Synthesis of 3-(2-Chloro-5-nitroanilino and 4-nitroanilino)-1-(2,4,6-trichlorophenyl)-2-pyrazolin-5-ones

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A new synthesis of 3-anilino-1-aryl-2-pyrazolin-5-ones in which the pyrazolinone ring is built *via* N-N bond formation is described. 2-Cyano-2',4',6'-trichloroacetanilide **1** was converted to imino ether hydrochloride **2** which was reacted with anilines in methanol to produce *N*-arylimino ether **3a,b**. Reaction of these *N*-arylimino ethers with hydroxylamine gave *N*-arylamidoximes **4a,b**. An 1,2,4-oxadiazol-5-one **6a** was prepared from the *N*-arylamidoxime **4a** and subjected to base-induced rearrangement. The desired 3-anilinopyrazolinone **7a** was obtained only in a very low yield. However, *O*-acetylation of the *N*-arylamidoximes **4a,b** followed by acid-catalyzed ring closure and rearrangement in the presence of excess acetic anhydride gave a mixture of *N*-acetylanilinopyrazolinones (*e.g.* **10**) and 4-acetyloxy-3-*N*-acetylanilinopyrazoles (*e.g.* **12**) which upon acid hydrolysis afforded the 3-anilinopyrazolinones **7a,b** in better yield.

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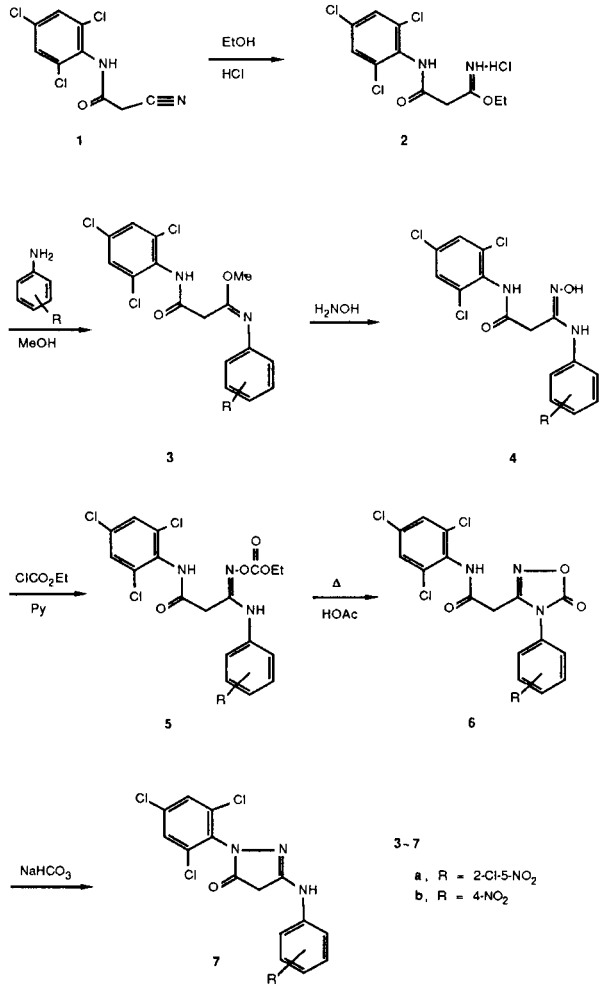
Pyrazolinones having 1-aryl and 3-nitrogen containing substituents are well known practical magenta couplers in color photography [1]. 3-Anilino-1-aryl-2-pyrazolin-5-ones are one type of such pyrazolinone couplers [2]. 3-Anilinopyrazolinones have been synthesized by the condensation of 3-amino- or 3-ethoxypyrazolinones [3,4] and anilines, by the Smiles rearrangement of 3-(2- or 4-nitrophenoxyacetamido)pyrazolinones [5], and by the reaction of ethyl 3-chloro- or 3-alkoxy-3-aryliminopropionate [2,6,7] and arylhydrazines. A common feature of all these known syntheses is that arylhydrazines are required as the source of two adjacent nitrogens in the heterocyclic ring. We reported a new synthesis of 3-acylaminopyrazolinones and its application to the synthesis of 3-(4-nitroanilino)pyrazolinone [8], which did not require arylhydrazine precursors. In the synthesis, an amidoxime was prepared and converted to 1,2,4-oxadiazole which underwent a base-induced rearrangement to afford the 3-acylaminopyrazolinone.

