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Total Synthesis of Pyrrolnitrin. II. Synthesis of Ethyl 3-Aryl-5-methyl-2-pyrrolecarboxylate. (1)[1,2]

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Ethyl 3-aryl-5-methyl-2-pyrrolecarboxylate (XXIII), a desirable intermediate for chlorination to prepare pyrrolnitrin, 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 intermedia te, 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_1,c) instead of the expected carboxylic acids (III). IIb was also condensed with acetophenone under basic condition to give IVb_2. These abnormal products were confirmed to be IV from the NMR spectra, that showed two olefinic protons ($CH_3COC\underline{H}=CH$: IVa 6.50; IVc 6.48 ppm, $CH_3COCH=C\underline{H}$: IVa 7.15; IVc 7.17 ppm in d_6-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 (XIb_1) 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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[1] Part I: S. Umio, K. Kariyone, K. Tanaka and H. Nakamura, *Chem. Pharm. Bull.* (Tokyo), **17**, 559 (1969).

[2] A part of this work was presented at the 9th Symposium of Chemistry of Natural Products at Osaka, Oct. 1965, and at the 87th Annual Meeting of the Pharmaceutical Society of Japan at Kyoto, April 1967.

[3] Location: *1, Kashimacho, Higashiyodogawa-ku, Osaka.*

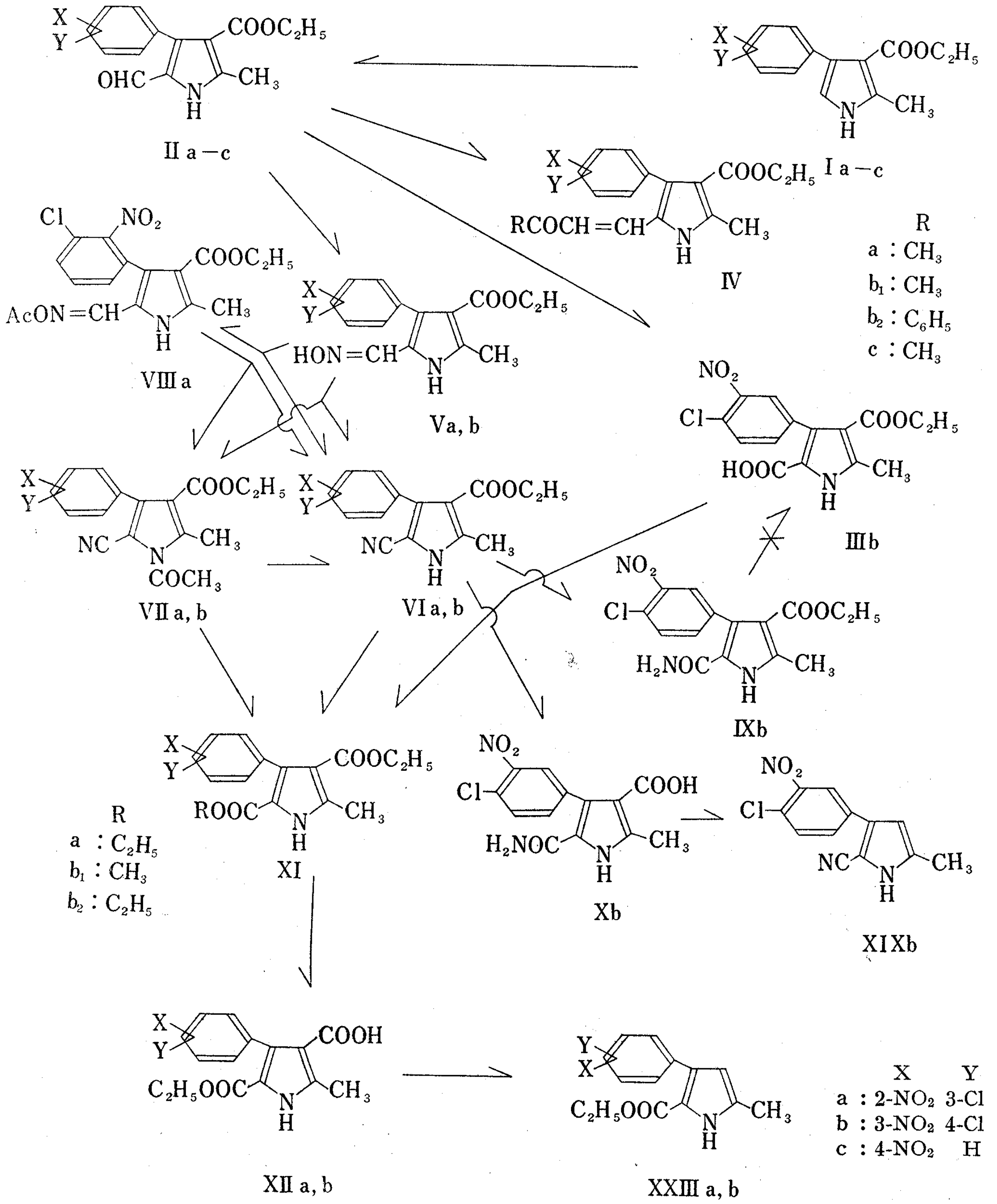

Chart I

frared spectrum of this by-product showed no NH absorption band in a 3300 cm^{-1} region. VIIa, b affroded 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 absorbtion 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-pyrrolecarboxylate (VIIIa) from the fact that treatment with boilling acetic anhydride afforded VIa.

In order to obtain IIIb *via* ethyl 2-carbamino-3-(3-nitro-4-chlorophenyl)-5-methyl-4-pyrrolecarboxylate (IXb), the cyanopyrrole derivative (VIb) was treated with hydrogen peroxide under a basic condition, but subsequent hydrolysis was not successful under any conditions. 2-Carbamino-3-(3-nitro-4-chlorophenyl)-5-methyl-4-pyrrolecarboxylic 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 alkoxycarbonyl 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.

