[Chem. Pharm. Bull. 17(3) 588—595 (1969)]

UDC 615.334.011.5 : 615.281 : 547.748.07

Total Synthesis of Pyrrolnitrin. V.[1] Synthesis of Pyrrolnitrin and Its Analogues. (1)[2]

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(Received June 10, 1968)

The structure for pyrrolnitrin by chemical degradation was established. Pyrrolnitrin, 3-(2-nitro-3-chlorophenyl)-4-chloropyrrole (XIIIa), and several 3-aryl-4-chloropyrroles (XIII) were derived from ethyl 3-aryl-5-trichloromethyl-4-chloro-2-pyrrolecarboxylates (VII) *via* 3-aryl-4-chloro-2,5-pyrroledicarboxylic acids (X). VII could be obtained by exhaustive chlorination of three kinds of starting materials, ethyl 3-aryl-5-methyl-2-pyrrolecarboxylates (I), 2-ethoxycarbonyl-3-aryl-5-methyl-4-pyrrolecarboxylic acids (III) and ethyl 3-(2-nitro-3-chlorophenyl)-4-chloro-5-methyl-2-pyrrolecarboxylate (IVa).

In the previous papers,[4] three preparative routes of alkyl 3-aryl-5-methyl-2-pyrrolecarboxylates from 2-aminoacetophenones or 1-aryl-1,3-butanediones were reported.

The present paper deals with investigation undertaken to synthesize pyrrolnitrin and its analogues from these intermediates.

In order to obtain 3-aryl-4-chloropyrrole (XIII), it is necessary that α and α' positions in the pyrrole nucleus are protected with suitable substituents against halogenation of β position, because these α and α' positions are more reactive than the β position.

Substituents such as hydrogen, acetyl or carboxyl in the β-position of pyrrole may be exchanged with halogen by halogenating reagents,[5,6] and a methyl group in α-position of the pyrrole nucleus can be converted to carboxylic acid *via* a trichloromethyl group by chlorination and subsequent solvolysis.

Ethyl 3-aryl-5-methyl-2-pyrrolecarboxylates (I), ethyl 3-aryl-4-acetyl-5-methyl-2-pyrrolecarboxylates (II)[7] and 2-ethoxycarbonyl-3-aryl-5-methyl-4-pyrrolecarboxylic acids (III)[8] were chosen as starting materials to synthesize pyrrolnitrin and its analogues.

The 4-position of the pyrrole ring of I was easily attacked with various reagents such as dirohdan, $(SCN)_2$, bromine or sulfuryl chloride to afford ethyl 3-aryl-4-thiocyanato-5-methyl-2-pyrrolecarboxylates (VIa,d), ethyl 3-aryl-4-bromo-5-methyl-2-pyrrolecarboxylates (Va,d) and ethyl 3-(2-nitro-3-chlorophenyl)-4-chloro-5-methyl-2-pyrrolecarboxylate (IVa) in good yields respectively.

Treatment of III with bromine, N-bromosuccinimide or sulfuryl chloride gave the corresponding halo pyrroles (IVa, Va,d). However, halogenation of II did not proceed under any conditions. The structure of Va was confirmed by the NMR spectrum which showed

1) Part IV: S. Umino, K. Kariyone, K. Tanaka, and H. Noguchi, *Chem. Pharm. Bull.* (Tokyo), **17**, 582 (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.*
4) Part II: *Chem. Pharm. Bull.* (Tokyo), **17**, 567 (1969); Part III: *Chem. Pharm. Bull.* (Tokyo), **17**, 576 (1969).
5) K. Yamamoto, Japan. Patent 254223 (1959).
6) H. Shinohara, A. Sugimoto, H. Segawa and A. Imoto, *Nippon Kagaku Zasshi*, **83**, 940 (1962).
7) Ethyl 3-(3-chlorophenyl)-4-acetyl-5-methyl-2-pyrrolecarboxylate (IId, mp 120—126°) was derived from ethyl (3-chlorobenzoyl)-isonitrosoacetate and acetylacetone by reductive cyclization.
8) IIIa was described in Part II in this series. IIId was described in Part IV.

