[Chem. Pharm. Bull. 17(3) 582—587 (1969)]

UDC 615.334.011.5 : 615.281 : 547.748.07

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

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(Received June 10, 1968)

Treatment of the crude-enamine (IV), prepared from 1-(3-chlorophenyl)-1,3-butanedione (II) and diethyl aminomalonate (III), with sodium ethoxide gave ethyl 3-(3-chlorophenyl)-5-methyl-2-pyrrolecarboxylate (VI) and ethyl 2-(3-chlorophenyl)-4-methyl-5-pyrrolecarboxylate (VII'), whose structures were confirmed by other synthetic methods. Mechanism of above reaction and ultraviolet absorption spectra of these pyrrole derivatives were discussed.

In the preceding paper,[1] the authors reported on the condensation of 1-(substituted-phenyl)-5-methyl-2-pyrrolecarboxylate, intermediate to synthesis pyrrolnitrin (I).

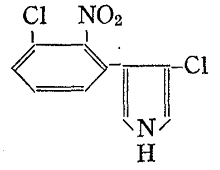

Chart 1

In this paper, two types of pyrrole derivatives were synthesized by condensation and cyclization reaction of 1-(3-chlorophenyl)-1,3-butanedione (II), which had no nitro group in the aryl group. The structure of these pyrrole derivatives were determined by comparison of the authentic compounds prepared by other methods, and the ultraviolet absorption spectra of these pyrrole were studied.

It seems that the nucleophilicity on carbonyl groups of 1-aryl-1,3-butanedione is determined by electronic and steric effects of the substituents in the phenyl group.

1-(3-Chlorophenyl)-1,3-butanedione (II) was treated with diethyl aminomalonate (III) to give a semi-solid condensation product (IV). IV was further treated with sodium ethoxide to give two products, colorless needles, mp 153—154° (VI) and colorless plates, mp 116—117° (VII), which were both analyzed correctly for $C_{14}H_{14}O_2NCl$.

This semi-solid product (IV) gave the pure enamine (V), colorless crystals, mp 54—56°, by recrystallization, which was treated with sodium ethoxide to give only one product (VI).[1]

The structures of these compounds were determined by the following chemical methods: ethyl 2-(3-chlorophenyl)-4-methyl-3-pyrrolecarboxylate (X) was obtained by treating ethyl 3-chlorobenzoylacetate (VIII) with 3-amino-2-propanone hydrochloride (IX) in an AcOH–AcONa buffer solution. X and colorless plates (VII) had the same composition, but their melting points were different and in the Ehrlich's test, X was positive but VII was negative, and therefore, it was considered that X was an isomer of VII. X was hydrolyzed and decarboxylated to yield 2-(3-chlorophenyl)-4-methyl-pyrrole (XII), and XII' was identified with XII after hydrolysis and decarboxylation of VII. From this fact, it was concluded that VII was the isomer of X in respect to the substituted position of the ethoxycarbonyl group, and the structure of VII was determined to be ethyl 2-(3-chlorophenyl)-4-methyl-5-pyrrolecarboxylate (VII').

Reductive cyclization of ethyl 2-(3-chlorobenzoyl)-2-oximinoacetate (XIII) with ethyl (or *tert*-butyl) acetoacetate (XIVa,b) yielded ethyl (or *tert*-butyl) 3-(3-chlorophenyl)-5-methyl-2,4-pyrroledicarboxylates (XVa,b). After hydrolysis and decarboxylation (or treatment with

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[1] Part III: S. Umino, K. Kariyone, K. Tanaka and T. Kishimoto, *Chem. Pharm. Bull.* (Tokyo), **17**, 576 (1969).

