New Syntheses of Pyrimido[4,5-*d*]pyrimidines[1]

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Novel conversions of pyrrolo-pyrimidines into pyrimido-pyrimidines are described. The treatment of 5-nitrosopyrrolo-pyrimidine (I) under Beckmann conditions causes ring expansion to give pyrimido-pyrimidine (II). Both the reduction of I with triphenylphosphine, potassium pyrosulfite, or sodium dithionite in dimethylformamide and the oxidation of 5-aminopyrrolo-pyrimidine with lead tetraacetate in dimethylformamide or acetic acid afford II. 5-Aminopyrimido-pyrimidine is prepared by the nucleophile-induced ring expansion of I. The possible mechanisms of these ring expansions are proposed.

The pyrimido[4,5-*d*]pyrimidine ring system not only resembles purine, but is isomeric with pteridine; it can, therefore, be expected to have biological activities similar to those of either purine or pteridine. In fact, certain pyrimido[4,5-*d*]pyrimidines have shown diuretic[2,3] and purine antagonistic[4] properties.

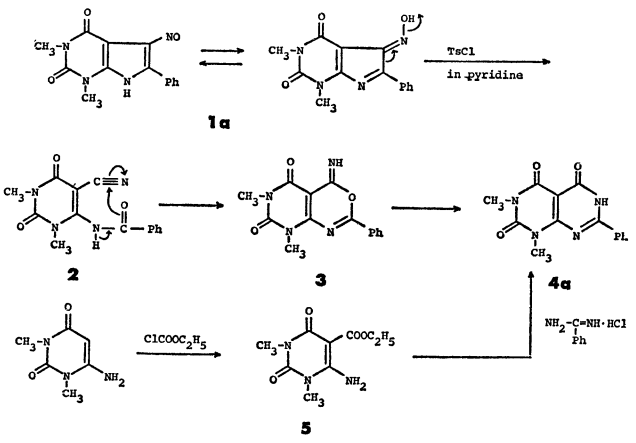
The known synthetic methods for the preparation of pyrimido[4,5-*d*]pyrimidines have involved the initial construction of suitably-substituted pyrimidine precursors and the subsequent annelation of the condensed pyrimidine ring in the reaction by using several carbon or carbon-nitrogen sources.[2–10] In this paper we will describe several new routes to the syntheses of pyrimido-[4,5-*d*]pyrimidines including ring expansions of pyrrolo-[2,3-*d*]pyrimidine derivatives.

Ring Expansion under Beckmann Conditions

It has been suggested that the ring expansion of 5-nitrosopyrrolo[2,3-*d*]pyrimidine to pyrimido[4,5-*d*]-pyrimidine by treatment under reflux with tosyl chloride or phosphorus oxychloride in dimethylformamide can be considered to occur *via* the usual Beckmann-type rearrangement.[11] Later we observed that the conversion of 3-nitrosoindole into quinazoline proceeds *via* the second-order Beckmann rearrangement.[12] This finding prompted us to look more closely into the ring expansion of 5-nitrosopyrrolo[2,3-*d*]pyrimidine described above.

The stirring of 1,3-dimethyl-5-nitroso-6-phenylpyrrolo[2,3-*d*]-2,4(1*H*,3*H*)-pyrimidinedione (**1a**)[11] with tosyl chloride in pyridine under cooling with ice water for 1 hr, followed by dilution with water, separated 6-(benzoylamino)-5-cyano-1,3-dimethyluracil (**2**), in which a nitrile absorption is present at 2215 cm^{-1} (Nujol) in the infrared spectrum. Compound **2** is extremely unstable, so even its purification by recrystallization from solvents or even its being maintained at room temperature for a few days results in cyclization into 4-iminopyrimido-1,3-oxazine (**3**). The heating of **1a** under a mild reflux with tosyl chloride or phosphorus oxychloride in pyridine formed **3** exclusively, while the refluxing of **1a** with the same reagents in dimethylformamide afforded 1,3-dimethyl-5-hydroxyl-7-phenylpyrimido[4,5-*d*]-2,4(1*H*,3*H*)-pyrimidinedione (**4a**), as has been described in the preceding paper.[11] The infrared spectra of **3** showed a strong imino absorption band at 3375 cm^{-1} (KBr). The heating of **3** under reflux in dimethylformamide resulted in the formation of **4a** *via* the Dimroth-type rearrangement. The treatment of **3** with an acid or base such as hydrochloric acid or benzylamine gave also **4a**. Compound **4a** was alternatively prepared by the following unequivocal synthesis. The heating of 6-amino-1,3-dimethyluracil with ethyl chloroformate in pyridine afforded 6-amino-1,3-dimethyl-5-(ethoxycarbonyl)uracil (**5**), which was then fused with benzamidine hydrochloride to give **4a**.

