[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY, ARIZONA STATE UNIVERSITY AND DEPARTMENT OF CHEMISTRY, NEW MEXICO HIGHLANDS UNIVERSITY]

Potential Purine Antagonists XXI. Preparation of Some 9-Phenyl-6-substituted Purines[1]

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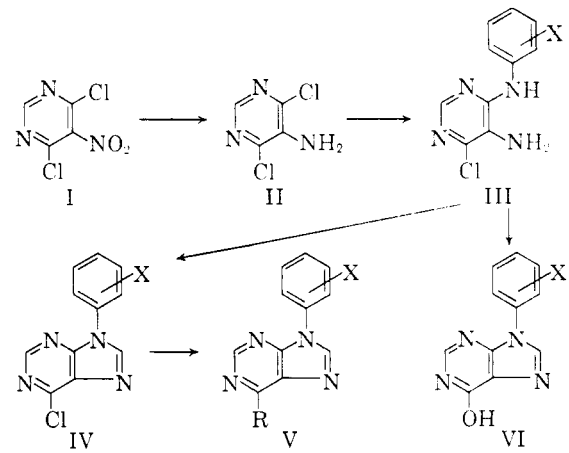
The synthesis of a number of new 9-aryl-6-substituted purines has been accomplished from the corresponding intermediate 5-amino-4-anilino-6-chloropyrimidine (III). The preparation of III was made possible by the reaction of 5-amino-4,6-dichloropyrimidine[2] with various anilines in the presence of a catalytic amount of hydrochloric acid.

A recent program involving the synthesis of certain 9-arylpurines[3,4] as potential anti-tumor agents has now been extended to include the preparation of a number of different 9-aryl-6-substituted purines. The general synthetic route of Daly and Christensen[5] has been extended to include the preparation of *p*-chlorophenyl-, *o*-chlorophenyl-, and (3,4-dichlorophenyl)-6-aminopurines.

Improvement of the synthesis of 4-amino-6-chloro-5-nitropyrimidine[6] in this laboratory by the reaction of 4,6-dichloro-5-nitropyrimidine[6] with a solution of ammonium acetate in dioxane and water makes this a practical synthetic route. This method however is limited to the preparation of 6-amino-9-arylpurines. Several other routes were investigated for the preparation of additional 9-aryl-6-substituted purine derivatives. The preparation of the desired 6-chloro-9-phenylpurine could conceivably be synthesized by the general route employed by Robins[7] and Lin for the synthesis of 6-chloro-9-methylpurine. The requisite intermediate pyrimidine, 4-anilino-6-chloro-5-nitropyrimidine, however, could not be prepared from 4,6-dichloro-5-nitropyrimidine (I). The only product isolated from the reaction of aniline and I was 4,6-bis-anilino-5-nitropyrimidine and unreacted I.

The preparation of 5-amino-6-chloro-4-methylaminopyrimidine by the method of Brown[8] from 5-amino-4,6-dichloropyrimidine[2] and the subsequent similar preparation of 4-alkylamino-5-amino-6-chloropyrimidine by Montgomery and Temple[9] suggested the possibility of the preparation of 5-amino-4-anilino-6-chloropyrimidine (III) from 5-amino-4,6-dichloropyrimidine. Preliminary reaction studies revealed that aniline and aniline derivatives substituted in the benzene ring did not react with II presumably because of the lower basicity of the amine. Maggioto and Phillips[10] have shown that amines of low basic strength can often be made to react with halogenated pyrimidines by the presence of mineral acid to result in acid catalyzed nucleophilic displacement of the chlorine atom. Following this lead it was found that aniline and various substituted anilines reacted readily with 5-amino-4,6-dichloropyrimidine[2] (II)



in an aqueous ethanol solution containing a small amount of hydrochloric acid. The 5-amino-6-chloro-4-substituted anilinopyrimidines (III) thus prepared were cyclized with ethyl orthoformate and acetic anhydride[7,9,11,12] to give the corresponding 6-chloro-9-substituted phenylpurines (IV). The reaction of several negatively substituted benzylamines with 5-amino-4,6-dichloropyrimidine (II)

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in the presence of acid was also successfully accomplished. These 5-amino-4-chloro-6-substituted benzylamines were similarly cyclized to give the corresponding 9-benzyl-6-chloropurines.