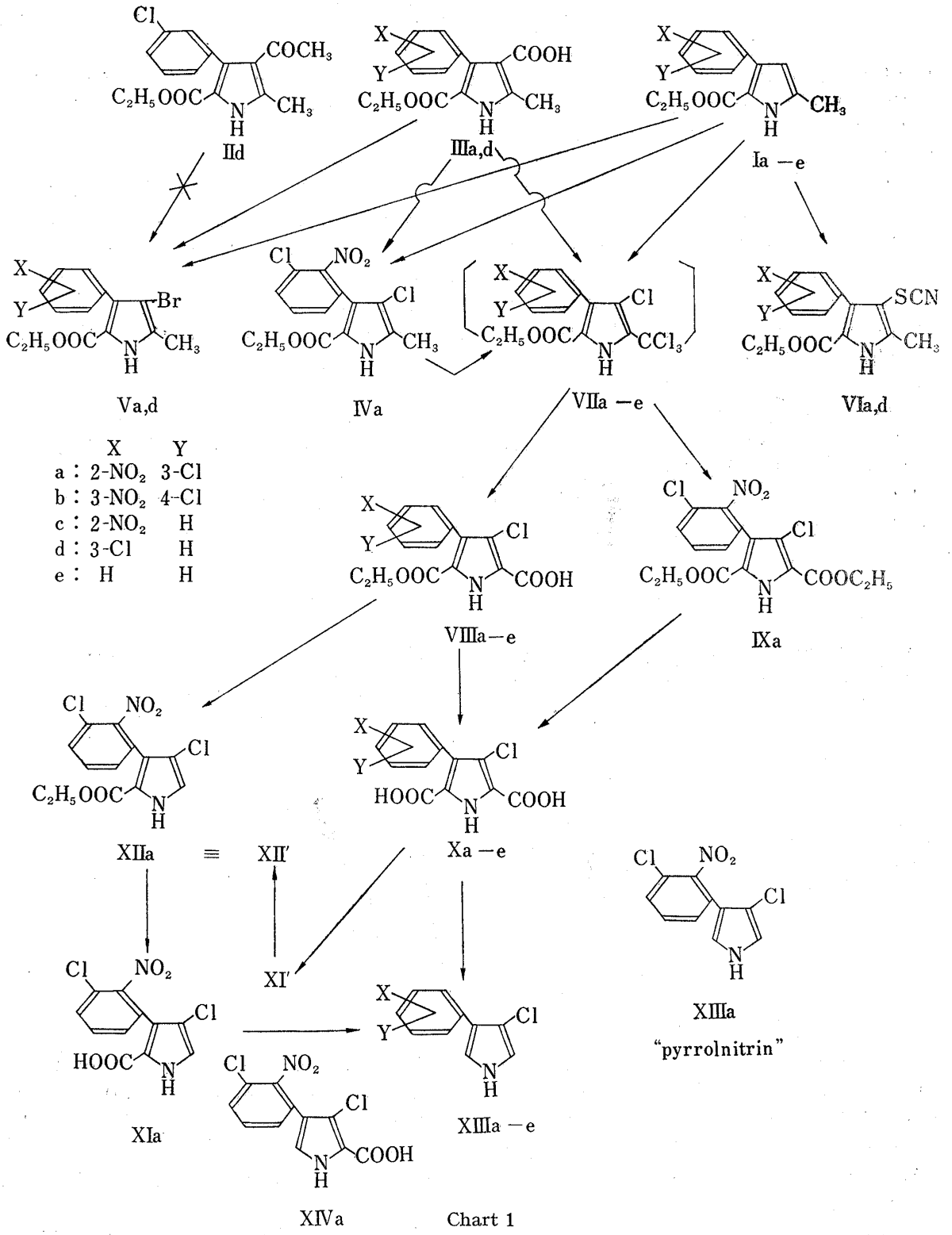


Chart 1

a singlet due to methyl protons at 2.2 ppm. IVa did not show any depression by admixture with an authentic sample, which will be reported in part XI.[9]

Corwin, *et al.*[10] have found that a methyl group in the α-position of pyrrole ring can be changed to a carboxylic acid *via* a trichloromethyl group by chlorination with sulfuryl chloride in the presence of bromine and subsequent hydrolysis in good yield.

9) Part XI: *Chem. Pharm. Bull.* (Tokyo), submitted.
10) A.H. Corwin ,W.A. Baily and P. Viohl, *J. Am. Chem. Soc.*, **64**, 1267 (1942).

However, when the intermediate (I) was treated with sulfuryl chloride and bromine, bromine was introduced to the 4-position of the pyrrole ring, because bromine was more reactive than sulfuryl chloride and the 4-position was more easily attacked by the halogenating reagent than the 2-methyl group, and therefore it was unfavorable for synthesizing pyrrolnitrin.

Shinohara, *et al.*[11] reported that chlorination of diethyl 2-methyl-3,5-pyrrolecarboxylate with sulfuryl chloride in acetic acid at 40—55° mainly afforded diethyl 2-formyl-4-chloro-3,5-pyrroledicarboxylate, which was derived from the resulting ethyl 2-dichloromethyl-4-chloro-3,5-pyrroledicarboxylate by solvolysis with acetic acid used as a solvent, giving small amount of 4-chloro-3,5-diethoxycarbonyl-2-pyrrolecarboxylic acid. From this observation, they concluded that solvolysis of a dichloromethyl group was more easily proceeded by acetic acid to give a formyl group than further chlorination by sulfuryl chloride.

On the contrary, it is probably possible that further chlorination of dichloromethyl group into trichloromethyl group is carried out in good yields under lower temperature condition in acetic acid.

Chlorination of alkyl 3-aryl-5-methyl-2-pyrrolecarboxylates (Ia—e) or 2-ethoxycarbonyl-3-aryl-5-methyl-4-pyrrolecarboxylic acids (IIIa,d) was carried out in acetic acid under cooling with 4 mole of sulfuryl chloride to give ethyl 3-aryl-4-chloro-5-trichloromethyl-2-pyrrolecarboxylates (VIIa—e), which were solvolyzed in excellent yields to 2-ethoxycarbonyl-3-aryl-4-chloro-5-pyrrolecarboxylic acids (VIIIa—e) with acetic acid or potassium bicarbonate without any side reaction.

