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Total Synthesis of Pyrrolnitrin. VII.[1] Synthesis of 2,5-Dimethyl-3-arylpyrrole[2]

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Preparation of 2,5-dimethyl-3-arylpyrrole (IX) was accomplished by three different routes: at first alkyl 3-aryl-5-methyl-4-pyrrolecarboxylate (IV) was converted to IX by the series of reactions containing Mannich reaction, reduction and decarboxylation, and secondly IX was also prepared by the ringclosure of 3-aryl-2,5-hexanedione (XIV) with ammonium acetate and thirdly the methiodide of a bis-Mannich base (XVIII) prepared by Mannich reaction of 3-arylpyrrole (XVII) was reduced with sodium borohydride to IX.

Following to the scheme for the total synthesis of pyrrolnitrin (I)[4] as described already[5] it was planned to synthesize 3-arylpyrrole with both α-positions protected by appropriate substituents, to chlorinate the 4-position of this pyrrole, and then to eliminate the protecting groups at both α-positions.

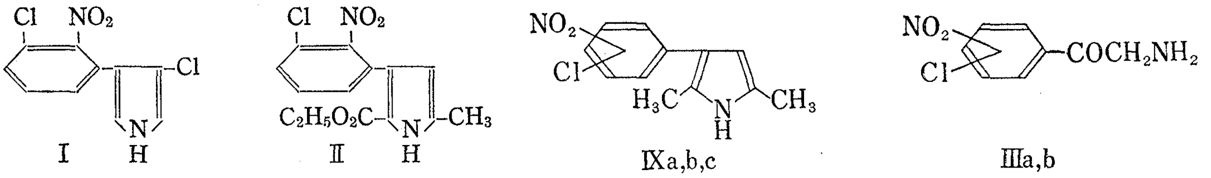

Chart 1

Alkoxycarbonyl and methyl groups were chosen as suitable protecting groups for this purpose, because the α-methyl group in a pyrrole ring has been known to be converted to a carboxyl group *via* a trichloromethyl group.[6] At the second[5] and third Parts[7] of this series synthesis of ethyl 3-(2-nitro-3-chlorophenyl)-5-methyl-2-pyrrolecarboxylate (II), an intermediate to synthesize pyrrolnitrin (I), was reported.

In this paper, we wish to report the synthesis of 2,5-dimethyl-3-arylpyrrole (IX) according to the same scheme.

Knorr condensation of 2′ (or 3′)-nitro-3′ (or 4′)-chloro-2-aminoacetophenones (IIIa,b) with ethyl acetoacetate, as described in the first Part,[8] afforded ethyl 3-[2(or 3)-nitro-3(or 4) chlorophenyl]-5-methyl-4-pyrrolecarboxylate (IVa,b).

Introduction of a methyl group to the 2-position of the pyrrole was investigated at first by using 3-nitro-4-chloroderivative as the preliminary experiment.

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1) Part VI: S. Umio, K, Kariyone, K. Tanaka, H. Noguchi and T. Ogino, *Chem. Pharm. Bull.* (Tokyo), **17**,

2) A part of this work was presented at the 9th Symposium of the Chemistry of Natural Products at
596 (1969).
Osaka, Oct. 1965. Preliminary communication of a part of this work appeared in *Tetrahedron Letters*, **1966**, 737, and in *Yakugaku Zasshi*, **86**, 159 (1966).

