TABLE IV

APPARENT EQUILIBRIUM CONSTANTS FOR $RHgX + OH^- \rightleftarrows RHgOH + X^-$ AT HALF-CONVERSION

Compound	Solvent[a]	(X^-)	pH	(OH^-)	$(X^-)/(OH^-)$
2 (Table II)	D	0.0013	11.8	1.0×10^{-5}	130
6 (Table II)	D	.0013	10.6	6.3×10^{-7}	2.1×10^{3}
	W	.0016	8.4	2.5×10^{-6}	640
8 (Table II)	D	.0017	8.20	2.5×10^{-9}	7×10^{5}
	W	.0036	8.14	1.4×10^{-6}	2.6×10^{3}
	W	.0008	7.5	3×10^{-7}	2.7×10^{3}
10 (Table II)	D	.0016	9.85	1.1×10^{-7}	1.5×10^{4}
	W	.0018	7.10	1.3×10^{-7}	1.4×10^{4}
11 (Table II)	D	.0013	9.95	1.4×10^{-7}	0.9×10^{4}
12 (Table III)	D	.0013	9.85	1.1×10^{-7}	1.2×10^{4}
	W	.0018	7.25	1.8×10^{-7}	1.0×10^{4}
13 (Table III)	D	.0017	11.0	1.6×10^{-6}	1.1×10^{3}
14 (Table III)	D	.0016	10.2	2.5×10^{-7}	6.4×10^{3}
15 (Table III)	D	.0015	12.3	3.2×10^{-5}	47
16 (Table III)	D	.0016	8.65	7.1×10^{-9}	2.3×10^{5}
17 (Table III)	D	.0013	10.0	1.6×10^{-7}	8.1×10^{3}
18 (Table III)	D	.0013	10.0	1.6×10^{-7}	8.1×10^{3}
19 (Exptl.)	D	.0016	9.95	1.4×10^{-7}	1.1×10^{4}
	W	.0017	7.25	1.8×10^{-7}	0.9×10^{4}
20 (Exptl.)	D	.0018	8.55	5.6×10^{-9}	3.2×10^{5}

[a] D = 66% dimethylformamide; W = water.

Anal. Calcd. for $C_{12}H_{16}HgN_4O_4S$: C, 28.10; H, 3.14; N, 10.92. Found: C, 28.11; H, 3.21; N, 10.69.

1,3-Dimethyl-5-N-allylcarbamyluracil.—One hundred grams (0.50 mole) of 1,3-dimethyl-5-carbethoxyuracil[2] was placed in a hydrogenation bomb with 300 ml. of dioxane and 60 g. (1.0 mole) of allylamine and heated overnight at 110°. The dioxane was removed under reduced pressure and the residue was dissolved in a minimum amount of water. The aqueous solution was decolorized with carbon, filtered, and the clear filtrate chilled. The solid was collected and again crystallized from a small volume of water. Forty grams (yield 36%) of white needles, m.p. 133°, was obtained.

Anal. Calcd. for $C_{10}H_{13}N_3O_3$: C, 53.80; H, 5.87; N, 18.83. Found: C, 54.00; H, 5.67; N, 18.59.

Mercurials from 1,3-Dimethyl-5-N-allylcarbamyluracil (Table III).—Eleven and one-tenth grams (0.05 mole) of 1,3-dimethyl-5-(N-allylcarbamyl)-uracil was added to 0.05 mole of chloromercuric acetate in 250 ml. of water, to 0.05 mole of chloromercuric acetate in 150 ml. of methanol, to 0.05 mole of chloromercuric acetate in 150 ml. of ethanol, to 0.05 mole of bromomercuric acetate in 150 ml. of methanol, to 0.05 mole of iodomercuric acetate in 150 ml. of methanol, to 0.05 mole of nitratomercuric acetate in 150 ml. of methanol, to 0.05 mole of thiocyanatomercuric acetate in 150 ml. of methanol, and to 0.05 mole of chloromercuric acetate in 40 ml. of methyl Cellosolve. The mixtures were heated to boiling and the solids dissolved. The resulting solutions were allowed to cool and stand at room temperature. The solid products were collected and separately recrystallized from ethylene dichloride.

