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Total Synthesis of Pyrrolnitrin. VIII.[1] A New Method of Pyrrole Ringclosure using Aminoacetal

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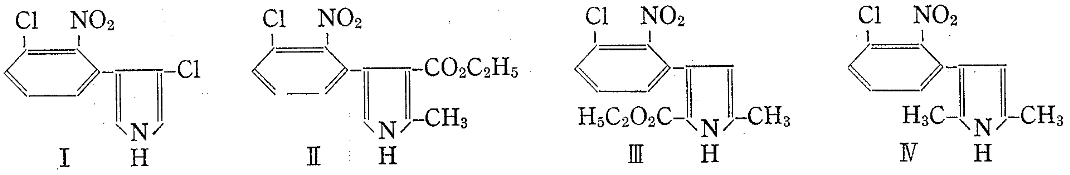
A new method of pyrrole ringclosure using an aminoacetal (V) was investigated. Condensation of 2-nitro-3-chlorophenylpyruvic acid (VIII) and 2-nitro-3-chlorophenylacetone (XVI) with V afforded 3-(2-nitro-3-chlorophenyl)pyrrole (XII) and 1-acetyl-2-methyl-3-(2-nitro-3-chlorophenyl)pyrrole (XX) respectively in an AcOH-AcONa·3H_2O mixture. Cyclization of an enamine (XIV), prepared from ethyl 2-nitro-3-chlorophenylpyruvate (XIII) and V, under anhydrous condition afforded ethyl 3-(2-nitro-3-chlorophenyl)-2-pyrrolecarboxylate (XV).

Hantzsch reaction was applied to VIII, which gave lastly XII.

The reaction mechanism of these reactions was proposed.

In the course of synthesizing pyrrolnitrin (I),[3] the extensive studies were carried out on the examination of several methods of pyrrole rigclosure; synthesis of β-arylpyrroles, II, III and IV, intermediates to I, has been investigated respectively by Knorr reaction in Part I,[4] the condensation of 1-aryl-1,3-butanediones with diethyl aminomalonate in Part III[5] and Paal Knorr reaction in Part VII[1] of this series.



I II III IV

Chart 1

In this paper, we wish to report on a new method of pyrrole ringclosure using an aminoacetal, and the extension of Hantzsch reaction.

All of the compounds synthesized by these new reactions in this paper are shown to play an important role in the synthesis of pyrrolnitrin (I), which will be reported in Parts IX[6] and X.[7]

Reaction of the Schiff base (IV), prepared from benzaldehyde and an aminoacetal (V), in sulfuric acid to give isoquinoline (VII) has been known as Pomerantz Fritsch reaction[8] (a).

It was anticipated that application of this reaction to 2-nitro-3-chlorophenylpyruvic acid (VIII) would afford the pyrrole ring, because α-position of the enamine intermediate (IX) would be so activated by an *o*-nitro group in a benzene ring that it might undergo the similar condensation.

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[1] Part VII: S. Umio, K. Kariyone, K. Tanaka and I. Ueda, *Chem. Pharm. Bull.* (Tokyo), **17**, 605 (1969).
[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] Part I: *Chem. Pharm. Bull.* (Tokyo), **17**, **559** (**1969**).
[5] Part III: *Chem. Pharm. Bull.* (Tokyo), **17**, **576** (**1969**).
[6] Part IX: *Chem. Pharm. Bull.* (Tokyo), **17**, **616** (**1969**).
[7] Part X: *Chem. Pharm. Bull.* (Tokyo), **17**, **622** (**1969**).

