hydroxy-6-mercaptopurine-2-sulfonic acid sodium salt prepared by another method.[13]

2,8-Dihydroxy-6-purinethiol (VI).[13,14] Twenty grams of 8-hydroxy-6-mercaptopurine-2-sulfonic acid sodium salt (V) was added to 220 ml. of concd. hydrochloric acid and 1500 ml. of water. The solution was refluxed for 4 hr. during which time the solid dissolved, and gradually the product crystallized from the hot solution. The solution was then filtered hot and the product washed with water. The yield of pure 2,8-dihydroxy-6-purinethiol was 11.2 g. The ultraviolet absorption spectrum of this compound was found to be essentially in agreement with that previously recorded.[13,14] $\lambda_{max}^{pH\ 1}$ 259, 358 mμ, ε 7,400, 30,200; $\lambda_{max}^{pH\ 11}$ 235, 346 mμ, ε 16,700; 21,700.

Anal. Calcd. for $C_5H_4N_4O_2S \cdot H_2O$: N, 27.7. Found: N, 27.8.

6-Chloro-2,8-dihydroxypurine (III). Two grams of 2,8-dihydroxy-6-purinethiol (VI) was added to 50 ml. of methanol-hydrochloric acid solution (see preparation of VII) and the solution cooled to 0° and stirred vigorously with a magnetic stirrer. Chlorine was carefully bubbled into the reaction mixture so that the temperature was kept below 5°. After approximately 5 min. all the solid was in solution, and the reaction was stopped (continued chlorination resulted in further oxidation of the desired product).

The reaction mixture was poured onto ice and the solution adjusted to *p*H 14 with concentrated aqueous ammonia. A precipitate of white needles of the ammonium salt of 6-chloro-2,8-dihydroxypurine gradually appeared in the solution. This product was filtered and dried to yield 1.6 g. The ammonium salt was dissolved in 100 ml. of boiling water and the solution acidified with hydrochloric acid and cooled to yield 1.1 g. of 6-chloro-2,8-dihydroxypurine (III). The product was recrystallized from water for final purification to give white crystals which gradually decomposed above 200° without melting. An attempt to convert the compound into an anhydrous product at 130° resulted in considerable decomposition.

Anal. Calcd. for $C_5H_3N_4ClO_2 \cdot H_2O$: C, 29.3; H, 2.4; N, 27.3. Found: C, 29.4; H, 2.5; N, 27.1.

8-Chloro-6-hydroxypurine (XIV). To 100 ml. of methanol-hydrochloric acid solution (see preparation of VII) was added 14.5 g. of 6-hydroxy-8-purinethiol hydrate (XIII).[4] The solution was cooled to 10° and chlorine passed into the reaction mixture for 40 min. until the reaction mass became too solid to stir. The crude product was added to ice and the solution made basic with concd. aqueous ammonia and finally acidified to *p*H 1 with hydrochloric acid. The solution was cooled and filtered, and the crude product was washed with water. 8-Chloro-6-hydroxypurine (XIV) was purified by reprecipitation from hot, dilute sodium hydroxide by the addition of acetic acid to yield 8.1 g. The ultraviolet absorption spectrum of the product was identical with that previously reported[4] for 8-chloro-6-hydroxypurine (XIV).

2-Chloro-6,8-dihydroxypurine (XII). Two grams of 2,8-dichloro-6-hydroxypurine (XI) was added to 100 ml. of concd. hydrochloric acid, and the mixture was heated for 2 hr. on the steam bath. The cooled solution was filtered and the product washed with distilled water. The crude product was added to 200 ml. of boiling water, and just enough potassium hydroxide was added to effect solution. The solution was treated with charcoal and boiled gently for 5 min. and filtered. The hot filtrate was acidified with hydrochloric acid and allowed to cool. The white crystals which slowly formed were filtered and washed with distilled water and dried at 110° to yield 1.1 g.

Anal. Calcd. for $C_5H_3N_4O_2Cl$: C, 32.1; H, 1.6; N, 30.0. Found: C, 32.0; H, 1.7; N, 29.5.