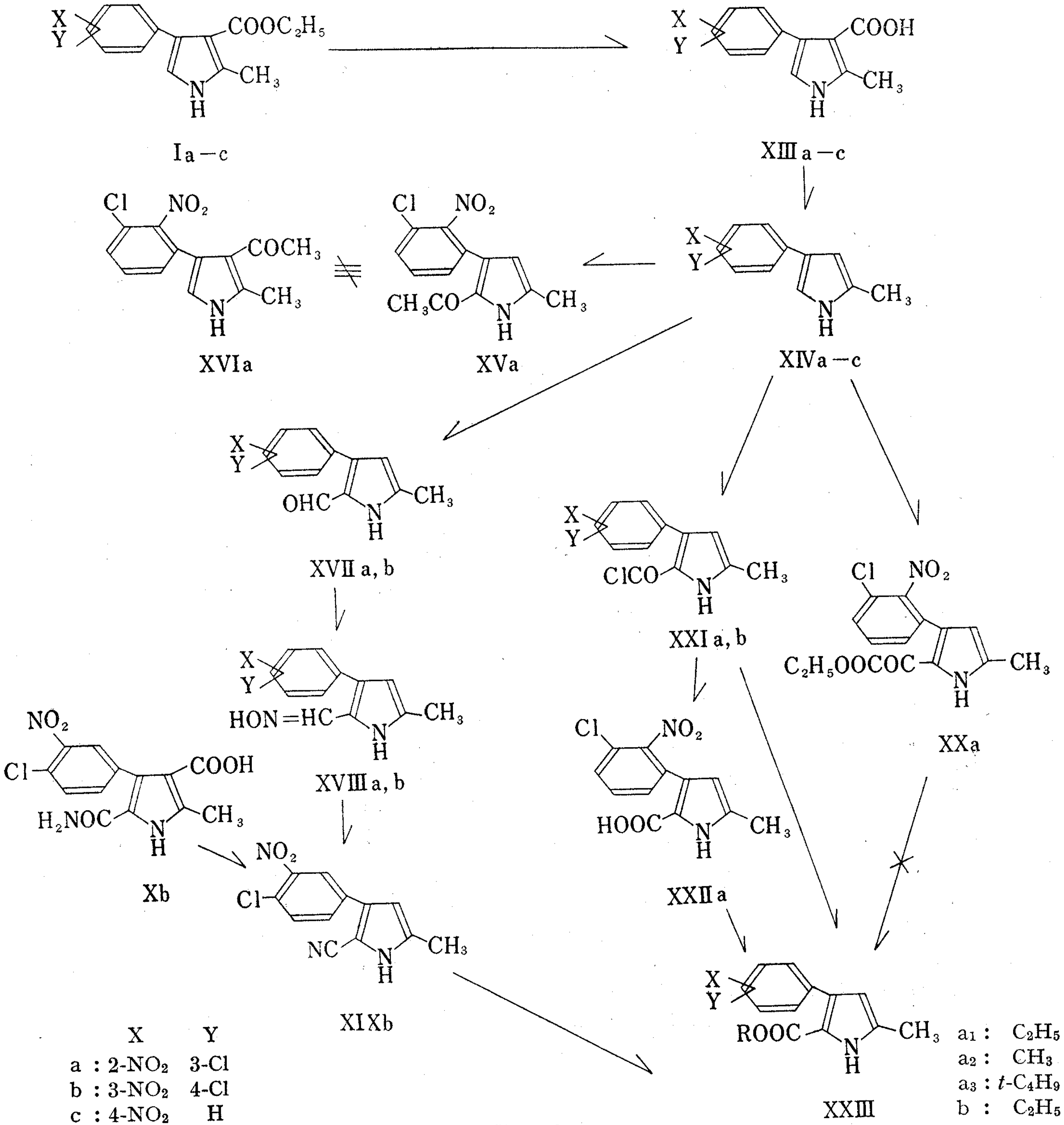

Chart 2

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[4] J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc. 1956, p. 299.

Using ethanol saturated with dry hydrogen chloride at −50°, the volume of ethanol increased about two times by hydrogen chloride, the cyano-pyrrole derivatives (VIa,b) afforded XIa,b_2, expected diethyl 3-aryl-5-methyl-2,4-pyrroledicarboxylate, in good yields. And the 1-acetyl-cyanopyrrole (VIIa,b) also gave XIa,b_2 under the same condition.

Selective hydrolysis of XIa,b_2 by treatment with concentrated sulfuric acid gave 2-ethoxycarbonyl-3-aryl-5-methyl-4-pyrrolecarboxylic acids (XIIa,b), and subsequent decarboxylation of resulting ester-acid afforded ethyl 3-aryl-5-methyl-2-pyrrolecarboxylate (XXIIIa_1,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 β-position of the pyrrole ring is known to be hydrolyzed with concentrated sulfuric acid through an acylinium ion, but ethyl 3-phenyl-5-methyl-4-pyrrolecarboxylate can not afford the corresponding carboxylic acid.[5]

On the contrary, under the above condition, ethyl 3-nitro-substituted phenyl-5-methyl-4-pyrrolecarboxylates (Ia—c) gave 3-aryl-5-methyl-4-pyrrolecarboxylic 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[1] 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-pyrrolecarboxyaldehyde (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-pyrrolecarboxylate (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-pyrroleoxalate (XXa) from XIVa and ethyl cyanoformate in the presence of zinc chloride, but subsequent decarbonylation 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-pyrrolecarbonyl 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-pyrrolecarboxylate (XXIIIa_1,a_2,a_3,b) with alcohols. XXIIIa_1,b did not show any depression in admixture with an authentic sample prepared from XIIa,b by the first route.

