time as:

Time, hr.	0	2.5	4.5	7	9
$\epsilon_{305} \times 10^{-3}$	5.15	4.18	3.48	2.46	1.88

The experiment was done under nitrogen. The solution turned gradually from yellow to dark brown in color.

BOSTON 11, MASS.

[CONTRIBUTION OF THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

Purines. VIII. The Aminolysis of Certain Chlorosubstituted Purines[1]

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RECEIVED DECEMBER 27, 1958

2,6-Dichloropurine and 2,6,8-trichloropurine were treated with a number of nitrogenous bases. The reactions were found to be stepwise with the 6-position being preferentially aminated. In the case of very active aminating agents the stepwise reaction was accomplished by using aqueous solutions of the amine. For complete aminolysis of the less reactive amines it was necessary to employ pressure equipment. The proof of structure of the partially aminated purines was established by the dehalogenation of the substituted chloropurine and comparison of the product with known compounds. The dehalogenation of 2,6,8-trichloropurine resulted in partial reduction of the nucleus, while 2,6-dichloropurine yielded the 2-chloropurine.

Largely through the efforts of Davoll,[2a] Bendich,[2b] Elion,[3] and their respective co-workers, 6-chloropurine, 2,6-dichloropurine and 2,6,8-trichloropurine have been made available as intermediates for the synthesis of purine derivatives.

The discovery of the effect of kinetin on cell division has stimulated activity in the search for methods for the synthesis of other 6-substituted purines, many of which have been prepared from 6-chloropurine.[4] Little attention, however, has been directed to the use of 2,6-[5] and 2,6,8-halogen substituted purines for such purposes.

TABLE I

COMPARISON OF DEHALOGENATED PURINES WITH KNOWN 6-SUBSTITUTED PURINES

	M.p., °C.	Mixed m.p., °C.	*p*H	λ_{max}	$E \times 10^4$
2-Chloropurine[12]	231–234		1	270.5	0.807
2-Chloropurine[c]	231–234		1	271	.800
6-Dimethylamino-purine·HCl[d]	251–253		1	277	1.56
6-Dimethylamino-purine·HCl[b]	249–250		1	277	1.47
6-Furfurylaminopurine[d]	265–266		1	274	1.69
6-Furfurylaminopurine[a]	264–266	264–266			
6-Furfurylaminopurine[b]	269–270		1	274	1.59
6-Morpholinopurine[d]	300–302		6	282	1.89
6-Morpholinopurine[a]	301–303	301–303			
6-Morpholinopurine[b]	299–301		[e]	282	1.77
6-Piperidinopurine[d]	274–275		1	281	1.70
6-Piperidinopurine[a]	273–275	272–274			
6-Piperidinopurine[b]	272–275	272–275			

[a] Obtained by dehalogenation of the 2-chloro-6-substituted purine. [b] Obtained by dehalogenation of the 2,8-dichloro-6-substituted purine. [c] Obtained by dehalogenation of the 2,6-dichloropurine. [d] Sample prepared by aminolysis of 6-chloropurine and product used for comparison purposes. [e] Distilled water.

Inasmuch as there is evidence that the activity of the chloro substituents at the 2,6- and 8-positions[6] in the purine molecule are markedly different thus permitting stepwise reactions, these intermediates offer interesting possibilities for the preferential aminolysis leading to the synthesis of possible purine antagonists. In order, therefore, to further study the aminolysis reactions of the chloropurines, to establish the structures of the partially aminated chloropurines and to investigate possible dehalogenation reactions of the chloropurines the work described herein was undertaken.