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

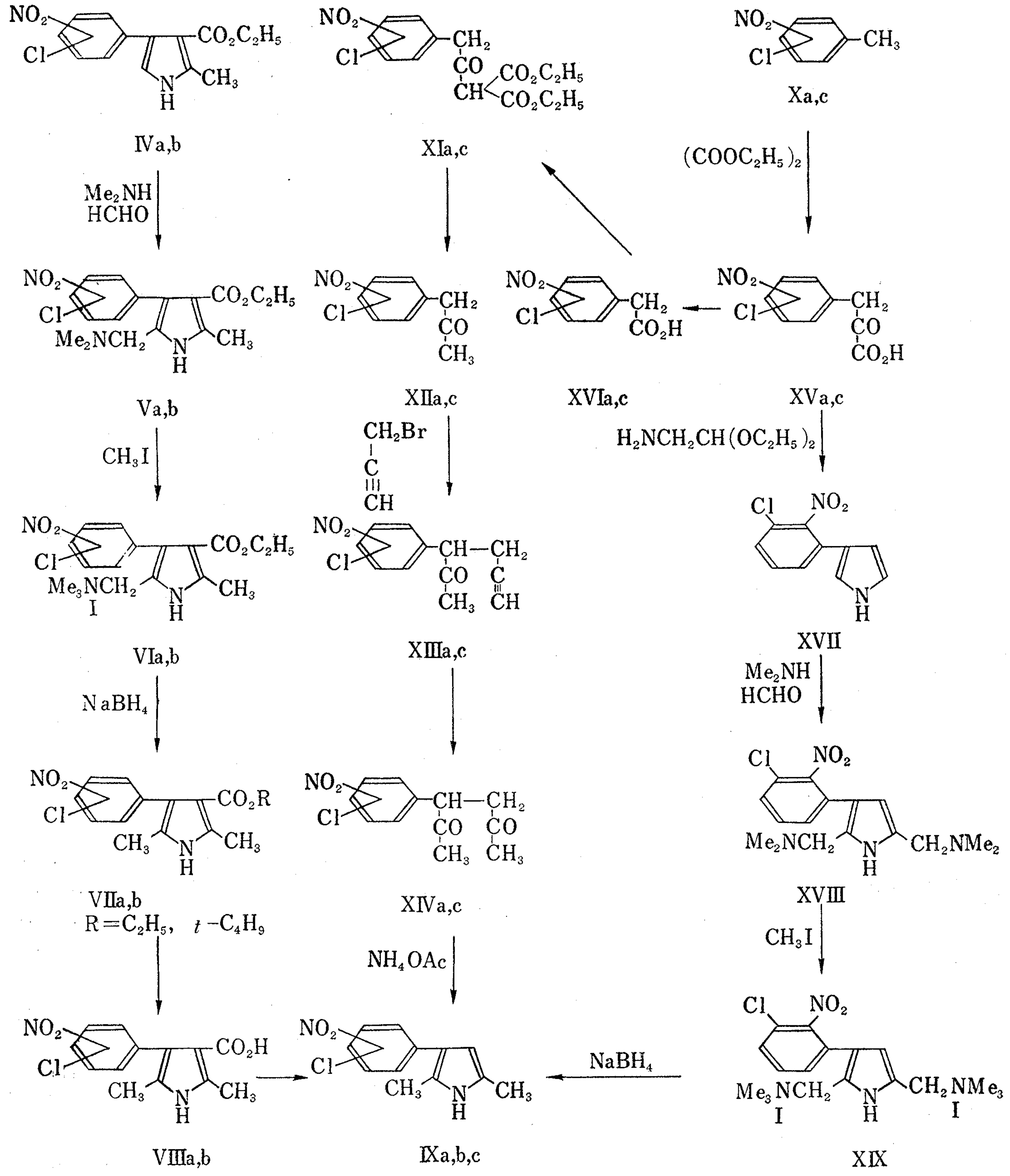
4) K. Arima, H. Imanaka, M. Kousaka and A. Fukuta, *Agr, Biol. Chem.*, **28**, 575 (1964).

5) Part II: *Chem. Pharm. Bull.* (Tokyo), **17**, 567 (1969).

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

7) Part III: *Chem. Pharm. Bull.* (Tokyo), **17**, 576 (1969).

8) Part I: *Chem. Pharm. Bull.* (Tokyo), **17**, 559 (1969).



	NO_2	Cl
a	: 2	3
b	: 3	4
c	: 2	4

Chart 2

Treatment of IVb with dimethylamine and formalin in acetic acid afforded 2-dimethylaminomethylpyrrole (Vb) in excellent yield.

The Mannich base (Vb) was transformed to its methiodide (VIb) by using methyl iodide in ethanol, and VIb was reduced with sodium borohydride to ethyl 2,5-dimethyl-3-(3-nitro-4-chlorophenyl)-4-pyrrolecarboxylate (VIIb: $R=C_2H_5$), the structure of which was ascertained by mixed melting point with a smaple of VIIb ($R=C_2H_5$) prepared in Part I.[8]

Similarly, ethyl 3-(2-nitro-3-chlorophenyl)-5-methyl-4-pyrrolecarboxylate (IVa) was converted to the Mannich base (Va), and this was treated with methyl iodide to give the methiodide (VIa), which yielded ethyl 2,5-dimethyl-3-(2-nitro-3-chlorophenyl)-4-pyrrolecarboxylate(VIIa: $R=C_2H_5$) by treatment with sodium borohydride.

