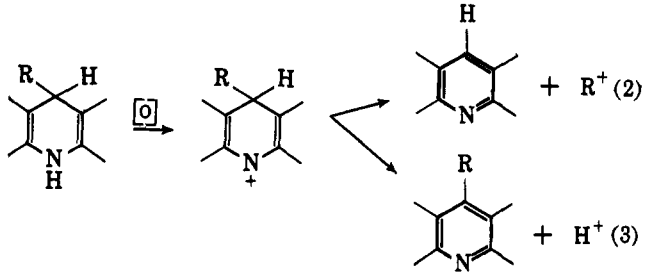
the 4-benzyl-4-isopropyl compound in the cyano series failed.

It is clear from the results described above that in the oxidation reaction the course of the reaction, *i.e.*, whether dealkylation (eq. 2) or proton loss (eq. 3) will occur, is governed both by the stability of the potential leaving carbonium ion and by steric factors, such as the size of the groups in the 3- and 5-positions (CO_2Et *vs.* CN) and the bulk of the leaving group R in the 4-position.



Experimental[9]

Synthesis of Dihydropyridines.—All of the dihydropyridines were prepared in the same manner, using the appropriate aldehyde, ammonia, and ethyl acetoacetate or aminocrotononitrile. A typical synthesis of an ester and of a nitrile is given.

4-Cyclohexenyl-3,5-dicarbethoxy-1,4-dihydrolutidine.—A solution of 22.0 g. (0.2 mole) of 3-cyclohexenecarboxaldehyde, 52.0 g. (0.4 mole) of ethyl acetoacetate, 40 ml. of ethanol, and 20 ml. (0.3 mole) of concentrated ammonium hydroxide was heated at reflux for 2 hr. The solution was cooled and poured into 500 ml. of ice–water. The oil which separated soon crystallized and was filtered to give 60.6 g. of crude product. One recrystallization from cyclohexane–hexane gave 48.8 g. (73.4% yield) of pure material, m.p. 139–140°. Attempted catalytic reduction of the cyclohexenyl ring using 0.5% palladium-on-carbon catalyst, in ethanol as the solvent, failed.

4-*t*-Butyl-3,5-dicyano-1,4-dihydrolutidine.—A mixture of 32.8 g. (0.4 mole) of *β*-aminocrotonitrile, 17.2 g. (0.2 mole) of pivaldehyde, and 100 ml. of glacial acetic acid was heated at boiling under reflux for 18 hr. The solution was chilled and the crude product was crystallized and filtered. One recrystallization from methanol gave 16.4 g. (38.2% yield) of pure product, m.p. 208–210°.

Dilution of the filtrate from the original reaction mixture with water or ether gave 4,6-dimethyl-5-cyano-2-pyridone, m.p. 300–302° dec. (from the self-condensation of *β*-aminocrotonitrile, lit.[10] m.p. 305°).

Oxidation of the Dihydropyridines.—All of the oxidations were carried out in the same manner. A typical oxidation is given.

Oxidation of 4-Benzyl-3,5-dicarbethoxy-1,4-dihydrolutidine.—To a solution of 5.0 g. (0.0146 mole) of 4-benzyl-3,5-dicarbethoxy-1,4-dihydrolutidine in 5.0 ml. of glacial acetic acid at 15–20° was added, with stirring, 5.0 g. (0.9725 mole) of sodium nitrite in small portions. When addition was complete, stirring was continued until all the brown fumes were gone. The mixture was poured into 200 ml. of ice–water. The mixture was then extracted with three 200-ml. portions of ether. The combined ether extracts were then extracted with dilute (1:3) hydrochloric acid. The combined acid extracts were neutralized with sodium bicarbonate to give a precipitate which was filtered to give 3.3 g. (90.4% yield) of pure 3,5-dicarbethoxy-2,6-dimethylpyridine, m.p. 69–71°.

The ethereal layer was washed with 5% sodium bicarbonate until neutral, then dried over magnesium sulfate, and evaporated at 100° to give a brown oil. Injection of the oil into an F and M Model 500 gas chromatograph using 3% Ucon Polar on Gas CromZ, programmed for 75 to 225°, showed the material to contain 47.3% benzaldehyde, 32.3% benzyl acetate, and 20% benzyl alcohol.

Acknowledgment.—The authors wish to thank Dr. James W. Wilson for helpful discussions.

(9) All melting points are corrected.

(10) J. Moir, *J. Chem. Soc.*, **81**, 100 (1902).

