[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

Studies on Condensed Pyrimidine Systems. VII. Some 8-Arylpurines

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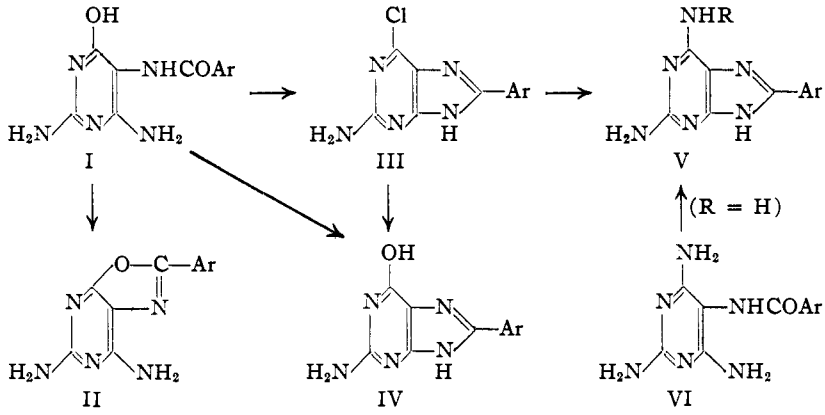
The preparation is described of a series of 2-amino-8-arylpurines bearing amino, halogen, hydroxyl, mercapto and substituted-amino groups in the 6-position. Treatment of 5-acylamino-2,4-diamino-6-hydroxy-pyrimidines with a phosphoryl halide results in the formation of 6-halogenopurines from which a variety of 6-substituted purines are obtainable. Cyclization of the 5-amidopyrimidines may also be effected in specific instances by fusion of the pyrimidine or its sodium salt or by heating the amide with the appropriate benzamide.

In connection with studies on the activities of unnatural purines as antimetabolites[1,2,3,4] the preparation of a series of 8-aryl-2-amino-6-hydroxy- and 2,6-diaminopurines was undertaken. Although a number of 8-alkylpurines have been prepared[5,6,7,8] the only 8-arylpurines recorded at the time this work was begun were a few xanthines which had been prepared by oxidation of the dibenzylidene derivatives of 4,5-diaminouracil.[9,10] Cyclization of 5-acylamino-4-aminopyrimidines appeared to be a feasible route to 8-aryl- as well as 8-alkylpurines[8] and was investigated first.

The pyrimidine-5-amides were readily obtained by conventional methods.[11] Investigation showed that no single method of ring closure was effective in all cases. The nearest approach to a general method is the treatment of the amide with a phosphoryl halide; however, this introduces some complications as described below. Heating of the amide (I, VI) or its sodium salt was effective in a number of instances, as was heating of the amide with the appropriate benzamide.[12]

Treatment of an amide (I, VI) with phosphoryl chloride led to closure of the imidazole ring in 19 of the 20 instances in which it was tried.[13] With 2-amino-4-hydroxypyrimidines (I) chlorination of the pyrimidine nucleus occurs, giving a 2-amino-6-chloropurine (III). Chlorination presumably precedes ring closure, since 2-amino-8-(4'-chlorophenyl)-6-hydroxypurine fails to chlorinate although the corresponding 2-amino-6-chloropurine was obtainable from the benzamidopyrimidine. This result is not unexpected in view of the failure of guanine to chlorinate under these conditions.[14] The 2-amino-6-chloropurines (III) may be converted to the 2-amino-6-hydroxy derivatives (IV)



by hydrolysis, to the 2,6-diamino- (V, R = H) and a variety of 2-amino-6-substituted-amino-8-arylpurines (V) by reaction with ammonia and amines, and to 2-amino-8-aryl-6-mercaptopurines with sodium hydrosulfide. The conditions for the replacement of the 6-chloro group are similar to those used for replacing the 6-chloro group of 2,6,8-trichloropurine.[15]

The advantages of using phosphoryl chloride are partly offset by several disadvantages. At first the most serious of these was the competing reaction whereby the oxazolo[5,4-d]pyrimidine[16] (II) usually is formed in variable amounts.[17] This is readily distinguished from the purine by its insolubility in alkali. This side-reaction can be minimized through the use of freshly distilled phosphoryl chloride and careful drying of the amide. A further disadvantage to the use of a phosphoryl halide lies in the formation of phosphorus-containing impurities which persist in the products. Acid hydrolysis is effective in removing these, but the 6-chloro and 6-bromopurines were not obtained in a completely pure state since this also leads to hydrolysis of the halogen. Treatment of 5-benzamido-2,4,6-triaminopyrimidines with phosphoryl chloride led to the formation of similar impurities, which could be re-

(1) G. H. Hitchings, G. B. Elion, E. A. Falco, P. B. Russell, M. B. Sherwood and H. VanderWerff, *J. Biol. Chem.*, **183**, 1 (1950).

