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Total Synthesis of Pyrrolnitrin. VI.[1] Synthesis of Nitro-chloro-2-aminoacetophenones and 1-Aryl-1,3-butanediones[2]

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Synthetic methods of nitro-chloro-2-aminoacetophenones (XV) and 1-(nitro-chlorophenyl)-1,3-butanediones (XXIII: R=H), starting materials for the synthesis of pyrrolnitrin (I) and its related compounds, were investigated. Neber rearrangement was shown to be suitable for the preparation of XV. Cleavage of ethyl 2-(nitro-chlorobenzoyl)-acetoacetate (XXI) and 2,4-pentanedione (XXII) led to XXIII (R=H).

In the first Part,[4] ethyl 3-(2-nitro-3-chlorophenyl)-5-methyl-4-pyrrolecarboxylate (II), an intermediate to pyrrolnitrin (I),[5] was synthesized by Knorr condensation of 2-nitro-3-chloro-2-aminoacetophenone (XVa) with ethyl acetoacetate.

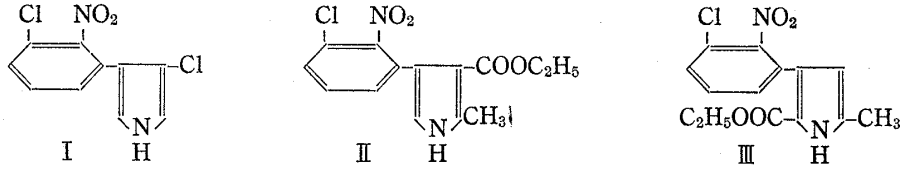


Chart 1

And in the third Part,[6] ethyl 3-(2-nitro-3-chlorophenyl)-5-methyl-2-pyrrolecarboxylate (III), another intermediate to I, was synthesized by the reaction between 1-(2-nitro-3-chlorophenyl)-1,3-butanedione (XXIIIa: R=H) and diethyl aminomalonate.

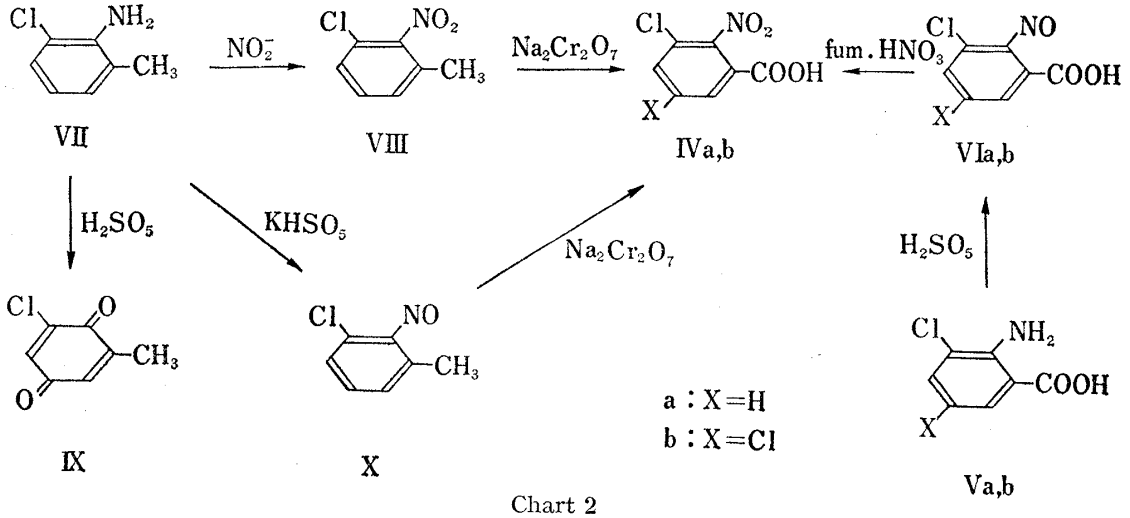


Chart 2

1) Part V: S. Umio, K. Kariyone, K. Tanaka, I. Ueda and Y. Morimoto, *Chem. Pharm. Bull.* (Tokyo), **17**, 558 (1969).
2) A part of this work was presented at the 87th annual meeting of the Pharmaceutical Society of Japan at Kyoto, April 1967.
3) Location: *1, Kashimacho, Higashiyodogawa-ku, Osaka.*
4) Part I: *Chem. Pharm. Bull.* (Tokyo), **17**, 559 (1969).
5) K. Arima, H. Imanaka, M. Kousaka and A. Fukuta, *Agr. Biol. Chem.*, **28**, 573 (1964).
6) Part III: *Chem. Pharm. Bull.* (Tokyo),**17**, 576 (1969).

The present paper describes the synthesis of these compounds, XVa and XXIIIa (R=H), and related compounds.

Our first effort was concentrated on the synthesis of 2-nitro-3-chlorobenzoic acid (IVa), an essential starting material to these compounds, XVa (R=H) and XXIIIa (R=H).

2-Nitro-3-chlorobenzoic acid (IVa) has been prepared by nitration[7] of 3-chlorobenzoic acid and by oxidation[8] of 2-nitro-3-chlorotoluene (VIII). These methods, however, appear to be unsuitable for the large scale production.

In an attempt to find a better method, the plan was chosen to substitute a nitro group for the amino group in 3-chloroanthranilic acid[9] (Va). It has been known that Caro's acid oxidation is the general method for oxidation of aromatic amines, and that *ortho*-substituted anilines, among them, gave the nitroso compounds instead of nitro compounds in good yield.

Bamberger[10] reported that *o*-nitrosobenzoic acid was obtainable in good yield by Caro's acid oxidation of anthranilic acid in a neutral solution.

However, the nitroso compound (VIa) was obtained in high yield in the case of 3-chloroanthranilic acid (Va), which was oxidized by Caro's acid prepared from sulfuric acid and potassium persulfate without neutralization.

Oxidation of VIa by fuming nitric acid afforded a quantitative yield of 2-nitro-3-chlorobenzoic acid (IVa).