INDIANAPOLIS 6, INDIANA

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Diuretics. III. 4,6-Diaminopyrimidines

BY CALVERT W. WHITEHEAD AND JOHN J. TRAVERSO

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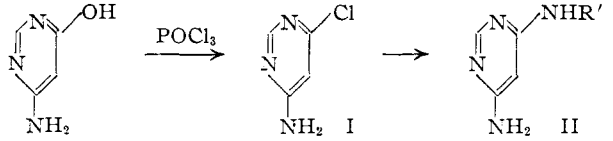
4-Amino-6-hydroxypyrimidine was chlorinated to yield 4-amino-6-chloropyrimidine. The latter was aminated to give 4-amino-6-alkylamino- and 4-amino-6-arylaminopyrimidines. Some of these aminopyrimidines were found to have diuretic activity. The reactions of diethyl malondiimidate with alkylamines yielded N,N″-dialkylmalondiamidines which were in turn cyclized with ethyl formate to 4,6-bis-alkylaminopyrimidines. The amination of 4,6-dichloropyrimidine also yielded 4,6-bis-alkylaminopyrimidines as well as intermediate 4-chloro-6-substituted aminopyrimidines. The pK_a's, the ultraviolet and infrared spectra were determined for a number of the 4,6-diaminopyrimidines and 4,6-bis-alkylaminopyrimidines

Although it has been reported that 4-amino-6-hydroxypyrimidine does not react successfully with phosphorus oxychloride[1] to yield 4-amino-6-chloropyrimidine (I), the latter was considered to be an appropriate intermediate in the synthesis of 4-amino-6-alkylamino- and 4-amino-6-arylaminopyrimidines. This reaction was reinvestigated and the product was found to be moderately soluble in water and easily hydrolyzed by acid. When precautions were taken to prevent this hydrolysis, compound I could be obtained in 48–62% yield. Condensations of I with alkylamines by conventional procedures yielded 4-amino-6-alkylaminopyrimidines (II, R′ = alkyl). The 4-amino-6-arylaminopyrimidines (II, R′ = aryl) were best obtained through their hydrochlorides by the reactions of arylamine hydrochlorides with I.



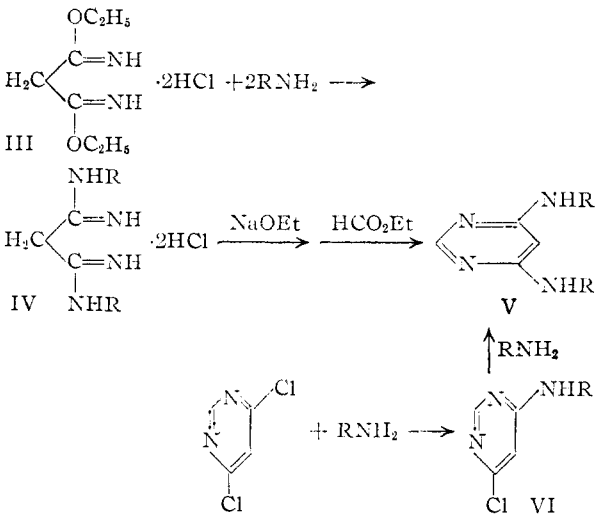
The parent 4,6-diaminopyrimidine was prepared by the method of Kenner through the condensation of malondiamidine with ethyl formate.[2] The possibility was considered that 4,6-bis-substituted aminopyrimidines could be prepared by a similar condensation of ethyl formate with N,N″-disubstituted malondiamidines (IV). The latter were prepared from diethyl malondiimidate (III) reactions with primary amines. When ethyl formate was allowed to react with IV the isolated products had the composition of 4,6-bis-substituted aminopyrimidines (V). The structure of V was confirmed by comparison with 4,6-bis-substituted aminopyrimidines obtained by the amination of 4,6-dichloropyrimidine. When 4,6-dichloropyrimidine was treated with amines the intermediate 4-chloro-6-substituted aminopyrimidines (VI) were also produced. The yields of both V and VI from the amination of 4,6-dichloropyrimidine depended upon the molar ratio of the reactants as well as the temperature of the reaction.

A number of the 4,6-diaminopyrimidines were titrated in 66% dimethylformamide and all showed one titratable group (Table III). It was impossible to determine pK'_a values of less than 2.5 because of the solvent blank. However, an at-

(1) D. J. Brown, *Rev. Pure Appl. Chem.*, **3**, 124 (1953).

(2) G. W. Kenner, B. Lythgoe, A. R. Todd and A. Topham, *J. Chem. Soc.*, 574 (1943).