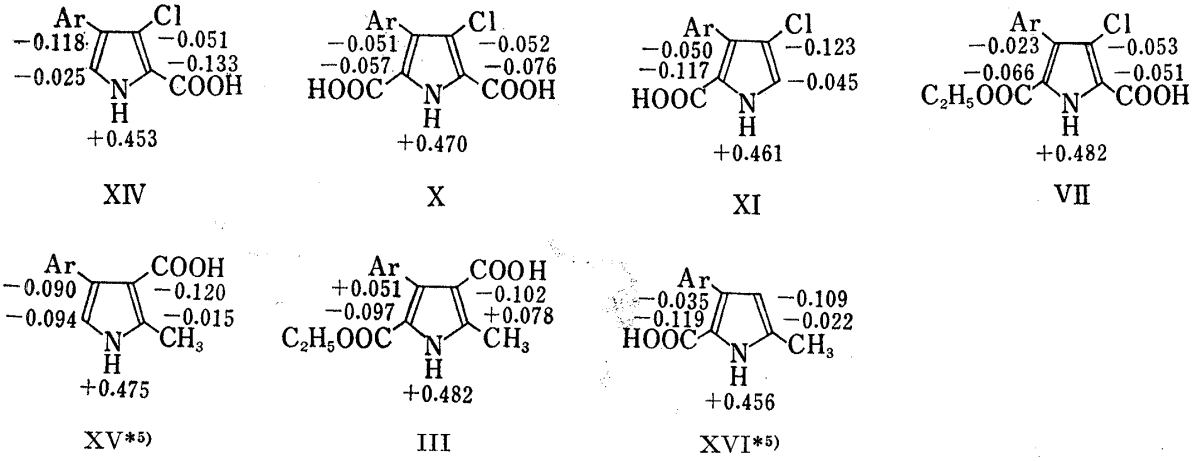


Chart 2

Treatment of ethyl 3-(2-nitro-3-chlorophenyl)-4-chloro-5-methyl-2-pyrrolecarboxylate (IVa) with sulfuryl chloride also afforded the trichloromethyl compound (VIIa) under the same conditions, but ethyl 3-(2-nitro-3-chlorophenyl)-4-bromo-5-methyl-2-pyrrolecarboxylate (Va) was partially converted to 4-chloro compound (VIIa).

Alcoholysis of the trichloro compound (VIIa) gave diethyl 3-(2-nitro-3-chlorophenyl)-4-chloro-2,5-pyrroledicarboxylate (IXa).

Hydrolysis of the half esters (VIIIa—e) and the diester (IXa) proceeded smoothly to give 3-aryl-4-chloro-2,5-pyrrole-dicarboxylic acids (Xa—e) under basic condition.

Decarboxylation of Xa by the usual manner in glycerin or ethanolamine gave corresponding pyrrole derivatives in poor yields.

Decarboxylation of Xa in dimethylaniline at 180° without stirring afforded an unexpected acidic product (XI'). This compound (XI') was supposed to be 3-(2-nitro-3-chlorophenyl)-

11) H. Shinohara, A. Sugimoto and A. Imoto, *Nippon Kagaku Zasshi*, **83**, 612 (1962).
12) K. Hattori and M. Hashimoto, unpublished data.

4-chloro-2-pyrrolecarboxylic acid (XIa) or 3-(2-nitro-3-chlorophenyl)-4-chloro-5-pyrrolecarboxylic acid (XIVa). And its ethyl ester of XI′ was obtained by the usual esterification.

In order to compare the ester of XI′ with one of the possible samples (ethyl ester of XIVa), 3-(2-nitro-3-chlorophenyl)-4-chloro-5-pyrrolecarboxylic acid (XIVa)[12] was esterified with boiling ethanol in the presence of hydrogen chloride, but abnormal decarboxylation afforded unexpected pyrrolnitrin (XIIIa) instead of the desired ester of XIVa.

The ethyl ester of XI′ was identified by comparison of its infrared spectrum and mixed melting point with that of an another possible compound (XIa) prepared from the half ester (VIIIa) by decarboxylation. Therefore, it became clear that the 5-position of the carboxyl group in Xa was eliminated at first under the decarboxylation conditions.

In order to explain the abnormal decarboxylation under acidic conditions, charge density of 3-arylpyrrolecarboxylic acids is calculated by Hückel LCAO-MO method using the parameters collected by Yonezawa, *et al.*[13]

According to these data, an α-carbon of pyrrole-monocarboxylic acid may be easily attacked by proton, because the charge density is larger than that of dicarboxylic acid.

Three kinds of monocarboxylic acids except XIa also gave the decarboxylation products under the similar esterification as XIVa, but three kinds of dicarboxylic acids afforded the corresponding diesters in good yields.

The difference between three kinds of monocarboxylic acids and XIa may be supposed that in the former the electronsupplying effect of methyl or chloro substituents to an α-carbon of the carboxylic acid is expected; however, in the latter, the same effect of chloro substituents can not be expected. In the latter case, the chlorine atom is oriented at the 4-position to the 2-positioned carboxyl group in a pyrrole ring, and only the chlorine atom of XIa can not be donated π-electron for the α-carbon of the carboxyl group. Therefore, we supposed following mechanism for these abnormal decarboxylation.