In an effort to develop a new synthetic route to 3-anilino-1-aryl-2-pyrazolin-5-ones which also would not require an arylhydrazine intermediate, we endeavored to prepare *N*-arylamidoximes **4a,b** and convert to 4-aryl-1,2,4-oxadiazolin-5-ones **6a,b** which may undergo base-catalyzed rearrangement to give the 3-anilinopyrazolinones **7a,b** liberating carbon dioxide.

2-Cyano-2',4',6'-trichloroacetanilide (**1**) was converted to imino ether hydrochloride **2** by the addition of alcohol in the presence of acid (the Pinner synthesis) [9]. The reaction of the imino ether **2** with 2-chloro-5-nitroaniline in methanol gave *N*-arylimino ether **3a**. The *N*-arylimino ether **3a** then reacted with hydroxylamine in anhydrous methanol to afford the *N*-arylamidoxime **4a**.



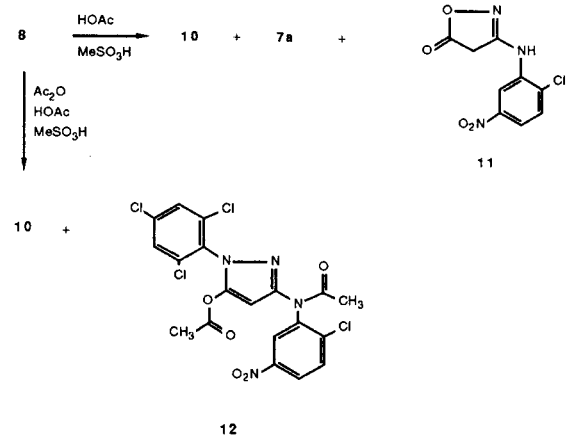
O-Acylation of *N*-arylamidoxime **4a** with ethyl chloroformate using pyridine as a base gave *O*-ethoxycarbonyl-*N*-

arylamidoxime **5a**, which was cyclized upon heating in acetic acid to give oxadiazolinone **6a**. When the oxadiazolinone **6a** was heated with potassium hydroxide in ethanol, it decomposed within 5 minutes under reflux temperature and gave multiple products. Only a trace of the desired pyrazolinone **7a** was detected by tlc. The reaction with a weaker base such as potassium carbonate or sodium bicarbonate in aqueous ethanol seemed to give a somewhat cleaner product mixture and the pyrazolinone **7a** was isolated in 20 ~ 25% yield. Several other bases, some inorganic such as sodium acetate, sodium phosphate, and sodium fluoride as well as some orgainc such as triethylamine and 1,4-diazabicyclo[2.2.2]octane, were tried under a variety of conditions, but the yield of **7a** never increased.