To ascertain the generality of this reaction, 3,5-dichloroanthranilic acid (Vb) was oxidized under the same condition to give also good yield of the nitroso compound (VIb), which was converted to 3,5-dichloro-2-nitrobenzoic acid (IVb) by fuming nitric acid.

Other synthetic methods of the acid (IVa) were investigated, with good results, using 2-amino-3-chlorotoluene (VII) as follows.

Sandmeyer reaction of 2-amino-3-chlorotoluene (VII) in the presence of nitrite-ion has been reported to give 2-nitro-3-chlorotoluene (VIII).[11]

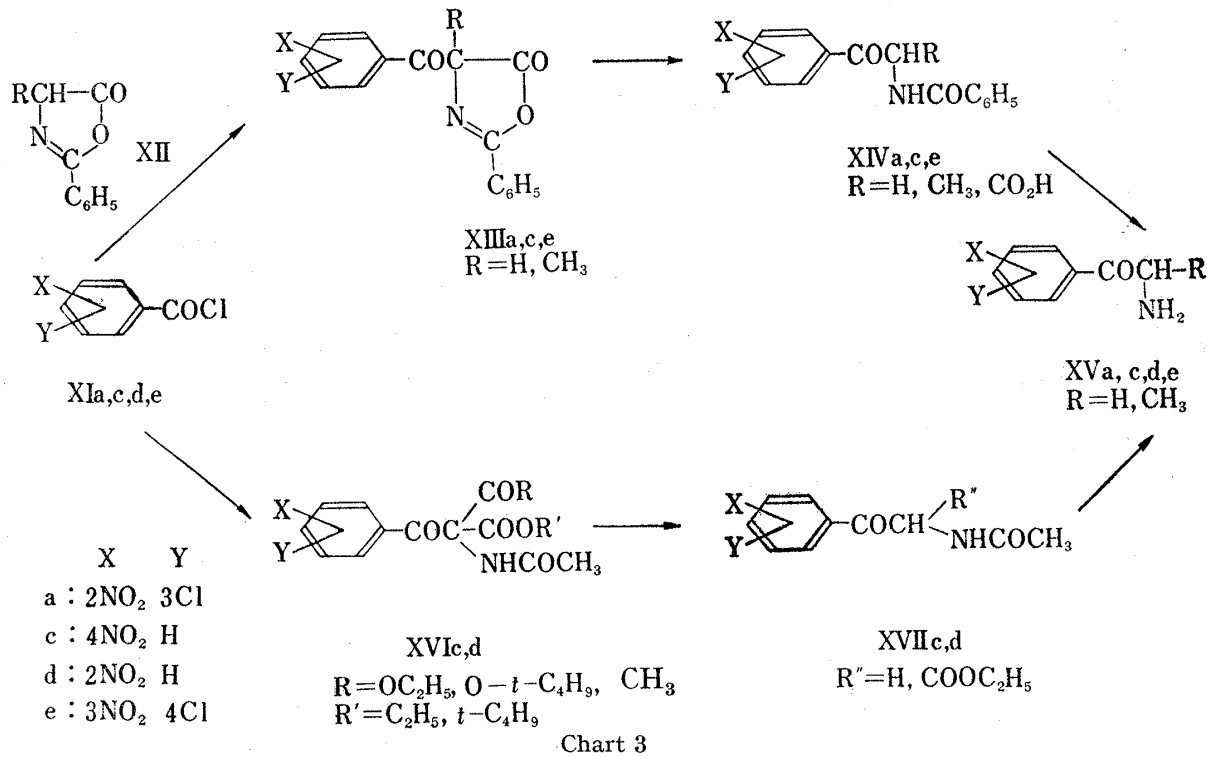


Chart 3

7) D. Pressman, *J. Am. Chem. Soc.*, **76**, 6337 (1954).
8) K. Brand and H. Zoller, *Chem. Ber.*, **40**, 3333 (1907).
9) B.R. Baker and R. E. Schaub, *J. Org. Chem.*, **17**, 141 (1952).
10) E. Bamberger, *Chem. Ber.*, **36**, 3645 (1913).
11) H. Singer and W. Shive, *J. Am. Chem. Soc.*, **77**, 5700 (1955).

Oxidation of VIII was re-examined and 2-nitro-3-chlorobenzoic acid (IVa) was obtained in high yield by dichromate oxidation.

It was expected that acidic Caro's acid would oxidize both amino and methyl group in VII. However, 2-chloro-6-methylbenzoquinone[12] (IX) was only the product obtained under an acidic condition, contrary to the expectation.

