Preparation of Pyrrole and Pyrrolidine Derivatives of Pyrimidine. 1-(2-Pyrimidinyl)pyrrole - an Inhibitor of *X. Phaseoli* and *X. Malvacearum*

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Pyrrole and pyrrolidine derivatives of pyrimidine were prepared in which the nitrogen atom of the pyrrole or pyrrolidine ring is bonded directly to the 2- or 4-carbon atom of the pyrimidine ring. Pyrrole derivatives were prepared by the dry distillation of an intimate mixture of an aminopyrimidine with mucic acid and by the reaction of a chloropyrimidine with potassium pyrrole. Pyrrolidine derivatives were prepared by the reaction of a chloropyrimidine with pyrrolidine and, in a single instance, by the catalytic hydrogenation of a pyrimidinylpyrrole. At a concentration of 200 mcg/mL, 1-(2-pyrimidinyl)pyrrole inhibited two plant pathogenic bacteria —*Xanthomanus phaseoli* (pathogenic on the bean plant) and *Xanthomanus malvacearum* (pathogenic on the cotton plant).

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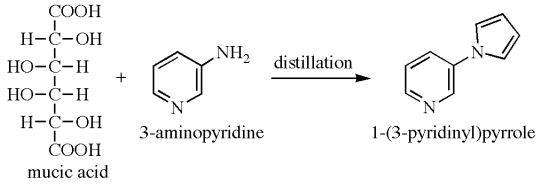
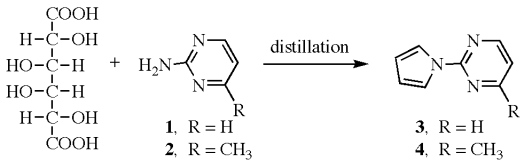
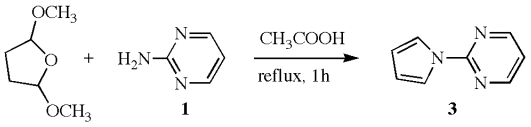
Just as Pictet and Crepieux [2] prepared 1-(3-pyridinyl)pyrrole by the dry distillation of a mixture of 3-aminopyridine with mucic acid in an early step in the synthesis of nicotine, we prepared 1-(2-pyrimidinyl)pyrrole



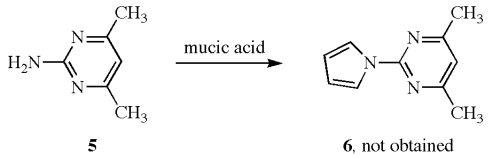
(**3**) and 1-(4-methyl-2-pyrimidinyl)pyrrole (**4**) by the distillation of a mixture of 2-aminopyrimidine (**1**) with mucic acid and by the distillation of a mixture of 2-amino-4-methylpyrimidine (**2**) with mucic acid, respectively. Subsequent to our work carried out in 1955, Nonoyama in



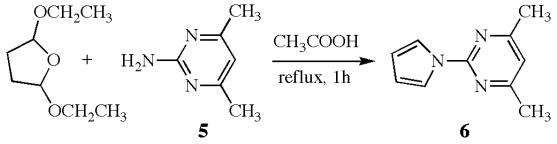
1987 prepared **3** by refluxing a solution of 2,5-dimethoxytetrahydrofuran and 2-aminopyrimidine (**1**) in acetic acid for 1 h [3]. The ^{1}H nmr spectrum of his product was identical to that of our product.



We obtained no 1-(4,6-dimethyl-2-pyrimidinyl)pyrrole (**6**) from the dry distillation of a mixture of 2-amino-4,6-dimethylpyrimidine and mucic acid. However, subsequent to our attempt made in 1955, Katritzky and coworkers in



1976 prepared **6** by the reaction of 2,5-diethoxytetrahyrofuran with **5** [4-6]. These same workers failed to prepare **6** by the reaction of 2-chloro-4,6-dimethylpyrimidine with potassium pyrrole [5].



The second method employed for the preparation of pyrimidinylpyrroles involved heating a mixture of a chloropyrimidine with potassium pyrrole in pyrrole as solvent. By this method we prepared 1-(2-pyrimidinyl)pyrrole (**3**) and 1-(2-amino-4-methyl-6-pyrimidinyl)pyrrole (**7**) from the requisite chloropyrimidine (see Table I). Replacement of a chlorine atom in the 2-, 4-, or 6-position of the pyrimidine ring by a nucleophile is well documented [7].

