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Structure-Activity Studies of Pyrrolnitrin Analogues[1,2]

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A number of de-chloro and de-nitro derivatives of pyrrolnitrin and the isomers as to the positions of the substituents were prepared and their antimicrobial activities were evaluated. Among the homologues having a nitro group, pyrrolnitrin has shown the strongest activity, in which the nitro group is suffered from steric hindrance. 2-Methyl-4-(2-nitro-3-chlorophenyl)pyrrole (**10a**) was also as effective as pyrrolnitrin. On the other hand, the de-nitro derivatives, 3-chloro-4-(3-chlorophenyl)pyrrole (**8o**), 3-chloro-4-(3-bromophenyl)pyrrole (**8g**) and 3-chloro-4-(3-trifluoromethyl)pyrrole (**8t**), showed stronger antimicrobial activities and broader spectra.

Pyrrolnitrin, a new antibiotic having a strong antifungal activity, was isolated from bacterial cell of *Pseudomonas pyrrocinia* and its structure was established to be 3-chloro-4-(2-nitro-3-chlorophenyl)pyrrole by Arima, *et al.*[4] in 1964. The total synthesis of this compound was accomplished by the present authors in 1965.[5b]

However, there has been no report regarding to the antifungal activities of group of compounds having the basic structure of 3-phenylpyrrole. In the present studies, a number of the pyrrolnitrin analogues were synthesized and their activities towards various bacteria were examined. The relation between the structure and antifungal activity was discussed.

For the preparation of ethyl 2-methyl-4-aryl-5-pyrrolecarboxylate (**4**) and 3-chloro-4-arylpyrrole (**8**), a sequence of reactions including the enamine intermediate (**2**) from 1-aryl-1,3-butandione (**1**) and diethyl aminomalonate[5] were employed.

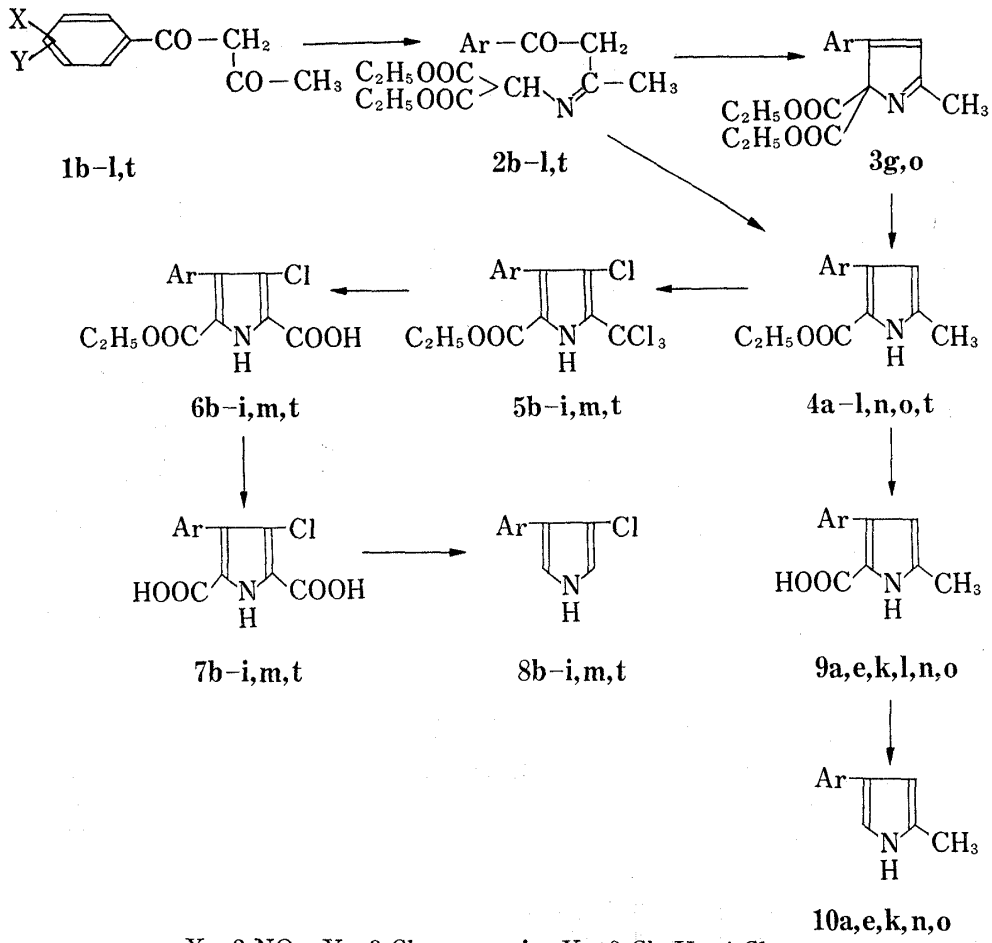
Cyclization of enamine (**2**) was unusual, which gave 2H-pyrrole (**3**) as in the case of the chloro analogue.[5b] Then ethyl 2-methyl-4-(3-bromophenyl)-5-pyrrolecarboxylate (**4**) was easily obtained by the treatment with sodium ethoxide.

When **4** was treated with sulfuryl chloride in acetic acid under cooling, 3-chloro-4-aryl-5-ethoxycarbonyl-2-pyrrolecarboxylicacid (**6**) was obtained instead of the expected polychlorinated compound (**5**). Under this con dition, **5** was formed initially which was then converted to **6** by the reaction with the acetic acid solvent.

Pyrrolnitrin analogues (**8b—i, m, t**) were derived from **6** by hydrolysis and the subsequent decarboxylation.

Various 2-alkyl-4-arylpyrroles were prepared, and their antimicrobial activities were compared with the activity of 2-methyl-4-(2-nitro-3-chlorophenyl)pyrrole (**10a**) and with that of pyrrolnitrin (**8a**). Chlorination of the diketone (**1**) by sulfuryl chloride gave 1-(2-nitro-3-

1) Total Synthesis of Pyrrolnitrin. XI. This work was presented at the 6th International Congress of Chemotherapy at Tokyo, Aug. 1969.
2) Part X: K. Tanaka, K. Kariyone and S. Umio, *Chem. Pharm. Bull.* (Tokyo), **17**, 622 (1969).
3) Location: *1, Kashimacho, Higashiyodogawa-ku, Osaka.*
4) K. Arima, H. Imanaka, M. Kousaka, A. Fukuta and G. Tamura, *Arg. Biol. Chem.*, **28**, 575 (1964).
5) *a*) S. Umio, K. Kariyone, K. Tanaka and T. Kishimoto, *Chem. Pharm. Bull.* (Tokyo), **17**, 576 (1969). *b*) H. Nakano, S. Umio, K. Kariyone, K. Tanaka, Y. Morimoto, T. Kishimoto, H. Noguchi, I. Ueda and H. Nakamura, The 9th Symposium of Chemistry of Natural Products at Osaka, Oct. 1965; S. Umio, K. Kariyone, K. Tanaka, I. Ueda and Y. Morimoto, *Chem. Pharm. Bull.* (Tokyo), **17**, 588 (1969).