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

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[5] S. Cusmano and V. Spiro, *Gazz. Chim. Ital.*, **82**, 576 (1952) [*C.A.*, **48**, 3959*h* (1954)].

Experimental[6]

Ethyl 2-Formyl-3-(2-nitro-3-chlorophenyl)-5-methyl-4-pyrrolecarboxylate (IIa)——To dimethyl formamide (0.3 g), 0.6 g of $POCl_3$ 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–$POCl_3$ 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 H_2O and recrystallized from benzene as colorless needles (0.4 g), mp 187°. *Anal.* Calcd. for $C_{15}H_{13}O_5N_2Cl$: 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 ($COOC_2H_5$), 1530, 1365 (NO_2).

Ethyl 2-Formyl-3-(2-nitro-4-chlorophenyl)-5-methyl-4-pyrrolecarboxylate (IIb)——Ib (0.5 g) was stirred with a mixture of dimethylformamide (0.3 g) and $POCl_3$ (0.6 g) as described above. The product was recrystallized from AcOEt to give colorless prisms, having mp 185°. *Anal.* Calcd. for $C_{15}H_{13}O_5N_2Cl$: 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-pyrrolecarboxylate (IIc)——Ic (1.0 g) was treated with a mixture of dimethylformamide (0.5 g) and $POCl_3$ (0.5 g) as described above. The product was recrystallized from EtOH to give pale yellow needles (1.0 g) , mp 184°. *Anal.* Calcd. for $C_{15}H_{14}O_5N_2$: 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 ($COOC_2H_5$), 1640 (CHO), 1515, 1345 (NO_2). NMR ($CDCl_3$) ppm: 1.12 (3H, triplet, $CH_2C\underline{H}_3$), 2.69 (3H, singlet, $C_3\underline{H}$), 4.17 (2H, quartet, $C\underline{H}_2CH_3$), 7.65, 8.35 (each of them 2H, doublet, arom–H), 9.24 (1H, singlet, CHO).