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

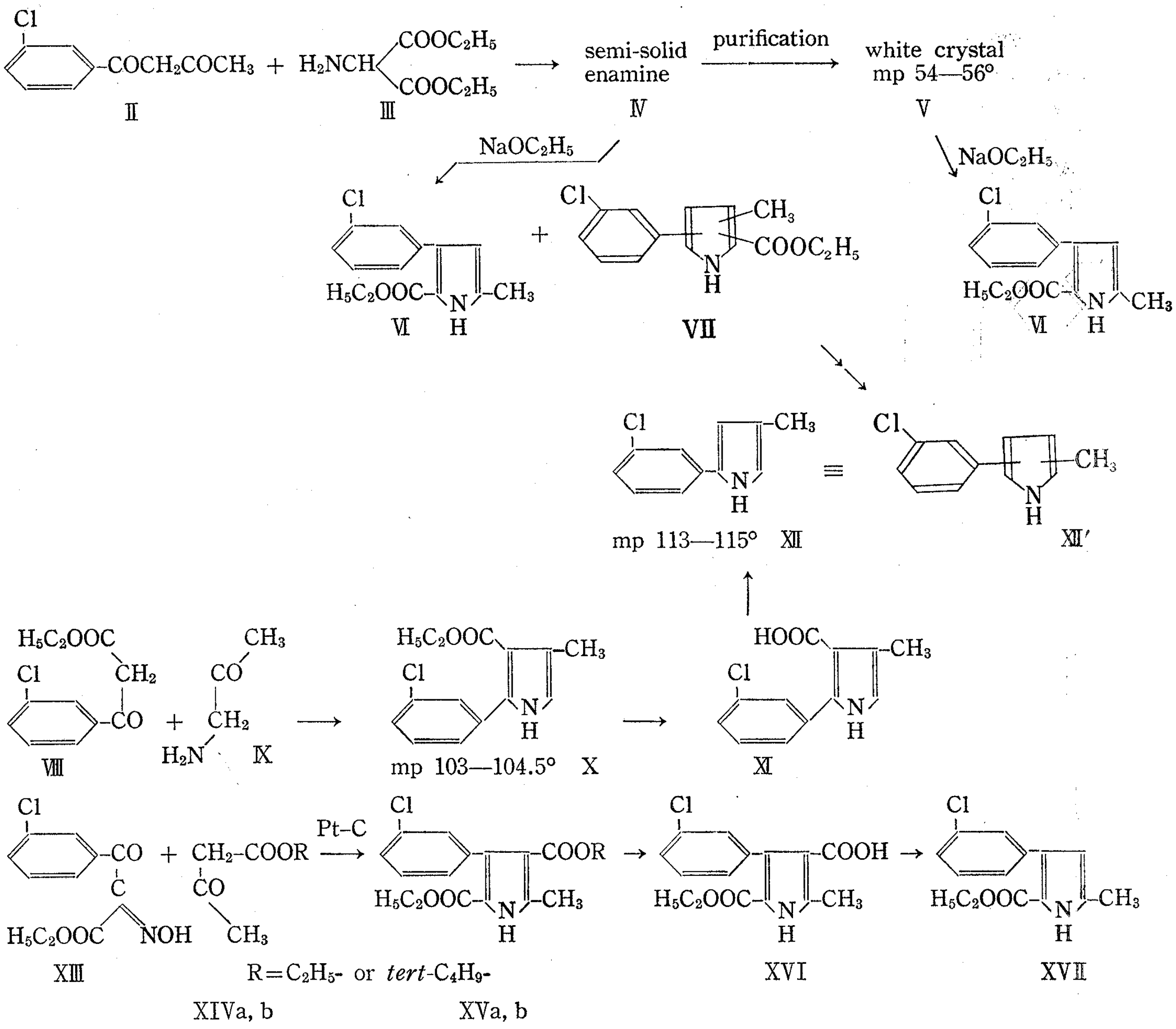


Chart 2

p-toluenesulfonic acid), XVab afforded ethyl 3-(3-chlorophenyl)-5-methyl-2-pyrrolecarboxylate (XVII).

A melting point of a mixture of VI and an authentic XVII was not depressed and also their infrared spectra were superimposable.