Dehydrocyclization of 4-Amino-5-arylamidopyrimidines to Purines with Polyphosphoric Acid[1a,b]

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Received November 23, 1964

Polyphosphoric acid was found to be an effective reagent for the dehydrocyclization of 4-amino-5-arylamidopyrimidines to purines. A number of 8-arylpurines were synthesized by this new procedure in high purity and yield. Cyclization to purines occurred with all pyrimidines, except in the case of 4-amino-6-mercapto-5-benzamidopyrimidine which resulted in a substituted thiazolo[5,4-*d*]pyrimidine. The ultraviolet absorption spectra of the arylamidopyrimidines and arylpurines synthesized were measured.

Several 8-arylpurines have been synthesized by cyclization of 4-amino-5-arylamidopyrimidines with phosphorus oxychloride[2,3] or phosphorus oxybromide,[2] by dry heating of the pyrimidines[2-4] and by other approaches.[2,5] However, no single method was found effective and applicable to the synthesis of all 8-arylpurines.

In conjunction with our investigation on antifolic acid agents, we found that polyphosphoric acid, which has been used previously for cyclization of other ring systems,[6] is an outstanding dehydrocyclization reagent for the formation of purines from 4-amino-5-arylamidopyrimidines. Substitutions on the C-2 and C-6 positions of the pyrimidine ring, and on the *para* position of the phenyl ring had little or no influence on cyclization. Accordingly, a number of previously

(1) (a) Presented in part before the Organic Chemistry Division, 147th National Meeting of the American Chemical Society, Philadelphia, Pa., April 1964, Abstracts of Papers, 108, p. 55N. (b) Supported in part by research grants from the National Institutes of Health, USPHS No. CY-3335 and C-6516.

(2) G. B. Elion, E. Burgi, and G. H. Hitchings, *J. Am. Chem. Soc.*, **73**, 5235 (1951).

(3) E. A. Falco, G. B. Elion, E. Burgi, and G. H. Hitchings, *ibid.*, **74**, 4897 (1952).

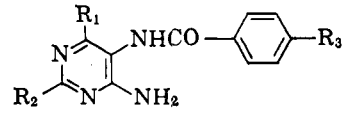
(4) A. Albert and D. J. Brown, *J. Chem. Soc.*, 2060 (1954).

(5) (a) G. M. Timmis, I. Cooke, and R. G. W. Spickett, "The Chemistry and Biology of Purines," G. E. Wolstenholme and C. M. O'Connor, Ed., Ciba Foundation Symposium, Little, Brown and Co., Boston, Mass., 1957, p. 134; (b) F. Bergmann and M. Tamari, *J. Chem. Soc.*, 4468 (1961); (c) H. Bredereck, H. G. v. Schuch, and A. Martini, *Ber.*, **83**, 201 (1950); (d) A. H. Cook and G. H. Thomas, *J. Chem. Soc.*, 1884 (1950).

(6) F. D. Popp and W. E. McEwen, *Chem. Rev.*, **58**, 321 (1958).

TABLE I

4-AMINO-5-ARYLAMIDOPYRIMIDINES

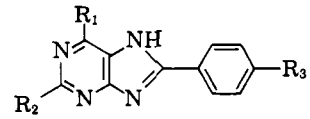


Compd.[a]	R_1	R_2	R_3	Formula	Recrystn. solvent[b]	Yield,[c] %	M.p. (dec.), °C.	R_f in solvent A	R_f in solvent B
I	CH_3	H	H	$C_{12}H_{12}N_4O$	A	41	195–196	0.65	0.86
II	H	H	H	$C_{11}H_{10}N_4O$	A	15	237–238[d]	0.51	0.86
III	NH_2	H	H	$C_{11}H_{11}N_5O \cdot 0.25H_2O$	A	32	285–286	0.50	0.68
IV	OH	CH_3	H	$C_{12}H_{12}N_4O_2$	B	52	>350	0.68	0.58
V	OH	NH_2	CH_3	$C_{12}H_{13}N_5O_2$	B	42	>350	0.49	0.45
VI	SH	SH	H	$C_{11}H_{10}N_4OS_2 \cdot 0.5H_2O$	B	52	288–290	0.62	0.48
VII	SH	H	H	$C_{11}H_{10}N_4OS$	C	61	283–286	0.41	0.22