TEMPE, ARIZ.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF BUFFALO]

Pyrazolono(3,4-d)pyrimidines. II. 6-Methylpyrazolono(3,4-d)pyrimidines and Some Reactions of Pyrazolono(3,4-d)pyrimidines[1,2]

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6-Methylpyrazolono(3,4-d)pyrimidines have been synthesized from 2-methyl-4-chloro-5-carbethoxypyrimidine and hydrazines. Several reactions of 6-methylthiopyrazolono(3,4-d)pyrimidines, including oxidation, hydrolysis, amination, chlorination, and alkoxylation, are described.

In the preceding paper in this series,[5] the preparation of several 4-substituted hydrazinopyrimidines and 6-methylthiopyrazolono(3,4-d)pyrimidines by the reaction of 2-methylthio-4-chloro-5-carbethoxypyrimidine (I) with substituted-hydrazines was described. The present paper discusses the reactions of 2-methyl-4-chloro-5-carbethoxypyrimidine (II)[6] with several of the same hydrazines and some reactions of 6-methylthiopyrazolono(3,4-d)pyrimidines.

When II was treated with *p*-bromophenyl- and *p*-carboxyphenylhydrazine, the corresponding pyrazolono(3,4-d)pyrimidines (XIII and XIV) were obtained directly. These results are identical with those obtained with I.

Treatment of II with methylhydrazine led to isolation of a low-melting solid which on heating in water gave 1,6-dimethylpyrazolono(3,4-d)-

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(2) In part from a dissertation submitted by Martin Hauser to the Graduate School of Arts and Sciences, the University of Buffalo, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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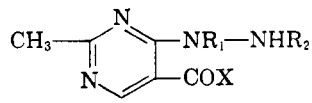
(5) M. Hauser, E. Peters, and H. Tieckelmann, *J. Org. Chem.*, 25, 1570 (1960).

(6) E. Peters, H. J. Minnemeyer, A. W. Spears, and H. Tieckelmann, *J. Org. Chem.*, 25, 2137 (1960).

TABLE I

2-METHYL-4-HYDRAZINO-5-SUBSTITUTED PYRIMIDINES



Compound	R_1	R_2	X	M.P.[13]	Yield, %	Formula	Calcd. / Found C	H	N
III	H	H	OC_2H_5	82–84	62	$C_6H_{12}N_4O_2$	48.97	6.17	28.55
							49.06	6.20	28.37
IV	H	H	OH	340 dec.	80	$C_6H_8N_4O_2$	42.85	4.80	33.32
							42.48	5.02	33.38
V	H	H	$NHNH_2$	205–207 dec.	61	$C_6H_{10}N_6O$	39.55	5.54	46.13
							39.84	6.09	46.43
VI	H	2-CH_3-5-$COOC_2H_5$-4-C_4N_2H	OC_2H_5	214–215	89	$C_{16}H_{20}N_6O_4$	53.32	5.59	23.32
							53.12	5.71	23.16
VII	H	C_6H_5	OC_2H_5	182–184	37	$C_{14}H_{16}N_4O_2$	61.75	5.92	20.58
							61.98	6.35	20.60
VIII	H	C_6H_5	$NHNHC_6H_5$	295–296	26	$C_{18}H_{18}N_6O$	64.65	5.43	25.14
							64.89	4.91	25.48
IX	CH_3	H	OC_2H_5	—	—	$C_9H_{14}N_4O_2$	—	—	—
							—	—	—

pyrimidine (XI). Attempts to purify this material by ordinary recrystallization procedures were unsuccessful, due to its conversion to XI. However, the similarity of the infrared spectrum of this material to that of the previously described 2-methylthio-4-(1-methylhydrazino)-5-carbethoxypyrimidine[5] and its cyclization to the pyrazolonopyrimidine (XI) indicate that the low melting solid was 2-methyl-4-(1-methylhydrazino)-5-carbethoxypyrimidine (IX). Attempts to prepare solid hydrazones of IX also failed. The hydrazones formed from aliphatic aldehydes in the cold were oils. Aromatic aldehydes did not react at room temperature.