Pyrrolidine derivatives of pyrimidine were prepared by the reaction of a chloropyrimidine with pyrrolidine (see Table II). In this way we prepared 1-(2-pyrimidinyl)pyrrolidine (**8**) [8,9], 1-(2-amino-4-methyl-6-pyrimidinyl)-pyrrolidine (**9**), and 1-(4,6-dimethyl-2-pyrimidinyl)pyrrolidine (**10**) [10] from the requisite chloropyrimidine. Reaction of 2-amino-4,6-dichloropyrimidine with a limited amount of pyrrolidine (2.3 mol pyrrolidine to 1 mol pyrimidine) with no heating gave 1-(2-amino-4-chloro-6-pyrimidinyl)pyrrolidine (**11**). At a much higher mol ratio (9:1) with heating, the disubstituted product, namely, 2-amino-4,6-di(1-pyrrolidinyl)pyrimidine (**12**), was obtained [11]. In a single instance, a pyrimidinylpyrrolidine was prepared

by the selective catalytic hydrogenation of the pyrrole ring of a pyrimidinylpyrrole. Specifically, 1-(2-pyrimidinyl)-pyrrolidine (**8**) was prepared by the catalytic hydrogenation of 1-(2-pyrimidinyl)pyrrole (**3**) which, in turn, was prepared by the dry distillation of a mixture of 2-aminopyrimidine (**1**) with mucic acid.

The reactions given in Scheme 1 support the structures of both 1-(2-pyrimidinyl)pyrrole (**3**) and 1-(2-pyrimidinyl)pyrrolidine (**8**). The synthesis of **8** from the reaction of 2-chloropyrimidine with pyrrolidine (reaction B) is considered to be an unambiguous synthesis of **8**. The products of reactions D and E had the same melting point. A mixture melting point of the two products was not depressed. The ^{1}H nmr spectra of the two products were identical to each other and indicated that the 2-pyrimidinyl moiety was bonded to the nitrogen atom of pyrrole. Other physical properties of the two products were the same. The products of reactions B and C were pale yellow oils and were characterized as picrates. The two picrates had the same melting point. A mixture melting point of the two picrates was not depressed. The ^{1}H nmr spectra of the two picrates were identical to each other and indicated that the structure of the two oils is given by **8**. In reaction C, the pyrrole ring was selectively reduced to the pyrrolidine ring.

At a concentration of 200 μg/mL, 1-(2-pyrimidinyl)pyrrole (**3**) inhibited two plant pathogenic bacteria – *Xanthomanus phaseoli* (pathogenic on the bean plant) and *Xanthomanus malvacearum* (pathogenic on the cotton plant) [12].

Table I

Pyrimidinylpyrroles

Pyrimidinylpyrrole	Method of prepn [a]	Pyrimidine ring of product C-2	C-4	C-6
1-(2-pyrimidinyl)pyrrole (**3**)	A, B		H-	H-
1-(4-methyl-2-pyrimidinyl)pyrrole (**4**)	A		CH_3-	H-
1-(2-amino-4-methyl-6-pyrimidinyl)-pyrrole (**7**)	B	NH_2-	CH_3-	

[a] Method A - dry distillation of a mixture of the requisite aminopyrimidine with mucic acid. Method B - reaction of the requisite chloropyrimidine with potassium pyrrole.

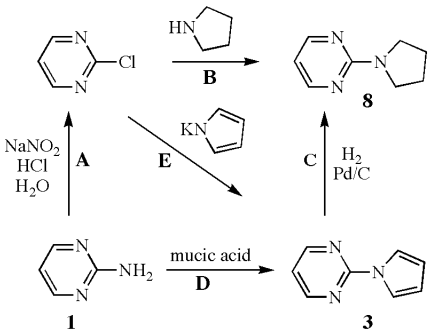
Table II

Pyrimidinylpyrrolidines

Pyrimidinylpyrrolidine	Method of prepn [a]	Pyrimidine ring of product C-2	C-4	C-6
1-(2-pyrimidinyl)pyrrolidine (**8**)	A,B		H-	H-
1-(2-amino-4-methyl-6-pyrimidinyl)-pyrrolidine (**9**)	A	NH_2-	CH_3-	
1-(4,6-dimethyl-2-pyrimidinyl)-pyrrolidine (**10**)	A		CH_3-	CH_3-
1-(2-amino-4-chloro-6-pyrimidinyl)-pyrrolidine (**11**)	A	NH_2-	Cl-	
2-amino-4,6-di(1-pyrrolidinyl)-pyrimidine (**12**)	A	NH_2-		

[a] Method A - reaction of a chloropyrimidine with pyrrolidine. Method B - selective catalytic hydrogenation of the pyrrole ring of a pyrimidinylpyrrole.

Scheme 1



EXPERIMENTAL

1-(2-Pyrimidinyl)pyrrole (**3**) from 2-Aminopyrimidine and Mucic Acid.

This compound was prepared in a manner similar to that described by Pictet and Crepieux for the preparation of 1-(3-pyridinyl)pyrrole from 3-aminopyridine and mucic acid [2]. In a typical experiment, an intimate mixture of 15.0 g (0.158 mol) of 2-aminopyrimidine and 15.0 g (0.0714 mol) of mucic acid was placed in a 200-mL round-bottomed flask fitted with a bent glass tube connected to a short air-cooled condenser (downward). The flask was heated in a Wood's metal bath (bath temperatures 145-335°). Most of the liquid distilled over at about 230° to about 270°. White fumes evolved from the condenser during distillation. The distillate solidified in the receiver (small beaker), forming yellow and white solids. The solids were broken up and mixed well with water (15 mL). The mixture was collected by vacuum filtration, using four small portions of water to complete the transfer. This crude product was dried by suction, by standing in air (45 min), and by heating in the air-oven at 50-55° (50 min), white crystals, 1.5 g (14%), mp 77-79°, soluble in cold ethanol, soluble in cold ether, insoluble in cold and hot water. For elemental analysis, the once-recrystallized products from four experiments were combined (0.54 g) and the combined lot was recrystallized from the solvent pair of 95% ethanol (10 mL) and water (22 mL), allowing crystals to form spontaneously over 1 h, white needles, mp 78-79°, dried in air-oven at 45-60° (31 h). ^{1}H nmr ($CDC1_3$): δ 6.38 (complex t, 2x β-H, pyrrole),7.82 (complex t, 2x α-H, pyrrole), 7.10 (t, 5-H, pyrimidine), 8.66 (d, 4-H & 6-H, pyrimidine).

