Ammonolysis of the Lactone-lactam XI.—The lactone-lactam XI (0.20 g.) was stirred with concentrated aqueous ammonia (35 ml.) at room temperature for 13 hours. The residue, a fluffy glass, obtained by evaporation *in vacuo* at 60°, was stirred with absolute methanol (4.0 ml.) for 10 minutes. Filtration gave a white solid, m.p. 193° with gas evolution. The infrared spectrum of this solid was identical to that of the solid XIII.

Preparation of the Oxime XV.—To a mixture of the solid XIV (29.1 g.) and water (300 ml.) was added hydroxylamine hydrochloride (13.9 g.) followed by sodium hydroxide (8.0 g.). The resulting solution was boiled over a free flame for 2.0 minutes and immediately cooled in an ice-bath to room temperature. Glacial acetic acid (50 ml.) was added to a *p*H of 3–4 and the solution was evaporated to dryness *in vacuo* with a heating bath temperature of 60°. Water (60 ml.) was added to the solid residue, the suspension shaken for 5 minutes and refrigerated overnight. Filtration gave the oxime XV, 22.2 g., m.p. 219° dec. This material was recrystallized 3 times from water to prepare a sample for analysis, m.p. 226° dec.; infrared spectrum: no bands around 5.7 μ.

Anal. Calcd. for $C_9H_{11}O_3N_3$: C, 51.67; H, 5.30; N, 20.09. Found: C, 51.25; H, 5.79; N, 19.97.

Dilactam of *endo-cis*-2,3-Dicarboxy-*endo-cis*-5,6-diaminonorbornane (IV).—The oxime XV (5.0 g. material which had not been recrystallized) in water (300 ml.) was shaken at room temperature in the presence of platinum oxide (0.5 g.) with hydrogen at 45 pounds per square inch for 64 hours. After removal of the catalyst the solution was refluxed for 0.5 hour[20] and evaporated *in vacuo* at 70° to give a crystalline residue (pink coloration). Recrystallization from water (about 20 ml., Norite) gave a crystalline product, the hydrate of the dilactam IV, which was dried *in vacuo* at 100° for 3 hours to give the dilactam (2.1 g., 49% yield), m.p. 202–207°. The analytical sample, m.p. 210.5–211°, was obtained by two recrystallizations from a methanol–water mixture. After each recrystallization the above drying procedure was necessary to remove the water of hydration. The dilactam IV was somewhat soluble in water to give a neutral solution (*p*H paper) and insoluble in organic solvents. The aqueous solubility was not appreciably increased in 5% sodium hydroxide or in 5% hydrochloric acid at room temperature within 1 hour (for longer periods *vide infra*); infrared spectrum: 2.89, 3.17, 5.92, 6.05, 6.24 μ.

(20) In an early run a compound, which gave a basic aqueous solution, was isolated. Pyrolysis of this compound (or more slowly by standing at room temperature in aqueous solution) gave the dilactam IV. The direct formation of the dilactam IV was assured by refluxing.

Anal. Calcd. for $C_9H_{10}O_3N_2$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.78; H, 5.64; N, 15.71.

Hydrate of the Dilactam IV.—The hydrate (prepared as above) when heated rapidly in a melting point tube typically bubbled at about 190° to form a new solid which melted at 205–210°; when heated more slowly from room temperature there was no evidence of change until the solid melted at about 205–210°. The hydrate was soluble in absolute methanol in contrast to the anhydrous dilactam, but otherwise the solubility characteristics were the same as the anhydrous dilactam. The hydrate (air-dried) typically lost from 0.56 to 1.1 moles of water when dried *in vacuo* at 100° for 3 hours (calculated from weight loss).

A portion of the anhydrous dilactam IV was dissolved in water at room temperature and evaporated at room temperature to dryness to give the hydrate as evidenced by the infrared spectrum; infrared spectrum: 2.9, 3.0, 3.1, 5.9, 6.2 μ. The over-all spectrum was quite similar to that of the anhydrous dilactam.

Monolactam of *endo-cis*-2,3-Dicarboxy-*endo-cis*-5,6-diaminonorbornane (XVI).—The dilactam IV (1.00 g.) and 5% hydrochloric acid (10 ml.) were stirred together at room temperature for 67 hours (after 44 hours and before 67 hours all of the solid dissolved). The solution was filtered to remove a trace of insoluble colored material and the filtrate was evaporated at room temperature. The crystalline residue was dissolved in water (100 ml.) and the chloride ions were removed by passage of the solution through Amberlite IR-4B (45 g.) in a manner analogous to that described by Meyers and Miller.[21] The residue from evaporation of the effluent at room temperature was a yellow, gummy solid (0.7 g.). Two recrystallizations (Norite) from water (3 parts by weight) gave the analytical sample. The compound XVI bubbled at about 235°, and was much more soluble in 5% sodium hydroxide and in 5% hydrochloric acid than in water. After drying the amino acid *in vacuo* at 100° for 3 hours the behavior on heating to about 235°, *i.e.*, bubbling, was unchanged; infrared spectrum: 2.9, 3.1, 6.0, 6.2, 6.6, 7.1 μ.

Anal. Calcd. for $C_9H_{12}O_3N_2$: C, 55.09; H, 6.17; N, 14.28. Found: C, 55.23; H, 6.37; N, 13.61.

Conversion of the Monolactam XVI to the Dilactam IV.—A portion of the monolactam XVI (0.10 g.) was heated in a small test-tube with an oil-bath at 250–255° for 3 minutes. At the end of this period gas evolution had about stopped. The melt was dissolved in hot water (0.5 ml.) and the precipitate obtained on cooling was dried *in vacuo* for 3 hours at 100° to give 0.060 g. of a solid, m.p. 208–209°. The mixed melting point with the dilactam IV was not depressed. The infrared spectrum was identical to that of the dilactam IV.

(21) C. Y. Meyers and L. E. Miller, *Org. Syntheses*, **32**, 13 (1952).

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY, PRINCETON, N. J., AND THE RESEARCH DIVISION OF PARKE, DAVIS AND CO., DETROIT, MICH.]

Pyrimido[4,5-d]pyrimidines. Part I

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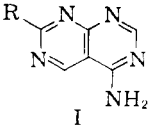
RECEIVED JANUARY 16, 1960

A number of pyrimido[4,5-d]pyrimidines have been prepared as potential diuretic agents. The synthesis of the requisite starting materials, 4-amino-5-cyanopyrimidines and 4-aminopyrimidine-5-carboxamides, and their conversion to pyrimido-[4,5-d]pyrimidines, are described. Many of the amino and substituted amino derivatives, unavailable by direct synthesis, were prepared by displacement of mercapto and alkylthio groups with amines.

In the search for new types of diuretic agents a variety of heterocyclic compounds were prepared and studied. One of the compounds prepared was 2,5-diaminopyrimido[4,5-d]pyrimidine (I, R = NH_2), which was found to be very active orally. Therefore, a series of aminopyrimido[4,5-d]pyrimidines was prepared and examined for diuretic activity and possible antagonistic activity in other biological systems.

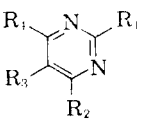


I

(1) Frick Chemical Laboratory, Princeton University.
(2) Parke, Davis and Co., Fellow, 1955–1957.
(3) Research Division, Parke, Davis and Co.

