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Total Synthesis of Pyrrolnitrin. I. Synthesis of 3-Arylpyrrole Derivatives by Knorr's Condensation[1]

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Alkyl 3-aryl-5-methyl-4-pyrrolecarboxylate (IIIa—j) and alkyl 2,5-dimethyl-3-aryl-4-pyrrolecarboxylate (IIIk—m), two kinds of key intermediates for synthesizing pyrrolnitrin (I), were obtained from 2-aminoacetophenones (IV) and alkyl acetoacetate by Knorr's pyrrole synthesis.

The mechanism of the pyrrole ringclosure of the above compounds was proposed since alkyl 3-substituted benzoylmethylaminocrotonates (VIII) could be isolated as intermediates presumably because of their difficult cyclization to the corresponding pyrroles; for which the infrared spectra of nitro and carbonyl group of VIII were discussed.

Pyrrolnitrin, a new antibiotic having a strong antifungal activity produced by a *Pseudomonas* culture, was reported by Arima and co-workers[3] in 1964. From the chemical degradation of this compound, Imanaka, *et al.* established the structure as 3-(2-nitro-3-chlorophenyl)-4-chloropyrrole (I).[4]

Total synthesis of this compound was communicated briefly by the present authors in 1966.[5]

This paper dealts with the detailed description of this synthesis by several methods including the above communications.

In order to synthesize pyrrolnitrin and its analogues, it is necessary that *α* and *α'* positions of the pyrrole nucleus should be protected with suitable groups before introducing a chlorine atom to the *β* position, because these positions are more reactive than the *β* positions.

For this purpose, ethyl 3-aryl-5-methyl-2-pyrrolecarboxylate (II, $R_1=COOC_2H_5$) and 2,5-dimethyl-3-arylpyrrole (II, $R_1=CH_3$) were chosen as a suitable key intermediates. Therefore, we try to synthesize alkyl 3-aryl-5-methyl-(or -2,5-dimethyl)-4-pyrrolecarboxylate (III, 5-methyl: $R_1=H$, 2,5-dimethyl: $R_1=CH_3$), which could be converted to the above key intermediates (II), by Knorr's pyrrole condensation.