These facts show that this ring expansion proceeds *via* the second-order Beckmann rearrangement of the imino oxime tautomeric form of **1a**, followed by cy-



Scheme 1.

1) A part of this paper has been reported in preliminary form: see F. Yoneda and M. Higuchi, *Chem. Commun.*, **1972**, 402; F. Yoneda and M. Higuchi, *Chem. Pharm. Bull.* (Tokyo), **20**, 2076 (1972).

2) E. C. Taylor, R. J. Knopf, R. F. Meyer, A. Holmes, and M. L. Hoefle, *J. Amer. Chem. Soc.*, **82**, 5711 (1960).

3) H. Grabeyes, G. E. Jaffé, I. J. Pachter, J. P. Rosenbloom, A. J. Villani, J. W. Wilson, and J. Weinstock, *J. Med. Chem.*, **11**, 568 (1968).

4) H. G. Mauter, *J. Org. Chem.*, **23**, 1450 (1958).

5) C. K. Chatterji and N. Anand, *J. Sci. Ind. Res.*, **17B**, 63 (1958).

6) C. K. Chatterji and N. Anand, *ibid.*, **18B**, 272 (1959).

7) H. Bredereck, F. Effenberger, and R. Suter, *Chem. Ber.*, **95**, 2049 (1962).

8) J. Druey, P. Schmidt, K. Eichenberger, and M. Wilhelm, U. S. 3055900 (1962).

9) H. Bredereck, G. Simchen, and H. Traut, *Chem. Ber.*, **100**, 3664 (1967).

10) H. Bredereck, G. Simchen, R. Wahl, and F. Effenberger, *ibid.*, **101**, 512 (1968).

11) F. Yoneda, M. Higuchi, K. Senga, M. Kanahori, and S. Nishigaki, *Chem. Pharm. Bull.* (Tokyo), **21**, 473 (1973).

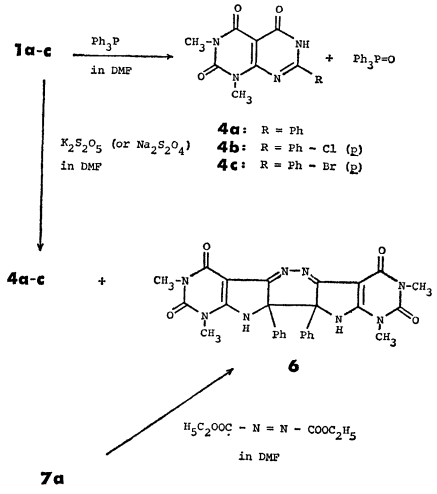
12) F. Yoneda, M. Higuchi, and R. Nonaka, *Tetrahedron Lett.*, 359 (1973).

clization into the 4-imino-1,3-oxazine intermediate (**3**) and subsequent Dimroth rearrangement, as is depicted in Scheme 1.

Reductive Ring Expansion

The stirring of **1a** under a mild reflux with excess triphenylphosphine in dimethylformamide for 1 hr, followed by cooling, caused the separation of **4a** in 45% yield. The mother liquor was evaporated in dryness under reduced pressure, and the residue was chromatographed to give triphenylphosphine oxide in a 76% yield. Similarly, the 6-*p*-chlorophenyl and 6-*p*-bromophenyl analogs (**1b** and **1c**) of **1a** yielded the corresponding pyrimido[4,5-*d*]pyrimidines (**4b** and **4c**) in almost the same yields.

