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

Purines. II. The Synthesis of Certain Purines and the Cyclization of Several Substituted 4,5-Diaminopyrimidines[1]

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A study of the cyclization methods for the preparation of purines has been made. On the basis of this work, a new improved procedure for the cyclization of the imidazole ring of the purine nucleus has been perfected. This method has been successfully applied to eleven different substituted 4,5-diaminopyrimidines. A number of new purines and improved procedures for preparation of pyrimidine derivatives are described.

In the course of chlorination studies of the purinones in the presence of tertiary amines a number of substituted alkylamino derivatives were obtained instead of the desired chlorination products.[2] Using this procedure both 2,6-bis-(diethylamino)-purine and 6-diethylaminopurine were prepared in good yield. Since 2,6-bis-(diethylamino)-purine gave promising tests in preliminary inhibition studies, it appeared desirable to prepare the 2-diethylaminopurine in order to complete the study of this series.

Starting with 2-diethylamino-4-amino-5-nitropyrimidine,[3] the 4,5-diamino derivative was obtained by catalytic reduction with Raney nickel. This product was in turn converted to 2-diethylamino-4-amino-5-formylaminopyrimidine, which when heated in boiling formamide, cyclized readily to yield the desired 2-diethylaminopurine. In view of the ease of this latter reaction, and the fact that the bottleneck to purine syntheses has been the difficulty usually encountered in the final step of cyclization, an investigation of the cyclizations of substituted 4,5-diaminopyrimidines in general was undertaken.

4,5-Diaminopyrimidone-6 with either a methyl, hydrogen or amino substituent in the 2-position can be cyclized in good yield by merely refluxing in 90–100% formic acid for 5–10 hours. However, with a considerable number of other 4,5-diaminopyrimidines this treatment results only in the formylation of the 5-position instead of yielding the desired purine. The cyclization of the formylamino derivative has been accomplished in the past by (1) slow fusion of the formylamino intermediate in an oil-bath,[4] (2) slow fusion of the corresponding sodium or potassium salt of the formyl derivative[5] or (3) fusion followed by removal of the purine product by sublimation procedures.[4b,c] These methods in general gave low yields and in many instances yield data were not even reported.

Todd and co-workers[6] modified the cyclization procedures by preparing the thioformylamino derivative which when heated in water, quinoline or pyridine was reported to yield purines. Although this method appears to be superior to the earlier cyclization procedures, several workers[7] found that the reaction was incomplete and yielded purine contaminated with uncyclized product.

Brown and co-workers[8] were the first investigators to employ formamide for cyclization purposes. Using the sulfates of the 4,5-diaminopyrimidines, formic acid and formamide in a sealed tube, these workers obtained good yields of the corresponding purine derivatives.[7b] Later Clark and Kalckar, using formylmorpholine as a solvent, reported[9] successful cyclization of 4,6-diamino-5-formamidopyrimidine by mere heating in an open system.

In view of the fact that several 4,5-diaminopyrimidines had been cyclized in this Laboratory by refluxing either the free base or the 5-formyl derivative in formamide, the general application of this procedure to other substituted diamines was investigated. It was observed that the 2,4,5-triaminopyrimidone-6,2-mercapto-4,5-diaminopyrimidone-6 and 2,4,5,6-tetraminopyrimidine were not cyclized by refluxing for 20 minutes in formamide; while 4-amino-5-formylaminopyrimidinedione-2,6 was only partially cyclized by this procedure.

Recently good yields have been reported for the synthesis of xanthine[10] in which the diamino sulfate had been used as the intermediate for the final step of cyclization. Following this lead it was discovered that merely refluxing the sulfates of the 4,5-diaminopyrimidines in formamide resulted readily in cyclization. Eleven different 4,5-diaminopyrimidines were investigated and all responded to this treatment, giving good yields of their respective purines. The cyclization of 6-chloro-4,5-diaminopyrimidine, however, yielded hypoxanthine rather than the chloro analog. The results of these studies are given in Table I.

