TABLE VI

ULTRAVIOLET ABSORPTION SPECTRA

Compound, pyrimidine	pH 1 Maximum λ, mμ	pH 1 Maximum E_m	pH 1 Minimum λ, mμ	pH 1 Minimum E_m	pH 11 Maxima λ, mμ	pH 11 Maxima E_m	pH 11 Minimum λ, mμ	pH 11 Minimum E_m
2-Amino-5-(4′-bromophenoxy)-4-hydroxy					233	14,500		
	270	7100	255	6350	280	6,600	260	3240
2-Amino-5-(4′-chlorophenoxy)-4-hydroxy-6-methyl					233	15,400		
	268	9550	253	8400	280	8,850	255	4650
5-(4′-Bromophenoxy)-2,4-diamino-					233	19,000		
	275	4500	265	3930	287	6,900	263	3500
5-(4′-Chlorophenoxy)-2,4-diamino-6-methyl-					233	17,800	259	2760
	277	8150	258	5000	286	8,500		

treated with carbon, filtered, neutralized with acetic acid, and allowed to stand while a yellow precipitate slowly formed. The precipitate was recrystallized from 75% ethanol, giving 6.2 g. (56.5%) of bright yellow crystals melting at 249–250°. *Anal.* Calcd. for $C_{10}H_8ClN_3OS$: C, 47.4; H, 3.2. Found: C, 47.7; H, 3.3.

5-(4′-Chlorophenoxy)-2,4-diaminopyrimidine.—The amination of the 2-amino-4-mercaptopyrimidine above was investigated at several temperatures using a ten-fold proportion of concentrated ammonium hydroxide and heating for 16 hours.[8] The yields of diamino compound increased with rising temperature, a maximum of 42.5% being obtained at 180–185°. Longer treatment (70 hours) at 145° gave a 49% yield. The replacement of the mercapto by an amino group is thus much more difficult in this instance than with the dimercaptopyrimidines previously studied.[8] Attention was then turned to alcoholic ammonia. This gave obviously superior results; a yield of 51% of the diaminopyrimidine was obtained in 16 hours treatment at 155°. In each instance the diaminopyrimidine was compared with an authentic specimen prepared by the general method above. Mixed melting points were undepressed, falling in the range 172–175°.

Ultraviolet Absorption Spectra.—Ultraviolet absorption spectra were determined using the Beckman model DU spectrophotometer, in aqueous solutions at a concentration of 10 mg. per l. in 0.1 *N* hydrochloric acid and Sørensen glycine–sodium hydroxide buffer at *p*H 11. Representative spectra are shown in Table VI.

Acknowledgments.—We are indebted to Samuel W. Blackman and N. Martinez, Jr., for microanalyses, Phoebe Lee Graham for absorption spectra and Shirley DuBreuil for technical assistance. We wish to express our gratitude to Dr. Charles H. Kellaway for advice and encouragement and for the correlation of the efforts of the two laboratories involved.

TUCKAHOE, N. Y. RECEIVED FEBRUARY 2, 1951

[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

2,4-Diaminopyrimidines as Antimalarials. II. 5-Benzyl Derivatives

BY ELVIRA A. FALCO, SHIRLEY DUBREUIL AND GEORGE H. HITCHINGS

2-Amino-5-benzyl-4-hydroxypyrimidines are prepared by the condensation of α-formyl-β-phenylpropionic esters or α-benzyl-β-ketoesters with guanidine. The conversion of these to 2,4-diaminopyrimidines *via* the 2-amino-4-chloro derivatives is described. Maximal antimalarial activity in this series is found when an electron-attractive substituent is present in the *para* position of the benzene ring and a methyl group is present in the pyrimidine-6 position.

The discovery of antimalarial activity in 5-(4′-chlorophenoxy)-2,4-diaminopyrimidine[1] and its 6-methyl homolog[2,3] indicated the desirability of the preparation and testing of various related structures. The oxygen atom of the phenoxypyrimidine was viewed as a connecting group of unknown importance between the pyrimidine and benzene nuclei. The preparation of similar substances with various atoms and groups, including nitrogen, sulfur and carbon in this position was therefore proposed for further investigation. The most readily accessible of these appeared to be the compounds with a methylene group in this position. Kast[4] had reported the preparation of 5-benzyl-2,4-diaminopyrimidine[5] by a rather roundabout and unfruitful method. However, Johnson and Ambelang[6] had formylated ethyl hydrocinnamate and condensed the resulting α-formyl derivative (I, R = H) with thiourea to give 5-benzyl-2-thiouracil. It seemed probable that α-formyl-β-phenylpropionic esters in general would condense with guanidine to give 2-amino-5-benzyl-4-hydroxypyrimidines (II, R = H) which could be converted to the diamino derivatives (IV, R = H) *via* the 4-chloropyrimidines (III, R = H) in the same manner as the 5-aryloxypyrimidines.

