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

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Cyclization of diethyl N-[1-methyl-3-(2-nitro-3- chlorophenyl)-3-oxopropylidene]-aminomalonate (XV) with polyphosphoric acid ethyl ester (PPE) gave ethyl 3-(2-nitro-3-chlorophenyl-5-methyl-2-pyrrolecarboxylate (XVI) in good yield. In such reaction, diethyl 3-(3-chlorophenyl)-5-methyl-2,2-(2H)-pyrroledicarboxylate (XX) was obtained easily by ring-close of diethyl N-[1-methyl-3-(3-chlorophenyl)-3-oxopropylidene]amino-malonate (XVIII) with PPE.

It may be concluded from this result that ethyl 3-aryl-5-methyl-2-pyrrolecarboxylate was prepared *via* the 2H-pyrrole compound from the corresponding enamine.

The synthesis and a study of 3-arylpyrroles were described in the previous part of this series.[2] The present investigation was undertaken to develop the commercial synthetic pathway of 3-arylpyrroles which are one of the most important intermediates to manufacture pyrrolnitrin.

Kleisphen[4] has reported that diethyl oximinomalonate (IV) was treated reductively with 2,4-pentanedione (V) to yield ethyl 3,5-dimethyl-2-pyrrolecarboxylate (VI). One of the authors[5] has reported the reaction of ethyl aminoisobutyroylacetate (I) with ethyl acetopyruvate (II) to afford diethyl 5-methyl-2,3-pyrroledicarboxylate (III) in good yield.

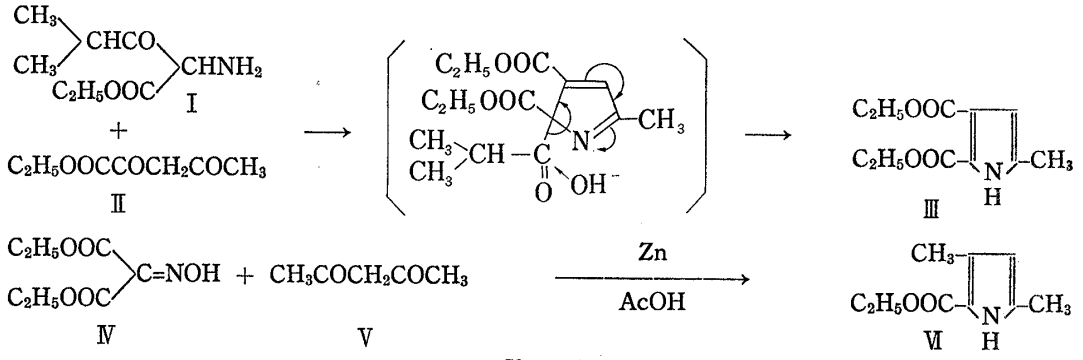

Chart 1

On the basis of these reports, new synthesis of ethyl 3-aryl-5-methyl-2-pyrrolecarboxylate was undertaken from 1-(substituted-phenyl)-1,3-butanedione as the starting material. Finar,[6] *et al.* have shown that *o*, *m* and *p*-nitrophenyl-butanedione were allowed to react with phenylhydrazine to form 3-methyl-5-*o*, *m* and *p*-nitrophenyl-1-phenylpyrazoles only, whereas phenylbutanedione and 2,4-dinitrophenylhydrazine gave both 5- and 3-phenylpyrazoles.

1) Part II: H. Nakano, S. Umio, K. Kariyone, K. Tanaka, I. Ueda and H. Nakamura, *Chem. Pharm. Bull.* (Tokyo), **17**, 567 (1969).
2) A part of this work was presented at the 87th Annual Meeting of the Pharmaceutical Soiety of Japan at Kyoto, April 1967.
3) Location: *1, Kashimacho, Higashiyodogawa-ku, Osaka.*
4) G.G. Kleisphen, *J. Am. Chem. Soc.*, **77**, 1546 (1955).
5) S. Umio, *Yakugaku Zasshi*, **79**, 1048 (1959).
6) L.L. Finar and A. B. Simmonds, *J. Chem. Soc.*, **1958**, 200.