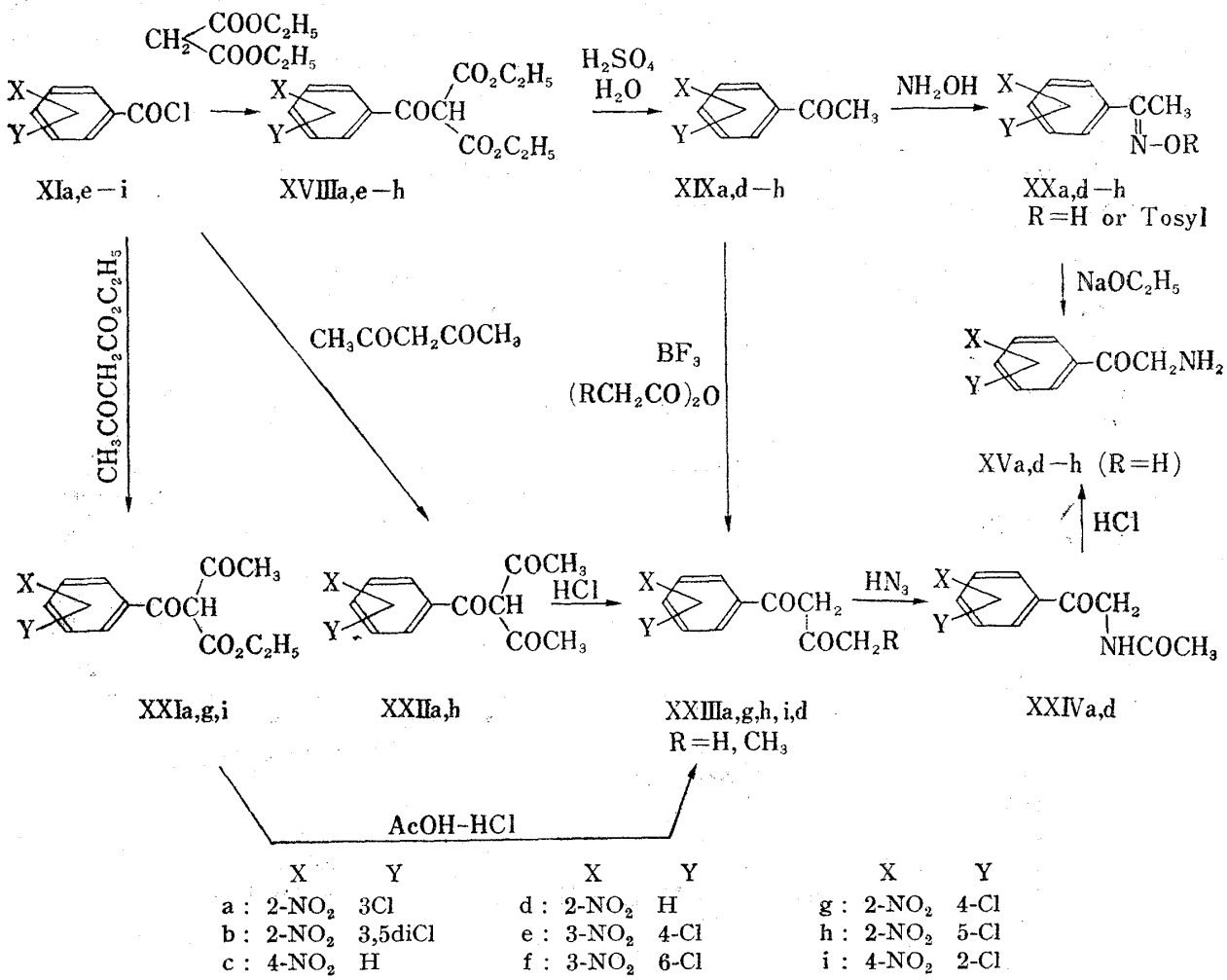
While neutral Caro's acid oxidation afforded 2-nitroso-3-chlorotoluene (X), X was further oxidized with potassium dichromate to give 2-nitro-3-chlorobenzoic acid (IVa) in excellent yield.

Using this 2-nitro-3-chlorobenzoic acid (IVa) a synthetic method of aminoketone (XV) was investigated.

As mentioned in the second Part,[13] it was desirable to synthesize β-arylpyrrole having substituents in both α-positions.

If we could prepare 2'-nitro-3'-chloro-2-aminopropiophenone (XVa: R=CH_3), Knorr condensation of this with ethyl acetoacetate might give the desired α,α'-disubstituted-3-arylpyrroles.

The reaction using the azlactone (XII) was chosen for this purpose. Tatsuoka, *et al.*[14] synthesized the benzoylaminoacetophenone (XIVc: R=H) by hydrolysis of the benzoylaz-



	X	Y		X	Y		X	Y
a :	2-NO_2	3Cl	d :	2-NO_2	H	g :	2-NO_2	4-Cl
b :	2-NO_2	3,5diCl	e :	3-NO_2	4-Cl	h :	2-NO_2	5-Cl
c :	4-NO_2	H	f :	3-NO_2	6-Cl	i :	4-NO_2	2-Cl

Chart 4

12) A. Claus and H. Achweitzer, *Chem. Ber.*, **19**, 928 (1886).
13) Part II: *Chem. Pharm. Bull.* (Tokyo), **17**, 567 (1969).
14) S. Tatsuoka, K. Osugi, *Yakugaku Zasshi*, **71**, 604 (1951).

lactone (XIIIc: R=H) prepared from the azlactone (XII: R=H) and *p*-nitrobenzoyl chloride (XIc).

The same kind of reaction of the methylated azlactone (XII: R=CH_3) with 3-nitro-4-chlorobenzoyl chloride (XIe) and 2-nitro-3-chlorobenzoyl chloride (XIa) gave the corresponding methylated benzoylazlactones (XIIIa,e: R=CH_3) respectively.

Both acidic and alkaline hydrolysis, however, resulted in debenzoylation prior to the desired ring opening accompanied with decarboxylation of XIVa,e (R=COOH), giving carboxylic acids corresponding to acid chlorides (XIa,c).

Being so difficult to synthesize XV (R=CH_3), we started to examine the synthetic method of 2-aminoacetophenone (XV: R=H).

It is reported by Schrecker[15] that, although an acidic hydrolysis of diethyl *p*-nitrobenzoylmalonate (XVc: R=OC_2H_5, R'=C_2H_5) resulted in cleavage of the *p*-nitrobenzoyl group, heating of the corresponding di-*tert*-butyl ester (XVIc: R=O *tert*-butyl, R'=*tert*-butyl) gave an acetamidoacetophenone (XVIIc: R=H) under anhydrous condition.

However, *o*-nitrobenzoyl chloride (XId) failed to react with di-*tert*-butyl acetamidomalonate, perhaps owing to steric hindrance by the *o*-nitrophenyl group.

Condensation of *o*-nitrobenzoyl chloride (XId) with ethyl acetamidoacetoacetate, in contrast, yielded ethyl acetamido-(*o*-nitrobenzoyl)acetoacetate (XVId: R=CH_3, R'=C_2H_5). An attempt to deacetylate XVId (R=CH_3, R'=C_2H_5) was unsuccessful, because cleavage of the *o*-nitrobenzoyl group preceded deacetylation.

On the basis of these preliminary experiments, it was found necessary, for synthesizing the desired 2'-nitro-3'-chloro-2-aminoacetophenone (XVa: R=H), to choose the reaction free from the steric hindrance.

After several investigations, Neber rearrangement was found to be suitable for this purpose and XVa: (R=H), as well as its analogues,[16] could be obtained by this reaction.

