# Displacement-Cyclization Reactions of Mono-substituted Hydrazines With Chloronitrobenzenes and Chloronitropyrimidines. New Routes to 8-Azapurine and Benzopyrazole Derivatives



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Reactions of different chloronitrobenzenes and chloronitropyrimidines with monosubstituted hydrazines, R-NHNH$_2$, where R is methyl, carbomethoxy and phenyl, are described. The reactivity of these hydrazines in displacement-*ortho* substituent cyclizations varies substantially, depending on the nature of the aromatic substrate and the hydrazine R group. New routes to 8-azapurine and benzopyrazole derivatives are described.

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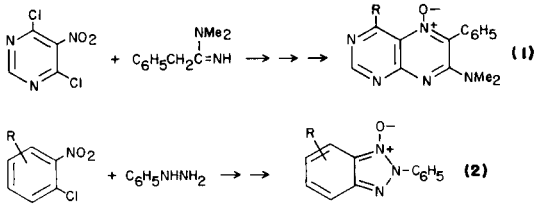
A variety of displacement-cyclization reactions of *ortho*-halonitroaromatics are useful routes to heterocyclic ring systems. Many of the important reactions have been summarized in a recent review by Preston and Tennant (1). We have recently described a new synthesis of the pteridine ring system *via* such a displacement-cyclization sequence involving amidines and chloronitropyrimidines (2) (equation 1). There are numerous early reports of a closely related sequence in which phenylhydrazine, when reacted



with appropriately structured halonitroaromatics, yields benzotriazole *N*-oxides (equation 2) (3-7). The reaction is base (8) as well as acid (9) catalyzed, and the insensitivity of the reaction to substituents on the ring supports a mechanism involving nucleophilic attack on the nitro group nitrogen atom (8).

In order to extend the scope of such reactions to other ring systems, we thought it of interest to examine this type of cyclization with severl types of hydrazines and aromatic substrates. The reactions of phenyl-, methyl- and carbomethoxyhydrazines with 1-chloro-2,6-dinitro-4-carboethoxybenzene (**1**) and 1-chloro-2,4-dinitro-6-carboethoxybenzene (**2**) are summarized in Figure I.

The reaction of phenylhydrazine with **1** yields the benzotriazole *N*-oxide **3**. An analogous product forms readily from picryl chloride and phenylhydrazine (10). Interestingly, both carbomethoxy- and methylhydrazine react with **1** to give only the displacement product. Cyclization cannot be induced to occur even under acidic or basic conditions. This is not surprising for **4**, since in base the anion **4a** will readily form, precluding cyclization. In

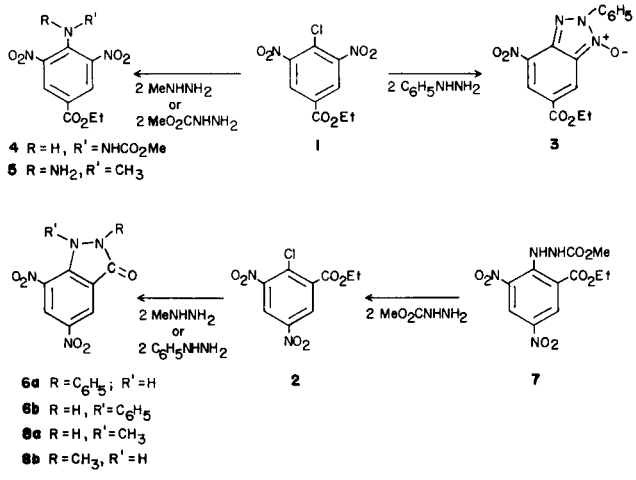
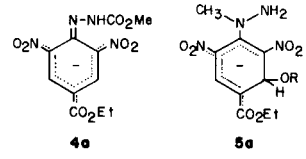


Figure 1. Reactions of **1** and **2** with 1-Substituted Hydrazines.

any case the basicity of nitrogen adjacent to the carbomethoxy group is dramatically reduced which does not favor cyclization (even under acidic conditions). The



reasons why **5** is reluctant to cyclize are puzzling. Under basic conditions addition to the ring may occur to yield **5a**. This is not an uncommon occurrence in such systems (11). The reason why cyclization does not occur under acidic conditions seems less obvious.