[a] *Anal.* Calcd. for I: C, 63.1; H, 5.3; N, 24.6. Found: C, 63.1; H, 5.4; N, 24.4. *Anal.* Calcd. for II: C, 61.7; H, 4.7; N, 26.3. Found: C, 61.9; H, 4.9; N, 26.2. *Anal.* Calcd. for III: C, 56.5; H, 5.0; N, 30.0. Found: C, 56.8; H, 5.1; N, 30.1. *Anal.* Calcd. for IV: C, 59.0; H, 5.0; N, 22.9. Found: C, 59.0; H, 4.9; N, 23.1. *Anal.* Calcd. for V: C, 55.6; H, 5.1; N, 27.0. Found: C, 55.6; H, 5.1; N, 26.8. *Anal.* Calcd. for VI: C, 46.0; H, 3.9; N, 19.5. Found: C, 46.5; H, 4.0; N, 19.3. *Anal.* Calcd. for VII: C, 53.6; H, 4.1; N, 22.8; S, 13.0. Found: C, 53.1; H, 4.5; N, 22.6; S, 13.3. [b] A, water; B, 50% acetic acid; C, methyl cellosolve–ether. [c] Purified yield. [d] Reported 225°; see ref. 4.

TABLE II

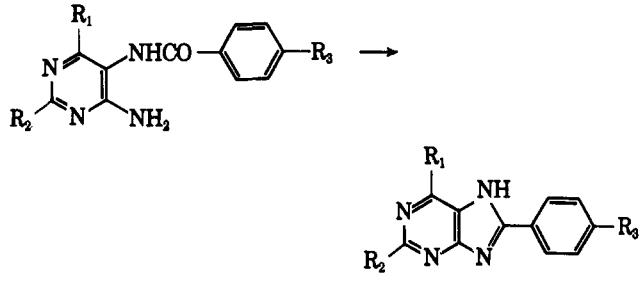
8-ARYLPURINES SYNTHESIZED BY THE POLYPHOSPHORIC ACID METHOD



Compd.[a]	R_1	R_2	R_3	Formula	Procedure	Recrystn. solvent[b]	Yield,[c] %	M.p. (dec.), °C.	R_f in solvent A	R_f in solvent B
VIII	CH_3	H	H	$C_{12}H_{10}N_4 \cdot 0.5H_2O \cdot HCl$	A	A	100	319	0.61	0.81
IX	H	H	H	$C_{11}H_8N_4$	B	D	60	264–265[d]	0.13	0.72
X	NH_2	H	H	$C_{11}H_9N_5 \cdot HCl$	A	A	94	310–311	0.46	0.70
XI	OH	CH_3	H	$C_{12}H_{10}N_4O \cdot H_2O$	B	C	54	>350	0.65	0.53
XII	OH	NH_2	CH_3	$C_{12}H_{11}N_5O \cdot HCl$	A	B	35	>350	0.27	0.38
XIII	SH	SH	H	$C_{11}H_8N_4S_2 \cdot 0.5HCl$	A	A	31	270	0.31	0.76

[a] *Anal.* Calcd. for VIII: C, 56.4; H, 4.7; Cl, 13.9; N, 21.9. Found: C, 56.8; H, 4.6; Cl, 14.4; N, 22.2. *Anal.* Calcd. for IX: C, 67.3; H, 4.1; N, 28.6. Found: C, 67.0; H, 4.0; N, 28.7. *Anal.* Calcd. for X: C, 53.3; H, 4.1; Cl, 14.3; N, 28.3. Found: C, 53.0; H, 4.3; Cl, 14.5; N, 28.2. *Anal.* Calcd. for XI: C, 59.0; H, 5.0; N, 22.9. Found: C, 58.8; H, 5.0; N, 23.1. *Anal.* Calcd. for XII: C, 51.9; H, 4.4; Cl, 12.8; N, 25.2. Found: C, 51.7; H, 4.4; Cl, 12.5; N, 25.0. *Anal.* Calcd. for XIII: C, 47.4; H, 3.1; Cl, 6.4; N, 20.1; S, 23.0. Found: C, 47.2; H, 3.3; Cl, 6.2; N, 19.9; S, 22.7. [b] A, 2 *N* hydrochloric acid; B, 1 *N* hydrochloric acid; C, 0.1 *N* hydrochloric acid; D, absolute ethanol. [c] Purified yield. [d] Melting point without decomposition; reported 261°; see ref. 4.

unknown mono- and disubstituted 8-arylpurines were prepared.



The required 4-amino-5-arylamidopyrimidines were prepared by acylation of the 4,5-diaminopyrimidines in sodium hydroxide or pyridine solutions. Wilson[7a] and others[7b,c] have demonstrated that the acylation of polyaminopyrimidines occurs on the 5-amino group. Other amino groups can be acylated but only under more drastic conditions.[7b,c] Few of the 4-amino-5-arylamidopyrimidines synthesized have actually been purified. All of the 5-arylamidopyrimidines reported here were purified and analyzed and, in the solvent systems[8] which we employed, appear as single spots on paper chromatograms; examples are given in Table I.