In the course of these investigations, a number of new purines were prepared together with several new procedures and new intermediates; these are reported for reasons of documentation. The starting material for the preparation of adenine was 4,6-dichloro-5-nitropyrimidine[11]; this was con-

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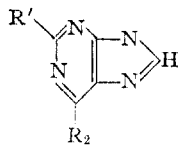
TABLE I



R_1	R_2	Method of cyclization	Yield based on purified material, %	M.p., °C.	Empirical formula	Nitrogen, % Calcd.	Nitrogen, % Found[h]	Recrystallization solvent
NH_2[4c]	H	A	49[a]	277–278	$C_5H_5N_5$	51.9	51.9	Water
H[7c]	NH_2	A	61	352–354 dec.	$C_5H_5N_5$[i]	51.9	51.2	Water
		C	95[b,f]					5% H_2SO_4
SH	H	B	62	Dec. over 280	$C_5H_4N_4S$	36.9	37.2	Water
$N(C_2H_5)_2$	H	B	73	228–230	$C_9H_{13}N_5$	36.7[j]	37.0	Ethanol–water
CH_3	OH	C	91	>350	$C_6H_6N_4O$	37.3	37.0	Water
CH_3[6,7]	NH_2	C	90	>350	$C_6H_7N_5$	46.9	46.8	.....
OH[5g]	CH_3	C	52	Darkens 300–310 m.p. >350	$C_6H_6N_4O$	37.3	37.0	Water
NH_2[4c]	CH_3	C	56[c]	Dec. 305–315	$C_6H_7N_5$	46.9	46.9	Water
SH[5c]	OH	C	89[e]	Dec. 325–340	$C_5H_4N_4OS$	33.3	33.5	.....
NH_2[20]	OH	C	96[g]	>350	$C_5H_5N_5O$	46.4	46.1	5% HCl
OH[10]	OH	C	76[e]	>350	$C_5H_4N_4O_2$	36.9	36.8	.....
SH[8]	NH_2	C	81[f]	>350	$C_5H_5N_5S$	41.9	42.2	5% H_2SO_4
NH_2[8]	NH_2	C	93[f]	300–302	$C_5H_6N_6$	56.0	56.2	5% H_2SO_4
H	OH	B	72[d]	>350	$C_5H_4N_4O$	41.1	40.8	Water
CH_3S[6]	NH_2	C	82[c]	294–295	$C_6H_7N_5S$	38.7	38.2	Ethanol

[a] Yield data have not been previously reported.[4c] [b] Adenine was isolated as the sulfate as described by Cavalieri.[7b] [c] The crude product was treated with dilute hydrochloric acid, boiled with Norit and the hot filtrate neutralized with dilute ammonium hydroxide which precipitated the free base on cooling. [d] 6-Chloro-4,5-diaminopyrimidine was the starting material in this cyclization. [e] Purification was effected by dissolving the crude product in dilute ammonium hydroxide, boiling with Norit and then acidifying the hot filtrate with acetic acid. [f] Yield data was based on sulfate. [g] Yield data based on hydrochloride. [h] All analytical samples were dried for 5–10 hours at 115°. [i] Picrate, m.p. 296°. [j] *Anal.* Calcd. for $C_9H_{13}N_5$: C, 56.5; H, 6.8. Found: C, 56.8; H, 6.7.

verted to the 4,6-diamino intermediate by an amination procedure which yielded 4,6-diamino-5-nitropyrimidine; this in turn was catalytically reduced with Raney nickel to the desired triamino intermediate. The melting point was 257° which agrees with that reported by Todd[5] who prepared this triamine from a different intermediate.

The synthesis of 6-methylpurinone-2 started from 2-chloro-4-amino-5-nitro-6-methylpyrimidine.[12] Hydrolysis gave the 2-hydroxy analog which was catalytically reduced by low pressure hydrogenation with Raney nickel to the desired 4,5-diamino intermediate in a 90% yield. This method appeared to be simpler than *via* the nitration route using 4-methylcytosine as described by Johns.[5e] The same reduction was reported in a 50–60% yield by Johns[5e] who employed aluminum amalgam.