From this fact, it seems reasonable to assume that since pyrrolnitrin possesses the nitro group in the benzene ring, 1-(2-nitro-3-chlorophenyl)-1,3-butanedione, the starting material of the pyrrolnitrin, may react with amino group at the 3-position carbonyl group of butanedione compounds selectively. At first preliminary experiments were initiated in order to prove the above assumption; namely, 1-(2-nitrophenyl)-1,3-butanedione was condensed with ethyl aminoacetoacetate in an alkaline medium, but the resulting product was apparently not the expected ring closing product, but a little amount of an unknown substance possessing mp 177—178.5° instead which indicated the following signals in NMR[7] (ppm): 1.35 (3H, triplet, $-COOCH_2C\underline{H}_3$) 4.35 (2H, quartet, $-COOC\underline{H}_2$) 2.22 (3H, singlet, CH_3 of α or β' position) 2.26 (3H, singlet, CH_3 or α of β' position) 8.2—7.3 (phenyl H, multiplet).

From the above NMR data added to the elemental analysis, IR, UV data on the unknown substance is concluded that ethyl 2-methyl-3-(2-nitrobenzoyl)-4-methyl-5-pyrrolecarboxylate (IX) was formed in this reaction condition. Accordingly, it has been found the carbonyl group of benzoyl group of butanedione compound (VII) could not react with the active methyne group of acetoacetate part but the carbonyl group of acetyl part was attacked by the active methylene group. Since this reaction had not proceeded to the expected direction (B route), it was thought advisable to investigate different methods which were used for other amino–compounds not containing the active carbonyl group such as acetyl group for avoiding the side reaction as in A route. For this purpose the diethyl aminomalonate was chosen as suitable amino-compounds.

Refluxing VII and diethyl aminomalonate in toluene gave diethyl N-[1-methyl-3-(2-nitrophenyl)-3-oxopropylidene]aminomalonate (XI) as yellow crystals in good yield; furthermore, ethyl 3-(2-nitrophenyl)-5-methylpyrrole-2-carboxylate (XII) was obtained when XI was refluxed in ethanol with sodium ethoxide.

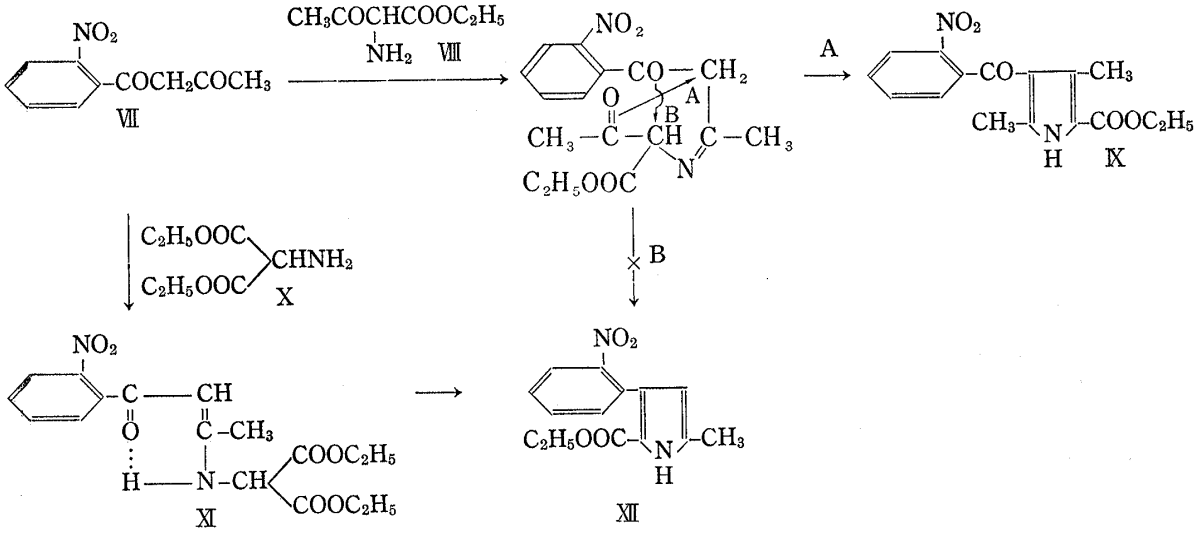

Chart 2

Keeping the above facts in mind, 1-(2-nitro-3-chlorophenyl)-1,3-butanedione was condensed with diethyl aminomalonate and the corresponding enamine compound (XV) was obtained in excellent yield. In the similar manner, boiling it with sodium ethoxide in ethanol produced ethyl 3-(2-nitro-3-chlorophenyl)-5-methyl-2-pyrrolecarboxylate (XVI). This substance was identified by comparison with an authentic sample.[1] Thus, it has been found that the reaction had occurred between 3-position the carbonyl group of 1-arylbutanediones possessing a nitro group in a benzene ring and an amino group selectively as Finar's report.[6]

7) The nuclear magnetic resonance spectra were measured with a Varian A-60 spectrometer using tetramethylsilane as internal standard.

