The Synthesis of Certain Alkyl and Aryl Pyrimido[4,5-*d*]pyrimidines

Shri Prakash Gupta (1), Roland K. Robins, and Robert A. Long

ICN Pharmaceuticals, Inc., Nucleic Acid Research Institute, 2727 Campus Drive, Irvine, California 92664

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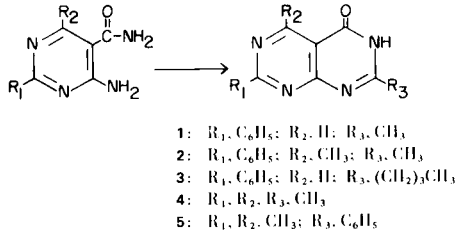
Recent studies on the purine metabolism in *Schistosoma mansoni* indicate (2-5) that schistosomes do not utilize the *de novo* pathway for the synthesis of purine nucleotides, but instead have a wide variety of salvage pathways for the utilization of preformed purines and purine nucleosides. A suggested (2-4) chemotherapy of schistosomiasis could involve the synthesis of purine analogs which would selectively inhibit the massive egg production of this trematode parasite without harm to the host.

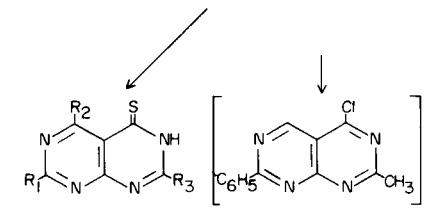
As part of a program of investigating several purine analogs, the synthesis of a 6,6-fused pyrimidine ring system containing aryl and alkyl groups was desired in order to obtain lipid solubility. The schistosomal parasite obtains its purine requirement by ingesting red blood cells and it seemed possible that increased lipid solubility might enhance the oral absorption and uptake by the red blood cells of these heterocycles.

Several reports (5-12) on the synthesis of pyrimido[4,5-*d*]pyrimidines are available and the procedures used for the preparation of the 4-amino-2,6-substituted pyrimidine-5-carboxamides are similar to those previously described (6). Refluxing an ethanol solution of 4-amino-2,6-dimethylpyrimidine-5-carboxamide with sodium ethoxide and ethyl acetate readily accomplished ring closure to provide 2,5,7-trimethylpyrimido[4,5-*d*]pyrimidin-4-one (**4**). When **4** was refluxed with purified phosphorus pentasulfide in dioxane, 2,5,7-trimethylpyrimido[4,5-*d*]-pyrimidine-4-thione (**7**) was obtained. The synthetic route from 4-amino-5-cyano-2,6-dimethylpyrimidine through **4** to **7** certainly is not the most direct or preferred, but we found that hydrolysis of 4-amino-5-cyano-2,6-dimethylpyrimidine with hydrogen sulfide under a variety of conditions was not successful in giving the desired product in good yield. Attempts to react the 4-amino-5-cyano-2,6-dimethylpyrimidine or a number of other *ortho*-aminonitrile substituted pyrimidines with ethylorthoformate-acetic anhydride followed by sodium hydrosulfide (12) yielded only unreacted starting materials. Treatment of **7** with methyl iodide in base readily yielded 2,5,7-trimethyl-4-methylthiopyrimido[4,5-*d*]pyrimidine (**8**).

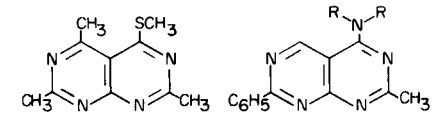
Previous workers (9,10) have reported attempts to chlorinate pyrimido[4,5-*d*]pyrimidin-4-one systems without success. We found that chlorination of such compounds as 2-methyl-7-phenylpyrimido[4,5-*d*]pyrimidin-4-one (**1**) was possible by reaction with phosphorus oxychloride and diethyl aniline. However, the chloro substituted product was found to be very reactive and could not be successfully obtained as an analytical sample. Initially, only starting material was isolated until conditions were found that permitted isolation of the chloro derivative as a syrup or gum. Treatment of the chloro intermediate with ammonia



