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# Total Synthesis of Pyrrolnitrin. X.[1] Synthesis of Pyrrolnitrin. (2)[2,3]

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Conversion of 2,5-disubstituted-3-arylpyrrole (II) to pyrrolnitrin (Ia) and the related compounds (I) was investigated. II was transformed by chlorination followed by hydrolysis and oxidation to 3-aryl-4-chloro-2,5-pyrroledicarboxylic acids (IV), which were decarboxylated to I in sulfuric acid.

Dialkyl 3-aryl-4-chloro-2,5-pyrroledicarboxylate (XI), alkyl β-aryl-4-chloropyrrolecarboxylates and halfesters of IV afforded Ia directly, when heated in sulfuric acid.

We have reported the synthetic methods of β-arylpyrroles (II) in Part II,[5] III,[6] VII[7] and IX.[1]

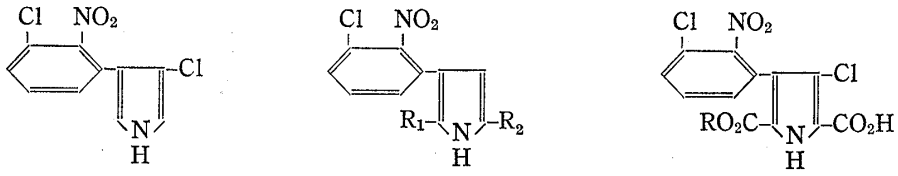


Chart 1

And in Part V[2] was reported the synthesis of pyrrolnitrin (Ia)[8] from ethyl 3-(2-nitro-3-chlorophenyl)-5-methyl-2-pyrrolecarboxylate (II: $R_1$=$COOC_2H_5$, $R_2$=$CH_3$), prepared in Part II[5] and III[6] *via* the halfester (III) and the dicarboxylic acid (IVa).

In this paper we wish to report the synthesis of Pyrrolnitrin (Ia) using the dimethylpyrroles, V and VI, prepared in Part VII,[7] and the pyrroles, VII, VIII and IX, prepared in Part IX.[1]

Treatment of the dimethylpyrroles, V and VI, with more than 7 moles of sulfuryl chloride in a mixture of acetic acid and propionic acid afforded the same octachloropyrrole at low temperature.

In the case of pyrrolecarboxylic acid (V), substitution of the carboxyl group by the chloro group occurred in this reaction.

Octachloropyrrole (X), when refluxed in an aqueous bicarbonate solution or in glacial acetic acid, was converted to 3-(2-nitro-3-chlorophenyl)-4-chloro-2,5-pyrroledicarboxylic acid (IVa) by solvolysis of the trichloromethyl groups in these solvents.

1) Part IX: K. Tanaka, K. Kariyone and S. Umino, *Chem. Pharm. Bull.* (Tokyo), **17**, 616 (1969).
2) Part V: *Chem. Pharm. Bull.* (Tokyo), **17**, 588 (1969).
3) A part of this work was presented at the 9th Symposium of the Chemistry of Natural Products at Osaka, Oct. 1965. Preliminary communication of a part of this work appeared in *Tetrahedron Letters*, **1966**, 737, and in *Yakugaku Zasshi*, **86**, 159 (1966).
4) Location: *1, Kashimacho, Higashiyodogawa-ku, Osaka.*
5) Part II: *Chem. Pharm. Bull.* (Tokyo), **17**, 567 (1969).
6) Part III: *Chem. Pharm. Bull.* (Tokyo), **17**, 576 (1969).
7) Part VII: *Chem. Pharm. Bull.* (Tokyo), **17**, 605 (1969).
8) K. Arima, H. Imanaka, M. Kousaka, and A. Fukuta, *Agr. Biol. Chem.*, **28**, 575 (1964).