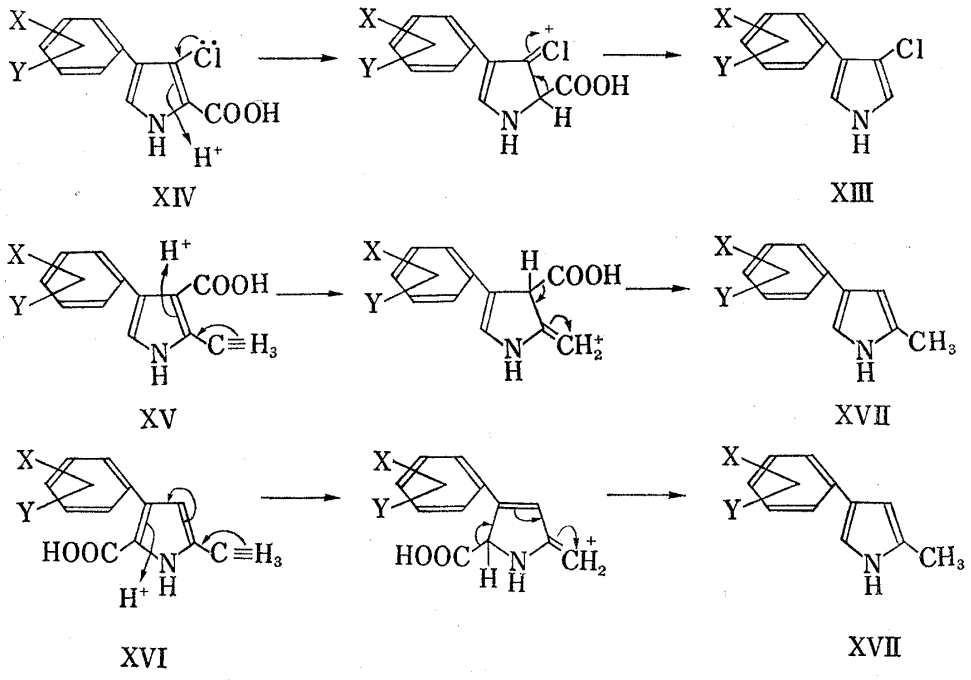


Chart 3

In the case of decarboxylation in dimethylaniline described above, these dicarboxylic acids (Xa—e) were vigorously refluxed to give 3-aryl-4-chloropyrroles (XIIIa—e) in excellent

13) T. Yonezawa, T. Nagata, H. Kato, A. Imamura and K. Morokuma, "Ryoshikagakunyumonjyo," Kagakudojin K.K., Kyoto, 1963, p. 55.

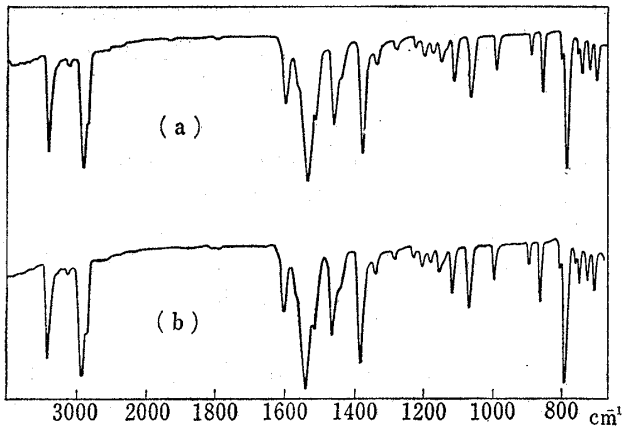
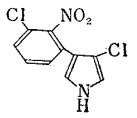


Chart 4. Infrared Spectra of 

a) natural *b*) synthetic

yields. One of them, 3-(2-nitro-3-chlorophenyl)-4-chloropyrrole (XIIIa) mp 124°, showed no depression in admixture with pyrrolnitrin. The infrared spectra (NH, 3340 cm^{-1}; NO_2, 1535, 1375 cm^{-1} in nujol) of XIIIa and pyrrolnitrin were perfectly superimosable. Furthermore, minimum inhibitory concentration of XIIIa against various microbes was quite similar with that of pyrrolnitrin isolated from Pseudomonas culture.

Thus, the structure for pyrrolnitrin by the chemical degradation[14] was established.

The structure–activity relationship of pyrrolnitrin and its various analogues will be reported in the near future.

Experimental[15]

Ethyl 3-(2-Nitro-3-chlorophenyl)-4-chloro-5-methyl-2-pyrrolecarboxylate (IVa)——i) From Ia: A solution of SO_2Cl_2 (0.23 g) in 2 ml of AcOH was added to a suspension of Ia (0.53 g) in 15 ml at 60° with stirring. After 1 hr, the reaction mixture was allowed to isolate crystals, which were filtered and recrystallized from EtOH to give IVa as colorless needles having mp 249°. IVa was identified with the authentic sample by mixed melting point comparison. IR (nujol) cm^{-1}: 3270 (NH), 1670 ($COOC_2H_5$), 1535, 1370 (NO_2). NMR (d_5-pyridine) ppm: 0.95 (3H, triplet, CH_2CH_3), 2.30 (3H, singlet, CH_3), 4.15 (2H, quartet, $C\underline{H}_2CH_3$).

ii) From IIIa: When IIIa (0.6 g) was treated as above, 0.2 g of IVa was obtained. It was identified by comparison of the infrared spectrum.