The available precedents were closer to the desired 5-benzyl-2,4-diamino-6-substituted pyrimidines, which were regarded as the more important series. Wheeler and McFarland[7] had prepared 5-benzyl-2-ethylmercapto-4-hydroxy-6-methylpyrimidine, and Curd, *et al.*,[8] had used this as an intermediate for the preparation of a series of 2-anilino-5-

(1) E. A. Falco, G. H. Hitchings, P. B. Russell and H. VanderWerff, *Nature*, **164**, 107 (1949).

(2) L. G. Goodwin, *ibid.*, **164**, 1133 (1949).

(3) E. A. Falco, P. B. Russell and G. H. Hitchings, THIS JOURNAL, **73**, 3753 (1951).

(4) H. Kast, *Ber.*, **45**, 3124 (1912).

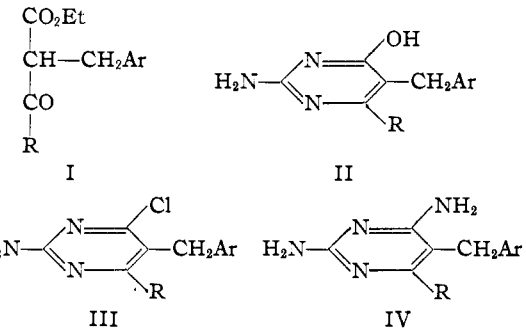
(5) The identity of Kast's substance is an open question since the melting point which he reports is about 50° lower than that of an authentic sample prepared from 2-amino-5-benzyl-4-hydroxypyrimidine (*cf.* Table V).

(6) T. B. Johnson and J. C. Ambelang, THIS JOURNAL, **60**, 2941 (1938).

(7) H. E. Wheeler and D. F. McFarland, *Am. Chem. J.*, **42**, 101 (1909).

(8) F. H. S. Curd, D. N. Richardson and F. L. Rose, *J. Chem. Soc.*, 382 (1946).

benzylpyrimidines with basic side chains in the 4-position. Furthermore Hall, *et al.*,[9] prepared 2-amino-5-benzyl-4-chloro-6-methylpyrimidine as an intermediate for the corresponding 4-dialkylaminoalkylamino derivatives. It appeared probable that the 2,4-diaminopyrimidines could be obtained by the reaction of the chloropyrimidines with ammonia. Experience with the 5-aryloxy-2,4-diaminopyrimidines[3] had indicated the importance to antimalarial activity of unsubstituted amino groups, an electron attraction group in the aromatic nucleus and an alkyl (methyl) group in the pyrimidine-6 position.[3] The investigation of the corresponding structural features in the benzyl series was therefore undertaken, and it was found that the desired substances were, in fact, readily obtainable by the proposed routes.



The condensation of guanidine with α-formyl-β-phenylpropionic esters (I, R = H) gave the 2-amino-5-benzyl-6-hydroxypyrimidines (II, R = H) in yields which, although not high, were satisfactory for the preparation of the diamino derivative for antimalarial testing. A few limitations were found. Ethyl β-*p*-nitrophenylpropionate could not be formylated satisfactorily. This was not unexpected and was at first attributed to reduction of the nitro group; however, similar difficulties were encountered with the β-*p*-aminophenylpropionate. The 2,4-diamino-5-*p*-nitrobenzylpyrimidine was obtained by nitration of the benzylpyrimidine and gave the amino derivative readily on catalytic reduction.

Many of the required β-phenylpropionic (hydrocinnamic) esters were known substances or were prepared from known cinnamic esters by reduction although a few new substances of each type were prepared. The most satisfactory method of reduction of the substituted ethyl cinnamates was with hydrogen and Raney nickel catalyst at room temperature and 2 atmospheres pressure. Apparently this is a new application of this versatile catalyst.

The β-ketoesters (I, R = alkyl or aryl) were most readily obtainable by the reaction of a suitable benzyl halide with the sodium derivative of a β-keto aliphatic ester.[10,11] Many of these esters (I) are new substances. In a few instances the condensation of a substituted benzaldehyde with the β-ketoester,[12] followed by catalytic reduction of the resulting benzal ester was employed.

(9) R. Hall, B. J. Lovell, H. T. Openshaw, L. C. Payman and A. R. Todd, *ibid.*, 357 (1946).