Anal. Calcd. for $C_8H_7N_3$: C, 66.19; H, 4.86. Found: C, 66.34; H, 5.04.

1-(2-Pyrimidinyl)pyrrole (**3**) from 2-Chloropyrimidine and Potassium Pyrrole.

The required 2-chloropyrimidine was prepared from 2-aminopyrimidine according to the directions given by Kogon, Minin, and Overberger [13]. The crude 2-chloropyrimidine had mp 56-65°.

The required potassium pyrrole was prepared by the reaction of pyrrole with potassium hydroxide. Thus, a mixture of 10.0 g (0.149 mol) of freshly distilled pyrrole and 6.0 g of 85% potassium hydroxide pellets, equivalent to 5.1 g (0.091 mol) of pure potassium hydroxide, was refluxed for a few minutes during which time all of the potassium hydroxide went into solution (yellow). The hot contents was poured into a copper flask and heated over a wire gauze for about 5 min while compressed air was directed into the flask, forming a crust. Then the flask was allowed to cool in a desiccator to room temperature. The crusty solid was quickly broken up and pulverized, giving tan potassium pyrrole. This product was stored in a vial under nitrogen.

1-(2-Pyrimidinyl)pyrrole was prepared by heating a mixture of 2.00 g (0.0174 mol) of crude 2-chloropyrimidine (mp 57-64°), 2.0 g (0.019 mol) of crude potassium pyrrole (tan), and 10.0 mL of freshly distilled pyrrole on a steam bath for about 3 min, giving an olive colored mixture. The mixture then was heated over a wire gauze until the mixture began to boil. At this point, heating was stopped and the flask was swirled until boiling ceased. This procedure of heating over a wire gauze and swirling was repeated eight times more. The dark mixture was filtered while still hot, using 3x3 mL absolute alcohol to complete the transfer. The solid in the funnel was washed with 3x5 mL absolute alcohol and then the solid was discarded. The combined filtrate was evaporated to a few milliliters. This liquid was cooled in an ice-water bath. The soft dark brown solid that formed was collected by vacuum filtration. A smaller portion of dark brown solid was obtained by evaporating the filtrate to near dryness, cooling, and filtering. Both portions of solid were combined and recrystallized (charcoal) from the solvent pair of 95% ethanol (10 mL) and water (20 mL). The hot ethanol-water solution was cooled in an ice-water bath. The purified product was collected by filtration and sucked dry (0.5 h), tan powder, 89 mg (3.5%), mp 80-82.5°.

Another experiment was carried out in the same way, except that 6.0 mL (not 10 mL) of freshly distilled pyrrole was used. The crude product was recrystallized from 50% ethanol-water, giving white flattened needles, 55 mg (2.2%), mp 81.5-84°. A mixture melting point of this product (mp 81.5-84°) and the product (mp 80-83°) from the dry distillation of a mixture of 2-aminopyrimidine and mucic acid was 80.5-82.5°. Since no depression of the melting points occurred, the identity of the two products was indicated. Additionally, the two products had the same musty odor, were both soluble in cold ethanol, were both insoluble in cold water, both consisted of white needles when precipitated from ethanol-water, and both had identical ^{1}H nmr spectra.

1-(2-Pyrimidinyl)pyrrolidine (**8**) from 2-Chloropyrimidine and Pyrrolidine.

To 3.5 g (0.049 mol) of pyrrolidine in a 50 mL erlenmeyer flask, 2.0 g (0.017 mol) of 2-chloropyrimidine (mp 56-65°) was added in small portions with swirling. The flask became extremely hot. After the addition was complete, the contents consisted of a clear yellow oil. The flask was fitted with a mini reflux condenser and the contents was heated on the steam bath for 1.5 h and then was gently refluxed over a wire gauze for 2.5 h, giving a dark brown viscous liquid. This liquid, in a 10 mL distillation flask, was distilled at the reduced pressure offered by the water aspirator while the flask was heated in an oil bath (bath temperatures 170-220°). A clear pale yellow oil, 1.44 g (54%), distilled over. This oil was again distilled, this time at 762 mmHg. A clear pale yellow oil was collected at about 230-240°. This oil was assumed to be 1-(2-pyrimidinyl)pyrrolidine. The crude picrate of this oil had mp 150-174°. After five recrystallizations from 95% ethanol, the picrate had mp 164-173°. This picrate, after drying in the air-oven at 80° for 16 h, was submitted for elemental analysis. ^{1}H nmr of picrate ($CDC1_3$): δ 2.15 (complex t, 4x β-H**,** pyrrolidine), 3.77 (complex t, 4x α-H, pyrrolidine), 6.80 (t, 5-H, pyrimidine), 8.50 (d, 4-H & 6-H, pyrimidine), 8.91 (s, 3-H & 5-H, picric acid), about 11.50 (very broad s, OH, picric acid).