Condensation of nitro-chlorobenzoyl chlorides (XIa,e—h) with diethyl malonate afforded benzoylmalonic ester (XVIIIa,e—h), which underwent acidic hydrolysis to give nitro-chloroacetophenones (XIXa,e—h) in good yield.

Acetophenones (XIXa,d—h) were converted to their oximes (XXa,d—h: R=H) using an ethanolic solution of hydroxylamine, the tosylation of which was examined in the presence of sodium ethoxide in ethanol. The reaction was found to be so sensitive to water that high yield of tosylates (XXa,d—h: R=tosyl) could not be obtained without careful dehydration of ethanol.

Aminoketones (XVa,d—h: R=H) were obtained by treating the tosylates with sodium ethoxide in anhydrous ethanol, followed by reaction with hydrogen chloride.

Moreover, aminoketones (XVa,d—h) were found also to be prepared by acidic hydrolysis of acetamidoacetophenones (XXIVa,d: R=H), which was obtained from 1-(nitro-chlorophenyl)-1,3-butanediones (XXIIIa,d: R=H), as described later, by Schmidt reaction.

The second objected synthesis of 1-(2-nitro-3-chlorophenyl)-1,3-butanediones (XXIIIa: R=H), as well as its analogues,[16] was achieved in the following way.

Condensation of nitro-chlorobenzoyl chlorides (XI) with the ethoxymagnesium salt of ethyl acetoacetate or acetylacetone afforded ethyl 2-(nitro-chlorobenzoyl)acetoacetates (XXIa, d,i) and 3-(nitro-chlorobenzoyl)-2,4-pentanediones (XXIIa, h) respectively in good yields.

Nitro-chlorobenzoyl group in these compounds was so reactive, perhaps owing to its strong steric and electronic effect, that both acidic and alkaline hydrolysis under the usual reaction conditions failed to afford XXIII (R=H) in excellent yield.

In order to avoid undersirable elimination of nitro-chlorobenzoyl group, an anhydrous reaction condition was chosen in the case of XXIa, g, i as follows: XXIa was heated in glacial

15) A.M. Schrecker and M.M. Trail, *J. Am. Chem. Soc.*, **80**, 6077 (1958).
16) These compounds were used for the synthesis of analogues of I.

acetic acid containing a little amount of dry hydrogen chloride to give good yield of 1-(nitro–chlorophenyl)-1,3-butanediones (XXIIIa,g,i: R=H), through the mechanism of ester–exchange followed by decarboxylation.

In the case of 3-(nitro–chlorobenzoyl)-2,4-pentanediones (XXIIa,h), after several experiments under acidic aqueous conditions, the reaction condition of refluxing XXIIa,h in 1/10N hydrochloric acid was found best, and 1-(nitro–chlorophenyl)-1,3-butanediones (XXIIIa,h: R=H) were obtained in good yields.

XXIIIa,h (R=H) was found also to be prepared by the reaction of the acetophenone (XIXa) with acetic anhydride in the presence of borontrifluoride. Substitution of propionic anhydride for acetic anhydride in this reaction afforded phenylpentanedione derivative (XXIIIa: R=H).

Experimental[17]

2-Nitroso-3-chlorobenzoic Acid (VIa)——Powdered 3-chloroanthranilic acid (Va) (34.9 g) was suspended in 1090 ml of Caro's acid solution[18] containing active oxygen (610 mg). The suspension was stirred at room temperature for 1—2 days, until the theoretical amount of Caro's acid was consumed.[19] The suspension was filtered and the solid was washed with H_2O. Recrystallization from 95% EtOH yielded colorless crystals (VIa) (30.3 g), mp 191°. *Anal.* Calcd. for $C_7H_4O_3NCl$: C, 45.33; H, 2.18; N, 7.55. Found: C, 45.19; H, 2.40; N, 7.68. IR (nujol) cm^{-1}: 1686 (COOH).

2-Nitroso-3,5-dichlorobenzoic Acid (VIb)——A suspension of powdered 3,4-dichloroanthranilic acid (Vb) (5 g) in Caro's acid (90 ml) containing active oxygen (48 mg) was stirred at room temperature, until a little more than theoretical amount of active oxygen was consumed. Filtration, washing and drying gave crude VIb (5 g), mp 122—123° (decomp.), which was shown by IR to contain a little mount of 2-nitro-3,5-dichlorobenzoic acid (IVb). This mixture was used in the next reaction without further purification.

Caro's Acid Oxidation of 2-Amino-3-chlorotoluene (VII)——i) In Acidic Solution: To a stirred solution of powdered VII (1.4 g) in H_2O (1 ml) and H_2SO_4 (6 ml) was added a Caro's acid solution, prepared from $K_2S_2O_4$ (10 g) and H_2SO_4 in the usual way. Stirring was continued for 2 hr and then K_2CO_3 (2.5 g) was added to this reaction mixture. The mixture was steamdistilled and yellow crystals of 2-chloro-6-methylbenzoquinone (IX), mp 88—89°, were collected by filtration from the coloed distillate. *Anal.* Calcd. for $C_7H_5O_2Cl$: C, 53.73; H, 3.68; Cl, 22.94. Found: C, 53.70; H, 3.22; Cl, 22.64.

ii) In Neutral Solution: A Caro's acid solution, prepared from $K_2S_2O_8$ (100 g), H_2SO_4 (66 ml) and H_2O (300 ml) in the usual way, was neutralized with solid K_2CO_3 to pH 5—6. A mixture of powdered VII (5.5 g) in this neutral Caro's acid solution (50 ml) was stirred in an ice-H_2O bath for 4.5 hr, during this time further 200 ml of the neutral Caro's acid solution was added in four portions. Precipitated crystals were collected by filtration and dissolved in ether. The ether solution was washed with H_2O, dried and evaporated to give 2-nitroso-3-chlorotoluene (X), mp 143—145°. Recrystallization from benzene yielded pale yellow crystals, mp 146—147.5°. *Anal.* Calcd. for C_7H_6ONCl: C, 54.04; H, 3.87; N, 9.00; Cl, 22.79. Found: C, 53.99; H, 3.90; N, 8.87; Cl, 22.92.