The ethoxycarbonyl group of ethyl 2,5-dimethyl-3-(nitro-chlorophenyl)-4-pyrrolecarboxylate (VII: $R=C_2H_5$) appeared to be resistant to saponification.

However, the carboxylic acid (VIIIa) was obtained in excellent yield by treating the ester (VIIa: $R=C_2H_5$) with concentrated sulfuric acid followed by reaction with water through AAC 1 mechanism.

Decarboxylation of this carboxylic acid (VIIIa) was carried out by heating it in glycerin to yield the desired 2,5-dimethyl-3-(2-nitro-3-chlorophenyl)pyrrole (IXa). Moreover, it was found that the 4-alkoxycarbonyl group of VII also could be eliminated by the following reaction: *tert*-butyl 2,5-dimethyl-3-(3-nitro-4-chlorophenyl)-4-pyrrolecarboxylate (VIIb: R= *tert*-butyl), prepared in Part I,[8] when refluxed in the presence of *p*-toluenesulfonic acid in benzene, was converted directly to 2,5-dimethyl-3-(3-nitro-4-chlorophenyl)pyrrole (IXb) by elimination of isobutylene followed by decarboxylation.

We, next, tried to examine other synthetic methods of dimethylpyrroles (IX) using 2-nitro-3(or 4)-chlorotoluene (Xa,c).

Ethoxalylation[9] of Xa,c has been known to yield 2-nitro-3(or 4)-chlorophenylpyruvic acid (XVa,c).

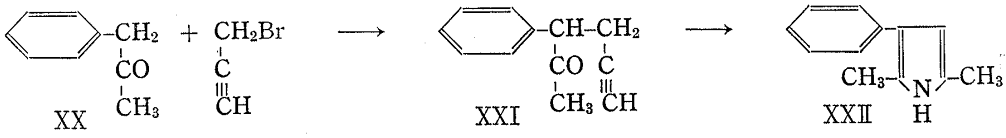


Chart 3

2-Nitro-3(or 4)-chlorophenylacetic acid (XVIa,c), prepared by hydrogen peroxide oxidation of XVa,c was condensed with the ethoxymagnesium salt of diethyl malonate to yield diethyl [2-nitro-3(or 4)-chlorophenyl]acetylmalonate (XIa,c) *via* the corresponding acid chlorides.

Refluxing XIa,c in aqueous acetic acid containing sulfuric acid gave 2-nitro-3(or 4)-chlorophenylacetone (XIIa,c).

Reisch[10] has reported the condensation of phenylacetone (XX) with propargyl bromide using sodium ethoxide in boiling ethanol to yield 4-phenyl-5-oxo-1-hexyne (XXI), which was transformed with ethanolic ammonia to 2,5-dimethyl-3-phenyl–pyrrole (XXII) in an autoclave.

2-Nitro-3(or 4)-chlorophenylacetone (XIIa,c), when treated with propargyl bromide in the presence of sodium ethoxide in hot ethanol in a similar way, afforded 4-[2-nitro-3(or 4)-chlorophenyl]-5-oxo-1-hexyne (XIIIa,c) in poor yield with a large quantity of tarry materials, owing to the instability of sodium salt of XIIa,c.

High yield of 4-(nitro–chlorophenyl)-5-oxo-1-hexyne (XIIIa,c), however, could be obtained by performing this reaction in absolute tetrahydrofuran instead of ethanol in an ice–salt bath.

An excellent yield of IX was obtained by the following method: hydration of XIIIa,c by treatment with mercuric sulfate in dilute sulfuric acid afforded 3-aryl-2,5-hexanediones (XIVa, c), which were transformed to 2,5-dimethyl-3-[2-nitro-3(or 4)-chlorophenyl]pyrrole (IXa,c) by treating with ammonium acetate in glacial acetic acid under the reaction condition of Paal Knorr reaction.

In such a way we could accomplish an excellent synthetic method of these compounds (IX a,c).