(2) G. B. Elion and G. H. Hitchings, *ibid.*, **185**, 651 (1950).

(3) G. B. Elion and G. H. Hitchings, *ibid.*, **187**, 511 (1950).

(4) G. B. Elion, G. H. Hitchings and H. VanderWerff, *ibid.*, in press.

(5) O. Isay, *Ber.*, **39**, 250 (1906).

(6) C. O. Johns, *J. Biol. Chem.*, **11**, 67 (1912); **12**, 91 (1912); **14**, 1 (1913).

(7) C. O. Johns and E. J. Baumann, *ibid.*, **15**, 515 (1913).

(8) W. Traube, *et al.*, *Ann.*, **432**, 266 (1923).

(9) W. Traube and W. Nithack, *Ber.*, **39**, 227 (1906).

(10) While this work was in progress the preparation of 8-phenylxanthine by fusion of 4,5-diaminouracil and benzamide was reported by H. Bredereck, H. G. v. Schuch and A. Martini, *ibid.*, **83**, 201 (1950).

(11) W. Wilson, *J. Chem. Soc.*, 1157 (1948).

(12) The substituted benzamide rather than benzamide or formamide was used to avoid exchange of the acyl radical. *Cf.* L. F. Cavalieri and G. B. Brown, THIS JOURNAL, **71**, 2246 (1949). An attempt to cyclize 5-(4'-chlorobenzamido)-2,4,6-triaminopyrimidine by heating it in formamide led to the formation of appreciable amounts of 2,6-diaminopurine.

(13) 2,4-Diamino-6-hydroxy-5-(4'-nitrobenzamido)-pyrimidine was recovered unchanged (50% yield) after eight hours heating under reflux conditions with phosphoryl chloride. No other product was recovered.

(14) R. R. Adams and F. C. Whitmore, THIS JOURNAL, **67**, 1271 (1945).

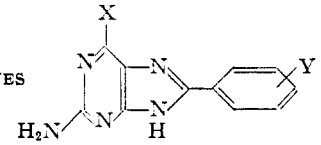
(15) E. Fischer, *Ber.*, **32**, 435 (1899).

(16) T. B. Johnson, *Am. Chem. J.*, **34**, 203 (1905).

(17) E. A. Falco, G. B. Elion, E. Burgi and G. H. Hitchings, to be published.

TABLE I

8-ARYLPURINES



Methods of Preparation: A, dry heating; B, dry heating of sodium salt; C, dry heating with benzamide or substituted benzamide; D, refluxing with phosphoryl chloride; E, hydrolysis of 6-chloropurine; F, reaction of 6-chloropurine with ammonia or amines; G, reaction of 6-chloropurine with sodium hydrosulfide at 120.°