Phenylhydrazine and II did not give the expected pyrazolonopyrimidine, but rather a mixture of 2-methyl-4-(2-phenylhydrazino)-5-carbethoxypyrimidine (VII) and 2-methyl-4-(2-phenylhydrazino)-5-pyrimidine-(2-phenylcarboxhydrazide)(VIII). VII, on heating in base, gave the pyrazolonopyrimidine (XII).

The reactions of II with various mole ratios of hydrazine gave several products. With two parts of hydrazine to one part of pyrimidine, the product isolated was the bipyrimidylhydrazine (VI). As the ratio was increased, the hydrazinopyrimidine (III) was obtained and at 4:1 was the only product. At higher ratios, mixtures of III and the hydrazinocarboxhydrazide (V) were obtained and at even higher ratios (6:1 and above) only V was isolated.

Treatment of III with base led to 6-methylpyrazolono(3,4-d)pyrimidine (X). However, hydrolysis of V with base did not give the pyrazolonopyrimidine (X), but 2-methyl-4-hydrazino-5-pyrimidinecarboxylic acid (IV). This indicates that ring closure of 4-hydrazino-5-carbethoxypyrimidines with base does not proceed through saponification, formation of the free acid on neutralization and cyclization of the 4-hydrazino-5-pyrimidinecarboxylic acids.

The position of the substituents in these compounds was established by methods previously described. The infrared spectrum of IX showed a medium absorption band at about 1640 $cm.^{-1}$ usually attributed to a free amino group.[7] This band was absent in the spectra of VII and VIII, but present with III–V. III–V gave a positive test for a free amino group with sodium pentacyanoammineferroate,[8] while VII and VIII were negative with this reagent. Therefore, the reaction of II with methylhydrazine leads to a 1-substituted hydrazinopyrimidine, while II gives 2-substituted hydrazinopyrimidines with arylhydrazines.

Two previously prepared compounds, 1-methyl-6-methylthiopyrazolono(3,4-d)pyrimidine (XV) and 6-methylthiopyrazolono(3,4-d)pyrimidine (XVI),[5] were used to study reactions of the pyrazolonopyrimidines. Oxidation of XV in dilute hydrochloric acid solution at 0° with chlorine water gave the 6-methylsulfonylpyrazolono(3,4-d)pyrimidine (XVII). XVII was then hydrolyzed to the corresponding 6-hydroxypyrazolonopyrimidine (XVIII), and was treated with ammonia and alkylamines to give 6-substituted aminopyrazolonopyrimidines (XIX–XXI).

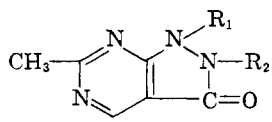
Attempts to oxidize XVI with chlorine water led to destruction of the pyrazole ring even at temperatures as low as −20°. The products isolated were 5-uracilcarboxylic acid or esters of 5-uracil-

(7) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, New York (1958), pp. 255–256.

(8) F. Feigl, V. Anger, and O. Frehden, *Mikrochemie*, **15**, 184 (1934). F. Feigl, *Spot Tests in Organic Analysis*, Elsevier Publishing Company, New York (1956), p. 292.

TABLE II

1- OR 2-SUBSTITUTED 6-METHYLPYRAZOLONO(3,4-d)PYRIMIDINES



Compound	R_1	R_2	M.P.[13]	Yield, %	Formula	Calcd. / Found C	H	N
X	H	H	340 dec.	88	$C_6H_6N_4O$	47.99	4.04	37.31
						47.93	4.55	36.86
XI	CH_3	H	236–237	59	$C_7H_8N_4O$	51.21	4.91	34.12
						51.06	5.45	33.85
XII	H	C_6H_5	345 dec.	63	$C_{12}H_{10}N_4O$	63.72	4.45	24.77
						63.66	4.90	24.74
XIII	H	C_6H_4-Br-*p*	360 dec.	78	$C_{12}H_9BrN_4O$	47.23	2.97	18.36
						47.66	2.78	18.33
XIV	H	C_6H_4-COOH-*p*	395 dec.	88	$C_{13}H_{10}N_4O_3$	57.78	3.73	20.73
						57.73	3.65	20.59

carboxylic acid depending upon whether dilute hydrochloric acid or alcohols were used as slurrying media.