Thus, it was concluded that the crude enamine (IV) had given ethyl 3-(3-chlorophenyl)-5-methyl-2-pyrrolecarboxylate (VI), mp 153—154° and ethyl 2-(3-chlorophenyl)-4-methyl-5-pyrrolecarboxylate (VII′), mp 116—117°, but the pure enamine, mp 54—56° (V), had given only one product (VI).[1]

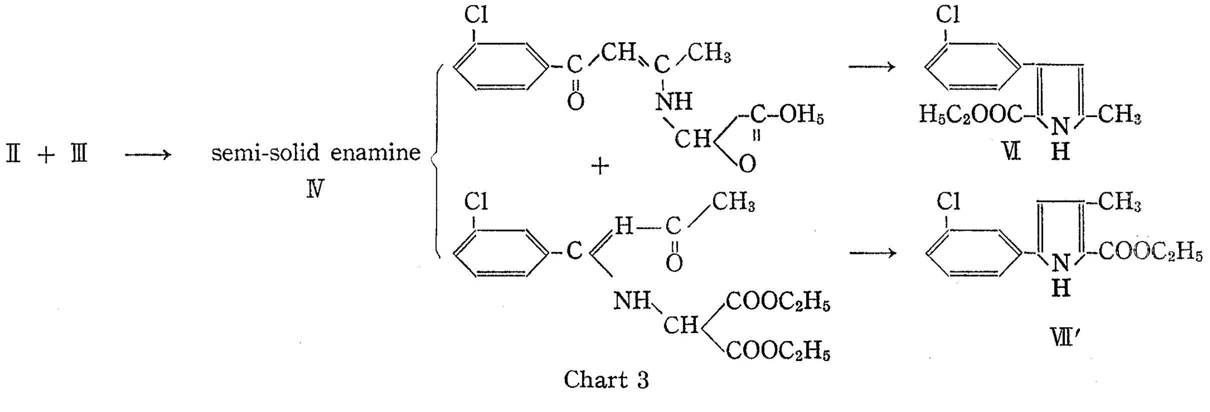
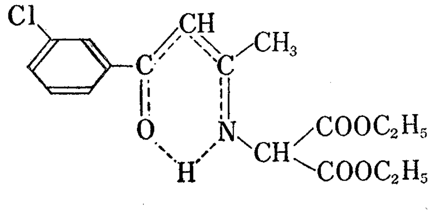


Chart 3

As a conclusion, the crude enamine (IV), as shown in Chart 3, is considered as a mixture of two enamines, diethyl N-[1-methyl-3-(3-chlorophenyl)-3-oxopropylidene]aminomalonate and diethyl N-[1-(3-chlorophenyl)-3-methyl-3-oxopropylidene]aminomalonate, which gave two pyrrole derivatives. Thus it was confirmed that there were no rearrangement reactions involved in this process.

We made spectroscopic observations of the pure enamine (V), and its structure was supported as shown in Chart 4. In the infrared spectra of enamine (V) in chloroform and in nujol, no imino band was observed, but in the NMR spectrum, a signal of an imino proton was observed as a broad doublet at 11.8 ppm (J=8 cps).

These observations indicated that the enamine (V) had a strong hydrogen bond in its structure. This was further confirmed by the fact that the imino band shifted to a lower frequency and its absorption strength became weaker in the infrared spectra and the signal of the imino proton shifted to a lower field in the NMR spectrum. These observations supported that the enamine (V) had the structure shown in the Chart 4.