Ethyl 2-(3-Oxo-1-butenyl)-3-(2-nitro-3-chlorophenyl)-5-methyl-4-pyrrolecarboxylate (IVa)——A mixture of IIa (1.2 g), KOH (0.36 g), acetone (60 ml) and H_2O (20 ml) was refluxed for 1.5 hr, condensed *in vacuo* to *ca.* 30 ml, and poured into H_2O. The resulting precipitate was collected by filtration, washed with 5% AcOH and crystallized from EtOH to afford 0.9 g of yellow needles having mp 199—200°. *Anal.* Calcd. for $C_{18}N_{17}O_5N_2Cl$: 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 ($COOC_2H_5$), 1670 (CH_3CO), 1530, 1370 (NO_2). NMR (d_6-acetone) ppm: 0.97 (3H, triplet, $COOCH_2$-$C\underline{H}_3$), 2.60 (3H, singlet, $C\underline{H}_3COCH{=}CH$), 2.87 (3H, singlet, $C\underline{H}_3$), 4.05 (2H, quartet, $COOC\underline{H}_2CH_3$), 6.50 (1H, doublet, $CH_3COC\underline{H}{=}CH$), 7.07 (1H, doublet, $CH_3COC{=}HCH$).

Ethyl 2-(3-Oxo-1-butenyl)-3-(3-nitro-4-chlorophenyl)-5-methyl-4-pyrrolecarboxylate (IVb_1)——IIb (1.8 g), KOH (0.24 g), acetone (30 ml) and H_2O (10 ml) were treated similarly as described above. The recrystallization from EtOH gave 1.9 g of yellow needles (mp 214—215°). *Anal.* Calcd. for $C_{18}H_{17}O_5N_2Cl$: 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-pyrrolecarboxylate (IVb_2)——A solution of IIb (0.2 g) and NaOH (0.06 g) in H_2O (0.5 ml)and EtOH (2 ml) was added acetophenone (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 H_2O. The resulting precipitate was filtered, washed, dried and crystallized from EtOH to give yellow prisms (0.32 g), mp 210—211°. *Anal.* Calcd. for $C_{23}H_{19}O_5N_2Cl$: 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 ($COOC_2H_5$), 1665 (C_6H_5CO), 1550, 1340 (NO_2).

Ethyl 2-(3-Oxo-1-butenyl)-3-(4-nitrophenyl)-5-methyl-4-pyrrolecarboxylate (IVc)——A solution of IIc (0.5 g) and $KHCO_3$ (0.45 g) and 2.5 ml of H_2O in 20 ml of acetone was stirred for 5 hr at 27°. The reaction mixture was evaporated in reduced pressure to small volume, and poured into H_2O. The aqueous layer was extracted with AcOEt and the organic layer was washed with H_2O and evaporated *in vacuo*. The residue was crystallized from EtOH to give 0.22 g of yellow needles (mp 222°). *Anal.* Calcd. for $C_{18}H_{18}O_5N_2$: C, 63.15; H, 5.30; N, 8.18. Found: C, 62.98; H, 5.43; N, 7.94. IR (nujol) cm^{-1}: 3280 (NH), 1710 ($COOC_2H_5$), 1640 (CH_3CO), 1510, 1340 (NO_2). NMR (d_6-acetone) ppm: 1.05 (3H, triplet, $CH_2C\underline{H}_3$), 2.50 (3H, singlet, $C\underline{H}_3CO$), 2.60 (3H, singlet, $C\underline{H}_3$), 4.10 (2H, quartet, $C\underline{H}_2CH_3$), 6.50 (1H, doublet, $CH_2COC\underline{H}{=}CH$), 7.20 (1H, doublet, $CH_3COCH{=}C\underline{H}$).