tempt was made to find a possible second pK'_a by determining a shift in ultraviolet absorption with change in pH. A shift does not occur for pH values between 3.7 and 0.4. Changes in both intensity and wave length occur between a pH of 4 and 5 for 4-amino-6-anilinopyrimidine. This shift corresponds to the pK'_a value of 4.9, as measured by titration, for the same compound. Changes



in λ_{max} and log a_M occur between pH 5 and 6 for the 4-amino-6-alkylaminopyrimidines. Ultraviolet spectra of all the 4,6-diaminopyrimidines show two maxima. The 4-amino-6-chloropyrimidines show only one maximum. These maxima and their intensities are given in Table III for both the free bases and their acid salts. Brown[3] showed that 2- and 4-aminopyrimidines exist in the amino-form by comparison of their base strengths, ultraviolet and infrared spectra with those of the corresponding nuclear and extra-nuclear N-methyl derivatives. Comparison of the ultraviolet spectra and pK'_a of 4,6-bis-*n*-butylaminopyrimidine with those of 4,6-bis-*n*-butylamino-3-methylpyrimidinium iodide led to similar conclusion for the 4,6-diaminopyrimidines. The great difference in the pK_a''s (Table III) of the above two compounds shows that both extra-nuclear nitrogens of 4,6-bis-*n*-butylaminopyrimidine exist in the amino-form. The near identity of the ultraviolet spectra (Table III) of 4,6-bis-*n*-butylamino-3-methylpyrimidinium iodide and the cation of 4,6-bis-*n*-butylaminopyrimidine shows that protonation occurs on a nuclear nitrogen. The infrared spectra of the 4,6-diaminopyrimidines showed that some bands were consistently present and these are characteristic of the 4,6-diaminopyrimidine moiety. These bands are at approximately 6.3, 6.7, 7.4, 7.9–8.0, 8.8, 10.2 and 12.3 μ.

Pharmacology.—Oral doses of 5 and 10 mg. per kg. of body weight were given to female dogs. The urine was collected over a three hour period starting one hour after dosage. The relative diuretic activity (Table I) was obtained by comparing the increase in urine volume per kg. of body weight over normal output. The greatest response was observed with the 4-amino-6-anilino-, 4-amino-6-toluidino-, 4-amino-6-phenoxyethylamino- and 4-amino-6-benzylaminopyrimidines. The 4-amino-6-anilinopyrimidine was assigned an arbitrary value of 100%. Substitution of a *p*-methoxy group in the aromatic ring destroyed the activity while *p*-chloro, and *o*- or *m*-methyl groups reduced the activity of both the 4-amino-6-anilino and 4-amino-6-benzylamino derivatives. Maximum activity of the 4-amino-6-alkylaminopyrimidines is found with C_4 and C_5 alkyl groups. Activity is lost when both the 4- and 6-amino groups are substituted or when one amino group is disubstituted. The mechanism of the diuretic action has not been determined; however, the 4,6-diaminopyrimidines do not inhibit carbonic anhydrase.

The toxicity in mice and rats varied from an LD_{50} value of 500 mg./kg. for 4-amino-6-anilinopyrimidine to 1500 mg./kg. for 4-amino-6-benzylaminopyrimidine. Daily doses of 25 mg./kg. of 4-amino-6-benzylaminopyrimidine, 4-amino-6-phenoxyethylaminopyrimidine, 4-amino-6-*n*-amylaminopyrimidine and 4-amino-6-anilinopyrimidine are well tolerated in dogs for six weeks without damage to organs or tissues and without signs of nausea, vomiting or crystalluria.

Acknowledgment.—The authors thank Wm. Brown, Howard L. Hunter, George Maciak and Miss Gloria Beckman for the microanalyses and Harold Boaz, Donald Wolf and Lee Howard for the ultraviolet, infrared and titration data and their interpretations.

Experimental

4-Amino-6-chloropyrimidine.[4]—4-Amino-6-hydroxypyrimidine[5] was dried in a vacuum oven at 130–140° for 24 hours. One mole or 111.1 g. of the dry pyrimidine was added to 1200 ml. of freshly distilled phosphorus oxychloride. The mixture was stirred carefully and 160 g. of redistilled N,N-diethylaniline was added. The mixture was boiled for 4.5 hours. After this time the solid had completely dissolved and the solution was of light brown color. Excess phosphorus oxychloride was distilled at 50–55° under reduced pressure. The thick brown sirup remaining was dissolved in an equal volume of ether, cooled in a Dry Ice–alcohol-bath and treated dropwise with 200 ml. of cold water while stirring. The temperature was maintained at −10–0° and ammonium hydroxide added when needed to maintain a pH of approximately 6. After stirring for 2 hours the mixture was allowed to warm to room temperature. Base was again added to maintain a pH of approximately 6. The final mixture, 2–2.5 l., was continuously extracted with ether for 2–5 days. The ether was evaporated, the solid washed with light petroleum ether, dissolved in approximately 4 l. of hot water, clarified with carbon, filtered and cooled. The white flakes were collected and dried. Concentration of the water filtrate yielded more product. The yields of 4-amino-6-chloropyrimidine from several runs ranged from 70–90 g., 48–62%, m.p. 215°.

Anal. Calcd. for $C_4H_4ClN_3$: C, 37.08; H, 3.10; N, 32.43. Found: C, 37.26; H, 3.30; N, 32.56.