TABLE II

Purine	*p*H	λ_{max}	$E \times 10^4$	λ_{min}	$E \times 10^3$
2-Chloro-6-furfurylamino-	95% EtOH	270	1.92	236	4.44
2-Chloro-6-morpholino-	95% EtOH	278	2.12	238	2.64
2-Chloro-6-piperidino-	95% EtOH	280	2.19	238	2.52
2,8-Dichloro-6-morpholino-	95% EtOH	282	2.10	244	3.27
2,6-Difurfurylamino-	95% EtOH	230	3.50	267	6.57
		287	1.18		
2,8-Difurfurylamino-6-morpholino-	95% EtOH	233	2.88	282	7.16
2,8-Dihydrazino-6-morpholino-	1	295	1.72	265	7.31
2,6-Dimorpholino-	1	244	1.86		
		266	2.21		
2,8-Di-*n*-hexylamino-6-morpholino	95% EtOH	235	2.49	283	5.58
2,6-Dipiperidino-	1	245	1.75		
		268	2.30		
2,8-Dipiperidino-6-morpholino-	1	226	2.35	288	6.94
2-Furfurylamino-6-morpholino-	1	287	1.73	247	10.71
2-Furfurylamino-6-piperidino-	1	288	1.94	245	5.58
2-Hydrazino-6-furfurylamino-	1	282	1.36	255	6.83
2-Hydrazino-6-morpholino-	1	231	1.34		
		289	1.47		
2-Hydrazino-6-piperidino-	1	231	1.46		
		290	1.72		
2-Morpholino-6-furfurylamino-	1	240	2.26		
		290	1.29		
2-Morpholino-6-piperidino-	1	245	1.63		
		268	2.14		
2-Piperidino-6-furfurylamino-	1	241	2.40		
		292	1.20		
2-Piperidino-6-morpholino-	1	244	1.91		
		266	2.26		

Using 2,6-dichloropurine four types of reactions were performed which included (1) preferential amination, (2) chemical reduction of 2-chloro-6-substituted purine, (3) total amination and (4) stepwise amination of 2-chloro-6-substituted purine.

(1) Published with the approval of the Monographs Publications Committee, Oregon State College as Research Paper No. 353, School of Science, Department of Chemistry.

(2) (a) J. Davoll and B. A. Lowy, THIS JOURNAL, **73**, 2936 (1951); (b) A. Bendich, *et al.*, *ibid.*, **76**, 6073 (1954).

(3) G. B. Elion and G. H. Hitchings, *ibid.*, **78**, 3509 (1956).

(4) J. Daly and B. E. Christensen, *J. Org. Chem.*, **21**, 117 (1956); M. L. Sutherland and B. E. Christensen, THIS JOURNAL, **79**, 2251 (1957).

(5) (a) J. A. Montgomery and L. Holum, *ibid.*, **79**, 2185 (1957); (b) **80**, 404 (1958).

(6) (a) E. Fischer, *Ber.*, **33**, 1371 (1900); (b) **30**, 2220 (1897); (c) R. K. Robins and B. E. Christensen, THIS JOURNAL, **74**, 3624 (1952).

TABLE III

AMINOLYSIS REACTIONS OF 2,6-DICHLOROPURINE 2-CHLORO-6-SUBSTITUTED PURINE AND 6-CHLOROPURINE

Purine	Halogen reactant[a]	Amine reactant	Reflux time, min.	Isolation procedure[b]	Yield, %
2-Chloro-6-furfurylamino-	1	5 ml. furfurylamine, 10 ml. H_2O	30	C	90
2-Chloro-6-morpholino-	1	5 ml. morpholine, 10 ml. H_2O	30	A	91
2-Chloro-6-piperidino-	1	5 ml. piperidine, 10 ml. H_2O	60	B	81
2,6-Difurfurylamino-	1	10 ml. furfurylamine	120	E	68
2,6-Dimorpholino-	1	10 ml. morpholine	120	D	93
2,6-Dipiperidino-	1	10 ml. piperidine	120	D	70
2-Furfurylamino-6-morpholino-	2	10 ml. furfurylamine	120	H	71
6-Furfurylamino-2-morpholino-	3	10 ml. morpholine	120	D	93
6-Furfurylamino-2-piperidino-	3	10 ml. piperidine	120	D	83
2-Furfurylamino-6-piperidino-	4	10 ml. furfurylamine	120	J	47
6-Furfurylamino-2-hydrazino-	3	10 ml. hydrazine hydrate	45	F	77
2-Hydrazino-6-morpholino-	2	10 ml. hydrazine hydrate	45	F	83
2-Hydrazino-6-piperidino-	4	10 ml. hydrazine hydrate	45	F	83
2-Morpholino-6-piperidino-	4	10 ml. morpholine	120	D	93
6-Morpholino-2-piperidino-	2	10 ml. piperidine	120	G	72
6-Piperidino-	5	10 ml. piperidine	30	I	71