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[9] H. Singer and W. Shive, *J. Am. Chem. Soc.*, **77**, 5700 (1955).

[10] J. Reisch, *Archiv. Pharm.*, **298**, 591 (1965).

The third method of synthesis of dimethylpyrrole (IXa) was attained, using the pyrrole prepared by the new method of pyrrole ringclosure employing an aminoacetal, which will be described in detail in Part VIII11) of this series.

Mannich reaction of 3-(2-nitro-3-chlorophenyl)pyrrole (XVII), prepared from 2-nitro-3-chlorophenylpyruvic acid (XVa) and an aminoacetal, afforded *α,α'*-bis-dimethylaminomethylpyrrole (XVIII). It is favorable to carry out this reaction below 60°, since N-acetylation of the pyrrole ring by acetic acid will take place at higher reaction temperature which will necessitate hydrolysis later.

N-Acetylation of a pyrrole compound with acetic acid used as a solvent is an unusual reaction, and similar acetylation will be described in Part VIII.11)

Now, the bis-Mannich base (XVIII) was transformed to its methiodide (XIX), which afforded 2,5-dimethyl-3-(2-nitro-3-chlorophenyl)pyrrole (IXa) by sodium borohydride reduction.

Conversion of 2,5-dimethyl-3-arylpyrroles, VIIIa and IXa, to pyrrolnitrin (I) will be described in Part X12) of this series.

Experimental13)

Ethyl 2-Dimethylaminomethyl-3-(3-nitro-4-chlorophenyl)-5-methyl-4-pyrrolecarboxylate (Vb)——To a stirred suspension of ethyl 3-(3-nitro-4-chlorophenyl)-5-methyl-4-pyrrolecarboxylate (IVb) (3 g) in glacial AcOH (60 ml), was added 24% ethanolic solution of Me_2NH (1.5 ml), followed by addition of 36% formalin (1.7 ml). After stirring was continued at 60° for 3 hr, most of AcOH was removed *in vacuo* and the residue dissolved in AcOEt. AcOEt extracts were washed with aqueous $NaHCO_3$ and H_2O, dried and evaporated to give a crude Vb (3.2 g). This was converted to its HCl-salt in the usual way. Recrystallization from EtOH yielded colorless crystals (Vb–HCl), mp 180—181°. *Anal.* Calcd. for $C_{17}H_{20}O_4Cl\cdot HCl$: C, 50.76; H, 5.26; N, 10.45. Found: C, 50.43; H, 5.23; N, 10.04.

Ethyl 2-Dimethylaminomethyl-3-(2-nitro-3-chlorophenyl)-5-methyl-4-pyrrolecarboxylate (Va)——A mixture of ethyl 3-(2-nitro-3-chlorophenyl)-5-methyl-4-pyrrolecarboxylate (IVa) (3 g), 24% ethanolic Me_2NH (1.5 ml) and 36% formalin (1.7 ml) in AcOH (60 ml) was stirred at 60° for 3 hr. The reaction mixture was worked up in the similar manner as in the preparation of Vb, to give a crude Va (3.2 g).

This was converted to its hydrochloride, which was recrystallized from AcOEt to yield colorless crystals, mp 225°. *Anal.* Calcd. for $C_{17}H_{20}O_4N_3Cl\cdot HCl$: C, 50.76; H, 5.26; N, 10.45.; Cl, 17.63. Found: C, 50.79; H, 5.51; N, 10.12; Cl, 17.28.

Ethyl 2,5-Dimethyl-3-(3-nitro-4-chlorophenyl)-4-pyrrolecarboxylate (VIIb)——A solution of the Mannich base (Vb) (3 g) and CH_3I (5 ml) in MeOH (10 ml) was allowed to stand for 30 min. Precipitated crystals were collected and recrystallized from MeOH to yield colorless needles (VIb) (3 g), mp 182—185°. *Anal.* Calcd. for $C_{18}H_{23}O_4N_3Cl$: C, 42.58; H, 4.57; N, 8.28. Found: C, 42.78; H, 4.58; N, 7.85.