Anal. Calcd. for $C_{14}H_{14}N_6O_7$: C, 44.45; H, 3.73. Found: C, 44.84; H, 3.69.

In another experiment, 3.5 g (0.049 mol) of practical pyrrolidine (clear, yellow) were caused to react with 2.0 g (0.017 mol) of 2-chloropyrimidine (mp 57-64°). After workup, a portion of the pale yellow oil (product) was converted to a picrate in 95% ethanol, mp 160-170°. After two recrystallizations from 95% ethanol, the picrate had mp 165-173°. This picrate was allowed to dry in the air for 35 days and dried in the air oven at 75° for 1 h.

Anal. Calcd. for $C_{14}H_{14}N_6O_7$: C, 44.45; H, 3.73; N, 22.22. Found: C, 44.69; H, 3.51; N, 22.21.

1-(2-Pyrimidinyl)pyrrolidine (**8**) by Catalytic Hydrogenation of 1-(2-Pyrimidinyl)pyrrole (**3**) from 2-Aminopyrimidine and Mucic Acid.

A mixture of 1-(2-pyrimidinyl)pyrrole (3.2 g, 0.022 mol, mp 78-80°, prepared from 2-aminopyrimidine and mucic acid), 0.8 g of 10% Pd/C, and 100 mL of ethanol was shaken in a Parr hydrogenation apparatus at 27° for 14.5 h at an initial pressure of hydrogen of 31 psi. The mixture then was filtered through an infusorial earth mat. The filtrate was distilled to remove ethanol, leaving a clear yellow-orange liquid (about 3 mL). Water (25 mL) was added to this liquid. The mixture was cooled in an ice-water bath. The solid in the mixture was collected by suction filtration and dried at 55° for 70 min, white and crystalline, 0.22 g, mp 74-81.5°. This solid was assumed to be unreacted 1-(2-pyrimidinyl)pyrrole. The clear pale yellow filtrate was evaporated on the steam bath to give a clear yellow oil above a yellow-brown scum. This mixture was put in a test tube and centrifuged. The top layer of clear yellow oil, assumed to be 1-(2-pyrimidinyl)-pyrrolidine, was converted to a picrate, mp 167-174.5°. This picrate was recrystallized from 95% ethanol. The picrate was sucked with the water aspirator for 2 h, mp 165.5-172.5°. This picrate was used for the elemental analysis, for the mixture melting point, and for the ^{1}H nmr spectrum. The mp of a mixture of the picrate (mp 165.5-172.5°) formed in this experiment with the once-recrystallized picrate (mp 166-174.5°) formed from the product of the reaction of 2-chloropyrimidine with pyrrolidine was 166-172.5°. Since no depression of the melting points occurred, the identity of the two picrates was indicated. The ^{1}H nmr spectrum of the picrate formed in this experiment was identical to the ^{1}H nmr spectrum of the picrate formed from the product of the reaction of 2-chloropyrimidine with pyrrolidine.

Anal. Calcd. for $C_{14}H_{14}N_6O_7$: C, 44.45; H, 3.73; N, 22.22. Found: C, 44.51; H, 3.64; N, 22.21.

1-(4-Methyl-2-pyrimidinyl)pyrrole (**4**).

The requisite 2-amino-4-methylpyrimidine was prepared in three steps. Condensation of guanidine carbonate with ethyl acetoacetate in refluxing ethanol gave 2-amino-4-methyl-6-hydroxypyrimidine [14]. This 6-OH compound was converted to the 6-Cl compound by refluxing with an excess of phosphorus oxychlo-

ride [15,16]. In this step, after the main reaction, excess phosphorus oxychloride was destroyed by pouring the reaction mixture onto cracked ice. The 6-Cl atom was removed by heating with zinc dust in aqueous ammonium chloride [17]. The crude 2-amino-4-methylpyrimidine so prepared consisted of yellow flattened needles, mp 156-158°.