[a] 1, 1 g. of 2,6-dichloropurine; 2, 1 g. of 2-chloro-6-morpholinopurine; 3, 1 g. of 2-chloro-6-furfurylaminopurine; 4, 1 g. of 2-chloro-6-piperidinopurine; 5, 1 g. of 6-chloropurine. [b] A, by reprecipitation from hot glacial acetic acid by dilution with water. B, by addition of 10 ml. of water followed by neutralization with acetic acid and filtered. Resolution in hot glacial acetic acid followed by dilution with water; process repeated. C, by dilution with 50 ml. of water, neutralized with acetic acid. Resolution in hot glacial acetic acid followed by dilution with water. D, by addition of 50 ml. of water to cooled reaction mixture. Resolution in hot ethanol and reprecipitated by dilution with water. E, by addition of 50 ml. of water to cold reaction mixture which was then neutralized with acetic acid. Resolution in ethanol followed by reprecipitation by dilution with water. F, product precipitated on cooling, was collected, washed and dried. The white needle-like crystals were recrystallized from ethanol. G, fifty ml. of water were added to cooled mixture. Product was removed by filtration, washed and dried, redissolved in ethanol and reprecipitated by addition of 100 ml. of water; filtered and dried. H, product was diluted with 50 ml. of water and neutralized with acetic acid, filtered, washed, dried and recrystallized from absolute alcohol. I, product was neutralized with acetic acid, collected, washed, dried and recrystallized from 50% aqueous ethanol. J, by addition of 50 ml. of water to cooled reaction mixture, neutralized by acetic acid, filtered, washed and dried; product recrystallized from absolute alcohol.

TABLE IV

Purine	M.p., °C.	Formula	Theory C, %	Theory H, %	Found C, %	Found H, %
2-Chloro-6-morpholino-	>260 d.	$C_9H_{10}N_5OCl$	45.2	4.18	45.2	4.15
2-Chloro-6-piperidino-	282–284	$C_{10}H_{12}N_5Cl$	50.6	5.06	50.5	4.81
2-Chloro-6-furfurylamino-	263–266	$C_{10}H_8N_5OCl$	48.1	3.21	48.0	2.99
2,6-Dimorpholino-	271–273	$C_{13}H_{18}N_6O_2$	53.8	6.21	53.5	6.07
2,6-Dipiperidino-	214–216	$C_{15}H_{22}N_6$	62.9	7.69	62.7	7.59
2,6-Difurfurylamino-	162–163	$C_{15}H_{14}N_6O_2$	58.1	4.52	58.3	4.48
2-Furfurylamino-6-morpholino-	225–226	$C_{14}H_{16}N_6O_2$	56.0	5.33	55.8	5.09
6-Furfurylamino-2-morpholino-	268–270	$C_{14}H_{16}N_6O_2$	56.0	5.33	56.1	5.02
6-Furfurylamino-2-piperidino-	249–250	$C_{15}H_{18}N_6O$	60.4	6.04	60.2	6.20
2-Furfurylamino-6-piperidino-	>215 d.	$C_{15}H_{18}N_6O$	60.4	6.04	60.2	5.85
6-Furfurylamino-2-hydrazino-	212–214	$C_{10}H_{11}N_7O$	48.0	4.49	47.7	4.15
2-Hydrazino-6-morpholino-	245–247	$C_9H_{13}N_7O$	46.0	5.53	45.9	5.37
2-Hydrazino-6-piperidino-	235–238	$C_{10}H_{15}N_7$	51.6	6.44	51.3	6.19
2-Morpholino-6-piperidino-	246–247	$C_{14}H_{20}N_6O$	58.3	6.94	58.3	6.70
6-Morpholino-2-piperidino-	228–231	$C_{14}H_{20}N_6O$	58.3	6.94	58.2	6.67
6-Piperidino-	274–275	$C_{10}H_{13}N_5$	59.1	6.41	59.1	6.39