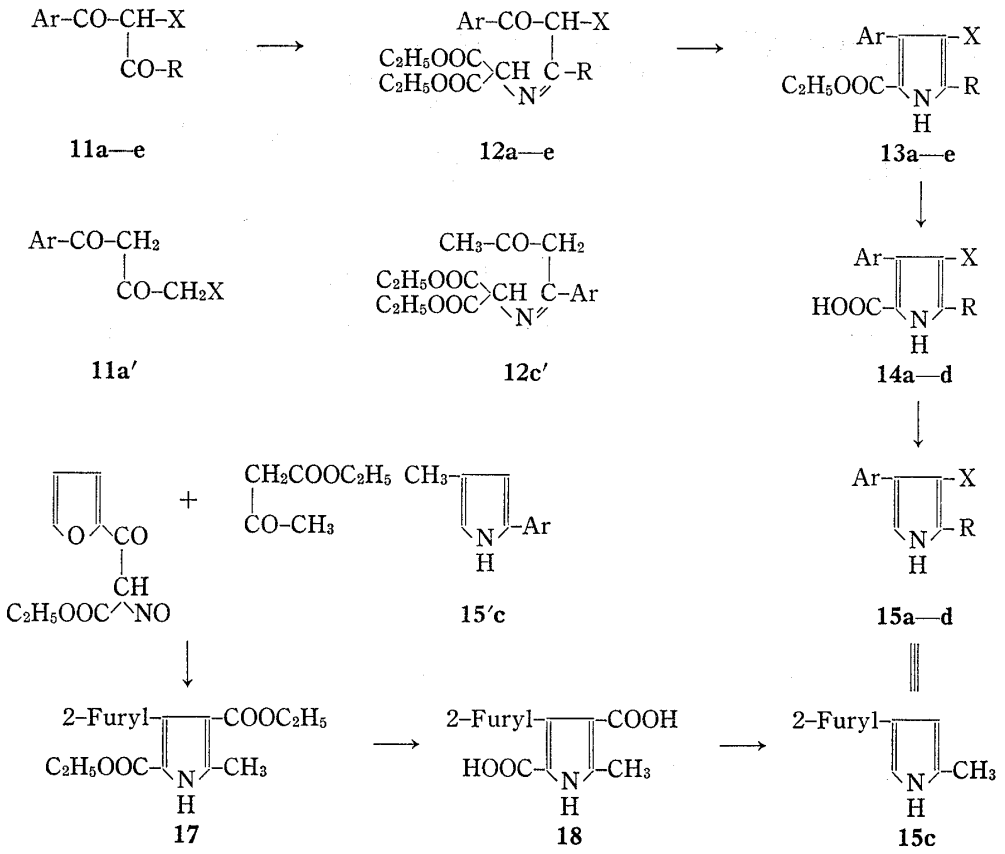
a : X=2-NO_2, Y=3-Cl
b : X=2-NO_2, Y=4-Cl
c : X=2-NO_2, Y=5-Cl
d : X=4-NO_2, Y=H
e : X=4-NO_2, Y=2-Cl
f : X=2-Cl, Y=H
g : X=3-Br Y=H
h : X=4-Cl, Y=H
i : X=3-Cl, Y=4-Cl
j : X=3-NO_2, Y=5-NO_2
k : X=4-CH_3O, Y=H
l : X=3-CH_3O, Y=4-CH_3O
m: X=2-Cl, Y=4-Cl
n : X=2-NO_2, Y=H
o : X=3-Cl, Y=H
t : X=3-CF_3, Y=H

Chart 1

chlorophenyl)-2-chloro-1,3-butandione (**11a**) in a good yield. The nuclear magnetic resonance (NMR) spectrum of the product showed a singlet at 2.4 ppm due to methyl group. This was consistent with the expected structure **11a** but not with the alternative structure of 1-aryl-4-chloro-1,3-butandione (**11′a**[3]).

Ethyl 2-alkyl-4-aryl-5-pyrrolecarboxylate (**13b—e**) and a 3-chloro derivative (**13a**) were derived from the corresponding 1-aryl-1,3-alkandiones (**11a—e**) and diethyl aminomalonate by the same technique descrived above. The ester group in **13a—d** was hydrolyzed and then removed by decarboxylation to produce 2-alkyl-4-arylpyrroles (**15b—d**) and a 3-chloro derivative (**15a**). 2-Methylpyrrolnitrin (**15a**), one of these alkylated analogues, was identified with the authentic sample derived from pyrrolnitrin.[6] In addition, the structure of **15c** was examined in order to exclude another possible structure, 2-(2-furyl)-4-methylpyrrole (**15′c**), which might be produced via another enamine intermediate (**12′c**). Diethyl 3-(2-furyl)-5-methyl-2,4-pyrroledicarboxylate (**17**) was prepared by the reductive cyclization of ethyl 3-(2-furyl)-3-oxo-2-nitrosobutyrate with ethyl acetoacetate over palladium-carbon, and it was converted to 2-methyl-4-(2-furyl)pyrrole (**15c**).

6) M. Hashimoto, K. Hattori and T, Takano, *Tetrahedron*, in press.



	Ar	X	R
a:	2-NO_2, 3-Cl-phenyl	Cl	CH_3
b:	2-NO_2, 3-Cl-phenyl	H	C_2H_5
e:	2-NO_2, 3-Cl-phenyl	H	n-C_3H_7
c:	2-furyl	H	CH_3
d:	2-thienyl	H	CH_3

Chart 2

By infrared (IR) and ultraviolet (UV) spectrum, the product **15c** from **14c** was shown to be identical with that from **18**.

