SYNTHESIS OF AZA ANALOGS OF AMRINONE

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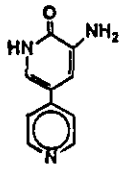
Abstract - The aldol condensation product (4) of 4-acetylpyridine (2) and diethyl mesoxalate (3) was converted to pyridazinecarboxylic acid hydrazide (6). Curtius reaction of 6 gave aminopyridazinone (7). The condensation of (4-pyridinyl)glyoxal (17) with aminomalonamide (9) yielded pyrazinecarboxamide (18) which was transformed to aminopyrazinone (19) by the Hofmann reaction. Curtius reaction of 1,2,4-triazinone-5-carboxylic acid (21b) gave aminotriazinone (22). Demethylation of methoxypyrimidine (29) prepared from methyl 2-methoxyformylacetate (25) and isonicotinamidine (26) gave pyrimidinol (30).

Several years ago, the search for a nonglycoside cardiotonic agent in our laboratory led to the development of amrinone (1).[2] Our continuing efforts to find an orally active and a more potent agent have led to the design and synthesis of several aza analogs of 1. The replacement of 2(1H)-pyridinone moiety of 1 by pyridazine, pyrazine, 1,2,4-triazine and pyrimidine ring systems has resulted in the synthesis of 7, 19, 22 and 30, respectively. The preparation of these compounds required the synthesis of novel intermediates depicted in schemes A, B, C and D, respectively. The key intermediates are 4, 17, 21b and 29.

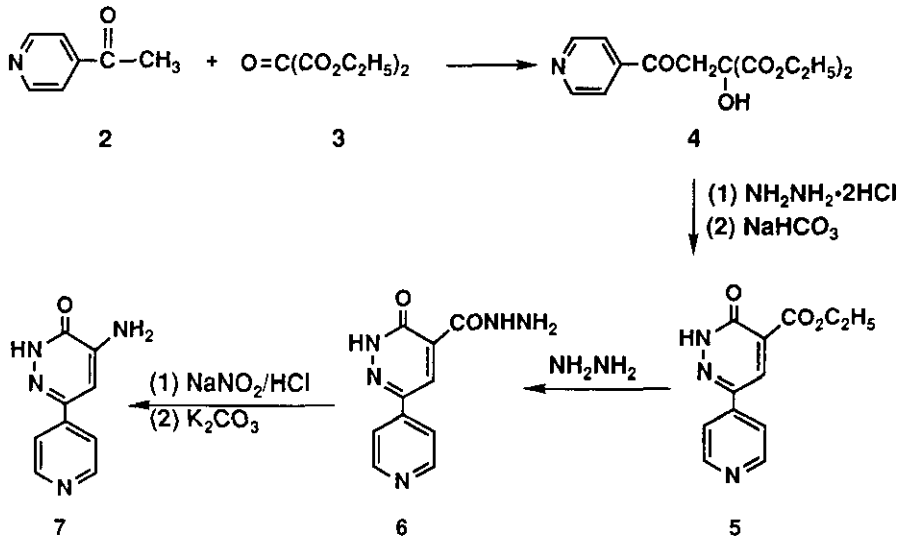


1
amrinone

RESULTS AND DISCUSSION

Aldol condensation of 4-acetylpyridine (2) with diethyl mesoxalate (3) gave diethyl malonate derivative (4) in a moderate yield. Reaction of 4 with hydrazine dihydrochloride followed by treatment with aqueous sodium bicarbonate yielded pyridazinecarboxylic acid ester (5), which was converted to hydrazide (6) in high yield. Curtius reaction of 6 gave the corresponding amino compound (7) identical with a sample previously prepared by a different method.[3]