The cyclization of 4-amino-5-arylamidopyrimidines to 8-arylpurines is effected readily by heating a mixture of the dry pyrimidines and polyphosphoric acid to 160–170°. The 8-arylpurines are insoluble in organic solvents, but are soluble in various strengths of hydrochloric acid from which most of them crystallize as hydrochlorides. In most cases, one recrystallization suffices to give analytically pure compounds which appear as single spots on paper chromatograms and the yields range from 31 to 100%; examples are given in Table II.

A number of 8-arylpurines have been prepared by cyclization of 4-amino-5-arylamidopyrimidines with phosphorus oxychloride.[2,3] However, the phosphorus oxychloride reacting with 4-amino-6-hydroxy-5-arylamidopyrimidines caused simultaneous cyclization to 6-chloropurines and oxazolo[5,4-*d*]pyrimidines. The proportion of oxazole was found to increase if a trace

(7) (a) W. Wilson, *J. Chem. Soc.*, 1157 (1948); (b) D. J. Brown, "Heterocyclic Compounds, The Pyrimidines," Interscience Publishers, Inc., Division of John Wiley and Sons, Inc., New York, N. Y., 1962, p. 324; (c) A. P Phillips and J. Mentha, *J. Am. Chem. Soc.*, **76**, 6200 (1954).

(8) The presence of an amino, methyl, or hydrogen substituent at the 6-position of the pyrimidines considerably increases the solubility in water from which these arylamidopyrimidines were recrystallized.

TABLE III

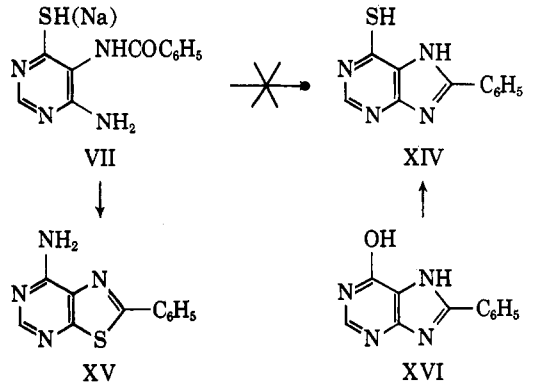
ULTRAVIOLET ABSORPTION SPECTRA OF 4-AMINO-5-ARYLAMIDOPYRIMIDINES AND OF 8-ARYLPURINES

Compd.	R_1	R_2	R_3	0.1 N HCl λ_{max}, mμ	0.1 N HCl ϵ_{max}	0.1 N NaCl λ_{max}, mμ	0.1 N NaCl ϵ_{max}	0.1 N NaOH λ_{max}, mμ	0.1 N NaOH ϵ_{max}
I	CH_3	H	H	235	17,400	229	18,250	231	12,900
						275	7,150	291	10,450
II	H	H	H	234	16,250	228	17,900	230[a]	12,800
				267.5[a]	10,500	280	7,050	285	9,100
III	NH_2	H	H	218	33,100	257[a]	10,400	270	9,500
				264	13,200				
IV	OH	CH_3	H	231[b]	10,800			259[a]	7,700
				258[b]	12,400				
V	OH	NH_2	CH_3	247[a]	20,300	242	17,000	241	18,000
				263	23,100	266	18,100	262[a]	13,600
VI	SH	SH	H	215	19,900	225	23,300	222	27,000
				285.5	27,000	262	21,000	269.5	26,500
				329	20,800	320	15,500	319	11,900
VII	SH	H	H		[c]			224.5	23,900
								245[a]	18,200
								292	13,000
VIII	CH_3	H	H	236	16,800	231	13,900	233	19,100
				301	27,100	292.5	26,800	304	27,400
						297.5	26,800	318[a]	16,200
						312[a]	13,000		
IX[d]	H	H	H	236	13,400	232	12,000	233	18,000
				302.5	24,100	298	25,300	304	26,400
						311[a]	16,600	318[a]	16,800
X	NH_2	H	H	232	14,200	234	19,600	238	20,400
				293	25,400	294	21,400	302.5	22,000
				299.5	25,000				
XI	OH	CH_3	H	233	12,300	236	17,000	237	19,900
				288	21,600	294.5	21,600	304	20,680
XII	OH	NH_2	CH_3	254	15,750	231	11,800	241	17,500
				308	19,600	254	13,350	317	17,350
						307	18,000		
XIII	SH	SH	H	220[b]	23,400			249[a]	12,300
				265[b]	6,100			344	17,300
				333[b]	26,300				
				352[a,b]	17,100				
XIV	SH	H	H	350[b]	20,700			223[a]	15,600
								258	18,600
								339	18,600