TABLE I

PYRIMIDINES



R_1	R_2	R_3	R_4	Yield, %	M.p.,[h] °C.	Recrystn. solvent	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
CH_3O	NH_2	CN	H	40[a]	221–222	Ethanol	$C_6H_6N_4O$	48.0	47.8	4.1	4.2
$C_5H_{10}N$[e]	NH_2	CN	H	25[a]	212–213	Ethanol	$C_{10}H_{13}N_5$	59.1	59.4	6.5	6.3
$C_5H_{11}N_2$[f]	NH_2	CN	H	49[a]	197	Ethanol	$C_{10}H_{14}N_6$	55.0	54.9	6.5	6.7
$CH_3(CH_2)_2NH$	NH_2	CN	H	76[b]	167–169	Ethanol	$C_8H_{11}N_5$	54.2	54.5	6.3	6.2
$CH_2{=}CHCH_2NH$	NH_2	CN	H	43[b]	171–172	Ethanol	$C_8H_9N_5$	54.8	54.6	5.2	5.3
$(CH_3)_2NCH_2CH_2NH$	NH_2	CN	H	55[b]	179–180	Ethanol	$C_9H_{14}N_6$	52.4	52.1	6.9	7.0
$CH_3(CH_2)_5NH$	NH_2	CN	H	44[b]	134–135	Ethanol	$C_{11}H_{17}N_5$	60.2	60.5	7.8	7.8
$C_6H_{11}NH$[g]	NH_2	CN	H	53[b]	182–183	Ethanol	$C_{11}H_{15}N_5$	60.8	60.9	7.0	6.9
$C_6H_5CH_2NH$	NH_2	CN	H	57[b]	177–179	Ethanol	$C_{12}H_{11}N_5$	64.0	64.3	4.9	5.0
o-$ClC_6H_4CH_2NH$	NH_2	CN	H	40[b]	185–187	Ethanol	$C_{12}H_{10}ClN_5$	55.5	55.2	3.9	3.7
C_6H_5NH	NH_2	CN	H	78[b]	234–235	Ethanol	$C_{11}H_9N_5$	62.5	62.8	4.3	4.4
H	NH_2	CN	CH_3	63[c]	217–219	Ethanol	$C_6H_6N_4$	53.7	53.9	4.5	4.7
CH_3S	NH_2	CN	CH_3	53[c]	238–240	Ethanol	$C_7H_8N_4S$	46.6	46.7	4.4	4.3
CH_3NH	NH_2	$CONH_2$	H	68[d]	268–270	H_2O	$C_6H_9N_5O$	43.1	43.1	5.4	5.4
$CH_3(CH_2)_5NH$	NH_2	$CONH_2$	H	88[d]	155	Ethanol	$C_{11}H_{19}N_5O$	55.7	55.5	8.1	8.0
$C_6H_5CH_2NH$	NH_2	$CONH_2$	H	62[d]	180–181	Ethanol	$C_{12}H_{13}N_5O$	59.2	59.5	5.3	5.3
o-$ClC_6H_4CH_2NH$	NH_2	$CONH_2$	H	71[d]	196–198	Ethanol	$C_{12}H_{12}ClN_5O$	51.9	52.0	4.3	4.6
$(CH_3)_2N$	NH_2	$CONH_2$	H	76[d]	289–290	H_2O	$C_7H_{11}N_5O$	46.4	46.7	6.1	6.0
C_6H_5NH	NH_2	$CONH_2$	H	89[d]	246–247	H_2O	$C_{11}H_{11}N_5O$	57.6	57.5	4.7	4.9
$C_5H_{11}N_2$[f]	NH_2	$CONH_2$	H	65[d]	222–223	H_2O	$C_8H_{11}N_6O$	49.7	49.5	5.7	5.4
$HOCH_2CH_2NH$	NH_2	$CONH_2$	H	66[b]	230	H_2O	$C_7H_{11}N_5O_2$	42.6	42.6	5.6	5.6
NH_2	NH_2	$CONH_2$	CH_3	74[d]	240–241	H_2O	$C_6H_9N_5O$	43.1	43.0	5.4	5.2

[a] Prepared from ethoxymethylenemalononitrile. [b] Prepared by the replacement of an ethylthio group by an amine. [c] Prepared from methylethoxymethylenemalononitrile. [d] Prepared by hydrolysis with concentrated sulfuric acid. [e] Piperidyl. [f] *n*-Methylpiperazyl. [g] Cyclohexylamino. [h] All melting points are uncorrected.

Since the completion of this work Chatterji and Anand have described the preparation of four 2-substituted 5-aminopyrimido[4,5-d]pyrimidines (I, R = H, CH_3, NH_2 and OH).[4,5] These compounds represent the first reported examples of this ring system bearing an amino substituent.

The key intermediates for the preparation of the pyrimido[4,5-d]pyrimidines desired in the present investigation were 4-amino-5-cyanopyrimidines (II). These compounds are conveniently prepared by the condensation of an amidine, guanidine, or thiourea with malononitrile[6,7] or ethoxymethylenemalononitrile.[8–10] Thus, the condensation of ethoxymethylenemalononitrile with O-methylisourea yielded 2-methoxy-4-amino-5-cyanopyrimidine. 4-Amino-5-cyano-6-methylpyrimidine was obtained by the condensation of methylethoxymethylenemalononitrile with alcoholic formamidine. Similarly, 2-methylthio-4-amino-5-cyano-6-methylpyrimidine was obtained by the condensation of methylethoxymethylenemalononitrile and thiourea followed by methylation of the crude product.

Condensation of ethoxymethylenemalononitrile and N,N-dialkylguanidines gave the corresponding 2-N,N-dialkylamino-4-amino-5-cyanopyrimidines in good yields. However, the use of monosubstituted guanidines resulted in mixtures from which the desired products were difficult to isolate. Hence, a series of 2-alkylamino-4-amino-5-cyanopyrimidines was prepared by treating 2-ethylthio-4-amino-5-cyanopyrimidine with an excess of the appropriate alkylamine. For the lower boiling amines it was necessary to heat the alcoholic solution of the reactants in an autoclave at 120–135°, but for *n*-propyl- and higher boiling alkylamines it was sufficient to use an excess of the amine as solvent and to heat at reflux until no more ethylmercaptan was evolved. In general, a reaction temperature higher than 135–140° resulted in decreased yields. However, in order to prepare 2-anilino-4-amino-5-cyanopyrimidine, it was necessary to heat the reaction mixture to 165°; a drop of hydrochloric acid was added as catalyst.

Hydrolysis of the 2-substituted-4-amino-5-cyanopyrimidines in concentrated sulfuric acid at room temperature yielded the corresponding 4-aminopyrimidine-5-carboxamides (VI). The yields were generally high, but it was found that 2-(2-hydroxyethyl)-amino-4-aminopyrimidine-5-carboxamide was best prepared by the alternative method of treating 2-ethylthio-4-aminopyrimidine-5-carboxamide with alcoholic ethanolamine in an autoclave.

The pyrimidines that were prepared in this work are listed in Table I.

The ring closure of the 4-amino-5-cyanopyrimidines (II) with formamide to yield the correspond-

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

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

(6) J. Baddiley, B. Lythgoe and A. R. Todd, *J. Chem. Soc.*, 386 (1943).

(7) G. W. Kenner, B. Lythgoe, A. R. Todd and A. Topham, *ibid.*, 388 (1943).

(8) W. Huber and H. A. Hölscher, *Ber.*, **71**, 87 (1938).

(9) W. Huber, THIS JOURNAL, **65**, 2222 (1943)

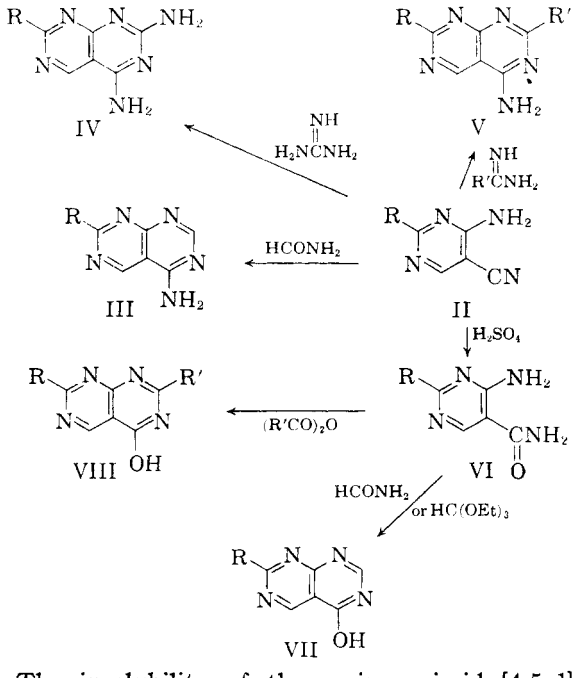
(10) R. Grewe, *Z. physiol. Chem.*, **242**, 89 (1936)

ing 5-aminopyrimido[4,5-d]pyrimidines (III) has been described by Chatterji and Anand.[5] In our work it was found advantageous to heat the reaction mixture at reflux for a short period of time or at 180° for 1–2 hours. In general, the yields obtained by this method were poor, but several of the 4-amino-5-cyanopyrimidines (II, R = H_2N, $(CH_3)_2N$ and N-methylpiperazyl) underwent this ring closure in quite acceptable yields. The results are summarized in Table II.