X	Y	Method of prepn.	Empirical formula	Analyses, % Calcd. C	H	N	H_2O	Found C	H	N	H_2O
NH_2	2-Cl	A	$C_{11}H_9N_6Cl\cdot{}^1/_2HCl\cdot{}^1/_2H_2O$	45.9	3.7	29.2	3.1	45.4	3.6	29.5	3.4
NH_2	3-Cl	A	$C_{11}H_9N_6Cl\cdot{}^1/_2HCl\cdot{}^1/_2H_2O$	45.9	3.7	29.2	3.1	45.5	3.4	28.8	3.3
NH_2	4-Cl	A, D, F	$C_{11}H_9N_6Cl\cdot{}^1/_2HCl\cdot{}^1/_2H_2O$	45.9	3.7	29.2	3.1[a]	46.3	3.8	29.0	3.1
NH_2	3-Br	D	$C_{11}H_9N_6Br\cdot HCl$			24.6				24.3	
NH_2	3-NO_2	A	$C_{11}H_9O_2N_7\cdot HCl\cdot H_2O$	40.5	3.7	30.1	5.5	40.7	3.8	29.6	5.4
NH_2	4-NO_2	A, D	$C_{11}H_9O_2N_7\cdot H_2O$	45.7	3.8		6.2	44.8	3.8		6.4
NH_2	4-OCH_3	D	$C_{12}H_{12}N_6O\cdot HCl\cdot 1^1/_2H_2O$	45.0	5.0	26.3	8.5	45.5	5.0	26.8	8.7
NH_2	4-$COOCH_3$	A	$C_{13}H_{12}O_2N_6\cdot HCl\cdot H_2O$	46.1	4.4	24.8	5.3	46.1	4.2	24.2	6.0
NH_2	3,5-$(NO_2)_2$	D	$C_{11}H_8O_4N_8\cdot HCl\cdot H_2O$	35.7	3.0	30.1		35.9	3.1	29.8	
NH_2	3,4-CH=CH—CH=CH—	A	$C_{15}H_{12}N_6$			30.4				30.4	
OH	H	B, C, E	$C_{11}H_9ON_5\cdot H_2O$	53.9	4.5	28.6	7.3	54.0	4.7	28.7	7.3
OH	2-Cl	E	$C_{11}H_8ON_5Cl$			26.8				26.8	
OH	3-Cl	E	$C_{11}H_8ON_5Cl\cdot HCl\cdot H_2O$	41.8	3.5	22.1	5.7	41.5	3.7	21.8	6.0
OH	4-Cl	E	$C_{11}H_8ON_5Cl\cdot{}^1/_2HCl\cdot H_2O$	44.3	3.5	23.5	6.0[b]	44.3	3.1	23.7	5.6
OH	4-NO_2	C	$C_{11}H_8O_3N_6\cdot H_2O$	45.5	3.4			44.9	3.5		
CH_3NH	4-Cl	F	$C_{12}H_{11}N_6Cl\cdot HCl$	46.3	3.9			46.1	4.0		
$(CH_3)_2N$	4-Cl	F	$C_{13}H_{13}N_6Cl\cdot HCl\cdot H_2O$	45.5	4.7	24.5		45.1	4.5	24.4	
$(HOCH_2CH_2)_2N$	4-Cl	F	$C_{15}H_{17}O_2N_6Cl$	51.6	4.9	24.1		51.1	4.9	24.1	
$CH_2CH_2OCH_2CH_2N$	4-Cl	F	$C_{15}H_{15}ON_6Cl\cdot HCl\cdot{}^1/_2H_2O$	47.9	4.5	22.4		47.5	4.0	22.5	
4-ClC_6H_4NH	4-Cl	F	$C_{17}H_{12}N_6Cl_2\cdot H_2O$	52.5	3.6	21.6	4.6	52.1	3.6	21.2	4.7
SH	4-Cl	G	$C_{11}H_8N_6SCl\cdot{}^1/_2H_2O$	46.0	3.1	24.4	3.1	45.9	3.3	24.5	3.3
Cl	3-Cl	D	$C_{11}H_7N_5Cl_2$	47.1	2.5	25.0		46.6	2.7	24.5	

[a] *Anal.* Calcd.: chloride, 6.2. Found: chloride, 5.9. [b] *Anal.* Calcd.: chloride, 6.0. Found: chloride, 6.1.

moved only by acid hydrolysis, leading in at least one instance to partial hydrolysis of the 6-amino group. These impurities though small in amount increase the difficulties (already considerable) in obtaining correct analytical data due to the difficulty with which complete combustion occurs.

The essential data for the 8-arylpurines are given in Table I. A few properties of these compounds deserve particular mention. None of them has a melting point. Hydration of both free purines and salts is common, and the anhydrous substances, obtained by heating the hydrate, usually regain water on exposure to air (*cf.* under Experimental). Basic hydrochlorides are frequently observed. The 8-aryl-2,6-diaminopurines, like the parent substance,[18] give basic hydrochlorides at *p*H 5.0. The 8-aryl-2-amino-6-hydroxypurines give normal hydrochlorides which are converted to the basic salts on washing with water.

The ultraviolet spectra of the 8-arylpurines are recorded in Table II.

Experimental

5-Benzamidopyrimidines.—The amides of 2,4,5,6-tetraaminopyrimidine[19] and 6-hydroxy-2,4,5-triaminopyrimidine[20] were prepared from the pyrimidine sulfates and one molar equivalent of the appropriate benzoyl chloride in a manner essentially the same as that described by Wilson.[11] The 5-benzamidopyrimidines thus obtained were identified by their ultraviolet absorption spectra (Table III) which are characterized by a narrow band in the 260–270 mμ region at *p*H 1 and a similar band, showing little or no shift in wave length but having a lower extinction value at *p*H 11. In this respect they are similar to other 5-amidopyrimidines.[21]

The spectra of 2,4,5,6-tetraaminopyrimidine[22] and 6-hydroxy-2,4,5-triaminopyrimidine,[21] on the other hand, are noticeably different in acid and alkaline solutions. Except where the spectra indicated gross contamination with the starting pyrimidine or with the benzoic acid derived from the benzoyl chloride, the 5-benzamidopyrimidines were used in their crude state for cyclization to the purines. The presence of small amounts of the substituted benzoic acid as an impurity is advantageous in ring closure by dry heating (Method A) since it lowers the melting point of the amide and thus minimizes the amount of decomposition accompanying this process.