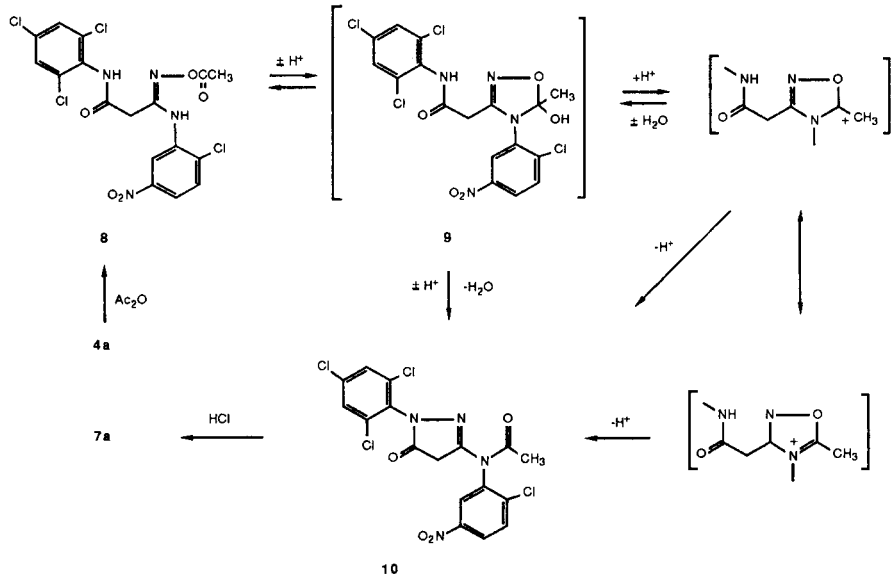
No attempts have been made to isolate and confirm byproducts formed in this reaction. The formation of many products may be due to the unstable nature of the oxadiazolinone **6a** toward a base. It is interesting to note that pyrolysis and photolysis of 3-benzyl-4-phenyl-1,2,4-oxadiazolin-5-one produced carbon dioxide and a mixture of products, some of which may be formed *via* an azomethine nitrene intermediate [10].

Thus, we pursued next *O*-acetylation of *N*-arylamidoxime **4a** followed acid-catalyzed ring closure and rearrangement which may give 3-*N*-acetylanilinopyrazolinone **10**. 4-Aryl-5-hydroxy-5-methyl-1,2,4-oxadiazoline **9**, an acid-catalyzed ring closure product of *O*-acetyl-*N*-arylamidoxime **8**, may not be isolable due to the reversible nature of its formation. However, the heterocycle formed *in-situ* may undergo acid-catalyzed rearrangement with loss of water to give **10**, as in the above scheme.

Indeed, there was obtained the acetylated pyrazolinone **10** [11] along with a small amount of desired pyrazolinone **7a** by heating the *O*-acetyl-*N*-arylamidoxime **8** in acetic acid with methanesulfonic acid as a catalyst. In addition to **10** and **7a**, isoxazolinone **11** was also formed as a byproduct. It must be derived from the starting material *O*-acetylamidoxime **8** by the action of water formed during the conversion of **8** to **10**. In fact, the same reaction in the presence of excess acetic anhydride gave **10** and 3-*N*-acetylanilino-5-acetoxy pyrazole **12** [11] without any trace of the isoxazolinone **11** according to tlc. Upon hydrolysis with hydrochloric acid in methanol, the crude mixture of **10** and **12** gave the desired pyrazolinone **7a** in 50% yield based on the *O*-acetyl-*N*-arylamidoxime **8**.



Interestingly, no reaction took place when 1,2,4-oxadiazolinone **6a** was treated in the same conditions as described on the previous page for **8**. Also, there was no



reaction when **8** was heated in acetic acid with or without acetic anhydride in the absence of methanesulfonic acid catalyst.

Since the acylating agent used in the first *O*-acylation step can be used in the second cyclization and rearrangement step as a dehydrating agent, the whole conversion of the *N*-arylamidoxime **4a** to anilinopyrazolinone **7a** could be carried out by a one-flask operation. Thus, after the *O*-acetylation reaction of *N*-arylamidoxime was done with an excess of acetic anhydride in acetic acid, methanesulfonic acid was simply added to the reaction mixture and the mixture was heated under reflux to effect cyclization and rearrangement. When the reaction was complete, the solvent was removed and the residue was subjected to the acid hydrolysis. The desired anilino pyrazolinone **7a** separated from the reaction mixture.