4,5,6-Triamino-2-methylpyrimidine used in the preparation of 2-methyl-6-aminopurine was obtained by the reduction of 4,6-diamino-5-benzeneazo-2-methylpyrimidine.[13] This intermediate gave a 44% yield using zinc dust as the reductant; Lythgoe[13] used a high pressure catalytic hydrogenation with Raney nickel, but reports no yield for the reaction.

2-Methylpurinone-6 was synthesized from 2-methyl-4-aminopyrimidone-6[14] which was nitrosated according to Traube's[15] procedure. This compound was in turn converted to the desired 4,5-diamino intermediate by means of a hydrosulfite reduction.

The starting material selected for the preparation of 2-amino-6-methylpurine was 2,4-dichloro-5-nitro-6-methylpyrimidine[16] which aminated more conveniently at atmospheric pressure than by the sealed tube technique described by Gabriel and Colman.[4c] The resulting 2,4-diamino-5-nitro-6-methylpyrimidine was then catalytically reduced using Raney nickel to the desired triamino intermediate.

The isoadenine used in these studies was synthesized from 2,4-dichloro-5-nitropyrimidine.[17] Conversion to the 2,4-diamino derivative was effected by essentially the same procedure as described for the preparation of the 6-methyl homolog. This method has the advantage of avoiding the use of phenol as a solvent[18] for the amination.

The synthesis of 2-mercaptopurine was accomplished through cyclization of 2-mercapto-4,5-diaminopyrimidine.[19]

The ultraviolet absorption maxima of all the purines prepared by these procedures were taken. In all instances where previous values had been reported, the data were confirmed (see Table II).

Experimental

Preparation of Purines. Method (A).—The appropriate 4,5-diaminopyrimidine, 1.0 g., together with 10 ml. of C.P. formamide, was boiled for 15 minutes under a hood.

(12) S. Gabriel and J. Colman, *Ber.*, **34**, 1244 (1901).

(13) B. Lythgoe, A. R. Todd and A. Topham, *J. Chem. Soc.*, 315 (1944).

(14) A. Maggiolo, A. P. Phillips and G. H. Hitchings, THIS JOURNAL, **73**, 107 (1951).

(15) W. Traube, *Ann.*, **432**, 287 (1923).

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(17) N. Whittaker, *ibid.*, 1586 (1951).

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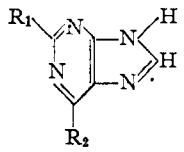
TABLE II



			Found			Reported		
R_1	R_2	Concn., mg./l[a]	*p*H	λ_{max}	ϵ	*p*H	λ_{max}	ϵ
NH_2	H	2.2	1	220	37,200			
		8.8	1	316	3,480			
H	NH_2	4.9	1	263	12,600	1.99[20,21]	264	12,500
SH	H	8.2	1	241	10,200			
		4.1	1	286.5	17,000			
$(C_2H_5)_2N$	H	3.1	1	229	37,600			
CH_3	OH	11.0	1	249.5	9,820			
CH_3	NH_2	8.6	1	266	12,200			
OH	CH_3	8.3	1	260	2,660			
				318	7,360			
NH_2	CH_3	2.3	1	219	39,100			
		9.2	1	313	4,490			
SH	OH	4.1	1	295	14,400			
NH_2	OH	5.8	5.9	246	13,900	5.9[21]	246	10,800
				275	10,400		275	8,660
OH	OH	5.4	1	227	5,620			
				266	9,340	2.01[21]	266	9,200
SH	NH_2	6.5	6.8	229	13,700	6.38[3]	230	9,640
				282	13,900		285	12,600
NH_2	NH_2	10.0	1.9	241	26,700	1.97[21]	241	10,000
				282	27,900		282	9,950
H	OH	14.3	6.5	251	10,200	6.44[21]	251	10,300
CH_3S	NH_2	7.3	1	221	9,940			
				246	13,300			
				284	11,200			

[a] Calculated as the free base.