4-Amino-6-chloropyrimidine Hydrochloride.—Five grams of 4-amino-6-chloropyrimidine was dissolved in 100 ml. of absolute ethanol. The alcohol solution was cooled in ice and was saturated with dry hydrogen chloride. The product separated, was collected and recrystallized from ethanol, yield 4 g. (65%), m.p. 193° dec.

Anal. Calcd. for $C_4H_5Cl_2N_3$: C, 28.94; H, 3.02; N, 25.32. Found: C, 29.09; H, 3.23; N, 25.18.

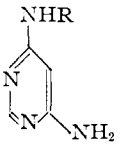
(3) D. J. Brown, Earl Hoerger and S. F. Mason, *J. Chem. Soc.*, 4035 (1955).

(4) The infrared spectrum has been reported for 4-amino-6-chloropyrimidine: L. N. Short and H. W. Thompson, *J. Chem. Soc.*, 168–187 (1952). A description of the synthesis or other physical properties could not be found.

(5) D. J. Brown, *J. Soc. Chem. Ind.*, **69**, 355 (1950).

TABLE I

4-AMINO-6-ALKYL(OR ARYL)AMINOPYRIMIDINES



R	Formula	Yield, %	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Diuretic activity,[h] %
CH_3	$C_5H_8N_4$	62	205					45.13	44.78	9
C_2H_5	$C_6H_{10}N_4$	74	193	52.15	52.21	7.30	7.36	40.55	40.32	
$CH_2{=}CHCH_2$	$C_7H_{10}N_4$	65	146					37.31	37.38	8
$HOOC(CH_2)_2$[a]	$C_7H_{10}N_4O_2$	21	225 d.	46.15	45.68	5.52	5.86			
n-C_3H_7	$C_7H_{12}N_4$	89	140	55.24	54.98	7.95	7.70	36.82	37.06	15
Iso-C_3H_7	$C_7H_{12}N_4$	81	177	55.24	55.65	7.95	7.90	36.82	36.33	11
n-C_4H_9	$C_8H_{13}N_3$	78	118	57.80	58.01	8.49	8.52	33.71	33.45	18
Iso-C_4H_9	$C_8H_{14}N_4$	70	125	57.80	58.04	8.49	8.48	33.71	33.96	16
C_5H_4O[b]	$C_9H_{10}N_4O$	30	172					29.46	29.64	11
n-C_5H_{11}	$C_9H_{16}N_4$	72	115	59.97	60.06	8.95	8.97	31.09	31.32	36
Iso-C_5H_{11}	$C_9H_{16}N_4$	50	145	59.97	59.49	8.95	9.31	31.09	30.84	16
p-ClC_6H_4	$C_{10}H_9ClN_4$	41	197	54.43	54.31	4.11	4.19	25.39	25.56	40
C_6H_5	$C_{10}H_{10}N_4$	74	179	64.50	63.70	5.41	5.49	30.09	30.35	100
C_6H_6N[c]	$C_{10}H_{11}N_5$	13	188	59.68	59.21	5.51	5.19	34.81	34.77	
C_6H_{11}[d]	$C_{10}H_{16}N_4$	54	203					29.14	29.04	7
n-C_6H_{13}	$C_{10}H_{18}N_4$	94	115	61.82	62.06	9.34	9.41	28.84	28.66	11
m-$CH_3C_6H_4$	$C_{11}H_{12}N_4$	35	132	65.98	66.28	6.04	6.22	27.98	28.20	68
p-$CH_3C_6H_4$	$C_{11}H_{12}N_4$	29	175	65.98	65.84	6.04	6.18	27.98	28.18	100
$C_6H_5CH_2$	$C_{11}H_{12}N_4$	78	211	65.98	65.70	6.04	5.91	27.98	27.69	69
p-$CH_3OC_6H_4$	$C_{11}H_{12}N_4O$	54	215–220	61.09	61.05	5.59	5.97	25.91	25.98	
$C_7H_{13}O$[e]	$C_{11}H_{18}N_4O$	70	197	59.43	59.93	8.16	8.33			
n-C_7H_{15}	$C_{11}H_{20}N_4$	53	119	63.42	63.68	9.68	9.93	26.90	26.94	16
o-$ClC_6H_4CH_2CH_2$	$C_{12}H_{13}ClN_4$	47	156					21.49	21.36	
$C_6H_5(CH_2)_2$	$C_{12}H_{14}N_4$	54	164	67.26	67.02	6.59	6.56	26.15	25.94	13
$C_6H_5CH(CH_3)$	$C_{12}H_{14}N_4$	67	171	67.26	67.54	6.59	6.70	26.15	26.27	
m-$CH_3C_6H_4CH_2$	$C_{12}H_{14}N_4$	94	175	67.26	67.12	6.59	6.72	25.15	26.68	21
p-$CH_3C_6H_4CH_2$	$C_{12}H_{14}N_4$	60	206	67.26	67.52	6.59	6.66	26.15	25.84	
o-$CH_3C_6H_4CH_2$	$C_{12}H_{14}N_4$	90	219	67.26	67.17	6.59	6.29	26.15	26.27	
p-$CH_3OC_6H_4CH_2$	$C_{12}H_{14}N_4O$	99	131 d.	62.59	62.53	6.13	6.26	24.33	24.51	
$C_6H_5O(CH_2)_2$	$C_{12}H_{14}N_4O$	98	190					23.71	23.67	86
$C_6H_{11}(CH_2)_2$[f]	$C_{12}H_{20}N_4$	60	183	65.42	65.70	9.15	9.18	25.43	25.18	
n-C_8H_{17}	$C_{12}H_{22}N_4$	76	100	64.82	64.59	9.97	9.88	25.20	25.08	
$C_9H_9O_2$[g]	$C_{13}H_{14}N_4O_2$	55	147	60.45	60.01	5.46	5.72	21.70	21.28	
$C_6H_5(CH_2)_3$	$C_{13}H_{16}N_4$	46	107					24.54	24.26	38
p-$CH_3OC_6H_4(CH_2)_2$	$C_{13}H_{16}N_4O$	95	165					22.94	22.91	
$C_6H_5(CH_2)_4$	$C_{14}H_{18}N_4$	98	108					23.12	22.86	
3,4-di-$CH_3OC_6H_3(CH_2)_2$	$C_{14}H_{18}N_4O_2$	61	152					20.43	20.18	
3,4-di-$CH_3OC_6H_3(CH_2)_3$	$C_{15}H_{20}N_4O_2$	45	153					19.57	19.08	
$C_6H_5C(C_4H_8)CH_2$	$C_{16}H_{20}N_4$	48	151	71.61	71.78	7.51	7.73	20.88	21.07	
$(C_6H_5)_2CHCH_2$	$C_{18}H_{18}N_4$	49	143	74.45	74.19	6.25	6.30	19.30	19.32	