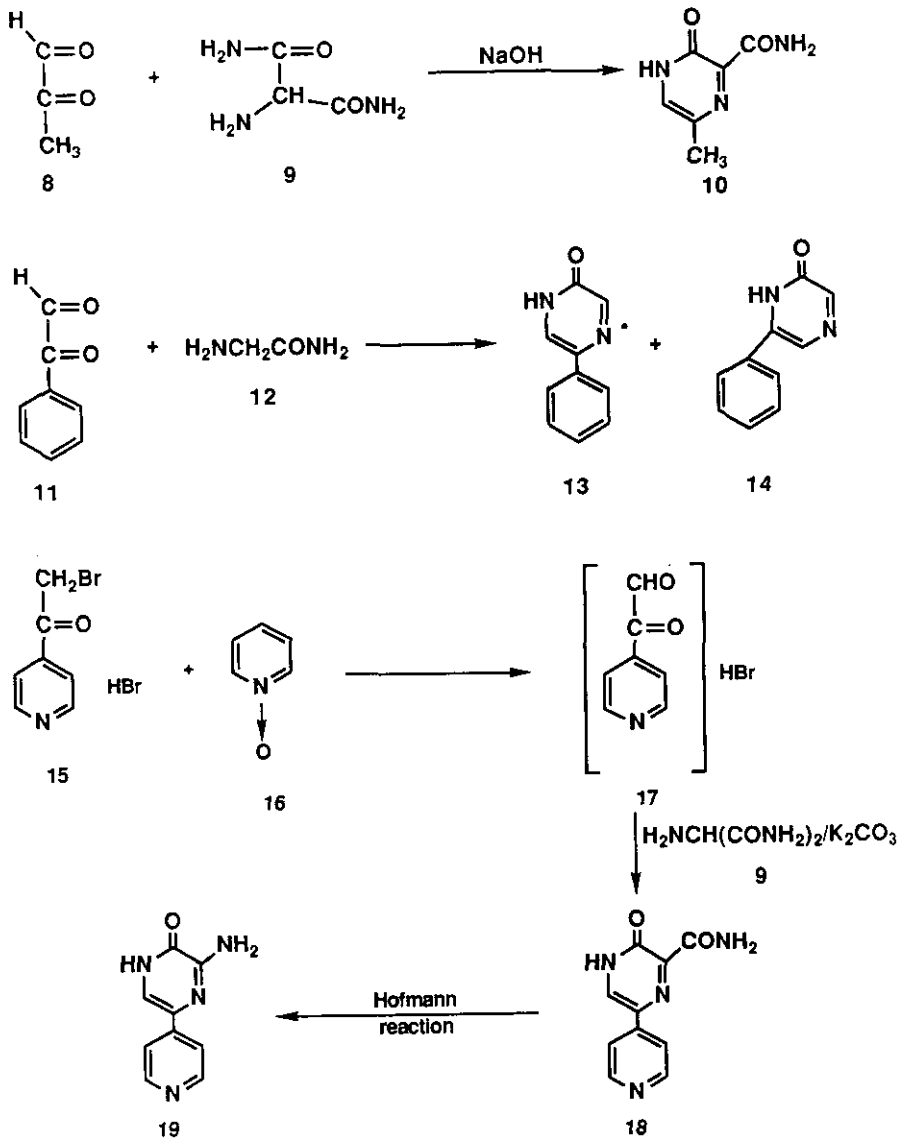
Scheme A



In 1949, Jones[4] reported that the condensation of methylglyoxal (**8**) with aminomalonamide (**9**) in the presence of sodium hydroxide gave only 1,2-dihydro-5-methyl-2-oxo-3-pyrazinecarboxamide (**10**) in 59% yield. In 1978, Sato[5] reported that the reaction between phenylglyoxal (**11**) and glycinamide (**12**) produced a mixture of 5-phenyl-2(1H)-pyrazinone (**13**) and 6-phenyl-2(1H)-pyrazinone (**14**) in a ratio of 20:1. The reaction of (4-pyridinyl)glyoxal (**17**) with aminomalonomide gave only one compound in 27% yield assigned structure (**18**) on the basis of the two