The mixture was allowed to cool, 5 ml. of water added and the solution then placed in the refrigerator for 48 hours. The crude product was removed by filtration, washed with a little ice-water and resuspended in 25 ml. of boiling water; the solution was acidified with dilute sulfuric acid and then decolorized with Norit. Neutralization of the hot filtrate with dilute ammonium hydroxide and cooling yielded the purine.

Method (B).—To 10 ml. of C.P. formamide was added 1.0 g. of the 5-formamido derivative, prepared by refluxing the corresponding 4,5-diaminopyrimidine with 90% formic acid. The formamide solution was gently boiled for 15 minutes, cooled, diluted with 10 ml. of water and filtered. The crude purine was dissolved in hot water or a hot ethanol–water mixture. The solution decolorized with Norit was allowed to stand to effect crystallization.

Method (C).—To 20 ml. of formamide was added 2.0 g. of the crystalline sulfate of the appropriate 4,5-diaminopyrimidine. The sulfate salt was prepared in all instances by the addition of dilute sulfuric acid to an aqueous solution or suspension of the 4,5-diamine. The sulfate appeared almost immediately in most instances; however, in some cases the salt crystallized slowly only after extended cooling of the aqueous solution. The formamide solution of the 4,5-diaminopyrimidine sulfate was boiled for 20–25 minutes. In all experiments solution was effected rapidly and often precipitation of the purine occurred after 10 minutes. The solution was finally cooled, diluted with 10 ml. of water and allowed to remain overnight in the refrigerator. The crude product was removed by filtration from the neutral solution and washed with cold water. The purification of the purine derivative varied somewhat with the nature of the product. All aminopurines were isolated after boiling the crude product with dilute mineral acid in the presence of Norit. The product was isolated either as the free base by neutralizing the acidic solution with dilute ammonium hydroxide or as the hydrochloride by cooling the acidic solution. The remaining purines were recrystallized from the solvents indicated in Table I.

4,6-Diamino-5-nitropyrimidine.[22]—Twenty ml. of an ethanol solution containing 4.0 g. of 4,6-dichloro-5-nitropyrimidine[11] was added to 20 ml. of ethanol which had been saturated with dry ammonia. The reaction mixture was warmed to 60° for 5 minutes and then allowed to stand at room temperature overnight. The filtered precipitate was washed with cold water; yield 3.1 g. (97%). A small sample which was recrystallized from acetic acid for analytical purposes turned brown above 300°, but did not melt up to 360°.

Anal. Calcd. for $C_4H_5N_5O_2$: C, 31.0; H, 3.22. Found: C, 31.1; H, 3.27.

4,5,6-Triaminopyrimidine.—To 40 ml. of methanol was added 1.3 g. of 4,6-diamino-5-nitropyrimidine and 0.5 g. of Raney nickel catalyst; the solution was shaken under a hydrogen pressure of 10 lb./sq. in. for 5 hours. The hot solution was filtered and then evaporated to dryness. The residue was dissolved in 20 ml. of boiling water, and the solution decolorized with a little Norit, and set aside to crystallize. Yield of colorless needles of 4,5,6-triaminopyrimidine was 1.0 g. (95.5%), m.p. 257°.

4,5-Diamino-6-chloropyrimidine.—To 150 ml. of boiling water containing 30 g. of zinc dust was added portionwise with caution 5.0 g. of 4-amino-5-nitro-6-chloropyrimidine.[11] The solution was heated for 10–15 minutes, then filtered immediately. The hot filtrate was brought to a *p*H of 10 with concentrated ammonium hydroxide and then set aside to cool. The yield of 4,5-diamino-6-chloropyrimidine was 2.1 g. (51%) of yellow needles, m.p. 251° dec. A small amount of material was decolorized with Norit and then recrystallized from water to give colorless needles, m.p. 252° dec.

Anal. Calcd. for $C_4H_5N_4Cl$: C, 33.3; H, 3.46; N, 38.7. Found: C, 33.8; H, 3.84; N, 38.3.

Catalytic reduction of 4-amino-5-nitro-6-chloropyrimidine using Raney nickel catalyst gave only 10–15% yield of the desired product.