2-Nitro-3-chlorobenzoic Acid (IVa)——i) From 2-Nitrosob nzoic Acid (VIa): Powdered VIa (30.2 g) was added in small portions with stirring to fuming HNO_3 (150 g) at 15—20°. After the reaction mixture was stirred for 20 min, the reaction mixture was poured into ice–H_2O (500 ml) and left to stand in a refrigerator for a few hr. Solid was filtered, washed with H_2O and dried to give colorless crystals (28.8 g) mp 237—239°. Recrystallization from aqeuous EtOH yielded colorless crystalline powders, mp 238—239°. *Anal.* Calcd. for $C_7H_4O_4NCl$: C, 40.90; H, 1.96; N, 6.81. Found: C, 41.15; H, 2.25; N, 7.09.

ii) From 2-Nitro-3-chlorotoluene (VIII): To a stirred mixture of VIII (1 g) and $K_2Cr_2O_7$ (4 g) in H_2O (10 ml) was added H_2SO_4 (15 ml) below 20°. Stirring was continued at room temperature for an hr and at 50—55° for 2 hr. The green reaction mixture was poured onto ice–H_2O (100 ml), and precipitated crystals were collected by filtration, washed with H_2O and dried to give colorless crystals (IVa) (1.1 g), mp 236—237°. No mixed melting point depression was observed with a sample from i).

iii) From 2-Nitroso-3-chlorotoluene (X): To a cooled mixture of X (0.6 g) and $K_2Cr_2O_7$ (2.5 g) in H_2O (10 ml) was added dropwise with stirring, H_2SO_4 (15 ml) below 20°. Stirring was continued at room temp. for an hr and at 50—55° for 2 hr. The green reaction solution was poured into ice–H_2O (100 ml). Precipitated crystals were collected by filtration and washed with H_2O to give IVa (0.75 g), mp 234—235°. This was identified with a sapmle from i) by mixed melting point.

17) All melting points are uncorrected. The infrared spectra were recorded on a Hitachi EPI S2.
18) Prepared from $K_2S_2O_8$ and H_2SO_4 according to the procedure of Willey: *Org. Synth., Coll. Vol.* III, p. 334.
19) The amount of Caro's acid was analysed by titrating an aliquot with $Na_2S_2O_3$ after addition of KI.

2-Nitro-3,5-dichlorobenzoic Acid (IVb)——Crude VI b (5 g) was oxidized with fuming HNO_3 (25 g) in the same manner as in the preparation of IVa, to give crude IVb (5 g). Recrystallization from aqueous EtOH yielded colorless crystals, mp 188—189°. *Anal.* Calcd. for $C_7H_3O_4NCl_2$: C, 35.62; H, 1.28; N, 5.49. Found: C, 35.54; H, 1.21; N, 5.73.

2-Phenyl-4-methyl-4-(3-nitro-4-chlorobenzoyl)-2-oxazolin-5-one (XIIIe: R=CH_3)——To a cooled mixture of 2-phenyl-4-methyl-2-oxazolin-5-one (XII) (3.7 g) and dry γ-collidine (5 ml), was added a solution of 3-nitro-4-chlorobenzoyl chloride (XIe) (4 g) in dry ether (25 ml) in an ice bath. After standing for 2—5 hr most of solvents were removed *in vacuo*, and the residue was triturated with dil. HCl and filtered. After washing with aqueous $NaHCO_3$ and H_2O, this solid was recrystallizee from acetone to yield yellow crystals (XIIIe: R=CH_3) (3.1 g), mp 110—112°. Anothe recrystallization raised the melting point to 113—114°. *Anal.* Calcd. for $C_{17}H_{11}O_5N_2Cl$: C, 56.91; H, 3.09; N, 7.81. Found: C, 57.12; H, 3.06; N, 7.92.

2-Phenyl-4-methyl-4-(2-nitro-3-chlorobenzoyl)-2-oxazolin-5-one (XIIIa: R=CH_3)——A mixture of XII (4.4 g) and dry γ-collidine (8 ml) was treated with a solution of 2-nitro-3-chlorobenzoyl chloride (XIa) (6.4 g) in abs. ether (30 ml) in the same manner as in the preparation of XIIIe (R=CH_3) to give yellow crystals(XIIIa) (3 g), mp 147—148°, after recrystallization from acetone. *Anal.* Calcd. for $C_{17}H_4O_5N_2Cl$: C, 56.90; H, 3.07; N, 7.81; Cl, 9.90. Found: C, 56.64; H, 3.14; N, 7.67; Cl, 9.87.

Attempted Condensation of *o*-Nitrobenzoyl Chloride (XId) with Di-*tert*-butyl Acetamidomalonate——A mixture of di-*tert*-butyl acetamidomalonate (4 g) and 50% NaH (0.82 g) in dry benzene (30 ml) was refluxed with stirring for 4 hr and then cooled in an ice bath. A solution of XId (3.47 g) in dry benzene (15 ml) was added to this stirred mixture and stirring was continued for an hr. The reaction mixture was poured onto ice–H_2O, and the organic layer was separated. Aqueous layer was extracted with benzene. The combined benzene extracts were washed with dil. aqueous NaOH and H_2O, dried and evaporated to give a yellow solid. Recrystallization from petroleumbenzine yielded *o*-nitrobenzoic anhydride, mp 131°. Di-*tert*-butyl acetamidomalonate was recovered from the mother liquor. Substitution of NaH by γ-collidine or $(EtO)_2Mg$ in this reaction gave the same result.