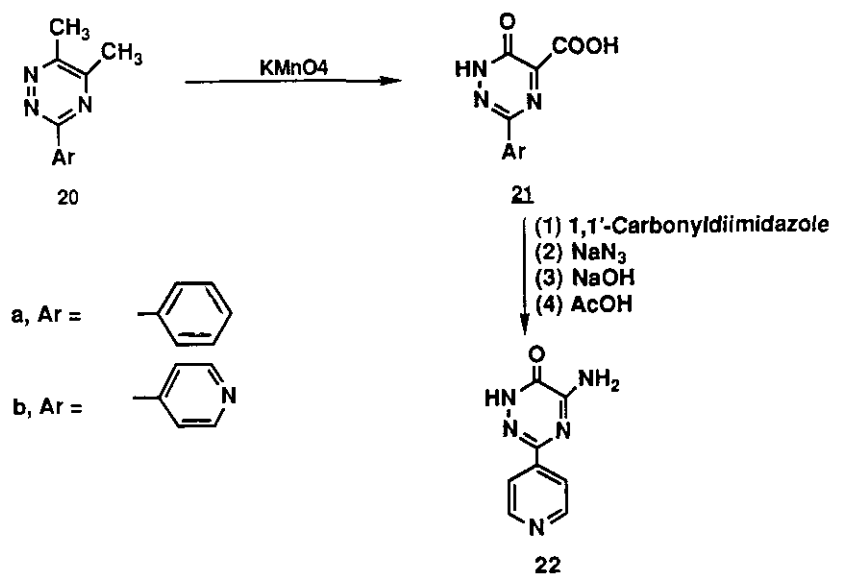
examples described above. The nmr spectrum is also consistent with this structure (experimental section). (4-Pyridinyl)glyoxal was prepared in situ by reacting 4-(bromoacetyl)pyridine with pyridine N-oxide.[6] Hofmann reaction of 18 gave the amino compound (19).

Scheme B



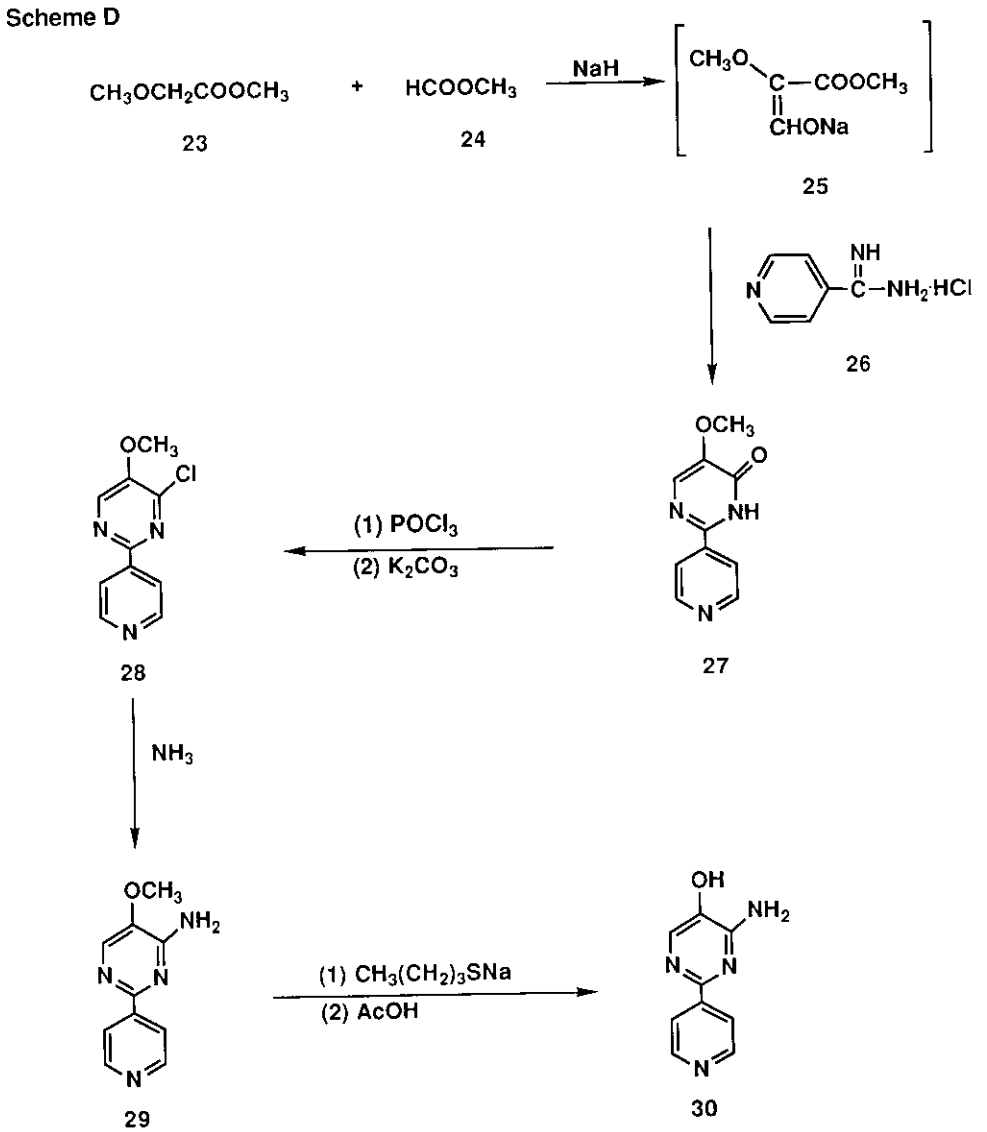
Metze and Meyer[7] showed that the oxidation of 5,6-dimethyl-3-phenyl-1,2,4-triazine (**20a**) with potassium permanganate resulted in the formation of 1,6-dihydro-6-oxo-3-phenyl-1,2,4-triazine-3-carboxylic acid (**21a**) in 59% yield. From the oxidation of 5,6-dimethyl-3-(4-pyridinyl)-1,2,4-triazine[8] (**20b**) with potassium permanganate, an acid was obtained in 61% yield which was assigned structure (**21b**) by analogy with 21a. The nmr spectrum supports this structural assignment (experimental section). Curtius rearrangement of this acid produced amino compound (22).