In contrast to the results of the ring closure with formamide, excellent yields were obtained by the cyclization of the *o*-aminonitriles with guanidine. Thus, the treatment of 4-amino-5-cyanopyrimidine with guanidine in refluxing ethanol or ethyl Cellosolve gave 2,4-diaminopyrimido[4,5-d]pyrimidine(IV, R = H) in 80% yield. When 2,4-diamino-5-cyanopyrimidine was treated with guanidine, N-methylguanidine or N,N-dimethylguanidine in refluxing ethyl Cellosolve, the same product was obtained in each case, namely, 2,4,7-triaminopyrimido[4,5-d]-pyrimidine (IV, R = NH_2). Benzamidine and acetamidine could be used in place of guanidine in the above ring closures, except that yields were lower. Thus, the condensation of 2-ethylthio-4-amino-5-cyanopyrimidine with benzamidine in refluxing ethyl Cellosolve yielded 2-phenyl-4-amino-7-ethylthio-pyrimido[4,5-d]-pyrimidine (V, R = $CH_3CH_2CH_2NH$ and R′ = C_6H_5).

Treatment of 2,4-diamino-7-ethylthiopyrimido-(4,5-d)pyrimidine with an alcoholic solution of an amine in an autoclave at 120–130° yielded the corresponding 2,4-diamino-7-(substituted-amino) pyrimido[4,5-d]pyrimidine. However, there did not appear to be any advantage in this procedure.

REACTION SCHEME I

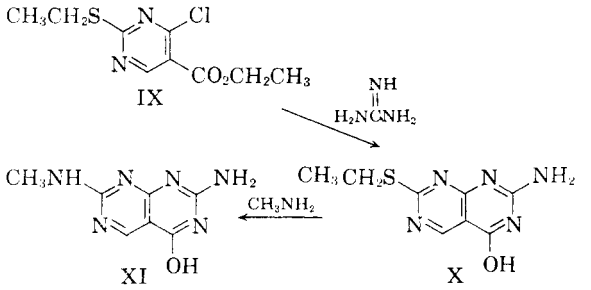


The insolubility of the aminopyrimido[4,5-d]-pyrimidines in the common organic solvents made purification difficult. In most cases the hydrochloride could be recrystallized from hot water, but an appreciable amount of hydrolysis occurred under these conditions. The substitution of larger alkyl- or arylamino groups yielded products which were readily purified by recrystallization from organic solvents.

The cyclization of the 4-aminopyrimidine-5-carboxamides (VI) with formamide or ethyl orthoformate proceeded smoothly to yield the corresponding 5-hydroxypyrimido[4,5-d]pyrimidines (VII). A mixture of ethyl orthoformate and acetic anhydride has been used previously for similar cyclizations[4,11,12] but it was found that similar results were obtained with ethyl orthoformate alone if the ethyl alcohol formed during the course of the reaction was continuously removed by distillation.

The 4-aminopyrimidine-5-carboxamides were also readily cyclized in good yield by heating with acid anhydrides (such as acetic, propionic and butyric anhydrides) to yield the corresponding 2-alkyl-4-hydroxypyrimido[4,5-d]pyrimidines (VIII, R′ = alkyl). Compounds prepared by these methods are listed in Table II.

The synthesis of 4-hydroxypyrimido[4,5-d]-pyrimidines bearing amino or alkylamino substituents in the 2- and 7-positions was also investigated. Addition of 2-ethylthio-4-chloro-5-carboethoxypyrimidine (IX) to a chilled solution of guanidine in ethanol yielded 2-amino-4-hydroxy-7-ethylthiopyrimido[4,5-d]pyrimidine (X). When



X was treated with methylamine in an autoclave, 2-amino-4-hydroxy-7-methylaminopyrimido[4,5-d]-pyrimidine (XI) was obtained. Pharmacological data on this compound indicated that the presence of a hydroxyl group on this nucleus decreased the diuretic activity.

Although the 2-(substituted-amino)-5-amino-pyrimido[4,5-d]pyrimidines (III) were readily obtained by the cyclization of the corresponding 2-substituted amino-4-amino-5-cyanopyrimidine, the introduction of a substituted amino group at the 5-position presented a more difficult problem. Treatment of 2-amino-5-hydroxypyrimido[4,5-d]-pyrimidine (XVII, R″ = hydrogen) with phosphorus pentasulfide in pyridine yielded an impure product which proved to be very difficult to purify. However, 2-benzylamino-5-hydroxypyrimido[4,5-d]-pyrimidine was readily thiolated under these same conditions to yield 2-benzylamino-5-mercapto-pyrimido[4,5-d]pyrimidine (XVIII, R″ = C_6H_5-CH_2). Treatment of this compound with alcoholic *n*-propylamine at 130° in an autoclave yielded 2-benzylamino-5-(*n*-propylamino)-pyrimido[4,5-d]-

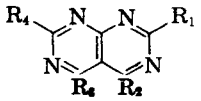
(11) H. G. Mautner, Abstr. of Papers, A.C.S. Meeting, N. Y., Sept. 8–13, 1957, p. 30-O.