Although the synthetic procedure of this compound (XVI) was excellent than the other with respect to simple process, yield was not so well. Therefore, experiments were undertaken to improve the reaction conditions.

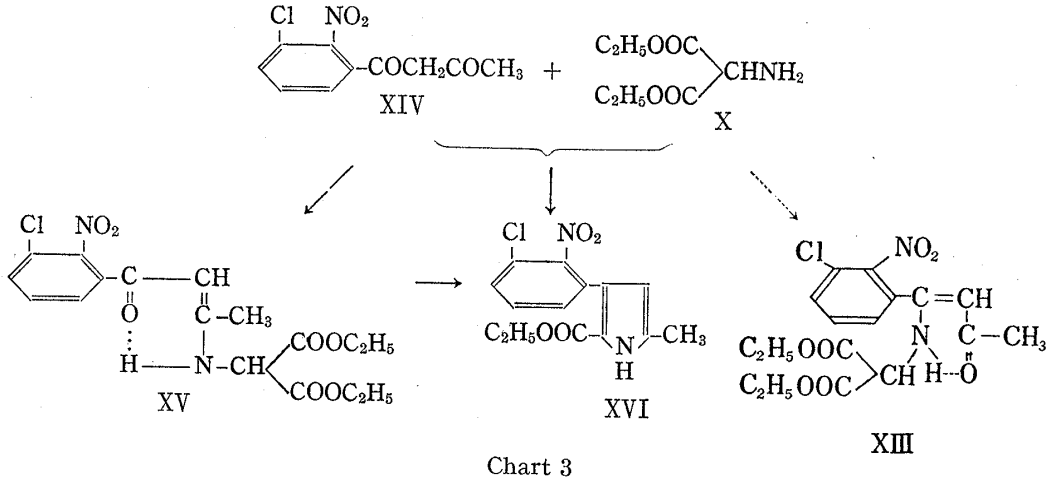

Chart 3

It has been shown that gentle heating the enamine compound (XV) in PPA as a condensing agent gives a little amount of the desired substance (XVI). Since PPA was a strong acid enough to decompose enamines, it was thought advisable to use polyphospholic acid ethyl