The refluxing of **1a** with excess potassium pyrosulfite in dimethylformamide for 1 hr and the subsequent cooling of the reaction mixture separated **4a** in a 50% yield. To our knowledge, the reaction is the first example in which potassium pyrosulfite has been successfully introduced into preparative origanic chemistry. In this reaction a dimeric product (**6**) was obtained as a by-product. The structure of **6** was assigned on the basis of an elemental analysis and a molecular-weight determination (a strong parent peak at *m/e* 536), and in consideration of its probable mode of formation. An analogous dimeric indole derivative is obtained in the oxidation of the 3-indoxyl derivative.[13] This dimeric product (**6**) was alternatively synthesized by the oxidative coupling of 3-aminopyrrolo[2,3-*d*]pyrimidine (**7a**) (*vide infra*) with diethyl azodicarboxylate in dimethylformamide.

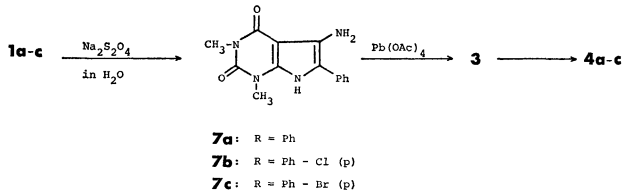


Scheme 2.

The treatment of **1b** and **1c** with potassium pyrosulfite under the same conditions gave, similarly, **4b** and **4c** in 58 and 40% yields respectively. The treatment of **1a** with sodium dithionite in dimethylformamide also yielded **4a**, although in a lower yield (34%), whereas this reaction in water gave the usual reduction-product, 5-aminopyrrolo[2,3-*d*]pyrimidines (**7**) (*vide infra*). When **1a** alone was refluxed in dimethylformamide, only a trace of **4a** was obtained, the starting material being almost entirely recovered.

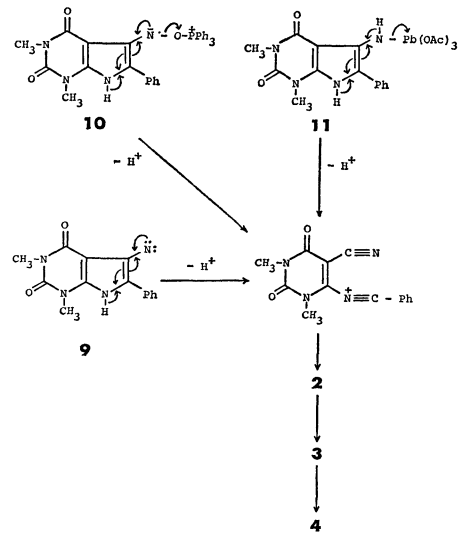
Oxidative Ring Expansion

It was found that the reaction of 5-amino-1,3-dimethyl-6-phenylpyrrolo[2,3-*d*]-2,4(1*H*,3*H*)-pyrimidinediones (**7a–c**) with lead tetraacetate gave **4a–c**. The starting materials, **7a–c**, were obtained by the reduction of **1a–c** with sodium dithionite in water. The heating of **7a–c** with excess lead tetraacetate in dimethylformamide or acetic acid at 90° for 3 hr, partial evaporation, and dilution with water caused the separation of **4a–c** in 90, 86, and 72% yields respectively. When the above reaction was carried out below 65°, an intermediate, the 4-imino-1,3-oxazine derivative (**3**), was obtained in a high yield.



Scheme 3.

Although a common intermediate, 5-nitrene (**9**), is formed in both the reductive and oxidative ring expansions described above, we could not demonstrate the presence of **9** by intermolecular trapping reaction with cyclohexene. Therefore, the more complex adducts, such as **10** and **11**, appear equally probable as precursors.



Scheme 4.