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

TABLE II: PYRIMIDO[4,5-d]PYRIMIDINES

R_1	R_2	R_3	R_4	Method of prepn.	Yield, %	M.p.,[e] °C.	Empirical formula
NH_2[d]	H	NH_2	H	Formamide	42	>300	$C_6H_6N_6 \cdot H_2O$
H[d]	H	NH_2	H	Formamide	16	>360	$C_6H_5N_5$
C_6H_5	H	NH_2	H	Formamide	25	>300	$C_{12}H_9N_5$
$C_5H_{11}N_2$[a]	H	NH_2	H	Formamide	70	>300	$C_{11}H_{15}N_7$
$C_5H_{10}N$[b]	H	NH_2	H	Formamide	29	>300	$C_{11}H_{14}N_6$
$(CH_3)_2N$	H	NH_2	H	Formamide	58	>300	$C_8H_{10}N_6 \cdot HCl \cdot H_2O$
$C_6H_5CH_2NH$	H	NH_2	H	Formamide	7	285–287	$C_{13}H_{12}N_6$
$CH_3(CH_2)_5NH$	H	NH_2	H	Formamide	23	276–278	$C_{12}H_{18}N_6$
CH_3S	H	NH_2	H	Formamide	19	>300	$C_7H_7N_5S$
NH_2	NH_2	H	H	Guanidine	78	>300	$C_6H_6N_6$
NH_2	NH_2	H	NH_2	Guanidine	68	>300	$C_6H_7N_7$
NH_2	NH_2	H	CH_3NH	[c]	35	>300	$C_7H_9N_7 \cdot HCl \cdot {}^1/_2H_2O$
NH_2	NH_2	H	$CH_3(CH_2)_2NH$	Guanidine	92	309–310	$C_9H_{13}N_7$
NH_2	NH_2	H	$CH_3(CH_2)_3NH$	Guanidine	72	272–273	$C_{10}H_{15}N_7$
NH_2	NH_2	H	$CH_3(CH_2)_5NH$	Guanidine	92	270–271	$C_{12}H_{19}N_7$
NH_2	NH_2	H	$HOCH_2CH_2NH$	Guanidine	33	>300	$C_6H_{11}N_7O \cdot HCl$
NH_2	NH_2	H	$CH_3)_2N$	Guanidine	61	>300	$C_8H_{11}N_7$
NH_2	NH_2	H	$C_5H_{10}N$[b]	Guanidine	50	>300	$C_{11}H_{15}N_7$
NH_2	NH_2	H	$(HOCH_2CH_2)_2N$	[c]	74	285	$C_{10}H_{15}N_7O_2$
NH_2	NH_2	H	$C_6H_5CH_2NH$	Guanidine	73	294–295	$C_{13}H_{13}N_7$
NH_2	NH_2	H	C_6H_5NH	Guanidine	78	>300	$C_{12}H_{11}N_7$
NH_2	NH_2	H	H_2NNH	[c]	88	>300	$C_6H_7N_8$
NH_2	NH_2	H	CH_3CH_2S	Guanidine	40	>300	$C_8H_{10}N_6S$
NH_2	NH_2	H	C_6H_5	Guanidine	94	>300	$C_{13}H_{10}N_6$
NH_2	NH_2	H	CH_3	Guanidine	74	>300	$C_7H_8N_6$
CH_3	NH_2	H	CH_3CH_2S	Acetamidine	25	279–280	$C_9H_{11}N_5S$
C_6H_5	NH_2	H	CH_3CH_2S	Benzamidine	15	226–228	$C_{14}H_{13}N_5S$
H	OH	H	CH_3NH	Formamide	57	>300	$C_7H_7N_5O$
H	OH	H	$CH_3(CH_2)_2NH$	Formamide	72	295–296	$C_9H_{11}N_5O$
H	OH	H	$CH_2{=}CHCH_2NH$	Formamide	58	278–280	$C_9H_9N_5O$
H	OH	H	$(CH_3)_2N$	Formamide	28	>300	$C_8H_9N_5O$
H	OH	H	*o*-$ClC_6H_4CH_2NH$	Formamide	71	>300	$C_{13}H_{10}N_5OCl$
H	OH	H	C_6H_5NH	Formamide	23	>300	$C_{12}H_9N_5O$
CH_3	OH	H	NH_2	$(CH_3CO)_2O$	78	>300	$C_7H_7N_5O$
CH_3CH_2	OH	H	NH_2	$(C_2H_5CO)_2O$	61	>330	$C_8H_9N_5O$
$CH_3CH_2CH_2$	OH	H	NH_2	$(C_3H_7CO)_2O$	52	>300	$C_9H_{11}N_5O$
$CH_3(CH_2)_4$	OH	H	NH_2	$(CH_3(CH_2)_4CO)_2O$	35	295–300	$C_{11}H_5N_5O$
CH_3	OH	CH_3	NH_2	$(CH_3CO)_2O$	74	>300	$C_8H_9N_5O$
CH_3	OH	H	$HO(CH_2)_2NH$	[c]	44	>300	$C_9H_{11}N_5O_2$
CH_3	OH	H	$CH_3(CH_2)_2NH$	$(CH_3CO)_2O$	18	294–295	$C_{10}H_{13}N_5O$
CH_3	OH	H	$CH_3(CH_2)_5NH$	$(CH_3CO)_2O$	23	267–268	$C_{13}H_{19}N_5O$
CH_3	OH	H	$(CH_3)_2N$	$(CH_3CO)_2O$	26	275–276	$C_9H_{11}N_5O$
CH_3	OH	H	$C_6H_5CH_2NH$	$(CH_3CO)_2O$	73	>300	$C_{14}H_{13}N_5O$
CH_3	OH	H	C_6H_5NH	$(CH_3CO)_2O$	62	>300	$C_{13}H_{11}N_5O$
CH_3	OH	H	CH_3CH_2S	$(CH_3CO)_2O$	75	247–248	$C_9H_{10}N_4OS$
CH_3	OH	H	CH_3S	$(CH_3CO)_2O$	57	288–290	$C_8H_8N_4OS$
CH_3	OH	H	CH_3	$(CH_3CO)_2O$	72	310–315	$C_8H_8N_4O$
CH_3	SH	H	CH_3S	P_2S_5	28	Dark, 260	$C_8H_8N_4S_2$
NH_2	OH	H	CH_3CH_2S	[f]	52	>300	$C_8H_9N_5OS$
NH_2	OH	H	CH_3NH	[c]	65	>300	$C_7H_8N_6O$
H	SH	H	$C_6H_5CH_2NH$	P_2S_5	80	290–291	$C_{13}H_{11}N_5S$
H	$CH_3(CH_2)_2NH$	H	$C_6H_5CH_2NH$	[g]	31	290–291	$C_{16}H_{18}N_6$
H	$CH_2{=}CHCH_2NH$	H	$C_6H_5CH_2NH$	[g]	41	274–275	$C_{16}H_{16}N_6$
H	SH	H	CH_3CH_2S	P_2S_5	68	280–283	$C_8H_8N_4S_2$
H	$C_6H_5CH_2NH$	H	CH_3CH_2S	[g]	35	231–232	$C_{15}H_{15}N_5S$
H	C_5H_5ONH[h]	H	CH_3CH_2S	[g]	52	219–220	$C_{12}H_{12}N_5OS$
H	C_6H_5NH	H	CH_3CH_2S	[g]	32	250–255	$C_{14}H_{17}N_5S$
H	CH_3NH	H	CH_3CH_2S	[g]	13	275–280	$C_9H_{11}N_5S$
H	CH_3NH	H	NH_2	[c]	50	>330	$C_7H_8N_6$
H	OH	H	CH_3S	[i]	72	225–229	$C_7H_6N_4OS$
H	SH	H	CH_3S	P_2S_5	75	290–297	$C_7H_6N_4S_2$
H	CH_3S	H	CH_3S	[j]	76	183–185	$C_8H_8N_4S_2$
H	$C_6H_5CH_2NH$	H	CH_3S	[k]	85	278–280	$C_{14}H_{12}N_5S$

[a] N-Methylpiperazyl. [b] Piperidyl. [c] Replacement of an ethylthio group by an amine. [d] Synthesis previously reported by Chatterji and Anand (ref. 4, 5). [e] All melting points are uncorrected. [f] 2-Ethylthio-4-chloro-5-carboethoxypyrimidine