Methyl 3-(3-Nitro-4-chlorophenyl)-4-ethoxycarbonyl-5-methyl-2-pyrrolecarboxylate (XIb_1)——To a solution of IIb (0.7 g) in dioxane (20 ml) a solution of $KMnO_4$ (0.27 g) was added with stirring at room temperature until the color of $KMnO_4$ vanished. After filtration, the filtrate was condensed *in vacuo* and the residue was poured in 5% H_2SO_4, and the resulting precipitate was collected by filtration. The crude product was dissolved in Na_2CO_3 solution in order to remove undissolved material. The crude carboxylic acid was separated from the solution by acidification, which was treated with CH_2N_2. The methyl ester was recrystallized from benzene–hexane to give pale yellow needles, mp 205—206°. *Anal.* Calcd. for $C_{16}H_{15}O_6N_2Cl$: 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 ($COOCH_3$, $COOC_2H_5$).

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[6] All melting points are uncorrected. The infrared spectra were recorded on a Hitachi EPI-S_2. 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-pyrrolecarboxylate (Va)——An ethanolic solution of NH_2OH prepared from $NH_2OH \cdot HCl$ (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 H_2O 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 dehydration to VIa as described later.

Ethyl 2-Hydroxyiminomethyl-3-(3-nitro-4-chlorophenyl)-5-methyl-4-pyrrolecarboxylate (Vb)——IIB (1.3 g) was treated with NH_2OH as described above to give Vb (0.9 g) as pale yellow needles, mp 189°. *Anal.* Calcd. for $C_{15}H_{14}O_5N_3Cl$: 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 ($COOC_2H_5$), 1530, 1345 (NO_2).

Ethyl 2-Cyano-3-(2-nitro-3-chlorophenyl)-5-methyl-4-pyrrolecarboxylate (VIa), and Ethyl 1-Acetyl-2-cyano-3-(2-nitro-3-chlorophenyl)-5-methyl-4-pyrrolecarboxylate (VIIa)——i) A mixture of Va (0.7 g) and Ac_2O (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 $C_{15}H_{12}O_4N_3Cl$: 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 ($COOC_2H_5$), 1535, 1375 (NO_2).

The mother liquor was concentrated and the residue was dissolved in Ac_2O, and the solution was refluxed again for 1.5 hr and evaporated in reduced pressure. The residue was dissolved in $CHCl_3$ and the solution was chromatographed on silicagel to give 0.3 g of VIIa, mp 106—107.5°. *Anal.* Calcd. for $C_{17}H_{14}O_5N_3Cl$: 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), 1750 ($COOC_2H_5$), 1720 (CH_3CO), 1535, 1375 (NO_2).

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 VIa by mixed melting point comparison.

iii) A solution of crude VIIIa (1.0 g) in Ac_2O (20 ml) was heated under reflux for 3 hr, and evaporated in reduced pressure, and the residue was dissolved in $CHCl_3$. The $CHCl_3$ 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—142°), which was identified with VIa by melting point of admixture.

Ethyl 2-Cyano-3-(3-nitro-4-chlorophenyl)-5-methyl-4-pyrrolecarboxylate (VIb) and Ethyl 1-Acetyl-2-cyano-3-(3-nitro-4-chlorophenyl)-5-methyl-4-pyrrolecarboxylate (VIIb)——Vb (1.0 g) was treated with Ac_2O as described above to give VIb (0.8 g) having mp 165° as colorless needles. *Anal.* Calcd. for $C_{15}H_{12}O_4N_3Cl$: 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 $C_{17}H_{14}O_5N_3Cl$: 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 ($COOC_2H_5$), 1710 (CH_3CO).

Ethyl 2-Acetoxyiminomethyl-3-(2-nitro-3-chlorophenyl)-5-methyl-4-pyrrolecarboxylate (VIIIa)——As olution of Va (1.5 g) in AcOH (10 ml) containing Ac_2O (2 ml) was heated at 100° for 5 min and evaporated in reduced pressure. After extraction with AcOEt, the organic layer was washed with H_2O, dried, and evaporated. The fractional crystallization from benzene gave colorless needles (0.3 g), mp 192—193°. *Anal.* Calcd. for $C_{17}H_{15}O_6N_3Cl$: 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 ($CH_3COON=$), 1710 ($COOC_2H_5$), 1535, 1375 (NO_2).

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

Ethyl 2-Carbamino-3-(3-nitro-4-chlorophenyl)-5-methyl-4-pyrrolecarboxylate (IXb)——To a solution of VIb (0.2 g) in 95% EtOH (3 ml) containing one drop of 5% NaOH, 30% H_2O_2 (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 95% EtOH as pale yellow needles, mp 198—199°. *Anal.* Calcd. for $C_{15}H_{14}O_5N_3Cl$: 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 ($CONH_2$), 1705 ($COOC_2H_5$), 1650 ($CONH_2$).