Scheme C



Sodium enolate[9] (25) was reacted with isonicotinamidine hydrochloride[10] to give pyrimidone (27) which in turn was converted to chloropyrimidine (28). Treatment of 28 with ammonia in an autoclave gave pyrimidinamine (29). Cleavage of the methyl ether with sodium butanethiolate yielded pyrimidinol (30) in a good yield.

Scheme D



Although 7, 19, 22 and **30** have close structural resemblance to amrinone (1), only aminopyridazinone (7) has cardiotonic activity equal to that of amrinone. The other three compounds are inactive.

EXPERIMENTAL

Melting points were determined in open capillaries in an oil bath and are uncorrected. The nmr spectra were obtained in deuteriotrifluoroacetic acid, unless indicated otherwise, on a Varian HA-100 spectrometer using tetramethylsilane as the internal standard, and chemical shifts are reported in parts per million and are given in δ units.

Diethyl hydroxy[2-oxo-2-(4-pyridinyl)ethylpropanedioate (4). A mixture of diethyl mesoxalate (99.7 g, 0.57 mol) and 4-acetylpyridine (55.4 g, 0.46 mol) was stirred and heated on a steam bath for 12 h and then left at room temperature overnight. The resulting solid was collected and recrystallized from EtOH to afford 79 g (58%) of tan crystals of **4**; mp 130-132°C; ms: M^+ m/z 295; ^{1}H nmr: δ 9.12, 8.60 (A_2B_2, J=5.8Hz, 4H, $-C_5H_4N$), 4.55 (q, J=7Hz, 4H, 2X-$OC\underline{H}_2CH_3$), 4.27 (s, 2H, O=C-CH_2-), 1.40 (t, J=7Hz, 6H, 2X-$OCH_2C\underline{H}_3$). Anal. Calcd for $C_{14}H_{17}NO_6$: C, 56.95; H, 5.80; N, 4.74. Found: C, 57.03; H, 5.85; N, 4.71.