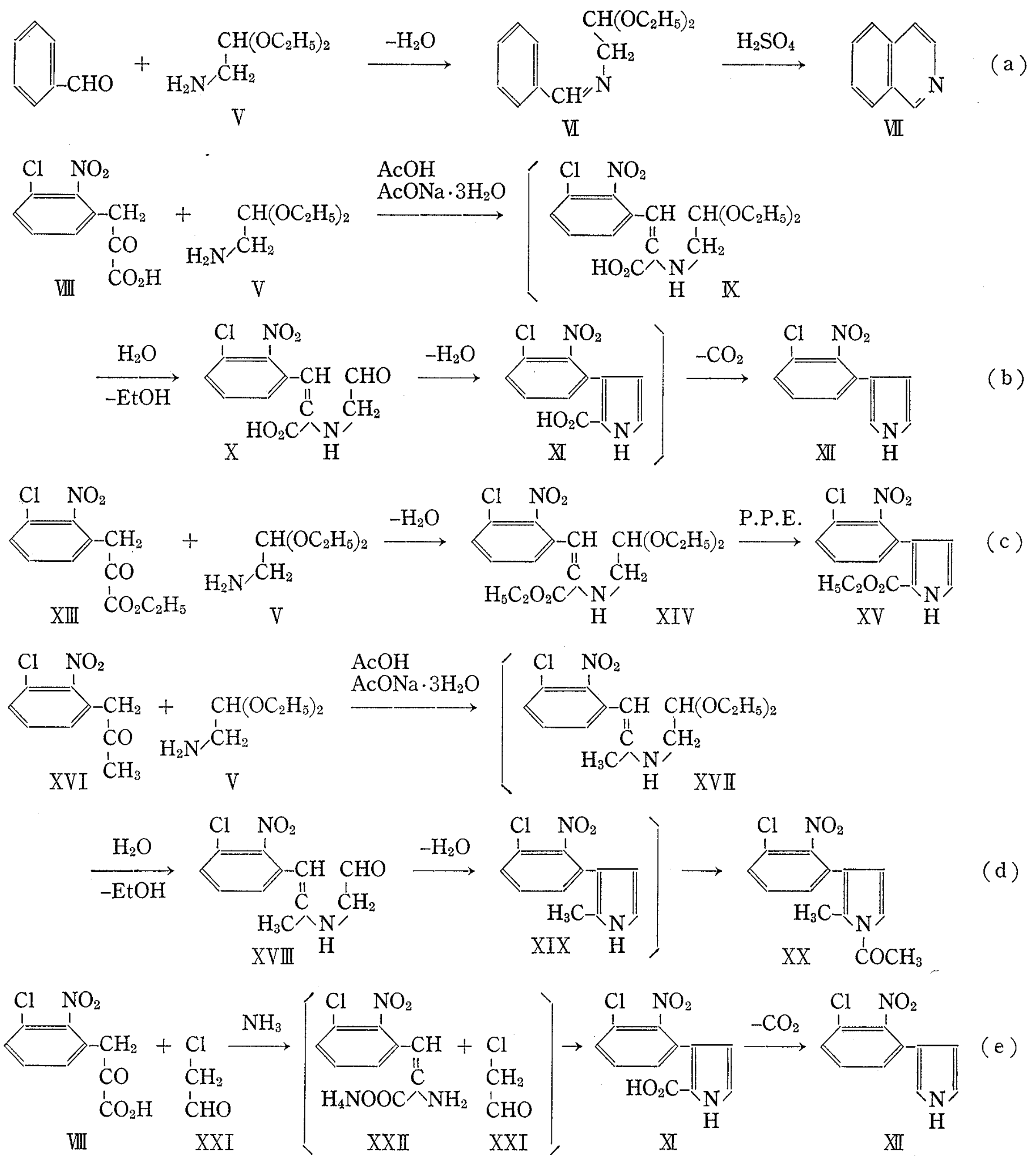

Chart 2

Two kinds of the mechanism were considered to be possible for this reaction: the mechanism by elimination of alcohol from an intermediate (IX) under anhydrous reaction condition, and that by dehydration of an intermediate (X) under the aqueous reaction condition.

First, examination was made to cyclize the enamine (IX), prepared from VIII and V in boiling xylene, under anhydrous reaction conditions using sodium ethoxide, sulfuric acid and polyphosphoric acid ethyl ester, but the yield was not so good.

So, we next tried the reaction under aqueous condition. 2-Nitro-3-chlorophenylpyruvic acid (VIII), when treated with an aminoacetal (V) in boiling acetic acid containing sodium acetate hydrate, gave yellow crystals of mp 121—122°.

This compound seems to be 3-(2-nitro-3-chlorophenyl)pyrrole (XII) from its elemental analysis, infrared (IR), nuclear magnetic resonance (NMR) and Ehrlich reaction, which showed a deep violet color similarly to that of pyrrolnitrin (I).

Moreover, the structure of this compound was ascertained by converting to the known 2,5-dimethyl-3-(2-nitro-3-chlorophenyl)pyrrole, as described in the part VII.[1]

It is to be noted that this reaction proceeds in an acidic aqueous solution, in which the acetal group is generally known to be unstable, and that a free aminoacetaldehyde is so labile that self-condensation might occur easily.

When this reaction was carried out at lower temperature, 3-(2-nitro-3-chlorophenyl)-2-pyrrolecarboxylic acid (XI) was isolated as its methyl ester.