Ethyl 2-Acetamido-2-(2-nitrobenzoyl)acetoacetate (XVId: R=CH_3, R′=Et)——A suspension of ethyl acetamidoacetoacetate (7.48 g) and 50% NaH (2.88 g) in dry benzene (20 ml) was stirred at room temperature for 4 hr and at 40° for an hr. After cooling, a solution of *o*-nitrobenzoyl chloride (XId) (7.44 g) in dry benzene (6 ml) was added to this stirred mixture over a period of an hr. Stirring was continued at room temperature for 2 hr and at 40° for 3 hr, and then the reaction mixture was allowed to stand overnight. The mixture was poured onto ice–H_2O, and the organic layer was separated and aqueous layer was extracted with benzene. Ccmbined benzene extracts were washed with H_2O, dried and evaporated to give a soild (8.5 g). Recrystallization from benzene yielded yellow crystals (XVId: R=CH_3, R′=Et) (1.2 g), mp 152—153°. *Anal.* Calcd. for $C_{15}H_{16}O_7N_2$: C, 53.57; H, 4.80; N, 8.33. Found: C, 52.93; H, 4.81; N, 8.44.

Nitro-chloroacetophenones (XIX)——Nitro-chlorobenzoyl chlorides (XI) were prepared by treating nitro-chlorobenzoic acids (IV) with a little excess of PCl_5 at 90—100°, followed by removing $POCl_3$ under vacuum.

CCl_4 (0.5 ml) was added to a suspension of Mg (21.4 g) in abs. EtOH (20 ml) and a vigorous reaction occured after a few minutes. After the reaction subsided, arolution of diethyl malonate (142 g) and abs. ether was added dropwiss, and the reaction mixture was refluxed with stirring for 3 hr. 20% H_2SO_4 was EtOH (80 ml) in abs ether (400 ml) was added dropwise to the stirred suspension at such a rate as gentle refluxing was maintained. After the addition, stirring and refluxing were continued in a warm water bath, until Mg dissolved completely. After cooling, nitro-chlorobenzoyl chlorides (XI) (176 g) dissolved in abs. ether was added dropwise, and the reaction mixture was refluxed with stirring for 3 hr. 10% H_2SO_4 was added to the cooled reaction mixture, and ether layer was separated and aqueous layer was etracted with ether. Combined ether extracts were washed with H_2O, dried and evaporated to give diethyl nitrochlorobenzoyl malonate (XVIII) almost quantitatively.

A mixture of above XVIII in AcOH (240 ml) and 25% H_2SO_4 (200 ml) was refluxed for 6—7 hr. The reaction mixture was made alkaline with aqueous NaOH and extracted with ether. Ether extracts were

Table I. Nitro-chloroacetophenones (XIX)

NO_2	Cl	No.	Crystd. from	mp (°C)	Yield (%)	Analysis					
						Calcd.			Found		
						C	H	N	C	H	N
2	3	a	EtOH	95—96	96	48.12	3.01	7.02	47.93	3.20	6.79
3	4	e	EtOH	98—100	94	48.12	3.01	7.02	47.98	3.18	7.06
3	6	f	EtOH	62	93	48.12	3.01	7.02	47.96	3.22	7.02
2	4	g	EtOH	64	98	48.12	3.01	7.02	48.07	3.25	6.98
2	5	h	EtOH	62	97	48.12	3.01	7.02	48.11	3.36	6.91

washed with H_2O, dried and evaporated to dryness. Recrystallization of the residue yielded nitro-chloroacetophenones (XIX), which are listed in Table I.

Nitro-chloroacetophenone Oximes (XX: R=H)——To a cooled solution of KOH (175 g) in H_2O (200 ml) was added slowly NH_2OH–HCl (200 g) dissolved in H_2O (250 ml) followed by 99% EtOH (2.5—3 liter), and precipitated KCl was filtered off. Nitro-chloroacetophenones (XIX) (98 g) were added to a half part of the filtrate, and the suspension was refluxed for 20 hr, during which the remainder of the filtrate was added in several portions. After most of EtOH was removed *in vacuo*, H_2O was added and the mixture was extracted with $CHCl_3$. The $CHCl_3$ extracts were washed, dried and evaporated to dryness. Recrystallization of the residue yielded oximes (XX: R=H), which were listed in Table II.

Table II. Nitro-chloroacetophenone Oximes (XX: R=H)

NO_2	Cl	No.	Crystd. from	mp (°C)	Yield (%)	Analysis					
						Calcd.			Found		
						C	H	N	C	H	N
2	3	a	50%EtOH	164—165	93.5	44.76	3.26	13.05	44.81	3.42	12.91
3	4	e	EtOH	164	73	44.76	3.26	13.05	44.99	3.55	12.36
3	6	f	C_6H_6-ligroin	158—162	63	44.76	3.26	13.05	44.81	3.43	13.14
2	4	g	C_6H_6-ligroin	155—156	63	44.76	3.26	13.05	44.95	3.51	13.05
2	5	h	C_6H_6-ligroin	150—151	58	44.76	3.26	13.05	44.82	3.48	13.21

Nitro-chloroacetophenone Oxime Tosylates (XX: R=Tosyl)——A solution of nitro-chloroacetophenone oximes (XXa: R=H) (98 g) in abs. EtOH (1400 ml) was treated with NaOEt solution, prepared from Na (11.7 g) and abs. EtOH (300 ml). Then a solution of *p*-toluenesulfonylchloride (94.5 g) in abs. EtOH (200 ml) was added dropwise to the stirred reaction mixture under ice-cooling, and stirring was continued for several hr. Precipitated crystals were collected by filtration and recrystallized to give the tosylates (XX: R=tosyl), which are listed in Table III.