(10) G. D. Goodall and R. D. Haworth, *J. Chem. Soc.*, 2482 (1903).

(11) H. Leuchs, *Ber.*, **44**, 1507 (1911).

(12) E. Knoevenagel and F. Albert, *ibid.*, **37**, 4476 (1904).

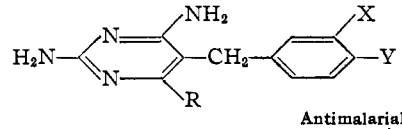
The condensation of α-benzyl-β-ketoesters with guanidine in general gave the aminohydroxypyrimidine (II) in good yields, no limitations with respect to the nature of the aromatic substituent being apparent.

Chlorination (III) and amination (IV) of both types of 5-benzylpyrimidines follow conventional techniques.[3]

A partial listing of the antimalarial activities[13] is shown in Table I. In compounds with an electron donor group in the *para* position of the benzene nucleus, the antimalarial activity is markedly enhanced by the introduction of a methyl group in the pyrimidine-6 position (Table I, 1 and 2). The 6-methyl derivative is more active than the higher homologs (Table I, 3 and 4). The 4-nitro derivative (Table I, 5) has an over-all activity comparable to that of the 4-chloro compound but is relatively more active against *Plasmodium gallinaceum* than against *P. berghei* while the pattern is the reverse with the 4-chloro derivative. The 3,4-dichloro derivative (Table I, 6) is much less active than the 4-chloro derivative in contrast to the results in the 5-aryl series of compounds.[14] Electron releasing substituents in the benzene nucleus in general depress antimalarial activity (Table I, 7 and 8) in this series as in the 5-aryloxy[3] series. It is of some interest that antibacterial activity is enhanced by substituents which depress the antimalarial activity.

TABLE I

ANTIMALARIAL ACTIVITIES OF 5-BENZYL-2,4-DIAMINOPYRIMIDINES



Compound	X	Y	R	Antimalarial activity against *P. gallinaceum* Quinine equivalent	*P. berghei* Quinine equivalent
1	H	Cl	H	1	3
2	H	Cl	CH_3	3.5	25
3	H	Cl	C_2H_5	3	1
4	H	Cl	C_3H_7	1	<1
5	H	NO_2	CH_3	22	7
6	Cl	Cl	CH_3	1	<1
7	H	CH_3	H	<1	0
8	H	OCH_3	CH_3	1	<1
9	H	H	CH_3	2	<1

A more complete survey of the antimalarial activities of the 5-benzyl-2,4-diaminopyrimidines is in press.[13] The biological work was carried out by L. G. Goodwin and I. M. Rollo at the Wellcome Laboratories of Tropical Medicine (London).

The activity of 5-benzyl-2,4-diamino-6-methylpyrimidines (Table I, 9) when compared to the corresponding activities of the 2-anilino-4-dialkylaminoalkylamino derivatives of Curd[8] and of the 2-amino-4-dialkylaminoalkylamino derivatives of Hull, *et al.*,[9] adds confirmation to the conclusion drawn from the biological results with members of the 5-phenoxy series,[3] namely, that the antimalarial activity with this type of substance is maximal when the amino groups are unsubstituted.

(13) E. A. Falco, L. G. Goodwin, G. H. Hitchings, I. M. Rollo and P. B. Russell, *Brit. J. Pharm.*, **6**, 185 (1951).

(14) P. B. Russell and G. H. Hitchings, THIS JOURNAL, **73**, 3763 (1951).

Experimental

Ethyl β-Phenylpropionates (Ethyl Hydrocinnamates).—These esters were prepared by the reduction of ethyl cinnamates with Raney nickel W5 catalyst[15] at 2 atmospheres hydrogen pressure. The known esters obtained by this procedure were the 4-methoxy-,[16] 4-chloro-,[17] 3-chloro-,[18] 4-methyl-,[18] 3,4-dimethoxy-[19] and 4-dimethylamino-.[20]

Formylation of β-Phenylpropionic Esters (Ethyl Hydrocinnamates).—The ethyl β-phenylpropionic esters were formylated with sodium and ethyl formate in ethereal solution. The method will be illustrated with ethyl β-(4-chlorophenyl)-propionate. To 12.6 g. (0.55 mole) of sodium wire in 500 ml. of sodium-dried ether was added in small portions a mixture of 116.5 g. (0.55 mole) of ethyl β-(4-chlorophenyl)-propionate and 44.6 g. (0.06 mole) of ethyl formate.[6] After standing overnight at room temperature the reaction was complete (disappearance of the sodium). The crude α-formyl derivative was condensed with guanidine as described below.