Previously, **19** could be successfully prepared from **27** *Via* **28**.[7] However, the Mannich's reaction of **20** and **4a** were difficult under the same reaction conditions. The Mannich's bases, **21** and **24** were prepared in decreased yields only by modified procedures. Two Mannich's bases, **21** and **24**, gave the corresponding methyl substituted pyrrole esters, **22** and **25**, respectively in the combination of two processes, the treatment with methyl iodide and the reduction with sodium borohydride. Methylated pyrroles (**23** and **26**) could be obtained by the method of hydrolysis and the subsequent decarboxylation as descrived above.

Discussions

For strong antifungal activity, it is necessary that pyrrolnitrin and its analogues should not be substituted by ester group at any position (**39**, **31**, **34**, **4a**), and furthermore, they should not have alkyl group at 1, or 2 and 5 positions of the pyrrole ring (**30**, **33**, **38**).

Some analogues having an alkyl group at either 2 or 5-position of the pyrrole ring (**10a**, **15b** and **32**), showed almost the same activities as the activity of pyrrolnitrin.

6) M. Hashimoto and K. Hattori, submitted.
7) S. Umino, K. Kariyone, K. Tanaka and I. Ueda, *Chem. Pharm. Bull.* (Tokyo), **17**, 605 (1969).

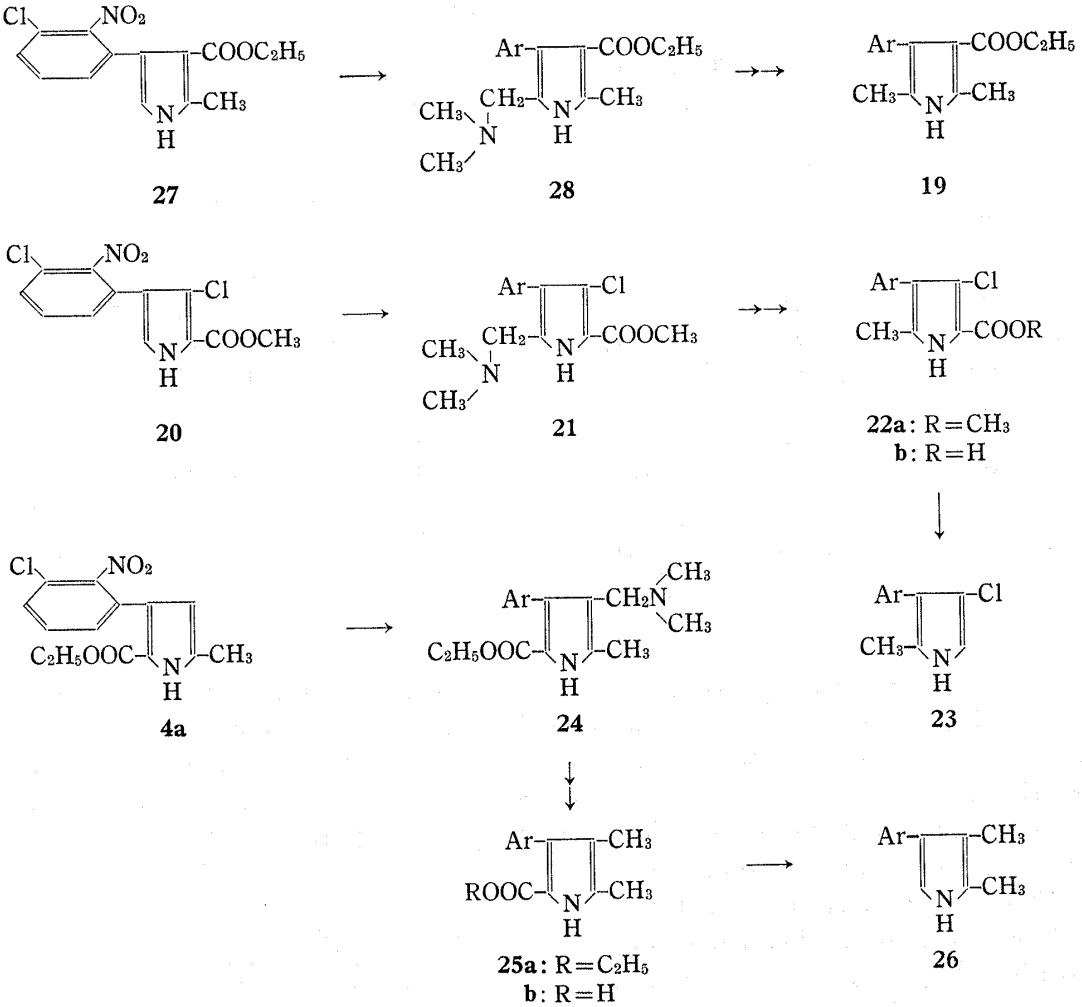
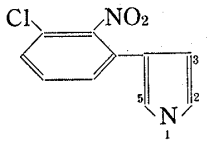


Chart 3

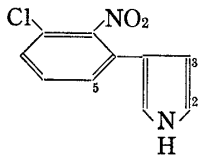
TABLE I-A.



Comp.	R 1	R 2	R 3	R 5	MIC (mcg/ml) A	B	C	D	E
8a	H	H	Cl	H	>40	>40	>40	2	10
30	CH_3	H	Cl	H	>40	>40	>40	>40	>40
33	H	CH_3	H	CH_3	>40	>40	>40	>40	>40
38	H	CH_3	Cl	CH_3	>40	>40	>40	>40	>40
39	H	$COOCH_3$	Cl	H	>40	>40	>40	>40	>40
31	H	H	Cl	$COOC_2H_5$	>40	>40	>40	>40	>40
34	H	CH_3	$COOC_2H_5$	H	>40	>40	>40	>40	>40
4a	H	CH_3	H	$COOC_2H_5$	>40	>40	>40	>40	>40

A: *Staphylococcus aureus* 209 P
B: *Escherichia coli* NIHJ
C: *Candida albicans* Yu-1200
D: *Trichophyton interdigitale*
E: *Mycobacterium tuberculosis* SP 607
30,38,39: M. Hashimoto and K. Hattori, submitted.
31,33,34: *Chem. Pharm. Bull.* (Tokyo), **17**, 588, 605, 559 (1969).

TABLE I-B.