Compound **2** also readily reacts with all three hydrazines. With this substrate however, only carbomethoxyhydrazine fails to yield a cyclized product. Interestingly, the cyclized products **6** and **8** result from attack on carbon in the adjacent carboethoxy function in **2**, rather than on the nitrogen of the adjacent nitro group, even though the

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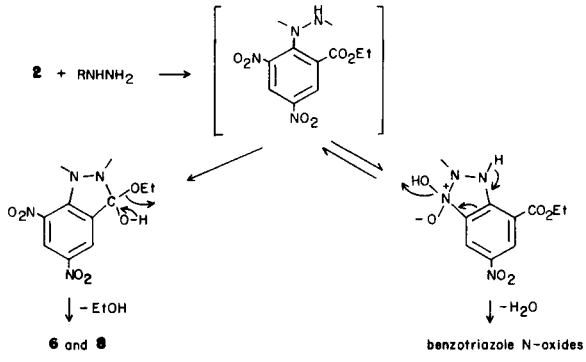
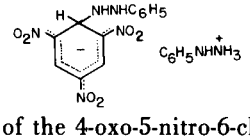
latter bears a formal positive charge. This is similar to our previous observations with amidine displacement-cyclizations (12), and may result from an initially reversible attack on the nitro group, which would lead to benzotriazole *N*-oxides, competing with a relatively irreversible attack on the carboethoxy group, leading to 3-oxopyrazoles. The latter contain fully conjugated benzene rings however, and would also likely be thermodynamically favored products.




On the basis of spectral characteristics of the isolated products it is difficult to unambigiously distinguish between **6a** and **6b**, and between **8a** and **8b**. We strongly favor **6a** and **8a**, however. The basicity of the unsubstituted nitrogen in phenylhydrazine is much greater than that of the nitrogen adjacent to the ring, and this strongly favors an initial substitution which leads only to **6a**. In contrast the basicity of the substituted nitrogen in methylhydrazine is greater than the unsubstituted nitrogen, favoring an initial substitution leading to **8a** (13,14). These arguments require substitution to occur initially in preference to direct attack on a ring substituent in **1** and **2**. There is evidence to support this latter possibility. While phenylhydrazine will slowly attack a nitro group in sym-TNB, attack on a ring carbon occurs even in this aromatic sybstrate to yield the corresponding anionic sigma complex (15).



The reactions of the 4-oxo-5-nitro-6-chloropyrimidine **9** and 4,6-dichloro-5-nitropyrimidine **10** are summarized in Figure II. The oxopyrimidine **9** reacts with 2 equivalents of 1-substituted hydrazine to yield the corresponding hydrazine substitution products **11a, 11b** and **11c**. Cyclization could not be effected with base, probably because of the acidity of the NH proton adjacent to the ring (R′ in **11a** and **11b**) and/or the NH adjacent to the carbonyl (in **11b**). In addition, cyclization could not be effected in acid (see Experimental).

The dichloronitropyrimidine **10** also reacts readily with 1-substituted hydrazines to yield the substitution products **12, 15** and **13**. With carbomethoxyhydrazine only the disubstituted product **12** was obtained, presumably because chlorine in the monosubstituted precursor of **12** is as labile as the chlorine in **10**. With methylhydrazine the monosubstitution product **13** is isolated. The chlorine in **13** is less susceptable to displacement because of the electron donating methylhydrazino group, which inhibits further substitution more strongly than the carbomethoxyhydrazino substituent in the monosubstituted precursor to **12**. Both **12** and **13** fail to cyclize under acidic or basic conditions (see Experimental). In fact, compound **13** forms **14** when treated with ethoxide.

Phenylhydrazine reacts with **10** to yield the monosubstituted product **15**, which upon treatment with acid does cyclize to the azapurine *N*-oxide **16**. Treatment of **16** with aqueous dithionite reduces the *N*-oxide and hydrolyzes chlorine to yield the 8-phenyl-8-azapurine **17**, identical in all respects with that prepared previously starting from phenylazomalonamide-amidine (16).