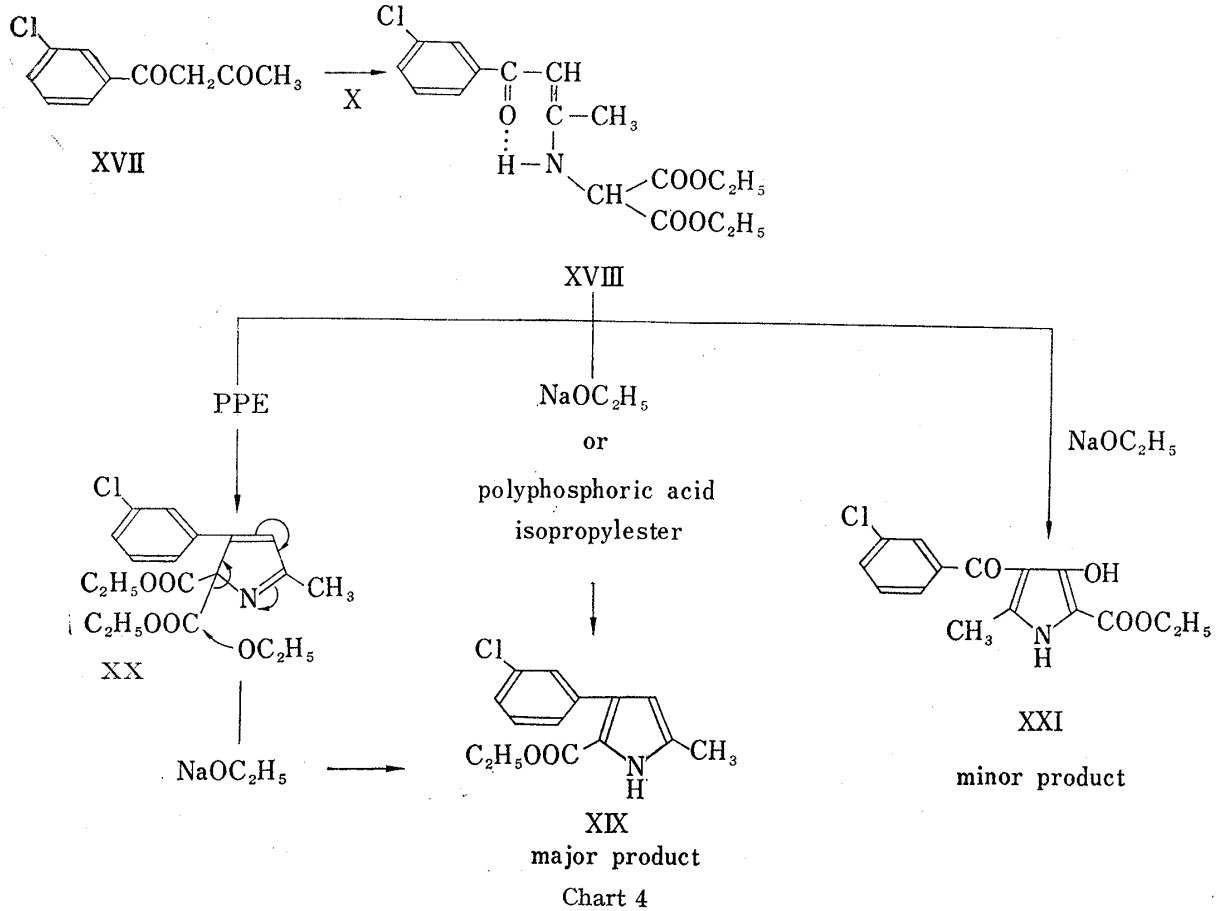

Chart 4

8) *a*) Y. Kanaoka, O. Yonemitsu, K. Tanizawa, and Y. Ban, *Chem. Pharm. Bull.* (Tokyo), **12**, 773 (1964); *b*) Y. Kanaoka, M. Machida, O. Yonemitsu, and Y. Ban, *ibid.*, **13**, 1065 (1965); *c*) Y. Kanaoka, Y. Ban, O. Yonemitsu, K. Irie, and K. Miyashita, *Chem. Ind.* (London), **1965**, 473; *d*) Y. Kanaoka, O.E. Sato, O. Yonemitsu, and Y. Ban, *Tetrahedron Letters*, **1964**, 2419.

ester (PPE) which was more harmless than PPA to –C=C–NH– bond such as enamines, though, Kanaoka, *et al.*[8a–d] noted on the applicability of PPE to organic reactions. However, there are no reports regarding to reaction with an active methylen group and a carbonyl group.

A mixture of diethyl N-[1-methyl-3-(2-nitro-3-chlorophenyl)-3-oxopropyliden]aminomalonate (XV), PPE and chloroform was heated for a long time to produce XVI in good yield. Also XVI was directly formed from a mixture of 1-(2-nitro-3-chlorophenyl)-1,3-butanedione (XIV), (X), PPE and chloroform by heating. Accordingly, a basis for the industrial possibility of pyrrolnitrin synthesis has been established.

Synthetic study of ethyl 3-(3-chlorophenyl)-5-methyl-2-pyrrolecarboxylate was attemtped to obtain further information on nucleophilicity of the amino group to both carbonyl groups of the corresponding 1,3-butanedione and also to prepare pyrrolnitrin derivatives, which is shown in Chart 4.

XVIII was obtained as a semi-solid mush by condensation of X with 1-(3-chlorophenyl)-1,3-butanedione (XVII) and it was purified by recrystallization. In a similar method, XIX was produced by cyclization of purified XVIII with sodium ethoxide. Contrarily, heating XVIII with PPE instead of sodium ethoxide gave a non-pyrrole compound, mp 78—80°. This substance indicated in IR cm^{-1}: 1730 (C=O), no absorption of NH group, NMR[7] ($CDCl_3$) (ppm): 1.2, (6H, triplet, $-OCH_2C\underline{H}_3$), 4.2 (4H, quartet, $-OC\underline{H}_2\ CH_3$), 2.4 (3H, singlet, $=C-C\underline{H}_3$), 6.8 (1H, singlet, =C–H) and UV λ_{max}^{EtOH}: 295 mμ.