In general the reactions with furfurylamine, hydrazine, morpholine and piperidine took place smoothly at the reflux temperatures of their respective reaction mixtures. Because of the variations in boiling points and the differences in the nucleophilicities of the various amines the reaction time ranged from twenty minutes to two hours. Since the products were extremely insoluble in water the problem of isolation was relatively simple. Purification was easily effected by recrystallization from aqueous ethanol.

Both halogen substituents were reactive when treated at reflux temperatures with morpholine, piperidine and furfurylamine. When the reactions were carried out in aqueous solutions of the amine the aminations were stepwise, leading to a 2-chloro-6-substituted purine. This observation made independently confirmed the recent report of Montgomery and Holum.[5] The 2-chloro-6-substituted purines were used in turn to prepare a number of polysubstituted derivatives.

The structures of the monoaminated products were established through dechlorination reactions. The dechlorinated products were then compared with the properties of the known 6-substituted purines or from newly prepared 6-substituted purines obtained by the aminolysis of 6-chlorpurine; see Table I. The comparisons were made on the basis of either mixed melting points or of ultraviolet spectra. The data in Table I show beyond

TABLE V

AMINOLYSIS REACTIONS 2,6,8-TRICHLOROPURINE AND 2,8-DICHLORO-6-SUBSTITUTED PURINES

Two grams of 2,6,8-trichloropurine and 10 ml. of amine were heated together for a period of time to effect amination. The conditions used for each experiment, method used for the isolation of the product and other data are recorded in Table V, while the analytical data are given in Table VI.

Purine	Halogen reactant[b]	Amine reactant	Temp., °C.	Time, hr.	Isolation procedure[c]	Yield, %
2,8-Dichloro-6-dimethylamino-	1	20 ml. H_2O, 20 ml. ethanol[3]	Reflux	2	D	67
2,8-Dichloro-6-furfurylamino-	1	10 ml. furfurylamine, 15 ml. H_2O	Reflux	0.75	A	71
2,8-Dichloro-6-morpholino-	1	10 ml. morpholine, 20 ml. H_2O	Reflux	1	B	65
2,8-Dichloro-6-piperidino-	1	10 ml. piperidine, 10 ml. H_2O	Reflux	1	C	98
2,8-Difurfurylamino-6-morpholino-	2	15 ml. furfurylamine	Reflux	6	E	52
2,8-Di-*n*-hexylamino-6-morpholino-	2	12 ml. *n*-hexylamine	180[a]	12	H	69
2,8-Dihydrazino-6-morpholino-	2	8 ml. hydrazine hydrate	Reflux	2	L	88
2,8-Dipiperidino-6-morpholino-	2	10 ml. piperidine	175[a]	20	K	85
2,6,8-Trifurfurylamino-	1	15 ml. furfurylamine	Reflux	4	E	77
2,6,8-Trihydrazino-	1	8 ml. hydrazine hydrate	Reflux	0.75	F	95
2,6,8-Tri-*n*-butylamino-	1	10 ml. *n*-butylamine	160[a]	5	G	78
2,6,8-Tri-*n*-hexylamino-	1	15 ml. *n*-hexylamine	Reflux	5	H	67
2,6,8-Trimorpholino-	1	10 ml. morpholine	175[a]	20	I	70
2,6,8-Tripiperidino-	1	10 ml. piperidine	175[a]	20	J	89