The method and apparatus used for the preparation of the title compound were the same as those used for the preparation of 1-(2-pyrimidinyl)pyrrole by the dry distillation of a mixture of 2-aminopyrimidine with mucic acid. Thus, an intimate mixture of 5.0 g (0.046 mol) of 2-amino-4-methylpyrimidine and 15.0 g (0.0714 mol) of mucic acid was heated at about 140-360° (bath temperatures) giving a yellow to dark orange distillate that solidified to white and yellow solids in the receiver cooled in an ice-water bath. Yellow-brown solid scraped from the condenser was combined with the solids in the receiver. The combined solid was recrystallized (charcoal) from the solvent pair of 95% ethanol (10 mL) and water (20 mL). The water-ethanol solution was refrigerated for 14.5 h, giving mostly colorless flat needles and some pale yellow crystals and grey particles. These solids were collected by filtration and sucked dry, 2.63 g, mp 37-130°. Another recrystallization (charcoal) was carried out using the solvent pair of 95% ethanol (17 mL) and enough hot water to reach the cloud point. The hot mixture was let stand at room temperature for 15 h and cooled in an ice-water bath for 1 h. The light grey long flat nacreous needles that precipitated were collected by filtration, 0.75 g (13%), mp 43-45°. A second crop was obtained from the filtrate by adding 2 mL of water and cooling in an ice-water bath for 2.5 h, 80 mg (1.3%), light tan flattened needles, mp 41-43.5°. Both crops were combined (0.83 g, 14%) and recrystallized from the solvent pair of 95% ethanol (10 mL) and enough hot water to reach the cloud point. The hot pale yellow alcohol-water mixture was allowed to stand for 14 h and then cooled in an ice-water bath for 1 h. The crystals that formed were collected by filtration, washed with 8x5 mL water, sucked dry, and dried in the air for nearly 4 h to give long flat transparent needles, mp 44-46°. For elemental analysis, a final recrystallization was carried out in the same manner as just described. The product was collected, washed with 3x5 mL water, and sucked dry for 3.25 h resulting in long transparent needles, mp 44.5-46°. ^{1}H nmr ($CDCl_3$): δ 6.38 (complex t, 2x β-H, pyrrole), 7.84 (complex t, 2x α-H, pyrrole), 2.54 (s, 4-CH_3, pyrimidine), 6.96 (d, 5-H, pyrimidine), 8.51 (d, 6-H, pyrimidine).

Anal. Calcd. for $C_9H_9N_3$: C, 67.90; H, 5.70. Found: C, 68.07; H, 5.67.

1-(2-Amino-4-methyl-6-pyrimidinyl)pyrrole (**7**).

In a 50-mL erlenmeyer flask, a mixture of 1.2 g (0.083 mol) of 2-amino-4-methyl-6-chloropyrimidine, 1.0 g (0.095 mol) of crude potassium pyrrole, and 10.0 mL of freshly distilled pyrrole was heated on the steam bath for 3 min, giving a dark brown mixture. The flask then was heated over a wire gauze until boiling started (foaming occurred). At this point heating was stopped and the flask was swirled and allowed to stand on the wire gauze until boiling ceased. This procedure of heating over the wire gauze, swirling, and standing was repeated twelve times more. The dark brown mixture was cooled in an ice-water bath for 1 h and allowed to stand at room temperature for 15 h. The dark brown partly crystalline solid was collected by filtration. The filtrate was concentrated to a few milliliters and the concentrate was cooled in an ice water bath to give about 0.1 g more of dark brown solid. Both solids were combined and extracted by adding absolute ethanol (10 mL) and charcoal and heating the mixture on the steam bath for about 5 min. The hot mixture was filtered by gravity. The solid on the filter paper was extracted again (no charcoal) in the same way, collecting both filtrates in the same container. The combined filtrate was heated on the steam bath and the hot brown solution was allowed to stand for 2 h and then cooled in an ice water bath for 5 min. The needles that separated were collected by filtration, washed with 3xl mL water, and sucked dry giving tan flat needles, 0.417 g, mp 153-155.5°. A third extraction (no charcoal) of the dark brown solid gave light tan short fine glistening needles, 0.056 g, mp 153-155°. Both portions of crude product were combined (0.473 g, 32.6%) and recrystallized (charcoal) from 50% ethanol-water (11 mL), letting the hot filtrate cool spontaneously for 12 h, followed by cooling in an ice water bath for nearly 4 h. The crystals that separated were collected by filtration, using 5x2 mL water to complete the transfer. The crystals, after being dried at 100-105° for about 2.5 h, had mp 152-154.5°. The Beilstein test was negative (no Cl). For elemental analysis, the product was recrystallized from 50% ethanol-water (8 mL), allowing the filtrate to cool spontaneously for nearly 2 h. The purified product was collected by filtration and washed with 2 mL of water, long flattened white needles, dried at 95-100° for 13 h, mp 152-154.5°. ^{1}H nmr ($CDCl_3$): δ 2.37 (s, 4-CH_3, pyrimidine), 5.25 (broad s, 2-NH_2, pyrimidine), 6.48 (s, 5-H, pyrimidine), 6.33 (complex t, 2x β-H, pyrrole), 7.47 (complex t, 2x α-H, pyrrole).

Anal. Calcd. for $C_9H_{10}N_4$: C, 62.05; H, 5.79. Found: C, 62.46; H, 6.03.

1-(2-Amino-4-methyl-6-pyrimidinyl)pyrrolidine (**9**).