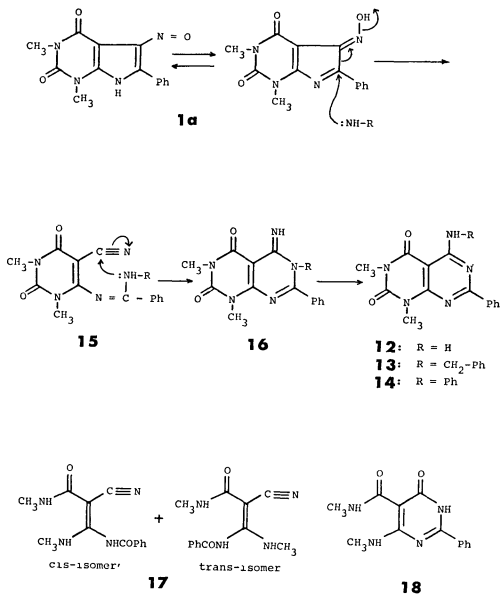
Nucleophile-induced Ring Expansion

The refluxing of **1a** in dimethylformamide while introducing dry ammonia over a 4-hr period yielded 5-amino-1,3-dimethyl-7-phenylpyrimido[4,5-*d*]-2,4(1*H*,3*H*)-pyrimidinedione (**12**) in a 60% yield. Re-

13) a) A. Hassner and M. Haddadin, *J. Org. Chem.*, **28**, 224 (1963). b) E. Giovannins, F. Farkas, and J. Rosales, *Helv. Chim. Acta*, **46**, 1326 (1963).

fluxing **1a** with urea in dimethylformamide also gave **12** in a 80% yield. The structure of **12** was assigned on the basis of the satisfactory elemental analysis and the spectral data, and finally by the conversion of **12** into **4a** by deamination with sodium nitrite in hydrochloric acid. Similarly, the refluxing of **1a** with benzylamine and aniline in dimethylformamide afforded 5-benzylamino- (**13**) and 5-anilino-1,3-dimethyl-7-phenylpyrimido[4,5-*d*]-2,4(1*H*,3*H*)-pyrimidinedione (**14**) in 59 and 64% yields respectively.

The following mechanism with the *N*-(5-cyanouracil-6-yl)amidine intermediate (**15**) rationalizes this ring expansion. A formal Beckmann-type rearrangement would also account directly for the formation of the 5-benzyl (**13**) and 5-anilino derivatives (**14**), without any need to postulate the subsequent Dimroth rearrangement of an imino intermediate (**16**). However, the formation of (benzoylamino)acrylonitrile (**17**) from **1a** by the action of alkali would eliminate the similar Beckmann process. That is, the refluxing of **1a** with 40% potassium hydroxide solution in a mixture of ethanol and water (1 : 1) for 1 hr yielded a nearly equimolar mixture of *cis*- and *trans*-isomers (**17**). The NMR spectra exhibited two pairs of three-proton singlets at 3.12 and 3.47 as well as those at 3.19 and 3.55. The former two singlets were assigned to the *N*-methyl groups of the *cis*-isomer, and the latter two, to those of the *trans*-isomer. The **17** mixture was converted into the corresponding pyrimidine derivative (**18**) in a quantitative yield by treatment with dry hydrogen chloride in ethanol. The characteristic nitrile band of **17** at 2190 cm^{-1} (Nujol) disappeared. The NMR spectrum displayed a pair of singlets at 3.10 and 3.45 corresponding to the *N*-methyl groups and phenyl protons at from 7.5 to 8.2.



Scheme 5.

Experimental

All the melting points are uncorrected. The NMR spectra were determined by means of a JNM 3H-60 spectrometer, using tetramethylsilane as the internal standard. The chemical shifts were expressed in δ values. The mass spectra (75 eV) were recorded on a Hitachi RMU-6D double-focusing spectrometer.

*6-(Benzoylamino)-5-cyano-1,3-dimethyluracil (**2**).* A mixture of 0.25 g (1 mmol) of **1a** and 0.6 g (3 mmol) of TsCl in 5 ml of pyridine was stirred under cooling with ice water for 4 hr. The subsequent dilution of the reaction mixture with H_2O gave 0.1 g (40%) of **2**.