Ring Closure by Dry Heating (Method A).—This method was used for closing most of the 5-benzamido-2,4,6-triaminopyrimidines to purines. In general, the compounds were heated in a Wood's metal bath at or near their melting points for one to two hours. Ring closure was considered to be complete when the soft reaction mass had resolidified. Yields varied from 30 to 60%. In cases where the melting point was high (*cf.* Table III) the yield was generally poor, due to decomposition. Two of the amides, 5-benzamido-2,4,6-triaminopyrimidine and 5-(4′-methoxybenzamido)-2,4,6-triaminopyrimidine, failed to close to the corresponding purines when heated at their melting points. An illustrative example of ring closure by dry heating is given below.

2,6-Diamino-8-(3′-nitrophenyl)-purine.—Fifteen grams of crude 5-(3′-nitrobenzamido-2,4,6-triaminopyrimidine was heated in an open flask in a Wood's metal bath at 240° for one hour. After cooling, the melt was dissolved in 600 ml. of 0.3 *N* sodium hydroxide solution and the alkaline solution filtered into 300 ml. of boiling water containing 50 ml. of glacial acetic acid. The crude purine precipitate was filtered off, after cooling, and redissolved in 3 liters of boiling 1 *N* hydrochloric acid. The acid solution was filtered hot. After standing at 4° overnight, the precipitate was collected, washed with water and alcohol and dried in a vacuum desiccator. The yield of 2,6-diamino-8-(3′-nitrophenyl)-purine hydrochloride hydrate was 3.0 g. When the acid filtrate from this precipitate was adjusted to *p*H 5 with sodium hydroxide solution, an additional 1.9 g. of the purine was isolated in the form of the basic hydrochloride.

(18) Unpublished observation.

(19) W. Traube, *Ber.*, **37**, 4544 (1904).

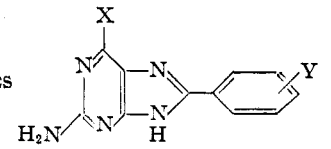
(20) W. Traube and H. W. Dudley, *ibid.*, **46**, 3839 (1913).

(21) G. H. Hitchings and G. B. Elion, THIS JOURNAL, **71**, 467 (1949).

(22) L. F. Cavalieri, A. Bendich, J. F. Tinker and G. B. Brown, *ibid.*, **70**, 3875 (1948).

TABLE II

ULTRAVIOLET ABSORPTION SPECTRA OF 8-ARYLPURINES



X	Y	pH 1 Maxima mμ	ε	Minima mμ	ε	pH 11 Maxima mμ	ε	Minima mμ	ε
NH_2	2-Cl	303	17,400	265	9,500	305	12,500	267	6,800
NH_2	3-Cl	315	20,200	265	8,950	240	19,200	280	5,750
						325	18,300		
NH_2	4-Cl	318	28,800	262	10,600	245	24,500	280	7,500
						325	24,500		
NH_2	3-Br	317	22,100	262	7,350	240	21,500	275	4,950
						325	19,500		
NH_2	3-NO_2	270	13,500	255	12,100	235	19,800	290	10,100
		315	18,200	285	13,000	325	15,600		
NH_2	4-NO_2	250[a]	15,300	295	8,500	255	12,500	245	11,900
		350	17,900			290	10,100	275	9,900
						405	13,100	330	5,950
NH_2	4-OCH_3	282	13,700	255	10,900	250	21,700	280	7,300
		325	28,200	290	12,500	322	24,800		
NH_2	4-$COOCH_3$	240	24,700	275	9,800	235	23,400	285	7,950
		330	28,100			332	27,000		
NH_2	3,5-$(NO_2)_2$	270[a]	18,700	295	14,500	240	36,300	285	11,500
		328	16,800			320	13,300		
						370–380[a]	9,600		
NH_2	3,4-CH=CH—CH=CH—	238	33,400	300	8,900	240	39,200	300	7,050
		330	16,000			335	15,700		
OH	H	238	15,400	257	11,500	238	19,100	270	8,800
		268	11,900	280	10,800	312	17,500		
		305	17,400						
OH	2-Cl	265	12,300	250	11,800	302	11,800	265	9,150
		295	13,400	280	11,200				
OH	3-Cl	271	10,750	260	10,300	240	22,100	275	7,600
		306	18,300	278	10,650	318	18,800		
OH	4-Cl	252	16,300	232	13,000	245	21,800	277	8,350
		310	19,200	280	10,700	322	20,200		
OH	4-NO_2	240[a]	14,200	290	8,000	252	15,200	240	14,300
		340	13,050			395	10,900	325	6,850
CH_3NH	4-Cl	242	16,000	280	9,800	245	20,000	280	7,800
		318	20,800			329	21,100		
$(CH_3)_2N$	4-Cl	243	18,900	268	11,300	247	24,600	282	8,300
		317	26,000			330	23,100		
$(HOCH_2CH_2)_2N$	4-Cl	247	19,800	278	11,300	246	23,800	282	7,000
		318	25,200			328	22,300		
$CH_2CH_2OCH_2CH_2N$	4-Cl	251	16,800	277	9,600	248	21,800	285	6,400
		320	22,200			332	20,700		
4-ClC_6H_4NH	4-Cl[b]					242[a]	24,500	262	14,400
						278	18,700	300	8,950
						350	35,800		
SH	4-Cl	268	18,000	235	11,500	250	20,000	300	9,150
		370	12,100	335	9,150	350	16,200		
Cl	3-Cl	250[a]	14,600	290	4,500	240	20,000	280	7,300
		342	19,300			335	18,600		