The lack of carbonyl activity in the infrared spectra of XV, XVI, and XIX indicated that the 3-keto was primarily in the enol form.[9] When these three compounds were treated with phosphorus oxychloride, the 3-chloro analogs, XXII–XXIV, respectively, were readily obtained. However, all attempts to replace these chlorine atoms with various nucleophiles were unsuccessful, the chlorine proving totally resistant to nucleophilic displacement.

When XXIV was heated for 48 hours at 200° in a steel bomb with ethanolic ammonia, the starting material was recovered. A similar result was obtained with sodamide in liquid ammonia. The chloro compound was again unchanged after heating XXII for 96 hours at 150° with ethanolic ammonia in a sealed tube, but there was some replacement of the methylthio group (about 25%) to give XXIV. Treatment of XXII with sodamide in liquid ammonia gave a 78% conversion to XXIV.

XV, the precursor of XXII, did not undergo this reaction, indicating that replacement of the 3-hydroxy with chloro had activated the 6-position toward nucleophilic displacements. When XXII was treated with sodium hydroxide and sodium ethoxide, the corresponding 6-hydroxy- (XXV) and 6-ethoxy- (XXVI) pyrazolonopyrimidines were formed. XV reacted with neither of these reagents. XXIII, while showing the same resistance to replacement of the 3-chlorine, did not undergo these replacement reactions at the 6-position.

The unreactivity to replacement of the chlorine in XXII–XXIV was not wholly unexpected. The chlorine atoms in 3-chloropyrazoles and in the isomeric 8-chloropurines are generally quite unreactive to nucleophilic displacement. Only in the case where there is a strong electron-withdrawing group at the 4-position of the pyrazole does the chlorine show some reactivity, and the pyrimidine ring cannot be considered such a group.[10]

Evaluation of the anti-tumor effects of a number of the compounds reported in this and the preceding paper[5] was carried out at the Roswell Park Memorial Institute, Buffalo, N. Y. The results were generally negative.[11]

EXPERIMENTAL[12]

2-Aryl-6-methylpyrazolono(3,4-d)pyrimidines (XIII *and* XIV). *General method.* A solution of 2.0 g. (0.01 mole) of II in 20 ml. of absolute alcohol was added to a solution of 0.02 mole of the arylhydrazine in the minimum amount of absolute alcohol. The resulting solution was warmed at 60° for 45 min. and allowed to stand 4 hr. at room temperature, diluted with three times its volume of water and refrigerated overnight at 1°. The precipitate was filtered, washed with water and recrystallized from *n*-butyl alcohol.

2-Methyl-4-(1-methylhydrazino)-5-carbethoxypyrimidine (IX). A solution of 0.92 g. (0.02 mole) of methylhydrazine in 10 ml. of absolute alcohol at 15° was added slowly to a solution of 2.0 g. (0.01 mole) of II in 30 ml. of absolute alcohol at 15°. The resulting solution was held at about 15° for 1 hr. and the alcohol then evaporated in a stream of dry air to leave an oily, yellow solid.

1,6-Dimethylpyrazolono(3,4-d)pyrimidine (XI). The residue in the above preparation was dissolved in 25 ml. of water and the solution boiled for 15 min. The precipitate which formed on overnight refrigeration was filtered and recrystallized from alcohol.

(9) For purposes of convenience, Table III represents all compounds in the enolic form, although in the discussion and experimental those pyrazolonopyrimidines not containing a 3-chloro atom are treated as the ketonic forms.

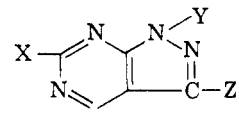
(10) R. C. Elderfield, *Heterocyclic Compounds*, Vol. V, John Wiley and Sons, New York (1957), pp. 102–103.

(11) E. Mihich, personal communication.

(12) Melting points are uncorrected. Analyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn.; and Geller Microanalytical Laboratories, Bardonia, N. Y.