*1,3-Dimethyl-5-imino-7-phenylpyrimido[4,5-d]-1,3-oxazine (**3**).* A mixture of 0.5 g (2 mmol) of **1a** and 1 g (5 mmol) of TsCl in 15 ml of pyridine was refluxed at 130—140 °C for 3 hr. The reaction mixture was then evaporated under reduced pressure, and to the residue 100 ml of H_2O was added. The crystals thus separated were recrystallized from DMF to give 0.45 g (90%) of colorless crystals; mp>285 °C (sublim.). *m/e* 284 (M^+). Found: C, 59.08; H, 4.21; N, 19.39%. Calcd for $C_{14}H_{12}N_4O_3$: C, 59.15; H, 4.26; N, 19.71%.

*Dimroth Rearrangement of **3** to **4a**.* *A.* A solution of 0.1 g (4 mmol) of **3** in 5 ml of DMF was refluxed for 3 hr and then allowed to stand overnight at room temperature. The crystals thus precipitated were washed with H_2O and dried to give 0.09 g (90%) of **4a**.

B. A solution of 0.05 g (0.2 mmol) of **3** in 10 ml of conc. HCl was refluxed for 3 hr. The reaction mixture was then diluted with H_2O and neutralized with aqueous NH_3 to separate 0.025 g (50%) of **4a**.

C. A solution of 0.25 g (1 mmol) of **3** and 0.16 g (2 mmol) of benzylamine in 50 ml of DMF was refluxed at 160° for 3 hr. After cooling, the crystals thus separated were washed with H_2O and dried to give 0.23 g (92%) of **4a**.

*6-Amino-1,3-dimethyl-5-(ethoxycarbonyl)uracil (**5**).* Three grams (19 mmol) of 6-amino-1,3-dimethyluracil were dissolved in 55 ml of pyridine, and to the solution we then added, drop by drop, 4.5 g (42 mmol) of ethyl chloroformate. After heating at 90 °C for 5 hr, the reaction mixture was evaporated *in vacuo*, and then 10 ml of H_2O was added. The crystals thus separated were recrystallized from EtOH to give 2.2 g (50.1 %) of colorless needles; mp 207—208 °C. Found: C, 47.74; H, 5.52; N, 18.68%. Calcd for $C_9H_{13}N_3O_4$: C, 47.57; H, 5.77; N, 18.49%.

*Reaction of **5** with Benzamidine Hydrochloride.* One gram (4 mmol) of **5** and 1.25 g (8 mmol) of benzamidine hydrochloride were thoroughly mixed, after which the mixture was fused at about 300 °C for 15 to 20 min. After cooling, reaction mixture was crushed in H_2O and washed with H_2O. The crushed mass was recrystallized from DMF to give 0.45 g (36%) of colorless plates (mp>300 °C), which were identical in all respects with the product (**4a**) prepared by the ring expansion of **1a**.

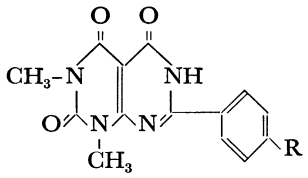
*Reductive Ring Expansion of **1a** with Triphenylphosphine.* A mixture of 1 g (4 mmol) of **1a** and 1.57 g (6 mmol) of triphenylphosphine in 20 ml of DMF was refluxed at 180 °C for 2.5 hr. After cooling, the crystals which separated were recrystallized from DMF to give 0.45 g (45%) of **4a**.

Similarly, 6-(*p*-chlorophenyl) (**1b**) and 6-(*p*-bromophenyl) (**1c**) analogs were converted into 7-(*p*-chlorophenyl)- (**4b**) and 7-(*p*-bromophenyl)-1,3-dimethylpyrimido[4,5-*d*]-2,4(1*H*,3*H*)-pyrimidinediones (**4c**) (see Table 1).

The evaporation of the mother liquor under reduced pressure and the column chromatography of the oily residue on alumina, using benzene–EtOH (7 : 3) as the eluant, gave triphenylphosphine oxide in a 75% yield.

*Reaction of **1a** with Potassium Pyrosulfite ($K_2S_2O_5$).* A mixture of 0.9 g (3 mmol) of **1a** and 0.9 g (4 mmol) of $K_2S_2O_5$ in 24 ml of DMF was heated under reflux at 180—190°C for 2.5 hr, during which time the color changed from red to

TABLE 1.