[a] Inflection. [b] In 95% ethanol.

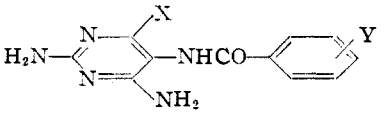
Ring Closure by Dry Heating of the Sodium Salt (Method B).—This method is suited to the ring closure of 5-benzamido-2,4-diamino-6-hydroxypyrimidines which are considerably higher melting than the corresponding 5-benzamido-2,4,6-triaminopyrimidines. The 6-hydroxy derivatives form sodium salts which can be isolated and which are lower melting than the free compounds. The conversion of 5-benzamido-2,4-diamino-6-hydroxypyrimidine to 2-amino-6-hydroxy-8-phenylpurine is illustrative of this method.

2-Amino-6-hydroxy-8-phenylpurine.—A solution of 4.9 g. of 5-benzamido-2,4-diamino-6-hydroxypyrimidine in 10 ml. of 2 *N* sodium hydroxide was evaporated to dryness on the steam-bath under reduced pressure. The sodium salt thus obtained was heated at 280° for 1.5 hours in a Wood's metal bath. Water evolved and the solid turned dark. After cooling, the residue was dissolved in 400 ml. of water containing 10 ml. of 2 *N* sodium hydroxide. The alkaline solution was filtered and acidified with acetic acid. The precipitate, after filtration, washing with water and drying at 100°, consisted of 2.4 g. of crude 2-amino-6-hydroxy-8-phenylpurine.

Ring Closure by Heating with a Benzamide (Method C).—Because of the extensive decomposition occurring when the high-melting amides are converted to purines by dry

TABLE III

CHARACTERISTICS OF 5-ACYLAMINOPYRIMIDINES



Substituents		M.p., °C., (dec.)	Ultraviolet absorption maxima, mμ	
X	Y		pH 1	pH 11
NH_2	H	266–270	272	270
NH_2	2-Cl	260–265	272	270
NH_2	3-Cl	270–280	272	270
NH_2	4-Cl	290–295	272	270
NH_2	3-NO_2	230–240	270	268
NH_2	4-NO_2	265–270	270	268
NH_2	4-OCH_3	264–267	270	265
NH_2	3-Br	265–270	273	268
NH_2	3,5-$(NO_2)_2$	280–285	270	250
NH_2	4-$COOCH_3$	280–285	245, 270	245, 268
NH_2	3,4-CH=CH—CH=CH	225–235	235, 272	235, 270
OH	H	293–298	235, 265	235, 263
OH	2-Cl	>350	265	255
OH	3-Cl	290–295	265	235, 265
OH	4-Cl	345–348	250	240
OH	4-NO_2	330–332	270	270
OH	2-Br	298–300	265	265
OH	4-Br	340–345	250	245
OH	2,4-Cl_2	315	265	262
OH	2-CH_3	>350	265	265
OH	4-$COOCH_3$	>350	250	245

heating, several of these amides were chosen for heating with the appropriate benzamides to effect ring closure. This method was successful with 5-benzamido-2,4-diamino-6-hydroxypyrimidine and benzamide, and with 2,4-diamino-6-hydroxy-5-(4′-nitrobenzamido)-pyrimidine and *p*-nitrobenzamide; with 5-benzamido-2,4,6-triaminopyrimidine and benzamide ring closure was not effected and the starting material was recovered unchanged.

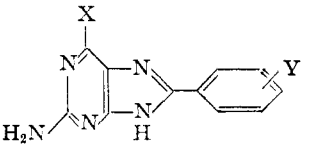
2-Amino-6-hydroxy-8-(4′-nitrophenylpurine).—A mixture of 8.4 g. of crude 2,4-diamino-6-hydroxy-5-(4′-nitrobenzamido)-pyrimidine and 9 g. of *p*-nitrobenzamide was heated at 290–300° in a Wood's metal bath for one hour. The mixture was cooled and leached with 500 ml. of ether in 5 portions to remove the *p*-nitrobenzamide. The dark brown residue was extracted with 1 liter of warm 1 *N* sodium hydroxide and the insoluble residue filtered off. The alkaline filtrate was acidified with acetic acid to *p*H 5 and the orange-red precipitate collected by centrifugation. After washing with water, alcohol and ether, and drying at 110°, the crude 2-amino-6-hydroxy-8-(4′-nitrophenyl)-purine weighed 3.5 g.