[a] Shoulder. [b] In 2 N hydrochloric acid. [c] Unstable. [d] Absorptions at pH 0, 5.40, and 10.28 were reported. See ref. 10.

amount of water was present in the reaction mixture.[8] The dehydrocyclization of 4-amino-5-arylamidopyrimidines with polyphosphoric acid, on the other hand, produced exclusively the 8-arylpurines. The only exception was the dehydrocyclization of 4-amino-6-mercapto-5-benzamidopyrimidine. The resulting products dissolved completely in alkali, demonstrating the absence of oxazolo[5,4-*d*]pyrimidines in the case of the 6-hydroxy-substituted pyrimidines[2,3] or thiazolo[5,4-*d*]pyrimidines in the case of the 6-mercapto-substituted compounds.[9] Furthermore, the ultraviolet absorption spectra and other physical properties are characteristic of the purine ring system.[10,11]

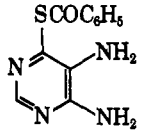
Cyclization of 4-amino-6-mercapto-5-benzamidopyrimidine (VII) gave a product insoluble in alkali, which indicates that the compound isolated was not a purine but the isomeric 2-phenyl-7-aminothiazolo[5,4-*d*]pyrimidine (XV), formed by cyclization through the mercapto group. A better yield of the thiazole was obtained in attempts to cyclize the sodium salt of the pyrimidine with polyphosphoric acid, analogous to the thermal cyclization of the sodium salt of 4-amino-6-mercapto-5-formamidopyrimidine to purine.[12] The expected product, 6-mercapto-8-phenylpurine (XIV) was synthesized by an independent method by thiation of 6-hydroxy-8-phenylpurine (XVI). The infrared and ultraviolet spectra of the thiazole are entirely different from those of the purine which is soluble in alkali.



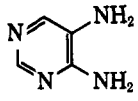
The anomalous cyclization of 4-amino-6-mercapto-5-benzamidopyrimidine to XV seemed to indicate that

(8) H. C. Koppel and R. K. Robins, *J. Org. Chem.*, **23**, 1457 (1958).
(9) S. F. Mason, *J. Chem. Soc.*, 2071 (1954).
(10) S. F. Mason, ref. 5a, p. 60.
(12) G. B. Elion and G. H. Hitchings, *J. Am. Chem. Soc.*, **76**, 4027 (1954).

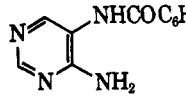
the benzoylation of 4,5-diamino-6-mercaptopyrimidine could have taken place at the mercapto group, forming 4,5-diamino-6-benzoylthiopyrimidine (XVII) analogous to the formation of 2-methyl-4-amino-6-benzoylthiopyrimidine.[13] The structure of the benzoylated pyrimidine was thus determined by dethiation with nickel catalyst.[14] If the product of benzoylation were indeed 4,5-diamino-6-benzoylthiopyrimidine (XVII), de-



XVII



XVIII



II

thiation should give 4,5-diaminopyrimidine (XVIII), while 4-amino-5-benzamidopyrimidine (II) should be obtained from 4-amino-6-mercapto-5-benzamidopyrimidine (VII). The dethiation gave a crystalline compound having m.p. 238–239° dec., identical with that of 4-amino-5-benzamidopyrimidine and not depressed on mixing with the authentic sample. Furthermore, the elementary analyses and infrared spectra of this compound were identical with those of 4-amino-5-benzamidopyrimidine (II). Therefore, the benzoylation of 4,5-diamino-6-mercaptopyrimidine took place at the 5-amino group with formation of 4-amino-6-mercapto-5-benzamidopyrimidine (VII). Cyclization through the mercapto group is known to occur with other 4-amino-5-amido-6-mercaptopyrimidines.[9,15] However, the cyclization of 2,6-dimercapto-4-amino-5-benzamidopyrimidine (VI) with polyphosphoric acid, reported here, and the thermal cyclization of 2,6-dimercapto-4-amino-5-formamidopyrimidine[16] formed purines exclusively.

The quantitative ultraviolet absorption spectra of both the pyrimidines and purines synthesized were measured in acidic, neutral, and basic solutions of constant ionic strength. In the absence of characteristic melting points, the absorption spectra of purines are invaluable for their identification (see Table III).