Usual nucleophilic replacement of the 6-chloro group was carried out with 6-chloro-9-phenylpurine to yield a number of 6-substituted-9-phenylpurines. Following standard reaction procedures previously employed in reactions of 6-chloro-9-methylpurine,[7] 9-phenyl-6-purinethiol, 6-methylthio-9-phenylpurine, 6-methylamino-9-phenylpurine, and 6-dimethylamino-9-phenylpurine were prepared. 9-Phenyl-6-purinethiol in a potassium hydroxide solution was treated with *p*-fluorobenzyl chloride to give 6-*p*-fluorobenzylthio-9-phenylpurine.

A new preparation of 9-phenylhypoxanthine was accomplished by cyclization of 5-amino-4-anilino-6-chloropyrimidine with formic acid. A similar reaction has previously been reported for the synthesis of 9-methylhypoxanthine.[7]

9-*p*-Chlorophenyl-6-hydroxypurine was prepared from 5-amino-6-chloro-4-*p*-chloroanilinopyrimidine and formic acid and also by deamination of 6-amino-9-*p*-chlorophenylpurine with hot nitrous acid. The ultraviolet absorption spectral data of the 9-substituted purines are listed in Table I.

EXPERIMENTAL[13]

Preparation of 5-Amino-4-anilino-6-chloropyrimidine (III, X = H). Four grams of 5-amino-4,6-dichloropyrimidine[2] was added to a solution containing 65 ml. of water, 10 ml. of ethanol, 1 ml. of concentrated hydrochloric acid, and 3 g. of aniline. The solution was refluxed for 8 hr.; then approximately 50 ml. of hot water was added, and the solution was allowed to stand overnight in the refrigerator. The product was filtered, washed with water, and recrystallized from a 2:1 water-methanol mixture to give 3.6 g. (67%) of white needles, m.p. 175–176°.

Anal. Calcd. for $C_{10}H_9ClN_4$: C, 54.4; H, 4.1; N, 25.4. Found: C, 54.4; H, 4.3; N, 25.3.

6-Chloro-9-phenylpurine (IV, X = H). Ten g. of dry 5-amino-4-anilino-6-chloropyrimidine (III, X = H) was added to a mixture of 50 ml. of ethyl orthoformate and 50 ml. of acetic anhydride. The solution was refluxed for 3 hr., and the excess solvents were removed under reduced pressure using a water-bath as the source of heat. The solid residue was dissolved in boiling benzene, and the solution was heated with charcoal and filtered. The cooled filtrate yielded 7.0 g. of crystals, m.p. 198–200°. Recrystallization of a small sample from benzene raised the melting point to 202–203°.

Anal. Calcd. for $C_{11}H_7ClN_4$: C, 57.3; H, 3.0; N, 24.3. Found: C, 57.6; H, 3.1; N, 24.6.

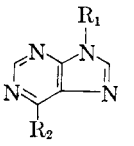
6-Hydroxy-9-phenylpurine (VI, X = H). A solution of 7 g. of 5-amino-4-anilino-6-chloropyrimidine and 70 ml. of formic acid was refluxed for 5 hr. The solution was then evaporated to near dryness under reduced pressure; then 100 ml. of boiling water was added. Concentrated ammonium hydroxide was added until a *p*H of 10 was reached. The solution was boiled with charcoal and filtered. The cooled filtrate yielded 3.4 g. of crude 9-phenylhypoxanthine. The product was recrystallized from water containing a small amount of methanol to give white needles, m.p. >300°.

Anal. Calcd. for $C_{11}H_8N_4O$: C, 62.3; H, 3.8; N, 26.4. Found: C, 62.2; H, 3.7; N, 25.9.

(13) All melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected.