Similar treatment on another *N*-arylamidoxime **4b** prepared *via* **3b** gave the corresponding 3-anilinopyrazolinone **7b**.

Thus, we accomplished a four-step synthesis of 3-anilino-1-aryl-2-pyrazolin-5-ones starting from cyanoacetanilide. This new synthetic route provides not only a method of preparing 3-anilino-1-aryl-2-pyrazolin-5-ones without using arylhydrazine precursors but also a convenient method of preparing them using inexpensive common reagents and solvents with simple operations.

EXPERIMENTAL

All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on Beckman 4220 Spectrophotometer. A Varian T-60 nuclear magnetic resonance spectrometer was used for ^{1}H nmr spectra with tetramethylsilane as an internal standard, and an AEI MS-9 mass spectrometer was used for mass spectra. Precoated silica gel 60F-254 plates made by EM Reagents were used for thin layer chromatography (tlc). Elemental analyses were performed by the Industrial Laboratory, Kodak Park, Eastman Kodak Co.

3-Ethoxy-3-imino-2',4',6'-trichloropropionanilide Hydrochloride **2**.

To a solution of 290 g (1.10 mole) of 2-cyano-2',4',6'-trichloroacetanilide [8] in 1750 ml of dried tetrahydrofuran and 500 ml of toluene was added 60 g (1.24 moles) of absolute ethanol and bubbled in 475 g of anhydrous hydrogen chloride gas maintaining the temperature between 25-35°. After the addition of gas was complete, the thick slurry was stirred at room temperature with protection from moisture for 20 hours. The resulting solid was collected, washed with toluene, and dried to give 277 g (73%) of **2** as colorless solids, mp 240° dec; ir (potassium bromide): 3430, 3220, 3030, 2950, 2870, 1680, 1575, 1540 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 1.36 (t, 3H, -CH_2CH_3), 4.12 (s, 2H, -$COCH_2$), 4.56 (q, 2H, -CH_2CH_3), 7.83 (s, 2H, -$C_6H_2Cl_3$), 10.50 (s, 1H, -N*H*CO-) and 11.65 (broad, 2H, -NH_2^+Cl-).

Anal. Calcd. for $C_{11}H_{12}Cl_4N_2O_2$: C, 38.2; H, 3.5; N, 8.1. Found: C, 37.9; H, 3.7; N, 8.3.

3-[*N*-(2-Chloro-5-nitrophenyl)imino]-3-methoxy-2',4',6'-trichloropropionanilide **3a**.

A mixture of 207.6 g (0.60 mole) of **2** and 103.5 g (0.60 mole) of 2-chloro-5-nitroaniline in 1500 ml of methanol was heated to 40° and stirred at that temperature for 18 hours. The thick slurry was cooled to room temperature and then to 5° in an ice-water bath. The product was collected, washed with methanol and water, and dried in air to give 173 g (64%) of **3a** as light tan solids, mp 183-185°; ir (potassium bromide): 3220, 3200, 1680 (sh), 1670, 1570, 1530 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 3.47 (s, 2H, -$COCH_2$-), 3.93 (s, 3H, -OCH_3), 7.80 (s, 2H, -$C_6H_2Cl_3$), 7.94 (m, 3H, -$C_6H_3ClNO_2$), and 10.15 (s, 1H, -N*H*CO-).

Anal. Calcd. for $C_{16}H_{11}Cl_4N_3O_4$: C, 42.6; H, 2.5; N, 9.3. Found: C, 42.5; H, 2.3; N, 9.5.

3-(2-Chloro-5-nitroanilino)-3-oximino-2',4',6'-trichloropropionanilide **4a**.