Diethyl 3-(2-Nitro-3-chlorophenyl)-5-methyl-2,4-pyrroledicarboxylate (XIa)——i) from VIa: A mixture of VIa (1.6 g) in 240 ml of EtOH saturated with HCl at −50° was allowed to stand for 3 days at 40° in a seald tube. The reaction mixture was concentrated *in vacuo*, and the residue was poured into H_2O (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 $C_{17}H_{17}O_6N_2Cl$: C, 53.62; 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 ($COOC_2H_5$), 1540, 1370 (NO_2).

ii) from VIIa: VIIa (0.3 g) was treated as described above. The product (0.12 g) was identified with XIa prepared from VIa.

Diethyl 3-(3-Nitro-4-chlorophenyl)-5-methyl-2,4-pyrroledicarboxylate (XIb_2)——VIb (0.2 g) gave XIb_2 (0.1 g) as colorless needles, mp 193°. *Anal.* Calcd. for $C_{17}H_{17}O_6N_2Cl$: 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 ($COOC_2H_5$), 1530, 1350 (NO_2).

2-Ethoxycarbonyl-3-(2-nitro-3-chlorophenyl)-5-methyl-4-pyrrolecarboxylic Acid (XIIa)——A suspension of XIa (1.2 g) in 2.4 ml of H_2SO_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_2SO_4 under cooling. The resulting precipitate was extracted with AcOEt, and the organic layer was washed with H_2O, 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-pyrrolecarboxylate ($XXIIIa_1$)——i) From XIIa: A mixture of XIIa (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 $C_{14}H_{13}O_4N_2Cl$: C, 54.46; H, 4.24; N, 9.08. Found: C, 54.46; H, 4.19; N, 8.78. IR (nujol) cm^{-1}: 3300 (NH), 1660 ($COOC_2H_5$), 1530, 1375 (NO_2). NMR (d_5-pyridine) ppm: 0.95 (3H, triplet, $CH_2C\underline{H}_3$), 2.28 (3H, singlet, $C_3\underline{H}$), 4.19 (2H, quartet, $C\underline{H}_2CH_3$), 6.26 (1H, singlet, 4-position of pyrrole).

ii) From XIVa *via* XXIa: To a solution of XIVa (0.475 g) and dimethylaniline (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, dimethylaniline (0.242 g) and abs. EtOH (1.0 g) was added during 30 min. After removal of excess $COCl_2$ by bubbling with air, the solution was concentrated. The residue was acidified 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-pyrrolecarboxylate ($XXIIIa_2$)——i) From XIVa: To a solution of XIVa (2.0 g) and dimethylaniline (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 dimethylaniline (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 reaction mixture was allowed to stand overnight. The resulting cyrstals 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 $C_{13}H_{11}O_4N_2Cl$: 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 ($COOCH_3$), 1535, 1375 (NO_2).

ii) From XXIIa: XXIIa (0.5 g) was treated with etheral solution of excess CH_2N_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-pyrrolecarboxylate ($XXIIIa_3$)**——XXIa prepared from XIVa (4.8 g) and dimethylaniline (2.4 g) and $COCl_2$ as described above was treated with a mixture of dimethylaniline (2.4 g) and abs. *tert*-BuOH (15 ml). The product was recrystallized from benzene to give 4.9 g of colorless needles having mp 224—225°. *Anal.* Calcd. for $C_{16}H_{17}O_4N_2Cl$: 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 ($COOC_4H_9$), 1540, 1370 (NO_2).

Ethyl 3-(3-Nitro-4-chlorophenyl)-5-methyl-2-pyrrolecarboxylate (XXIIIb)——i) From XIb_2 *via* XIIb: XIb_2 (2.0 g) was hydrolyzed similarly as described in XIIa. The crude product was decarboxylated in glycerin as described in XXIIIa (i). The recrystallization from benzene gave pale yellow needles (0.06 g), mp 167°. *Anal.* Calcd. for $C_{14}H_{13}O_4N_2Cl$: 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 ($COOC_2H_5$), 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_2O, 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_2 by infrared spectrum comparison.

iii) From XIVb *via* XXIb: A solution of XIVb (0.476 g) described in $XXIIIa_1$ (ii). 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 XIIb by comparison of mixed melting point and infrared spectrum.