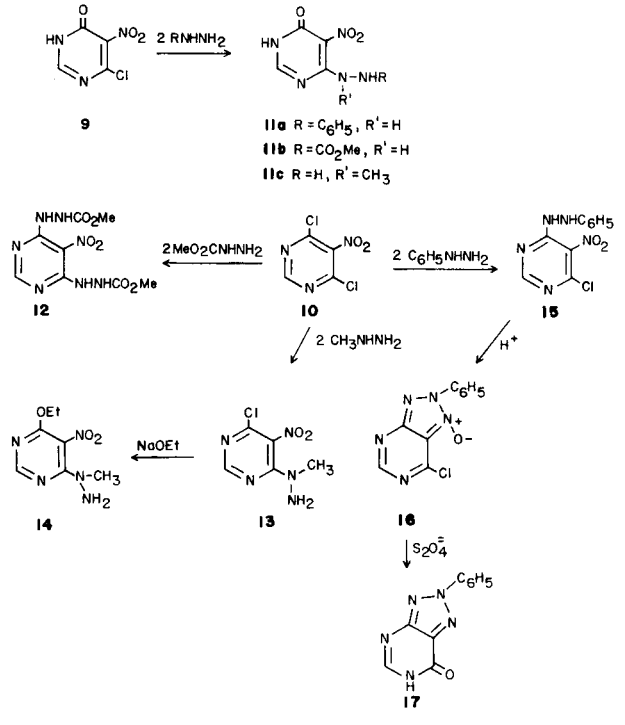
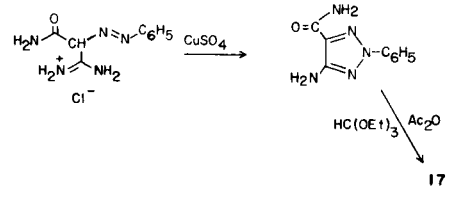



Figure II. Reactions of Pyrimidines with Hydrazines.




## EXPERIMENTAL

All melting points are uncorrected. $^1$H Nmr spectra were run on JEOL C-60 HL and MH-100 spectrometers with TMS as an internal reference. Visible and ultraviolet spectra were recorded on a Perkin-Elmer Model 402 UV-visible spectrophotometer. Infrared spectra were recorded on a

Perkin-Elmer Model 237 B infrared spectrophotometer. Mass spectra were obtained on a Perkin-Elmer RMU-6D mass spectrometer. Elemental analyses were cross-checked by Galbraith Laboratories, Inc., Knoxville, TN, G. I. Robertson Laboratories, Florham Park, NJ, and Integral Microanalytical Laboratories, Inc., Raleigh, NC.

Compounds **1** and **2** were obtained from the corresponding carboxylic acids as described previously (17). Compound **10** was obtained from Aldrich Chemical Co. and was used without further purification.

Preparation of **3**.

A solution of 0.04 mole of phenylhydrazine (Aldrich) in 50 ml. of dry ethanol was added to a solution of 5 g. (0.02 mole) of **1** in dry ethanol. The reaction mixture was stirred at room temperature for two days and the orange-red crystalline product was filtered, added to 100 ml. of fresh anhydrous ethanol and refluxed for 1 hour. Upon cooling the orange crystalline material was filtered to give 6.2 g. (95%) of compound **3**, m.p. 184-186° dec.; $^1$H nmr (deuteriochloroform): δ 9.15 (1H, s, ArH), 9.05 (1H, s, ArH), 8.40 and 6.70 (5H, two multiplets, $C_6H_5$), 4.55 (2H, q, $CO_2CH_2CH_3$) and 1.50 (3H, t, $CO_2CH_2CH_3$).

*Anal.* Calcd. for $C_{15}H_{12}N_4O_5$: C, 54.88; H, 3.68; N, 17.07. Found: C, 55.00; H, 3.54; N, 17.09.

Preparation of **4**.

A solution of 0.04 mole of carbomethoxy hydrazine (Aldrich) in 50 ml. of dry ethanol was added to a solution of 5.0 g. (0.02 mole) of **1** in dry ethanol. The reaction mixture was stirred for two days at room temperature and the crystalline product was filtered to give 4.2 g. (65%) of **4**, m.p. 160-161° dec.; $^1$H nmr (deuteriochloroform): δ 9.50 (1H, br s, $NHCO_2$), 8.65 (2H, s, ArH), 6.75 (1H, br s, ArNH), 4.40 (2H, q, $CO_2CH_2CH_3$), 3.75 (3H, s, $CO_2CH_3$) and 1.40 (3H, t, $CO_2CH_2CH_3$).

*Anal.* Calcd. for $C_{11}H_{12}N_4O_6$: C, 40.25; H, 3.69; N, 17.07. Found: C, 40.27; H, 3.62; N, 16.84.

Heating compound **4** for three days in an ethanol solution saturated with hydrogen chloride gas gives only starting material. Refluxing a methanol solution of **4** in with one equivalent of sodium methoxide for 3 hours followed by neutralization with concentrated hydrochloric acid also yields only starting material.

Preparation of **5**.