Ethyl 3-(2-Nitro-3-chlorophenyl)-4-bromo-5-methyl-2-pyrrolecarboxylate (Va)——i) From Ia and Br_2: A solution of Br_2 (1.5 g) in 10 ml of AcOH was added to a suspension of Ia (2.6 g) in 25 ml of AcOH at 60° under stirring for 1 hr. After cooling, separated crystals were collected by filtration. Recrystallization from EtOH gave colorless prisms (1.8 g), mp 255° (decomp.). *Anal.* Calcd. for $C_{14}H_{12}O_4N_2BrCl$: C, 43.38; H, 3.12; N, 7.23. Found: C, 43.45; H, 3.19; N, 6.93. IR (nujol) cm^{-1}: 3270 (NH), 1672 ($COOC_2H_5$), 1540, 1357 (NO_2). NMR (d_5-pyridine) ppm: 0.95 (3H, triplet, $CH_2C\underline{H}_3$), 2.30 (3H, singlet, $C\underline{H}_3$), 4.15 (2H, quartet, $C\underline{H}_2CH_3$), 7.60 (3H, singlet, arom–$\underline{H}$).

ii) From Ia and N-Bromosuccinimide: A mixture of Ia (0.5 g), N-bromosuccinimide (0.3 g) and 30 ml of tetrachloroethane was heated under reflux for 1 hr. After evaporation of the filtrate, the residue was recrystallized from EtOH to give 0.2 g of Va (mp 255° decomp.). The infrared spectrum of it is similar to that of the sample described above.

iii) From IIIa and Br_2: IIIa (0.35 g) and Br_2 (0.14 g) were treated similarly as described in (i). Va (0.22 g, mp 225° decomp.) was obtained. It is identified with the infrared spectrum.

Ethyl 3-(3-Chlorophenyl)-4-bromo-5-methyl-2-pyrrolecarboxylate (Vd)——i) From Id: A mixture of Id (2.0 g), 1.4 g of Br_2 and AcOH (20 ml) was treated similarly as Va (i). 1.7 g of Va (mp 155° decomp., colorless needles) was obtained. *Anal.* Calcd. for $C_{14}H_{13}O_2NBrCl$: C, 49.22; H, 3.54; N, 4.11. Found: C, 47.88; H, 3.84; N, 4.11.

ii) From IIId: IIId (0.5 g), Br_2 (0.4 g) and AcOH (5 ml) were treated as similar Va (i). 0.3 g of Va was obtained.

Ethyl 3-(2-Nitro-3-chlorophenyl)-4-thiocyanato-5-methyl-2-pyrrolecarboxylate (VIa)——A solution of Br_2 (1.7 g) in AcOH (15 ml) was added dropwise to a suspension of Ia (2.1 g) and NH_4SCN (3.2 g) in 30 ml of AcOH at 12—15° with stirring for 20 min. After further stirring for 2 hr, the reaction mixture was poured

14) H. Imanaka, M. Kousaka, G. Tamura and K. Arima, *J. Antibiotics, Ser. A*, **18**, 207 (1965).

15) 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 internal standard.

into 400 ml of H_2O, and a separated precipitate was collected by filtration, washed with H_2O, and dried. It was recrystallized from AcOEt–ligroin to give colorless needles (2.4 g) having mp 194.5°. *Anal.* Calcd. for $C_{15}H_{12}O_5N_3ClS$: C, 49.25; H, 3.31; N, 11.49; Cl, 9.69; S, 8.77. Found: C, 49.13; H, 3.38; N, 12.22; Cl, 9.79; S, 9.44. IR (nujol) cm^{-1}: 3350 (NH), 2150 (SCN), 1715 ($COOC_2H_5$), 1535, 1375 (NO_2).

Ethyl 3-(3-Chlorophenyl)-4-thiocyanato-5-methyl-2-pyrrolecarboxylate (VId)——To a mixture of Id (2.0 g), NH_4SCN (2.3 g) and AcOH (30 ml), a solution of Br_2 (1.2 g) in 15 ml of AcOH was added under stirring at 12—15°, and stirring was continued additional 2.5 hr. The reaction mixture was poured into H_2O, resulting crystals were collected by filtration, and recrystallized from EtOH to give yellow needles (2.35 g) having mp 158—159°. *Anal.* Calcd. for $C_{15}H_{13}O_2N_2ClS$: C, 56.16; H, 4.08; N, 8.73; Cl, 11.05; S, 10.00. Found: C, 55.92; H, 4.37; N, 8.86; Cl, 11.11; S, 10.09. IR (nujol) cm^{-1}: 3280 (NH), 2120 (SCN), 1685 ($COOC_2H_5$). NMR ($CDCl_3$) ppm: 1.15 (3H, triplet, $CH_2C\underline{H}_3$), 2.55 (3H, singlet, $C\underline{H}_3$), 4.23 (2H, quartet, $C\underline{H}_2CH_3$).

2-Ethoxycarbonyl-3-(2-nitro-3-chlorophenyl)-4-chloro-5-pyrrolecarboxylic Acid (VIIIa)——i) From Ia: To a suspension of Ia (1.2 g) in 12 ml of AcOH was added a solution of SO_2Cl_2 (2.1 g) in AcOH (3 ml) with stirring at (5—10° for 3 hr. The reaction mixture became clear during addition of SO_2Cl_2, and was kept standing overnight at room temperature. The solution was warmed to 50° for 2 hr, and poured in cold H_2O. The aqueous layer was twice extracted with AcOEt. The organic layer was dried and evaporated *in vacuo*. The residue was dissolved in 10 ml of AcOH again, and the solution was heated under reflux for 0.5 hr, and then evaporated in reduced pressure. The residue was washed with a small volume of AcOH, collected by filtration, and recrystallized from AcOH to give 0.95 g of VIIIa as colorless needles, mp 262° (decomp.). *Anal.* Calcd. for $C_{14}H_{10}O_6N_2Cl_2$: C, 45.06; H, 2.07; O, 25.75; N, 7.51; Cl, 19.00. Found: C, 45.32; H, 2.90; O, 25.85; N, 7.75; Cl, 19.17. IR (nujol) cm^{-1}: 3250 (NH), 1720 ($COOC_2H_5$), 1680 (COOH), 1535, 1370 (NO_2).