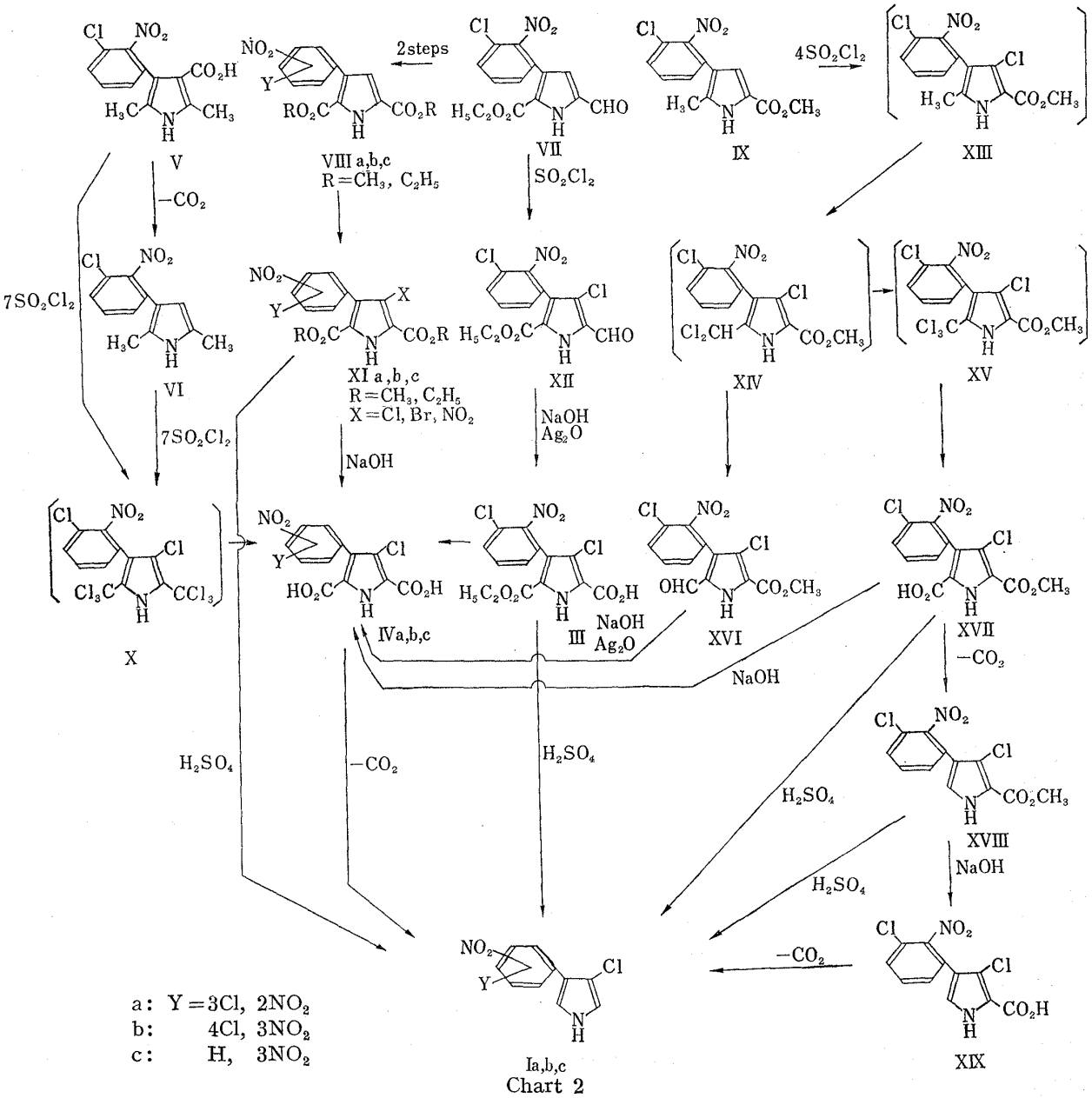


Chart 2

At room temperature as employed for chlorination of II ($R_1$=$COOC_2H_5$, $R_2$=$CH_3$), the yield fell down owing to the side-production of tarry materials.

This difference was consistent with the fact that Ehrlich reaction was positive in the dimethylpyrrole (VI), although this was negative in the pyrrolecarboxylic ester (II: $R_1$=$COOC_2H_5$, $R_2$=$CH_3$), and this color reaction was supposed to show the tendency of V and VI to suffer from side reactions.

On the contrary, 2,5-pyrroledicarboxylic ester (VIII) were so unreactive that heating might be necessary for chlorination of these compounds in acetic acid.

Chlorination of dimethyl 3-(3-nitro-4-chlorophenyl)-2,5-pyrroledicarboxylate (VIIIb: R=$CH_3$) and dimethyl 3-(3-nitrophenyl)-2,5-pyrroledicarboxylate (VIIIc: R=$CH_3$) with sulfuryl chloride yielded 4-chloro compounds, XIb (R=$CH_3$, X=Cl) and XIc (R=$CH_3$, X=Cl), at 60°—70° in acetic acid.

This chlorination is supposed to proceed by an ionic reaction mechanism, because this reaction was prompted by addition of iodine. Similarly, bromination and nitration of VIIIb (R=$CH_3$) gave 4-bromo- (XIb: R=$CH_3$, X=Br) and 4-nitro-compound (XIb: R=$CH_3$, X=$NO_2$) respectively.

Diethyl 3-(2-nitro-3-chlorophenyl)-2,5-pyrroledicarboxylate (VIIIa: R=$C_2H_5$), however, was not chlorinated in good yield under this reaction condition.

Because benzene and pyrrole ring are not in the same plane in VIIIa (R=$C_2H_5$), the difference is not explainable from mesomeric effect of the nitro group, but rather from a steric hindrance of this group.

Chlorination of VIIIa (R=$C_2H_5$) was attained by addition of benzoylperoxide to this reaction mixture to give diethyl 3-(2-nitro-3-chlorophenyl)-4-chloro-2,5-pyrroledicarboxylate (XIa: R=$C_2H_5$, X=Cl), which was identified with a sample prepared in Part V.[2)]

The chlorinated diesters, XIb (R=$CH_3$, X=Cl), XIc (R=$CH_3$, X=Cl) and XIa (R=$C_2H_5$, X=Cl), thus obtained, were easily hydrolyzed to the corresponding 2,5-pyrroledicarboxylic acids, IVa,b,c. 3-(2-Nitro-3-chlorophenyl)-4-chloro-2,5-pyrroledicarboxylic acid (IVa) was also prepared from ethyl 3-(2-nitro-3-chlorophenyl)-5-formyl-2-pyrrolecarboxylate (VII) in the following way: chlorination of VII with sulfuryl chloride gave ethyl 3-(2-nitro-3-chlorophenyl)-4-chloro-5-formyl-2-pyrrolecarboxylate (XII), which was oxidized to the halfester (III) with silver oxide in aqueous ethanolic sodium hydroxide.