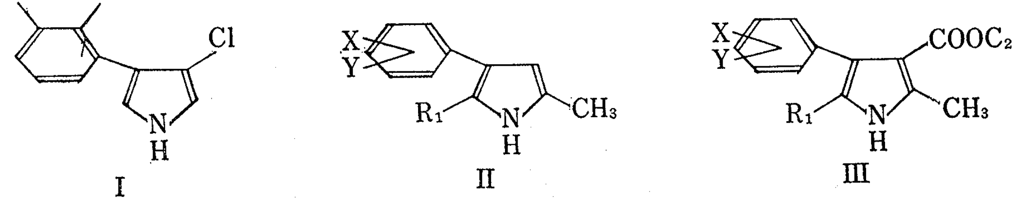

Chart 1

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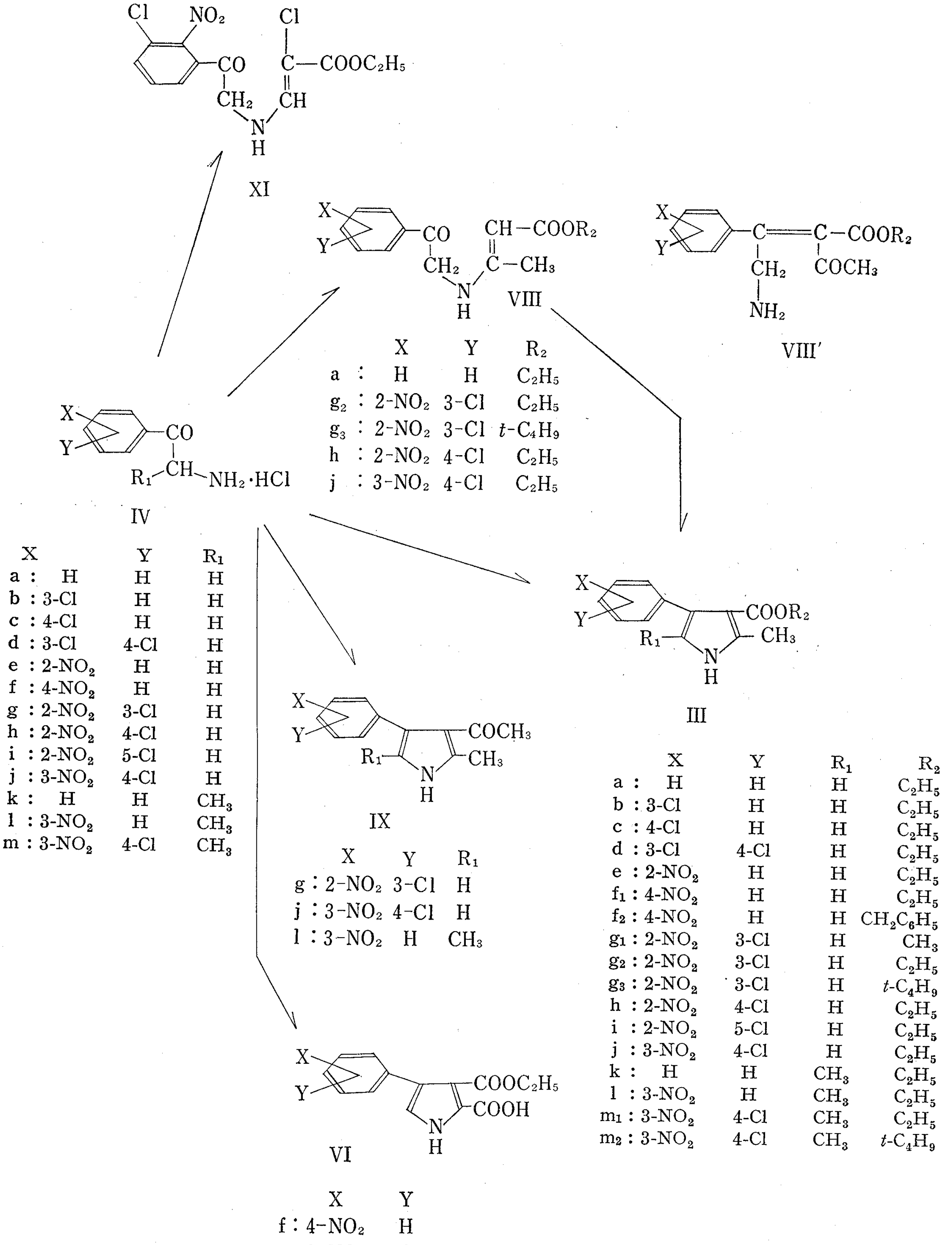
[1] A part of this work was presented at the 9th Symposium of Chemistry of Natural Products at Osaka, Oct. 1965, and at the 87th Annual Meeting of the Pharmaceutical Society of Japan at Kyoto, April 1967.

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

[3] K. Arima, H. Imanaka, M. Kousaka, A. Fukuta and G. Tamura, *Agr. Biol. Chem.*, **28**, 575 (1964).

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

[5] H. Nakano, S. Umio, K. Kariyone, K. Tanaka, T. Kishimoto, H. Noguchi, I. Ueda, H. Nakamura and Y. Morimoto, *Yakugaku Zasshi*, **86**, 159 (1966); *Tetrahedron Letters*, **1966** 737.



VIII

	X	Y	R_2
a	H	H	C_2H_5
g_2	$2\text{-}NO_2$	3-Cl	C_2H_5
g_3	$2\text{-}NO_2$	3-Cl	$t\text{-}C_4H_9$
h	$2\text{-}NO_2$	4-Cl	C_2H_5
j	$3\text{-}NO_2$	4-Cl	C_2H_5

IV

	X	Y	R_1
a	H	H	H
b	3-Cl	H	H
c	4-Cl	H	H
d	3-Cl	4-Cl	H
e	$2\text{-}NO_2$	H	H
f	$4\text{-}NO_2$	H	H
g	$2\text{-}NO_2$	3-Cl	H
h	$2\text{-}NO_2$	4-Cl	H
i	$2\text{-}NO_2$	5-Cl	H
j	$3\text{-}NO_2$	4-Cl	H
k	H	H	CH_3
l	$3\text{-}NO_2$	H	CH_3
m	$3\text{-}NO_2$	4-Cl	CH_3

IX

	X	Y	R_1
g	$2\text{-}NO_2$	3-Cl	H
j	$3\text{-}NO_2$	4-Cl	H
l	$3\text{-}NO_2$	H	CH_3

VI

	X	Y
f	$4\text{-}NO_2$	H
j	$3\text{-}NO_2$	4-Cl

III

	X	Y	R_1	R_2
a	H	H	H	C_2H_5
b	3-Cl	H	H	C_2H_5
c	4-Cl	H	H	C_2H_5
d	3-Cl	4-Cl	H	C_2H_5
e	$2\text{-}NO_2$	H	H	C_2H_5
f_1	$4\text{-}NO_2$	H	H	C_2H_5
f_2	$4\text{-}NO_2$	H	H	$CH_2C_6H_5$
g_1	$2\text{-}NO_2$	3-Cl	H	CH_3
g_2	$2\text{-}NO_2$	3-Cl	H	C_2H_5
g_3	$2\text{-}NO_2$	3-Cl	H	$t\text{-}C_4H_9$
h	$2\text{-}NO_2$	4-Cl	H	C_2H_5
i	$2\text{-}NO_2$	5-Cl	H	C_2H_5
j	$3\text{-}NO_2$	4-Cl	H	C_2H_5
k	H	H	CH_3	C_2H_5
l	$3\text{-}NO_2$	H	CH_3	C_2H_5
m_1	$3\text{-}NO_2$	4-Cl	CH_3	C_2H_5
m_2	$3\text{-}NO_2$	4-Cl	CH_3	$t\text{-}C_4H_9$