1: R_1, C_6H_5; R_2, H; R_3, CH_3
2: R_1, C_6H_5; R_2, CH_3; R_3, CH_3
3: R_1, C_6H_5; R_2, H; R_3, $(CH_2)_3CH_3$
4: R_1, R_2, R_3, CH_3
5: R_1, R_2, CH_3; R_3, C_6H_5



6: R_1, C_6H_5; R_2, H; R_3, $(CH_2)_3CH_3$
7: R_1, R_2, R_3, CH_3



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9: R, H
10: R, CH_3

or dimethylamine yielded the products **9** and **10**, respectively. Attempts to chlorinate 2,5,7-trimethylpyrimido-[4,5-*d*]pyrimidin-4-one (**4**) using a variety of methods were not successful. This is possibly due to the steric hindrance from the 5-methyl group.

Table I

Physical Data of Some Pyrimido[4,5-*d*]pyrimidines

Compound	M.p., °C	Yield %	Molecular Formula	Analysis Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1	>300	68	$C_{13}H_{10}N_4O$	65.54	4.20	23.52	65.35	4.37	23.36
2	>300	75	$C_{14}H_{12}N_4O$	66.66	4.76	22.22	66.72	4.79	22.50
3	272-273	64	$C_{16}H_{16}N_4O$	68.57	5.71	20.00	68.72	5.91	20.37
4	>300	68	$C_9H_{10}N_4O$	60.00	5.55	31.11	60.27	5.73	31.33
5	>300	46	$C_{14}H_{12}N_4O\cdot\frac{1}{4}H_2O$	65.50	4.87	21.82	65.51	4.79	21.49
6	262	41	$C_{16}H_{16}N_4S$	64.86	5.40	18.91	64.71	5.63	18.79
7	275-277	26	$C_9H_{10}N_4S$	52.42	4.85	27.18	52.29	5.21	26.95
8	178	69	$C_{10}H_{12}N_4S\cdot\frac{1}{2}H_2O$	52.40	5.67	24.54	52.49	5.87	24.24
9	>300	62	$C_{13}H_{11}N_5$	65.82	4.64	29.53	65.98	4.79	29.43
10	174	58	$C_{15}H_{15}N_5$	67.92	5.66	26.41	68.09	5.57	26.57

EXPERIMENTAL

Melting points were determined on a Thomas Hoover apparatus and are uncorrected. Evaporations were accomplished with a Buckner rotating evaporator under reduced pressure. The pmr spectra were recorded at 60 MHz on a Perkin-Elmer Hitachi R-20A spectrometer and were found to be consistent with the assigned structures. Analytical results were determined by MHW Laboratories, Garden City, Michigan and Het. Chem. Co., Harrisonville, Missouri.

2,5,7-Trisubstitutedpyrimido[4,5-*d*]pyrimidin-4-ones (**1-5**).

To a solution of one equivalent of the 4-amino-2,6-disubstituted pyrimidine-5-carboxamide in 5-equivalents of sodium in absolute ethanol was added 5-equivalents of the appropriate ester (ethyl acetate; ethyl valerate; ethyl benzoate) and the resulting solution refluxed overnight. The solvent was evaporated *in vacuo*, the solid dissolved in water and filtered. The filtrate was neutralized to *p*H-4 with glacial acetic acid. The precipitate that formed was collected by filtration, washed well with water and air dried. Purification of the solid was either by recrystallization or by repeated dissolutions in base followed by neutralization with acid. For analysis, the compounds were dried *in vacuo* at 110° over phosphorus pentoxide.

7-Phenyl-2-*n*-butylpyrimido[4,5-*d*]pyrimidine-4-thione (**6**).