Comp.	R			MIC (mcg/ml)				
	2	3	5	A	B	C	D	E
8a	H	Cl	H	>40	>40	>40	2	10
23	H	Cl	CH_3	>40	>40	>40	>40	>40
10a	CH_3	H	H	>40	>40	>40	5	10
15b	C_2H_5	H	H	>40	>40	>40	5	20
32	H	H	CH_3	>40	>40	>40	5	20
26	CH_3	CH_3	H	>40	>40	>40	>40	>40

A: *Staphylococcus aureus* 209P B: *Escherichia coli* NIHJ
C: *Candida albicans* Yu-1200 D: *Trichophyton interdigitale*
E: *Mycobacterium tuberculosis* SP 607
32: *Chem. Pharm. Bull.* (Tokyo), **17**, 619 (1969).

This may be explained by assuming the following mechanism. Either α or α' position of pyrrole, having a high reactivity as a nucleophile, could be supposed as a active site to micro-örganisms. Chlorine atom of 3-position of pyrrole (pyrrolnitrin **8a**) could donate electron to the 2-position to increase the reactivity of α-position. Thus such compounds may be more activated than those without electron donating group on the pyrrole ring.

In 2-methyl-4-(2-nitro-3-chlorophenyl) pyrrole (**10a**), one of effective compounds, electron is released to another α-position, the 5-position of pyrrole, by the methyl group at the 2-position.

On the other hand, 2,3-dimethyl-4-(2-nitro-3-chlorophenyl)pyrrole (**29**) was inactive. The activating effect of the methyl group at the 2-position was weakend by the effect of methyl group at 3-position of pyrrole ring.

On the basis of this assumption, 3-chloro-5-methyl-4-(2-nitro-3-chlorophenyl) pyrrole (**23**) might be effective among pyrrolnitrin type compounds, because both 3-position of chlorine and 5-position of methyl group donate electron to the 2-position. However, the proposed compound was apparently inactive. This discrepancy may be explained by the assumption that the activation by the substituents of pyrrole ring of this compound exceeds an optimum extent.

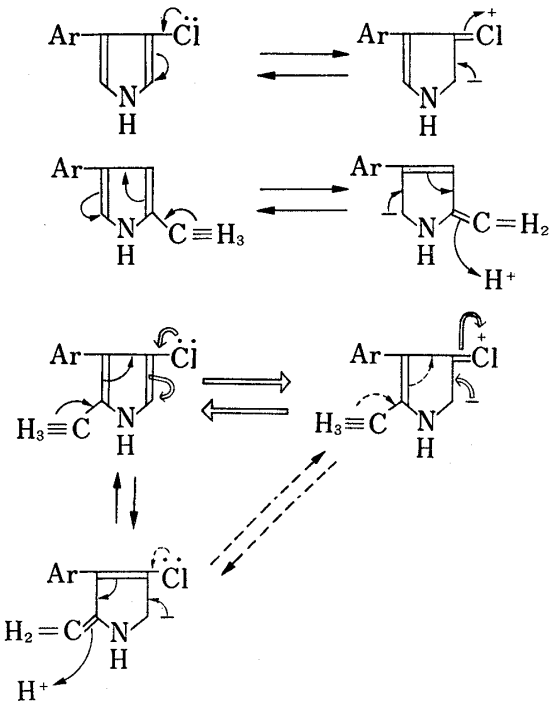
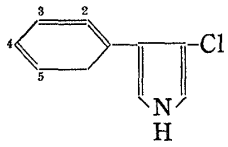


Chart 4

By the IR spectra, it was interesting observed that each compound of the nitro-substituted derivatives showed a symmetric vibration band of nitro group of different frequency.

On the other hand, the shift of symmetric stretching vibration band of nitro group to higher frequency indicated that the benzene ring and the nitro group were not co-planer to

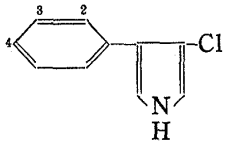
Table II.



Comp.	R 2	R 3	R 4	R 5	MIC D	MIC E	IR spectra ν_{NO_2}(symmetric) (cm^{-1})
8n	NO_2	H	H	H	5	>40	1350
8a	NO_2	Cl	H	H	2	10	1375
8b	NO_2	H	Cl	H	5	20	1345
8c	NO_2	H	H	Cl	>40	>40	1345
8p	H	NO_2	H	H	10	>40	1345
8q	H	NO_2	Cl	H	10	>40	1350
8d	H	H	NO_2	H	5	>40	1345
8e	Cl	H	NO_2	H	>40	>40	1345

D: *Trichophyton interdigitale* E: *Mycobacterium tuberculosis* SP 607
8n and **8—9**: *Chem. Pharm. Bull.* (Tokyo), **17**, 588 (1969).
8p and **q**: *Chem. Pharm. Bull.* (Tokyo), **17**, 623 (1969).

Table III.



Comp.	R 2	R 3	R 4	MIC (mcg/ml) A	B	C	D	E
8a	NO_2	Cl	H	>40	>40	>40	2	10
8r	H	H	H	20	20	20	2.5	20
8f	Cl	H	H	>40	>40	20	1	20
8o	H	Cl	H	10	20	1	1	10
8g	H	Br	H	10	10	10	0.25	5
8t	H	CF_3	H	10	10	10	0.25	20
8h	H	H	Cl	20	20	10	10	20
8m	Cl	H	Cl	>40	>40	20	5	10
8i	H	Cl	Cl	20	20	10	10	20

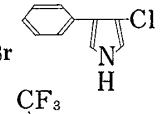
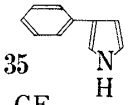
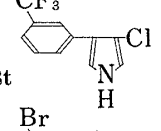
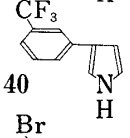
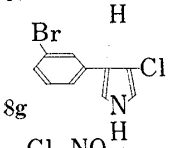
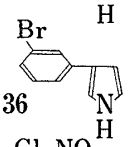
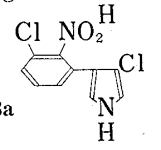
A: *Staphylococcus aureus* 209 P B: *Escherichia coli* NIHJ
C: *Candida albicans* Yu-1200 D: *Trichophyton interdigitale*
E: *Mycobacterium tuberculosis* SP 607
8r and **8o**: *Chem. Pharm. Bull.* (Tokyo), **17**, 588 (1969).

each other. By the IR spectra of ortho nitro group, the nitro group of pyrrolnitrin (**8a**) was more strongly twisted from benzene plane than the other ortho nitro compounds (**8n, b** and **c**). The antifungal activity became stronger as the shift of nitro group was increased.