To a solution of 23.3 g (0.431 mole) of sodium methoxide in 750 ml of methanol was added 30.5 g (0.439 mole) of finely pulverized hydroxylamine hydrochloride. The mixture was stirred for 30 minutes at room temperature and to the mixture was added 169.5 g (0.376 mole) of **3a** and 750 ml of tetrahydrofuran. The mixture was heated under reflux for 7 hours, and concentrated to a thick slurry under a reduced pressure to remove THF. To the slurry was added 750 ml of fresh methanol and the mixture was allowed to stand at room temperature overnight. The solid was collected, washed with methanol and water, and dried in air. There was obtained 118.5 g (70%) of **4a** as bright yellow crystals, mp 205-207° dec; ir (potassium bromide): 3450, 3330, 3240, 1650, 1610, 1575 (sh), 1550, 1520 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 3.95 (s, 2H, -$COCH_2$-), 7.77 (m, 3H, -$C_6H_3ClNO_2$), 7.80 (s, 2H, -$C_6H_2Cl_3$), 9.30 (s, 1H, -N*H*-Ar), and 10.33 (s, 1H, -N*H*CO-).

Anal. Calcd. for $C_{15}H_{10}Cl_4N_4O_4$: C, 39.9; H, 2.2; N, 12.4. Found: C, 40.1; H, 2.1; N, 12.3.

3-(2-Chloro-5-nitroanilino)-3-ethoxycarbonyloximino-2',4',6'-trichloropropionanilide **5a**.

To a mixture of 9.0 g (20 mmoles) of **4a** and 2.3 g of pyridine in 90 ml of tetrahydrofuran was added slowly 3.0 g (28 mmoles) of ethyl chloroformate with an ice bath cooling. The mixture was stirred at room temperature for 1½ hour, and concentrated to a thick slurry, to which 150 ml of methanol was added. The mixture was stirred for 15 minutes and cooled to 5°. The solid was collected, washed with methanol, and dried in air. There was obtained 9.2 g (88%) of **5a** as pale yellow solids, mp 203-205° dec; ir (potassium bromide): 3270, 1755, 1645, 1540, 1525 cm^{-1} nmr (DMSO-d_6): δ 1.26 and 1.30 (t and t, 3H, -OCH_2CH_3), 4.08 (s, 2H, $COCH_2$-), 4.22 and 4.26 (q and q, 2H, -OCH_2CH_3), 7.78 (m, 3H, -$C_6H_3ClNO_2$), 7.83 (s, 2H, -$C_6H_2Cl_3$), 9.00 (s and s, 1H, -N*H*Ar-), and 10.42 (s, 1H, -N*H*CO-).

Anal. Calcd. for $C_{18}H_{14}Cl_4N_4O_6$: C, 41.2; H, 2.7; N, 10.7. Found: C, 41.0; H, 2.7; N, 10.9.

4-(2-Chloro-5-nitrophenyl)-3-[2-oxo-2-(2,4,6-trichloroanilino)ethyl]-1,2-,4-oxadiazolin-5-one **6a**.

A solution of 7.85 g (15 mmoles) of **5a** in 100 ml of glacial acetic acid was heated under reflux for 2 hours. After cooled to room temperature, the mixture was diluted with 150 ml of water. The resulting solid was collected and recrystallized from methanol to give 5.8 g (81%) of **6a** as colorless crystals, mp 213-215° dec; ir (potassium bromide): 3220, 1700, 1670, 1620, 1575, 1565, 1530 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 4.10 (s, 2H, -$COCH_2$-), 7.74 (s, 2H, -$C_6H_2Cl_3$), 8.14 (d, 1H, C-3*H* of -$C_6H_3ClNO_2$), 8.52 (d and d, 1H, C-4*H* of -$C_6H_3ClNO_2$), 9.00 (d, 1H, C-6*H* of -$C_6H_3ClNO_2$), and 10.27 (s, 1H, -N*H*CO-).

Anal. Calcd. for $C_{16}H_8Cl_4N_4O_5$: C, 40.2; H, 1.7; N, 11.7. Found: C, 40.2; H, 1.7; N, 12.0.