Chart 2

Condensation of diethyl oxaloacetate (V) with nitro-aminoketones (IVf, g) gave 3-aryl-4-ethoxycarbonyl-5-pyrrolecarboxylic acid (VIf, j), whose structures were confirmed by infrared spectra (VIf: 3280 cm^{-1} pyrrole NH, 1680 cm^{-1} ester carbonyl, 1625 cm^{-1} carboxylic acid carbonyl; VIj: 3250 cm^{-1} NH, 1670 cm^{-1} ester, 1630 cm^{-1} carboxylic acid) and by a positive Ehrlich's color reaction. But since nitro group was introduced on the phenyl ring of aminoacetophenone, the ring-closure reaction did proceed in the lower yield than that of the procedure by Yamamoto, *et al.*[6] in which no nitro group was involved.

Halley, *et al.*[7] reported that ethyl 3-phenyl-5-methyl-4-pyrrolecarboxylate (IIIa) was easily obtained in a buffer solution at pH 6.5—6.9 from 2-aminoacetophenone and ethyl acetoacetate (VII).

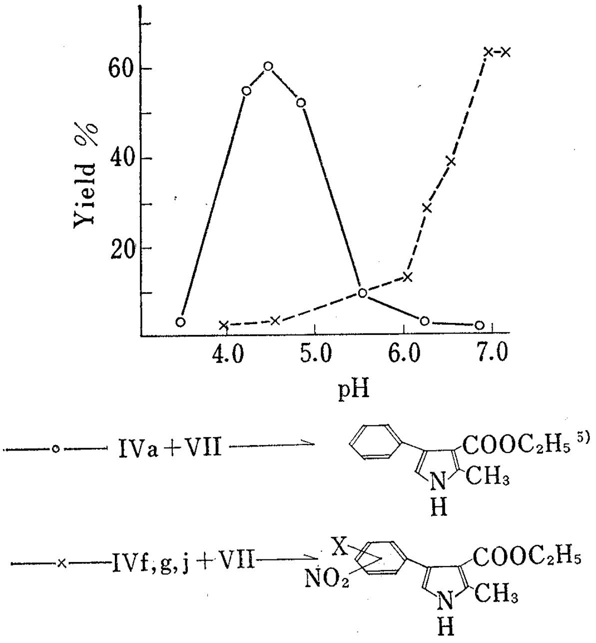


Chart 3

3′-Chloro-, 4′-chloro- and 3′,4′-dichloro-2-aminoacetophenones (IVb—d) could be converted to ethyl 3-aryl-5-methyl-4-pyrrolecarboxylates (IIIb—d) under the above conditions.

When nitro-2-aminoacetophenones were employed under Halley's condition, the ring-closure was not realized, but was carried out successfully with a buffer solution at pH 4.5—4.2 as shown in chart 3. However, under milder condition in the same buffer solution, an unexpected product, alkyl 3-(substituted benzoylmethylamino)-crotonate (VIIIa,g_2,g_3,h,j), could be isolated.

The structure of VIII was confirmed by the following data: the infrared spectrum of VIIIg_2 showed the NH band at 3300 cm^{-1} and the keto carbonyl at 1690 cm^{-1}, and the ester carbonyl band was strongly shifted to 1655 cm^{-1} by the α-double bonding. 2′-Nitro-3′-chloro-2-aminoacetophenone (IVg) was easily recovered from VIIIg_2 by treatment with dilute hydrochloric acid, and VIIIg_2 was converted to the desired pyrrole (IIIg_2)under the drastic conditions described below. In order to exclude the posibility of the another structure (VIII′) for VIII, a model compound, ethyl 2-chloro-3-(2-nitro-3-chlorobenzoylmethylamino)acrylate (XI) was prepared from ethyl 2-chloroformylacetate and IVg. From the similar character of XI to VIII (3350 cm^{-1} NH, 1710 cm^{-1} keto carbonyl, 1630 cm^{-1} ester, and IVg was easily recovered from XI), the structure of VIII was suggested to be alkyl 3-(substituted benzoylmethylamino)crotonate.