[a] These reactions were carried out in a Parr bomb 20 ml. capacity, heated in an oven at the indicated temperature. [b] 1, 2 g. of 2,6,8-trichloropurine; 2, 2 g. of 2,8-dichloro-6-morpholinopurine; 3, 5 g. of dimethylamine hydrochloride and 4 g. of sodium acetate trihydrate. [c] A, by addition of 50 ml. of water, neutralized with acetic acid, filtered, washed, dried and recrystallized from glacial acetic acid. B, by addition of 20 ml. of water, neutralized with acetic acid, filtered, washed, dried, redissolved in hot glacial acetic acid and reprecipitated by addition of water. C, same procedure as B using 100 ml. of water initially. D, by filtration, washed, dried and recrystallized from ethanol. E, by addition of 100 ml. of water, neutralized with acetic acid, filtered, washed, dried and recrystallized from ethanol. F, by filtration, washed, resuspended in water, filtered and dried. G, same as E but recrystallized twice from ethanol. H, by steam distillation to remove excess *n*-hexylamine, cooled, filtered and recrystallized twice from absolute ethanol. I, by dilution with 100 ml. of water, filtered, washed, dried, redissolved in hot ethanol and reprecipitated with water. J, the reaction product was dissolved in a minimum amount of absolute alcohol and 100 ml. of water was added. The product was removed by filtration, washed, dried, redissolved in hot ethanol and then reprecipitated with water. K, the reaction product was dissolved in a minimum amount of absolute alcohol and 100 ml. of water was added. The solution was then neutralized with acetic acid and filtered. The filtrate was treated with an excess of ammonium hydroxide to precipitate the product, which was recovered by filtration, redissolved in hot ethanol and reprecipitated by addition of water. L, by dilution with 50 ml. water, cooling, filtration, resuspension in water, filtration and drying.

doubt that the initial aminolysis of 2,6-dichloropurine was stepwise and involved the 6-position preferentially to yield a 2-chloro-6-substituted purine. This marked activity of the 6-chloro substituent in purine compounds has been observed in 4-chloroquinazolines[7] in which the 4-position has similar structural features to that of the 6-position in the purine molecule.

Supporting the data in Table I is the fact that several workers[6b,8] have shown that the melting points and ultraviolet spectra of the 6-substituted purines are different from those of their 2-substituted isomers.

Dechlorination by catalytic methods such as those described by Bendich[2b] *et al.*, for dechlorination of 6-chloropurine or by Smith and Christensen[9] for nuclear dehalogenation of pyrimidines were not successful with 2,6-dichloropurine. The chemical procedure of Fischer[6b] employing hydriodic acid and phosphonium iodide gave the best results. The procedure of Boehringer[10] using tetrahydronaphthalene and iodine was attempted but later abandoned due mainly to problems of isolation.

2,6,8-Trichloropurine was subjected to a similar series of experiments. The extent of the reactions of the nucleophilic agents were likewise found to be dependent on temperature and the presence of moisture to an even more marked degree. The reactions in the lower thermal ranges were carried out at reflux temperatures. However it was found that in certain reactions it was necessary to employ a Parr bomb to reach the necessary thermal range for the complete amination of the 2,6,8-positions. Furthermore, as in the experience with 2,6-dichloropurine, the addition of water to the reaction mixture resulted in the preferential amination of the 6-position, which was the most reactive, thus permitting stepwise amination. However the presence of a third chloro substituent in the 8-position influenced the activity of the 2-chloro substituent to the extent that in general it would not aminate at the reflux temperatures of the anhydrous amine.

2,8-Dichloro-6-dimethylaminopurine was prepared by refluxing dimethylamine hydrochloride, sodium acetate, ethanol, water and 2,6,8-trichloropurine together. Experiments with the same reaction mixture using pressure equipment at 160° for five hours failed to effect amination of the 2- or 8-positions.

Inasmuch as the data in Table I indicate that the dechlorinated x,y-dichloro-z-substituted purine to be identical with the corresponding 6-substituted purine as judged by ultraviolet and melting point data, it is evident that the 6-position is sufficiently reactive as to permit stepwise amination. The ultraviolet data of other purines prepared in this investigation are given in Table II and show that the substitution of a morpholino for a piperidino

(7) A. J. Tomisek and B. E. Christensen, THIS JOURNAL, **67**, 2112 (1945).

(8) S. F. Mason, *J. Chem. Soc.*, 2071 (1954); R. K. Robins, K. J. Dille, C. H. Willits and B. E. Christensen, THIS JOURNAL, **75**, 263 (1953).