Hydrolysis of this halfester (III) yielded 3-(2-nitro-3-chlorophenyl)-4-chloro-2,5-pyrroledicarboxylic acid (IVa).

Next, chlorination of methyl 2-methyl-3-(2-nitro-3-chlorophenyl)-5-pyrrolecarboxylate (IX) was investigated.

We have reported the chlorination of II ($R_1$=$COOC_2H_5$, $R_2$=$CH_3$) with 4 moles of sulfuryl chloride at room temperature in acetic acid to give the halfester (III) in good yield.[2)]

When IX was chlorinated under the same reaction condition as used for II ($R_2$=$COOC_2H_5$, $R_2$=$CH_3$), a mixture of the formylester (XVI) and the halfester (XVII) was obtained.

Good yield of the halfester (XVII), however, was obtained accompanied with a trace of the aldehyde (XVI), when this chlorination was carried out at −5°——10° in an acetic acid–propionic acid mixture.

Oxidation of the aldehyde (XVI) with silver oxide in aqueous ethanolic sodium hydroxide afforded the 2,5-pyrroledicarboxylic acid (IVa) directly, which was also prepared by hydrolysis of the halfester (XVII).

The halfester (XVII), when heated in glycerin, was decarboxylated to methyl 3-(2-nitro-3-chlorophenyl)-4-chloro-5-pyrrolecarboxylate (XVIII), which was hydrolyzed to the corresponding acid (XIX).

By the way, we have chosen $\alpha,\alpha'$-substituted-$\beta$-arylpyrroles (II) as intermediates to pyrrolnitrin (Ia) as often described already, because $\alpha$-positions are usually more reactive than $\beta$-in pyrrole rings.

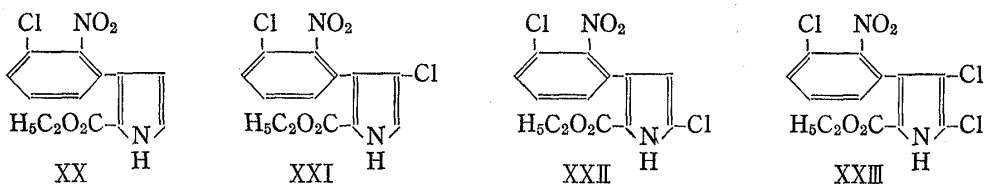


Chart 3

The pyrrolecarboxylate (XX), when treated with a little excess of sulfuryl chloride in an acetic acid–propionic acid mixture, afforded ethyl 3-(2-nitro-3-chlorophenyl)-4-chloro-2-pyrrolecarboxylate (XXI) preferentially, accompanied with only small amounts of 5-chloro-(XXII) and 4,5-dichloro-compound (XXIII).

Synthesis of pyrrolnitrin (Ia) using the pyrrole derivatives prepared in this paper was investigated in the following way.

3-(2-Nitro-3-chlorophenyl)-4-chloro-2,5-pyrroledicarboxylic acid (IVa), obtained from pyrroles, V, VI, VII, VIII and IX, was decarboxylated to 3-(2-nitro-3-chlorophenyl)-4-chloro-

pyrrole (Ia) in boiling dimethylaniline as described in Part V,[9] which was identified with pyrrolnitrin (Ia) by the mixed melting point and IR *etc.*

Ia was also prepared by decarboxylation of 3-(2-nitro-3-chlorophenyl)-4-chloro-5-pyrrolecarboxylic acid (XIX) under similar reaction condition.

Moreover, it was found that treatment of the dicarboxylic acid (IVa) in hot sulfuric acid acid gave Ia.

Similarly, 2,5-pyrroledicarboxylic acids (IVb,c) were decarboxylated in sulfuric acid to give analogues of Ia.

Furthermore, it was found that the similar treatment of pyrroles, III, XVII, XIa, XVIII and XX, in sulfuric acid afforded Ia, without passing through the corresponding carboxylic acids.

This type of dealkoxycarbonylation in concentrated sulfuric acid has not been reported and was supposed to proceed directly by substitution of the alkoxycarbonyl group by a proton of sulfuric acid.