According to the above data, as the nitro group of pyrrolnitrin is not co-planer to the benzene ring, the nitro group influences the electronic structure of arylpyrrole only by inductive effect without mesomeric effect. Consequently, it may be assumed that the nitro group of pyrrolnitrin is dispensable for antifungal activity.

By this inference, several analogues activities were examined. In this series, these analogues showed broader and stronger antimicrobial activities than those of the original nitrophenyl compounds. Denitro–pyrrolnitrin (**8o**), its bromo analogue (**8g**) and trifluoromethyl derivative (**8t**) were the most effective in all pyrrolnitrin derivatives.

Table IV.

	C	D (MIC)		C	D (MIC)
8r 	20	2.5	35 	>40	20
8t 	10	1	40 	>40	12.5
8g 	10	0.25	36 	>40	12.5
8a 	>40	2	37 	20	2

C: *Candida albicans* Yu-1200 D: *Trichophyton interdigitale*
35, 36, and **40**: K. Kariyone and H. Nakamura submitted.
8r: K. Kariyone and H. Nakamura, *Chem. Pharm. Bull.* (Tokyo), **17**, 588 (1969)

When the 3-position of pyrrole is not chlorine-substituted, the antifungal activity is decreased in comparison with the corresponding chlorinated derivatives. Thus, the assumption, based on the data of Table I-B is supported.

Experimental[8]

Diethyl N-(1-Alkyl-3-aryl-3-oxopropyliden)aminomalonate (2b—l,t, 12a—e,)——General Method: A mixture of *a* g of 1-aryl-1,3-alkandione, *b* g of diethyl aminomalonate, *c* ml of EtOH and two drops of piperidine was refluxed for 5 hr. Solvent was evaporated *in vacuo*. The residue was recrystallized from a suitable solvent. The results are shown in Table V.

Ethyl 2-Methyl-3-(3-bromophenyl)-(5H)-5,5-pyrroledicarboxylate (3 g)——A solution of diethyl N-[1-methyl-3-(3-bromophenyl)-3-oxopropyliden]aminomalonate (**2 g**, 1.0 g), 20 g of PPE and 20 ml of $CHCl_3$ was refluxed for 17 hr. Chloroform was removed under reduced pressure. To the residue was added ice-water and the mixture was extracted with ether. The ether layer was washed with 5% NaOH solution and with water, and then the ether solution was dried over Na_2SO_4. After removing ether, a crude product was obtained. The product was recrystallized from a mixture of ether and *n*-hexane, yielding 3 g as colorless needles, mp 77.5—78° (0.5 g). *Anal.* Calcd. for $C_{17}H_{18}O_4NBr$: C, 53.70; H, 4.77; N, 3.68. Found: C, 53.69; H, 4.85; N, 3.50.

Ethyl 2-Alkyl-4-aryl-5-pyrrolecarboxylate (4b—l,t, 13b—e) and Its 3-Chloro Derivative (13a)——General Method: i) with PPE: A mixture of *a* g of **2**, $20\times a$ g of PPE and $20\times a$ ml of $CHCl_3$ was gently refluxed for 15 hr. Chloroform was evaporated under reduced pressure, the residue was added to an ice-water to decompose PPE. The solution was extracted with ether. The ether extract was washed with 5% NaOH solution and water, dried over $MgSO_4$, and then evaporated. The residue was recrystallized. The results were described in Table VI.

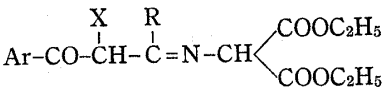
ii) with NaOEt: A solution of **2** or **3** g (*a* g) in $a\times 4$ ml of tetrahydrofuran was added dropwise with stirring to a solution of NaOEt prepared from $a\times 40$ ml of EtOH and $a\times 1.4$ g of metallic sodium. The reaction mixture was refluxed for 4.5 hr, and the solvent was evaporated *in vacuo*.

The residue was added into 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 organic solvent. The results are shown in Table VI.

5-Ethoxycarbonyl-4-aryl-3-chloro-2-pyrrolecarboxylic Acid (6b—i,m,t)——General Method: To a suspension of 4 (*a* g) in $a\times 10$ ml of AcOH was added a solution of SO_2Cl_2 (*b* g) in AcOH (*b* ml) with stirring at

8) All melting point are uncorrected. The infrared spectra were recorded on Hitachi EPI-S_2. The NMR spectra were measured with a Varian A-60 spectrometer using tetramethylsilane as internal standard.

Table V.



Comp.	Ar.	X	R	*a*g	*b*g	*c*ml	2 or 12	Recry.[a] solv.	Cryst.[b] form
2 b	2-NO_2 4-Cl	H	CH_3	1.2	1.1	10	1.2	A	F
c	2-NO_2 5-Cl	H	CH_3	20.0	18.0	100	32.5		G
d	4-NO_2 H	H	CH_3	30.0	30.4	100	31.7	B	F
e	4-NO_2 2-Cl	H	CH_3	20.0	18.0	100	29.5	C	F
f	2-Cl H	H	CH_3	20.0	21.4	100	38.0	B	H
g	3-Br H	H	CH_3	17.2	15.3	70	20.0	D	I
h	4-Cl H	H	CH_3	23.0	24.5	150	30.5		G
i	3-Cl 4-Cl	H	CH_3	6.0	6.0	35	8.9	E	H
j	3-NO_2 5-NO_2	H	CH_3	8.0	5.6	50	9.0	A	F
k	4-MeO H	H	CH_3	3.9	4.3	20	6.6	C	H
l	3-MeO 4-MeO	H	CH_3	23.0	21.8	350	9.0	C	H
t	3-CF_3 H	H	CH_3	9.6	7.4	50	10.0		G
12 a	2-NO_2 3-Cl	Cl	CH_3	2.0	1.5	20	2.3	E	F
b	2-NO_2 3-Cl	H	C_2H_5	5.0	4.5	25	6.0	E	F
c	2-furyl	H	CH_3	7.0	9.7	50	14.9		G
d	2-thienyl	H	CH_3	5.0	5.5	35	9.6		G
e	2-NO_2 3-Cl	H	*n*-C_3H_7	1.2	1.0	6	2.0		G