[a] Prepared by heating the sodium salt of β-alanine with 4-amino-6-chloropyrimidine in aqueous solution. [b] Furfuryl. [c] 2-Pyridylmethyl. [d] Cyclohexyl. [e] 1-Hydroxycyclohexylmethyl. [f] β-Cyclohexylethyl. [g] 3,4-Methylenedioxyphenethyl. [h] The diuretic activity was determined by R. B. Robbins of this Laboratory. The values were obtained by comparing the increase in urine volume per kg. of body weight over normal output during three hours starting 1 hour after dosage. The diuretic response was from doses of 5 and 10 mg. per kg. A value of 10% was obtained for a 20 mg./kg. dose of 1-allyl-3-ethyl-6-aminouracil.

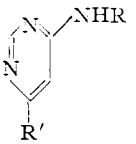
4-Amino-6-alkylaminopyrimidines. Table I.—Ten grams (0.068 mole) of 4-amino-6-chloropyrimidine was mixed with 0.14 mole of the appropriate alkylamine alone or dissolved in 50–100 ml. of water, alcohol, dioxane or toluene. The reaction was completed by boiling under reflux for 8–12 hours. Low boiling amines were heated at 110–120° with the chloropyrimidine in sealed glass tubes. Best results were obtained with the higher boiling amines by using dioxane or toluene as the solvent. After completion of the reaction the mixture was cooled and filtered. The filtrate was concentrated and the resulting solid 4-amino-6-alkylaminopyrimidine purified by recrystallization from ethyl acetate, alcohol or mixtures of ethyl acetate and petroleum ether or alcohol and water.

4-Amino-6-arylaminopyrimidines, Table I.—Ten grams (0.068 mole) of 4-amino-6-chloropyrimidine was added to 0.068 mole of the arylamine hydrochloride in a mixture of 200 ml. of dioxane and 30 ml. of ethanol. The solution was boiled under reflux for 24 hours. The hydrochloride of the 4-amino-6-arylaminopyrimidine separated when cooled. It was dissolved in water, clarified with carbon, filtered and made basic with ammonium hydroxide. The precipitated 4-amino-6-arylaminopyrimidine was recrystallized from a mixture of alcohol and water. The reaction also was carried out with the free arylamine and 4-amino-6-chloropyrimidine, but this gave lower yields and products that were more difficult to purify.