## Experimental[10]

**Dimethyl 3-(3-Nitro-4-chlorophenyl)-4-chloro-2,5-pyrroledicarboxylate (XIb: R=$CH_3$, X=Cl)**——To a suspension of dimethyl 3-(3-nitro-4-chlorophenyl)-2,5-pyrroledicarboxylate (VIIIb: R=$CH_3$) (230 mg) in AcOH (12 ml) was added a solution of $SO_2Cl_2$ (190 mg) in AcOH (2 ml) followed by addition of a drop of solution of $I_2$ in AcOH. After the mixture was warmed at 60° (bath temp.) for 6 hr, most of AcOH was removed *in vacuo*, the residual solution was diluted with $H_2O$ and extracted with AcOEt. The AcOEt extracts were washed with $H_2O$, aqueous $NaHCO_3$ and $H_2O$, dried and evaporated to dryness. Recrystallization of the residue from MeOH yielded colorless crystals (XIb: R=$CH_3$, X=Cl) (130 mg), mp 207—209°. *Anal.* Calcd. for $C_{14}H_{10}O_6N_2Cl_2$: C, 45.05; H, 2.71; N, 7.51; Cl, 19.00. Found: C, 44.85; H, 2.66; N, 7.31; Cl, 19.22. IR (nujol) $cm^{-1}$: 3260 (NH), 1735, 1710 ($COOCH_3$), 1531, 1345 ($NO_2$).

**Dimethyl 3-(3-Nitro-4-chlorophenyl)-4-bromo-2,5-pyrroledicarboxylate (XIb: R=$CH_3$, X=Br)**——To a stirred suspension of VIIIb (R=$CH_3$) (0.20 g) in AcOH (25 ml) was added a solution of $Br_2$ (110 mg) in AcOH (5 ml). Stirring was continued at 70° (bath temp.) for 9 hr. After cooling, the resulting solution was diluted with $H_2O$ and extracted with AcOEt. The AcOEt extracts were washed with aqueous $NaHCO_3$ and $H_2O$, dried and evaporated to dryness. Recrystallization of the residue from benzene yielded colorless crystals (XIb: R=$CH_3$, X=Br) (150 mg), mp 189—191°. *Anal.* Calcd. for $C_{14}H_{10}O_6N_2BrCl$: C, 40.24; H, 2.42. Found: C, 40.49; H, 2.70. IR (nujol) $cm^{-1}$: 3280 (NH), 1708, 1730 ($COOCH_3$), 1530, 1350 ($NO_2$).

**Dimethyl 3-(3-Nitro-4-chlorophenyl)-4-nitro-2,5-pyrroledicarboxylate (XIb: R=$CH_3$, X=$NO_2$)**——A solution of $HNO_3$ ($d$=1.52) (0.2 ml) in $Ac_2O$ (0.8 ml) was added to a stirred suspension of VIIIb (50 mg) in $Ac_2O$ (3 ml). Stirring was continued at 80—85° for 1 hr and then on a boiling water bath for 3 hr. After cooling, reaction mixture was diluted with $H_2O$ and extracted with AcOEt. The AcOEt extracts were washed with aqueous $NaHCO_3$ and $H_2O$, dried and evaporated to dryness. Recrystallization of the residue from benzene yielded colorless crystals (XIb: R=$CH_3$, X=$NO_2$)(21 mg), mp 214—215°. *Anal.* Calcd. for $C_{14}H_{10}O_8N_3Cl$: C, 43.82; H, 2.63; N, 10.98. Found: C, 43.86; H, 2.93; N, 10.63.

**Dimethyl 3-(3-Nitrophenyl)-4-chloro-2,5-pyrroledicarboxylate (XIc: R=$CH_3$, X=Cl)**——A solution of $SO_2Cl_2$ (12.4 mg) in AcOH (1.6 ml) was added to a solution of dimethyl 3-(3-nitrophenyl)-2,5-pyrroledicarboxylate (XIc: R=$CH_3$) (20 mg) in AcOH (1.6 ml), and the mixture was warmed at 60° for 8 hr. The reaction solution was diluted with $H_2O$ and extracted with AcOEt. The AcOEt extracts were washed with $H_2O$, aqueous $NaHCO_3$ and $H_2O$, dried and evaporated to give colorless crystals (XIc: R=$CH_3$, X=Cl) (24 mg), mp 181—185°. Recrystallization from MeOH yielded colorless crystals, mp 202. *Anal.* Calcd. for $C_{14}H_{11}O_6N_2Cl$: C, 49.64; H, 3.27; N, 8.28. Found: C, 49.87; H, 3.56; N, 8.16. IR (nujol) $cm^{-1}$: 3320 (NH), 1730, 1708 ($COOCH_3$), 1522, 1353 ($NO_2$).

**Diethyl 3-(2-Nitro-3-chlorophenyl)-4-chloro-2,5-pyrroledicarboxylate (XIa: R=Et, X=Cl)**——To a suspension of diethyl 3-(2-nitro-3-chlorophenyl)-2,5-pyrroledicarboxylate (VIIIa: R=$C_2H_5$) (0.1 g) in AcOH (2 ml) was added a solution of $SO_2Cl_2$ (0.06 g) in AcOH (2 ml), followed by addition of a little amount of $(PhCOO)_2$. The reaction mixture was warmed at 60°(bath temp.) for 42 hr, poured into $H_2O$ and extracted with AcOEt. The AcOEt extracts were washed with $H_2O$ and aqueous $NaHCO_3$ , dried and evaporated

9) Part V: *Chem. Pharm. Bull.* (Tokyo), **17**, 588 (1969).