Compound No.	R	Mp (°C)	Yield (%) Ph_3P	Yield (%) $K_2S_2O_5$	Appearance (Recryst. solvent)	Formula	Analysis Calcd (%) C	Calcd (%) H	Calcd (%) N	Found (%) C	Found (%) H	Found (%) N
4a	H	>300	45	50	Colorless plates (DMF)	$C_{14}H_{12}N_4O_3$	59.15	4.26	19.71	59.37	4.28	19.49
4b	Cl	>300	48	58	Colorless plates (DMF)	$C_{14}H_{11}N_4O_3Cl$	52.75	3.48	17.58	52.75	3.45	17.48
4c	Br	>300	42	40	Colorless plates (DMF)	$C_{14}H_{11}N_4O_3Br$	46.29	3.05	15.40	46.60	3.16	15.17

yellow. After cooling, the crystals which separated were recrystallized from DMF to give 0.45 g (50%) of colorless plates of **4a**.

The mother liquor was allowed to stand for 2 days to separate yellow crystals, which were then collected by filtration. The filtrate was concentrated *in vacuo* and diluted with H_2O to separate more yellow crystals. The combined crystals were recrystallized from DMF to give 0.15 g (17.6%) of colorless prisms of the dimer (**6**); mp 287—289 °C. *m/e* 536 (M^+). Found: C, 57.01; H, 5.07; N, 18.58%. Calcd for $C_{28}H_{24}N_8O_4.3H_2O$: C, 56.95; H, 5.09; N, 18.98%.

Under the same conditions, **1b** and **1c** were converted into **4b** and **4c** (see Table 1).

*Reaction of **7a** with Diethyl Azodicarboxylate.* To a solution 0.75 g (3 mmol) of **7a** in 30 ml of DMF, we added 0.5 g (3 mmol) of diethyl azodicarboxylate; the mixture was then heated under stirring at 130—135 °C for 6 hr. After cooling, the reaction mixture was evaporated to dryness. The residue was collected by filtration, washed with EtOH, and recrystallized from DMF to give 0.3 g (40.3%) of colorless plates (mp 287—289 °C) which were in all respects identical with the byproduct (**6**) formed by the reaction of **1a** with $K_2S_2O_5$.

*5-Amino-1,3-dimethyl-6-phenylpyrrolo[2,3-d]-2,4(1H,3H)-pyrimidinedione (**7a**).* A mixture of 6 g (21 mmol) of **1a** and 7.3 g (42 mmol) of $Na_2S_2O_4$ in 30 ml of H_2O was heated under reflux for 30 min. After cooling, the crystals which separated were recrystallized from EtOH to give 2.2 g (38.6 %) of pale yellow needles; mp 249—250 °C. *m/e* 270 (M^+). Found: 62.04; H, 5.37; N, 20.71%. Calcd for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.73%.

Similarly, 6-(*p*-chlorophenyl) (**7b**) (mp 250 °C, 40%) and 6-(*p*-bromophenyl) (**7c**) (mp 268 °C, 35%) analogs were obtained.

*Ring Expansion of **7a** with Lead Tetraacetate.* *A.* To a suspension of 0.81 g (3 mmol) of **7a** in 30 ml of acetic acid, we added, little by little, 2 g (5 mmol) of $Pb(OAc)_4$, after which the mixture was heated under stirring at 90 °C for 3 hr, during which time the color changed to a yellowish brown. After the solvent had been evaporated under reduced pressure, a small amount of H_2O was added to the resulting residue; the crystals which were thus separated were recrystallized from DMF to give 0.77 g (90%) of **4a**.

B. To a solution of 0.75 g (3 mmol) of **7a** in 30 ml of DMF, we added, little by little, 2 g (5 mmol) of $Pb(OAc)_4$, after which the mixture was heated at 65 °C for 3 hr. The reaction mixture was then diluted with H_2O to precipitate 0.08 g (91%) of **3**.