TABLE III

1,3,6-TRISUBSTITUTED PYRAZOLO(3,4-d)PYRIMIDINES



Compound	X	Y	Z	M.P.[13]	Yield, %	Formula	Calcd. / Found C	H	N	Cl
XVII	SO_2CH_3	CH_3	OH	210–212 dec.	71	$C_7H_8N_4O_3S$	36.84	3.53	24.56	—
							36.86	3.55	24.55	—
XVIII	OH	CH_3	OH	350–352 dec.	90	$C_6H_6N_4O_2$	43.38	3.64	33.72	—
							43.23	3.91	33.71	—
XIX	NH_2	CH_3	OH	330 dec.	85	$C_6H_7N_5O$	43.63	4.27	42.41	—
							43.94	4.67	42.73	—
XX	$NHCH_3$	CH_3	OH	259–260	92	$C_7H_9N_5O$	46.92	5.06	39.09	—
							46.75	5.10	39.10	—
XXI	NHC_2H_5	CH_3	OH	255–256	74	$C_8H_{11}N_5O$	49.73	5.74	36.25	—
							49.62	5.84	36.59	—
XXII	SCH_3	CH_3	Cl	104–105	66	$C_7H_7ClN_4S$	39.16	3.29	—	16.52
							39.35	3.43	—	16.32
XXIII	SCH_3	H	Cl	234–235	82	$C_6H_5ClN_4S$	35.91	2.51	—	17.67
							36.08	2.35	—	17.68
XXIV	NH_2	CH_3	Cl	230–231	72	$C_6H_6ClN_5$	39.25	3.29	—	19.31
							39.49	3.37	—	19.20
XXV	OH	CH_3	Cl	320 dec.	71	$C_6H_5ClN_4O$	39.04	2.73	—	19.21
							38.82	2.59	—	19.28
XXVI	OC_2H_5	CH_3	Cl	67–69	66	$C_8H_9ClN_4O$	45.18	4.28	—	16.68
							44.87	4.88	—	16.27

2-Methyl-4-(2-phenylhydrazino)-5-carbethoxypyrimidine (VII). A solution of 3.2 g. (0.030 mole) of phenylhydrazine in 25 ml. of absolute alcohol was added to a solution of 30 g. (0.015 mole) of II in 25 ml. of absolute alcohol. After standing at room temperature, the precipitate was filtered, washed with water and stirred 15 min. with 25 ml. of 10% potassium hydroxide. The solution was filtered and the insoluble residue washed with water and recrystallized from *n*-butyl alcohol.

2-Methyl-4-(2-phenylhydrazino)-5-pyrimidine-(2-phenylcarboxhydrazide) (VIII). The alkaline filtrate from the previous experiment was acidified with 25% acetic acid; the precipitate was filtered, washed with water and recrystallized from alcohol.

2-Phenyl-6-methylpyrazolono(3,4-d)pyrimidine (XII). Compound VII (0.075 g., 0.0027 mole) was added to 10 ml. of boiling 10% potassium hydroxide. Boiling was continued until solution was complete. The solution was cooled, acidified with 25% acetic acid; the precipitate was filtered, washed with water and recrystallized from alcohol.

1,2-Bis(2-methyl-5-carbethoxy-4-pyrimidyl)hydrazine (VI). Solutions of 2.0 g. (0.010 mole) of II in 10 ml. of absolute alcohol and 0.65 g. (0.020 mole) of hydrazine in 10 ml. of absolute alcohol were mixed and allowed to stand 2 hr. at room temperature. The alcohol was evaporated in a stream of dry air and the residue washed with water and recrystallized from *n*-butyl alcohol.

2-Methyl-4-hydrazino-5-carbethoxypyrimidine (III). A solution of 0.24 g. (0.0075 mole) of hydrazine in 5 ml. of absolute alcohol was added to a solution of 0.50 g. (0.0025 mole) of II in 10 ml. of absolute alcohol at 15°. The temperature was maintained at about 15° for 30 min. After standing 12 hr. at room temperature, the alcohol was evaporated and the residue was treated with 25 ml. of boiling water. The insoluble material (VI, 0.04 g., 5%) was filtered and the filtrate chilled overnight at 1°. The precipitate which formed on cooling was recrystallized from water (yield of III, 0.31 g., 62%).