To 1.0 g (0.014 mol) of practical pyrrolidine (pale yellow) in a 50 mL erlenmeyer flask was added 1.0 g (0.0070 mol) of 2-amino-4-methyl-6-chloropyrimidine in portions with stirring and heating on the steam bath. Additional pyrrolidine (40 drops) was added in portions along the way inasmuch as the mixture became very dry. The white mixture was heated strongly on the steam bath for 7 min and then allowed to cool to room temperature. Water (10 mL) was added with vigorous stirring. The chalky white solid was collected by filtration, using 12 mL of water to complete the transfer. The solid was washed with 2x5mL of water, sucked with the vacuum, and allowed to dry in air for 13 h, 0.95 g (79%), mp 170-173°. This crude product was recrystallized from the solvent pair of 95% ethanol (10 mL) and water (110 mL), allowing the hot ethanol-water solution to cool spontaneously for 1 h, adding 53 drops of water, and stirring the solution with scratching to cause precipitation of fine white crystals. The product was collected by filtration, using three small portions of water to complete the transfer. The product was sucked dry for 1.75 h, 0.58 g, mp 171-172°. A second crop was obtained by cooling the filtrate (3.75 h), collecting the product by filtration, and sucking the product with the vacuum (40 min), fine white crystals, 0.10 g, mp 170-171.5°. Both crops were combined (0.68 g, 57%). For elemental analysis, the product was recrystallized from the solvent pair of 95% ethanol (10 mL) and water (about 45 mL), allowing the solution to cool in an ice-water bath for 1 h, stirring the solution vigorously to cause precipitation of crystals, cooling for 25 min more, and letting the mixture stand at room temperature for 22 h. The product was collected by filtration, using a small portion of water to complete the transfer, and dried at 100-105° for 28 h, fine white crystals, mp 169-170°. ^{1}H nmr ($CDCl_3$): δ 1.96 (broad complex t, 4x β-H, pyrrolidine), 3.41

(broad s, 4x α-H, pyrrolidine), 2.21 (s, 4-CH_3, pyrimidine), 5.63 (s, 5-H, pyrimidine), 4.75 (broad s, 2-NH_2, pyrimidine).

Anal. Calcd. for $C_9H_{14}N_4$: C, 60.64; H, 7.92. Found: C, 60.67; H, 7.95.

1-(4,6-Dimethyl-2-pyrimidinyl)pyrrolidine (**10**).

The requisite 2-chloro-4,6-dimethylpyrimidine was prepared in two steps. Condensation of guanidine carbonate with 2,4-pentanedione (acetylacetone) in refluxing 95% ethanol afforded 2-amino-4,6-dimethylpyrimidine [18]. Diazotization of this aminopyrimidine with aqueous sodium nitrite in an excess of hydrochloric acid gave the 2-chloro compound [13].

To 3.0 g (0.021 mol) of 2-chloro-4,6-dimethylpyrimidine, 7.5 g (0.11 mol) of practical pyrrolidine was added in two portions. About half of the pyrrolidine was added with shaking. The mixture became progressively warmer and spontaneously boiled, forming an orange-brown viscous liquid. When boiling ceased, the remainder of the pyrrolidine was added with shaking. The mixture was concentrated by heating on steam and the concentrate was cooled to room temperature. An excess of 10% sodium hydroxide was added, giving two layers. The lower aqueous layer was separated from the upper dark orange-brown layer. The aqueous layer was extracted with two portions of ether and both extracts were added to the dark orange-brown layer. The ether was removed by heating the solution on the steam bath. The remaining dark orange-brown viscous liquid was distilled at 3 mmHg, giving a pale yellow distillate (bp 114-116°/3 mmHg) and hard white waxy solid that collected in the condenser. The pale yellow distillate, upon scratching, solidified completely, forming pale yellow crystals. These crystals were combined with the hard white waxy solid removed from the condenser, 2.5 g (67%), mp 49.5-51°, negative Beilstein test (no Cl), soluble in cold 95% ethanol, insoluble in cold water, insoluble in 5% sodium hydroxide, soluble in cold 5% hydrochloric acid. This product was recrystallized (charcoal) from the solvent pair of 95% ethanol (about 7 mL) and water (about 6 mL), allowing the ethanol-water solution to cool in an ice-water bath. Upon seeding, crystals formed rapidly. The mixture was cooled for 0.5 h more. The soft white glistening needles (larger portion) were collected, washed with water, and dried at room temperature over calcium chloride for 22 h, 1.57 g (42%), mp 49.5-50.5°. The pale yellow needles in the filtrate (smaller portion) were collected, washed with water, and dried in the same way, 0.14 g (3.8%), mp 49.5-51.2°. The larger portion was recrystallized from the solvent pair of ethanol and water, allowing the solution to cool in an ice-water bath for 1.75 h. The crystals (major crop) that formed were collected and washed with water, long white needles with a faint yellowish color. The soft long white needles (minor crop) that formed in the filtrate were collected and washed twice with water. Both crops were dried at room temperature over phosphorus pentoxide *in vacuo* for 67.5 h. The major crop had mp 49.7-51°. The minor crop had mp 49-50°. ^{1}H nmr ($CDC1_3$): δ 1.98 (broad complex t, 4x β-H, pyrrolidine), 3.62 (broad complex t, 4x α-H, pyrrolidine), 2.31 (s, 4-CH_3 & 6-CH_3, pyrimidine), 6.30 (s, 5-H, pyrimidine).