(9) V. H. Smith and B. E. Christensen, *J. Org. Chem.*, **20**, 829 (1955).

(10) Boehringer, German Patent 576,604, May 12, 1933; *C.A.* **27**, 5757 (1933).

TABLE VI

Purine	M.p., °C.	Formula	Theory C, %	Theory H, %	Theory N, %	Found C, %	Found H, %	Found N, %
2,8-Dichloro-6-dimethylamino-	287–288	$C_7H_7N_5Cl_2$	36.2	3.02	30.2	36.4	3.57	30.6
2,8-Dichloro-6-furfurylamino-	248–249	$C_{10}H_7N_5OCl_2$	42.3	2.46	24.6	42.4		24.2
2,8-Dichloro-6-morpholino-	280–282	$C_9H_9N_5OCl_2$	39.5	3.29		39.4	3.45	
2,8-Dichloro-6-piperidino-	264–265	$C_{10}H_{11}N_5Cl_2$	44.2	4.05	25.7	44.2	4.58	25.5
2,8-Difurfurylamino-6-morpholino-	>137 d.	$C_{19}H_{21}N_7O_3\cdot H_2O$	55.2	5.57		55.2	5.44	
2,8-Di-*n*-hexylamino-6-morpholino-	>216 d.	$C_{21}H_{37}N_7O\cdot H_2O$	59.8	9.26		59.7	9.31	
2,8-Dihydrazino-6-morpholino-	>172 d.	$C_9H_{15}N_9O$	40.8	5.67		40.7	5.67	
2,8-Dipiperidino-6-morpholino-	>117 d.	$C_{19}H_{29}N_7O$	61.4	7.84		61.2	7.81	
2,6,8-Trifurfurylamino-	160–161	$C_{20}H_{19}N_7O_4\cdot H_2O$	56.7	4.97	23.1	56.8	4.90	22.9
2,6,8-Trihydrazino-	209 d.	$C_5H_{10}N_{10}$	28.6	4.76	66.8	28.5	4.69	65.0
2,6,8-Tri-*n*-butylamino-	206–207	$C_{17}H_{31}N_7\cdot H_2O$	58.2	9.40	27.9	58.3	9.13	27.6
2,6,8-Tri-*n*-hexylamino-	159–160	$C_{23}H_{43}N_7\cdot H_2O$	63.3	10.45	22.5	63.4	10.4	22.8
2,6,8-Trimorpholino-	246–248	$C_{17}H_{25}N_7O_3$	54.4	6.67	26.1	54.9	6.54	25.8
2,6,8-Tripiperidino-	115–117	$C_{20}H_{31}N_7$	65.1	8.40	26.6	65.0	8.75	26.1

substituent alters only slightly the position of the maximum absorption or magnitude of the extinction coefficient.

Fischer[11] long ago attempted to reduce trichloropurine by treating it with hydriodic acid only to get 2,6-diiodopurine. Since Smith[9] had successfully dehalogenated a number of pyrimidine derivatives catalytically using two-phase ether–sodium hydroxide media, attempts were made to adapt this process to the current problem. Using glacial acetic acid as a solvent, the trichloropurine was reduced to a tetrahydropurine. The tetrahydropurine was extremely hygroscopic. Attempts to prepare derivatives for characterization purposes failed.

When the same reaction conditions were applied to the reduction of 2,6-dichloropurine the reactions were unsuccessful. However in aqueous media the 6-chloro substituent was removed yielding 2-chloropurine in a 40% yield.

Experimental

One gram of 2,6-dichloropurine and 5–10 ml. of amine were refluxed for various periods of time. The specific conditions used in each experiment and other experimental details are given in Table III while the analytical data are to be found in Table IV.

Two hundred mg. of pulverized substituted mono- and dichloropurine was added to 2 g. of hydroiodic acid (sp. gr. 1.96). The mixture became warm with a considerable portion of the compound going into solution; the reaction was evident by the strong brown color in the liquid. Pulverized phosphonium iodide in excess was added and the mixture stirred for two hours at room temperature. The reduction was nearly complete by this time as judged by the disappearance of the solid phase. The mixture was then heated to boiling until a clear, almost colorless solution was obtained; if separation of iodine occurred, further addition of phosphonium iodide was necessary. The colorless solution was evaporated under vacuum to almost dryness. The isolation procedures for each of the 6-substituted purines are given in Table VII.