Ring Closure with Phosphoryl Chloride (Method D).—The closure of 5-benzamido-2,4,6-triaminopyrimidines to 2,6-diamino-8-phenylpurines and of 5-benzamido-2,4-diamino-6-hydroxypyrimidines to 2-amino-6-chloro-8-phenylpurines was effected by refluxing the amide with phosphoryl chloride. When the solid was completely in solution, after two to eight hours, the excess phosphoryl chloride was removed under reduced pressure, and the residue treated as described in the illustrative examples below. The two amides which had failed to close to purines by dry heating, 5-benzamido-2,4,6-triaminopyrimidine and 5-(4′-methoxybenzamido)-2,4,6-triaminopyrimidine, were converted to the corresponding 2,6-diaminopurines with phosphoryl chloride. However, 2,4-diamino-6-hydroxy-5-(4′-nitrobenzimido)-pyrimidine could not be transformed to the corresponding 2-amino-6-chloropurine by this method. In general, the yields of 2-amino-6-chloropurines are good, 65–85%, in those cases where the amount of oxazolopyrimidine formed is small. They are, however, difficult to purify and only one has been obtained in sufficiently pure form for analysis (Table I). The others are identified by their ultraviolet absorption spectra (Tables II and IV).

2,6-Diamino-8-(4′-methoxyphenyl)-purine.—Eight grams of crude 5-(4′-methoxybenzamido)-2,4,6-triaminopyrimidine was boiled with 250 ml. of phosphoryl chloride, under reflux, for four hours. The excess phosphoryl chloride was distilled off under reduced pressure and the residue poured onto 300 g. of ice. The precipitate was filtered off, dissolved in 200 ml. of 0.5 *N* sodium hydroxide and the alkaline solution filtered into 300 ml. of boiling water containing 25 ml. of glacial acetic acid. After cooling, the precipitate was collected, washed with water, alcohol and ether and dried at 110°. The crude purine thus obtained (5.7 g.) contained some bound phosphorus. This phosphorus was removed by boiling the product in 2 *N* hydrochloric acid for one-half hour and subsequent recrystallization from 1 *N* hydrochloric acid. The hydrochloride crystallizes with 1.5 molecules of water of crystallization (see Table I) which is lost after two hours at 140°. On exposure to air the anhydrous hydrochloride regains one molecule of water of crystallization within one hour; there is no further gain after several days.

TABLE IV

ULTRAVIOLET ABSORPTION SPECTRA OF 8-ARYLPURINES



X	Y	*p*H 1 maxima, mμ	*p*H 11 maxima, mμ
Cl	H	255, 342	242, 335
Cl	2-Cl	250,[a] 330	320
Cl	4-Cl	260, 345	245, 335
Cl	2-Br	325	315
Cl	4-Br	265, 342	250, 335
Cl	2,4-Cl_2	250,[a] 330	320
Cl	2-CH_3	320	235, 315
Cl	4-$COOCH_3$	245, 340	240, 340
Br	4-Cl	260, 345	250, 340
Br	H	250, 338	242, 332

[a] Inflection.

2-Amino-6-chloro-8-(3′-chlorophenyl)-purine.—A suspension of 12.1 g. of 5-(3′-chlorobenzamido)-2,4-diamino-6-hydroxypyrimidine in 250 ml. of phosphoryl chloride was heated, under reflux, for 3.5 hours. At the end of this time, all the solid material had dissolved. The excess phosphoryl chloride was removed under reduced pressure and the residue treated with 250 g. of crushed ice. The precipitate was collected, washed with cold water, dissolved in 300 ml. of 0.5 *N* sodium hydroxide and reprecipitated by acidification with acetic acid. After filtration, washing with water and drying in a vacuum desiccator, the yield of crude 2-amino-6-chloro-8-(3′-chlorophenyl)-purine was 9.7 g. A sample was purified for analysis by solution in dilute sodium hydroxide solution and reprecipitation with acetic acid (see Table I).

Eight additional 6-chloro- and two 6-bromo-8-arylpurines were prepared by the above method. The preparation of analytically pure samples of these was not attempted. They are characterized by the preparation of 6-substituted amino derivatives (Table I) and by their ultraviolet absorption spectra (Table IV). The spectra of these substances may be readily distinguished from those of 6-amino and 6-hydroxy derivatives by the fact that at *p*H 11 the bands lie at shorter wave lengths than at *p*H 1.