Some variation in the time required for formylation was noted with different esters. The reaction was allowed to proceed at room temperature as long as any unreacted sodium could be found on breaking up the lumpy product with a rod; in some instances as long as 72 hours of standing was necessary.

Ethyl α-Benzyl-β-ketobutyrates (Ethyl α-Acetyl Hydrocinnamates).—For the most part these esters were prepared by the reaction of a benzyl halide and sodium with ethyl acetoacetate. The method of Leuchs[11] in which 2 equivalents of acetoacetic ester are employed is preferable to that of Goodall[10] using 1 equivalent, in that it minimized the formation of the α,α-bis-benzylacetoacetic ester. Ethyl α-4-methoxybenzyl-β-ketobutyrate was prepared previously by Goodall,[10] ethyl 4-nitrobenzyl-β-ketobutyrate by Burgess,[21] and ethyl α-benzylbenzoylacetate by Perkin.[22] Also prepared by this method were the following ethyl α-benzyl-β-ketobutyrates: 2-chloro-, b.p. 172–185° at 48 mm.; 4-chloro-, b.p. 190–197° at 18 mm.; 2,4-dichloro-, b.p. 201–203° at 20 mm.; 4-bromo-, a solid not further purified (from 4-bromo-benzyl bromide[23]); 3-methyl-, b.p. 175–177° at 18 mm. (from 3-methylbenzyl bromide[24]); 3,4-methylenedioxy-, b.p. 210–211° at 25 mm. (from piperonyl bromide[25]); and *x*-bromo-4-methyl-, b.p. 190–196° at 15 mm. (from *x*-bromo-ω-bromoxylene, see text below).

***x*-Bromo-ω-bromoxylene.**—To 24 g. (0.13 mole) of 2-bromo-1,4-dimethylbenzene (bromo-*p*-xylene) heated at 125–135° under a reflux condenser, 24 g. (0.15 mole) of bromine was added dropwise, under the level of the liquid over a period of one hour. The liquid was distilled at 15 mm. pressure and 19.5 g. (57%) of a colorless liquid boiling at 190–196° was obtained. The resulting product is probably a mixture of the two isomeric bromomethyl derivatives but separation and identification of these was not attempted.

Ethyl α-(4-Hydroxy-3-methoxybenzyl)-acetoacetate.—This substance was prepared *via* ethyl α-acetyl-4-hydroxy-3-methoxycinnamate.[12] The reduction was carried out catalytically using platinized-charcoal catalyst.[26] To a solution of 10 g. of ethyl α-acetyl-4-hydroxy-3-methoxycinnamate[12] in 100 ml. of ethanol, platinized-charcoal catalyst was added and the solution shaken with hydrogen at 30 lb. pressure. The theoretical amount of hydrogen was absorbed in six hours. After filtration the ethanol was removed under reduced pressure. The ester distilled at 140–141° at 3.5 mm. The yield was 9.5 g. (95%).

Anal. Calcd. for $C_{14}H_{18}O_5$: C, 63.2; H, 6.8. Found: C, 63.1; H, 6.5.

Ethyl α-acetyl-3,4-dimethoxycinnamate was prepared from veratric aldehyde and ethyl acetoacetate by the Knoevenagel[12] procedure, as a yellow viscous oil boiling in the range 180–189° at 3 mm. It was reduced to **ethyl α-(3,4-dimethoxybenzyl)-acetoacetate** (ethyl α-acetyl-3,4-dimethoxyhydrocinnamate) as described immediately above. The reduction gave a 75% yield of ester boiling at 200–210° at 15 mm.

Anal. Calcd. for $C_{15}H_{20}O_5$: C, 64.2; H, 7.1. Found: C, 64.5; H, 6.9.

Ethyl α-4-Chlorobenzyl-β-ketovalerate.—This ester was prepared from 4-chlorobenzyl chloride and ethyl β-ketovalerate by the general method outlined above. The product boiled at 175–195° at 15 mm. pressure.

Ethyl α-4-Chlorobenzyl-β-ketocaproate.—This ester was prepared from 4-chlorobenzyl chloride and ethyl β-ketocaproate. The product boiled at 196–204° at 24 mm. From 25 g. of the benzyl chloride (0.15 mole) and 24.5 g. (0.15 mole) of the β-keto ester the yield was 27 g. (61%).