ii) From IIIa: A mixture of IIIa (0.352 g), 7 ml of AcOH and 0.57 g of SO_2Cl_2 was employed instead of that of example (i). The residue was recrystallized from AcOH to yield 0.21 g of a product having mp 262° (decomp.). The infrared spectrum of it was identical with that of the above sample.

iii) From IVa: A suspension of IVa (0.2 g), 2.5 ml of AcOH and 0.266 g of SO_2Cl_2 was treated similarly as described in (i). Recrystallization from AcOH afforded 0.16 g of product, mp 262° (decomp.) as colorless needles, which was identified with an authentic sample described in (i) by comparison of infrared spectra.

2-Ethoxycarbonyl-3-(3-nitro-4-chlorophenyl)-4-chloro-5-pyrrolecarboxylic Acid (VIIIb)——A solution of SO_2Cl_2 (2.16 g) in 3 ml of AcOH was added dropwise to a suspension of Ib (0.5 g) in AcOH (5 ml) with stirring at 10—15°. The reaction mixture was allowed to stand overnight at room temperature, and poured in to cold H_2O. The aqueous solution was extracted with AcOEt, and then the organic layer was dried and evaporated under reduced pressure. The residue was dissolved again in AcOH (10 ml), and the solution was heated under reflux for 1 hr. The reaction mixture was concentrated *in vacuo*, and the residual crystals were recrystallized from AcOH for analysis, mp 239° (decomp.), pink needles (0.2 g). *Anal.* Calcd. for $C_{14}H_{10}O_6N_2Cl_2$: N, 7.51. Found: N, 7.80.

2-Ethoxycarbonyl-3-(2-nitrophenyl)-4-chloro-5-pyrrolecarboxylic Acid (VIIIc)——Ic (2.0 g), 20 ml of AcOH and 4.4 g of SO_2Cl_2 were employed similarly as above VIIIa (i).

The product was recrystallized from AcOH to give 1.5 g of colorless needles, mp 259° (decomp.). *Anal.* Calcd. for $C_{14}H_{11}O_6N_2Cl$: C, 49.64; H, 3.27; N, 8.27. Found: C, 49.40; H, 3.55; N, 8.03. IR (nujol) cm^{-1}: 3250 (NH), 1710 ($COOC_2H_5$), 1670 (COOH), 1530, 1345 (NO_2).

2-Ethoxycarbonyl-3-(3-chlorophenyl)-4-chloro-5-pyrrolecarboxylic Acid (VIIId)——i) From Id: A mixture of Id (1.6 g), SO_2Cl_2 (3.8 g) and 16 ml of AcOH was treated as described in VIIIa (i). Recrystallization of the product from AcOH afforded 1.2 g of slightly pink needles having mp 235° (decomp.). *Anal.* Calcd. for $C_{14}H_{11}O_4NCl_2$: C, 51.24; H, 3.38; N, 4.27; Cl, 21.61. Found: C, 51.31; H, 3.64; N, 4.51; Cl, 21.93. IR (nujol) cm^{-1}: 3250 (NH), 1710 ($COOC_2H_5$), 1670 (COOH).

ii) From IIId: IIId (1.4 g), SO_2Cl_2 (4.6 g) and AcOH (14 ml) afforded by similar treatment described as above 0.6 g of VIIId having mp 235° (decomp.). *Anal.* Calcd. for $C_{14}H_{11}O_4NCl_2$: C, 51.24, H, 3.38; N, 4.27. Found: C, 51.45; H, 3.66; N, 4.60.

2-Ethoxycarbonyl-3-phenyl-4-chloro-5-pyrrolecarboxylate (VIIIe)——Ethyl 3-phenyl-5-methyl-2-pyrrolecarboxylate (Ie)[16] (3.7 g), SO_2Cl_2 (9.4 g) and 74 ml of AcOH was treated similarly described as VIIIa (i) 1.1 g of product (colorless needles from AcOH, mp 252° decomp.). *Anal.* Calcd. for $C_{14}H_{12}O_4NCl$: C, 57.26; H, 4.12; N, 4.77; Cl, 12.07. Found: C, 57.44; H, 4.22; N, 4.62; Cl, 12.36. IR (nujol) cm^{-1}: 3270 (NH), 1715 ($COOC_2H_5$), 1675 (COOH).