3-(2-Nitro-3-chlorophenyl)-5-methyl-4-pyrrolecarboxylic Acid (XIIIa)——A suspension of Ia (1.0 g) in 93% H_2SO_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 $KHCO_3$ solution. After removal of the undissolved material by filtration, 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-Nitro-4-chlorophenyl)-5-methyl-4-pyrrolecarboxylic Acid (XIIIb)——A suspension of Ib (1.0 g) in 93% H_2SO_4 (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 $C_{12}H_9O_4N_2Cl$: C, 51.35; H, 3.23; N, 9.98; Cl, 12.63. Found: C, 51.21; H, 3.23; N, 9.89; Cl, 12.63.

3-(4-Nitrophenyl)-5-methyl-4-pyrrolecarboxylic Acid (XIIIc)——A suspension of Ic (1.0 g) in 93% H_2SO_4 (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% Na_2CO_3 in order to exclude undissolved materials. Acidification of the filtrate of Na_2CO_3 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% H_2SO_4 was employed instead of 93% H_2SO_4, XIIIc was similarly obtained in the same yield as above, but the starting material could not be recovered in pure form.

3-(2-Nitro-3-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, and 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 $C_{11}H_9O_2N_2Cl$: 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 (NO_2).

ii) A suspension of XIIIa (10.0 g) in glycerin (10 ml) was stirred at 200° until the evolution of CO_2 was ceased, 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 $C_{11}H_9O_2N_2Cl$: C, 55.83; H, 3.83; N, 11.84. Found: C, 55.84; H, 4.05; N, 11.84.

3-(3-Nitro-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 CO_2 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 $C_{11}H_9O_2N_2Cl$: 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 (NO_2).

3-(4-Nitrophenyl)-5-methylpyrrole (XIVc)——A mixture of XIIIc (0.5 g) and soda asbesto (0.5 g) was heated under reduced pressure at 150—180° for 40 min in a combustion tube. The sublimated product was collected and purified by re-sublimation to give yellow granules (0.03 g mp 232°). *Anal.* Calcd. for $C_{11}H_{10}O_2N_2$: 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 (NO_2).

3-(2-Nitro-3-chlorophenyl)-5-methyl-2-pyrrolecarboxaldehyde (XVIIa)——$POCl_3$ (0.6 g) was added dropwise 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 $C_{12}H_9O_3N_2Cl$: 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 (NO_2).

3-(3-Nitro-4-chlorophenyl)-5-methyl-2-pyrrolecarboxaldehyde (XVIIb)——XIVb (0.6 g) was treated with a mixture of dimethylformamide and $POCl_3$ as described above. Recrystallization of the product from AcOEt gave pale yellow needles (0.5 g), mp 192°. *Anal.* Calcd. for $C_{12}H_9O_3N_2Cl$: 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 (NO_2).

2-Acetyl-3-(2-nitro-3-chlorophenyl)-5-methylpyrrole (XVa)——A solution of XIVa (0.4 g) in dichloroethane (2 ml) was added slowly to a mixture of $POCl_3$ (0.6 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 206.5—207°. *Anal.* Calcd. for $C_{13}H_{11}O_3N_2Cl$: 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 (CH_3CO), 1535, 1370 (NO_2).

3-(3-Nitro-4-chlorophenyl)-5-methylpyrrole-2-carbonitrile (XIXb)——i) From VIb *via* Xb: A stirring mixture of VIb (200 mg) and 98% H_2SO_4 (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_2OH (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 XVIIIb (1.0 g) in Ac_2O (15 ml) was refluxed for 3 hr, and evaporated in vacuo. The resulting viscouse liquid was sublimated under reduced pressure at 200—230° in a sublimation tube to give slight yellow needles (0.6 g) having mp 202° after twice sublimation. *Anal.* Calcd. for $C_{12}H_8O_2N_3Cl$: 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°. *Anal.* Calcd. for $C_{15}H_{13}O_5N_2Cl$: 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 XXIa prepared from XIVa (0.476 g) and dimethylaniline (0.242 g) and $COCl_2$ as described in XXIIIa$_1$ (ii), 20 ml of 5% K_2CO_3 was added with stirring at 0—5°, 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_2SO_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° decomp.). *Anal.* Calcd. for $C_{12}H_9O_4N_2Cl$: 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).