XVIII

Chart 4

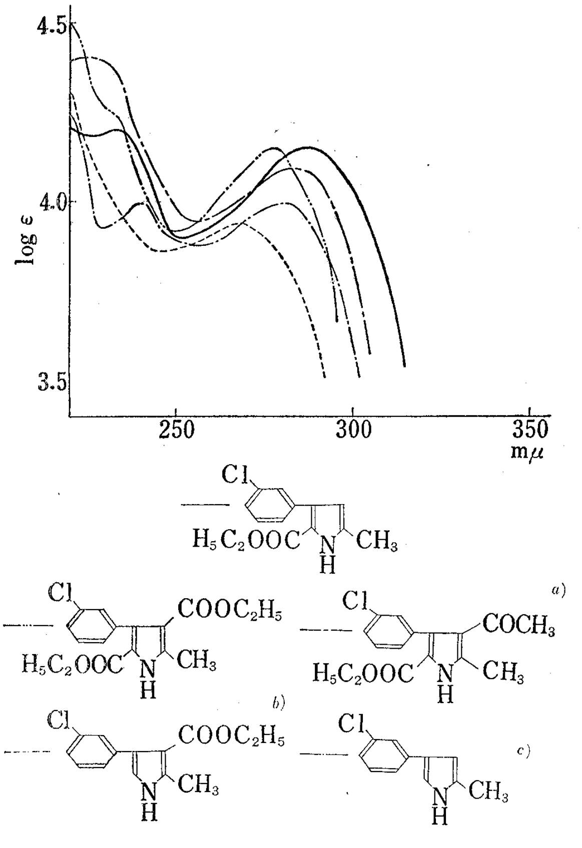


Fig. 1. Ultraviolet Spectra of 3-Aryl-pyrroles

a) Part V: *Chem. Pharm. Bull.* (Tokyo), **17**, 588(1969).
b) Part I: *Chem. Pharm. Bull.* (Tokyo), **17**, 559(1969).
c) Part XI: *Chem. Pharm. Bull.* (Tokyo), submitted.

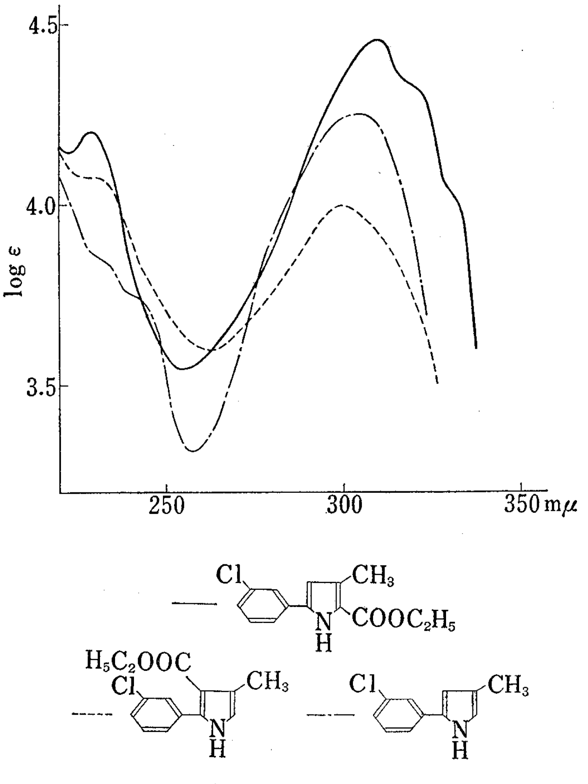


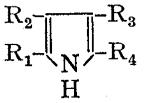
Fig. 2. Ultraviolet Spectra of 2-Aryl-pyrroles

We also studied relationships between the ultraviolet absorption spectra and the substituted position of the aryl group in the aryl-pyrroles.

The ultraviolet absorption spectra of 3-aryl-pyrrole were extremely differed from 2-aryl-pyrrole, as shown in Fig. 1 and Fig. 2. In these ultraviolet absorption spectra, two absorption bands were observed near 290 mμ (band I) and 220 mμ (band II).

It is known[3] that the band I of 2-pyrrolecarboxylate is observed in a longer wavelength region than that of 3-pyrrolecarboxylate, but it was considered that the aryl group in the pyrrole ring was more effective than carbonyl group in the pyrrole ring in this shift, as shown in Fig. 1 and Fig. 2. So it is obviously concluded that the aryl group is key substituents in the ultraviolet absorption spectra of the aryl-pyrroles. Band I of ethyl 3-(3-chlorophenyl)-5-methyl-2-pyrrolecarboxylate (VI) was observed at 286 mμ and band I of ethyl 2-(3-chlorophenyl)-4-methyl-5-pyrrolecarboxylate (VII′) was observed at 310 mμ.