Malondiamidines.—To 75 ml. of absolute ethanol was added 23 g. (0.1 mole) of diethyl malondiimidate. Two-tenths mole of the appropriate amine was added and the mix-

TABLE II

4,6-BIS-AKLYLAMINOPYRIMIDINES AND 4-AMINO-6-DISUBSTITUTED AMINOPYRIMIDINES



R	R′	Formula	Yield, %	M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
C_2H_5	C_2H_5NH	$C_8H_{14}N_4$	79	187					33.71	33.92
$H_2C{=}CHCH_2$	$H_2C{=}CHCH_2NH$	$C_{10}H_{14}N_4$	19.5	163					29.45	29.41
C_5H_5O[a]	C_5H_5ONH[a]	$C_{14}H_{14}N_4O_2$	14	185	62.21	62.45	5.22	5.34	20.73	20.92
n-C_8H_{17}	n-$C_8H_{17}NH$	$C_{20}H_{38}N_4$	48	112					16.85	16.72
H	$(CH_3)_2N$	$C_6H_{10}N_4$	93	202					40.55	40.83
H	C_4H_8N[b]	$C_8H_{12}N_4$	95	243					34.12	34.39
H	$(C_2H_5)_2N$	$C_8H_{14}N_4$	39	132	57.80	57.79	8.49	8.58	33.71	33.50
H	C_4H_8NO[c]	$C_8H_{12}N_4O$	72	197	53.32	53.59	6.71	6.74	31.09	30.83
H	$C_5H_{10}N$[d]	$C_9H_{14}N_4$	97	185	60.64	60.88	7.92	8.03	31.44	31.85
H	$C_6H_{12}N$[e]	$C_{10}H_{16}N_4$	81	208	62.47	62.58	8.39	8.74	29.14	29.41
H	$(n$-$C_3H_7)_2N$	$C_{10}H_{18}N_4$	33	99	61.82	62.02	9.34	9.21	28.84	28.62
H	$C_6H_5(CH_3)N$	$C_{11}H_{12}N_4$	82	181	65.98	65.96	6.04	6.06	27.98	27.97

[a] Furfuryl. [b] Pyrrolidino. [c] Morpholino. [d] Piperidino. [e] Homopiperidino.

TABLE III

ULTRAVIOLET AND pK'_a DATA FOR 4,6-DIAMINOPYRIMIDINES AND 4-AMINO-6-CHLOROPYRIMIDINES

Pyrimidine	Solvent and pH	λ_{max}	log a_M	pK'_a[a]
4-Amino-6-n-butylamino-	MeOH	258	3.74	5.7
		223	4.62	
4-Amino-6-diethylamino-	MeOH	230	4.53	5.7
	7.9, 13.3	263	3.94	
	0.45	229	4.35	
		274	4.25	
4-Amino-6-homo-piperidino	H_2O	229	4.32	5.7
	4	274	4.27	
4,6-Bis-ethylamino	H_2O	230	4.45	5.6
	4	273	4.18	
4,6-Bis-allylamino-	MeOH	231	4.68	5.2
	7.4, 13.2	264	3.83	
	0.3	231	4.48	
		274	4.21	
4,6-Bis-furfurylamino-	MeOH a	232	4.71	4.7
		263	3.86	
4,6-Bis-n-octylamino-	MeOH	232	4.68	
	7.35, 13.2	264	3.80	
	0.3	232	4.46	
		274	4.19	
4-Amino-6-(β-cyclohexyl-ethylamino)-	MeOH	224	4.64	
		260	3.75	
4-Amino-6-(cyclohexanol-1-methylamino)-	H_2O	224	4.41	5.6
	4	268	4.18	
4-Amino-6-(cyclopentyl-1-phenylamino)-	MeOH	224	4.67	5.5
		258	3.81	
4-Amino-6-anilino-	MeOH	247	4.24	4.9
	7.6, 13.1	280	4.27	
	0.3	239	4.15	
		284	4.19	
4-Amino-6-N-methyl-anilino-	H_2O	210	4.32	5.0
	4	225	4.31	
		276	4.24	
4-Amino-6-(β,β-diphenyl-ethylamino)-	MeOH	224	4.70	
		261	3.86	
4-Amino-6-benzylamino-	MeOH	224	4.62	5.5
		260	3.79	
4,6-Bis-n-butylamino-3-methylpyrimidinium iodide	MeOH	223	4.58	12.8
	4	275	4.16	
4-Benzylamino-6-chloro-	MeOH	246	4.30	
4-Chloro-6-phenoxyethyl-	MeOH	244	4.28	
4-Chloro-6-piperidino-	MeOH	255	4.32	
4-Chloro-6-furfuryl-amino-	MeOH	244	4.30	

[a] The pK'_a's were determined in 66% N,N-dimethylformamide.

ture shaken until the solid had dissolved. The solution was allowed to stand several days until the product crystallized. The crystalline malondiamidine dihydrochloride was then collected and recrystallized from alcohol. The following malondiamidines were prepared.