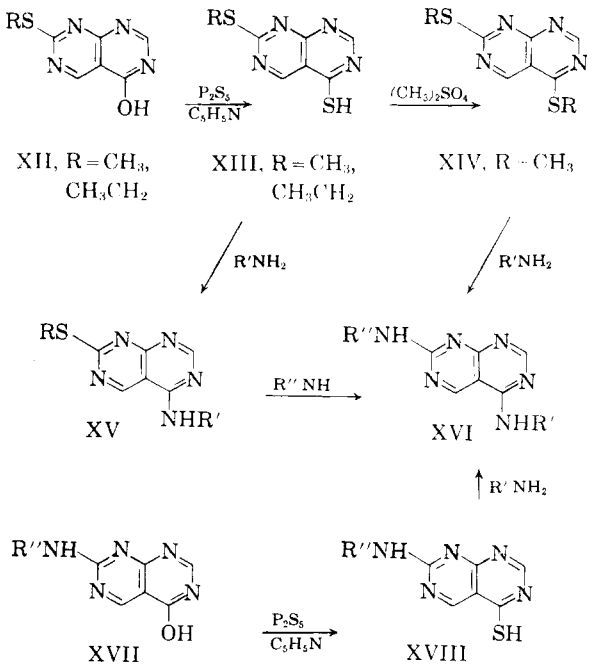
Recrystn. solvent	Analyses, % Calcd. C	H	N	Found C	H	N	λ_{max}, mμ	Ultraviolet spectra log ϵ_{max}	Solvent
1:1 H_2O–ethanol	40.0	4.5	46.7	39.8	4.3	46.7	244, 314	4.47, 3.81	*p*H 7
(Subl.)	49.0	3.4	47.4	49.6	3.1	47.4	232, 302	3.86, 3.70	0.1 *N* HCl
Ethanol	64.6	4.1		64.3	4.0		263, 324.5	4.37, 4.28	0.1 *N* HCl
Ethanol	53.9	6.2		54.0	6.2		259, 316	4.65, 3.87	*p*H 7
Ethanol	57.4	6.1		57.4	6.1		269, 312, 348	4.60, 3.67, 3.60	*p*H 7
H_2O	39.3	5.3	34.4	39.5	5.3	34.4	264, 312	4.61, 3.75	*p*H 7
Ethanol	61.9	4.8		62.1	5.0		256, 316	4.64, 3.87	*p*H 7
Ethanol	58.5	7.4		58.7	7.5		257, 313	4.62, 3.82	*p*H 7
(Subl.)	43.3	3.6	36.2	43.4	3.7	36.2	255, 270, 328	3.72, 3.66, 3.44	0.1 *N* HCl
H_2O	44.4	3.7		44.2	3.7		234, 278	4.23, 4.02	0.1 *N* HCl
H_2O	40.6	4.0		40.6	4.2		221, 248, 311	3.72, 3.66, 3.44	0.1 *N* HCl
H_2O	35.5	4.7	41.5	35.8	4.5	41.2	238, 324	4.49, 4.15	*p*H 7
Ethanol	49.3	6.0		49.1	5.8		239, 327	4.62, 4.17	*p*H 7
Ethanol	51.4	6.5		51.1	6.6		238, 327	4.62, 4.16	*p*H 7
Ethanol	55.2	7.3		55.2	7.4		238, 324	4.66, 4.17	*p*H 7
H_2O	37.3	4.7		37.1	4.5		238, 324	4.63, 4.17	*p*H
Ethanol	46.8	5.4		46.8	5.3		238, 253, 333	4.40, 4.38, 3.98	*p*H 7
Ethyl Cellosolve	53.9	4.4		53.7	4.4		240, 257, 337	4.53, 4.53, 4.11	*p*H 7
Ethanol	45.2	5.7		45.0	5.9		240, 253, 332	4.45, 4.45, 4.12	*p*H 7
Ethanol	58.4	4.9		58.6	5.0		239, 325.5	4.67, 4.20	*p*H 7
Ethanol	56.9	4.4		57.0	4.4		242, 265, 334	4.46, 4.44, 4.25	*p*H 7
H_2O	37.5	4.2		37.5	4.2		236.5, 323	4.60, 4.14	*p*H 7
Ethyl Cellosolve	43.2	4.5		43.5	4.5		248, 330	4.48, 4.07	*p*H 7
Ethyl Cellosolve	60.5	4.2		60.3	4.2		261, 333	4.53, 3.98	*p*H 7
H_2O	47.7	4.6	47.7	47.6	4.7	47.9	232, 302	3.94, 3.78	0.1 *N* HCl
Ethyl Cellosolve	48.8	5.0		48.6	5.1		215, 271, 333	4.18, 4.34, 4.14	0.1 *N* HCl
Ethanol	59.3	4.6		59.5	4.7		271, 334	4.62, 4.15	*p*H 7
Acetic acid	47.5	4.0		47.7	4.0		256, 325	4.55, 3.56	*p*H 7
Acetic acid	52.6	5.4		52.9	5.4		257, 327	4.55, 3.55	*p*H 7
H_2O	53.2	4.5	34.5	53.0	4.2	34.4	256, 323	4.58, 3.61	*p*H 7
Acetic acid	50.3	5.8		50.0	6.0		262, 280, 336	4.52, 4.17, 3.50	*p*H 7
Acetic acid	54.3	3.5		54.4	3.8		256, 322	4.63, 3.67	*p*H 7
Acetic acid	60.2	3.8		60.1	4.0		219, 270	4.23, 4.36	*p*H 7
Acetic acid	47.5	4.0		47.2	4.2		243, 312	4.57, 3.72	*p*H 7
Acetic acid	50.3	4.8		50.0	4.8		244, 312	4.57, 3.72	*p*H 7
Ethanol	52.7	5.4		52.5	5.6		243, 312	4.57, 3.72	*p*H 7
1:1 H_2O–ethanol	56.6	6.5		56.7	6.4		244, 312	4.60, 3.75	*p*H 7
Acetic acid	50.3	4.8		50.0	4.6		246, 306	4.67, 3.74	*p*H 7
H_2O	48.9	5.0		49.2	4.9		255, 323	4.69, 3.68	*p*H 7
Ethanol	54.8	6.0		54.8	6.0		256, 327	4.53, 3.74	*p*H 7
Ethanol	59.8	7.3		59.8	7.2		256, 325	4.58, 3.83	*p*H 7
Ethanol	52.7	5.4		52.7	5.4		261, 336	4.40, 3.58	*p*H 7
Acetic acid	62.9	4.9		63.0	5.0		256, 324	4.61, 3.70	*p*H 7
Ethanol	61.6	4.4		61.4	4.4		218, 268, 296	4.25, 4.36, 4.24	*p*H 7
Ethanol	48.6	4.5		48.6	4.8		263, 314	4.48, 3.91	*p*H 7
Methanol	46.2	3.9		46.1	4.0		260, 318	4.39, 3.00	0.1 *N* NaOH
Methanol	54.5	4.6		54.6	4.4		234, 306	4.34, 3.99	.1 *N* NaOH
Methanol	42.9	3.6	25.0	42.9	3.7	25.3	241, 269	4.25, 4.21	.1 *N* NaOH
Acetic acid	43.0	4.1		43.0	4.1		255, 322	4.49, 4.11	.1 *N* NaOH
H_2O	43.7	4.2		43.8	4.1		234, 319	4.65, 4.14	.1 *N* NaOH
Acetic acid	58.0	4.1		58.0	4.2		225, 263, 283, 373	4.42, 4.41, 4.07, 4.08	.1 *N* NaOH
Ethanol	65.3	6.2		65.4	6.1		269, 346	4.56, 4.05	.1 *N* HCl
Ethanol	65.7	5.5		65.5	5.8		269, 344	2.56, 4.04	.1 *N* HCl
Ethanol	42.8	3.6		43.0	3.6		238, 272, 380	4.11, 4.25, 4.13	*p*H 7
i-PrOH	60.6	5.1		60.9	5.0		270, 336	4.44, 4.14	*p*H 7
i-PrOH	54.3	4.6		54.6	4.7		269, 335	4.46, 4.13	*p*H 7
Ethanol	59.3	4.6		59.1	4.5		272, 344	4.34, 4.12	*p*H 7
i-PrOH	48.9	5.0		48.9	5.0		269, 337	4.45, 4.10	*p*H 7
Ethanol	47.7	4.6		47.7	4.6		243, 327	4.49, 3.98	*p*H 7
H_2O	43.3	3.1	28.9	43.4	2.9	28.5	261, 317	4.46, 4.04	0.1 *N* NaOH
Pyridine	40.0	2.9	26.7	39.7	2.8	27.0	236, 268	3.87, 4.09	0.1 *N* NaOH
(Subl.)	42.9	3.6		43.2	3.5		274, 342	4.27, 4.02	Ethanol
1:1 H_2O–ethanol	59.4	4.6		59.7	4.5		268, 334	4.36, 4.07	Ethanol

plus guanidine. [g] Replacement of a mercapto group by an amine. [h] Furfurylamino. [i] Ethyl orthoformate plus acetic anhydride. [j] Alkylation with dimethyl sulfate. [k] Replacement of a methylthio group by an amine.

pyrimidine (XVI, R'' = $C_6H_5CH_2$, R' = $CH_3CH_2CH_2$).