2-Amino-5-benzyl-4-hydroxypyrimidines. General Method.—The appropriate ester was condensed with guanidine or guanidine carbonate in alcoholic solution by heating for six to 12 hours on the steam-bath under a reflux condenser. After removal of the alcohol the residue was diluted with water and acidified (to *p*H 6) with acetic acid. The resultant 2-amino-5-benzyl-4-hydroxypyrimidine was purified by solution in dilute aqueous sodium hydroxide and reprecipitation with acetic acid. The method will be exemplified by the preparations of 5-(4-chlorobenzyl)-2,4-diaminopyrimidine and its 6-methyl homolog. The aminohydroxypyrimidines prepared by this method are listed in Table II. Several of the crude 2-amino-4-hydroxypyrimidines were chlorinated and aminated as described below without further purification.

2-Amino-5-(4′-chlorobenzyl)-4-hydroxypyrimidine.—To the crude formylation mixture (from 0.55 mole of ethyl 4-chlorohydrocinnamate) a solution of guanidine (from 52.3 g. (0.55 mole) of guanidine hydrochloride and 12.6 g. (0.55 mole) of sodium in 500 ml. of ethanol) was added. The ether was then distilled off and the solution was heated, under a reflux condenser, on the steam-bath for eight hours. About half of the alcohol was distilled off and the mixture was poured into 2 liters of water and neutralized with acetic acid (*p*H 6). After standing several hours the aminohydroxypyrimidine was filtered, sucked as dry as possible and washed with several small portions of ether (to remove a brown oil). The compound was purified by solution in dilute aqueous sodium hydroxide followed by precipitation with acetic acid (*p*H 6). The yield was 33 g. (26%) of compound melting at 280–283°.

2-Amino-5-(4′-chlorobenzyl)-4-hydroxy-6-methylpyrimidine.—Ethyl α-4-chlorobenzylacetoacetate (α-acetyl-4-chlorohydrocinnamate) (199 g., 0.78 mole) was dissolved in ethanol (500 ml.), guanidine carbonate (70 g., 0.78 mole) was added, and the mixture was heated for six hours on the steam-bath under a reflux condenser. The product was worked up as for 2-amino-5-(4′-chlorobenzyl)-4-hydroxypyrimidine, giving 145 g. (74%) of material melting at 330–333°.

5-Benzyl-2,4-diaminopyrimidines. General Method.—The aminohydroxypyrimidines from the previous step were dissolved in an excess of phosphoryl chloride by heating under reflux conditions. The excess phosphoryl chloride was removed *in vacuo* and the resulting sirup was poured over ice and the solution neutralized with ammonia. The crude 2-amino-4-chloropyrimidine was treated with an alcoholic solution of ammonia at elevated temperatures and pressures. The 2,4-diaminopyrimidine was isolated by evaporation of the alcohol. It was purified by solution in aqueous acid followed by precipitation with alkali or by recrystallization from ethanol or methanol. The pertinent properties of these diaminopyrimidines are presented in Table III.

The method will be illustrated by that used for **5-(4′-chlorobenzyl)-2,4-diaminopyrimidine.** 2-Amino-5-(4′-chlorobenzyl)-4-hydroxypyrimidine (10 g.) was heated with 100 ml. of phosphoryl chloride under reflux conditions until a clear solution was obtained (about 30 minutes) and for an additional 30 minutes. The excess phosphoryl chloride was removed by distillation under reduced pressure and the sirup was poured over cracked ice (600 g.). The mixture was stirred and ammonium hydroxide solution was added from time to time until a stable *p*H value of about 10 was maintained (two hours). The mixture was filtered by suction and

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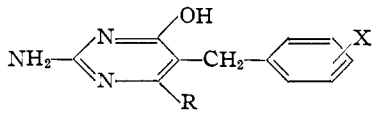
(17) S. Gabriel and M. Herzberg, *Ber.*, **16**, 2036 (1883).
(18) C. Willgerodt and W. Hambrecht, *J. prakt. Chem.*, [2] **81**, 74 (1910).
(19) F. Zetzsche and K. Huggler, *Helv. Chim. Acta*, **10**, 472 (1927).
(20) L. Weil, *Monatsh.*, **29**, 895 (1908).
(21) H. Burgess, *J. Chem. Soc.*, 2017 (1927).
(22) W. H. Perkin and J. Stenhouse, *ibid.*, **59**, 1006 (1891).
(23) J. Schramm, *Ber.*, **17**, 2922 (1881).
(24) E. F. J. Atkinson and J. F. Thorpe, *J. Chem. Soc.*, **91**, 1687 (1907).
(25) G. M. Robinson and R. Robinson, *ibid.*, **105**, 1456 (1914).
(26) R. Baltzly and A. P. Phillips, THIS JOURNAL, **68**, 261 (1946).