Rearrangement of **6a** to 3-(2-Chloro-5-nitroanilino)-1-(2,4,6-trichlorophenyl)-2-pyrazolin-5-one **7a**.

To a solution of 1.3 g of sodium bicarbonate in 20 ml of water and 40 ml of methanol was added 2.4 g (5 mmoles) of **6a** and the mixture was heated under reflux for 2 hours. Methanol was removed and the mixture was acidified with dilute hydrochloric acid. The resulting solid was collected and redissolved in 15 ml of methanol and 1.5 g of 50% NaOH solution. The mixture was acidified with 6*N* hydrochloric acid and cooled in an ice bath. The crude product was collected and recrystallized from THF-methanol. There was obtained 0.55 g (25%) of **7a** as yellow needles, whose mp, ir and nmr spectra were identical with those of an authentic sample of **7a** prepared by known procedure [2].

3-(2-Chloro-5-nitroanilino)-3-acetyloximino-2',4',6'-trichloropropionanilide **8**.

A mixture of 13.6 g (30 mmoles) of **4a** and 5 g of acetic anhydride in 100 ml of glacial acetic acid was stirred at room temperature for 18 hours. The solid was collected, washed with acetic acid, and dried. This was recrystallized from THF-methanol to give 13.5 g (91%) of **8** as a colorless solid, mp 205-206° dec; ir (potassium bromide): 3325, 3200, 3180, 3100, 2995, 1745, 1675, 1630, 1615, 1580, 1545, 1525 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.00 and 2.12 (s and s, 3H, -COCH_3), 3.95 (s, -COCH_2), 7.72 (s, 2H, -$C_6H_2Cl_3$), 7.80 (m, 3H, -$C_6H_3ClNO_2$), 8.80 (broad s, 1H, -N*H*Ar), and 10.15 (broad s, 1H, -N*H*CO-).

Anal. Calcd. for $C_{17}H_{12}Cl_4N_4O_5$: C, 41.3; H, 2.4; N, 11.3. Found: C, 41.1; H, 2.4; N, 11.1.

Cyclization and Rearrangement of **8**.

(a) Without Acetic Anhydride.

A solution of 5 g (10 mmoles) of **8** and 0.5 g of methanesulfonic acid in 60 ml of glacial acetic acid was heated under reflux for 20 minutes. Analysis (tlc) of the reaction mixture showed three major spots identified later as *N*-acetylanilinopyrazolinone **10** [11], anilinopyrazolinone **7a** [2], and isoxazolinone **11** with a few minor impurities. After cooling, the reaction mixture was concentrated under a reduced pressure keeping the temperature around 40° and the residual oil was stirred with 100 ml of water. The resulting solid was collected, washed, and dried. This solid was slurried in 40 ml of methanol, collected, and recrystallized from THF-methanol. There was obtained 1.4 g of **10** as the first crop and 0.4 g of **7a** as the second crop. The latter was recrystallized once more to give pure **7a**. These two products were identified by the comparison with authentic samples prepared by the known procedure [2,11]. The filtrate from the methanol slurry of crude solid was concentrated to its ⅓ volume and cooled in an ice bath to give 0.6 g of **11** as yellow crystals, mp 188-190° dec; ir (potassium bromide): 3600, 3480, 3350, 3100, 1805, 1630, 1600, 1580, 1550, 1510 cm^{-1}; ^1H nmr (DMSO-d_6): δ 4.00 (s, 2H, -COCH_2-), 7.74 (d, 1H, C-3*H* of -$C_6H_3ClNO_2$), 7.85 (d and d, 1H, C-4*H* of -$C_6H_3ClNO_2$), 8.93 (d, 1H, C-6*H* of -$C_6H_3ClNO_2$), and 9.40 (s, 1H, -N*H*Ar); ms: m/e 255 and 257 (M^+).

Anal. Calcd. for $C_9H_6ClN_3O_4$: C, 42.3; H, 2.4; N, 16.4. Found: C, 42.2; H, 2.3; N, 16.6.