N,N′′-Diethylmalondiamidine dihydrochloride, yield 71%, m.p. 280° dec. *Anal.* Calcd. for $C_7H_{18}Cl_2N_4$: C, 36.69; H, 7.92; N, 24.45. Found: C, 36.63; H, 8.00; N, 24.70.

N,N′′-Di-n-butylmalondiamidine dihydrochloride, yield 49%, m.p. 290–295°. *Anal.* Calcd. for $C_{11}H_{26}Cl_2N_4$: C, 46.31; H, 9.19. Found: C, 46.87; H, 9.26.

N,N′′-Diallylmalondiamidine dihydrochloride, yield 95%, m.p. 255° dec. *Anal.* Calcd. for $C_9H_{18}Cl_2N_4$: C, 42.69; H, 7.16. Found: C, 42.54; H, 7.41.

N,N′′-Di-(γ-methoxypropyl)-malondiamidine dihydrochloride, yield 59%, m.p. 230° dec. *Anal.* Calcd. for $C_{11}H_{26}Cl_2N_4O_2$: C, 41.65; H, 8.30. Found: C, 41.85; H, 8.34.

N,N′′-Di-n-octylmalondiamidine dihydrochloride, yield 78%, m.p. 280–290° dec. *Anal.* Calcd. for $C_{19}H_{42}Cl_2N_4$: C, 57.41; H, 10.65; N, 14.10. Found: C, 57.65; H, 10.70; N, 14.29.

N,N′′-Difurfurylmalondiamidine dihydrochloride, yield 60%, m.p. 280° dec. *Anal.* Calcd. for $C_{13}H_{18}Cl_2N_4O_2$: C, 46.99; H, 5.46. Found: C, 46.81; H, 5.45.

N,N′′-Diphenethylmalondiamidine dihydrochloride, yield 61%, m.p. 300° dec. *Anal.* Calcd. for $C_{15}H_{26}Cl_2N_4$: C, 60.10; H, 6.85. Found: C, 60.38; H, 6.85.

4,6-Diaminopyrimidines from Malondiamidines, Table II.—A solution of 5.4 g. (0.1 mole) of sodium methylate in 75 ml. of ethanol was cooled in an ice-bath and 0.05 mole of the appropriate N,N′′-disubstituted malondiamidine dihydrochloride was added. The precipitated sodium chloride was collected on a filter. The filtrate was concentrated under reduced pressure. The remaining sirup was dissolved in 20 ml. of ethyl formate and allowed to stand at room temperature for 12 hours. The alcohol was concentrated on the steam-bath and cooled. The crystalline product was collected and recrystallized from 50% ethanol.

4-Amino-6-disubstituted Aminopyrimidines, Table II.—One-tenth mole of 4-amino-6-chloropyrimidine was treated with 0.2 mole of the appropriate secondary amine in the same manner described for the preparation of 4-allylamino-6-aminopyrimidine.

Amination of 4,6-Dichloropyrimidine. 4,6-Bis-benzylaminopyrimidine.—Seven and four-tenths grams (0.05

mole) of 4,6-dichloropyrimidine[2] was mixed with 21.5 g. (0.20 mole) of benzylamine. The mixture became hot and a solid separated. The mixture was then heated on the steam-bath for 3 hours. The resulting solid was dissolved in hot alcohol and cooled to yield 6.5 g. (46%) of 4,6-bis-benzylaminopyrimidine, m.p. 234–235°.

Anal. Calcd. for $C_{18}H_{18}N_4$: C, 74.45; H, 6.25; N, 19.30. Found: C, 74.09; H, 6.52; N, 19.54.

4-Benzylamino-6-chloropyrimidine.—The alcohol filtrate from the above crystallization was concentrated and the solid residue was recrystallized from a mixture of ethyl acetate and petroleum ether; yield 2 g. (18.2%), m.p. 121°.

Anal. Calcd. for $C_{11}H_{10}ClN_3$: N, 19.13. Found: N, 18.74.

4,6-Bis-*n*-butylaminopyrimidine.—Six and seven-tenths grams of 4,6-dichloropyrimidine was treated with 14.6 g. of *n*-butylamine in the manner described above; yield 6.7 g. (67%), m.p. 154°.

Anal. Calcd. for $C_{12}H_{22}N_4$: C, 64.82; H, 9.97; N, 25.20. Found: C, 64.63; H, 9.93; N, 25.05.

4-Chloro-6-β-phenoxyethylaminopyrimidine.—To a solution of 6.85 g. (0.05 mole) of β-phenoxyethylamine in 60 ml. of 20% alcohol was added 3.95 g. (0.026 mole) of 4,6-dichloropyrimidine. The solution was heated on the steam-bath for 12 hours. Upon cooling 4-chloro-6-β-phenoxyethylaminopyrimidine crystallized and was recrystallized from a mixture of ethyl acetate and petroleum ether; m.p. 98–100°, yield 6 g. (90%).