2-Methyl-4-hydrazino-5-pyrimidinecarboxhydrazide (V). A solution of 0.40 g. (0.0125 mole) of hydrazine in 5 ml. of absolute alcohol at 15° was added to a solution of 0.50 g. (0.0025 mole) of II in 10 ml. of absolute alcohol at 15°. The resulting solution was allowed to stand at 15° for 30 min. and overnight at room temperature. The alcohol was evaporated and the residue treated with 10 ml. of hot benzene. The insoluble material was filtered and the benzene evaporated to give 0.24 g. (48%) of III. The benzene-insoluble material was recrystallized from alcohol (yield of V, 0.07 g., 16%).

2-Methyl-4-hydrazino-5-pyrimidinecarboxylic acid (IV). A solution of 0.50 g. (0.0027 mole) of V in 10 ml. of 10% potassium hydroxide was boiled for 10 min., cooled, and acidified with 25% acetic acid. The precipitate was filtered and recrystallized from water.

6-Methylpyrazolono(3,4-d)pyrimidine (X). A solution of 0.30 g. (0.0015 mole) of III in 10 ml. of 5% potassium hydroxide was boiled for 15 min., cooled, and acidified with 25% acetic acid; then refrigerated overnight at 1°. The precipitate was filtered, washed with ice water and recrystallized from water.

1-Methyl-6-methylsulfonylpyrazolono(3,4-d)pyrimidine (XVII). A solution of 2.0 g. (0.010 mole) of XV in 150 ml. of 5% hydrochloric acid was cooled to 1° and dry chlorine gas bubbled through for 10 min. A yellow precipitate formed. To the cold solution was then added, with agitation, 3.5 g. of sodium bisulfite. The precipitate was filtered, washed ice water and recrystallized from dry isopropyl alcohol.

1-Methyl-6-substituted aminopyrazolono(3,4-d)pyrimidines (XIX–XXI). *General method.* A mixture of 0.5 g. (0.0022 mole) of XVII, 5 ml. of amine, and 50 ml. of dry *n*-butyl alcohol in a sealed tube was heated 6 hr. at 140°. After evaporation of the solvent, the residue was washed with water and recrystallized (XIX from *n*-butyl alcohol; XX–XXI from alcohol-water).

1-Methyl-6-hydroxypyrazolono(3,4-d)pyrimidine (XVIII). *A. Acidic hydrolysis.* A solution of 1.0 g. (0.0044 mole) of XVII in 10 ml. of concd. hydrochloric acid was evaporated to dryness on the steam bath and the residue recrystallized from water (90%).

B. Basic hydrolysis. A solution of 1.0 g. (0.0044 mole) of

XVII in 10 ml. of 10% sodium hydroxide was refluxed 10 min., cooled, acidified with 25% acetic acid, and chilled overnight at 1°. The precipitate was filtered, washed with ice water and recrystallized from water (76%).

1,6-Disubstituted-3-chloropyrazolo(3,4-d)pyrimidines (XXII–XXIV). *General method.* Two grams of 1,6-disubstituted-pyrazolono(3,4-d)pyrimidine and 30 ml. of phosphorus oxychloride were heated for 6 hr. at 140° in a sealed tube. The solution was added slowly to 300 g. of cracked ice, cooled, and made basic with concd. ammonium hydroxide. The precipitate was filtered and washed with water. XXII was recrystallized from alcohol-water; XXIII and XXIV were purified by sublimation at 175°/15 mm.

Preparation of XXIV *from* XXII. Ferric nitrate (0.1 g.) and 1.0 g. (0.043 mole) of sodium were added to 100 ml. of vigorously stirred liquid ammonia. After 10 min., 2.0 g. (0.0095 mole) of XXII was added and stirring continued for 90 min. The ammonia was allowed to evaporate and 100 ml. of water was added to the residue. After filtering, the water-insoluble material was washed with water and sublimed at 175°/15 mm. The yield by this method was 70% as compared to 72% by the preceding method.