Facile convertibility of VIIIa,g_2,g_3,h to pyrrole (IIIa,g_2,g_3,h) indicates VIII was an intermediate of Knorr's pyrrole ringclosure, and therefore we proposed the following mechanism.

Concerning to substitutions on the phenyl ring of 2-aminoacetophenone, some relationship was observed between the difficulty of pyrrole cyclization and the wave number of streching vibration of the keto carbonyl and nitro groups.

The experimental results showed that the ringclosure became progressively difficult in the following order. 4′-NO_2 (IVf)$<$3′-NO_2-4′-Cl (IVj)$<$2′-NO_2-3′-Cl (IVg)$<$2′-NO_2 (IVe)$<$ 2′-NO_2-4′-Cl (IVh)$<$2′-NO_2-5′-Cl (IVi)

While 4′-nitro-2-aminoacetophenone (IVf) afforded ethyl 3-(4-nitrophenyl)-5-methyl-4-pyrrolecarboxylate (IIIf_1) in a 0.1 mole buffer solution (pH 4.5—4.2) at room temperature

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6) K. Yamamoto and K. Kariyone, *Yakugaku Zasshi*, **75**, 1222 (1955).

7) C.A.C. Halley and P. Maitland, *J. Chem. Soc.*, **1951**, 3155.

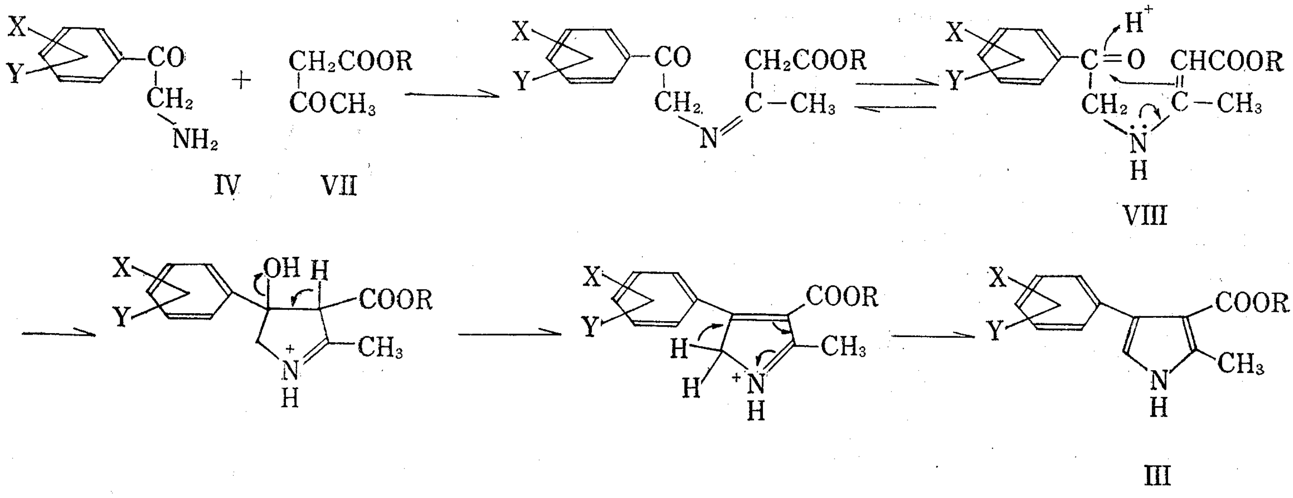
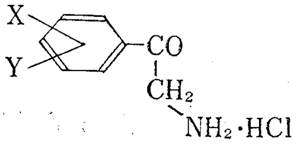


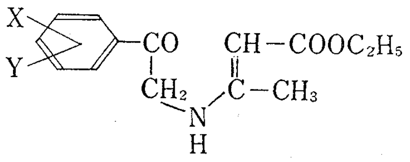
Chart 4

for a few hours, and 3′-nitro-4′-chloro-2-aminoacetophenone (IVj) afforded IIIj after few days under the same condition. But 2′-nitro-3′-chloro (IVg) and 2′-nitro-4′-chloro-2-aminoacetophenones (IVh) were only converted to the intermediate (VIII).

Conversion of IVg and IVe to pyrrolecarboxylic esters (IIIg,e) was successfully carried out at 60° in a mixture of glacial acetic acid and sodium acetate (at pH 4.5), which was more drastic condition than the above described.

Pyrrole cyclization of 2′-nitro-4′-chloro- and 2′-nitro-5′-chloro-2-aminoacetophenones (IVh, i) became progressively difficult. The yield of corresponding ester (IIIi) from the latest aminoketone (IVi) was the lowest.