Considering of these data, it seems to be concluded that the structure of the non-pyrrole compound is 2H-pyrrole (XX). The chemical proof for this assumption is as follows: ethyl 3-(3-chlorophenyl)-5-methyl-2-pyrrolecarboxylate was obtained easily from 2H-pyrrole (XX) by treatment with sodium ethoxide in good yield as might be expected.

In view of the above fact the most reasonable structure of 2H-pyrrole compound was diethyl 3-(3-chlorophenyl)-5-methyl-2,2-(2H)-pyrroledicarboxylate. Thus, we defined the reaction mechanism of pyrrole ring-closure of enamine compounds.

On the other hand, when XVIII was heated with polyphosphoric acid isopropyl ester, ethyl 3-(3-chlorophenyl)-5-methyl-2-pyrrolecarboxylate (XIX) was obtained directly. PPE also may give the same result under more drastic conditions.

Using the enamine compounds containing a nitro group in the benzene ring, the corresponding 2H-pyrroles could not be obtained. Consequently, it was presumed that such intermediates were more unstable owing to the inductive effect of a nitro group. When XVIII was treated with sodium ethoxide in an usual way, a small amount of an unknown substance of mp 191—192.5° was isolated from the reaction mixture. This substance showed in IR cm^{-1}: 3250 (OH or NH), 1678, 1605 (C=O) and gave an intense color by blue ferric. From these data and the value of elemental analysis, it was assumed the structure of this substance might be a hydroxypyrrole such as XXI, namely Dieckmann condensation having taken place to XVIII. When a nitro group was present in a benzene ring the corresponding hydroxy pyrrole compound was not isolated at all which was shown by its negative ferric chlorid test. Further, the enamine isomer (XIII) could not be found in the reaction mixture.

Experimental[9]

Diethyl N-[1-Methyl-3-(2-nirtophenyl)-3-oxopropylidene]aminomalonate (XI)——A mixture of 4.0 g of 1-(2-nitrophenyl)-1,3-butanedione, 4.5 g of diethyl aminomalonate, 30 ml of EtOH and two drops of piperidine was refluxed for 5 hr. Solvent was evaporated *in vacuo*. The residue was treated with ether and the separated crystals were collected by filtration, washed with ether and dried, yielding 4.3 g of yellow crystals. The crystals were recrystallized from a mixed solvent of benzene and ether to obtain faint yellow granules, XI, mp 85.5—87.5° (4.1 g). *Anal.* Calcd. for $C_{17}H_{20}O_7N_2$: C, 56.04; H, 5.53; N, 7.69. Found: C, 56.01; H, 5.44; N, 7.75.

9) All melting points were uncorrected.

Ethyl 3-(2-Nitrophenyl)-5-methyl-2-pyrrolecarboxylate (XII)——A solution of 0.5 g of diethyl N-[1-methyl-3-(2-nitrophenyl)-3-oxopropylidene]aminomalonate (XI) in 2 ml of tetrahydrofuran was added dropwise with stirring to a solution of NaOEt prepared from 6 ml of EtOH and 70 mg of metallic sodium. After the reaction mixture was refluxed for 5 hr, the solvents were evaporated *in vacuo*. The residue was added with water and the solution was extracted with ether. The ether layer was washed with water, dried over $MgSO_4$, and evaporated to yield an oily substance. The oily substance was treated with ether to afford solid. The product was recrystallized from EtOH to obtain yellow prisms of XII. mp 161.5—163° (15 mg). *Anal.* Calcd. for $C_{14}H_{14}O_4N_2$: C, 61.31; H, 5.15; N, 10.21. Found: C, 61.60; H, 5.46; N, 10.26.