Hydrolysis of 2-Amino-6-chloro-8-phenylpurines (Method E).—The hydrolysis of the 6-chloro to the corresponding 6-hydroxypurine is accomplished by boiling the 6-chloropurine with 2 *N* hydrochloric acid for two hours. This method likewise appears to hydrolyze the phosphorus-containing impurities and to make possible the purification of the 2-amino-6-hydroxy-8-phenylpurines, either as free bases or as hydrochlorides.

2-Amino-8-(3′-chlorophenyl)-6-hydroxypurine.—A suspension of 1.8 g. of crude 2-amino-6-chloro-8-(3′-chlorophenyl)-purine in 100 ml. of 2 *N* hydrochloric acid was refluxed for two hours. The nature of the precipitate changed without complete solution taking place at any time. The reaction mixture was diluted with 100 ml. of water, chilled, and the yellow solid (1.55 g.) filtered off, washed with water and dried at 110°. The ultraviolet absorption spectrum of this product revealed that the 6-chloro group had been hydrolyzed. A sample was recrystallized for analysis by solution in 1000 parts hot 2 *N* hydrochloric acid and slow cooling overnight. The crystals of the hydrochloride hydrate were filtered off, washed with 2 *N* hydrochloric acid, alcohol and ether and dried at room temperature (Table I).

Reaction of 6-Chloropurines with Ammonia or Amines (Method F).—The 2-amino-6-chloro-8-phenylpurines prepared by Method D were treated with ammonia and amines to prepare the corresponding 6-amino or 6-substituted aminopurines. The example with morpholine will serve to illustrate the procedure used with diethylamine, piperidine and *n*-butylamine. Since the reactions with ammonia, methylamine, dimethylamine, bis-β-hydroxyethylamine and *p*-chloroaniline were carried out under varied conditions, they are described individually.

2-Amino-8-(4′-chlorophenyl)-6-N-morpholinopurine.—A mixture of 1 g. of crude 2-amino-6-chloro-8-(4′-chlorophenyl)-purine, 3 ml. of morpholine, 0.1 ml. of concentrated hydrochloric acid and 5 ml. of absolute ethanol were heated on the steam-bath, under reflux, for one hour. The reaction mixture was cooled, diluted with 100 ml. of water, and the crude 2-amino-8-(4′-chlorophenyl)-6-N-morpholinopurine (0.85 g.) filtered off. A 100-mg. sample was recrystallized for analysis by solution in 50 ml. of 0.1 *N* sodium hydroxide solution and filtration into 100 ml. of boiling 1 *N* hydrochloric acid. After standing overnight at 4°, the hydrochloride of the purine was collected, washed with water, alcohol and ether and dried at room temperature (Table I).

8-(4′-Chlorophenyl)-2,6-diaminopurine.—A mixture of 13.3 g. of crude 2-amino-6-chloro-8-(4′-chlorophenyl)-purine, 150 ml. of concentrated aqueous ammonium hydroxide and 2 ml. of concentrated hydrochloric acid was heated in a sealed tube for 6 hours at 150°. The contents of the tube were evaporated to dryness on the steam-bath and the residue leached with 400 ml. of water. The crude product (10.0 g.) was dissolved in 5 liters of boiling 1 *N* hydrochloric acid, and the hot solution cautiously brought to *p*H 5 by the addition of concentrated ammonium hydroxide. The 8-(4′-chlorophenyl)-2,6-diaminopurine precipitated as the basic hydrochloride. It was collected, washed with water and dried at 100° (7.8 g.) (Table I).

2-Amino-8-(4′-chlorophenyl)-6-methylaminopurine.—A solution of 1 g. of crude 2-amino-6-chloro-8-(4′-chlorophenyl)-purine in 10 ml. of a 25% aqueous solution of methylamine containing 0.1 ml. of concentrated hydrochloric acid was allowed to stand at room temperature for two days. The mixture was then boiled for ten minutes, to remove some of the excess methylamine, diluted to 100 ml. with water, made strongly acidic with hydrochloric acid and cooled. The precipitate of 2-amino-8-(4′-chlorophenyl)-6-methylaminopurine hydrochloride (0.85 g.) was collected, washed with water and dried at 110°. A 150-mg. sample was purified for analysis by solution in 25 ml. of 0.2 *N* sodium hydroxide, filtration into 100 ml. of boiling 2 *N* hydrochloric acid. After cooling, the hydrochloride was collected, washed with water and dried at 110° (Table I).