Experimental[17a,b]

4-Amino-5-arylamidopyrimidines. General Method.—To a vigorously stirred solution or suspension of 5 g. of 4,5-diaminopyrimidine or its salt in 2 molar equiv. of 1 *N* sodium hydroxide at 0°, an equimolar quantity of benzoyl chloride was added dropwise over a period of 1 hr. The mixture was then stirred continuously for an additional 0.5 hr. and the pH of the solution was kept at 10–11 by dropwise addition of 1 *N* sodium hydroxide solution. The reaction mixture was then acidified with 6 *N* hydrochloric acid to pH 5. After cooling at 4° for a few hours, the precipitate was filtered and washed thoroughly with cold water and ether. Purification was effected by recrystallization from an appropriate solvent.

4-Amino-6-methyl-5-benzamidopyrimidine (I).—This compound was prepared according to the general method. The solution, after acidification to pH 5, was evaporated to dryness *in vacuo* and the residue was extracted with boiling ethanol. Upon addition of ether, the benzamidopyrimidine was deposited. Concentration of the ethanol–ether filtrate gave an additional yield of the pyrimidine.

4-Amino-5-benzamidopyrimidine (II).—This compound was prepared by condensation of benzoyl chloride with 4,5-diaminopyrimidine in dry pyridine, essentially according to the procedure of Albert and Brown.[4]

The by-product, **4,5-dibenzamidopyrimidine**,[4] upon recrystallization from 25% acetic acid, deposited brown crystalline plates: m.p. 179–180° (lit.[4] 179°); $\lambda_{max}^{0.1\ N\ HCl}$ 230 mμ (ϵ_{max} 21,300) and 287 (11,400), $\lambda_{max}^{0.1\ N\ NaCl}$ 230 mμ (ϵ_{max} 23,000) and 266 (12,200), and $\lambda_{max}^{0.1\ N\ NaOH}$ 226 mμ (ϵ_{max} 21,000) and 289 (14,000).

2,6-Dimercapto-4-amino-5-benzamidopyrimidine (VI).—This compound was prepared according to the general method. At the end of the reaction, the solution was diluted with an equal volume of water and then acidified to pH 5. The precipitate was recrystallized from 50% acetic acid. Upon concentration of the acetic acid filtrate an additional yield was obtained.

Dethiation of 4-amino-6-mercapto-5-benzamidopyrimidine.—A solution of 0.8 g. of 4-amino-6-mercapto-5-benzamidopyrimidine in 50 ml. of 2 *N* ammonium hydroxide and 8 g. of Davison sponge nickel (grade 986)[14] was refluxed with continuous stirring for 1.5 hr. At the end of this period, the nickel was filtered and washed with 20 ml. of hot water. The combined filtrate and washings on cooling deposited 0.2 g. of white crystals, m.p. 238–239° dec. A mixture melting point determination with an authentic sample of 4-amino-5-benzamidopyrimidine showed no depression.

Anal. Calcd. for $C_{11}H_{10}N_4O$: C, 61.7; H, 4.7; N, 26.2. Found: C, 61.6; H, 4.7; N, 26.4.

8-Arylpurines. General Method.—The purines were prepared by two procedures which differed only in the manner of isolating the crude product. The reaction mixtures were protected from moisture during the reaction by means of a calcium chloride drying tube. The detailed description of the procedures are given below.

Procedure A.—To a mixture of 3 g. of dry 4-amino-5-arylamidopyrimidine and 25 g. of phosphorus pentoxide, cooled to 0°, 18 ml. of 85% phosphoric acid was added. The mixture was then heated to 160–170° and stirred for 1.5 hr. By this time, the slowly dissolving amidopyrimidine had gone into solution. After cooling to room temperature, the thick sirup was poured onto crushed ice with vigorous stirring. After standing at 4° for 18 hr., the precipitate was filtered and washed thoroughly with water and ether. The crude product was recrystallized from an appropriate solvent.

Procedure B.—The reaction was carried out as in procedure A, except that the purine, which was soluble in the aqueous solution, was precipitated by treatment with 6 *N* sodium hydroxide solution to pH 5. The product was isolated by cooling first to room temperature, and then at 4° for 18 hr. The filtered crude product was thoroughly washed with water and ether, and recrystallized.

6-Mercapto-8-phenylpurine (XIV).—A mixture of 1.5 g. of 6-hydroxy-8-phenylpurine, 6 g. of phosphorus pentasulfide, and4 5 ml. of dry pyridine was refluxed under anhydrous conditions for 3.5 hr. The pyridine was removed *in vacuo*, 60 ml. of water was added to the residue, and the mixture was boiled for 15 min. After cooling at 4° for 18 hr., the precipitate was filtered and washed thoroughly with cold water. The crude product, 1.3 g., was recrystallized from 300 ml. of 2 *N* hydrochloric acid to deposit 0.52 g. (33.5%) of yellow crystals. The compound turned black at 280° and would not melt above this temperature.