10) 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.

to dryness. Recrystallization of the residue from EtOH yielded white crystals (XIa: R=$C_2H_5$, X=Cl) (0.05 g), mp 128—130°. Further recrystallization raised the melting point to 134°, and no mixed melting point depression was observed with a sample prepared in Part V.[9] *Anal.* Calcd. for $C_{16}H_{14}O_6N_2Cl_2$: C, 47.89; H, 3.52; N, 6.98; Cl, 17.68. Found: C, 47.73; H, 3.45; N, 6.87; Cl, 17.61.

**Ethyl 3-(2-Nitro-3-chlorophenyl)-4-chloro-5-formyl-2-pyrrolecarboxylate (XII)**——To a suspension of ethyl 3-(2-nitro-3-chlorophenyl)-5-formyl-2-pyrrolecarboxylate (VII) (0.4 g) in AcOH (8 ml) was added a solution of $SO_2Cl_2$ (0.4 g) in AcOH (2 ml), and the mixture was warmed at 65° (bath temp.) for 17 hr. After cooling, the solution was diluted with $H_2O$ and extracted with AcOEt. The AcOEt extracts were washed with $H_2O$ and aqueous $NaHCO_3$, dried and evaporated. The residue was dissolved in benzene and chromatographed on silicagel using benzene as eluent to give, after evaporation of the solvent, colorless crystals (XII) (0.25 g). Recrystallization from AcOEt–*n*-hexane yielded colorless crystals, mp 183—185°. *Anal.* Calcd. for $C_{14}H_{10}O_5N_2Cl_2$: C, 47.07; H, 2.83; N, 7.84; Cl, 19.86. Found: C, 46.85; H, 2.85; N, 7.80; Cl, 19.55. NMR ($CDCl_3$) ppm: 1.10 (3H, triplet, $OCH_2\underline{CH_3}$), 4.20 (2H, qualtet, $O\underline{CH_2}CH_3$), 7.2—7.7 (3H, multiplet, phenyl), 9.87 (1H, singlet, CHO).

**2-Ethoxycarbonyl-3-(2-nitro-3-chlorophenyl)-4-chloro-5-pyrrolecarboxylic Acid (III)**——To a stirred suspension of 3-(2-nitro-3-chlorophenyl)-4-chloro-5-formyl-2-pyrrolecarboxylate (XII) (0.2 g) in abs. EtOH (8 ml) was added under cooling $Ag_2O$ (prepared from 0.4 g of $AgNO_3$), followed by dropwise addition of a solution of NaOH (0.09 g) in $H_2O$ (8 ml). Stirring was continued in an ice–$H_2O$ bath for 8 hr and then allowed to stand overnight in a refrigerator. The reaction mixture was filtered and the solid washed with EtOH and $H_2O$. The filtrte and washing were combined, acidified with HCl and extracted with AcOEt. Acidic substances were extracted with dil. aqueous NaOH, acidified with HCl and extracted with AcOEt. The extracts were washed with $H_2O$, dried and evaporated to leave a colorless solid (III) (0.2 g). Twice recrystallizations from AcOH yielded colorless crystals (0.15 g), mp 272—274° (decomp.). This was identified with a sample prepared in Part V[2] by IR and was furthermore ascertained by esterification to XIa (R=$C_2H_5$, X=Cl). *Anal.* Calcd. for $C_{14}H_{10}O_6N_2Cl_2$: C, 45.06; H, 2.71; N, 7.51; Cl, 19.00. Found: C, 44.79; H, 2.71; N, 7.52; Cl, 18.79.

**Chlorination of Methyl 2-Methyl-3-(2-nitro-3-chlorophenyl)-5-pyrrolecarboxylate (IX)**——i) Reaction in an Ice–$H_2O$ Bath: A solution of $SO_2Cl_2$ (0.4 g) in AcOH–EtCOOH (1:1) (2 ml) was added dropwise to a stirred suspension of IX (0.2 g) in AcOH–EtCOOH (1:1) (2 ml) in an ice–$H_2O$ bath over the period of ½ hr. The suspension was stirred at this temperature for 5 hr, during this time IX was once dissolved and then new crystals began to precipitate. Stirring was continued at room temperature for 180 hr, until the precipitated crystals were completely dissolved. Then the solution was stirred at 60° for 3 hr, poured into $H_2O$ and extracted with AcOEt. The AcOEt extracts were washed with $H_2O$ and evaporated to dryness. The residue was dissolved in AcOH (7 ml) and refluxed for 1½ hr. Most of AcOH was removed *in vacuo*, and the residue was diluted with $H_2O$ and the mixture was extracted with AcOEt. Acidic substances were extracted with dil. aqueous NaOH from the AcOEt extracts, acidified with HCl and extracted with AcOEt. AcOEt extracts were washed with $H_2O$, dried and evaporated to leave a colorless solid (0.08 g). Recrystallization from AcOH yielded white crystals (XVII) (0.055 g), mp 279° (decomp.). Further recrystallization raised the melting point to 282° (decomp.). *Anal.* Calcd. for $C_{13}H_{18}O_6N_2Cl_2$: C, 43.47; H, 2.25; N, 7.80; Cl, 19.75. Found: C, 43.57; H, 2.49; N, 7.73; Cl, 19.71.