To a suspension of 7-phenyl-2-*n*-butylpyrimido[4,5-*d*]pyrimidin-4-one (**3**) (1.54 g., 5.79 mmoles) in pyridine (50 ml.) was added purified phosphorus pentasulfide (11.1 g., 50 mmoles). The resulting mixture was refluxed 3 hours and reduced to a syrup *in vacuo*. The syrup was chromatographed over silica gel (200 g.) using chloroform. The fraction containing **6** was reduced to dryness and the resulting solid recrystallized from ethanol to yield 0.7 g.

2,5,7-Trimethylpyrimido[4,5-*d*]pyrimidine-4-thione (**7**).

Finely powdered 2,5,7-trimethylpyrimido[4,5-*d*]pyrimidin-4-one (**4**) (1.0 g., 5.6 mmoles) and purified phosphorus pentasulfide (12.2 g., 55 mmoles) were added to dioxane (70 ml.) and the resulting mixture refluxed 14 hours. The solvent was removed *in vacuo* and the residual gum extracted with boiling 0.25 *N* sodium hydroxide. The extract was charcoaled, filtered through celite and neutralized with acetic acid. The solid was collected by filtration, dried *in vacuo* and recrystallized from ethanol to yield 0.297 g.

4-Methylthio-2,5,7-trimethylpyrimido[4,5-*d*]pyrimidine (**8**).

To a solution of **7** (2.06 g., 10 mmoles) in water (20 ml.) containing sodium hydroxide (0.44 g., 11 mmoles) was added methyl iodide (4.26 g.). The resulting mixture was stirred for 1 hour at room temperature, the solid collected by filtration and recrystallized from ethanol-water to yield 1.51 g.

4-Amino-2-methyl-7-phenylpyrimido[4,5-*d*]pyrimidine (**9**) and 4-Dimethylamino-2-methyl-7-phenylpyrimido[4,5-*d*]pyrimidine (**10**).

A mixture of phosphorus oxychloride (10 ml.), diethyl aniline (redistilled, 2 ml.) and **1** was stirred at room temperature for 20 minutes, then heated on a steam bath until the solid dissolved (20 minutes). The resulting solution was poured over ice and quickly extracted with chloroform. The chloroform was washed twice with water and dried over anhydrous sodium sulfate. After removal of the chloroform *in vacuo*, the resulting gum was treated with ammonium hydroxide (15 ml., 29.8%) or dimethylamine (15 ml.), respectively. The separated solid was collected by filtration and **9** recrystallized from ethanol-water and **10** from benzene.

REFERENCES

(1) Present address: Department of Biopharmaceutical Sciences, University of Utah, Salt Lake City, Utah 84112.

(2) A. W. Senft, R. P. Miech, P. R. Brown, and D. G. Senft, *Int. J. Parasit.*, **2**, 249 (1972).

(3) A. W. Senft, D. G. Senft, and R. P. Miech, *Biochem. Pharmacol.*, **22**, 437 (1973).

(4) A. W. Senft, G. W. Crabtree, K. C. Agarwal, E. M. Scholar, R. P. Agarwal, and R. E. Parks, Jr., *ibid.*, **22**, 449 (1973).

(5) R. J. Stegman, A. W. Senft, P. R. Brown, and R. E. Parks, Jr., *ibid.*, **22**, 459 (1973).

(6) E. C. Taylor, R. J. Knoff, R. F. Meyer, A. Holmes, and M. L. Hoefle, *J. Am. Chem. Soc.*, **82**, 5711 (1960).

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

(8) T. Yoneda and M. Higuchi, *Bull. Chem. Soc.*, **46**, 3849 (1973).

(9) R. Niess and E. Eilingsfeld, *Ann. Chem.*, 2019 (1974).

(10) H. G. Mautner, *J. Org. Chem.*, **23**, 1450 (1958).

(11) S. K. Chatterji and N. Anand, *J. Sci. Ind. Res. (India)*, **17B**, 63 (1958).

(12) E. C. Taylor, A. McKillop, and S. Vromen, *Tetrahedron*, **23**, 885 (1967).