Anal. Calcd. for $C_{11}H_8N_4S$: C, 57.9; H, 3.5; N, 24.5; S, 14.0. Found: C, 57.8; H, 3.6; N, 24.3; S, 14.1.

2-Phenyl-7-aminothiazolo[5,4-*d*]pyrimidine (XV). **A. From 4-Amino-6-mercapto-5-benzamidopyrimidine.**—This compound was prepared from 1.7 g. of 4-amino-6-mercapto-5-benzamidopyrimidine, 14 g. of phosphorus pentoxide, and 10 ml. of 85% phosphoric acid by a method similar to procedure A for the preparation of purines. The crude material, weighing 1.5 g., was recrystallized first from 1200 ml. of 2 *N* hydrochloric acid and then from 300 ml. of 2 *N* hydrochloric acid to give 0.9 g. (57%): m.p. 260–262°; $\lambda_{max}^{0.1\ N\ HCl}$ 219.5 mμ (ϵ_{max} 19,400), 232 (shoulder)

(13) *Cf.* ref. 7b, p. 286.

(14) H. N. Schlein, M. Israel, S. Chatterjee, and E. J. Modest, *Chem. Ind.* (London), 418 (1964).

(15) (a) D. J. Brown, ref. 5a, p. 50; (b) G. B. Elion, W. H. Lange, and G. H. Hitchings, *J. Am. Chem. Soc.*, **78**, 2858 (1956).

(16) (a) K. L. Dille and B. E. Christensen, *ibid.*, **76**, 5087 (1954); (b) A. G. Beaman, *ibid.*, **76**, 5633 (1954).

(17) (a) All melting points are corrected. The yields given are the purified compounds. The elementary analyses were performed by Dr. C. K. Fitz, Needham Heights, Mass. (b) We acknowledge the generous samples of 6-hydroxy-2,4,5-triaminopyrimidine sulfate and phosphorus pentasulfide from the Takeda Pharmaceutical Co., Japan, and Monsanto Chemical Co., respectively.

(16,400), 302 (16,200), 317.5 (shoulder) (14,300), and 336 (shoulder) (7200).

Anal. Calcd. for $C_{11}H_8N_4S$: C, 57.9; H, 3.5; N, 24.5; S, 14.0. Found: C, 58.3; H, 3.2; N, 24.2; S, 14.2.

B. From the Sodium Salt of 4-Amino-6-mercapto-5-benzamidopyrimidine.–4-Amino-6-mercapto-5-benzamidopyrimidine (3 g.) was dissolved in 32 ml. of 0.5 *N* sodium hydroxide and the solution was evaporated to dryness *in vacuo*. The residue was mixed with 25 g. of phosphorus pentoxide and to this mixture, cooled to 0°, 18 ml. of 85% phosphoric acid was added. The mixture was heated to 160–170° and stirred for 1.5 hr. After cooling to room temperature, the sirup was poured over crushed ice and the precipitate was collected after cooling at 4° for 18 hr. This crude material, weighing 2.6 g., was extracted with 150 ml. of 2 *N* sodium hydroxide, which upon acidification to pH 5 with glacial acetic acid deposited 0.3 g. of a yellow solid. It was not 6-mercapto-8-phenylpurine as shown by comparison of its ultraviolet and infrared spectra with those of an authentic sample. The residue left from the extraction, weighing 2 g., was recrystallized with the help of Darco from 600 ml. of 2 *N* hydrochloric acid to deposit 2 g. (61.9%) of light yellow needles, m.p. 272–273° dec.

Anal. Calcd. for $C_{11}H_8N_4S \cdot HCl$: C, 49.9; H, 3.4; Cl, 13.4; N, 21.2; S, 12.1. Found: C, 50.0; H, 3.3; Cl, 13.2; N, 21.4; S, 11.9.

Neutralization of this compound with 1 *N* sodium hydroxide gave a product which was identical with the one obtained in A.

Ultraviolet Absorption Spectra.—The quantitative ultraviolet absorption spectra of both the pyrimidines and purines synthesized were measured at 0.1 *N* hydrochloric acid, 0.1 *N* sodium chloride (by neutralization of equal volumes of 0.1 *N* HCl and 0.1 *N* NaOH solutions), and 0.1 *N* sodium hydroxide. A Cary Model 11 spectrophotometer, employing 1-cm. silica cells, was used.

Infrared Absorption Spectra.—The infrared absorption spectra of the various compounds were determined in the solid state in potassium bromide disks, using a Perkin-Elmer Model 137B spectrophotometer.