Ethyl 2,3-dihydro-3-oxo-6-(4-pyridinyl)-4-pyridazinecarboxylate (5). A mixture of **4** (29.5 g, 0.1 mol), hydrazine dihydrochloride (10.6 g, 0.1 mol), and EtOH (1 l) was heated under reflux with stirring for 18 h and then cooled to room temperature. The resulting mixture was concentrated under reduced pressure and the residue was quenched with aqueous $NaHCO_3$. The resulting white solid was collected, washed with water and dried. This solid was suspended in boiling EtOH and then filtered off to give 17.4 g (71%) of the title compound; mp 196-197°C; ms: M^+ m/z 245; ^{1}H nmr: δ 9.10, 8.75 (A_2B_2, J=6Hz, 4H, $-C_5H_4N$), 8.99 (s, 1H, 5-H), 4.70 (q, J=7Hz, 2H, $-OC\underline{H}_2CH_3$), 1.60 (t, J=7Hz, 3H, $-OCH_2C\underline{H}_3$). Anal. Calcd for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.68; H, 4.64; N, 17.19.

2,3-Dihydro-3-oxo-6-(4-pyridinyl)-4-pyridazinecarboxylic acid hydrazide (6). A stirred mixture of **5** (24.5 g, 0.1 mol), 95% hydrazine hydrate (30 ml), and EtOH (475 ml) was heated under reflux for 3.5 h and then chilled in an ice bath. The resulting crystals were collected and dried to afford 19.5 g (84%) of **6**; mp 212-213°C; ms: M^+ m/z 231; ^{1}H nmr: δ 9.30 (s, 1H, 5-H), 8.94, 8.78 (A_2B_2, J=6Hz, 4H, $-C_5H_4N$). Anal. Calcd for $C_{10}H_9N_5O_2$: C, 51.95; H, 3.92; N, 30.29. Found: C, 52.05; H, 3.97; N, 30.16.

4-Amino-6-(4-pyridinyl)-3(2H)-pyridazinone (7). To a stirred mixture of **6** (28 g, 0.12 mol) and 6N aqueous HCl (1.1 l) was added a solution of sodium nitrite (20 g, 0.29 mol) in water (75 ml) below 5°C over a 30 min period. The reaction mixture was stirred further below 5°C for 45 min at room temperature for 30 min and then at 50-60°C for 2 h. The resulting mixture was concentrated to near dryness under vacuo. The residue was dissolved in aqueous NaOH and precipitated by acidifying with AcOH. The tan product was collected, washed with water and recrystallized from MeOH to give 14.2 g (63%) of 7[3]; mp 304-306°C (lit.,[3] mp 305-307°C); ^{1}H nmr: δ 9.03, 8.63 (A_2B_2, J=6Hz, 4H, $-C_5H_4N$), 7.44 (s, 1H, 5-H).

1,2-Dihydro-2-oxo-5-(4-pyridinyl)-3-pyrazinecarboxamide (**18**). To a stirred solution of 4-(bromoacetyl)pyridine hydrobromide (56 g, 0.2 mol) in MeOH (350 ml) cooled in an ice bath was added pyridine N-oxide (37 g, 0.39 mol). The ice bath was removed and the reaction mixture was allowed to stir at room temperature for 24 h. Aminomalonamide (24 g, 0.2 g) was added and the reaction mixture was cooled again in an ice bath. The reaction mixture was then treated with 20% aqueous K_2CO_3 (140 ml) in a dropwise manner. After stirring the reaction mixture at room temperature for 24 h, the MeOH was removed under reduced pressure and the tan crystalline solid was collected. It was suspended in boiling MeOH and then filtered off to give 11.7 g (27%) of **18**; mp 298-301°C; ms: M^+ m/z 216; ^{1}H nmr: δ 9.10, 8.85 (A_2B_2, J=5.8Hz, 4H, $-C_5H_4N$), 9.03 (s, 1H, 6-H). Anal. Calcd for $C_{10}H_8N_4O_2$: C, 55.56; H, 3.73; N, 25.91. Found: C, 55.16; H, 3.70; N, 25.91.