2-Hydroxy-4-amino-5-nitro-6-methylpyrimidine.—Six grams of 2-chloro-4-amino-5-nitro-6-methylpyrimidine[12] was added to a solution consisting of 50 ml. of glacial acetic acid, 50 ml. of water and 20 g. of sodium acetate. The solution was refluxed for 2.5 hours, cooled and filtered. The precipitate was rinsed with a little cold water, yield of a light yellow product 4.1 g. (76%), m.p. 280–285° dec.

Anal. Calcd. for $C_5H_6N_4O_3$: N, 33.0. Found: N, 33.0.

2-Hydroxy-4,5-diamino-6-methylpyrimidine.—A solution consisting of 80 ml. of methanol and 4 g. of 2-hydroxy-4-amino-5-nitro-6-methylpyrimidine in which was suspended 2–3 g. of Raney nickel catalyst was treated with hydrogen at 15 lb. pressure/sq. in. for 10 hours.

The hot solution was filtered and the insoluble residue extracted with three 200-ml. portions of boiling methanol. The methanolic solution was then concentrated to 60 ml. and allowed to cool; yield of white crystals was 3.1 g. (94%), m.p. 280° dec.

Anal. Calcd. for $C_5H_8N_4O$: N, 40.0. Found: N, 39.6.

4,5,6-Triamino-2-methylpyrimidine.—A boiling solution of 300 ml. of water and 100 ml. of ethanol containing 24 g. of 4,6-diamino-5-benzeneazo-2-methylpyrimidine[13] and 24 g. of zinc dust was stirred while 100 ml. of dilute sulfuric acid was added slowly. After all the azo compound had dissolved (5 minutes) the solution was decolorized with Norit and filtered immediately. The cooled filtrate yielded 11.0 g. (44%) of the light yellow needles of the sulfate 4,5,6-triamino-2-methylpyrimidine.

Anal. Calcd. for $C_5H_9N_5 \cdot H_2SO_4$: N, 29.5. Found: N, 29.3.

4,5-Diamino-2-methylpyrimidone-6 Sulfate.—Fifty-five grams of 2-methyl-4-aminopyrimidone-6[14] was nitrosated according to the directions of Traube.[15] The crude blue-green derivative was washed with water and then suspended in 1500 ml. of 60° water. To the solution was then added slowly with stirring sufficient sodium hydrosulfite to decolorize the product completely. An additional 40 g. of sodium hydrosulfite was then added and the solution brought to 80°, stirred with Norit and filtered. The warm filtrate was carefully acidified with dilute sulfuric acid and set aside to cool; yield 42 g. white plates (50.4% over-all). A small sample for analytical purposes was recrystallized from water.

Anal. Calcd. for $(C_5H_8N_4O)_2 \cdot H_2SO_4$: N, 29.6. Found: N, 29.4.

(20) W. Traube, *Ber.*, **33**, 1373 (1900).

(21) L. F. Cavalieri, A. Bendich, J. F. Tinker and G. B. Brown, THIS JOURNAL, **70**, 3878 (1948).

(22) This compound has been previously reported as a by-product[11] in another preparation.

2,4-Diamino-5-nitro-6-methylpyrimidine.—A solution of 15.0 g. of 2,4-dichloro-5-nitro-6-methylpyrimidine[16] in 50 ml. of ethanol was added to 150 ml. of 95% ethanol previously saturated with dry ammonia. The solution was heated to boiling while aerated with a continuous stream of ammonia for a period of one-half hour. The solution was then cooled, filtered, and the precipitate repeatedly washed with cold water to remove the ammonium chloride; yield of light tan product 10 g. (82%), m.p. 235° dec.