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA OF THE 9-ARYL-6-SUBSTITUTED PURINES



		*p*H 1		*p*H 11	
R_1	R_2	λ_{max}, mμ	ε	λ_{max}, mμ	ε
C_6H_5	OH	249[a]	14,100	254	14,800
C_6H_5	Cl	227	18,000	231	17,480
		265	11,540	265	10,060
C_6H_5	SH	223	15,960	230	24,000
		322	27,300	311	27,500
C_6H_5	SCH_3	336	12,750	319	13,200
C_6H_5	$NHCH_3$	263	18,900	267	16,200
C_6H_5	$N(CH_3)_2$	270	21,000	275	18,800
C_6H_5	$SCH_2C_6H_4pF$	287[b]	11,950	...	...
p-ClC_6H_4	OH	235	11,500	235	9,600
		...	...	255	6,650
p-ClC_6H_4	Cl	233	12,000	235	11,000
p-ClC_6H_4	SH	323	4,050	312	24,100
3,4-$Cl_2C_6H_3$	Cl	237	8,725	239	15,250
$CH_2C_6H_5$	Cl	266	9,700	266	9,900
3,4-$Cl_2CH_2C_6H_3$	Cl	266	10,200	267	11,500
NH_2	*p*-ClC_6H_4	235	21,000	260	16,660
		255	18,000	...	...
NH_2	2,4-$Cl_2C_6H_3$	257	19,800	260	17,885
NH_2	*o*-ClC_6H_4	258	15,700	260	15,190

[a] Point of inflection. [b] Run in ethanol.

9-Phenyl-6-purinethiol. Ten g. of 6-chloro-9-phenylpurine and 5 g. of thiourea were dissolved in 200 ml. of absolute ethanol. The solution was refluxed for 3 hr. and then cooled and filtered. The precipitate was washed with a small amount of cold water. The light tan crystals were dissolved in hot dilute potassium hydroxide. The solution was boiled gently for a few minutes with charcoal and filtered. The filtrate was acidified while hot with acetic acid. The resulting precipitate (8.2 g.), m.p. >300°, was washed and dried at 125°.

Anal. Calcd. for $C_{11}H_8N_4S$: C, 57.9; H, 3.5; N, 24.6. Found: C, 57.6; H, 3.5; N, 24.4.

6-Methylthio-9-phenylpurine. Ten g. of 9-phenyl-6-purinethiol was dissolved in 200 ml. of 0.5*N* potassium hydroxide, and the solution was stirred and cooled in an ice bath. To the cold solution was added 6.22 g. (2.72 ml.) of methyl iodide, and stirring was continued for 2 hr. The resulting solid was collected and recrystallized from 200 ml. of boiling water to give a product, m.p. 148–149°.

Anal. Calcd. for $C_{12}H_{10}N_4S$: C, 59.7; H, 4.1; N, 23.1. Found: C, 60.0; H, 4.1; N, 23.4.

6-Methylamino-9-phenylpurine. To a suspension of 10 g. of 6-chloro-9-phenylpurine in 100 ml. of water was added 100 ml. of 40% aqueous methylamine. The mixture was heated on a steam bath for 2 hr., cooled, and filtered to give 8.4 g. of white crystalline product, m.p. 155–156°. The product was recrystallized from a water-ethanol mixture and dried at 85° for several days.

Anal. Calcd. for $C_{12}H_{11}N_5$: C, 64.0; H, 4.9; N, 31.1. Found: C, 63.8; H, 5.1; N, 31.2.

6-Dimethylamino-9-phenylpurine. To 10 g. of 6-chloro-9-phenylpurine, dissolved in 200 ml. of ethanol, was added 60 ml. of dimethylamine. The mixture was heated on a steam bath until the volume was reduced to approximately 100 ml. The mixture was cooled and filtered to give 8.6 g. of white crystals, m.p. 166–168°. Recrystallization from ethanol raised the melting point to 168–169°.

Anal. Calcd. for $C_{13}H_{13}N_5$: C, 65.3; H, 5.4; N, 29.3. Found: C, 65.8; H, 6.2; N, 29.2.