*5-Amino-1,3-dimethyl-7-phenylpyrimido[4,5-d]-2,4(1H,3H)-pyrimidinedione (**12**).* *A.* Three grams (11 mmol) of **1a** were dissolved in 30 ml of DMF, and to this solution we introduced dry ammonia at 140° over an 8-hr period, during which time the color changed to red. After the solvent had been evaporated, the resulting residue was recrystallized from DMF to yield 1.8 g (60%) of colorless needles; mp 259—260 °C. *m/e* 283 (M^+). Found: C, 59.70; H, 4.34; N, 25.15%. Calcd for $C_{14}H_{13}N_5O_2$: C, 59.35; H, 4.63: N, 24.72%.

B. A mixture of 0.5 g (2 mmol) of **1a** and 0.5 g (8 mmol) of urea in 10 ml of DMF was refluxed at 150—160 °C for 3 hr. The reaction mixture was evaporated under reduced pressure, and the resulting residue was diluted with H_2O. The crystals thus precipitated were recrystallized from DMF to give 0.4 g (80%) of **12**.

*Deamination of **12** into **4a**.* To a suspension of 0.1 g (0.4 mmol) of **12** in 20 ml of 10% dilute HCl, we added, portion by portion, excess $NaNO_2$ (0.5 g) under stirring and cooling with ice water; the mixture was then heated on a water bath for 1 hr. After cooling, the crystals which separated were washed with H_2O and dried to yield **4a** in a quantitative yield.

*5-(Benzylamino)-1,3-dimethyl-7-phenylpyrimido[4,5-d]-2,4(1H,3H)-pyrimidinedione (**13**).* To a solution of 0.5 g (2 mmol) of **1a** in 10 ml of DMF, we added 0.32 g (3 mmol) of benzylamine under stirring. The mixture was heated under reflux at 180 °C for 3 hr, during which time the color changed from yellow to red. After cooling, the product which separated were recrystallized from EtOH to give 0.38 g (58.5%) of colorless prisms; mp 228—229 °C. *m/e* 373 (M^+). Found: C, 67.39; H, 5.07; N, 18.51%. Calcd for $C_{21}H_{19}N_5O_2$: C, 67.54; H, 5.13; N, 18.76%.

*5-Anilino-1,3-dimethyl-7-phenylpyrimido[4,5-d]-2,4-(1H,3H)-pyrimidinedione (**14**).* To a solution of 0.5 g (2 mmol) of **1a** in 10 ml of DMF, we added 0.28 g (3 mmol) of aniline under stirring, after which the mixture was treated as has been described above to give 0.4 g (64%) of colorless needles; mp>300 °C. *m/e* 359 (M^+). Found: C, 66.73; N, 4.65; N, 19.40%. Calcd for $C_{20}H_{17}N_5O_2$: C, 66.84; H, 4.77; N, 19.49%.

1-Cyano-1-(N-methylcarbamoyl)-2-(benzoylamino)-2-(methylamino)ethylene (a Mixture of cis- *and* trans-*Isomers) (**17**).* To a solution of 0.75 g (3 mmol) of **1a** in 60 ml of EtOH, we added 15 ml of an aqueous solution including 1.5 g of KOH. After the mixture had been refluxed for 2 hr, the EtOH was evaporated and H_2O was added to the resulting residue. The undissolved material was filtered off, and the

filtrate was acidified with acetic acid to precipitate pale yellow crystals. Recrystallization from aqueous DMF gave 0.4 g (58%) of colorless needles; mp 189 °C. *m/e* 258 (M^+). Found: C, 60.41; H, 5.10; N, 21.82%. Calcd for $C_{13}H_{14}H_4O_2$: C, 60.45; H, 5.46; N, 21.70%.

Ring Closure of ***17*** *to 4-Hydroxy-6-(methylamino)-5-(*N*-methylcarbamoyl)-2-phenylpyrimidine (****18****).* A solution of 0.5 g (2 mmol) of **17** in 20 ml of absolute EtOH was introduced with dry HCl for 4 hr at room temperature, during which time colorless crystals were isolated. The crystals were then recrystallized from DMF to give 0.3 g (60%) of colorless mp>300 °C. *m/e* 258 (M^+). Found: C, 60.55; H, 5.10; N, 21.47%. Calcd for $C_{13}H_{14}N_4O_2$: C, 60.45; H, 5.46; N, 21.70%.