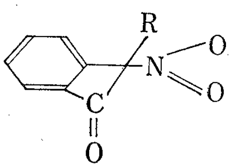
	X	Y	ν_{CO}	$\nu_{s\,NO_2}$	ν_{CO}	$\nu_{s\,NO_2}$
f	: 4-NO_2	H	1685	1345		
j	: 3-NO_2	4-Cl	1705	1350	1700	1355
g	: 2-NO_2	3-Cl	1705	1375	1700	1375
e	: 2-NO_2	H	1725	1350		
h	: 2-NO_2	4-Cl	1730	1345	1725	1350
i	: 2-NO_2	5-Cl	1735	1345		

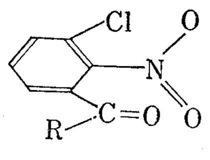
Chart 5

The infrared spectral data suggested that the order of carbonyl stretching vibration in wave number was parallel with the order of difficulty of ringclosure as shown in chart 5.

It is of interest that the carbonyl group of IVg is supposed to receive the strongest steric hindrance with such bulky groups as nitro and chloro at the 2′ and the 3′ position among 2′-nitro-2-aminoacetophenones (IVe, g, h, i). However IVg was more easily converted to the pyrrole than other 2′-nitro derivatives (IVe, h,i).

Accordingly to the infrared spectral data, the nitro group of IVg (symmetric stretching: 1375 cm^{-1}) was suggested to be more strongly twisted from the benzene ring plane than othert





IVg

Chart 6

2′-nitro-2-aminoacetophenones (N–O symmetric stretching: 1345—1350 cm^{-1}), because the symmetric stretching vibration of the nitro group shifted to a lower frequency, indicating benzene and N–O bonding to be more coplanar.[8,9] Therefore, as the carbonyl group of IVg was effected a weaker steric hindrance than carbonyl group of other 2′-nitro derivatives (IVe,h,i), the cyclization of IVg took place more easily than other aminoketones.

Knorr's condensation with 2-aminopropiophenones (IVk,l,m)[10] and alkyl acetoacetate (VII) gave alkyl 2,5-dimethyl-3-aryl-4-pyrrolecarboxylates (IIIk,l,m$_1$,m$_2$), all suitable key intermediates to synthesize 3-aryl-4-chloropyrroles.

3-Aryl-4-acetyl-5-methylpyrroles (IXg,j) and 2,5-dimethyl-3-(3-nitrophenyl)-4-acetylpyrrole (IX 1) were derived from 2-aminoacylophenones (IVg,j,l) and acetylacetone (X) by the Knorr's pyrrole ringclosure similar to the above.

Experimental[11]

Alkyl 3-Aryl-5-methyl-4-pyrrolecarboxylate (IIIa—j) and Alkyl 2,5-Dimethyl-3-aryl-4-pyrrolecarboxylate (IIIk—m)

i) From IV and VII

General Method: A) A mixture of 2-aminoacylophenone hydrochloride (IVb—d) (a g), alkyl acetoacetate (VII) (a g) and 0.1 mole of buffer solution (pH 6.5, adjusted with K_2HPO_4–KOH, 100×a ml) was stirred at room temperature for 3 days. The separated crystals were collected by filtration, dried and recrystallized from EtOH. The results are shown in Table I–A.

B) To a solution of 2-aminoacylophenone hydrochloride (IVe—j, l, m) (a g)[12] in 0.1 mole of buffer solution (100×a ml, adjusted with AcOH–AcONa at pH 4.5), alkyl acetoacetate (VII) (a g) was added in one portion. The mixture was stirred at room temperature for 3 days. A brown solid was isolated, and crystallized from EtOH or benzene. The results are shown in Table I–A.

C) A mixture of 2-aminoacetophenone hydrochloride (IVe—j) (a g), alkyl acetoacetate (VII) (a g), AcONa·3H_2O (12.5×a g) and glacial AcOH (20×a g) was stirred at 50° for 3 hr and at 75° for additional 3 hr.

After cooling, the reaction mixture was poured into ice–water (400×a ml), and separated precipitate was collected by filtration, and crystallized from EtOH, AcOH or benzene. The results are shown in Table I–A.

ii) from VIII

General Method: C) Alkyl 3-(substituted benzoylmethylamino)crotonate (VIIIa, g$_2$,g$_3$,h,j) (a g) was employed instead of the corresponding 2-aminoacetophenones and alkyl acetoacetate described in (i) (C). The results are shown in Talbe I–B.

D) A mixture of ethyl 3-(2-nitro-3-chlorobenzoylmethylamino) crotonate (VIII g$_2$) (a g) and ethyl polyphosphate (20×a g) was stirred at 80° for 1.5 hr. The reaction mixture was poured into cold water (*ca.* 400×a ml) and extracted with AcOEt. The organic layer was washed with 10% HCl and 5% $KHCO_3$, dried over $MgSO_4$. The solvent was removed under reduced pressure and the brown residue was crystallized from benzene. The results is described in Table I–B.