Table III. Nitro-chloroacetophenone-oxime Tosylates (XX: R=tosyl)

NO_2	Cl	No.	Crystd. from	mp (°C)	Yield (%)	Analysis					
						Calcd.			Found		
						C	H	N	C	H	N
2	3	a	AcOEt petr. ether	147—148	87	48.85	3.55	7.60	48.76	3.64	7.41
2	H	d	AcOEt-ligroin	98—104	60	44.35	4.19	12.92	44.12	4.38	12.68
3	4	e	AcOEt-ligroin	135—137	58	48.85	3.55	7.60	48.79	3.67	7.53
3	6	f	AcOEt	157—158	58	48.85	3.55	7.60	48.59	3.66	7.32
2	4	g	AcOEt-ligroin	118—119	62	48.85	3.55	7.60	48.63	3.68	7.69
2	5	h	AcOEt-ligroin	114—115	80	48.85	3.55	7.60	48.98	3.69	7.69

Table IV. Nitro-chloro-2-amino Acetophenone Hydrochlorides (XV: R=H)

NO_2	Cl	No.	Crystd. from	mp (°C)	Yield (%)	Analysis					
						Calcd.			Found		
						C	H	N	C	H	N
2	3	a	EtOH	213 (decomp.)	76	38.27	3.21	11.16	38.49	3.39	11.38
2	H	d	EtOH	202—5 (decomp.)	69	44.35	4.19	12.93	44.02	4.42	12.80
3	4	e	EtOH	201—2 (decomp.)	88	38.27	3.21	11.16	38.38	3.36	11.27
3	6	f	EtOH	224—5 (decomp.)	77	38.27	3.21	11.16	38.39	3.34	11.09
2	4	g	EtOH	191 (decomp.)	83	38.27	3.21	11.16	38.41	3.37	11.35
2	5	h	10%HCl	187—8 (decomp.)	54	38.27	3.21	11.16	38.01	3.43	11.02

Nitro-chloro-2-aminoacetophenones (XV: R=H)——By Neber Rearrangement: To a stirred suspension of nitro-chloroacetophenone oxime tosylates (XX: R=tosyl) (98 g) in abs. EtOH (800 ml) was added dropwise a solution of NaOEt, prepared from Na (8.8 g) and abs. EtOH (300 ml). Stirring was continued until the suspension turned to a solution once and again new crystals precipitated. The reaction mixture was cooled and precipitated crystals were filtered off. The filtrate was diluted with ether and extracted with 10% HCl. HCl extracts were evaporated to dryness and the residue was recrystallized from EtOH to yield nitro-chloro-2-aminoacetophenone hydro chloride (XV·HCl: R=H), which are listed in Table IV.

***o*-Nitro-2-aminoacetophenone Hydrochloride (XVd·HCl: R=H)**——By Schmidt Reaction: To a stirred solution of 1-(2-nitrophenyl)-1,3-butanedione (XXIIId: R=H) (3 g) in $CHCl_3$ (3 ml) was added H_2SO_4 (100 ml), followed by dropwise addition of HN_3 (0.64 g) dissolved in $CHCl_3$ (7.5 ml), at room temp. Stirring was continued until the evolution of N_2 cesaed. The reaction mixture was poured onto ice–H_2O and extracted with AcOEt. The AcOEt extracts were washed with H_2O, dried and evaporated to give a colorless solid (XXIVd) (2.4 g). Recrystallization from EtOH yielded colorless needles, mp 128 —129°. *Anal.* Calcd. for $C_{10}H_{10}O_4N_2$·HCl: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.38; H, 4.62; N, 12.04. A suspension of XXIVd (0.02 g) in 10% HCl (10 ml) was heated at 95° for an hr. A resulting solution was evaporated to dryness. Recrystallization of the residue yielded colorless crystals (XVd·HCl: R=H), mp 202—205° (decomp). No mixed melting point depression was observed with a sample from the above Neber rearrangement.

2′-Nitro-3′-chloro-2-aminoacetophenone Hydrochloride (XVa·HCl: R=H)——By Schmidt reaction: To a stirred solution of 1-(2-nitro-3-chlorophenyl)-1,3-butanedione (XXIIIa: R=H) (1.0 g) in $CHCl_3$ (3 ml) was added NH_3 (0.215 g) dissolved in $CHCl_3$ (2.5 ml) followed by H_2SO_4 (2.5 ml). After a small amount of NaN_3 was added, stirring was continued for an hr. The reaction mixture was poured onto ice–H_2O, and $CHCl_3$ layer was separated and aqueous layer was extracted with $CHCl_3$. Combined $CHCl_3$ solution were washed, dried and evaporated to dryness. Recrystallization from EtOH yielded colorless crystals (XXIVa) (0.8 g), mp 158—159°. *Anal.* Calcd. for $C_{10}H_9O_2N_4Cl$·HCl: C, 46.80; H, 3.53; N, 10.92. Found: C, 46.91; H, 3.58; N, 10.91. XXIVa was hydrolyzed with 10% HCl in the similar manner as in the hydrolysis of XXIVd, to give 2′-nitro-3′-chloro-2-aminoacetophenone hydrochloride (XVa: R=H), mp 199° (decomp.). No mixed melting point depression was observed with a sample from Neber rearrangement.

Ethyl 2-(2-Nitro-3-chlorobenzoyl)acetoacetate (XXIa)——CCl_4 (0.5 g) was added to a mixture of Mg (2.64 g) and abs. EtOH (2.64 g). After vigorous reaction subsided, a solution of ethyl acetoacetate (16.3 g) and abs. EtOH (6.96 ml) in abs. ether (51.7 ml) was added dropwise to the stirred reaction mixture over a period of an hr. Immediately after the addition was completed, CCl_4 (0.5 ml) was added and stirring and refluxing were continued until Mg dissolved completely. A solution of 2-nitro-3-chlorobenzoyl chloride (XIa), prepared from IVa (20 g) and PCl_5 (22.7 g), in abs. ether (90 ml) was added dropwise to the cooled reaction mixture, and was stirred under reflux for 4 hr. After cooling, 10% H_2SO_4 (220 ml) was added, and ether layer was separated and aqueous layer was extracted with ether. Acidic substances were extracted from the combined ether solution, acidified with HCl and extracted with ether. The extracts were washed, dried and evaporated to give pale brown solids (XXIa) (30.5 g), mp 68°. Recrystallization from EtOH yielded colorless crystals, mp 72°. *Anal.* Calcd. for $C_{13}H_{12}O_6NCl$: C, 49.77; H, 3.86; N, 4.47. Found: C, 49.64; H, 4.11; N, 4.45.