3-Amino-5(4-pyridinyl)-2(1H)-pyrazinone (**19**). To a stirred solution of 35% aqueous NaOH (100 ml) and water (400 ml) cooled to 0°C was added bromine (10.5 ml, 0.2 mol) dropwise followed by finely powdered **18** (15 g, 70 mmol). The resulting mixture was further stirred at 0-5°C for 4 h and then acidified with AcOH. The yellow product was collected and recrystallized from DMF to give 8.2 g (63%) of a tan solid; mp >290°C dec.; ms: M^+ m/z 188; ^{1}H nmr: δ 8.95, 8.42 (A_2B_2, J=5.6Hz, 4H, $-C_5H_4N$), 7.93 (s, 1H, 6-H). Anal. Calcd for $C_9H_8N_4O$: C, 57.46; H, 4.28; N, 29.77. Found: C, 57.34; H, 4.12; N, 29.52.

1,6-Dihydro-6-oxo-3-(4-pyridinyl)-1,2,4-triazine-5-carboxylic acid (**21b**). To an ice cold stirred mixture of **20b**[8] (18.6 g, 0.1 mol), 35% aqueous NaOH (140 ml), and water (500 ml) was added solid $KMnO_4$ (97 g, 0.61 mol) below 15°C over 2 h. The ice bath was removed, and the

reaction mixture was stirred at room temperature for 22 h and then treated with 27% aqueous formaldehyde until the purple color of $KMnO_4$ was discharged. The resulting thick brown mixture was filtered through a Celite pad. The filtrate was acidified with concentrated HCl whereupon a yellow solid crystallized. The product was collected, washed with water and dried to give 13.4 g (61%); mp 228-230°C; ^1H nmr: δ 9.27, 9.04 (A_2B_2, J=6.6Hz, 4H, $-C_5H_4N$). Anal. Calcd for $C_9H_6N_4O_3$: C, 49.55; H, 2.74; N, 25.68. Found: C, 49.44; H, 2.82; N, 25.47.

5-Amino-3-(4-pyridinyl)-1,2,4-triazin-6(1H)-one (22). To a solution of **21b** (10.9 g, 50 mmol), triethylamine (7.2 ml) and DMF (75 ml) was added 1,1'-carbonyldiimidazole (10.2 g, 63 mmol). The resulting mixture was stirred for 1 h and then treated with sodium azide (4.1 g, 63 mmol). After heating on a steam bath for 1.5 h, the resulting mixture was concentrated under reduced pressure. The residue was treated with 10% aqueous NaOH (50 ml) and stirred for 1 h. The resulting solution was acidified with AcOH. The precipitate was collected, washed with water, dried and recrystallized from DMF to give 4.4 g (44%) of a tan solid; mp >330°C; ms: M^+ m/z 189; ^1H nmr: δ 9.16, 8.75 (A_2B_2, J=6.4Hz, 4H, $-C_5H_4N$). Anal. Calcd for $C_8H_7N_5O$: C, 50.79; H, 3.73; N, 37.20. Found: C, 50.70; H, 3.84; N, 36.97.