Talbe II summarizes the infrared absorption bands of those pyrrole esters prepared above.

Alkyl 3-(Substitutedbenzoylmethylamino)crotonate (VIIIa,g$_2$,g$_3$,h,j) and Ethyl 2-Chloro-3-(2-nitro-3-chlorobenzoylmethylamino)acrylate (XI)

General Method: A) A solution of 2-aminoacetophenone hydrochloride (IVa) (a g) in 0.1 mole buffer solution (at pH 6.5, adjusted with K_2HPO_4–KOH) (100×a ml) was added ethyl acetoacetate (a g) under stirring at room temperature for 1—3 hr until the reaction mixture became cloudy. The precipitate was separated, dried and crystallized from AcOEt. The result was shown in Table III.

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[8] N. Ida, *Kagaku no Ryoiki Zokan* (*Journal of Japanese Chemistry, supplement*), **45**, 43 (1961).

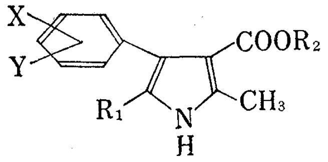
[9] This observation was supported with crystal structure analysis of pyrrolnitrin by Morimoto, *et al.* (Y. Morimoto, M. Hashimoto and K. Hattori, *Tetrahedron Letters*, **1968**, 201).

[10] 2-Aminopropiophenone (IVk) derived from alanine and benzoic anhydride by Dakin–West reaction and subsequent hydrolysis. 3′-Nitro-2-aminopropiophenone (IVl) was obtained from 3′-nitro-2-bromopropiophenone by Gabriel's method. 3′-Nitro-4′-chloro-2-aminopropiophenone (IVm) was prepared from 3′-nitro-4′-chloropropiophenone oxime by tosylation, followed by Neber rearrangement.

[11] All melting points are uncorrected. The infrared spectra were recorded on a Hitachi EPI S$_2$. The nuclear magnetic resonance spectra were measured with a Varian A-60 spectrometer using tetramethylsilane as an internal standard.

[12] Preparation of unkown 2-aminoacylophenone will be reported in Part VI [*Chem. Pharm. Bull.* (Tokyo), **17**, 596 (1969)].

Table I-A.



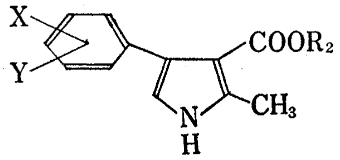
Product NO.	X	Y	R_1	R_2	Method	a (g)	III (g)	mp (°C)
IIIb	3-Cl	H	H	C_2H_5	A	5.0	4.5	129
c	4-Cl	H	H	C_2H_5	A	24.5	22.5	169
d	3-Cl	4-Cl	H	C_2H_5	A	0.4	0.06	155
e	2-NO_2	H	H	C_2H_5	C	0.3	0.2	159
f_1	4-NO_2	H	H	C_2H_5	B	1.5	1.3	165
f_2	4-NO_2	H	H	$CH_2C_6H_5$	C	1.8	1.1	165
g_1	2-NO_2	3-Cl	H	CH_3	C	20.0	8.0	186
g_2	2-NO_2	3-Cl	H	C_2H_5	B	1.0	0.1	188
g_2	2-NO_2	3-Cl	H	C_2H_5	C	20.0	10.0	188
g_3	2-NO_2	3-Cl	H	t-C_4H_9	C	20.0	6.0	167
h	2-NO_2	4-Cl	H	C_2H_5	B	1.5	0.1	184
h	2-NO_2	4-Cl	H	C_2H_5	C	1.5	0.02	184
i	2-NO_2	5-Cl	H	C_2H_5	B	1.5	0.03	175
i	2-NO_2	5-Cl	H	C_2H_5	C	1.5	0.01	175
j	3-NO_2	4-Cl	H	C_2H_5	B	1.5	0.9	155
j	3-NO_2	4-Cl	H	C_2H_5	C	20.0	12.0	155
k	H	H	CH_3	C_2H_5	A	5.5	5.0	bp 170(0.35mmHg)
l	3-NO_2	H	CH_3	C_2H_5	B	2.0	0.8	147
m_1	3-NO_2	4-Cl	CH_3	C_2H_5	B	0.5	0.11	152
m_2	3-NO_2	4-Cl	CH_3	t-C_4H_9	B	4.2	4.9	209

Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found. C	Found. H	Found. N
$C_{14}H_{14}O_2NCl$	63.76	5.35	5.31	63.94	5.46	5.24
$C_{14}H_{14}O_2NCl$	63.76	5.35	5.31	63.64	5.61	5.29
$C_{14}H_{13}O_2NCl_2$	56.39	4.40		56.06	4.39	
$C_{14}H_{14}O_4N_2$	61.31	5.15	10.21	61.07	5.34	10.40
$C_{14}H_{14}O_4N_2$	61.31	5.15	10.21	61.42	5.33	10.09
$C_{19}H_{16}O_4N_2$	67.85	4.80	8.33	67.70	4.84	8.14
$C_{13}H_{11}O_4N_2Cl$	52.98	3.76	9.51	52.90	3.97	9.22
$C_{14}H_{13}O_4N_2Cl$	54.46	4.24	9.08	54.33	4.29	
				54.25	4.11	9.04
$C_{16}H_{17}O_4N_2Cl$	57.06	5.09	8.32	57.19	5.36	8.39
$C_{14}H_{13}O_4N_2Cl$	54.46	4.24	9.08	54.44	4.16	9.01
	identified by comparison of IR					
$C_{14}H_{13}O_4N_2Cl$	54.46	4.24	9.08	54.64	4.18	9.23
	identified by comparison of IR					
$C_{14}H_{13}O_4N_2Cl$	54.46	4.24	9.08	54.58	4.10	9.11
				54.60	4.16	8.99
$C_{15}H_{17}O_2N$	74.05	7.04	5.76	73.99	7.32	5.41
$C_{15}H_{16}O_4N_2$	62.49	5.59	9.72	62.28	5.71	9.57
$C_{15}H_{15}O_4N_2Cl$	55.82	4.68	8.68	55.70	4.75	8.61
$C_{17}H_{19}O_4N_2Cl$	58.20	5.40	7.99	58.31	5.41	7.77

B) Ethyl 2-chloroformylacetate (a g) or ethyl acetoacetate (VII) (a g) and 2-aminoacetophenone (IVg) (a g) were dissolved in buffer solution (0.1 mole, pH 4.5, adjusted with AcOH–AcONa) (100 × a ml) and the reaction mixture was treated in the same manner as above. The results are shown in Table III.

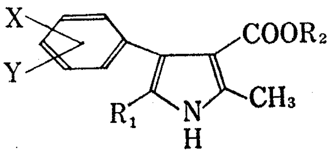
3-(2-Nitro-3-chlorophenyl)-4-acetyl-5-methylpyrrole (IXg)——Five grams of IVg, acetylacetone (5.0 g), AcONa·3H_2O (62.5 g) were dissolved in 100 ml of glacial AcOH with stirring at 50°. The reaction mixture

TABLE I-B.



Product No.	X	Y	R_2	Method	a (g)	III (g)	mp (°C)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found. C	Found. H	Found. N
IIIa	H	H	C_2H_5	A	0.3	0.2	105	lit. mp 106						
g_2	2-NO_2	3-Cl	C_2H_5	C	0.3	0.2	188	$C_{14}H_{13}O_4N_2Cl$	54.46	4.24	9.08	54.25	4.11	9.04
g_2	2-NO_2	3-Cl	C_2H_5	D	0.5	0.2	187					54.21	4.05	9.00
g_3	2-NO_2	3-Cl	t-C_4H_9	C	0.3	0.1	167	$C_{16}H_{17}O_4N_2Cl$	57.06	5.09	8.32	57.22	5.31	8.43
j	3-NO_2	4-Cl	C_2H_5	C	0.5	0.3	152	$C_{14}H_{13}O_4N_2Cl$	54.46	4.24	9.08	54.39	4.15	9.26

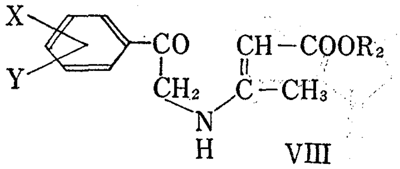
TABLE II.



	X	Y	R_1	R_2	IR(nujol) cm^{-1} ν_{NH}	ν_{CO}	ν_{NO_2} as	ν_{NO_2} s
a	H	H	H	C_2H_5	3350	1670		
b	3-Cl	H	H	C_2H_5	3330	1667		
c	4-Cl	H	H	C_2H_5	3340	1660		
d	3-Cl	4-Cl	H	C_2H_5	3330	1660		
e	2-NO_2	H	H	C_2H_5	3280	1665	1520	1340
f_1	4-NO_2	H	H	C_2H_5	3330	1670	1500	1335
f_2	4-NO_2	H	H	$CH_2C_6H_5$	3350	1670	1500	1335
g_1	2-NO_2	3-Cl	H	CH_3	3310	1685	1530	1370
g_2	2-NO_2	3-Cl	H	C_2H_5	3275	1670	1535	1370
g_3	2-NO_2	3-Cl	H	t-C_4H_9	3350	1670	1535	1370
h	2-NO_2	4-Cl	H	C_2H_5	3320	1660	1520	1350
i	2-NO_2	5-Cl	H	C_2H_5	3320	1670	1520	1345
j	3-NO_2	4-Cl	H	C_2H_5	3320	1670	1535	1347
k	H	H	CH_3	C_2H_5	3300	1660		
l	3-NO_2	H	CH_3	C_2H_5	3320	1670	1535	1350
m_1	3-NO_2	4-Cl	CH_3	C_2H_5	3350	1670	1540	1350
m_2	3-NO_2	4-Cl	CH_3	t-C_4H_9	3340	1665	1535	1360