Table I. Ultraviolet Spectra of 2- or 3-Aryl-pyrroles

	Compounds 			λ_{max}(band I) (in 95% EtOH)
R_1	R_2	R_3	R_4	mμ (log ε)
C_2H_5OOC-	2-chloro-C_6H_4-	H-	CH_3-	*b*) 281 (4.19)
C_2H_5OOC-	4-chloro-C_6H_4-	H-	CH_3-	*b*) 283 (4.20)
C_2H_5OOC-	3-bromo-C_6H_4-	H-	CH_3-	*b*) 288 (4.14)
C_2H_5OOC-	3,4-dichloro-C_6H_3-	H-	CH_3-	*b*) 283 (4.20)
C_2H_5OOC-	4-methoxy-C_6H_4-	H-	CH_3-	*b*) 282 (4.21)
C_2H_5OOC-	3,4-dimethoxy-C_6H_3-	H-	CH_3-	*b*) 287 (4.26)
C_2H_5OOC-	C_6H_5-	H-	CH_3-	*b*) 293 (4.22)
C_2H_5OOC-	C_6H_5-	CH_3O-	C_2H_5OOC-	*d*) 283 (4.24)
H-	3,4-dichloro-C_6H_3-	C_2H_5OOC-	CH_3-	*a*) 278 (3.98)
H-	4-methoxy-C_6H_4	H-	CH_3-	*b*) 273 (4.02)
3,4-Dichloro-C_6H_3-	H-	CH_3-	C_2H_5OOC-	*c*) 300 (4.36)
3-Chloro-C_6H_4-	H-	H-	C_2H_5OOC-	*c*) 308 (4.50)
3-Methoxy-C_6H_4-	H-	H-	C_2H_5OOC-	*c*) 310 (4.44)
C_6H_5-	H-	H-	C_2H_5OOC-	*c*) 308 (4.39)

a) Part I: *Chem. Pharm. Bull.* (Tokyo), **17**, 559 (1969)
b) Part XI: *Chem. Pharm. Bull.* (Tokyo), submitted
c) Part XII: *Chem. Pharm. Bull.* (Tokyo), submitted
d) unpublished

The absorption maxima of other 2- and 3- aryl-pyrroles as shown in Table I, were correlated to the substituted position of the aryl group on the pyrrole ring. Therefore, it is concluded that the band I of 3-aryl-pyrrole are observed at a shorter wavelength than 290 mμ and band I of 2-aryl-pyrroles are observed at a longer region than 300 mμ.

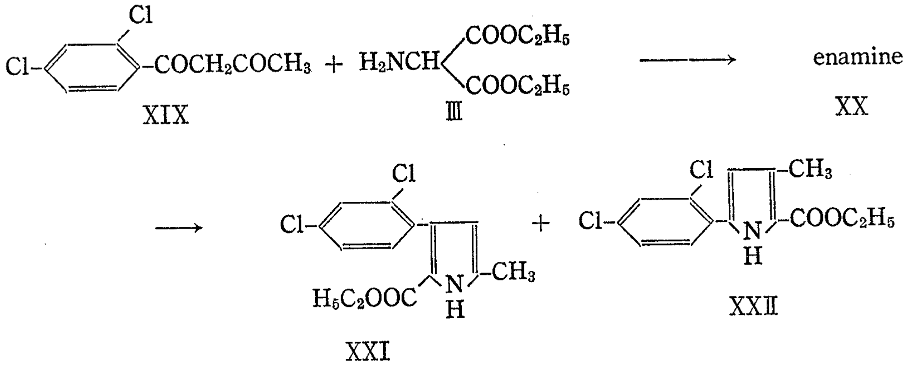


Chart 5

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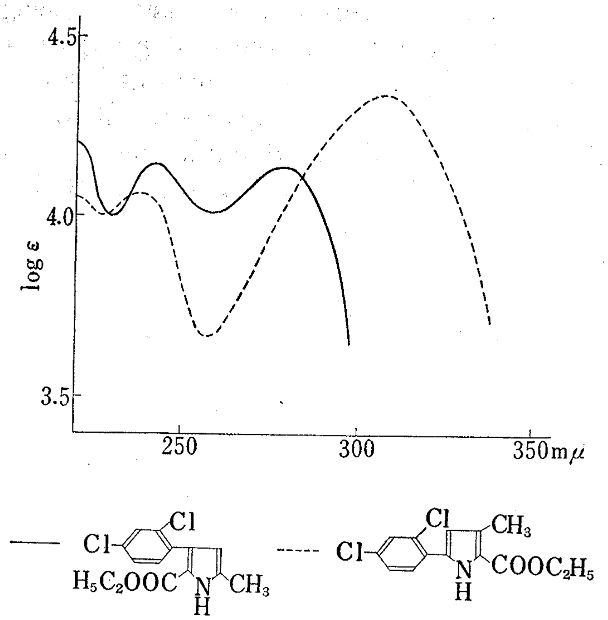
[3] H.H. Jafeé and Milton Orchin, "Theory and Applications of Ultraviolet Spectroscopy," John Wiley & Sons, Inc., New York, N.Y., 1962, p. 350.