5-Methoxy-2-(4-pyridinyl)-4(3H)-pyrimidinone (27). To a stirred mixture of 50% NaH/oil dispersion (5 g, 0.1 mol) in THF (150 ml) at room temperature was added dropwise a solution of methyl methoxyacetate (10.4 g, 0.1 mol) and methyl formate (8 g, 0.12 mol) over a period of 20 min. The resulting mixture was continuously stirred for 2 h and then Et_2O (200 ml) was added and the solid was collected. This solid was added to a stirred mixture of isonicotinamidine hydrochloride (15.8 g, 0.1 mol) and EtOH (200 ml). The resulting mixture was stirred at room temperature for 24 h and refluxed for 1 h. Water (200 ml) was added and the mixture was heated until most of the solid dissolved. The hot solution was filtered and the filtrate was acidified with AcOH. Removal of EtOH under reduced pressure resulted in crystallization. The tan crystals were collected, washed with EtOH and dried to yield 11.1 g (55%) of **27**; mp 249-251°C dec.; ms: M^+ m/z 203; ^1H nmr: δ 9.30, 8.70 (A_2B_2, J=6Hz, 4H, $-C_5H_4N$), 8.23 (s, 1H, 6-H), 4.18 (s, 3H, OCH_3). Anal. Calcd for $C_{10}H_9N_3O$: C, 59.11; H, 4.66; N, 20.68. Found: C, 59.14; H, 4.47; N, 20.60.

4-Chloro-5-methoxy-2-(4-pyridinyl)pyrimidine (28). A stirred mixture of 27 (10 g, 49.2 mmol) and phosphorous oxychloride (85 ml, 0.91 mol) was heated under reflux for 1.5 h and then most of the unreacted phosphorous oxychloride was removed under reduced pressure. The residue was poured over ice and neutralized by treating with solid K_2CO_3. The product was extracted with $CHCl_3$ (2 x 200 ml). The combined $CHCl_3$ extract was concentrated to dryness and the residue was crystallized from 2-PrOH to afford 9.7 g (90%) of a light pink solid; mp 129-131°C dec.; ms: M^+ m/z 221; ^1H nmr (DMSO-d_6): δ 8.71 (s, 1H, 6-H), 8.68, 8.08 (A_2B_2, J=6Hz, 4H, -C_5H_4N), 4.10 (s, 3H, OCH_3). Anal. Calcd for $C_{10}H_8ClN_3O$: C, 54.19; H, 3.64; N, 18.96. Found: C, 54.30; H, 3.67; N, 18.97.

5-Methoxy-2-(4-pyridinyl)-4-pyrimidinamine (29). A mixture of 28 (44.2 g, 0.2 mol), liquid ammonia (100 ml) and EtOH (450 ml) was heated at 130°C in an autoclave for 8 h. After cooling to room temperature, the resulting dark solution was treated with charcoal and filtered. The filtrate was concentrated to dryness. The residue was washed with aqueous K_2CO_3 and water. Recrystallization from 2-PrOH gave 28.5 g (65%) of a tan solid; mp 175-177°C; ms: M^+ m/z 202; ^1H nmr: δ 9.20, 8.80 (A_2B_2, J=6Hz, 4H, -C_5H_4N), 7.99 (s, 1H, 6-H), 4.22 (s, 3H, -OCH_3). Anal. Calcd for $C_{10}H_{10}N_4O$: C, 59.40; H, 4.98; N, 27.71. Found: C, 59.06; H, 4.86; N, 27.44.

4-Amino-2-(4-pyridinyl)-5-pyrimidinol (30). To a stirred mixture of 29 (15 g, 74.2 mmol), 50% NaH/oil dispersion (4.8 g, 0.1 mol), and DMF (200 ml) was added butanethiol (9.5 ml, 0.1 mol) dropwise over 15 min. The reaction mixture was stirred at room temperature for 21 h and then heated on a steam bath for 5 h. The resulting solution was concentrated to near dryness. The residue was washed with hexane to remove oil and then treated with water (100 ml) and AcOH (10 ml). The resulting tan solid was collected, washed with water, suspended in boiling MeOH and then filtered off to yield 10.8 g (77%) of the title compound; mp 282-285°C dec.; ms: M^+ m/z 188; ^1H nmr: δ 9.15, 8.90 (A_2B_2, J=5.8Hz, 4H, -C_5H_4N), 8.08 (s, 1H, 6-H). Anal. Calcd for $C_9H_8N_4O$: C, 57.44; H, 4.28; N, 29.77. Found: C, 57.40; H, 4.37; N, 29.79.

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REFERENCES

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