Diethyl 3-(2-nitro-3-chlorophenyl)-4-chloro-2,5-pyrroledicarboxylate (IXa)——i) From Ia: To a suspension of Ia (1.5 g) in 15 ml of AcOH, a solution of SO_2Cl_2 (6.5 g) in AcOH (10 ml) was added slowly with stirring at 10—15°. After standing overnight at room temperature, 10 ml of abs. EtOH was added to the reaction mixture. The mixture was evaporated *in vacuo* to give a viscous residue. After refluxing an ethanolic solution (10 ml) of the residue for 3 hr, EtOH was removed under reduced pressure. A solution of the residue in AcOEt was washed with aqueous $KHCO_3$ and H_2O, and then evaporated *in vacuo*. The

16) E.J. Chu and T.C. Chu, *J. Org. Chem.*, **19**, 266 (1954).

residue was crystallized from benzene-ligroin, and recrystallized from EtOH to give 0.3 g of colorless prisms having mp 137°. *Anal.* Calcd. for $C_{16}H_{14}O_4N_2Cl$: C, 47.90; H, 3.52; N, 6.98. Found: C, 48.02; H, 3.67; N, 6.93. IR (nujol) cm^{-1}: 3350 (NH), 1720 ($COOC_2H_5$), 1545, 1370 (NO_2).

ii) From VIIIa: An ethanolic solution of VIIIa (0.5 g) containing 5% of HCl gas was heated under reflux for 3 hr. The reaction mixture was evaporated to dryness under reduced pressure. A solution of the residue in AcOEt was washed with 5% K_2CO_3 and H_2O, dried over $MgSO_4$, and concentrated *in vacuo* to give the crude diester (0.4 g). Recrystallization of the crude diester afforded 0.2 g of colorless prisms having mp 137°. It was identified by mixed melting point comparison with an authentic sample described in (i).

iii) From Xa: Under similar conditions described above, Xa (0.5 g) gave rise to 0.2 g of a product melting at 137° after recrystallization from EtOH. It was identical by infrared spectrum comparison with that of above (i).

3-(2-Nitro-3-chlorophenyl)-4-chloro-2,5-pyrroledicarboxylic Acid (Xa)——i) From VIIIa: A 90% ethanolic solution (100 ml) of VIIIa (0.6 g) containing 0.75 g of KOH was heated under reflux for 5 hr, and evaporated *in vacuo*. The aqueous solution of the residue was acidified with conc. HCl and extracted with AcOEt. The organic layer was washed with H_2O, dried over $MgSO_4$, evaporated *in vacuo* to dryness. The crude acid was obtained almost quantitatively, and recrystallized from 50% EtOH for analysis, mp 280° (decomp.) as colorless needles. *Anal.* Calcd. for $C_{12}H_6O_6N_2Cl$: C, 41.76; H, 1.76. Found: C, 42.03; H, 1.99.

ii) From IXa: A mixture of IXa (1.0 g) and 15 ml of EtOH in 15 ml of 10% NaOH was treated similarly as described above. A crude dicarboxylic acid (0.9 g) was obtained and identified by comparison of its infrared spectrum with that of an authentic sample prepared from VIIIa.

3-Phenyl-(or Substitued phenyl)-4-chloro-2,5-pyrroledicarboxylic Acid (Xb—e)——General Method: A mixture of VIII (a g), $10\times$a ml of EtOH and $30\times$a ml of 10% NaOH solution was refluxed for 4 hr. After cooling, the reaction mixture was poured $30\times$a ml of 10% H_2SO_4, and the resuting acidic suspension was extracted with AcOEt. The organic layer was washed with H_2O, dried over $MgSO_4$ and evaporated *in vacuo* to give a crude dicarboxylic acid almost quantitatively. The crude dicarboxylic acid was employed in next step without further purification. The results are described below.

Xb (0.3 g) derived from VIIIb (0.5 g).
Xc (0.8 g) derived from VIIIc (1.3 g).
Xd (0.5 g) derived from VIIId (0.9 g).
Xe (0.5 g) derived from VIIIe (0.7 g).

3-(2-Nitro-3-chlorophenyl)-4-chloro-2-pyrrolecarboxylic Acid (XIa)——A mixture of Xa (1.0 g) and dimethylaniline (40 ml) was heated at 180° (inner temperature) for 45 min without stirring, and poured into 400 ml of 10% HCl. The mixture was extracted with AcOEt and the extract was treated with 10% Na_2CO_3. Crude XIa (0.7 g, mp 265° decomp.) was obtained by extraction of the above aqueous layer after acidification, followed by concentration. Treatment of XIa with etheral CH_2N_2 gave methyl ester of it, which was recrystallized from benzene-ligroin to give slightly yellow needles having mp 170—172°. *Anal.* Calcd. for $C_{12}H_8O_4N_2Cl_2$: C, 45.74; H, 2.56. Found: C, 45.72; H, 2.77. IR (nujol) cm^{-1}: 3400 (NH), 1710 ($COOC_2H_5$), 1535, 1375 (NO_2).

Ethyl 3-(2-Nitro-3-chlorophenyl)-4-chloro-2-pyrrolecarboxylate (XII)——i) From XIa: Esterification of XIa (0.1 g) with EtOH–HCl gave 0.08 g of colorless needles (mp 170—171°) after recrystallization from EtOH. The product was identified with an authentic sample described below by mixed melting point comparison.

ii) From VIIIa: A solution of VIIIa (1.5 g) in 20 ml of dimethylaniline was heated under vigorous reflux for 1 hr with stirring. The reaction mixture was poured in 200 ml of HCl, and extracted with benzene. The benzene layer was washed with H_2O, dried, and passed through a thin-layer of silicagel on a Buchner's funnel, and evaporated *in vacuo*.