XXI XXII

Fig. 3. Ultraviolet Spectra of XXI and XXII

These results are useful to decide the substituted position of an aryl group in the pyrrole derivatives.

For example, 2,4-dichlorophenyl-1,3-butanedione (XIX) was treated with diethyl aminomalonate (III) and the resulting enamine (XX) gave two kind of pyrroles who compositions were the same as $C_{14}H_{13}O_2NCl_2$ by their microanalyses, and the respective ultraviolet absorption spectra were shown in Fig. 3.

We could confirm from the ultraviolet absorption spectra that these were ethyl 3-(2,4-dichlorophenyl)-5-methyl-2-pyrrolecarboxylate (XXI) and ethyl 2-(2,4-dichlorophenyl)-4-methyl-5-pyrrolecarboxylate (XXII).

As described above, it was confirmed that nucleophilicity of 1-aryl-1,3-butanedion was decided by electronic and steric effects of the substituted group in the benzene ring. This led to that 3-aryl-1,3-butanedione which had a nitro group in the benzene ring condensed with an amine at the 3-carbonyl group of the 1,3-butanedione to yield diethyl N-[1-methyl-3-(2-nitro-3-chlorophenyl)-3-oxopropylidene]aminomalonate, and then 3-aryl-pyrrole was obtained. But 3-aryl-1,3-butanedione which had a chloro group in the benzene ring condensed with the 1-, or 3-carbonyl group to give two enamines and consequently, to yield two pyrroles, the 3-aryl-pyrrole (VI) and the 2-aryl-pyrrole (VII′).

Experimental⁴⁾

Cyclization of the Semi-solid Enamine (IV)——A solution of semi-solid enamine (IV) (79.1 g) in abs. EtOH (50 ml) was added dropwise with stirring to a solution of NaOEt prepared from abs. EtOH (200 ml) and metallic sodium (10.4 g). The mixture was refluxed for 5 hr. The solution was diluted with water, and extracted with ether. The extracts were washed with water, dried and condensed to dryness to give a semi-solid residue, which was recrystallized from EtOH to give ethyl 3-(3-chlorophenyl)-5-methyl-2-pyrrolecarboxylate (VI), mp 153—155°, (20.2 g).¹⁾

The mother liquor of recrystallization was chromatographed over silicagel. Elution with benzene gave a crystalline material, which was recrystallized from EtOH to afford colorless plates (VII), mp 116—117° (4 g). *Anal.* Calcd. for $C_{14}H_{14}O_2NCl$: C, 63.76; H, 5.35; N, 5.31. Found: C, 63.62; H, 5.50; N, 5.19. IR (nujol) cm^{-1}: 3280 (NH), 1660 (EtOOC). UV λ_{max}^{EtOH} mμ (log ε): 232 (4.20), 310 (4.48). NMR ($CDCl_3$) ppm: 6.38 (1H, doublet, $J=3$ cps, H_3 in pyrrole), 9.35 (1H, H_1 in pyrrole).

Ethyl 2-(3-Chlorophenyl)-4-methyl-3-pyrrolecarboxylate (X)——A mixture of ethyl 3-chlorobenzoylacetate (VIII) (6.81 g), 3-amino-2-propanone hydrochloride (IX) (3.39 g), $AcONa \cdot 3H_2O$ (75 g) and AcOH (120 ml) was warmed with stirring at 50° for 4 hr. After stirring was continued at 70° for additional 4 hr the reaction mixture was poured into water and extracted with ether. The extracts were washed with 5% NaOH and water, dried and condensed to dryness to give a semi-solid product, which was recrystallized from benzene–ligroin to afford X, mp 103—104.5°, (1.1 g) (Ehrlich's test was positive). *Anal.* Calcd. for $C_{14}H_{14}O_2NCl$: C, 63.76; H, 5.35; N, 5.31. Found: C, 63.53; H, 5.41; N, 5.22. IR (nujol) cm^{-1}: 3290 (NH), 1673 (EtOOC). UV λ_{max}^{EtOH} mμ (log ε): 300 (4.0). NMR ($CDCl_3$) ppm: 6.54 (multiplet, H_5 in pyrrole), 8.68 (1H, H_1 in pyrrole).