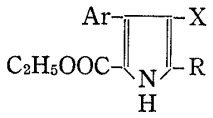
Comp.	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Cl	Found C	H	N	Cl
2 a	111.5	$C_{17}H_{19}O_7N_2Cl$	51.20	4.80	7.02		51.49	4.85	6.99	
b	employed in next step without further purification									
c	87	$C_{17}H_{20}O_7N_2$	56.04	5.54	7.67		56.29	5.74	7.67	
d	79	$C_{17}H_{19}O_7N_2Cl$	51.20	4.80	7.02	18.89	51.21	4.98	7.07	19.12
e	63	$C_{17}H_{20}O_5NCl$	57.71	5.70	3.96		57.69	5.67	3.93	
f	55	$C_{17}H_{20}O_5NBr$	51.26	5.03	3.52		51.17	5.23	3.63	
g	employed in next step without further purification									
h	61	$C_{17}H_{19}O_5NCl$	52.59	4.93	3.61		52.84	4.69	3.54	
i	165.5	$C_{17}H_{19}O_9N_3$	49.88	4.68	10.27		49.86	4.96	10.05	
j	71	$C_{18}H_{23}O_6N$	61.88	6.64	4.01		61.58	6.76	3.88	
k	102	$C_{19}H_{25}O_7N$	60.15	6.64	3.69		59.88	6.82	3.84	
l	employed in next step without further purification									
12 a	108.5	$C_{17}H_{18}O_7N_2Cl_2$	47.13	4.19	6.47	16.37	47.00	4.31	6.20	16.23
b	83	$C_{18}H_{21}O_7N_2Cl$	52.55	5.31	6.59	8.86	52.37	5.13	6.79	8.59
c	employed in next step without further purification									
d	employed in next step without further purification									
e	employed in next step without further purification									

a) A: benzene–ligroin B: MeOH C: EtOH D: benzene–petroleum ether E: benzene–petroleum benzine
b) F: yellow needles G: liquid H: colorless needles I: light yellow needles

5—10° for 3 hr. The reaction mixture became clear during the addition of SO_2Cl_2, and was kept standing overnight at room temperature. The solution was poured into ice–water. The aqueous layer was extracted twice with AcOEt. The organic layer was dried and evaporated *in vacuo*. The residue was dissolved again in $a \times 10$ ml of AcOH, and the solution was heated under reflux for 0.5 hr, and then evaporated under reduced pressure. The residue was washed with a small volume of AcOH, collected by filtration, and recrystallized from AcOH. The results were described in Table VII.

Diethyl 2-Methyl-4-(2-furyl)-3,5-pyrroledicarboxylate (17)——A mixture of ethyl 3-(2-furyl)-3-oxo-2-nitrosopropionate (3.9 g), ethyl acetoacetate (3.1 g) and AcOH (60 ml) was hydrogenated over 10% Pd–C (0.4 g) by the usual procedure. The catalyst was removed by filtration and the filtrate was evaporated.

TABLE VI.

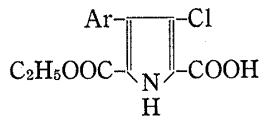


Comp.	Ar	X	R	2, 12 (ag)	Method	4, 13 (g)	Recry[a] solv.	Cryst.[b] form
4 b	2-NO_2 4-Cl	H	CH_3	0.7	i	0.1	A	F
c	2-NO_2 5-Cl	H	CH_3	17.8	i	6.1	A	F
d	4-NO_2 H	H	CH_3	20.0	i	2.4	A	G
e	4-NO_2 2-Cl	H	CH_3	14.0	i	5.2	A	F
f	2-Cl H	H	CH_3	15.0	i	4.0	B	H
				22.0	ii	9.9	B	
g	3-Br H	H	CH_3	7.4	ii	1.6	A	I
	(from 3 g 0.1)				ii	0.05	A	I
h	4-Cl H	H	CH_3	30.0	ii	4.6	A	H
i	3-Cl 4-Cl	H	CH_3	4.0	ii	1.1	A	H
j	3-NO_2 5-NO_2	H	CH_3	8.0	i	1.8	C	F
k	4-MeO H	H	CH_3	6.0	i	0.2	A	H
l	4-MeO 3-MeO	H	CH_3	21.0	i	11.0	A	J
t	3-CF_3 H	H	CH_3	18.0	i	7.0	B	I
				1.1	ii	0.2	B	I
13 a	2-NO_2 3-Cl	Cl	CH_3	1.0	i	0.2	D	F
b	2-NO_2 3-Cl	H	C_2H_5	7.4	i	0.3	E	F
c	2-furyl	H	CH_3	11.9	ii	1.5	A	H
d	2-thienyl	H	CH_3	9.6	ii	0.7	A	H
e	2-NO_2 3-Cl	H	n-C_3H_7	20.0	i	2.0	A	F

Comp.	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Cl	Found C	H	N	Cl
1 b	159	$C_{14}H_{13}O_4N_2Cl$	54.47	4.24	9.08		54.53	4.28	9.28	
c	156	$C_{14}H_{13}O_4N_2Cl$	54.47	4.24	9.08		54.36	4.62	9.32	
d	191	$C_{14}H_{14}O_4N_2$	61.31	5.15	10.21		61.26	5.16	10.27	
e	203	$C_{14}H_{13}O_4N_2Cl$	54.47	4.24	9.08		54.48	4.49	8.93	
f	142	$C_{14}H_{14}O_2NCl$	63.75	5.35	5.31		63.56	5.65	5.43	
	142									
g	161	$C_{14}H_{14}O_2NBr$	54.56	4.58			54.27	4.56		
	161						54.39	4.44		
h	149	$C_{14}H_{14}O_2NCl$			5.31				5.43	
i	143	$C_{14}H_{13}O_2HCl_2$	56.39	4.40	4.70	23.78	56.34	4.69	4.79	23.45
j	212	$C_{14}H_{13}O_6N_3$	52.66	4.10	13.16		52.84	4.38	13.37	
k	130	$C_{15}H_{16}O_3N$	69.48	6.61	5.40		69.49	6.64	5.21	
l	123	$C_{16}H_{18}O_4N$	66.42	6.62	4.84		66.12	6.60	4.87	
t	149	$C_{15}H_{13}O_2NCl_2F_3$	54.31	3.95	4.22		53.98	3.66	4.10	
	149									
13 a	250	$C_{14}H_{12}O_4N_2Cl_2$	48.99	3.53	8.16	20.66	49.16	3.68	8.31	20.52
b	192	$C_{15}H_{16}O_4N_2Cl$	55.81	4.68	8.68	10.99	55.56	4.89	8.68	11.08
c	141	$C_{12}H_{13}O_3N$	65.71	5.98	6.39		65.77	6.07	6.65	
d	127	$C_{12}H_{13}O_2NS$	61.25	5.57	5.96		61.11	5.76	5.84	
e	169	$C_{16}H_{17}O_4N_2Cl$	57.07	5.09	8.32	10.56	56.87	5.06	8.29	10.81

a) A: EtOH B: benzene–hexanee C: acetone D: benzene E: MeOH
b) F: yelolow needles G: yellow plates H: colorless needles I: colorless plates J: colorless prisms

TABLE VII.