VIb (1 g) was dissolved in abs. MeOH (20 ml) and the solution was warmed to 55—60°. $NaBH_4$ (156 mg) was added to this stirred solution and, after vigorous evolution of Me_3N subsided, stirring was continued at this temp. for 20 min. Most of MeOH was removed *in vacuo* and the residue was dissolved in AcOEt. The AcOEt solution was washed with H_2O, dried and evaporated to give a colorless solid. Recrystallization from C_6H_6–ligroin yielded pale yellow crystals (VIIb) (0.4 g), mp 151—152°. *Anal.* Calcd. for $C_{15}H_{15}O_4N_2Cl$: C, 55.82; H, 4.68; N, 8.68. Found: C, 55.65; H, 4.83; N, 8.53.

Ethyl 2,5-Dimethyl-3-(2-nitro-3-chlorophenyl)-4-pyrrolecarboxylate (VIIa)——A solution of Va (3 g), CH_3I (5 ml) in MeOH (10 ml) was allowed to stand for 30 min and precipitated crystals were collected. Recrystallization from MeOH yielded pale yellow needles of VIIa (3.1 g), mp 231°. *Anal.* Calcd. for $C_{18}H_{23}O_4N_3Cl$: C, 42.58; H, 4.57; N, 8.28. Found: C, 42.28; H, 4.97; N, 7.86.

This methiodide (VIa) (1 g) was dissolved in abs. MeOH (20 ml) and reduced with $NaBH_4$ (0.4 g) in the similar manner as in the preparation of VIIb. Recrystallization of crude VIIa from C_6H_6–ligroin yielded pale yellow crystals (0.4 g), mp 192°. *Anal.* Calcd. for $C_{15}H_{15}O_4N_2Cl$: C, 55.82; H, 4.68; N, 8.68. Found: C, 55.99; H, 4.76; N, 8.47.

2,5-Dimethyl-3-(2-nitro-3-chlorophenyl)-4-pyrrolecarboxylic Acid (VIIIa)——A suspension of VIIa (0.6 g) in conc. H_2SO_4 (1.5 ml) was stirred at 15° for 12 hr. Reaction mixture was poured into ice–H_2O, and precipitated solid was filtered and then dissolved in 10% aqueous NaOH. The alkaline solution was washed with AcOEt, acidified with dil. H_2SO_4 and the precipitated solid was extracted with AcOEt. The

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11) Part VIII: *Chem. Pharm. Bull.* (Tokyo), **17**, 611 (1969).

12) Part X: *Chem. Pharm. Bull.* (Tokyo), **17**, 622 (1969).

13) All melting points are uncorrected. The infrared spectra were recorded on a Hitachi EPI S2.

extracts were washed with H_2O, dried and evaporated to give a colorless soild (VIIIa) (0.3 g). This showed no absorption band at 1130 cm^{-1}, which was attributable to ester group in VIIa, and a new absorption band at 1665 cm^{-1}.

2-Nitro-3-chlorophenylacetic Acid (XVIa)——2-Nitro-3-chlorophenylpyruvic acid (XVa) (32.1 g) was dissolved in H_2O (620 ml) by adding enough amount of aqueous NaOH to adjust pH to 8—9. 30% H_2O_2 (32.1 g) was added dropwise with stirring to this solution, and stirring was continued for 1 hr. After addition of 30% H_2O_2 (4.68 g) to a solution again adjusted to pH 8—9, stirring was continued for another hour. Then the reaction mixture was acidified with HCl, and precipitated crystals were collected and washed with H_2O. Recrystallization from 95% EtOH yielded pale yellow crystals (XVIa) (22.9 g), mp 165—167°. *Anal.* Calcd. for $C_8H_6O_4NCl$: C, 44.57; H, 2.81; N, 6.50; Cl, 16.45. Found: C, 44.73; H, 2.87; N, 6.58; Cl, 16.57. IR (nujol) cm^{-1}: 1715 (COOH), 1528, 1362 (NO_2).

Diethyl 2-(2-Nitro-4-chlorobenzoyl)acetylmalonate (XIc)——To a mixture of Mg (0.99 g) and abs. EtOH (1 ml) were added several drops of CCl_4, and the mixture was allowed to stand for 10—20 min, until vigorous reaction subsided. To this stirred mixture was added dropwise a solution of diethyl malonate (7.8 g) and abs. EtOH (4.5 ml) in abs. ether (25 ml) at such a rate that gentle refluxing was maintained. After addition was completed, stirring and refluxing were continued in an warm water bath until Mg was dissolved. 2-Nitro-4-chlorophenylacetic acid (XVIc) (8.7 g) was refluxed in $SOCl_2$ (22.2 ml) and excess $SOCl_2$ was removed completely *in vacuo* below 40° to leave crude acid chloride.