Anal. Calcd. for $C_{10}H_{15}N_3$: C, 67.76; H, 8.53. Found: C, 67.15; H, 8.44.

1-(2-Amino-4-chloro-6-pyrimidinyl)pyrrolidine (**11**).

To 1.0 g (0.0061 mol) of 2-amino-4,6-dichloropyrimidine (mp 216-217°), 1.0 g (0.014 mol) of practical pyrrolidine (pale yellow) was added in two portions. About half of the pyrrolidine was added. An immediate exothermic reaction ensued, causing the contents to boil. When this reaction subsided, the remainder of the pyrrolidine was added, causing the same exothermic reaction. After the reaction subsided, the solid was broken up and 5 mL of water were added with swirling. The tan solid was collected by filtration, using several small portions of water (total of 15 mL) to complete the transfer. The tan solid was allowed to dry in air for 1 h and dried at 80-85° for 100 min, mp softened at 137-144° and melted only partially above 144°. The solid was recrystallized (charcoal) from 95% ethanol (20 mL), allowing the yellow filtrate to cool in an ice-water bath for 1.5 h. The white solid that formed was collected and sucked dry, mp 155-170°, positive Beilstein test (Cl present), dried in air overnight, 0.27 g (23%). The solid was recrystallized from the solvent pair of 95% ethanol (15 mL) and water (10 mL), allowing the ethanol-water solution to cool in the ice-water bath for 3.5 h. The product was collected and sucked dry, soft fine white crystals, mp 165-172°. To these crystals 10 mL of 95% ethanol were added and the mixture was heated on the steam bath until it was slightly turbid. The mixture was filtered. The turbid filtrate was cooled in an ice-water bath for 15 min. Flocculent solid formed. The mixture was filtered. To the nearly clear filtrate 10 mL of water were added, giving a milky suspension that was heated briefly on the steam bath with stirring. The flocculent solid that formed was removed by filtration. The slightly cloudy filtrate was let stand for 1.5 h whereupon more flocculent solid formed. The mixture was filtered. The clear filtrate was cooled in an ice-water bath for nearly 3 h during which time fine white nacreous needles formed. These needles were collected and dried at 95-100° for 2.5 h, mp 177.5-179.5°. For elemental analysis the sample was dried for an additional 17.5 h at 95-100°. No sample was available for a ^{1}H nmr spectrum.

Anal. Calcd. for $C_8H_{11}N_4Cl$: C, 48.37; H, 5.58. Found: C, 48.74; H, 5.48.

2-Amino-4,6-di(1-pyrrolidinyl)pyrimidine (**12**).

To 1.02 g of 99% pure 2-amino-4,6-dichloropyrimidine, equivalent to 1.00 g (0.00610 mol) of 100% pure compound, cooled in an ice water bath, were added 1.77 g (2.06 mL) of 99% pure pyrrolidine. A vigorous exothermic reaction occurred. The ice-water bath was removed and the mixture was heated on the steam bath for 32 min. Then 1.1 g (1.3 mL) of 99% pyrrolidine was added through the top of the condenser and the mixture was heated for 28 min. Then 1.1 g (2.06 mL) of 99% pyrrolidine was added and the mixture was heated for 2 h 21 min more. Thus the reactants were heated on the steam bath for a total of 3 h 21 min. A total of 3.99 g of 99% pyrrolidine, equivalent to 3.93 g (0.0553 mol) of 100% pure pyrrolidine, was used in the reaction. The resulting heterogeneous mixture was allowed to stand at room temperature in the dark for 43.5 h. The solids were broken up and collected by filtration, using 2x4 mL water to complete the transfer. The cream-colored solid was washed with 2x6 mL water and dried at 62° for 2.5 h, 1.29 g, mp 204-211° with softening and sintering occurring over many degrees before 204°. This solid was recrystallized from the solvent pair of 95% ethanol and water. About one-third of the solid did not dissolve in the hot 95% ethanol. This insoluble solid was discarded. The ethanol-water mixture was let stand at room temperature for 111 min. The soft nacreous off-white crystals that separated were collected by filtration, using 4x3 mL water to complete the transfer. The crystals were washed with 7 mL water, sucked with the vacuum for

11 min, and dried in the air-oven at 60-61° for 128 min, 0.239 g (16.8%), negative Beilstein test (no Cl), mp 207-213.5° with most of the melting occurring at 211-213.5°. The product was again recrystallized from the solvent pair of 95% ethanol and water, allowing the hot ethanol-water mixture to stand at room temperature for 160 min. The nacreous off-white crystals that separated were collected by filtration, using 2x2 mL water to complete the transfer, washed with 2x4 mL water, sucked with the vacuum for 10 min, and dried in the air-oven at 75° for 5.75 h, long flat narrow rectangular transparent needles (x100), 96 mg (6.8%), negative Beilstein test (no Cl), mp 209-212.5°. ^{1}H nmr ($CDC1_3$): δ 1.91-1.96 (broad complex t, 8x β-H, pyrrolidine), 3.35-3.44 (broad complex t, 8x α-H, pyrrolidine), 4.49 (broad s, 2-NH_2, pyrimidine), 4.69 (s, 5-H, pyrimidine).