Comp.	Ar X	Ar Y	4 (*a*g)	SO_2Cl_2 (*b*g)	6 (g)	mp (decomp.)	Form[1]
6 b	2-NO_2	4-Cl	1.0	1.9	1.0	220	A
c	2-NO_2	5-Cl	2.0	3.8	2.1	222	B
d	4-NO_2	H	2.3	4.4	1.2	271	A
e	4-NO_2	2-Cl	2.0	3.8	1.1	250	A
f	2-Cl	H	1.7	3.7	1.3	264	C
g	3-Br	H	1.5	2.9	1.0	270	A
h	4-Cl	H	4.7	9.6	3.1	265	A
i	3-Cl	4-Cl	1.6	3.3	1.5	270	A
t	3-CF_3	H	2.0	3.8	2.4	270	A

Comp.	Formula	Analysis (%) Calcd. C	H	N	Cl	Found C	H	N	Cl
6 b	$C_{14}H_{10}O_6N_2Cl_2$	45.06	2.70	7.51	19.00	45.11	2.85	7.59	18.89
c	$C_{14}H_{10}O_6N_2Cl_2$	45.06	2.70	7.51	19.00	45.08	2.75	7.61	18.84
d	$C_{14}H_{11}O_6N_2Cl$	49.64	3.27		10.47	50.41	3.64		10.54
e	$C_{14}H_{10}O_6N_2Cl_2$	45.06	2.70	7.51	19.00	45.09	2.83	7.70	18.77
f	$C_{14}H_{11}O_4NCl_2$	51.24	3.36	4.27	21.61	51.19	3.45	4.22	21.85
g	$C_{14}H_{11}O_4NClBr$	45.13	3.38	3.76		44.95	3.17	3.91	
h	$C_{14}H_{11}O_4NCl_2$	51.24	3.36	4.27	21.61	51.03	3.56	4.17	21.75
i	$C_{14}H_{10}O_4NCl_3$	46.37	2.78	3.86	29.33	46.32	2.95	3.76	29.19
t	$C_{15}H_{11}O_4NClF_3$	49.81	3.07	3.87		49.62	3.00	3.77	

1) A: colorless needles B: yellow needles C: pink needles

The residue was diluted with water and extracted with ether. The extracts were washed with dil.HCl, with dil.NaOH and with water successively and dried to give colorless crystals. Recrystallization from benzene–hexane afforded **17**, mp 134.5—136°, (2.7 g). *Anal.* Calcd. for $C_{15}H_{17}O_5N$: C, 61.85, H, 5.88, N, 4.81. Found: C, 62.01, H, 5.98, N, 4.74.

Pyrrolecarboxylic Acids (7b—i,m,t, 9a,e,k,l,n,o, 14a—d, 18, 22b and 25b)——General Method: A mixture of corresponding pyrrolester (*a* g), $a \times 10$ ml of EtOH and $a \times 30$ ml of 10% NaOH solution was refluxed for 5 hr. After cooling, the reaction mixture was poured into $30 \times a$ ml of 10% Na_2SO_4, and the resulting acidic suspension was extracted with AcOEt. The organic layer was washed with water, dried over $MgSO_4$ and evaporated *in vacuo* to give a crude pyrrolecarboxylic acid in almost quantitative yields.

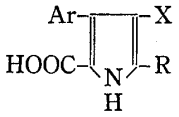
The crude acid was employed in the next step without further purification. Some of them was recrystallized for elemental analysis (Table VIII).

Decarboxylation of Pyrrolecarboxylic Acids (8b—i,m,t,10a,e,k,n,o, 15a—d, 23 and 26)——General Method: A solution of corresponding carboxylic acid (*a* g) in $40 \times a$ ml of dimethylaniline was heated under reflux for 0.5 hr with vigorous stirring. The mixture was evaporated under reduced pressure to *ca.* 1/5 volume, poured into $100 \times a$ ml of 10% H_2SO_4 and extracted with benzene. The benzene layer was washed with 10% H_2SO_4 and water, dried over $MgSO_4$, filtered through a thin-layer of silica gel, and the resulted solution was evaporated under reduced pressure of N_2.

The results are described in Table IX.

Methylation of Pyrrole-Esters (22a and 25a)——i) Dimethylaminomethylation: Pyrrole ester (**20** or **4a**, 6.0 g) was dissolved in 130 ml of AcOH containing Me_2NH HCl (9.5 g), 37% HCHO aq. (11 ml) and NaOAc 3 H_2O (9.5 g).

Table VIII.

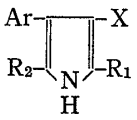


Comp.	Ar	X	R	4, 13, (ag)	9, 14 (g)	Recry.[a] solv.	Cryst.[b] form
9k	4-MeO H	H	CH_3	0.7	0.3	A	C
l	3-MeO 4-MeO	H	CH_3	0.4	0.2	A	C
14a	2-NO_2 3-Cl	Cl	CH_3	0.5	0.25	A	D
b	2-NO_2 3-Cl	H	C_2H_5	1.0	0.55	A	C
c	2-furyl	H	CH_3	0.8	0.2	B	C
d	2-thienyl	H	CH_3	0.9	0.2	B	C

Comp.	mp (decomp.)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
9k	154	$C_{13}H_{13}O_3N$	67.52	5.67	6.06	67.65	5.88	6.30
l	147	$C_{14}H_{15}O_4N$	64.36	5.79	5.36	64.65	5.82	5.39
14a	249	$C_{12}H_8O_4N_2Cl_2$						
b	189	$C_{13}H_{11}O_4N_2Cl$	52.98	3.76	9.51	52.74	3.75	9.28
c	129	$C_{10}H_9O_3N$						
d	132	$C_{10}H_9O_2NS$	57.95	4.38	6.76	57.64	4.44	6.60

a) A: benzene–EtOH B: benzene
b) C: colorless needles D: yellow needles

Table IX.