It is obvious from these observations that this pyrrole ringclosure proceeds by the following mechanism: 2-nitro-3-chlorophenylpyruvic acid (VIII) should condense with the aminoacetal (V) to give an enamine intermediate (IX) under this reaction condition. Then the acetal group of IX should be hydrolysed in the presence of water to the formyl intermediate (X), which was cyclized to yield 3-(2-nitro-3-chlorophenyl)-2-pyrrolecarboxylic acid (XI). Finally, XI should be decarboxylated to 3-(2-nitro-3-chlorophenyl)pyrrole (XII) in the presence of the strongly acidic starting material (VIII) in boiling acetic acid.

Treatment of the enamine (IX), prepared beforehand from VIII and V under the same reaction condition gave a similar result.

The above-mentioned new method of pyrrole ringclosure made this reaction extended to ethyl 2-nitro-3-chlorophenylpyruvate (XIII). When XIII was treated in boiling acetic acid containing sodium acetate hydrate similarly as in the reaction of VIII, only the same pyrrole (XII) was isolated, perhaps because of that the ethoxycarbonyl group was hydrolyzed before condensation.

Then cyclization of the enamine (XIV), prepared beforehand from XIII and V, was investigated in several anhydrous reaction conditions. After some examinations with other reagents, it was found that ethyl 3-(2-nitro-3-chlorophenyl)-2-pyrrolecarboxylate (XV) could be obtained in good yield by using polyphosphoric acid ethyl ester in boiling chloroform.

The structure of XV was ascertained by elemental analysis, IR, NMR and conversion to a known ethyl 3-(2-nitro-3-chlorophenyl)-5-methyl-2-pyrrolecarboxylate (III), which will be reported in Part IX[6] of this series.

It is supposed that this reaction should proceed directly by elimination of ethanol from an acetal intermediate (XIV) as shown in (c), being clearly different from the mechanism (b).

Next, further extension of this reaction to 2-chloro-3-nitrophenylacetone (XVI) was tried. The color reaction of VIII and XIII with an ethanolic ferric chloride solution was so strong as to show the reactivity of these compounds, which was not observed in the case of 2-nitro-3-chlorophenylacetone (XVI). However, formation of a sodium salt in an anhydrous solution was supposed to show enough reactivity of this compound.

Condensation of an enamine (XVII), prepared from XVI and V, was examined using polyphosphoric acid ethyl ester in boiling chloroform as in (c), and a large quantity of tarry materials were isolated from this reaction product, although positive Ehrlich reaction showed a slight formation of a pyrrole compound.

However, treatment of 2-nitro-3-chlorophenylacetone (XVI) with an aminoacetal (V) in boiling acetic acid containing sodium acetate hydrate produced colorless crystals of mp 85.5—86.5°. Considering from the presence of a carbonyl and absence of an imino absorption of the pyrrole ring in the IR, the positive Ehrlich reaction, the elemental analysis and the NMR data, this compound was assumed to be 1-acetyl-2-methyl-3-(2-nitro-3-chlorophenyl)-pyrrole (XX).

This reaction was considered to proceed through the following mechanism, judged from the data that N-acetylation was not observed in reaction (b), and that N-acetylation occurred in bis-Mannich reaction of the related pyrrole compound under similar reaction condition.[1] Namely, the formyl intermediate (XVIII) should be formed similarly as in reaction (b), and

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8) E. Schlitter and J. Muller, *Helv. Chim. Acta*, **31**, 914 (1948)

then XVIII should be cyclized to give 2-methyl-3-(2-nitro-3-chlorophenyl)pyrrole (XIX). And finally, XIX should be acetylated by acetic acid in the presence of sodium acetate under this reaction condition to give XX.

Difference of N-acetylation between (b) and (d) can be explained by the electron-releasing character of the methyl group.

The success in establishing the new method of pyrrole ringclosure made several synthetic routes of pyrrolnitrin (I) possible.

Furthermore, after searching for other synthetic methods of β-arylpyrroles, extension of Hantzsch reaction⁹⁾ was found also to give 3-(2-nitro-3-chlorophenyl)pyrrole (XII); namely, 2-nitro-3-chlorophenylpyruvic acid (VIII), when treated with chloroacetaldehyde in aqueous ammonia, afforded a product with strong Ehrlich reaction, indicating the formation of a pyrrole compound (XI).

In order to isolate XI from the accompanying starting material (VIII), the crude reaction product was refluxed in acetic acid to effect selective decarboxylation of XI to XII (e).

3-(2-Nitro-3-chlorophenyl)pyrrole (XII), thus obtained, was identical with a sample from (b).