6-p-Fluorobenzylthio-9-phenylpurine. To a solution of 10 g. of 9-phenyl-6-purinethiol in 100 ml. of 4% potassium hydroxide was added 6.2 g. of *p*-fluorobenzylchloride. The mixture was heated, with stirring, on a steam bath for 2 hr. The resulting mixture was cooled, filtered, and washed with a small amount of distilled water to give 13.3 g. of white crystalline product, m.p. 167–169°. Recrystallization from ethanol raised the melting point to 169–171°.

Anal. Calcd. for $C_{18}H_{13}FN_4S$: C, 64.3; H, 3.9; N, 16.6. Found: C, 64.3; H, 3.9; N, 17.0.

5-Amino-6-chloro-4-(p-chloroanilino)pyrimidine (III, X = *p*-Cl). Four g. of 5-amino-4,6-dichloropyrimidine[2] (II) was added to a solution containing 65 ml. of water, 10 ml. of ethanol, 1 ml. of concentrated hydrochloric acid, and 3.5 g. of *p*-chloroaniline. The solution was refluxed for 7 hr. Approximately 50 ml. of hot water was then added to the solution, and the solution was allowed to stand overnight in the refrigerator. The product was filtered, washed with water, and recrystallized from a 1:1 water-methanol mixture to give 3.8 g. (62%) of white needles, m.p. 222°.

Anal. Calcd. for $C_{10}H_8Cl_2N_4$: C, 47.2; H, 3.1; N, 21.9. Found: C, 47.5; H, 3.0; N, 22.1.

6-Chloro-9-(p-chlorophenyl)purine (IV, X = *p*-Cl). Thirty g. of dry 5-amino-6-chloro-4-(*p*-chlorophenyl)pyrimidine was added to a mixture of 150 ml. of ethyl orthoformate and 150 ml. of acetic anhydride. The solution was refluxed for 3 hr., and the excess solvent was removed under reduced pressure using a water bath as the source of heat. The solid residue was dissolved in boiling benzene, and the solution was heated with charcoal and filtered. The cooled filtrate yielded 27 g. of crystals, m.p. 220–222°.

Anal. Calcd. for $C_{11}H_6Cl_2N_4$: C, 49.9; H, 2.3; N, 21.1. Found: C, 50.3; H, 2.5; N, 21.1.

9-(p-Chlorophenyl)-6-hydroxypurine (VI, X = *p*-Cl). *Method 1.* A solution of 8 g. of 5-amino-6-chloro-4-(*p*-chloroanilino)pyrimidine and 75 ml. of formic acid was refluxed for 10 hr. The solution was then evaporated to near dryness under reduced pressure, and dilute ammonium hydroxide was added to the residue until *p*H 10 was reached. The cooled solution yielded 3.6 g. of crude 9-(*p*-chlorophenyl)-hypoxanthine. The crude product was recrystallized from water containing a small amount of methanol to give white needles, m.p. >300°.

Anal. Calcd. for $C_{11}H_7ClN_4O$: C, 53.7; H, 2.8; N, 22.7. Found: C, 53.5; H, 3.0; N, 22.4.

Method 2. Three g. of 6-amino-9-(*p*-chlorophenyl)purine was added to a solution of 5 ml. of concentrated sulfuric acid and 50 ml. of water. The mixture was then boiled on a hotplate until solution was completed. The solution was allowed to cool to 90°; then 15 g. of a 33% aqueous solution of sodium nitrite was added. This solution was boiled for 10 min., cooled, and filtered. The solid material was then dissolved in 2*N* sodium hydroxide, and the solution was then treated with Norit and filtered. The filtrate was acidified with glacial acetic acid, and the precipitate was collected. The yield was 1 g. (33%) of product, m.p. >300°. The ultraviolet absorption spectra of this product and that prepared by method 1 were identical.

Anal. Calcd. for $C_{11}H_7ClN_4O$: C, 53.7; H, 2.8; N, 22.7. Found: C, 53.5; H, 3.1; N, 22.4.