2-(3-Chlorophenyl)-4-methyl-3-pyrrolecarboxylic Acid (XI)——A suspension of X (0.5 g) in 95% H_2SO_4 (1 ml) was warmed with stirring at 31° for 3.5 hr. The reaction mixture was poured onto ice, and extracted

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4) All melting points are uncorrected. The infrared spectra were recorded on a Hitachi EPI S2. The ultraviolet absorption spectra were recorded on a Hitachi EP S2. The nuclear magnetic resonance spectra were measured with a Varian A–60 spectrometer using tetramethylsilane as an internal standard.

with benzene. The extracts were washed with water, dried, and condensed to dryness to yield a carboxylic acid (XI), mp 137—146° (decomp.) (0.04 g).

2-(3-Chlorophenyl)-4-methyl-pyrrole (XII)——A mixture of XI (20 mg) and glycerin (1 ml) was heated with stirring at 170° for 30 min. The sublimed crystals were collected. The crystals were purified by sublimation to give a pyrrole derivative (XII), mp 114—115°, (6 mg). *Anal.* Calcd. for $C_{11}H_{10}NCl$: C, 68.93; H, 5.64. Found: C, 68.89; H, 5.28. IR (nujol) cm^{-1}: 3400 (NH). UV λ_{max}^{EtOH} $m\mu$ ($\log \varepsilon$): 305 (4.27). NMR ($CDCl_3$) ppm: 2.14 (3H, singlet, Me), 6.39 (1H, singlet, H_5 in pyrrole), 6.65 (1H, singlet, H_3 in pyrrole).

Hydrolysis and Decarboxylation of Colorless Plates (VII)——A mixture of VII (0.5 g), 10% NaOH (4 ml) and 95% EtOH (2 ml) was refluxed for 4 hr. The reaction mixture was filtrated, and the filtrate was acidified with dil.HCl. The resulting precipitates were collected by filtration to give a carboxylic acid, mp 165—168° (decomp.) (0.4 g).

A mixture of the carboxylic acid (100 mg) and glycerin (2 ml) was heated for 30 min at 160°. The reaction mixture was poured into water and extracted with AcOEt. The extracts were washed with dil. NaOH and water, dried and condensed to dryness to afford a crystalline product, which was recrystallized from benzene–ligroin to give a pyrrole derivative (XII′), mp 114—115°. (60 mg). *Anal.* Calcd. for $C_{11}H_{10}NCl$: C, 68.93; H, 5.64; N, 7.31. Found: C, 68.95; H, 5.29; N, 7.31. This compound was identified to be XII by the mixed melting point determination and infrared spectral comparison.

Ethyl 3-(3-Chlorophenyl)-5-methyl-2,4-pyrroledicarboxylate (XVa)——A mixture of ethyl 2-(3-chlorobenzoyl)-2-oximinoacetate (XIII) (2 g), ethyl acetoacetate (XIVa) (1.33 g) and AcOH (30 ml) was hydrogenated over 10% Pd-C (0.2 g) in the usual manner. The catalyst was removed by filtration and the filtrate was evaporated. The residue was diluted with water and extracted with ether. The extracts were washed with dil. HCl, dil. NaOH and water, dried, and condensed to dryness to give colorless crystals, which were recrystallized from EtOH to afford XVa, mp 138—139°, (1.5 g). *Anal.* Calcd. for $C_{17}H_{18}O_4NCl$: C, 60.81; H, 5.40; N, 4.17; Cl, 10.75. Found: C, 61.08; H, 5.67; N, 4.07; Cl, 10.75. IR (nujol) cm^{-1}: 3270 (NH); 1700, 1663 (EtOOC). UV λ_{max}^{EtOH} $m\mu$ ($\log \varepsilon$); 277 (4.17).