Comp.	Ar	X	R_1	R_2	7, 9, 14 (ag)	8, 10, 15 (g)
8b	2-NO_2 4-Cl	Cl	H	H	0.2	0.06
c	2-NO_2 5-Cl	Cl	H	H	1.0	0.2
d	4-NO_2 H	Cl	H	H	0.2	0.1
e	4-NO_2 2-Cl	Cl	H	H	0.7	0.3
f	2-Cl H	Cl	H	H	0.1	0.05
g	3-Br H	Cl	H	H	0.2	0.05
h	4-Cl H	Cl	H	H	2.0	0.6
i	3-Cl 4-Cl	Cl	H	H	0.1	0.03
m	2-Cl 4-Cl	Cl	H	H	0.1	0.02
t	3-CF_3 H	Cl	H	H	1.8	0.5
10a	2-NO_2 3-Cl	H	CH_3	H	1.0	0.3
e	4-NO_2 2-Cl	H	CH_3	H	0.5	0.3
k	4-MeO H	H	CH_3	H	0.3	0.01
n	2-NO_2 H	H	CH_3	H	0.6	0.05
o	3-Cl H	H	CH_3	H	0.2	0.15
15a	2-NO_2 3-Cl	Cl	CH_3	H	0.2	0.05
b	2-NO_2 3-Cl	H	C_2H_5	H	0.5	0.01
c	2-furyl	H	CH_3	H	0.15	0.03
					(18 0.18)	0.02
d	2-thienyl	H	CH_3	H	0.2	0.03
23	2-NO_2 3-Cl	Cl	H	CH_3	(13 0.8)	**23**=0.2
29	2-NO_2 3-Cl	CH_3	CH_3	H	(28 1.9)	**29**=0.2

Comp.	Recry. solv.[a]	Cry. form[b]	mp	Formula	Anaysis (%) Calcd. C	H	N	Cl	Found C	H	N	Cl
8 b	A	D	118	$C_{10}H_6O_2N_2Cl_2$	46.71	2.35			46.46	2.64		
c	A	E	106	$C_{10}H_6O_2N_2Cl_2$			10.89				11.06	
d	A	E	174	$C_{10}H_7O_2N_2Cl$	53.59	3.13	12.62	15.93	54.11	3.41	12.76	16.19
e	A	F	184	$C_{10}H_6O_2N_2Cl_2$			10.89				10.99	
f	A	G	75	$C_{10}H_7NCl_2$	56.63	3.33			56.93	3.46		
g	liquid, could not be distilled without decomposition											
h	A	G	63	$C_{10}H_7NCl_2$	56.63	3.33			56.85	3.49		
i	A	G	confirmed with IR and Ehrlich's color reaction									
m	A	G	confirmed with IR and Ehrlich's color reaction									
t	liquid, bp 0.1		129	$C_{11}H_7NClF_3$	53.70	2.87	5.69		53.74	3.02	5.83	
10 a	B	H	84	$C_{11}H_9O_2N_2Cl$	55.83	3.83	11.84		55.89	4.16	12.01	
e	A	I	167	$C_{11}H_9O_2N_2Cl$	55.83	3.83	11.84	14.88	55.80	3.99	11.86	14.90
k	C	J	108	$C_{12}H_{13}ON$	76.97	7.00			77.29	7.33		
n	liquid, confirmed with IR and Ehrlich's color reaction											
o	A	K	61	$C_{11}H_{10}NCl$	68.95	5.26			68.83	5.39		
15 a	A	E	165	$C_{12}H_{11}O_2N_2Cl$	57.49	4.42			57.37	4.39		
b	liquid, confirmed with IR and Ehrlich's color reaction											
c	liquid, confirmed with IR and Ehrlich's color reaction											
	liquid, identified with above sample by IR											
d	liquid, confirmed with IR and Ehrlich's color reaction											
23	D	E	165	$C_{11}H_8O_2N_2Cl_2$	48.73	2.97	10.33		48.95	3.06	10.10	
29	A	E	139	$C_{12}H_{11}O_2N_2Cl$	57.49	4.42	11.76		57.51	4.63	11.55	

a) A: benzene–ligroin B: ether–hexane C: benzene–hexane D: benzene–petroleum ether
b) E: yellow needles F: orange needles G: colorless needles H: yelllow prisms I: orange prisms
J: colorless prisms K: colorless plates

The reaction mixture was heated at 95° for 50 hr with stirring, then evaporated under reduced pressure to dryness. The EtOAc solution of the residue was washed with 10% K_2CO_3 and water, dried over $MgSO_4$, evaporated *in vacuo* to give crude dimethylaminomethyl compounds (**21**, **24**).

21: powder 3.7 g.

24: 4.0 g, mp 174—179° colorless needles after recrystallization from EtOH.

ii) Methiodide of the Base: A MeOH solution (50 ml) of the Mannich's base (4 g) was added 8 ml of methyl iodide, then allowed to stand overnight, and evaporated to give methiodide of the Mannich's base (5.9 g).

iii) Reduction of the Methiodide (**22a** and **25a**): The above methiodide was dissolved in 100 ml of EtOH, reduced by 1.2 g of $NaBH_4$ by the usual procedure. The reaction mixture was evaporated *in vacuo*, and the residue was dissolved in EtOAc. The organic layer was washed with dil.HCl and H_2O, dried over $MgSO_4$ and evaporated *in vacuo*.

22a was recrystallized from benzene as yellowish green plates having mp 228—229.5° (2.4 g). *Anal.* Calcd. for $C_{13}H_{10}O_4N_2Cl_2$: C, 47.44, H, 3.06, N, 8.15, Cl, 21.54. Found: C, 47.30, H, 3.12, N, 8.72, Cl, 21.41.

25a was recrystallized from EtOH, but was purified by preparative thin-layer chromatography for elemental analysis. (yellow prisms, mp 264—266°). *Anal.* Calcd. for $C_{15}H_{15}O_4N_2Cl$: C, 55.82, H, 4.69, N, 8.68. Found: C, 55.67, H, 4.86, N, 8.66.