A solution of this acid chloride in abs. ether (20 ml) was added dropwise under cooling to the stirred solution of diethyl ethoxymagnesium-malonate, and stirring was continued under reflux in a warm water bath for 4 hr. 10% H_2SO_4 was added to the cooled reaction mixture, and the ether layer was separated and the aqueous layer was extracted with ether. Combined ether extracts were washed with H_2O, dried and evaporated to give a yellow oil (XIc) quantitatively. This was used in the next reaction without further purification.

Diethyl (2-Nitro-3-chlorophenylacetyl)malonate (XIa)——A solution of diethyl ethoxymagnesium-malonate was prepared from diethyl malonate (10.1 g) and Mg (2.32 g) in the similar manner as in the preparation of XIc. This solution was treated with crude acid chloride [prepared from 2-nitro-3-chlorophenylacetic acid (XVIa) (20.2 g) and $SOCl_2$], and worked up in the similar manner to give crude XIa almost quantitatively. This was used in the next reaction without further purification.

2-Nitro-4-chlorophenylacetone (XIIb)——A mixture of crude XIc (12 g) and AcOH (38 ml) in 20% H_2SO_4 (127 ml) was refluxed for 20 hr. After cooling, the reaction mixture was diluted with H_2O and extracted with benzene. Benzene extracts were washed with dil. aqueous NaOH and H_2O, dried and evaporated to give a pale brown solid (5.3 g). Recrystallization from CCl_4 yielded pale yellow crystals (XIIc) (5.3 g), mp 76—77°. Another recrystallization raised the melting point to 78—79°. *Anal.* Calcd. for $C_9H_8O_3NCl$: C, 50.60; H, 3.77; N, 6.56; Cl, 16.60. Found: C, 50.44; H, 3.82; N, 6.76; Cl, 16.79. IR (nujol) cm^{-1}: 1710 (CO), 1517, 1350 (NO_2).

2-Nitro-3-chlorophenylacetone (XIIa)——A mixture of XIa (28 g) and AcOH (65 ml) in 20% H_2SO_4 (290 ml) was refluxed for 16 hr. The resulting mixture was worked up in the similar manner as in the preparation of (XIIc) to give a colorless solid (XIIa) (17 g). Recrystallization from EtOH gave colorless crystals (14 g), mp 70—74°. Another recrystallization raised its melting point to 74.5—76°. *Anal.* Calcd. for $C_9H_8O_3NCl$: C, 50.60; H, 3.77; N, 6.56; Cl, 16.60. Found: C, 50.44;H, 3.77; N, 6.76; Cl, 16.66. IR (nujol) cm^{-1}: 1710 (CO), 1515, 1348 (NO_2).

4-(2-Nitro-4-chlorophenyl)-5-oxo-1-hexyne (XIIIc)——Na (0.34 g) was dissolved in abs. EtOH and the resulting solution was evaporated to dryness and abs. tetrahydrofuran (40 ml) was added to the powdered residue. This mixture was cooled to −10——15° in an ice-salt bath, and to this was added with stirring 2-nitro-4-chlorophenylacetone (XIIc) (3 g) followed by dropwise addition of propargyl bromide (1.7 g) dissolved in abs. tetrahydrofuran (3 ml) at this temp. Stirring was continued for 30 min at −5——10° for 3 hr and then the reaction mixture was allowed to stand overnight at room temp. Most of tetrahydrofuran was removed *in vacuo*, H_2O was added and the mixture was extracted with ether. Ether extracts were washed with H_2O, dried and evaporated to give a pale orange solid (2.8 g). Recrystallization from CCl_4 yielded colorless crystals (XIIIc) (2.1 g), mp 106—108°. Further recrystallization raised the melting point to 107—108°. *Anal* Calcd. for $C_{12}H_{10}O_3NCl$: C, 57.26; H, 4.01; N, 5.57; Cl, 14.01. Found: C, 56.87; H, 3.99; N, 5.62; Cl, 14.50. IR (nujol)cm^{-1}.: 3280 (H C≡C–), 1705 (CO), 1520, 1352 (NO_2).