4-Amino-2-diethylamino-5-formylaminopyrimidine.—Eight grams of 4-amino-2-diethylamino-5-nitropyrimidine,[3] m.p. 110°, was dissolved in 100 ml. of absolute methanol, 2–3 g. of Raney nickel catalyst added and the solution hydrogenated at a pressure of 10 lb./sq. in. for 5 hours. The solution was then filtered and evaporated to dryness. To the residue was added 25 ml. of 90% formic acid and the solution refluxed gently for 15 minutes; the excess formic acid was then evaporated and the residue redissolved in 50 ml. of hot slightly ammoniacal solution. Upon cooling a crude yield of 5.1 g. of dark brown material was deposited. The crude material was then boiled with 200 ml. of water which left a small amount of dark, gummy residue; the aqueous solution was clarified by boiling with Norit. The cooled filtrate yielded 2.9 g. (36.7%) of white crystals, m.p. 175–177°. Recrystallization from ethanol–water mixture gave a product, m.p. 177–179°.

Anal. Calcd. for $C_9H_{16}N_5O$: N, 33.5. Found: N, 33.7.

CORVALLIS, OREGON

[CONTRIBUTION FROM THE CHEMICAL AND BIOCHEMICAL RESEARCH DIVISIONS OF SCHERING CORPORATION]

11-Oxygenated Steroids. I. Partial Syntheses of 11-Ketotestosterone and of Adrenosterone

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A new partial synthesis of adrenosterone is described. Adrenosterone has been converted by two independent methods to 11-ketotestosterone.

Adrenosterone (I) (Reichstein's Substance G) is one of the "inactive" companion cortical steroids which were isolated from cortical extracts by Reichstein.[1,2] No processes have been described for its preparation other than chromic acid or alkaline cleavage of the side chain of cortical steroids, which have been used to make small amounts in the process of proving their structures.[2,3]

A five-step synthesis of adrenosterone is outlined in formulas II–VI, and from I the closely related 11-ketotestosterone (VII) has been prepared for the first time. The 17-carbonyl of I has been reduced biochemically with yeast to form VII, whose structure was established by the somewhat longer independent synthesis shown in formulas VIII–XI, from V.

Pregnan-3α,17α-diol-11,20-dione (II) is available from desoxycholic acid,[4,5] and its 20-carbonyl group was hydrogenated selectively with Adams platinum catalyst in methanol to which a trace of pyridine had been added in order to inhibit the reduction of the 11-carbonyl group. The triol III was isolated only as a crude mixture which was then oxidized with lead tetraacetate in acetic acid to etiocholan-3α-ol-11,17-dione (IV).[3a] The oxidation of IV with N-bromoacetamide[6] (NBA) in aqueous acetone gave etiocholan-3,11,17-trione (V).[7] Alternately V was obtained by the reduction of II with sodium borohydride[8] to give the tetrol (IIIa), which was then cleaved at the 17-position with lead tetraacetate to etiocholan-3α,11β-diol-17-one (IVa)[9] followed by oxidation to the triketone (V) with N-bromoacetamide. Bromination of V in acetic acid followed by dehydrobromination–semicarbazone formation introduced the C-4 double bond. Adrenosterone (I) was then regenerated from its semicarbazone with pyruvic acid.[10] The over-all yield of I through II and III was 33%.

Adrenosterone was converted into 11-ketotestosterone (VII) by the highly specific yeast reduction.[11] This method of reduction attacks neither the 3-keto-Δ^4-system nor the 11-carbonyl group. The structure of VII was established by an independent synthesis.

The trione V was converted to the corresponding 3-dioxolane (VIII) by refluxing in benzene with one mole of ethylene glycol in the presence of *p*-toluenesulfonic acid. The resulting mixture of starting material, 3-dioxolane and 3,17-bisdioxolane was separated chromatographically.[12] Catalytic reduction of VIII in the presence of a trace of pyridine afforded etiocholan-17β-ol-3,11-dione 3-dioxolane (IX), which was hydrolyzed to etiocholan-17β-ol-3,11-dione (X), with an over-all yield from VIII to X of 69%. Bromination of X and dehydrobromination of the bromide (XI) gave 11-ketotestosterone (VII), identical with the product from yeast reduction of adrenosterone (I).

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(5) T. H. Kritchevsky, D. L. Garmaise and T. F. Gallagher, *ibid.*, **74**, 483 (1952).

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