This compound was prepared in the same fashion as **4** using methyl hydrazine (Aldrich) and was obtained in 74% yield, m.p. 139° dec.; $^1$H nmr (DMSO-$d_6$): δ 8.20 (2H, s, ArH), 5.20 (2H, s, $NH_2$), 4.30 (2H, q, $CO_2CH_2CH_3$), 3.00 (3H, s, $NCH_3$) and 1.30 (3H, t, $CO_2CH_2CH_3$).

*Anal.* Calcd. for $C_{10}H_{12}N_4O_6$: C, 42.36; H, 4.26; N, 19.71. Found: C, 42.18; H, 4.28; N, 19.63.

Heating compound **5** in methanol for three days in the presence of a ten-fold molar excess of concentrated hydrochloric acid affords only starting material. Furthermore, refluxing a mixture of **1** equivalent of compound **1** and 2.05 equivalents of methylhydrazine for 48 hours in ethanol gives an 80% yield of **5** and a 20% yield of a mixture of unidentified products based on the total weight of isolated material.

Preparation of **6a**.

A solution of 0.008 mole of phenylhydrazine (Aldrich) in 50 ml. of dry ethanol was added to a solution of 1 g. (0.004 mole) of **2** in dry ethanol. The reaction mixture was stirred for two days at room temperature and the crystalline product was filtered to give 0.99 g. (82%) of **6a**, m.p. 270° dec.; $^1$H nmr (DMSO-$d_6$): δ 9.85 (1H, br s, NH), 9.15 (1H, d, ArH), 8.95 (1H, d, ArH), 8.00 and 7.65 (5H, two separate multiplets, $C_6H_5$); ir (potassium bromide): $cm^{-1}$ at 3100 (NH stretch), 1640 (CO stretch), 1530, 1480 and 1340.

*Anal.* Calcd. for $C_{13}H_8N_4O_5$: C, 52.01; H, 2.69; N, 18.66. Found: C, 52.22; H, 2.67; N, 18.84.

Preparation of **7**.

This compound was prepared in the same fashion as **6a** using carbomethoxy hydrazine (Aldrich) and was obtained in 82% yield, m.p. 153° dec.; $^1$H nmr (deuteriochloroform): δ 10.15 (1H, br s, $NHCO_2$), 8.90 (1H, d, ArH), 8.70 (1H, d, ArH), 6.65 (1H, br s, ArNH), 4.40 (2H, q, $CO_2CH_2CH_3$), 3.65 (3H, s, $CO_2CH_3$) and 1.40 (3H, t, $CO_2CH_2CH_3$).

*Anal.* Calcd. for $C_{11}H_{12}N_4O_6$: C, 40.25; H, 3.69; N, 17.07. Found: C, 40.26; H, 3.61; N, 17.03.

Stirring compound **7** in methanol for three days in the presence of a ten-fold molar excess of concentrated hydrochloric acid affords only star-

Table I

Chemical Shifts (δ) in DMSO-$d_6$ and Elemental Analyses of **11a**, **11b** and **11c**

| | Pyrimidone CONH | Pyrimidone H | Hydrazine NH | Hydrazine Moiety |
|---|---|---|---|---|
| **11a** | 12.40, br s | 8.00, s | 5.65 (1H, br s, pyrimidone NH), 5.55 (1H, br s, pyrimidone NHN*H*) | 7.50 (5H, m, $C_6H_5$) |
| **11b** | 12.40, br s | 8.20, s | 10.40 (1H, br s, pyrimidone NH), 9.65 (1H, br s, pyrimidone NHN*H*) | 3.60 (3H, s, $CO_2CH_3$) |
| **11c** | 12.40, br s | 8.00, s | 2.90 (2H, br s, pyrimidone $NNH_2$) | 3.35 (3H, s, $NCH_3$) |

| | Theoretical % | | | Found % | | |
|---|---|---|---|---|---|---|
| | C | H | N | C | H | N |
| **11a** | 48.58 | 3.67 | 28.33 | 48.19 | 3.41 | 28.02 |
| **11b** | 31.45 | 3.08 | 30.56 | 31.22 | 3.21 | 30.34 |
| **11c** | 32.44 | 3.81 | 37.83 | 32.22 | 3.58 | 37.59 |

ting material. Refluxing **7** in a solution of methanol and one equivalent of sodium methoxide for 3 hours followed by neutralization with concentrated hydrochloric acid affords **7** as the only product.

Preparation of **8a**.