***tert*-Butyl 3-(3-Chlorophenyl)-5-methyl-2,4-pyrroledicarboxylate (XVb)**——A mixture of XIII (6.52 g), *tert*-butyl acetoacetate (XIVb) (5.28 g) and AcOH (100 ml) was hydrogenated over 10% Pd–C (0.7 g) as described in the synthesis of XVa to give XVb as yellow crystals, which were recrystallized from EtOH to give colorless crystals, mp 145—145.5°, (5.6 g). *Anal.* Calcd. for $C_{19}H_{22}O_4NCl$: C, 62.72; H, 6.10; N, 3.85; Cl,9.75. Found: C, 63.12; H, 6.26; N, 3.72; Cl, 9.94. IR (nujol) cm^{-1}: 3260 (NH); 1693, 1662 (EtOOC).

2-Ethoxycarbonyl-3-(3-chlorophenyl)-5-methyl-4-pyrrolecarboxylic Acid (XVI)——(i) From Ethyl Ester (XVa): A suspension of XVa (3 g) in conc. H_2SO_4 (6 ml) was warmed with stirring at 30° for 4 hr. The reaction mixture was poured onto ice and the resulting precipitates were collected by filtration to afford a carboxylic acid (XVI), mp 220—225 (decomp.), (1 g).

ii) From *tert*-Butyl Ester (XVb): A mixture of XVb (0.5 g), *p*-toluenesulfonic acid (0.05 g) and abs. toluene (20 ml) was refluxed for 5 hr. After cooling, water and AcOEt were added to the reaction mixture, and the resulting organic layer was extracted with dil.NaOH. The water layer was acidified and extracted with AcOEt. The extracts were washed with water, dried and condensed to dryness to give a carboxylic acid (XVI), (0.1 g).

The organic layer, which was obtained after extraction with dil.NaOH, was washed with water, dried and evaporated to give XVII, mp 153—154° (0.3 g).

Ethyl 3-(3-Chlorophenyl)-5-methyl-2-pyrrolecarboxylate (XVII)——A mixture of XVI (500 mg) and glycerin (5 ml) was heated with stirring at 240° for 1 hr. The reaction mixture was poured in water and extracted with AcOEt. The extracts were dried and evaporated. The residue was dissolved into benzene, and decolored over silicagel. The solvent was evaporated to dryness to give XVII, mp 154—155° (100 mg).

Enamine (XX)——The mixture of 1-(2,4-dichlorophenyl)-butanedione (XIX) (7.0 g), diethyl aminomalonate (6.0 g) and abs. benzene (35 ml) was treated in the same manner as described in the synthesis of IV[1] to give a semi-solid enamine (XX), (5.0 g).

Cyclization of the Enamine (XX)——The solution of the enamine (XX) (4.0 g) and sodium ethoxide prepared from abs. EtOH and Na was treated in the same manner as described above. The product was separated by preparative TLC into two materials which showed fluorescence under radiation of ultraviolet ray. The crystalline product, which was obtained from the first fraction, was recrystallized from EtOH to give ethyl 2-(2,4-dichlorophenyl)-4-methyl-5-pyrrolecarboxylate (XXII), mp 126°, (0.1 g). *Anal.* Calcd. for $C_{14}H_{13}O_2NCl$: C, 56.39; H, 4.40; N, 4.70; Cl, 23.78. Found: C, 56.52; H, 4.26; N, 4.87; Cl, 23.43. UV λ_{max}^{EtOH} $m\mu$ ($\log \varepsilon$): 240 (4.06), 305 (4.37).

The second fraction gave ethyl 3-(2,4-dichlorophenyl)-5-methyl-2-pyrrolecarboxylate (XXI), mp 193°, (0.4 g). *Anal.* Calcd. for $C_{14}H_{13}O_2NCl$: C, 56.39; H, 4.40; N, 4.70; Cl, 23.78. Found: C, 56.35; H, 4.45; N, 4.61; Cl, 23.57. UV λ_{max}^{EtOH} $m\mu$ ($\log \varepsilon$): 245 (4.14), 282 (4.13).