2-Amino-8-(4′-chlorophenyl)-6-dimethylaminopurine.—A mixture of 1 g. of crude 2-amino-6-chloro-8-(4′-chlorophenyl)-purine, 0.1 ml. of concentrated hydrochloric acid and 25 ml. of a 33% solution of dimethylamine in methanol was heated at 60° for one hour, under reflux. The methanol and excess dimethylamine were evaporated off in a boiling water-bath until the volume of the reaction mixture was 5 ml. The mixture was then diluted with water, made strongly acidic with hydrochloric acid and the precipitate of crude 2-amino-8-(4′-chlorophenyl)-6-dimethylaminopurine hydrochloride (0.86 g.) collected. The hydrochloride was purified for analysis in the same manner as the 6-methylamino derivative described above.

2-Amino-8-(4′-chlorophenyl)-6-bis-(β-hydroxyethyl)-aminopurine.—A mixture of 20 g. of crude 2-amino-6-chloro-8-(4′-chlorophenyl)-purine, 25 ml. of bis-β-hydroxyethylamine, 0.15 ml. of 36% ethanolic hydrogen chloride and 100 ml. of absolute alcohol was heated in a sealed tube for 3.5 hours at 120°. The reaction mixture was taken almost to dryness on the steam-bath, diluted to 400 ml. of water, acidified to *p*H 6 with acetic acid, and the precipitate filtered off (21.3 g.). A 16.1-g. portion of this precipitate was treated with 100 ml. of water and 75 ml. of 2 *N* sodium hydroxide. A small insoluble residue was filtered off and the alkaline filtrate added slowly to 800 ml. of boiling water containing 30 ml. of glacial acetic acid. The mixture was allowed to cool slowly before the precipitate was collected, washed with water and dried at 120° (13.1 g.) (Table I).

2-Amino-6-(4′-chloroanilino)-8-(4′-chlorophenyl)-purine.—A mixture of 1.2 g. of 2-amino-6-chloro-8-(4′-chlorophenyl)-purine and 1.4 g. of *p*-chloroaniline was heated in an oil-bath at 160° for 15 minutes and then at 200° for 20 minutes. The reaction mixture was allowed to cool and was then leached with 100 ml. of ether, followed by 100 ml. of 1 *N* sodium hydroxide. The insoluble residue (1 g.) was recrystallized by solution in 350 ml. of boiling absolute ethanol, filtration and dilution with 350 ml. of water. After cooling, the precipitate (0.8 g.) was collected, washed with 50% ethanol and dried at room temperature (Table I).

2-Amino-8-(4′-chlorophenyl)-6-mercaptopurine (Method G).—A mixture of 2 g. of crude 2-amino-6-chloro-8-(4′-chlorophenyl)-purine and 50 ml. of 2 *N* aqueous sodium hydrosulfide was heated in a sealed tube at 120° for three hours. The insoluble material was filtered off, washed with water and dissolved in 200 ml. of 0.2 *N* sodium hydroxide. The alkaline solution was filtered, acidified with acetic acid and the yellow precipitate (2.1 g.) collected, washed with water and dried at 100° (Table I). The hemihydrate loses its water of crystallization at 140° and regains it on exposure to air.

Preparation of 2-Amino-6-bromo-8-phenylpurines.—The 6-bromopurines are prepared by heating 5-benzamido-2,4-diamino-6-hydroxypyrimidines with phosphoryl bromide[23] in a manner analogous to the synthesis of the 6-chloropurines with phosphoryl chloride (Method D). Great difficulty was encountered in the purification of these 6-bromopurines, but their identity is established by the close resemblance of their ultraviolet absorption spectra (Table IV) to those of the corresponding 2-amino-6-chloro-8-phenylpurines. An illustrative example is given below.

2-Amino-6-bromo-8-(4′-chlorophenyl)-purine.—A mixture of 4 g. of crude 5-(4′-chlorobenzamido)-2,4-diamino-6-hydroxypyrimidine and 40 g. of phosphoryl bromide was heated, in a Wood's metal bath at 170° for one hour. The excess phosphoryl bromide was distilled off under reduced pressure and the solid residue was treated with 150 g. of crushed ice. The precipitate was filtered off, dissolved in 300 ml. of 0.2 *N* sodium hydroxide and the solution filtered into 200 ml. of water containing 20 ml. of glacial acetic acid. The 2-amino-6-bromo-8-(4′-chlorophenyl)-purine (3.65 g.) was collected by centrifugation, washed with water and dried in a vacuum desiccator.

Ultraviolet absorption spectra were determined using the Beckman model DU spectrophotometer. Measurements were made at a concentration of 10 mg. per liter in 0.1 *N* hydrochloric acid and in Sørensen's glycine–sodium hydroxide buffer at *p*H 11.0.

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