Experimental10)

Reaction of 2-Nitro-3-chlorophenylpyruvic Acid11) (VIII) with Aminoacetal (V)——i) At Higher Temperature: A mixture of VIII (1.55 g), aminoacetal (V) (1.5 g) and AcONa·3H_2O (20 g) in AcOH (32 ml) was stirred under gentle refluxing for 12 hr. After most of AcOH was removed *in vacuo* from the dark reaction mixture, H_2O was added and the mixture was extracted with ether. The ether extracts were washed with H_2O, dil. aqueous NaOH and H_2O, dried and evaporated to give a brown solid (0.4 g). This was dissolved in benzene and passed through a column of silicagel. Elution with benzene followed by evaporation of the solvent gave yellow crystals (0.3 g), mp 115—118°, which were recrystallized from benzene-*n*-hexane to yield 3-(2-nitro-3-chlorophenyl)pyrrole (XII) as yellow crystals (0.25 g), mp 121—122°. This showed a positive Ehrlich test. *Anal.* Calcd. for $C_{10}H_7O_2N_2Cl$: C, 53.94; H, 3.17; N, 12.63; Cl, 15.92. Found: C, 54.08; H, 3.31; N, 12.45; Cl, 16.16. IR (nujol) cm^{-1}: 3440 (NH), 1530, 1378 (NO_2).

ii) At Lower Temperature: A mixture of VIII (3 g), V (4 g) and AcONa·3H_2O (39 g) in AcOH (62 ml) was stirred at 70° (bath temp.) for 22 hr. After removal of AcOH *in vacuo* and addition of H_2O, the mixture was extracted with ether. Acidic compounds were extracted from the ether solution with dil. aqueous NaOH, acidified with HCl and extracted with ether. The ether extracts were washed with H_2O, dried and evaporated to give a brown solid (1 g). Trituration of this solid with C_6H_6, filtrating off the insoluble starting material (VIII) and evaporation of the filtrate left a brown solid (0.45 g), which showed a positive Ehrlich test. This was treated with etherial solution of CH_2N_2 and, after standing overnight, the resulting solution was evaporated to dryness. This was dissolved in benzene and chromatographed on a silica-gel column. Elution with C_6H_6 and evaporation of the solvent afforded a little amount of enol-ether of methyl 2-nitro-3-chlorophenylpyruvate accompanied with colorless crystals (0.2 g), mp 178—180°, of methyl 3-(2-nitro-3-chlorophenyl)-2-pyrrolecarboxylate (methyl ester of XI). Recrystallization of the latter from CCl_4 yielded colorless crystals (0.05 g), mp 185—186°. *Anal.* Calcd. for $C_{12}H_9O_4NCl$: C, 51.34; H, 3.24; N, 9.98; Cl, 12.63. Found: C, 51.63; H, 3.48; N, 9.88; Cl, 12.77. IR (nujol) cm^{-1}: 3300 (NH), 1675 ($COOCH_3$), 1533 1370 (NO_2).

Ethyl 2-Nitro-3-chlorophenylpyruvate (XIII)——A solution of 2-nitro-3-chlorophenylpyruvic acid (VIII) (20 g) and conc. H_2SO_4 (2 ml) in abs. EtOH (400 ml) was warmed at 50° (bath temp.)for 9 hr. Most EtOH was removed *in vacuo*, H_2O was added and the mixture was extracted with AcOEt. The AcOEt extracts were washed several times with aqueous $NaHCO_3$ and H_2O, dried and evaporated to give yellow crystals (20.2 g). Recrystallization from CCl_4-*n*-hexane yielded yellow crystals (XIII) (18.4 g), mp 105—107°. Further recrystallization provided pale yellow crystals, mp 109—110°. *Anal.* Calcd. for $C_{11}H_{10}O_5NCl$: C, 48.63; H, 3.71; N, 5.16; Cl, 13.05. Found: C, 48.90; H, 3.74; N, 5.52; Cl, 13.34.

Ethyl 3-(2-Nitro-3-chlorophenyl)-2-pyrrolecarboxylate (XV)——A solution of XIII (10 g) and aminoacetal (V) (4.9 g) in toluene (200 ml) was heated under reflux for 7 hr. During this reaction water formed

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9) A. Hantzsch, *Chem. Ber.*, 23, 1474 (1890).

10) All melting points are uncorrected. The infrared spectra were recorded on a Hitachi EPI S2. The nuclear magnetic resonance spectra were measured with a Varian A-60 spectrometer using tetramethylsilane as an internal standard.