The original, non–alkali–extractable fractions were washed with $H_2O$, dried and evaporated to give a pale brown solid (0.15 g). Twice recrystallizations from $C_6H_6$–*n*-hexane yielded pale yellow crystals (XVI-$H_2O$), mp 173—174°. *Anal.* Calcd. for $C_{13}H_{18}O_5N_2Cl_2 \cdot H_2O$: C, 43.23; H, 2.80; N, 7.76; Cl, 19.64. Found: C, 43.60; H, 3.10; N, 7.52; Cl, 19.82. IR (nujol) $cm^{-1}$: 3370, 3260 (NH), 1725, 1708, 1675 ($COOCH_3$ CHO), 1538, 1370 ($NO_2$). NMR ($CDCl_3$) ppm: 4.05 (3H, singlet, $OCH_3$), 7.50—7.82 (3H, multiplet, phenyl), 9.58 (1H, singlet, CHO).

ii) At −10°: A solution of $SO_2Cl_2$ (1.7 g) in AcOH–EtCOOH (1:1) (9 ml) was added dropwise to a stirred suspension of IX (0.85 g) in AcOH–EtCOOH (1:1) (9 ml) at −10° over a period of 1 hr. Stirring was continued at −10——−15° for 3½hr, at room temperature for 170 hr and at 60° for 3 hr. The reaction mixture was worked up as above to give crude XVI (0.05 g) and XVII (0.8 g). Recrystallization of XVII from AcOH yielded colorless crystals (0.6 g), mp 281—282° (decomp.).

**Methyl 3-(2-Nitro-3-chlorophenyl)-4-chloro-5-pyrrolecarboxylate (XVIII)**——A suspension of 5-methoxycarbonyl-3-(2-nitro-3-chlorophenyl)-4-chloro-2-pyrrolecarboxylic acid (XVII) (0.2 g) in glycerin (10 ml) was heated with stirring under $N_2$ stream at 230—240° for 1½ hr. After cooling, the mixture was diluted with $H_2O$ and extracted with benzene. The benzene extracts were washed with $H_2O$, dried and evaporated to dryness. The residue was dissolved in benzene and chromatogrphed on a silicagel column using benzene as an eluent. Evaporation of the solvent gave colorless crystals (XVIII) (0.02 g). Recrystallization from benzene yielded colorless crystals, mp 197—198°. *Anal.* Calcd. for $C_{12}H_{18}O_4N_2Cl$: C, 45.73; H, 2.56; N, 8.89; Cl, 22.50. Found: C, 45.56; H, 2.36; N, 8.78; Cl, 22.69. IR (nujol) $cm^{-1}$: 3220 (NH), 1788, 1670 ($COOCH_3$), 1530, 1380 ($NO_2$).

**3-(2-Nitro-3-chlorophenyl)-4-chloro-5-pyrrolecarboxylic Acid (XIX)**——A mixture of methyl 3-(2-nitro-3-chlorophenyl)-4-chloro-5-pyrrolecarboxylate (XVIII) (0.3 g), NaOH (0.1 g), $H_2O$ (4 ml) and 95% EtOH (5 ml) was refluxed for 4 hr. Most of EtOH was removed *in vacuo*, and the residue was diluted with $H_2O$ and

the mixture was extracted with AcOEt. Washing, drying and evaporating of the extracts gave a colorless solid (XIX) (0.28 g). Recrystallization from AcOEt yielded colorless crystals (0.25 g), mp 215°. IR (nujol) $cm^{-1}$: 3370 (NH), 1670 (COOH), 1538, 1372 ($NO_2$).

**3-(3-Nitro-4-chlorophenyl)-4-chloro-2,5-pyrroledicarboxylic Acid (IVb)**——A mixture of dimethyl 3-(3-nitro-4-chlorophenyl)-4-chloro-2,5-pyrroledicarboxylate (IXb: R=$CH_3$, X=Cl) (0.12 g), KOH (0.15 g), $H_2O$ (10 ml) and 95% EtOH (20 ml) was refluxed for 5½ hr. Most of EtOH was removed *in vacuo*, the residue was diluted with $H_2O$, acidified with HCl and extracted with EtOAc. Washing, drying and evaporation of the extracts gave a colorless solid (IVb) quantitatively. Recrystallization from aqueous EtOH yielded colorless crystals, mp 280° (decomp.). *Anal.* Calcd. for $C_{12}H_6O_6N_2Cl_2$: C, 41.76; H, 1.76. Found: C, 42.03; H, 1.99.

**3-(3-Nitrophenyl)-4-chloro-2,5-pyrroledicarboxylic Acid (IVc)**——A mixture of dimethyl 3-(3-nitrophenyl)-4-chloro-2,5-pyrroledicarboxylate (IXc: R=$CH_3$, X=Cl) (198 mg), KOH (287 mg), 95% EtOH (8 ml) and $H_2O$ (2.4 ml) was refluxed for 6 hr. The reaction mixture was worked up in the usual way to give a colorless solid (172 mg). Recrystallization from aqueous EtOH yielded colorless crystals (IVc) (148 mg), mp 292—294° (decomp.). IR (nujol) $cm^{-1}$: 3500 (NH), 1690 (COOH), 1520, 1350 ($NO_2$).