This compound was prepared in the same fashion as **6a** using methyl hydrazine (Aldrich) and was obtained in 98% yield, m.p. 260° dec.; $^1$H nmr (DMSO-$d_6$): δ 12.00 (1H, br s, NH), 8.70 (1H, d, ArH), 8.60 (1H, d, ArH) and 4.80 (3H, s, $NCH_3$); ir (potassium bromide): $cm^{-1}$ at 3050 (NH stretch), 1590 (CO stretch), 1530, 1480, 1340, 1290, 1240, and 1190.

*Anal.* Calcd. for $C_8H_6N_4O_5$: C, 40.35; H, 2.54; N, 23.52. Found: C, 40.35; H, 2.36; N, 23.45.

Preparation of **11a, 11b** and **11c**.

These compounds were prepared from the known 6-chloro-5-nitro-4-(3*H*)pyrimidone (18) as follows. A solution of 0.0036 mole of the corresponding hydrazine (Aldrich) in 15 ml. of dry methanol was added dropwise to a solution of 0.31 g. (0.0018 mole) of **9** in 20 ml. of dry methanol. The reaction mixture was stirred for 5.5 hours at room temperature and the products were filtered. The yields and melting points are as follows: **11a**, 51%, m.p. 218° dec.; **11b**, 83%, 216-220° dec.; **11c**, 81%, 193° dec. The $^1$H nmr spectra and elemental analyses are summarized in Table I. Addition of a solution of one equivalent of sodium methoxide in dry methanol to a refluxing solution of **11a, 11b** or **11c** in dry methanol with subsequent refluxing for 5 hours followed by neutralization with dilute aqueous hydrochloric acid affords only recovered reactants **11a, 11b** and **11c**. Furthermore, stirring **11a, 11b** or **11c** for four days in methanol in the presence of a ten-fold molar excess of concentrated hydrochloric acid gives only recovered **11a, 11b** and **11c**.

Preparation of **12**.

A solution of 0.041 mole of carbomethoxy hydrazine (Aldrich) in 50 ml. of dry chloroform was added portionwise to a solution of 2 g. (0.01 mole) of **10** (Aldrich) in dry chloroform. The reaction mixture was heated for 2.5 days at 65-70° and was filtered warm. The remaining solid was washed five times with 100 ml. of hot chloroform. Evaporation of the filtrate and recrystallization of the remaining solid three times from dry ethanol afforded 1.54 g. (50%) of compound **12**, m.p. 205-208° dec.; $^1$H nmr (deuteriochloroform): δ 10.00 (2H, br s, $CO_2NH$), 8.00 (1H, s, pyrimidine H), 7.20 (2H, br s, pyrimidine-NH) and 3.70 (6H, s, $CO_2CH_3$); ms: m/e 301 (parent peak), 269, 181, 169, 131 and 119.

*Anal.* Calcd. for $C_8H_{11}N_7O_6$: C, 31.90; H, 3.68; N, 32.55. Found: C, 32.01; H, 3.56; N, 32.16.

Addition of a solution of one equivalent of sodium methoxide in dry methanol to a refluxing solution of **12** in dry methanol with subsequent refluxing for 17.5 hours and neutralization of the reaction mixture with dilute aqueous hydrochloric acid afforded only recovered **12**. Furthermore, heating compound **12** in a methanol solution saturated with hydrogen chloride gas for 4 days affords only recovered **12**.

Preparation of **13**.

A solution of 0.0056 mole of methylhydrazine (Aldrich) in 20 ml. of dry chloroform was added dropwise to a solution of 0.55 g. (0.0028 mole) of **10** (Aldrich) in dry chloroform cooled to 0-5°. The reaction mixture was stirred at room temperature for four days. The precipitate was filtered and washed with 5 ml. of dry chloroform. Evaporation of the filtrate and recrystallization of the remaining yellow solid from dry ethanol afforded 0.55 g. (97%) of **13**, m.p. 157-158° dec.; $^1$H nmr (deuteriochloroform): δ 8.45 (1H, s, pyrimidine H), 3.92 (2H, br s, $NH_2$) and 3.50 (3H, s, $NCH_3$).

*Anal.* Calcd. for $C_5H_4ClO_2$: C, 24.50; H, 2.97; N, 34.40. Found: C, 24.49; H, 2.76; N, 34.51.

Heating compound **13** in a dry ethanol solution saturated with hydrogen chloride gas affords only the hydrochloride salt of **13**, m.p. 180° dec.; $^1$H nmr (DMSO-$d_6$): δ 9.00 (3H, br s, NH), 8.15 (1H, s, pyrimidine H) and 3.40 (3H, s, $NCH_3$).

Preparation of **14**.