A more general method for the preparation of this type of compound was investigated and is shown in Reaction Scheme II. 2-Ethylthio-5-hydroxypyrimido[4,5-d]pyrimidine and 2-methylthio-5-hydroxypyrimido[4,5-d]pyrimidine (XII) were thiolated to yield XIII. Treatment of XIII

REACTION SCHEME II



(R = CH_3CH_2) with two equivalents of benzylamine in boiling water resulted in the preferential replacement of the mercapto group to yield 2-ethylthio-5-benzylaminopyrimido[4,5-d]pyrimidine (XV, R = CH_3CH_2, R' = $C_6H_5CH_2$). When this product was heated with alcoholic ammonia in an autoclave at 140°, 2-amino-5-benzylaminopyrimido(4,5-d)pyrimidine (XVI, R' = $C_6H_5CH_2$, R'' = H) was obtained. Similarly, 2,5-bis-(methylthio)-pyrimido[4,5-d]pyrimidine (XIV) was prepared by treating a solution of 2-methylthio-5-mercaptopyrimido[4,5-d]pyrimidine in aqueous sodium carbonate with dimethyl sulfate. When XIV was stirred with an excess of benzylamine in absolute alcohol at room temperature for 15 hours, the product was 2-methylthio-5-benzylaminopyrimido-[4,5-d]pyrimidine (XV, R = CH_3, R' = $C_6H_5CH_2$).

The compounds which showed the greatest diuretic activity in this series were the 2-amino-5-alkylaminopyrimido[4,5-d]pyrimidines (XVI, R'' = H, R' = alkylamino). These compounds showed excellent diuretic activity in dogs when administered in oral doses of 10 mg. per kg. of body weight. The isomeric 2-alkylamino-5-aminopyrimido[4,5-d]pyrimidines were slightly less active, as were the 2,4-diamino-7-alkylaminopyrimido[4,5-d]pyrimidines (IV, R = alkylamino). It has been noted already that the introduction of a hydroxy group in this nucleus reduces diuretic activity. The pharmacology of these compounds will be reported elsewhere.

A number of these compounds were selected and screened as possible anticancer agents but none showed any interesting activity.

Experimental

The preparations given below are representative of the procedures indicated in Tables I and II.

2-Methoxy-4-amino-5-cyanopyrimidine (II, R = CH_3O).—To a chilled solution of 10.8 g. of sodium methoxide in 200 ml. of absolute ethanol was added 50 g. of O-methylisourea *p*-toluenesulfonate.[13] The suspension was stirred for 15 minutes and then 24.4 g. of ethoxymethylenemalononitrile was added in 2-g. portions. The reaction mixture was stirred at room temperature for 1 hour, heated at reflux for an additional hour, cooled and filtered. The collected solid was washed with 150 ml. of water, dissolved in 100 ml. of cold 2 *N* hydrochloric acid, treated with charcoal, and the filtrate neutralized with concentrated ammonium hydroxide to yield 12.2 g. of product.

4-Amino-5-cyano-6-methylpyrimidine.—To a solution of 2.5 g. of sodium in 100 ml. of absolute ethanol was added 8.05 g. of formamidine hydrochloride. The mixture was stirred at room temperature for 15 minutes and the sodium chloride was removed by filtration. To the stirred filtrate was added 13.6 g. of methylethoxymethylenemalononitrile, and the mixture was heated on a steam-bath for 10 minutes. Cooling caused the separation of 8.4 g.

2-Methylthio-4-amino-5-cyano-6-methylpyrimidine.—To a solution of 2.5 g. of sodium in 100 ml. of absolute ethanol was added 7.6 g. of thiourea and the mixture was warmed until solution was complete. It was cooled to 40° and 13.6 g. of methylethoxymethylenemalononitrile added in small portions with stirring. The mixture was heated on the steam-bath for 1 hour and then chilled to yield 12.3 g. of the yellow sodium salt of 2-mercapto-4-amino-5-cyano-6-methylpyrimidine. This salt was dissolved in 200 ml. of water with stirring and treated with 10 g. of methyl iodide. After 30 minutes the product which had separated was collected by filtration and dried to give 9.4 g. of pale-yellow needles.

2-*n*-Propylamino-4-amino-5-cyanopyrimidine.—A solution of 54.0 g. of 2-ethylthio-4-amino-5-cyanopyrimidine[4] in 177 g. of *n*-propylamine was heated at reflux for 18 hours. The excess amine was removed by distillation and the crude material was recrystallized from ethanol to give 40.2 g. of product.

2-Methylamino-4-amino-5-cyanopyrimidine.—A mixture of 10.0 g. of 2-ethylthio-4-amino-5-cyanopyrimidine, 25 ml. of 25% aqueous methylamine and 40 ml. of ethanol was heated in an autoclave at 130° for 3 hours. After cooling, the autoclave was opened and 5.7 g. of product was collected.

2-Anilino-4-amino-5-cyanopyrimidine.—A mixture of 20.0 g. of 2-ethylthio-4-amino-5-cyanopyrimidine and 50 ml. of aniline containing two drops of concentrated hydrochloric acid was heated at 150° for 3 hours and finally at 175° for 1 hour. The solid cake which separated on cooling was suspended in 150 ml. of ethanol and filtered to give 17.3 g. of a yellow solid.

2-Methylamino-4-aminopyrimidine-5-carboxamide (VI, R = CH_3NH).—To 40 ml. of concentrated sulfuric acid was added 12.5 g. of 2-methylamino-4-amino-5-cyanopyrimidine in portions and with occasional cooling so that the temperature did not exceed 30°. The resulting solution was allowed to stand at room temperature for 2 hours and was then poured into 150 g. of crushed ice. Upon scratching, a solid sulfate salt separated that was removed by filtration and dissolved in 150 ml. of boiling water. Neutralization with concentrated ammonium hydroxide yielded 9.6 g. of product.

The 4-amino-5-cyanopyrimidines can also be hydrolyzed with alkaline hydrogen peroxide.[4] However, most of the pyrimidine-5-carboxamides employed in this study were prepared by hydrolysis with concentrated sulfuric acid as described in the above example. It was necessary to prepare 2-(2-hydroxyethyl)-amino-4-aminopyrimidine-5-carboxamide by a different route because of its marked solubility in dilute sulfuric acid.

2-(2-Hydroxyethyl)-amino-4-aminopyrimidine-5-carboxamide.—Twenty grams of 2-ethylthio-4-aminopyrimidine-5-carboxamide and 35 ml. of monoethanolamine were heated at 110–115° for 4 hours. Then 100 ml. of water was added

(13) J. W. Janus, *J. Chem. Soc.*, 3552 (1955).

and the crude product was collected by filtration after chilling. Recrystallization from 300 ml. of water yielded 12.2 g. of product.

2,5-Diaminopyrimido(4,5-d)pyrimidine (III, R = NH_2).—Twenty-seven grams of 2,4-diamino-5-cyanopyrimidine and 100 g. of redistilled formamide were heated at gentle reflux for 0.5 hour. The reaction mixture was cooled and 100 ml. of ethanol was added. The light-tan product which separated was collected by filtration and purified by dissolving in 400 ml. of hot 1 *N* hydrochloric acid and treating with decolorizing charcoal. Neutralization of the hot filtrate with concentrated ammonium hydroxide yielded 15.1 g. of light-tan crystals: m.p. > 300°. This compound is reported to melt at 265° with decomposition.[5]

The other 2-substituted-5-aminopyrimido(4,5-b)pyrimidines listed in Table II were prepared in a similar manner. In those cases where the substituent in the 2-position was a monosubstituted alkylamine (*e.g.*, III, where R = $C_6H_5CH_2NH$) a purer product was obtained by heating the reaction mixture at 185° for 2 hours. Because of the insolubility of these compounds in the ordinary organic solvents, the purification of large amounts was most simply effected by recrystallizing the hydrochlorides from hot water. However, this was usually accompanied by an appreciable loss due to hydrolysis.