**3-(2-Nitro-3-chlorophenyl)-4-chloro-2,5-pyrroledicarboxylic Acid (IVa)**——i) From 2,5-Dimethyl 3-(2-nitro-3-chlorophenyl)-4-pyrrolecarboxylic Acid (V): $SO_2Cl_2$ (4.5 g) was added dropwise to a stirred suspension of V (1.2 g) in AcOH (20 ml) in an ice–$H_2O$ bath. Stirring was continued in ice–$H_2O$ bath for 5 hr and at room temperature for 2—3 days. The solution was diluted with $H_2O$ and extracted with AcOEt. The AcOEt extracts were washed with $H_2O$, dried and evaporated to dryness. The residue was dissolved in AcOH (20 ml) was refluxed for an hr. Most of AcOH was removed *in vacuo*, $H_2O$ was added and the mixture was extracted with AcOEt. AcOEt extracts were washed with $H_2O$, dried and evaporated to dryness. Recrystallization of the residue from AcOH yielded colorless crystals (IVa) (0.4 g), mp 283°. This was identified with a sample of IVa, prepared in Part V,[2] by IR.

ii) From 2,5-Dimethyl-3-(2-nitro-3-chlorophenyl)pyrrole (VI): A solution of $SO_2Cl_2$ (8.65 g) in AcOH–EtCOOH (1:1) (20 ml) was added dropwise to a stirred suspension of VI (2 g) in AcOH–EtCOOH (1:1) (20 ml) at −20——25° over a period of an hr. Stirring was continued at −20——25° for 5 hr, at −10——20° for 14 hr, at room temperature for 48 hr and at 60° for 3 hr. The reaction mixture was worked up in the usual way to give a colorless solid (IVa) (1.45 g). Recryizastalltion from AcOH yielded colorless crystals (0.9 g), mp 296° (decomp.). Further recrystallization raised the melting point to 303° (decomp.). *Anal.* Calcd. for $C_{12}H_6O_6N_2Cl_2$: C, 41.76; H, 1.76; N, 8.12; Cl, 20.55. Found: C, 41.82; H, 1.93; N, 7.90; Cl, 20.71.

iii) From Methyl 2-Formyl-3-(2-nitro-3-chlorophenyl)-4-chloro-5-pyrrolecarboxylate (XVI): To a stirred and cooled solution of XVI (105 mg) in abs. EtOH (4 ml) was added $Ag_2O$ (prepared from 0.21 g of $AgNO_3$) followed by the dropwise addition of a solution of NaOH (48 mg) in $H_2O$ (1 ml). Stirring was continued in an ice–$H_2O$ bath for 2 hr and at room temperature for 16 hr. The reaction mixture was filtered, the filtrate was diluted with $H_2O$, acidified with HCl and extracted with AcOEt. Acidic substances were extracted with dil. aqueous NaOH, acidified with HCl and extracted with AcOEt. The AcOEt extracts were washed with $H_2O$, dried and evaporated to leave colorless crystals (IVa) (0.10 g). Recrystallization from AcOEt yielded colorless crystals (0.08 g), mp 300° (decomp.).

iv) From 3-(2-Nitro-3-chlorophenyl)-4-chloro-5-methoxycarbonyl-2-pyrrolecarboxylic Acid (XVII): A mixture of XVII (0.3 g), NaOH (0.15 g), $H_2O$ (4 ml) and 99% EtOH (5 ml) was refluxed for 5 hr. Most of EtOH was removed *in vacuo* and the residue was diluted with $H_2O$ acidified with HCl and extracted with AcOEt. Washing, drying and evaporating the solvent gave a colorless solid (IVa) (0.25 g). Recrystallization from AcOH yielded colorless crystals (0.22 g), mp 307° (decomp.). *Anal.* Calcd. for $C_{12}H_6O_6N_2Cl_2$: C, 41.76; H, 1.76; N, 8.12; Cl, 20.55. Found: C, 41.20; H, 1.70; N, 8.33; Cl, 20.78.

**Chlorination of Ethyl 3-(2-Nitro-3-chlorophenyl)-2-pyrrolecarboxylate (XX)**——To a stirred solution of XX (0.5 g) in AcOH–EtCOOH (1:1) (30 ml) was added dropwise a solution of $SO_2Cl_2$ (0.27 g) in AcOH–EtCOOH (1:1) (5 ml) in an ice–$H_2O$ bath over a period of 30 min. Stirring was continued in an ice–$H_2O$ bath for 5 hr and then the solution was allowed to stand at room temperature for 40 hr. The solution was diluted with $H_2O$ and extracted with benzene. The benzene extracts were washed with $H_2O$, aqueous $NaHCO_3$ and $H_2O$, dried and evaporated to give a colorless solid (0.6 g). This was dissolved in $C_6H_6$, chromatographed on $Al_2O_3$ using benzene as an eluent and the eluted fractions were analysed by thin-layer chromtography (TLC). Those fractions containing the disired product were combined and evaporated to give crude XX (0.45 g), mp 145—150°. Twice recrystallizations from $CCl_4$ yielded colorless crystals (0.4 g), mp 163—165°. No mixed melting point depression was observed with an authentic sample of XXI.