Recrystallization from EtOH gave colorless needles (0.25 g), mp 170—171°. *Anal.* Calcd. for $C_{13}H_{10}O_4N_2Cl_2$: C, 47.44; H, 3.06; N, 8.51; Cl, 21.54. Found: C, 47.57; H, 3.10; N, 8.57; Cl, 21.10. IR (nujol) cm^{-1}: 3280 (NH), 1685 ($COOC_2H_5$), 1535, 1380 (w), 1370 (NO_2).

3-(2-Nitro-3-chlorophenyl)-5-methylpyrrole (XVIIa) by Abnormal Decarboxylation——i) From XVa: A solution of 0.3 g of XVa in 30 ml of EtOH containing 4% of HCl was refluxed on a water bath for 3 hr. The solvent was removed *in vacuo*. The benzene solution of the residue was washed with H_2O, dried and evaporated under reduced pressure. Recrystallization from benzene-ligroin gave 0.2 g of yellow granules having mp 82°, which was identified with an authentic sample described in part II[4] by comparison of infrared spectrum and mixed melting point.

ii) From XVIa: XVIa (0.3 g) was treated as described in (i), 0.15 g of XVIIa (mp 82°) was obtained.

3-(2-Nitro-3-chlorophenyl)-4-chloropyrrole (XIIIa, "Pyrrolnitrin")——i) From Xa in Dimethylaniline: A solution of Xa (5.0 g) in 200 ml of dimethylaniline was heated under reflux for 1.5 hr with vigorous stirring. The mixture was evaporated under reduced pressure to *ca.* 1/5 volume, poured into 800 ml of 10% HCl and extracted with benzene. The benzene layer was washed with 10% HCl and H_2O, dried over $MgSO_4$,

filtered through a thin-layer of silicagel, and a resulted yellow solution was evaporated under reduced pressure of N_2. The residue was recrystallized from benzene–ligroin to give yellow granules (3.4 g) having melting point 124°. *Anal.* Calcd. for $C_{10}H_6O_2N_2Cl_2$: C, 46.72; H, 2.35; N, 10.89; Cl, 27.53. Found: C, 46.96; H, 2.54; N, 10.85; Cl, 27.29. IR (nujol) cm^{-1}: 3340 (NH), 1535, 1375 (NO_2).

ii) From Xa in Glycerin: A mixture of 1.0 g of Xa and 20 ml of glycerin was heated at 210° for 15 min. The mixture was poured into 300 ml of H_2O, and the water layer was saturated with NaCl and extracted with benzene. The extracts were washed with H_2O, dried and chromatographed on a silicagel column. The second fraction was collected and evaporated under reduced pressure. The residue was crystallized from benzene–ligroin, and yellow granules (0.2 g) were obtained. The product did not show any depression in mixed melting point with natural pyrrolnitrin, the infrared and NMR spectra was perfectly superimposable with that of pyrrolnitrin.

iii) From XIa: A mixture of XIa (20 mg) and 5 ml of glycerin was heated at 250° for 10 min and poured into 50 ml of ice–water. The solution was extracted with benzene and treated as described in (ii), to give 15 mg of yellow solids. The infrared spectrum of the solid was the same as that of an authentic sample.

iv) From XIVa: A solution of XIVa (0.3 g) of 30 ml of EtOH containing 4% of HCl was refluxed for 3 hr. The solvent was removed under reduced pressure, and the residue was dissolved in benzene. The benzene solution was treated as described in (ii), to give 0.15 g of yellow granules (mp 124°). It was identified with an authentic sample by mixed melting point comparison.

3-(3-Nitro-4-chlorophenyl)-4-chloropyrrole (XIIIb)——Xb (0.3 g) was dissovled in 30 ml of dimethylaniline and the solution was treated as described in XIIIa (i). Recrystallization from benzene–ligroin gave 0.1 g of light yellow needles, mp 114°. It was identified with an authentic sample[9] by mixed melting point comparison. IR (nujol) cm^{-1}: 3450 (NH), 1525, 1345 (NO_2).

3-(2-Nitrophenyl)-4-chloropyrrole (XIIIc)——Xc (0.8 g) was treated as described in XIIIa (i). Recrystallization from benzene–ligroin afforded 0.06 g of light yellow needles, mp 111°. *Anal.* Calcd. for $C_{10}H_7O_2N_2Cl$: C, 53.95; H, 3.17. Found: C, 53.97; H, 3.33. IR (nujol) cm^{-1}: 3450 (NH), 1517, 1360 (NO_2).

3-(3-Chlorophenyl)-4-chloropyrrole (XIIId)——A solution of Xd (0.5 g) in 20 ml of dimethylaniline was heated under reflux with stirring for 1 hr, and poured in 200 ml of 10% HCl, and extracted with benzene. The organic layer was washed with H_2O and 5% NaOH, dried, evaporated under reduced pressure. The residue was distilled to give 0.3 g of colorless liquid at bp 145—147° (0.15 mmHg). *Anal.* Calcd. for $C_{10}H_7NCl_2$: C, 56.63; H, 3.33; Cl, 33.44. Found: C, 56.88; H, 3.46; Cl, 33.13. IR (nujol) cm^{-1}: 3450 (NH).

3-Phenyl-4-chloropyrrole (XIIIe)——Xe (0.5 g) was treated as described in XIIId. The residue was purified by silicagel chromatography to give 0.2 g of colorless liquid which could not be distilled without decomposition. The infrared spectra of it was very similar to that of XIIId, and Ehrlich's color reaction was strongly positive.