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

was sometimes distilled off as azeotropic mixture. Removal of toluene *in vacuo* left an oily product (crude XIV) (14.2 g), which was used for the following reaction without further purification. The crude enamine (XIV) (14.2 g) and P.P.E. (286 g) was dissolved in dry $CHCl_3$ (715 ml), and the solution was heated under reflux in a stream of N_2 for 10 hr. $CHCl_3$ was removed *in vacuo*, H_2O was added and the mixture was extracted with ether. The ether extracts were washed several times with dil. aqueous NaOH and H_2O, dried and evaporated to give a yellow solid (5.55 g). Recrystallization from benzene yielded pale yellow crystals (XV) (3.0 g), mp 190—191°. Further recrystallization raised the melting point to 191.5—192.5°. *Anal.* Calcd. for $C_{13}H_{11}O_4N_2Cl$: C, 52.98; H, 3.77; N, 9.51; Cl, 12.03. Found: C, 53.21; H, 4.07; N, 9.61; Cl, 12.11. IR (nujol) cm^{-1}: 3310 (NH), 1672 ($COOC_2H_5$), 1531, 1370 (NO_2). NMR ($CDCl_3$) ppm: 1.13 (3H, triplet, $COOCH_2C\underline{H}_3$), 4.20 (2H, quartet, $COOC\underline{H}_2CH_3$), 6.33 (1H, triplet, H_4 in pyrrole), 6.98 (1H, triplet, H_5 in pyrrole), 7.35—7.7 (3H, multiplet, phenyl).

1-Acetyl-2-methyl-3-(2-nitro-3-chlorophenyl)pyrrole (XX)——To a stirred, boiling mixture of 2-nitro-3-chlorophenylacetone (XVI) (2 g) and $AcONa \cdot 3H_2O$ (26.3 g) in AcOH (40 ml), was added dropwise a solution of V (2.66 g) in AcOH (10 ml) over a period of 1.5 hr. After stirring and refluxing were continued for 3 hr, most of AcOH was removed *in vacuo*, H_2O was added and the mixture was extracted with ether. The ether extracts were washed with dil. HCl, dil. aqueous NaOH and H_2O, dried and evaporated to give a pale brown solid (1.4 g). This was dissolved in C_6H_6 and passed through a column of silicagel. Elution with C_6H_6 gave pale pinky crystals (XX) (0.2 g), mp 85—86°, and further elution gave the starting material (XV). Recrystallization of crude XX from *n*-hexane yielded colorless crystals, mp 85.5—86.5°, which gave a positive Ehrlich test. *Anal.* Calcd. for $C_{13}H_{11}O_3N_2Cl$: C, 56.03; H, 3.98; N, 10.05; Cl, 12.72. Found: C, 56.13; H, 4.13; N, 9.99; Cl, 12.91. IR (nujol) cm^{-1}: 1742 ($COCH_3$) 1542, 1372 (NO_2). NMR ($CDCl_3$) ppm: 2.44 (3H, singlet, C–CH_3), 2.59 (3H, singlet, N–$COCH_3$), 6.26 (1H, doublet, H_4 in pyrrole), 7.18 (1H, doublet, H_5 in pyrrole) 7.3—7.7 (3H, multiplet, phenyl).

Reaction of 2-Nitro-3-chlorophenylpyruvic Acid (VIII) and Chloraldehyde (XXI)——Chloraldehyde (XXI) (2.28 g) was added dropwise to a stirred solution of VIII (1.5 g) in 20% NH_3 (50 ml) in an ice–H_2O bath over a period of 30 min. Stirring was continued in an ice–H_2O bath for 22 hr and then at room temperature for 4½ hr. The reaction mixture was acidified with HCl and extracted with ether. The ether extracts were washed with H_2O, dried and evaporated to give a brown solid (1.4 g), which was composed of the starting material (VIII) and 3-(2-nitro-3-chlorophenyl)-2-pyrrolecarboxylic acid (XI). The mixture was heated in AcOH (40 ml) with stirring for 2 hr to be decarboxylated to XI selectively. After cooling, the reaction mixture was diluted with H_2O and extracted with ether. The ether extracts were washed with dil.aqueous NaOH and H_2O, dried and evaporated to give crude XII (0.2 g). This was chromatographed on a silicagel column using C_6H_6 as eluent, and evaporation of the solvent yielded yellow cryatals (0.1 g), mp 121.5—122°, which showed no melting point depression with an authentic sample of XII.