2,4,7-Triaminopyrimido(4,5-d)pyrimidine (IV, R = NH_2).—To a solution of 5.4 g. of sodium methoxide in 200 ml. of ethyl Cellosolve was added 9.6 g. of guanidine hydrochloride and 13.5 g. of 2,4-diamino-5-cyanopyrimidine. The reaction mixture was then stirred at reflux for 20 hours. During this time ammonia was continuously evolved. The hot reaction mixture was filtered and the crude product was washed with 100 ml. of warm water. After drying, this crude product weighed 16.5 g. Purification was effected by recrystallization (with charcoal) from 600 ml. of water containing 20 ml. of concentrated hydrochloric acid. The product weighed 9.1 g. and analyzed for the monohydrochloride monohydrate. The analytical sample of the free base was prepared by adding a small sample of the above product to dilute ammonium hydroxide and then recrystallizing the resulting product from water.

The other 7-substituted-2,4-diaminopyrimido(4,5-d)pyrimidines listed in Table II were prepared in a similar manner. 2,4-Diamino-7-ethylthiopyrimido(4,5-d)pyrimidine (IV, R = CH_3CH_2S) was prepared in ethanol to avoid the replacement of the ethylthio group. 2,4-Diaminopyrimido(4,5-d)pyrimidine (IV, R = H) was prepared in both ethanol and ethyl Cellosolve and almost identical yields were obtained. In those cases where the products were soluble in ethyl Cellosolve (IV, R = $C_6H_5CH_2NH$ and R = *n*-$CH_3(CH_2)_5NH$), excess solvent was removed under reduced pressure and the product was recrystallized from ethanol.

2-Phenyl-4-amino-7-ethylthiopyrimido(4,5-d)pyrimidine (V, R = CH_3CH_2S, R′ = C_6H_5).—To a solution of 5.4 g. of sodium methoxide in 200 ml. of absolute ethanol was added 15.5 g. of benzamidine hydrochloride and 18.0 g. of 2-ethylthio-4-amino-5-cyanopyrimidine. The reaction mixture was stirred at reflux for 24 hours and ammonia was evolved. The reaction mixture was filtered while hot to remove insoluble inorganic material, and the excess solvent was removed from the filtrate under reduced pressure to yield a gummy material which solidified upon the addition of 100 ml. of water. The yellow product obtained in this manner was quite impure. After four recrystallizations from ethanol, 4.6 g. of product was obtained.

2-Methyl-4-amino-7-ethylthiopyrimido(4,5-d)pyrimidine (V, R = CH_3CH_2S, R′ = CH_3).—To a solution of 5.4 g. of sodium methoxide in 200 ml. of anhydrous ethanol was added 9.5 g. of acetamidine hydrochloride and 18.0 g. of 2-ethylthio-4-amino-5-cyanopyrimidine. The reaction mixture was stirred at reflux for 24 hours and during this time ammonia was evolved and a precipitate separated. The cooled reaction mixture was filtered, and the product was washed thoroughly with water to remove inorganic material. Recrystallization from ethyl Cellosolve yielded 5.5 g.

2-Methylamino-5-hydroxypyrimido(4,5-d)pyrimidine (VII, R = CH_3NH).—A mixture of 9.6 g. of 2-methylamino-4-aminopyrimidine-5-carboxamide and 25 ml. of formamide was heated at reflux for 0.5 hour. The reaction mixture was allowed to cool, 75 ml. of ethanol was added and the product was removed by filtration. Recrystallization from 300 ml. of glacial acetic acid gave 5.7 g.

2-Ethylthio-5-hydroxypyrimido(4,5-d)pyrimidine (VII, R = CH_3CH_2S).—A solution of 100 g. of 2-ethylthio-4-aminopyrimidine-5-carboxamide in 500 ml. of ethyl orthoformate was heated at reflux for 3 hours. The ethanol which formed during the course of the reaction was removed by fractionation through a short distillation column. After cooling, the product was removed by filtration and washed with 200 ml. of ether to give 81 g., m.p. 237–239°. Recrystallization from glacial acetic acid yielded 61.5 g. of product, m.p. 244–246°. This compound is reported[4] to melt at 238°.

2-Ethyl-4-hydroxy-7-aminopyrimido(4,5-d)pyrimidine (VIII, R = NH_2, R′ = CH_3CH_2).—A mixture of 14.0 g. of 2,4-diaminopyrimidine-5-carboxamide and 100 ml. of propionic anhydride was stirred at reflux for 1 hour. After several minutes a yellow precipitate began to separate from the solution. The reaction mixture was cooled and filtered and the collected solid was washed with 100 ml. of ether to yield 18 g. of 2-ethyl-4-hydroxy-7-propionylaminopyrimido(4,5-d)pyrimidine. This material was then dissolved in 200 ml. of water containing 3.5 g. of sodium hydroxide, and the solution was heated at reflux for 1 hour. After 10 minutes the hydrolyzed product began to separate out. The mixture was cooled and the product removed by filtration and washed with water. Recrystallization from glacial acetic acid gave 9.5 g.

2-Amino-4-hydroxy-7-ethylthiopyrimido(4,5-d)pyrimidine (X).—Thirty grams of powdered guanidine hydrochloride was added to a solution of 16.8 g. of sodium methoxide in 200 ml. of anhydrous ethanol. The resulting mixture was stirred at room temperature for 0.5 hour and then filtered to remove inorganic material. The filtrate was cooled in an ice-bath to 5–10° and 38.5 g. of 2-ethylthio-4-chloro-5-carboethoxypyrimidine[14] was added dropwise. The reaction mixture was stirred at room temperature for 2 hours and then concentrated under reduced pressure. The residue was added to 150 ml. of warm water and an insoluble neutral fraction was removed by filtration. Neutralization of the filtrate with glacial acetic acid yielded 18.2 g. of product.

The 2-Amino-4-hydroxy-7-methylaminopyrimido(4,5-d)-pyrimidine (XI).—Five grams of 2-amino-4-hydroxy-7-ethylthiopyrimido(4,5-d)pyrimidine was dissolved in 20 ml. of 25% aqueous methylamine and 30 ml. of water and the resulting solution was heated in an autoclave at 140° for 4 hours. Upon cooling, the product which had separated out was removed by filtration and dried in a vacuum oven at 65° overnight; yield 3.5 g.

2-Benzylamino-5-mercaptopyrimido(4,5-d)pyrimidine (X-VIII, R″ = $C_6H_5CH_2$).—A mixture of 14.2 g. of 2-benzylamino-5-hydroxypyrimido(4,5-d)pyrimidine and 13.6 g. of phosphorus pentasulfide in 130 ml. of pyridine was heated at reflux for 4 hours. After cooling, the yellow solid was removed by filtration and washed with 25 ml. of ethanol; yield 12.0 g., m.p. 288°. The addition of 200 ml. of water to the filtrate gave an additional 3.2 g. of product which upon recrystallization from glacial acetic acid yielded a bright yellow solid.

2-Benzylamino-5-*n*-propylaminopyrimido(4,5-d)pyrimidine (XVI, R′ = $CH_3CH_2CH_2$, R″ = $C_6H_5CH_2$.—Five grams of 2-benzylamino-5-mercaptopyrimido(4,5-d)pyrimidine, 10 ml. of *n*-propylamine and 50 ml. of ethanol were sealed in an autoclave and heated at 140° for 4 hours. After cooling, the solid which had separated was removed by filtration and washed with 10 ml. of dilute sodium hydroxide solution. The product was purified by recrystallization from ethanol to give 1.7 g.

2-Ethylthio-5-mercaptopyrimido(4,5-d)pyrimidine (XIII, R = CH_3CH_2).—One hundred grams of 2-ethylthio-5-hydroxypyrimido(4,5-d)pyrimidine, 110 g. of phosphorus pentasulfide and 500 ml. of pyridine were stirred at reflux for 3 hours. The solvent was removed by distillation under reduced pressure and the residue was dissolved in 1 l. of 5% sodium hydroxide solution. The resulting solution was treated with decolorizing charcoal, filtered and the filtrate acidified with glacial acetic acid to give 112 g. of golden yellow crystals.