9-(p-Chlorophenyl)-6-purinethiol. Five g. of 6-chloro-9-(*p*-chlorophenyl)purine and 4.6 g. of thiourea were dissolved in 150 ml. of absolute ethanol. The solution was refluxed for 3 hr., then cooled and filtered, and the precipitate was washed with a small amount of cold water. The light tan crystals were dissolved in hot dilute potassium hydroxide. The solution was boiled gently for a few minutes with charcoal, and the filtrate was acidified while hot with acetic acid. The resulting precipitate (4.8 g.), m.p. >300°, was washed and dried at 125° for analysis.

Anal. Calcd. for $C_{11}H_7ClN_4S$: C, 50.3; H, 2.7; N, 21.3. Found: C, 50.6; H, 2.6; N, 21.6.

5-Amino-4-benzylamino-6-chloropyrimidine. Ten g. of 5-amino-4,6-dichloropyrimidine was added to a solution containing 165 ml. of water, 25 ml. of ethanol, 1 ml. of concentrated hydrochloric acid, and 7 g. of benzylamine. The solution was refluxed for 5 hr.; then approximately 125 ml. of hot water was added to the solution. The solution was allowed to stand overnight in the refrigerator The product was filtered, washed with water, and recrystallized from a benzene-heptane mixture to give 9.0 g. of white needles, m.p. 207–209°.

Anal. Calcd. for $C_{11}H_{10}ClN_4$: C, 56.7; H, 4.3; N, 23.9. Found: C, 56.9; H, 4.7; N, 24.1.

6-Chloro-9-benzylpurine. Three g. of dry 5-amino-4-benzylamino-6-chloropyrimidine was added to a mixture of 25 ml. of ethyl orthoformate and 25 ml. of acetic anhydride. The solution was refluxed for 3 hr., and the excess solvent was removed under reduced pressure using a water bath as the source of heat. The gummy residue was extracted three times with 25 ml. portions of boiling heptane. The heptane was allowed to cool in the refrigerator overnight to give 1.1 g. of white needles, m.p. 84–85.5°.

Anal. Calcd. for $C_{12}H_9ClN_4$: C, 58.9; H, 3.7; N, 22.9. Found: C, 58.8; H, 3.9; N, 23.3.

5-Amino-4-(3,4-dichlorobenzylamino)-6-chloropyrimidine. Four g. of 5-amino-4,6-dichloropyrimidine[2] was added to a solution containing 65 ml. of water, 10 ml. of ethanol, 1 ml. of concentrated hydrochloric acid, and 5 g. of 3,4-dichlorobenzylamine. The solution was refluxed for 3 hr.; then approximately 50 ml. of water was added to the solution. The solution was allowed to cool, and the product was filtered, washed with water, dried, and recrystallized from benzene to yield 4.4 g. of tan crystals, m.p. 198–200°.

Anal. Calcd. for $C_{11}H_9Cl_3N_4$: C, 43.6; H, 3.0; N, 18.5. Found: C, 43.4; H, 3.4; N, 18.8.

6-Chloro-9-(3,4-dichlorobenzyl)purine. Four g. of dry 5-amino-6-chloro-4-(3,4-dichlorobenzylamino)pyrimidine was added to a mixture of 25 ml. of ethyl orthoformate and 25 ml. of acetic anhydride. The solution was refluxed for 3 hr.; the excess solvent was removed, and the gummy residue was extracted three times with 25 ml. portions of boiling heptane. The heptane solution was allowed to cool overnight in the refrigerator to give 1.7 g. of white crystals, m.p. 149–151°.

Anal. Calcd. for $C_{12}H_7Cl_3N_4$: C, 46.1; H, 2.2; N, 17.9. Found: C, 46.3; H, 2.3; N, 17.8.

5-Amino-6-chloro-4-(3,4-dichloroanilino)pyrimidine. Ten g. of 5-amino-4,6-dichloropyrimidine was added to a solution containing 165 ml. of water, 25 ml. of ethanol, 1 ml. of concentrated hydrochloric acid, and 11 g. of 3,4-dichloroaniline. The solution was refluxed for 3 hr.; then approximately 125 ml. of hot water was added to the solution, and it was allowed to stand overnight in the refrigerator. The product was filtered and washed with water to give 19.5 g. of crude product. A purified sample, m.p. 214°, was obtained by recrystallizing a small amount of the product from benzene.