4-(2-Nitro-3-chlorophenyl)-5-oxo-1-hexyne (XIIIa)——To a stirred suspension of powdered NaOEt (prepared from 1 g of Na and abs. EtOH) in 100 ml of abs. tetrahydrofuran, was added 2-nitro-3-chlorophenylacetone (XIIa) (8.8 g) at −10——15° followed by dropwise addition of a solution of propargyl bromide (5 g) in abs. tetrahydrofuran (15 ml). The reaction mixture was worked up in the similar manner as in the preparation of XIIIc to give a pale pink solid (XIIIa) (9.5 g). Recrystallization from CCl_4 yielded colorless crystals (7.1 g), mp 91—93°. Further recrystallization provided colorless crystals, mp 95—96°. *Anal.* Calcd. for $C_{12}H_{10}O_3NCl$: C, 57.26; H, 4.01; N, 5.57; Cl, 14.01. Found: C, 57.44; H, 4.31; N, 5.42,; Cl, 14.23. IR ($CHCl_3$) cm^{-1}: 3310 (HC≡C–), 1722 (CO), 1534, 1365 (NO_2).

3-(2-Nitro-4-chlorophenyl)-2,5-hexanedione (XIVc)——A solution of $HgSO_4$ (0.3 g) and H_2SO_4 (0.3 g) in 70% MeOH (40 ml) was stirred and warmed to 70°, and to this was added 4-(2-nitro-4-chlorophenyl)-5-

oxo-1-hexyne (XIIIc) (2.2 g). After stirring was continued at 70° for 3 hr, most of MeOH was removed *in vacuo*. H_2O was added to the residue and the mixture was extracted with ether. The ether extracts were washed with H_2O, dried and evaporated to give a colorless syrup (XIVc) (2.2 g). IR (nujol) cm^{-1}: 1712 (CO), 1528, 1352 (NO_2). This was used in the next reaction without further purification.

3-(2-Nitro-3-chlorophenyl)-2,5-hexanedione (XIVa)——4-(2-Nitro-3-hlorophenyl)-5-oxo-1-hexyne (XIIIa) (2.3 g) was added with stirring to a warm solution of $HgSO_4$ (0.8 g) and H_2SO_4 (0.8 g) in 70% MeOH (80 ml) at 70°. After stirring was continued at this temperature for 3 hr, the reaction mixture was worked up as in the preparation of (XIVc) to give a pale brown syrup (2.4 g). Recrystallization from light petroleum ether yielded colorless crystals (XIVa) (2 g), mp 62—66°. Further recrystallization raised the melting point to 64—66°. *Anal.* Calcd. for $C_{12}H_{12}O_4NCl$: C, 53.44; H, 4.49; N, 5.19; Cl, 13.15. Found: C, 53.24; H, 4.50; N, 5.23; Cl, 13.15. IR (nujol) cm^{-1}: 1724, 1716 (CO), 1547, 1373 (NO_2).

2,5-Bis-(dimethylaminomethyl)-3-(2-nitro-3-chlorophenyl)pyrrole (XVIII)——A mixture of 3-(2-nitro-3-chlorophenyl)pyrrole (XVII) (0.5 g), 36% formalin (0.85 ml), $Me_2NH\cdot HCl$ (0.75 g) and AcONa (0.75 g) in glacial AcOH (12 ml) was stirred at 60° for 48 hr. After most of AcOH was removed *in vacuo*, a large excess of dil. HCl was added and the mixture was washed with ether. The acidic solution was made strongly alkaline with powdered K_2CO_3 and extracted with AcOEt. The AcOEt extracts were washed with H_2O, dried and evaporated to give a brown syrup (crude XVIII) (0.75 g), which was used for the nest reaction without further purification.

2,5-Dimethyl-3-(3-nitro-4-chlorophenyl)pyrrole (IXb)——A mixture of *tert*-butyl 2,5-dimethyl-3-(3-nitro-4-chlorophenyl)-4-pyrrolecarboxylate (VIIb: R=*tert*-Bu) (1 g) and *p*-toluenesulfonic acid (0.1 g) in abs. benzene (30 ml) was refluxed for 5 1/3 hr. After cooling, the reaction mixture was diluted with AcOEt, the solution was washed with dil. aqueous NaOH and H_2O, dried and evaporated to give a semisolid (0.8 g). Twice recrystallizations from ligroin yielded yellow crystals (IXb) (0.55 g), mp 86—87.5°. *Anal.* Calcd. for $C_{12}H_{11}O_2N_2Cl$: C, 57.49; H, 4.42; N, 11.18. Found: C, 57.58; H, 4.45; N, 11.36.