2-Chloropurine.—2,6-Dichloropurine (1 g.) and 0.72 g. of sodium acetate in 50 ml. of water were shaken at room temperature with 0.15 g. of 10% palladium–charcoal catalyst under 30 p.s.i. of hydrogen for three hours. The mixture was filtered. The filtrate was concentrated down to about 10 ml. and refiltered. The crude product of 2-chloropurine was purified by recrystallization from water; yield 0.35 g. (41%). The product melted at 231–234° when it was heated rapidly from 200° on an aluminum block. The ultraviolet absorption spectrum of the 2-chloropurine was found to be identical to that reported earlier by Montgomery.[12]

(11) E. Fischer, *Ber.*, **31**, 2550 (1898).

(12) J. A. Montgomery, THIS JOURNAL, **78**, 1928 (1956).

Tetrahydropurine Dihydrochloride.—2,6,8-Trichloropurine (2 g., 0.0085 mole), 1 g. of 10% palladium-on-charcoal, 75 ml. of glacial acetic acid and just enough water to wet the palladium catalyst were mixed together in a low pressure hydrogenation bottle and allowed to react at 42 pounds pressure of hydrogen for 24 hours. A hydrogen uptake of 0.04[13] mole was noted at this time. The reaction mixture was filtered and evaporated to 3 ml. at which time 50 ml. of dry ether was added. This precipitated the tetrahydropurine dihydrochloride, which was filtered and dried; yield 1.75 g. (98%), m.p. gradual decomposition above 160°.

TABLE VII

DEHALOGENATION REACTIONS OF CHLOROPURINES

Dehalogenated purine	Substituted chloropurine	Wt. of purine, g.	Yield, %	Isolation procedure[a]
6-Dimethylamino-	2,8-Dichloro-6-dimethylamino-	0.2	71.0	B
6-Furfurylamino-	2-Chloro-6-furfurylamino-	.2	65	E
6-Furfurylamino-	2,8-Dichloro-6-furfurylamino-	.2	13.3	A
6-Morpholino-	2-Chloro-6-morpholino-	.2	81	D
6-Morpholino-	2,8-Dichloro-6-morpholino-	.2	83	C
6-Piperidino-	2-Chloro-6-piperidino-	.2	88	D
6-Piperidino-	2,8-Dichloro-6-piperidino-	.2	80	D

[a] A, The free base was precipitated from aqueous solution by addition of 28% ammonium hydroxide, filtered and recrystallized from ethanol. B, The free base was prepared by addition of 28% ammonium hydroxide and then evaporated to dryness 25°. The residue was converted to its hydrochloride in absolute alcohol and then precipitated with ether. C, The free base was precipitated by the addition of 28% ammonium hydroxide to a warm water solution, filtered and recrystallized from 50% ethanol. D, The solid residue was dissolved in 20 ml. of boiling water which in turn was made slightly alkaline with concd. ammonia yielding the crystalline free base. The base was recrystallized from 50% ethanol. E, Same as D except for the final recrystallization from absolute ethanol.

Anal. Calcd. for $C_5H_{10}N_4Cl_2$: C, 30.4; H, 5.08; N, 28.4; Cl, 36.0. Found: C, 30.1; H, 5.00; N, 27.6; Cl, 36.4.

The free base was prepared by adding a theoretical amount of 5% sodium hydroxide to the salt and evaporating it to dryness. This mixture was then extracted with hot absolute ethanol, cooled and then dry ether added, which precipitated out the free base. This was filtered and tested for chloride by sodium fusion and was found to be negative. The free base was extremely hygroscopic and became liquid after a few minutes.

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(13) The hydrogen absorbed was so small that it could not be accurately measured by the pressure gauge of the hydrogenation apparatus.