Anal. Calcd. for $C_{12}H_{12}ClN_3O$: N, 16.83. Found: N, 16.37.

4-Chloro-6-furfurylaminopyrimidine.—A mixture of 5.9 g. (0.06 mole) of furfurylamine and 4.46 g. (0.03 mole) of 4,6-dichloropyrimidine in 50 ml. of water was heated on the steam-bath for several hours. An oil separated that readily crystallized upon cooling. This was recrystallized from a mixture of ethyl acetate and petroleum ether; yield 3.5 g. (58%), m.p. 130°.

Anal. Calcd. for $C_9H_8ClN_3O$: N, 20.05. Found: N, 20.25.

4-Chloro-6-piperidinopyrimidine was prepared by the procedure described above; yield 93%, m.p. 78°.

Anal. Calcd. for $C_9H_{12}ClN_3$: C, 54.68; H, 6.12; N, 21.26. Found: C, 54.82; H, 5.97; N, 21.35.

4,6-Bis-*n*-butylamino-3-methylpyrimidinium Iodide.—One gram each of 4,6-bis-*n*-butylaminopyrimidine and methyl iodide was added to 25 ml. of ethyl acetate. After refluxing for one hour, a crystalline solid was collected from the cooled solution. Recrystallization from ethanol gave 1.2 g. (43%) of solid, m.p. 121°.

Anal. Calcd. for $C_{13}H_{25}IN_4$: C, 42.80; H, 6.92; N, 15.37. Found: C, 43.16; H, 6.78; N, 15.38.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Studies in the Synthesis of the Antirachitic Vitamins. VI. The Synthesis of 2-Cholestanylidene-ethan-1-al

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Several methods for the synthesis of 2-cholestanylidene-ethan-1-al, a key intermediate in the synthesis of biologically active vitamin D homologs, have been studied. Of all these, the method in which the Grignard of ethoxyacetylene is allowed to react with cholestanone with subsequent partial hydrogenation followed by acid-catalyzed rearrangement gives the best yields and minimum by-products.

In the synthesis of biologically active vitamin D homologs[2] one of the key intermediates is 2-cholestanylidene-ethan-1-al (IX). It is the purpose of this communication to describe the various methods used for the synthesis of this intermediate.

The first method used for the synthesis of 2-cholestanylidene-ethan-1-al is outlined in a sequence of reactions shown in Fig. 1. The reaction between cholestanone[3,4] and lithium acetylide in liquid ammonia was studied under a variety of conditions before optimum yields of the acetylenic carbinol II were obtained. Only negligible quantities of this carbinol were obtained when cholestanone was added as a solid or in ether solution to liquid ammonia containing only 10% excess of lithium acetylide. A 22% yield was realized when toluene was substituted for ether and a fourfold excess of lithium acetylide used. Optimum yields of 75–80% of the acetylenic carbinol were obtained when cholestanone was added in a 50–50 mixture of ether–toluene to liquid ammonia containing sevenfold excess of lithium acetylide. Girard reagent P was advantageous in removing the unreacted ketone.

The acetylenic carbinol was partially hydrogenated in ethanol to 3-ethenylcholestan-3-ol (III) in quantitative yields using palladium-on-calcium carbonate as the catalyst. Both compounds II and III gave, upon catalytic hydrogenation using platinum oxide, 3-ethylcholestan-3-ol (IV). Following the method of Dimroth[6] and Grab and Rumpf[7] the carbinol III was treated with phosphorus tribromide in pyridine to yield a mixture consisting of 82% of 1-bromo-2-cholestanylidene-ethane (V) and 18% of 3-ethenylcholest-3-ene (VI). The bromide V was difficult to purify so the mixture was treated directly with potassium acetate in acetic acid to produce another mixture consisting of 67% of 1-acetoxy-2-cholestanylidene-ethane (VII) and an additional 33% of the diene VI through a dehydrobromination reaction. The over-all yield of the ester for the two reactions was 55%. Most of the diene could be separated by crystallization, but the ester was obtained free from the diene only by chromatography in efficiencies of 25–30%.

An attempt then was made to by-pass the bro-

(1) From the Ph.D. Thesis of C. P. Priesing, M.I.T., April, 1957.

(2) N. A. Milas and C. P. Priesing, THIS JOURNAL, **79**, 3610 (1957); also presented before the 132nd Meeting of A.C.S., New York, N. Y., September 8–13, 1957.

(3) W. F. Bruce and J. O. Ralls, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 191.

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