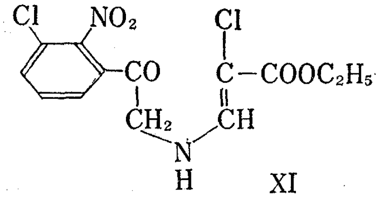
was kept at 50° for 3 hr and then at 70° for additional 3 hr. The mixture was poured into cold H_2O (500 ml), and resulting precipitate was collected by filtration and dried. Recrystallization from EtOH gave yellow needles (1.5 g), mp 190°. *Anal.* Calcd. for $C_{13}H_{11}O_3N_2Cl$: C, 56.02; H, 3.98; N, 10.05; Cl, 12.72. Found: C, 55.90; H, 3.87; N, 9.99; Cl, 12.48. IR (nujol) cm^{-1}: 3280 (NH), 1630 ($COCH_3$), 1535, 1370 $(NO)_2$.

TABLE III.



VIII

and



XI

Compound No.	X	Y	R_2	Method	IV, VII (g)	Buffer (ml)	VIII (g)	mp	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found. C	Found. H	Found. N
VIII a	H	H	C_2H_5	A	0.5	50	0.1	106	$C_{14}H_{17}O_3N$	67.99	6.93	5.66	67.87	6.85	5.46
g_2	2-NO_2	3-Cl	C_2H_5	B	0.5	50	0.2	156(d)	$C_{14}H_{15}O_5N_2Cl$	51.46	4.63	8.57	51.45	4.59	8.39
g_3	2-NO_2	3-Cl	t-C_4H_9	B	0.5	50	0.2	150(d)	$C_{16}H_{19}O_5N_2Cl$	54.17	5.40	7.90	54.30	5.68	7.62
XI	2-NO_2	3-Cl	C_2H_5	B	0.5	50	0.3	136(d)	$C_{13}H_{12}O_5N_2Cl_2$	44.98	3.48	8.07	45.40	3.79	7.46
VIII h	2-NO_2	4-Cl	C_2H_5	B	0.5	50	0.08	130(d)	$C_{14}H_{15}O_5N_2Cl$	51.46	4.63	8.57	51.59	4.80	8.74
j	3-NO_2	4-Cl	C_2H_5	B	0.5	50	0.2	139(d)	$C_{14}H_{15}O_5N_2Cl$	51.46	4.63	8.57	51.24	4.54	8.54

All compounds were recrystallized from AcOEt to give colorless leaves. (d): decomp.

3-(3-Nitro-4-chlorophenyl)-4-acetyl-5-methylpyrrole (IXj)——The reaction of IVj (0.5 g) with acetylacetone (0.5 g) was carried out in 10 ml of AcOH containing AcONa·$3H_2O$ (6.25 g) in the same manner as described above, giving 0.3 g of a product. It was recrystallized from AcOEt to give yellow granules: mp 197°. *Anal.* Calcd. for $C_{13}H_{11}O_3N_2Cl$: C, 56.02; H, 3.98; N, 10.05. Found: C, 55.71; H, 4.02; N, 9.08. IR (nujol) cm^{-1}: 3220 (NH), 1623 ($COCH_3$), 1525, 1355 (NO_2).

2,5-Dimethyl-3-(3-nitrophenyl)-4-acetylpyrrole (IXl)——To a solution of IVl (2.0 g) in 0.1 mole acetate buffer solution (at pH 4.5, 200 ml) was added 1.6 g of acetylacetone.

The slight yellow reaction mixture was stirred for about 3 days until a crude product was separated. The crystals were recrystallized from EtOH to give yellow needles (1.3 g) having mp 208°. *Anal.* Calcd. for $C_{14}H_{14}O_3N_2$: C, 65.10; H, 5.46; N, 10.85. Found: C, 65.34; H, 5.41; N, 10.67. IR (nujol) cm^{-1}: 3200 (NH), 1620 ($COCH_3$), 1530, 1345 (NO_2).