Ethyl 2,4-Dimethyl-3-(2-nitrobenzoyl)-5-pyrrolecarboxylate (IX)——A solution of 0.4 g of 1-(2-nitrophenyl)-1,3-butanedione (VII), 0.37 g of ethyl α-amino-acetoacetate hydrochloride (VIII), 20 mg of K_2CO_3 and 3 ml of 60% EtOH were added with 3 drops of 2% NaOH. The solution was allowed to stand for 2 days at 37° and then the reaction mixture was poured into an ice-water, and extracted with ether, dried over $MgSO_4$ and evaporated, yielding dark brown needles containing an oily substance.

A benzene solution of this product was chromatographed on silicagel, to obtain needles mp 160—167°. This crystals were recrystallized from a mixture of benzene and petroleum ether three times, to give IX as colorless needles mp 177—178.5° (110 mg). *Anal.* Calcd. for $C_{16}H_{16}O_5N_2$: C, 60.75; H, 5.10; N, 8.86. Found: C, 60.48; H, 5.25; N, 9.24.

Diethyl N-[1-Methyl-3-(2-nitro-3-chlorophenyl)-3-oxopropylidene]aminomalonate (XV)——A mixture of 2.0 g of 1-(2-nitro-3-chlorophenyl)-1,3-butanedione (XIV), 1.8 g of diethyl aminomalonate (X) and 10 ml of benzene was refluxed for 10 hr using Dean Stark's apparatus. After benzene was distilled off *in vacuo*, the residue was treated with ether, and then solid was separated.

The solid was collected by filtration, washed with ether and dried over $MgSO_4$. The solid was recrystallized from a mixed solvent of benzene and ligr oin,affording, XV, mp 135—136° (2.86 g). *Anal.* Calcd.for $C_{17}H_{19}O_7N_2Cl$: C, 51.20; H, 4.80; N, 7.02. Found: C, 51.24; H, 4.90; N, 7.07.

Ethyl 3-(2-Nitro-3-chlorophenyl)-5-methyl-2-pyrrolecarboxylate (XVI)——A mixture of 0.8 g of diethyl N-[1-methyl-3-(2-nitro-3-chlorophenyl)-3-oxopropylidene]aminomalonate (XV), 16.0 g of PPE and 20 ml of $CHCl_3$ was gently boiled for 15 hr. Chloroform was evaporated *in vacuo*. The residue was added to an ice-water to decompose PPE. The solution was extracted with ether. The extract was washed with 5% NaOH solution, with water and dried over $MgSO_4$, and evaporated. The residue was recrystallized from benzene to give XVI as colorless prisms, mp 222—223° (0.32 g). This substance was undepressed by admixture with an authentic sample[1] and infrared spectra were superimposable.

Diethyl N-[1-Methyl-3-(3-chlorophenyl)-3-oxo-propylidene]aminomalonate (XVIII)——A mixture of 20 g of 1-(3-chlorophenyl)-1,3-butanedione (XVII), 18 g of diethyl aminomalonate (X) and 100 ml of C_6H_6 was refluxed for 10 hr.

The reaction mixture was washed four times with dil. NaOH and twice with water. The dried extract on evaporation gave crude semi-solid enamines (31.3 g). The products were recrystallized from a mixture of ether and *n*-hexane to obtain XVIII as colorless needles, mp 54—56° (20.4 g). *Anal.* Calcd. for $C_{17}H_{20}O_5NCl$: C, 57.71; H, 5.69; N, 3.96. Found: C, 57.93; H, 5.72; N, 4.17.

Ethyl 3-(3-Chlorophenyl)-5-methyl-2-pyrrolecarboxylate (XIX)——A solution of 9.5 g of diethyl N-[1-methyl-3-(3-chlorophenyl)-3-oxopropylidene]aminomalonate (XVIII) in 38 ml of tetrahydrofuran was added dropwise with stirring to a solution of NaOEt prepared from 130 ml of EtOH and 13.3 g of metallic sodium. The reaction mixture was refluxed for 4.5 hr, and the solvent were evaporated *in vacuo*.

The residue was added to an ice–water and the solution was extracted with ether. The organic layer was washed with water, dried over $MgSO_4$, and evaporated. The residue was recrystallized from a mixture of C_6H_6 and *n*-hexane, to obtain XIX, colorless needles, mp 154—155° (4.1 g). *Anal.* Calcd. for $C_{14}H_{14}O_2NCl$: C, 63.76; H, 5.36; N, 5.32. Found: C, 63.99; H, 5.50; N, 5.47.