**3-(3-Nitro-4-chlorophenyl)-4-chloropyrrole (Ib)**——3-(3-Chloro-4-nitrophenyl)-4-chloro-2,5-pyrroledicar boxylic acid (IVb) (40 mg) was suspended in conc. $H_2SO_4$ (1 ml) and heated at 120° (bath temp.) for 5 min. Resulting purple solution was poured into ice–$H_2O$ and extracted with AcOEt. The AcOEt extracts were washed with $H_2O$, aqueous $NaHCO_3$ and $H_2O$, dried and evaporated to dryness. The yellow residue was chromatographed on silica-gel column using benzene as an eluent and the eluted $C_6H_6$ was evaporated to give yellow crystals (Ib). Recrystallization from $C_6H_6$–light peteroleum yielded yellow crystals (20 mg), mp 114—115°. *Anal.* Calcd. for $C_{10}H_6O_2N_2Cl_2$: C, 46.71; H, 2.36; N, 10.90; Cl, 27.58. Found: C, 46.99; H, 2.57; N, 11.07; Cl, 27.54. IR (nujol) $cm^{-1}$: 3455 (NH), 1523, 1346 ($NO_2$).

**3-(3-Nitrophenyl)-4-chloropyrrole (Ic)**——A suspension of 3-(3-nitrophenyl)-4-chloro-2,5-pyrroledicarboxylic acid (IVc) (75.5 mg) in conc. $H_2SO_4$ (2 ml) was heated at 120° (bath temp.) for 10 min. The hot solution was poured onto ice and worked up in the usual way to give yellow crystals (Ic) (58 mg). Recrystallization from $C_6H_6$–light petroleum yielded yellow crystals (31 mg), mp 105°. *Anal.* Calcd. for $C_{10}H_7O_2N_2Cl$: C, 53.95; H, 3.17; N, 12.63; Found: C, 54.08; H, 3.38; N, 12.81. IR (nujol) $cm^{-1}$: 3320 (NH), 1520, 1340 ($NO_2$).

**Synthesis of Pyrrolnitrin (Ia)**——i) From 3-(2-Nitro-3-chlorophenyl)-4-chloro-2,5-pyrroledicarboxylic Acid (IVa): A suspension of IVa (0.10 g) in conc. $H_2SO_4$ (3 ml) was heated with stirring at 110° (bath temp.) for 20 min. The hot solution was poured onto ice, and the mixture was extracted with benzene. The extracts were washed with $H_2O$, aqueous NaOH and $H_2O$, dried and evaporated to dryness. The residue was dissolved in benzene and passed through a filter fillted with silicagel. The filtrate and washings were combined and evaporated to give yellow crystals of Ia (0.035 g). Recrystallization from ligroin yielded yellow crystals (0.03 g), mp 120—122°. No mixed melting point derpession was observed with an authentic sample of pyrrolnitrin (Ia). IR (nujol) $cm^{-1}$: 3430 (NH), 1532, 1371 ($NO_2$).

ii) From 3-(2-Nitro-3-chlorophenyl)-4-chloro-5-pyrrolecarboxylic Acid (XIX): A suspension of XIX (30 mg) in conc. $H_2SO_4$ (2 ml) was stirred at 90° (bath temp.) for 10 min. This solution was worked up in the similar manner as in i), to yield Ia (6 mg), mp 120°.

iii) From 2-Ethoxycarbonyl-3-(2-nitro-3-chlorophenyl)-4-chloro-5-pyrrolecarboxylic Acid (III): A suspension of III (0.5 g) in conc. $H_2SO_4$ (10 ml) was heated with stirring at 110° (bath temp.) for 25 min. The reaction mixture was worked up in the usual manner to give Ia (0.202 g). Recrystallization from ligroin yielded Ia (0.145 g), mp 121—122°.

iv) From 3-(2-Nitro-3-chlorophenyl)-4-chloro-5-methoxycarbonyl-2-pyrrolecarboxlic Acid (XVII): A suspension of XVII (40 mg) in conc. $H_2SO_4$ (2 ml) was heated with stirring at 130° (bath temp.) for 20 min and the reaction solution was worked up in the usual manner to give Ia (13 mg), mp 118—120°.

v) From Diethyl 3-(2-Nitro-3-chlorophenyl)-4-chloro-2,5-pyrroledicarboxylate (XIa: $R=C_2H_5$, X=Cl): A suspension of XIa ($R=C_2H_5$, X=Cl) (0.10 g) in conc. $H_2SO_4$ (1 ml) was heated with stirring at 130° (bath temp.) for 10 min. Working up in the usual manner gave yellow crystals of Ia (34 mg), mp 120—122°.

vi) From Methyl 3-(2-Nitro-3-chlorophenyl)-4-chloro-5-pyrrolecarboxylate (XVIII): Similar treatment of XVIII (0.5 g) in conc. $H_2SO_4$ (13 ml) at 110° for 12 min yielded Ia (0.17 g), mp 120—121°.

vii) From Ethyl 3-(2-Nitro-3-chlorophenyl)-4-chloro-2-pyrrolecarboxylate (XXI): Similar treatment of XXI (0.5 g) in conc. $H_2SO_4$ (10 ml) at 110° for 15 min yielded Ia (0.16 g), mp 120—122°.

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