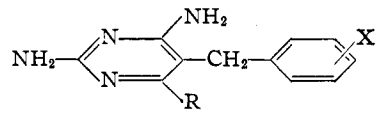
TABLE II



R	X	Formula	M.p., °C.[a]	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H	H	$C_{11}H_{11}N_3O$	214–219	65.7	5.5		66.0	5.3	
H	2-Cl	$C_{11}H_{10}ClN_3O$	253–258			17.8			17.5
H	4-Cl	$C_{11}H_{10}ClN_3O$	280–283			17.8			17.3
H	4-OCH_3	$C_{12}H_{13}N_3O_2$	255–259	62.3	5.6	18.1	62.3	5.7	18.1
H	3,4-diOCH_3	$C_{13}H_{15}N_3O_3$	242–244	59.8	5.7	16.1	60.4	5.4	16.0
H	4-CH_3	$C_{12}H_{13}N_3O$	248–249	67.0	6.0	19.5	66.5	5.6	19.5
H	4-$N(CH_3)_2$	$C_{13}H_{16}N_4O$	263–266	63.9	6.6		63.9	6.4	
CH_3	2-Cl	$C_{12}H_{12}ClN_3O$	307–308	57.7	4.8	16.8	58.0	4.7	17.3
CH_3	4-Cl	$C_{12}H_{12}ClN_3O$	330–333			16.8			16.9
CH_3	4-Br	$C_{12}H_{12}BrN_3O$	332–334	49.0	4.1	14.3	49.4	4.0	14.0
CH_3	2,4-diCl	$C_{12}H_{11}Cl_2N_3O$	330–333			14.8			14.4
CH_3	3,4-diCl	$C_{12}H_{11}Cl_2N_3O$	290–292			14.8			15.0
CH_3	4-OCH_3	$C_{13}H_{15}N_3O_2$	300–305			17.1			17.2
CH_3	3,4-diOCH_3	$C_{14}H_{17}N_3O_3 \cdot {}^1/_2H_2O$	226–228	59.2	6.4	14.8	59.6	6.2	14.8
CH_3	3,4-OCH_2O–	$C_{13}H_{13}N_3O_3$	293–294			16.2			16.5
CH_3	3-OCH_3-4-OH	$C_{13}H_{15}N_3O_3$		59.8	5.7	16.1	59.9	5.7	16.0
CH_3	3-CH_3	$C_{13}H_{15}N_3O$	233–234			18.3			18.2
CH_3	x-Br-4-CH_3	$C_{13}H_{14}BrN_3O$	242–244	50.6	4.5	13.6	50.6	4.6	13.1
CH_3	4-NO_2	$C_{12}H_{12}N_4O_3 \cdot {}^1/_2H_2O$	305–310			20.8			20.8
C_2H_5	4-Cl	$C_{13}H_{14}ClN_3O$				15.9			15.3
C_3H_7	4-Cl	$C_{14}H_{16}ClN_3O$	286–287			15.1			15.1
C_6H_5	H	$C_{17}H_{15}N_3O$	334			15.2			15.3

[a] Melting points uncorrected. In all cases decomposition occurs.