Anal. Calcd. for $C_{12}H_{19}N_5$: C, 61.77; H, 8.21; N, 30.02. Found: C, 61.81; H, 7.87; N, 30.00.

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REFERENCES AND NOTES

[1] The major portion of this work was carried out in 1954-1956 in the College of Liberal Arts and Sciences of Temple University, Philadelphia, PA, as part of my requirements for the degree of Master of Arts, under the direction of Professor William T. Caldwell, now deceased. A minor portion of this work was subsequently carried out in the School of Pharmacy, Temple University, and in the Department of Chemistry, Villanova University. None of this work has heretofore been submitted for publication. This paper is dedicated to the memory of my parents — Myer and Tootsie (Yetta) Becker.

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[3] M. Nonoyama, *Transition Metal Chemistry*, **12**, 1 (1987). Nonoyama's method seemingly is patterned after the procedure described by N. Clauson-Kaas and Z. Tyle, *Acta Chem. Scand*., **6**, 667 (1952) for the preparation of N-substituted pyrroles by the reaction of a 2,5-dialkoxytetrahydrofuran with a primary amine.

[4] A. R. Katritzky, J. Lewis, G. Musumarra, and G. Ogretir, *La Chimica e L'Industria*, **58**, 381 (1976).

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[6] Katritzky and coworkers [4,5] state that they used the method of R. A. Jones, *Austral. J. Chem.*, **19,** 289 (1966) for the preparation of N-substituted pyrroles. Jones's method is the same as that devised by Clauson-Kaas and Tyle in 1952. See [3].

[7] See, for example, D. J. Brown, The Pyrimidines, Interscience Publishers, NY, 1962, pp 181-182 and pp 187-201.

[8] We prepared 1-(2-pyrimidinyl)pyrrolidine (**8**) from 2-chloropyrimidine and pyrrolidine in 1956. N. Chatani, T. Asaumi, S. Yorimitsu, and S. Murai, *J. Am. Chem. Soc*., **123**, 10,935 (2001) state that they prepared **8** (no experimental details are given) by the reaction of 2-chloropyrimidine with pyrrolidine according to A. Hassner, A. L. R. Krepski, and V. Alexanian, *Tetrahedron*, **34**, 2069 (1978). Hassner's paper, however, does not mention **8**.

[9] A paper by J. W. Liebescheutz and coworkers, *Pesticide Science*, **50**, 250 (1997) states that 1-(2-pyrimidinyl)pyrrolidine (**8**) was prepared from 2-chloropyrimidine and pyrrolidine but the usual experimental details are lacking. However, ^{1}H nmr data for the product are given: (90 MHz): δ 8.37 (2H, d, J=4.5 Hz), 6.50 (1H, t, J=4.5 Hz), 3.60 (4H, m), 2.0 (4H, m).

[10] Subsequent to our work carried out in 1965, H. Grube and H. Suhr, *Ber*., **102**, 1570 (1969) prepared 1-(4,6-dimethyl-2-pyrimidinyl)-pyrrolidine (**10**) by the same method used in this work. The mp of their product (mp 51-52°) was virtually the same as the mp of our product (mp 49.7-51° uncorrected). Grube and Suhr prepared **10** in 88% yield by heating the reactants at 50° for 3 h. They determined the rate constant of the reaction.

[11] We prepared 2-amino-4,6-di(l-pyrrolidinyl)pyrimidine (**12**) in 2003. Subsequently we discovered that two groups of workers – designated (a) and (b) – had prepared **12** earlier. (a) W. B. Cowden and N. W. Jacobsen, *Austral. J. Chem.*, **32**, 2049 (1979) had prepared **12** by essentially the same method we used. Our mol ratio of pyrrolidine to pyrimidine was 9:1 whereas Cowden and Jacobsen's mol ratio was 38:1. We gently heated the reactants on the steam bath for 3 h 21 min whereas Cowden and Jacobsen refluxed the reactants for 4 h. The mp of our analytically pure product was 209-212.5° whereas the mp of Cowden and Jacobsen's product was 221-222°. The ^{1}H nmr spectrum of our product confirmed its structure. Cowden and Jacobsen give no spectral data. (b) J. N. Low and coworkers, *Acta Crystallographica*, **C58,** 289 (2002) also had prepared **12** but under conditions of reaction different from ours. They refluxed a solution of 2-amino-4,6-dichloropyrimidine, pyrrolidine, triethylamine, and butanol, with stirring, for 56 h. The mol ratio of pyrrolidine to pyrimidine was 3.5:1. They characterized their product by mp (224°), by ^{1}H nmr and ^{13}C nmr spectra, and by X-ray crystallography. Their single crystal X-ray diffraction data indicated that the molecules of **12** take the form of a chain of fused rings, that the molecules are associated through hydrogen bonds involving donor hydrogen atoms of the 2-amino group and acceptor nitrogen atoms in the pyrimidine ring, that the nitrogen atoms of the pyrrolidine moieties do not participate in hydrogen bonds, and that aromatic π - π stacking interactions are absent.

[12] Biological testing was carried out by Eli Lilly and Co.

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