1-(2-Nitro-3-chlorophenyl)-1,3-butanedione (XXIIIa: R=H)——i) From XXIa: A solution of XXIa (3 g), dry HCl (0.2 g) in AcOH (60 ml) was heated at 115° for 17 hr. After most of AcOH was removed *in vacuo*, H_2O was added and the mixture was extracted with ether. Acidic substances were extracted with dil. aqueous NaOH from the ether solution, acidified with HCl and extracted with ether. Ether extracts were washed several times with aqueous $NaHCO_3$ and H_2O, dried and evaporated to give pale brown solids (XXIIIa: R=H) (1.8 g), mp 97—99°. Recrystallization from EtOH yielded colorless crystals, mp 99.5°. *Anal.* Calcd. for $C_{10}H_8O_4NCl$: C, 49.70; H, 3.34; N, 5.80. Found: C, 49.66; H, 3.26; N, 5.97.

1-(2-Nitro-4-chlorophenyl)-1,3-butanedione (XXIIIg: R=H)——*via* XXIg: Similar condensation of 2-nitro-4-chlorobenzoyl chloride (XIg), prepared from IVg (40 g), with ethoxymagnesium salt of ethyl acetoacetate gave ethyl 2-(2-nitro-4-chlorobenzoyl)acetoacetate (XXIg) (61.7 g). Then XXIg was refluxed in a mixture of AcOH and dry HCl to yield colorless crystals (XXIIIg: R=H), mp 79—80° after recrystallization from EtOH. *Anal.* Calcd. for $C_{10}H_8O_4NCl$: C, 49.71; H, 3.34; N, 5.84; Cl, 14.67. Found: C, 49.83; H, 3.46; N, 5.91; Cl, 14.87.

1-(2-Chloro-4-nitrobenzoyl)-1,3-butanedione (XXIIIi: R=H)——via XXI: Similarly, from XIi (50 g) was obtained ethyl 2-(2-chloro-4-nitrobenzoyl)acetoacetate (XXIi) (78.2 g). XXIi (78.2 g) was refluxed in a mixture of AcOH and dry HCl to give 1-(2-chloro-4-nitrobenzoyl)1,3-butanedione (XIIIi: R=H), 79—80°. *Anal.* Calcd. for $C_{10}H_8O_4NCl$: C, 49.71; H, 3.34; N, 5.84; Cl, 14.67. Found: C, 49.41; H, 3.35; mp N, 5.92; Cl, 14.48.

3-(2-Nitro-3-chlorobenzoyl)-2,4-pentanedione (XXIIa)——A solution of ethoxymagnesium-acetylacetone was prepared from Mg (0.85 g), abs. EtOH (3.07 ml), CCl_4 (4 drops) and abs. ether (16.5 ml) in the usual manner. To this stirred solution was added dropwise a solution of 2-nitro-3-chlorobenzoyl chorlide (XIa) (7 g) in abs. ether (50 ml) at 5—10°, and stirring was continued under reflux for 5 hr. After coloing, 10% H_2SO_4 (125 ml) was added to the reaction mixture and the ether layer was separated and aqueous layer was

extracted with ether. The ether extracts were worked up in the similar manner as in the preparation of XXIa, to give pale brown solids (XXIIa) (10.7 g).

1-(2-Nitro-3-chlorophenyl)-1,3-butanedione (XXIIIa: R=H)——ii) *via* XXIIa: A suspension of XXIIa (1.0 g) in 1/10 N HCl (20 ml) was refluxed for 4 hr. After cooling the reaction mixture was extracted with ether. The extracts were washed with aqueous $NaHCO_3$ and H_2O, dried and evaporated to give colorless crystals (XXIIIa: R=H) (0.80 g), mp 97—99°. No melting point depression was observed with a sample of XXIIIa obtained from XXIa.

1-(2-Nitro-5-chlorophenyl)-1,3-butanedione (XXIIIh: R=H)——Similar treatment of XIh, prepared from 2-nitro-5-chlorobenzoic acid (IVh) (17.5 g), with ethoxymagnesium-acetylacetone in the usual way gave 3-(2-nitro-5-chlorobenzoyl)-1,3-pentanedione (XXIIh) (20 g), mp 65—75°. XXIIh (20 g) was refluxed in N/10 HCl to give XXIIIh: (R=H) (11 g), mp 89—91°. *Anal.* Calcd. for $C_{10}H_8O_4NCl$: C, 49.71; H, 3.34; N, 5.84; Cl, 14.67. Found: C, 49.89; H, 3.53; N, 5.59; Cl, 14.69.

1-(2-Nitro-3-chlorophenyl)-1,3-butanedione (XXIIIa: R=H)——iii) By Acetylation: BF_3-etherate (600 g) was added dropwise to a stirred solution of XIXa (150 g) in Ac_2O (500 ml) in an ice bath, and stirring was continued at 40° for 15 hr. After cooling, $AcONa \cdot 3H_2O$ (500 g) and H_2O (2.5 liter) was added to the reaction mixture, ether was distilled off and the residual solution was refluxed for 20 min. The cooled reaction mixture was extracted with ether. Acidic substances was extracted from the ether solution, acidified with HCl and extracted with ether. Ether extracts were washed with H_2O, dried and evaporated to give colorless crystals (XXIIIa: R=H) (13.8 g), mp 97—98°. No mixed melting point depression was observed with a sample from i).

1-(2-Nitro-3-chlorophenly)-1,3-pentanedione (XXIIIa: R=CH_3)——Gaseous BF_3 was saturated in a mixture of XIXa (20 g) and $(EtCO)_2O$ (25 g) in dichloroethane (40 ml).

After the mixture was stirred at room temperature for an hr, a solution of $AcONa \cdot 3H_2O$ (33 g) in H_2O (165 ml) was added and stirring was continued under reflux for 25 min. This mixture was worked up in the similar manner as in the preparation of XIIIa (R=H), to give colorless crystals (XXIIIa: R=CH_3) (4.7 g), mp 97—98°. *Anal.* Calcd. for $C_{11}H_{10}O_4NCl$: C, 51.68; H, 3.94; N, 5.48; Cl, 13.87. Found: C, 51.91; H, 3.94; N, 5.42; Cl, 13.60.