Anal. Calcd. for $C_{10}H_7Cl_3N_4$: N, 19.3. Found: N, 19.6.

6-Chloro-9-(3,4-dichlorophenyl)purine. Dry crude 5-amino-6-chloro-4-(3,4-dichloroanilino)pyrimidine (19.5 g.) was added to a mixture of 100 ml. of ethyl orthoformate and 100 ml. of acetic anhydride. The solution was refluxed for 6 hr., and the excess solvent was removed under reduced pressure using a water bath as a source of heat. The solid residue was dissolved in boiling benzene, and the solution was heated with charcoal and filtered. The cooled filtrate yielded 11.3 g. of crystals, m.p. 234–235°. Recrystallization of a small sample from benzene raised the melting point to 236–237°.

Anal. Calcd. for $C_{11}H_5Cl_3N_4$: C, 44.2; H, 1.7; N, 18.7. Found: C, 44.6; H, 1.6; N, 18.4.

4-Amino-6-chloro-5-nitropyrimidine. Ninety g. of 4,6-dichloro-5-nitropyrimidine[6] was dissolved in 500 ml. of dioxane. To this solution, which was stirred and cooled to 5°, was added dropwise a freshly prepared solution of ammonium acetate prepared as follows: To fresh, commercial concentrated ammonium hydroxide (28% ammonia) (350 ml.) was

carefully added, with cooling, a little at a time, 200 ml. of glacial acetic acid. The solution was cooled to 0° before use. This ammonium acetate solution was added dropwise at such a rate that the inside temperature was maintained at 10° with external cooling in an ice bath. After the addition was complete, the reaction mixture was stirred an additional hr., and finally 2 l. of ice-water was added slowly, with stirring, to precipitate the product. The solution was then filtered, and the product was washed with water and dried at room temperature. The crude product was recrystallized from benzene to give 55 g. of yellow crystals, m.p. 156–157°; reported[6] m.p. 155–156°.

4-Amino-6-(o-chloroanilino)-5-nitropyrimidine. Five g. (0.04 mole) of 4-amino-6-chloro-5-nitropyrimidine was added to a solution of 10 g. (0.07 mole) of *o*-chloroaniline in 30 ml. of *n*-butanol. The solution was placed on the steam bath for 30 min.; during this time 7 g. (92%) of 4-amino-6-(*o*-chloroanilino)-5-nitropyrimidine precipitated. The precipitate was filtered and then recrystallized from a 2:1 mixture of dioxane and absolute ethanol to give a melting point of 268°.

Anal. Calcd. for $C_{10}H_8N_5O_2Cl$: C, 45.2; H, 3.0; N, 26.4. Found: C, 45.1; H, 3.0; N, 26.2.

6-(o-Chloroanilino)-4,5-diaminopyrimidine sulfate. One g. (0.003 mole) of 4-amino-6-*o*-chloroanilino-5-nitropyrimidine was suspended in 40 ml. of methanol containing 1 g. of Raney nickel. The mixture was hydrogenated at a pressure of 40 lb./sq. in. for approximately 2 hr. After 2 hr. the reaction was found to be completed since no further absorption of hydrogen gas was observed. The solution was removed from the hydrogenator and filtered. The filtrate was made strongly acidic with dilute sulfuric acid, and upon cooling 1.1 g. (91%) of the salt was collected, m.p. >300°.

6-Amino-9-(o-chlorophenyl)purine. One g. (0.004 mole) of 6-(*o*-chloroanilino)-4,5-diaminopyrimidine sulfate was boiled in 10 ml. of formamide for 20 min. The flask was removed from the hot plate, and 50 ml. of water was added to the hot solution. The solution was allowed to stand in the refrigerator overnight; during this time 0.4 g. (55%) of 6-amino-9-(*o*-chlorophenyl)purine precipitated. Recrystallization from absolute ethanol gave a product having a melting point of 285°.

Anal. Calcd. for $C_{11}H_8N_5Cl$: C, 53.8; H, 3.3; N, 28.8. Found: C, 53.8; H, 3.6; N, 29.4.