2,5-Dimethyl-3-(2-nitro-4-chlorophenyl)pyrrole (IXc)——A mixture of 3-(2-nitro-4-chlorophenyl)-2,5-hexanedione (XIVc) (2.2 g) and $AcONH_4$ (4.4 g) in glacial AcOH (25 ml) was stirred and refluxed for 1 hr. After cooling, the resulting brown solution was diluted with H_2O and extracted with ether. The extracts were washed with H_2O, dried and evaporated to give a yellow solid (1.95 g). This was dissolved in benzene and passed through a filter containing silicagel. The filtrate and washings were combined and evaporated to give IXc (1.9 g). Recrystallization from CCl_4 gave yellow crystals (1.55 g), mp 112—114°. Further recrystallization raised the melting point to 115—116°. *Anal.* Calcd. for $C_{12}H_{13}O_2N_2Cl$: C, 57.50; H, 4.42; N, 11.17; Cl, 14.14. Found: C, 57.85; H, 4.40; N, 11.48; Cl, 14.48.

2,5-Dimethyl-3-(2-nitro-3-chlorophenyl)pyrrole (IXa)——i) From 2,5-Dimethyl-3-(2-nitro-3-chlorophenyl)-4-pyrrolecarboxylic Acid (VIIIa): A suspension of VIIIa (2.5 g) in glycerin (25 ml) was heated and stirred at 190—200° under N_2 for 1 hr. The hot reaction mixture was poured into a large amount of H_2O and was extracted with benzene. The benzene extracts were filtered to remove unreacted VIIIa. The filtrate was washed with dil. aqueous NaOH and H_2O,dried and passed through a filter filled with silicagel. The filtrate was evaporated to give a yellow solid, which was recrystallized from benzene-ligroin to yield (IXa) (0.5 g), mp 136—137°. *Anal.* Calcd. for $C_{12}H_{11}O_2N_2Cl$: C, 57.79; H, 4.92; N, 11.14; Cl, 14.26. Found: C, 57.70; H, 4.42; N, 11.17; Cl, 14.14. IR (nujol) cm^{-1}: 3430 (NH), 1528, 1376 (NO_2).

ii) From 3-(2-Nitro-3-chlorophenyl)-2,5-hexane Dione (XIVa): A solution of XIVa (1.9 g) and $AcONH_4$ (6.3 g) in glacial AcOH (35 ml) was refluxed with stirring for 1 hr. The reaction mixture was worked up in the similar manner as in the preparation of IX to give a yellow solid (1.6 g). Recrystallization from CCl_4 yielded yellow crystals (IXa) (1.4 g), mp 137—138°. No mixed melting point depression was observed with a sample prepared in i).

iii) From Bis-Mannich Base (XVIII): A mixture of the crude Mannich base (XVIII) (0.75 g) and CH_3I (3 ml) in abs. EtOH (3 ml) was allowed to stand overnight, and evaporated to yield a brown semisolid (crude XIX). A part of this was triturated with ether, the solvent was removed by decantation and the remaining solid was recrystallized from abs. EtOH to give pale yellow crystals (XIX), mp 300°. *Anal.* Calcd. for $C_{18}H_{27}O_2N_4ClI_2$: C, 34.82; H, 4.39; N, 9.03. Found: C, 34.03; H, 4.73; N, 8.73.

A solution of the crude methiodide (XIX) (1 g) in abs. EtOH (15 ml) was stirred at 55—60°. After addition of $NaBH_4$ (0.3 g), stirring was continued at this temperature for 30 min. After cooling, most of EtOH was removed *in vacuo*, H_2O was added and the mixture was extracted with ether. The ether extracts were washed with dil. HCl and H_2O, dried and evaporated to give a yellow solid (0.3 g). Recrystallization from benzene-*n*-hexane gave yellow crystals (IXa) (0.2 g), mp 137—138°, which showed no mixed melting point depression with a sample prepared in i).