A freshly prepared solution of 0.003 mole of sodium ethoxide in 10 ml. of dry ethanol was added dropwise to a solution of 0.61 g. (0.003 mole) of compound **13** cooled to 0-5°. After stirring for 4.5 hours at room temperature, the reaction mixture was reduced to half its volume and cooled in an ice/water bath. The precipitate was filtered and washed with 5 ml. of dry ethanol twice to afford crystalline **14**. A second crop of crystals afforded a total of 0.33 g. (51%) of **14**, m.p. 181-185° dec.; $^1$H nmr (DMSO-$d_6$): δ 8.30 (1H, s, pyrimidine H), 5.00 (2H, br s, $NH_2$), 4.40 (2H, q, $OCH_2$), 3.40 (3H, s, $NCH_3$) and 1.20 (3H, t, $OCH_2CH_3$).

*Anal.* Calcd. for $C_7H_{11}N_5O_3$: C, 39.43; H, 5.20; N, 32.85. Found: C, 39.12; H, 5.08; N, 32.90.

Addition of a solution of one equivalent of sodium ethoxide in dry ethanol to a refluxing solution of **14** in dry ethanol, subsequent refluxing for 21 hours and neutralization of the reaction mixture with dilute aqueous hydrochloric acid afforded a red glass which is a mixture (tlc) of three or more products which were not further identified.

Preparation of **15**.

A solution of 0.052 mole of phenylhydrazine (Aldrich) in 75 ml. of dry chloroform was added dropwise to a solution of 5.0 g. (0.026 mole) of **10** (Aldrich) in 75 ml. of dry chloroform cooled to 0-5°. The reaction mixture was maintained at 0-5° for the duration of the addition period and was then allowed to slowly warm to room temperature where it was stirred for three days. The resulting precipitate was filtered off and washed three times with 50 ml. of dry chloroform. The chloroform was evaporated under reduced pressure and the remaining black tar was stirred with 50 ml. of dry ethanol until **15** precipitated as a fine yellow powder. The product was filtered and recrystallized from dry ethanol to give 2.02 g. (30%) of crystalline **15**, m.p. 163-164° dec.; $^1$H nmr (deuteriochloroform): δ 8.30 (1H, s, pyrimidine H), 7.35 (5H, m, $C_6H_5$) and 4.40 (2H, s, NHNH).

*Anal.* Calcd. for $C_{10}H_8ClN_5O$: C, 45.21; H, 3.04; N, 26.36. Found: C, 45.19; H, 3.07; N, 26.30.

Preparation of **16**.

A hot solution of 1 g. (0.0038 mole) of **15** in 20 ml. of dry ethanol was added in one portion to a solution of 60 ml. of ethanol saturated with hydrogen chloride gas at 65-75° and the mixture was stirred for four days. The yellow precipitate that formed was filtered and dried (0.3 mm) over phosphorus pentoxide at 100° to give 0.90 g. (97%) of crystalline **16** coordinated with two equivalents of water, m.p. 200-203° dec.; $^1$H nmr (DMSO-$d_6$): δ 8.70 (4H, br s, water), 8.05 (1H, s, pyrimidine H) and 7.50 (5H, m, $C_6H_5$); ms: m/e 247 (parent peak) 232, 213, 201, 187 and 158.

*Anal.* Calcd. for $C_{10}H_6ClN_5O\cdot 2H_2O$: C, 42.33; H, 3.56; N, 24.69. Found: C, 42.26; H, 3.70; N, 24.34.

Preparation of **17** (17).

A mixture of 0.18 g. (0.007 mole) of **16** and 0.41 g. (0.0023 mole) of sodium dithionite in 20 ml. of 50% aqueous ethanol was heated at reflux for two hours. The ethanol was then removed on a rotary evaporator and the lime green solid was filtered and washed with 10 ml. of water. The solid was suspended in 20 ml. of a fresh 50% aqueous ethanol solution, made acidic and then heated until all the solid dissolved. Upon cooling, compound **17** precipitated as white crystals. A second crop of crystals dried (0.3 mm) over phosphorus pentoxide at 100° gave a total of 0.023 g. (15%) of **17**, m.p. 280° dec.; lit. m.p. 281° dec.; $^1$H nmr (DMSO-$d_6$): δ 13.00 (1H, br s, pyrimidone (CONH), 8.40 (1H, s, pyrimidone H) and 8.10 and 7.65 (5H, two separate multiplets, $C_6H_5$); ms: m/e 213, 185, 130, 103 and 77.

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