Paper Chromatography.—The R_f values of both the pyrimidines and purines were determined by ascending paper chromatography using Whatman No. 1 paper. The solvents used were methanol–concentrated hydrochloric acid–water (70:20:10, v./v.; solvent A) and *n*-butylalcohol–2 *N* ammonium hydroxide–ethanol (20:5:2, v./v.; solvent B).

Synthesis and Properties of α-Aminothiol Esters[1,2]

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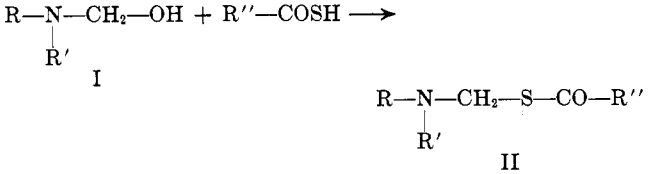
Received December 24, 1964

Acetate esters of one aromatic and five aliphatic α-aminothiols and the benzoate esters of two of these were synthesized by condensation of the appropriate dialkylaminomethanol and thiolcarboxylic acid in the presence of potassium carbonate. The reaction appears to have considerable generality. All of the α-aminothiol esters were found to undergo rearrangement on heating to the corresponding N,N-disubstituted amide and (poly)-thioformaldehyde. Hydrolysis of diethylaminomethanethiol acetate in dilute hydrochloric acid gave diethylaminomethanethiol hydrochloride, accompanied by diethylamine hydrochloride, while basic hydrolysis gave diethylamine, thioformaldehyde, and acetate, accompanied by some diethylacetamide.

Esters of aliphatic α-aminothiols have not been previously described[3] although an ester of an aromatic α-aminothiol is known, the adduct of benzalanthranilic acid and thiolacetic acid.[5] We were interested in this class of compounds for possible antioxidant and anti-radiation drug activity, and as possible synthetic precursors for α-aminothiols.

The synthesis of α-aminothiol esters was accomplished by the reaction of dialkylaminomethanols (I) with thiolcarboxylic acids in the presence of potassium carbonate. The dialkylaminomethanols were



prepared *in situ* from formaldehyde and dialkylamines, and the method is analogous to the synthesis of α-aminosulfides from I and mercaptans and thiophenols[6–8] and to the only reported synthesis of α-aminothiols,[4] employing the reaction of I with hydrogen sulfide. Unfortunately the scope of the latter reaction seems to be very limited.[4,9]

This synthesis of α-aminothiol esters has been successful in each case taken where the amino group is tertiary, as listed in Table I. It is of interest that the diethylamino and dimethylamino derivatives IIa and IIb were obtained in moderate yields, since attempted synthesis of the corresponding α-aminothiols was unsuccessful.[4] The synthesis was successful also for diisopropylaminomethanethiol acetate (IIc) indicating that steric hindrance in the amine is not a serious factor. The method is capable of extension to arylamino derivatives, as shown by the formation of N-methylanilinomethanethiol acetate (IIh), but it is not practical for monoalkylaminomethanethiol esters, *e.g.*, IIi, due to predominance of polymer formation.

Except in this last case, purification of the products was achieved by low-pressure distillation or by crystallization, as shown in Table III. In some cases difficulty was encountered from the tendency to undergo a rearrangement which is described below, and it was generally best to carry out the distillation quickly and at as low a temperature as possible without use of a fractionating column. Because of its high boiling point, diethylaminomethanethiol benzoate (IIc) could

(1) Presented at the Kansas City Chemistry Conference, Kansas City, Mo., Nov. 20, 1964.

(2) This work was supported by National Institutes of Health Grant RN-00300-02 and U. S. Army Medical Command Contract MD-2026.

(3) Since this work was completed, E. E. Smissman and J. R. J. Sorenson [*J. Org. Chem.*, **30**, 300 (1965)] of the University of Kansas synthesized 1-piperidinemethanethiol acetate and benzoate by acylation of 1-piperidinemethanethiol[4] with the corresponding thiolcarboxylic acid. We thank Dr. Smissman for advising us of this work before it was published.

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(5) G. W. Stacy and R. J. Morath, *ibid.*, **74**, 3885 (1952).

(6) C. M. McLeod and G. M. Robinson, *J. Chem. Soc.*, **119**, 1470 (1921).

(7) G. F. Grillot, H. R. Felton, B. R. Garrett, H. Greenburg, R. Green, R. Clementi, and M. Moskowitz, *J. Am. Chem. Soc.*, **76**, 3969 (1954).

(8) G. F. Grillot and R. E. Schaffraht, *J. Org. Chem.*, **24**, 1035 (1959).

(9) Unpublished experiments in this laboratory.