(b) With Acetic Anhydride.

A mixture of 5 g (10 mmoles) of **8**, 1 g of acetic anhydride, and 0.5 g of methanesulfonic acid in 60 ml of glacial acetic acid was heated under reflux for 15 minutes. Analysis (tlc) of the reaction mixture showed **10** [11] and **12** [11] with a few minor impurities, but no trace of **11** could be detected. After cooling, the reaction mixture was concentrated under a reduced pressure keeping the temperature around 40° and the residual oil was stirred with 100 ml of water. The resulting solid was collected and dried. This solid was heated in 10 ml of concentrated hydrochloric acid and 10 ml of methanol under reflux for 1 hour. After cooling, the mixture was allowed to stand overnight. The resulting solid was collected, washed well with water and methanol, and dried. There was obtained 2.2 g (50%) of **7a** as yellow crystals, mp 278-280° (lit [2] 274-278°).

3-(2-Chloro-5-nitroanilino)-1-(2,4,6-trichlorophenyl)-2-pyrazolin-5-one **7a** from **4a**.

A slurry of 22.6 g (0.05 mole) of **4a** in 50 ml of acetic anhydride and 200 ml of glacial acetic acid was stirred at room temperature for 21 hours. To the mixture was added 5 g of methanesulfonic acid and the mixture was heated as quickly as possible to its boiling point and kept under reflux for only 10 minutes. The solvent was removed by distillation under a reduced pressure keeping the temperature below 50°. The residual thick greenish brown oil was heated with 200 ml of methanol and 50 ml of concentrated hydrochloric acid under reflux for 1 hour. The mixture was cooled to room temperature and allowed to stand overnight. The solid was collected, washed well with water and methanol, and dried. There was obtained 9.1 g (42%) of **7a** as yellow solid, mp 278-280°.

3-[*N*-(4-Nitrophenyl)imino]-3-methoxy-2',4',6'-trichloropropionanilide **3b**.

This compound was prepared from **2** and 4-nitroaniline in 48% yield by following a procedure similar to that described for **3a**, mp 192-194°; ir (potassium bromide): 3220, 3180, 3065, 3010, 1670, 1655, 1595, 1585, 1560, 1525, 1505 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.45 (s, 2H, -COCH_2-), 3.86 (s, 3H, -OCH_3), 7.16 and 8.29 (AB q, 4H, -$C_6H_4NO_2$), 7.82 (s, 2H, -$C_6H_2Cl_3$), and 10.23 (s, 1H, -N*H*CO-).

Anal. Calcd. for $C_{16}H_{12}Cl_3N_3O_4$: C, 46.1; H, 2.9; N, 10.1. Found: C, 46.4; H, 2.7; N, 9.9.

3-(4-Nitroanilino)-3-oximino-2',4',6'-trichloropropionanilide **4b**.

This was prepared from **3b** in 57% yield by following a procedure similar to that described for **4a**, mp 194-195.5° dec; ir (potassium bromide): 3320, 3220, 3180, 1665, 1650, 1590, 1550, 1520, 1500 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.80 (s, 2H, -COCH_2-), 7.78 and 8.24 (AB q, 4H, -$C_6H_4NO_2$), 7.82 (s, 2H, -C_6HCl_3), 9.32 (s, 1H, -N*H*Ar), and 10.16 (s, 1H, -N*H*CO-).

Anal. Calcd. for $C_{15}H_{11}Cl_3N_4O_4$: C, 43.1; H, 2.7; N, 13.4. Found: C, 43.4; H, 2.7; N, 13.3.

3-(4-Nitroanilino)-1-(2,4,6-trichlorophenyl)-2-pyrazolin-5-one **7b**.

This was prepared from **4b** in 45% yield by following a procedure similar to that described for the direct preparation of **7a** from **4a**, mp 299-303° (lit [5] 299-304°).

Acknowledgement.

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