4-Amino-6-(2,4-dichloroanilino)-5-nitropyrimidine. One g. (0.004 mole) of 4-amino-6-chloro-5-nitropyrimidine was added to a solution of 2 g. (0.06 mole) of 2,4-dichloroaniline in 50 ml. of methanol. The mixture was placed on the steam bath for 20 min. During this time 1.5 g. (75%) of 4-amino-6-(2,4-dichloroanilino)-5-nitropyrimidine precipitated. The compound was recrystallized from dioxane to give a melting point >300°.

Anal. Calcd. for $C_{10}H_7N_5O_2Cl_2$: C, 39.9; H, 2.3; N, 23.4. Found: C, 40.1; H, 2.7; N, 23.1.

4,5-Diamino-6-(2,4-dichloroanilino)pyrimidine sulfate. Five g. (0.016 mole) of 4-amino-6-(2,4-dichloroanilino)-5-nitropyrimidine was suspended in 150 ml. of methanol containing 4 g. of Raney nickel. The mixture was then hydrogenated at a pressure of 40 lb./sq. in. After approximately 2 hr. the hydrogenation was found to be complete since there was no further absorption of hydrogen gas. The solution was then removed from the hydrogenator and filtered. The filtrate was made strongly acidic with dilute sulfuric acid. The acid solution was cooled, and 8 g. (94%) of the salt was collected, m.p. >300°.

6-Amino-9-(2,4-dichlorophenyl)purine. One g. (0.002 mole) of 4,5-diamino-6-(2,4-dichloroanilino)pyrimidine sulfate was boiled with 10 ml. of formamide for 30 min. The flask was then removed from the hot plate and cooled; 150 ml. of water was then added to the solution. The solution was placed in the refrigerator and allowed to stand overnight. During this time 0.45 g. (63%) of 6-amino-9-(2,4-dichlorophenyl)purine precipitated. The product was recrystallized from dioxane to give a product melting >300°.

Anal. Calcd. for $C_{11}H_7N_5Cl_2$: C, 47.1; H, 2.5; N, 25.1. Found: C, 47.5; H, 3.0; N, 25.1.

4-Amino-6-p-chloroanilino-5-nitropyrimidine. One g. of 4-amino-6-chloro-5-nitropyrimidine was added to a solution of 2 g. of *p*-chloroaniline in 20 ml. of *n*-butanol. The solution was placed on the steam bath for 20 min.; during this time 1.2 g. (86%) of 4-amino-6-*p*-chloroanilino-5-nitropyrimidine precipitated. The product was filtered and recrystallized from a 1:1 mixture of dioxane and absolute methanol to give a compound with a melting point 285–286°.

Anal. Calcd. for $C_{10}H_8N_5O_2Cl$: C, 45.2; H, 3.0; N, 26.4. Found: C, 45.1; H, 3.0; N, 26.2.

6-Amino-9-(p-chlorophenyl)purine. Four g. (0.015 mole) of 4-amino-6-(*p*-chloroanilino)-5-nitropyrimidine was suspended in 150 ml. of methanol. To this mixture was added 3 g. of Raney nickel, and the solution was hydrogenated at a pressure of 40 lb./sq. in. for approximately 3 hr. The Raney nickel was removed and washed with small amounts of methanol. The combined filtrates were made strongly acidic with dilute sulfuric acid. After the solution was cooled, the sulfate salt was collected to yield 6 g. (78%), m.p. >300°. This crude product was boiled in 60 ml. of formamide for 30 min. The flask was removed from the hot plate, and to the hot solution was added 300 ml. of water. The solution was allowed to stand in the refrigerator overnight during which time 2.4 g. (57%) of 6-amino-9-(*p*-chlorophenyl)-purine precipitated. The crude product was filtered and recrystallized from a 3:1 mixture of *N,N*-dimethylformamide and water.

Anal. Calcd. for $C_{11}H_8N_5Cl$: C, 53.8; H, 3.3; N, 28.8. Found: C, 53.4; H, 3.8; N, 28.5.

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