TABLE III



R	X	Formula	M.p., °C.[a]	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H	H	$C_{11}H_{12}N_4$	194–196	66.0	6.0	28.0	66.0	5.7	27.8
H	2-Cl	$C_{11}H_{11}ClN_4$	228–229	56.3	4.7	23.9	55.9	4.3	24.0
H	4-Cl	$C_{11}H_{11}ClN_4$	205–208	56.3	4.7	23.9	56.5	4.4	23.8
H	4-OCH_3	$C_{12}H_{14}N_4O$	198–202 dec.	62.6	6.1	24.3	63.0	5.8	23.8
H	3,4-diOCH_3	$C_{13}H_{16}N_4O_2$	228–233 dec.			21.5			21.7
H	4-CH_3	$C_{12}H_{14}N_4$	166–171			26.2			26.1
H	4-NO_2	$C_{11}H_{11}N_5O_2$	238–239 dec.			28.6			28.5
H	4-$N(CH_3)_2$	$C_{13}H_{17}N_5 \cdot H_2O$	231–235			26.8			26.7
CH_3	H	$C_{12}H_{14}N_4$	181–185	67.2	6.5		66.7	6.1	
CH_3	2-Cl	$C_{12}H_{13}ClN_4$	222–228	57.9	5.2	22.5	57.9	5.2	22.8
CH_3	4-Cl	$C_{12}H_{13}ClN_4$	235–236	57.9	5.2	22.6	57.4	5.3	22.3
CH_3	4-Br	$C_{12}H_{13}BrN_4$	239–241	49.2	4.4	19.1	48.9	4.4	18.9
CH_3	2,4-diCl	$C_{12}H_{12}Cl_2N_4$	244–245	50.9	4.3	19.8	50.9	3.9	19.4
CH_3	3,4-diCl	$C_{12}H_{12}Cl_2N_4$	257–262	50.9	4.3	19.8	50.4	3.9	20.0
CH_3	4-OCH_3	$C_{13}H_{16}N_4O$	231–234 dec.	63.9	6.5	22.9	63.2	6.0	22.6
CH_3	3,4-diOCH_3	$C_{14}H_{18}N_4O_2$	259–261 dec.			20.4			20.4
CH_3	3,4-OCH_2O–	$C_{13}H_{14}N_4O_2$	273 dec.	60.5	5.4	21.7	60.4	5.3	22.0
CH_3	3-OCH_3-4-OH	$C_{13}H_{16}N_4O_2$	254–258 dec.			21.5			21.3
CH_3	3-CH_3	$C_{13}H_{16}N_4$	162–163	68.4	7.0	24.6	68.8	7.3	24.1
CH_3	x-Br-4-CH_3	$C_{13}H_{15}BrN_4$	183–189	50.8	4.9	18.2	51.2	5.3	18.2
CH_3	4-NO_2	$C_{12}H_{13}N_5O_2$	244–245 dec.	55.6	5.0	27.0	55.2	4.6	27.0
CH_3	4-NH_2	$C_{12}H_{15}N_5$	193–195			30.6			30.3
CH_3	4-$NHCOCH_3$	$C_{14}H_{17}N_5O$	255–258			25.8			26.2
C_2H_5	4-Cl	$C_{13}H_{15}ClN_4$	198–200	59.4	5.7	21.3	59.4	5.5	21.6
C_3H_7	4-Cl	$C_{14}H_{17}ClN_4$	166–167	60.7	6.1	20.3	60.5	5.9	20.3
C_6H_5	H	$C_{17}H_{16}N_4$	222–223	73.9	5.8		74.0	5.9	

[a] Melting points uncorrected. The compounds melt reversibly except as noted.

sucked as dry as possible. The crude chloro compound and 70 ml. of an alcoholic ammonia solution (saturated at 5°) were placed in a sealed vessel and heated at 155° for 16 hours. The alcohol was removed by evaporation on the steam-bath. The residue was dissolved in water (150 ml.) by the addition of an excess of acetic acid, the solution filtered and the filtrate was made strongly alkaline by the addition of saturated sodium hydroxide solution. The precipitate was filtered off, washed with water, and recrystallized from 95% ethanol. The yield was 6 g. (60%) of colorless crystals melting at 205–208°.

5-Benzyl-2,4-diaminopyrimidine.—Ethyl hydrocinnamate (113 g., 0.63 mole) was formylated as described above and the product condensed with guanidine by heating in alcoholic solution for eight hours, giving 24 g. (19%) of 2-amino-5-benzyl-4-hydroxypyrimidine (Table II). The aminohydroxypyrimidine (15 g.) was converted to the chloro derivative by heating with 150 ml. of phosphoryl chloride. The crude chloro compound was heated with 100 ml. of alcoholic ammonia (saturated at 0°) at 155° for 16 hours and the 5-benzyl-2,4-diaminopyrimidine (Table III) (8.2 g., 55% from the aminohydroxypyrimidine) was isolated as described for the 4-chloro derivative. After recrystallization from ethanol, it melted at 194–196°, and a second recrystallization failed to change the melting point. Kast[4] gives a melting point of 145° for material prepared by the reduction of 5-benzyl-2,4-diamino-6-iodopyrimidine.

2,4-Diamino-5-(4′-nitrobenzyl)-6-methylpyrimidine (Table III) was prepared by nitration of the unsubstituted benzyl derivative. A solution of 5-benzyl-2,4-diamino-6-methylpyrimidine (8.0 g.) in sulfuric acid (60 ml.) was cooled to 0° and finely powdered potassium nitrate (3.8 g.) was added with stirring over the course of one hour, the temperature being maintained below 5°. The mixture was stirred for an additional one-hour period during which time the temperature rose to 22°. The reaction mixture was poured over ice (200 g.). After standing about an hour the colorless sulfate was collected, washed with cold water, suspended in *N* ammonium hydroxide solution, filtered and washed with water. The product was purified by solution in dilute acetic acid followed by precipitation with sodium hydroxide, and then recrystallized from 95% ethanol. The yield was 6.3 g. (64%) of yellow needles melting at 243–245°.