2-Ethylthio-5-methylaminopyrimido(4,5-d)pyrimidine (XV, R = CH_3CH_2, R′ = CH_3).—A solution of 12.5 g. of 2-ethylthio-5-mercaptopyrimido(4,5-d)pyrimidine and 14 g. of 25% aqueous methylamine in 300 ml. of water was

(14) H. L. Wheeler and C. O. Johns, *Am. Chem. J.*, **38**, 594 (1907).

heated at reflux for 0.5 hour. After cooling, the product was removed by filtration and purified by recrystallization from isopropyl alcohol to give 2.65 g.

2-Amino-5-methylaminopyrimido(4,5-d)pyrimidine (XVI, R'' = H, R' = CH_3).—One gram of 2-ethylthio-5-methylaminopyrimido(4,5-d)pyrimidine was heated with 30 ml. of ethanol saturated with ammonia in an autoclave at 135° for 5 hours. The product which had separated out of solution was purified by recrystallization from aqueous ethanol to give 0.5 g.

2,5-Bis-(methylthio)-pyrimido(4,5-d)pyrimidine, (XIV, R = CH_3).—To 15 ml. of 7.5% aqueous sodium carbonate was added 0.4 g. of 2-methylthio-5-mercaptopyrimido(4,5-d)pyrimidine and the mixture was heated to 35–40° in an oil-bath. To the resulting solution was added 0.5 ml. of dimethyl sulfate and the two-phase system was stirred manually until homogeneous. At this time a light yellow solid began to separate from the reaction mixture. The flask was removed from the oil-bath and the mixture stirred vigorously with a magnetic stirrer for 5 minutes. The mixture was refrigerated overnight and the solid product collected by filtration, washed with alcohol and dried to give 0.32 g. of a pale yellow solid.

2-Methylthio-5-benzylaminopyrimido(4,5-d)pyrimidine (XV, R = CH_3, R' = $C_6CH_5CH_2$).—To a suspension of 0.07 g. of 2,5-bis-(methylthio)-pyrimido(4,5-d) pyrimidine in 8 ml. of absolute ethanol was added 0.5 ml. of benzylamine. The mixture was stirred for 15 hours at room temperature. The solid which had formed was collected by filtration, washed with ethanol and ether and dried to give 0.075 g. of pale yellow material, which yielded white needles upon recrystallization from ethanol.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STATE UNIVERSITY OF IOWA, IOWA CITY, IOWA]

The Rearrangement of 1,1-Dimethyl-1-*p*-nitrobenzylamine-2-acetimide

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RECEIVED MAY 9, 1960

1,1-Dimethyl-1-benzylamine-2-acetimide and 1,1-dimethyl-1-*p*-nitrobenzylamine-2-acetimide rearrange to 1,1-dimethyl-2-benzyl-2-acetylhydrazine and 1,1-dimethyl-2-*p*-nitrobenzyl-acetylhydrazine, respectively. The structure of the latter was demonstrated by synthesis from the dimethylhydrazone of *p*-nitrobenzaldehyde. Alkylation of 1,1-dimethyl-1-*p*-nitrobenzylamine-2-acetimide with methyl iodide gave 1,1-dimethyl-1-*p*-nitrobenzyl-2-α-methoxyethylidenehydrazonium iodide. Hydrolysis of the acetimide with hydrochloric acid gave 1,1-dimethyl-1-*p*-nitrobenyzlhydrazonium chloride. Treatment of the latter with sodium methoxide gave dimethyl-*p*-nitrobenzylamine, formaldehyde and ammonia.

The successful synthesis of trimethylamine-*p*-toluenesulfonimide (I)[2] and trimethylaminebenzimide (II)[3] suggested a study of the chemical

$(CH_3)_3\overset{+}{N}-\overset{-}{N}SO_2C_6H_4CH_3$-*p* $(CH_3)_3\overset{+}{N}-\overset{-}{N}COC_6H_5$

properties of these compounds and a comparison of their behavior with the sulfilimines

In this work the rearrangement of 1,1-dimethyl-1-benzylamine-2-acetimide (III) and 1,1-dimethyl-1-*p*-nitrobenzylamine-2-acetimide (IV) has been investigated. Since the benzyl derivative III was

$(CH_3)_2\overset{+}{N}(CH_2C_6H_5)-\overset{-}{N}COCH_3$ (III) $(CH_3)_2\overset{+}{N}(CH_2C_6H_4NO_2\text{-}p)-\overset{-}{N}COCH_3$ (IV)

an oil, most of the reactions were carried out with the *p*-nitrobenzyl compound IV.

Both compounds were prepared from 1,1-dimethyl-2-acetylhydrazine (V)[4] through the corresponding hydrazonium salt VI. The 1,1-dimethyl-1-*p*-nitrobenzylamine-2-acetimide (IV) rearranged when distilled under reduced pressure to 1,1-dimethyl-2-*p*-nitrobenzyl-2-acetylhydrazine (VII). The structure of the rearranged product (VII) was demonstrated by conversion to 1,1-dimethyl-2-*p*-acetaminobenzyl-2-acetylhydrazine (IX) which was synthesized from the dimethylhydrazone of *p*-nitrobenzaldehyde (X) by the steps

$(CH_3)_2NNHCOCH_3$ (V) $\xrightarrow{p\text{-}NO_2C_6H_5CH_2Br}$ $(CH_3)_2\overset{+}{N}(CH_2C_6H_4NO_2\text{-}p)NHCOCH_3\ Br^-$ $\xrightarrow{OH^-}$ $(CH_3)_2\overset{+}{N}(CH_2C_6H_4NO_2\text{-}p)-\overset{-}{N}COCH_3$ (IV) $\xrightarrow{heat}$ $(CH_3)_2NN(CH_2C_6H_4NO_2\text{-}p)COCH_3$ (VIII)

(1) Abstracted in part from the Ph.D. Thesis of E. Yeakey, August, 1960 and presented at the 138th Meeting of the American Chemical Society, New York, N. Y., Sept., 1960.

(2) S. Wawzonek and D Meyer, THIS JOURNAL, **76**, 2918 (1954).

(3) R. L. Hinman and M. Flores, *J. Org. Chem.*, **24**, 660 (1959).

(4) R. L. Hinman, THIS JOURNAL, **78**, 1645 (1956).

$(CH_3)_2NN=CHC_6H_4NO_2$-*p* (X) $\xrightarrow[H_2]{Pt}$ $(CH_3)_2NN(C_6H_4NH_2\text{-}p)=CH$ (XI) $\xrightarrow{LiAlH_4}$ $(CH_3)_2NNHCH_2C_6H_4NH_2$-*p* (XII) $\xrightarrow{(CH_3CO)_2O}$ $(CH_3)_2NN(COCH_3)CH_2C_6H_4NHCOCH_3$-*p* (IX)

Acid hydrolysis of 1,1-dimethyl-2-*p*-nitrobenzyl-2-acetylhydrazine gave 1,1-dimethyl-2-*p*-nitrobenzylhydrazine.

Proof for the structure of the aminimide IV was the acid hydrolysis to 1,1-dimethyl-1-*p*-nitrobenzylhydrazonium chloride (XIII) which was difficult to purify. This salt (XIII) was converted into

IV $\xrightarrow{HCl}$ $(CH_3)_2\overset{+}{N}(CH_2C_6H_4NO_2\text{-}p)NH_2\ Cl^-$ (XIII) $\longrightarrow$ $(CH_3)_2\overset{+}{N}(CH_2C_6H_4NO_2\text{-}p)N=CHC_6H_5\ Cl^-$ (XIV) $\leftarrow$ $(CH_3)_2NN=CHC_6H_5$ (XV)

the picrate and formed a hydrazone (XIV) with benzaldehyde. The latter compound was also synthesized by the alkylation of the dimethylhydrazone of benzaldehyde (XV) with *p*-nitrobenzyl chloride.

Prolonged acid treatment of the aminimide IV gave *p*-nitrobenzyl chloride.

Reduction of the aminimide IV with tin and hydrochloric acid gave 1,1-dimethylhydrazine; cleav-