Ethyl 2-Methyl-3-(3-chlorobenzoyl)-4-hydroxy-5-pyrrolecarboxylate (XXI)——A solution of 7.9 g of diethyl N-[1-methyl-3-(3-chlorophenyl)-3-oxopropylidene]aminomalonate (XVIII) in 10 ml of EtOH was heated with NaOEt prepared from EtOH 25 ml and 1.04 g of metallic sodium, in a similar manner as above.

The reaction mixture was poured into an ice–water and filtered. The filtrate was treated with active carbon, filtered and dried over $MgSO_4$. The ether solution was evaporated, yielding crude product (0.2 g). mp 159—170°.

This solid was recrystallized from EtOH, to afford ethyl 2-methyl-3-(3-chlorobenzoyl)-4-hydroxy-5-pyrrolecarboxylate (XXI). mp 191.5—192.5°. *Anal.* Calcd. for $C_{15}H_{14}O_4NCl$: C, 58.54; H, 4.59; N, 4.55; Cl, 11.52. Found: C, 58.28; H, 4.63; N, 4.43; Cl, 11.65.

Diethyl 3-(3-Chlorophenyl)-5-methyl-2*H*-pyrrole-2,2-dicarboxylate (XX)——A solution of diethyl N-[1-methyl-3-(3-chlorophenyl)-3-oxopropylidene]aminomalonate (XVIII), 20 g of PPE and 20 ml of $CHCl_3$ was refluxed for 17 hr. Chloroform was removed under reduced pressuure. To the residue was added an ice–water and extracted with ehter.

The ether layer was washed with 5% NaOH solution, and with water and then ether solution was dried over $MgSO_4$. After removing ether a crude porudct (0.7 g) was obtained. The product was recrystallized from a mixture of ether and *n*-hexane, yielding diethyl 3-(3-chlorophenyl)-5-methyl-2*H*-pyrrole-2,2-dicarboxylate as colorless needles, mp 79—80° (0.6 g). *Anal.* Calcd. for $C_{17}H_{18}O_4NCl$: C, 60.80; H, 5.41; N, 4.17; Cl, 10.56. Found: C, 61.10; H, 5.50; N, 4.22; Cl, 10.70.

Reaction of XX with NaOEt——A solution of 500 mg of diethyl 3-(3-chlorophenyl)-5-methyl-2*H*-pyrrole-2,2-dicarboxylate (XX) in 3 ml of tetrahydrofuran was added dropwise to a solution of NaOEt prepared from 40 mg of metallic sodium and 5 ml of EtOH and then mixture was refluxed for 3 hr. The solvents were evaporated *in vacuo*. The residue was added with an ice–water, and extracted with ether.

The organic layer was dried over $MgSO_4$, and ether was removed. The residual solid was recrystallized from a mixed solvent of C_6H_6 and *n*-hexane, yielding ethyl 3-(chlorophenyl)-5-methyl-2-pyrrolecarboxylate (XIX), mp 154—155° (390 mg). This substance was identified by comparison with an authentic sample prepared from ethyl N-[1-methyl-3-(3-chlorophenyl)-3-oxopropylidene]aminomalonate (XVIII) with NaOEt by means of admixture and infrared spectra.

Cyclization of XVIII with Polyphosphoric Acid Isopropyl Ester——P_2O_5 (50 g) was added slowly to isopropanol (100 ml) with stirring and ice cooing, and then the solution was stirred at 90—95° for 2 hr. To this polyphosphoric acid ester solution was added dimethyl N-[1-methyl-3-(3-chlorophenyl)-3-oxopropylidene]aminomalonate (XVIII) (7.1 g) dissolved in small amount of isopropanol. Then the reaction mixture was stirred at 90—95° for 20 hr. After cooling the mixture was poured into ice–water (600 ml) and extracted with AcOEt. The extracts were washed with water, 10% aqueous Na_2CO_3, water, 10% aqueous H_2SO_4 and water successively, and dried over $MgSO_4$. After removing the solvent, a mixture of solid and oil was obtained. The solid was filtered, washed with cold EtOH and then recrystallized from EtOH to give colorless needles (2.5 g), mp 153—154°, undepresseed by admixture with an authentic sample of ethyl 3-(3-chlorophenyl)-5-methyl-2-pyrrolecarboxylate (XIX).