The same substance was prepared by the general method described above from 4-nitrobenzyl chloride and acetoacetic ester. When prepared in this way the substance melted at 244–245° and a mixture of the two melted undepressed at 243–245°.

2,4-Diamino-5-(4′-nitrobenzyl)-pyrimidine (Table III) was prepared by nitration as described immediately above. The allocation of the nitro group is based on the degradation to 4-nitrobenzoic acid, since attempts at formylation of β-4-nitrophenylpropionic ester gave only intractable products which failed to yield isolable amounts of pyrimidine when condensation with guanidine was attempted.

Degradation of 2,4-Diamino-5-nitrobenzylpyrimidine to 4-Nitrobenzoic Acid.—2,4-Diamino-5-(4′-nitrobenzyl)-pyrimidine (600 mg.) was dissolved in 100 ml. of concentrated hydrochloric acid on the steam-bath and potassium chlorate was added in small portions—a total of 2 g. in the course of one hour. The mixture was allowed to evaporate to dryness, dissolved in 50 ml. of water and made strongly alkaline with sodium hydroxide. A saturated solution of potassium permanganate (50 ml.) was added and the solution was heated for two hours on the steam-bath. The excess permanganate was destroyed with methanol, the solution was filtered and the filtrate acidified with hydrochloric acid. The pale yellow crystals of 4-nitrobenzoic acid (150 mg., 50%) were collected. The melting point was 239–240°, undepressed on admixture with authentic 4-nitrobenzoic acid.

5-(4′-Aminobenzyl)-2,4-diamino-5-methylpyrimidine was prepared by reduction of the 4-nitro derivative above. To 3.0 g. of the above nitro compound in 100 ml. of ethanol was added 100 mg. of Adams platinum catalyst, a few drops of hydrochloric acid and 10 ml. of water. The theoretical amount of hydrogen was taken up in three hours. The catalyst was filtered off, washed with 50 ml. of water and the filtrate was concentrated *in vacuo*. The residue was taken up in 50 ml. of water and the product was precipitated by adjusting the *p*H to 10 with sodium hydroxide. The precipitate was then recrystallized from 95% ethanol. The yield was 2.3 g. (86%), m.p. 193–195°. This compound gave a red color on diazotization followed by treatment with β-naphthol.

5-(4′-Acetamidobenzyl)-2,4-diamino-6-methylpyrimidine.—To 2.2 g. of the 4-aminobenzyl derivative (above) suspended in 20 ml. of water an excess of acetic anhydride (15 ml.) and enough dilute ammonium hydroxide solution to keep the *p*H about 8 were added alternately with shaking over about one hour. At this point the *p*H was adjusted to 9.0 and the precipitate removed by filtration. This crude diacetyl compound (2.3 g.) was then boiled for one hour under reflux with 2 molar equivalents of 0.1 *N* sodium hydroxide solution. The precipitate was removed by filtration and recrystallized from 300 ml. of boiling water. The yield was 1.5 g. of needles melting at 255–258°. Analysis (Table III) indicates the presence of one acetyl group. Since the diazo test with β-naphthol is negative the acetyl group is allocated to the aromatic amino group.

Ultraviolet Absorption Spectra.—Representative ultraviolet absorption spectra are shown in Table IV. The absorption was measured at a concentration of 10 mg. per liter on the Beckman model DU spectrophotometer in 0.1 *N* hydrochloric acid and Sørensen glycine–sodium hydroxide buffer at *p*H 11.0.

TABLE IV

ULTRAVIOLET ABSORPTION SPECTRA

Compound, pyrimidine	*p*H = 1 Maximum λ mμ	*E*m	*p*H = 1 Minimum λ mμ	*E*m	*p*H = 11 Maximum λ mμ	*E*m	*p*H = 11 Minimum λ mμ	*E*m
2-Amino-5-(4′-chlorobenzyl)-4-hydroxy-	262	9050	245	7400	280	7900	257	4250
2-Amino-5-(4′-chlorobenzyl)-6-methyl-4-hydroxy-	265	8850	248	6200	280	8100	255	4380
5-(4′-Chlorobenzyl)-2,4-diamino-	270	5300	255	4450	287	6850	258	2350
5-(4′-Chlorobenzyl)-2,4-diamino-6-methyl-	285	7000	258	4350	276	8700	255	2740

Acknowledgments.—The authors are indebted to Samuel W. Blackman and to N. Martinez, Jr., for the microanalyses reported here and to Phoebe Lee Graham for the determination of ultraviolet absorption spectra. The many helpful suggestions of our colleague, Dr. Richard Baltzly, are gratefully acknowledged.

TUCKAHOE, N. Y. RECEIVED FEBRUARY 2, 1951