1-Methyl-3-chloro-6-ethoxypyrazolo(3,4-d)pyrimidine (XXVI). One gram (0.043 mole) of sodium was added to 150 ml. of absolute alcohol. After solution had taken place, 1.0 g. (0.0043 mole) of XXII was added and the solution then refluxed for 2 hr. After diluting with 150 ml. of water, the solution was neutralized with 5% hydrochloric acid and the solvent evaporated in a stream of dry air. The residue was stirred with 75 ml. of water and the water-insoluble material recrystallized from ligroin (b.p. 30–60°).

1-Methyl-3-chloro-6-hydroxypyrazolo(3,4-d)pyrimidine (XXV). One gram (0.0043 mole) of XXII and 25 ml. of 10% potassium hydroxide were refluxed for 2 hr. The solution was cooled and acidified with 25% acetic acid. The precipitate was filtered, washed with ice-water and recrystallized from water.

Oxidation of XVI. *A. Hydrochloric acid slurry.* A slurry of 2.0 g. (0.011 mole) of XVI in 150 ml. of 10% hydrochloric acid was cooled to 0° and dry chlorine gas bubbled through for 30 min., at which time solution was complete. To the cold solution was added 10.5 g. of sodium bisulfite and the solution concentrated to 25 ml. on the steam bath. After chilling overnight at 1°, the precipitate was filtered, washed with water and recrystallized from alcohol to give 0.95 g. (55%) of solid identical with (ultraviolet, infrared) an authentic sample of 5-uracilcarboxylic acid.[12]

B. Ethyl alcohol slurry. A slurry of 1.0 g. (0.0055 mole) of XVI in 100 ml. of alcohol was cooled to −20° and dry chlorine gas bubbled through until solution was complete (20 min.). The solution was concentrated to 15 ml. by boiling and chilled several hours at 1°. The precipitate was recrystallized from alcohol to give 0.65 g. (65%) of solid identical with (ultraviolet, infrared, mixed melting point) an authentic sample of 5-carbethoxyuracil.[12]

C. n-Butyl alcohol slurry. A slurry of 2.0 g. (0.11 mole) of XVI in 150 ml. of *n*-butyl alcohol was cooled to −20° and dry chlorine gas bubbled through until solution was complete (30 min.). The solution was concentrated to 20 ml. and chilled overnight at 1°. The precipitate was recrystallized from *n*-butyl alcohol to give 1.4 g. (62%) of 5-carbutoxyuracil; m.p. 237–239°. Saponification of this material gave a solid identical with 5-uracilcarboxylic acid.[12]

Anal. Calcd. for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.66; N, 13.21. Found: C, 50.91; H, 5.63; N, 13.01.

BUFFALO 14, N. Y.

[CONTRIBUTION FROM THE ORGANIC CHEMISTRY DEPARTMENT, RESEARCH DIVISION, ABBOTT LABORATORIES]

Heterocyclic Compounds Containing Adjacent Nitro and Guanidino Groups. A Novel Rearrangement of 4-Amino-5-nitro-6-guanidino-(and 6-ureido)pyrimidine

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5-Guanidino-1-methyl-4-nitroimidazole (V) has been prepared by reaction of the corresponding 5-chloro compound (III) with guanidine. Treatment of V with aqueous alkali under the conditions of the Arndt benzotriazine 1-oxide synthesis[1] results only in fragmentation of the imidazole ring. Subjection of either 4-amino-6-guanidino-5-nitropyrimidine (XII) or the corresponding 6-ureido compound (XX) to either aqueous acid or alkali produces a novel rearrangement in which the pyrimidine ring has been opened at position 2, a carbon atom lost as formic acid, followed by ring closure onto the guanidino or ureido group to form a 2,4,6-trisubstituted 5-nitropyrimidine. The various products of this rearrangement have also been synthesized for comparison purposes by direct nitration of the appropriate pyrimidine. A ring-opened intermediate in this rearrangement, 3-guanidino-3-imino-2-nitropropionamide (XVII), has been isolated and characterized, and converted to 2,4-diamino-6-hydroxy-5-nitropyrimidine (XVIII) by base catalyzed ring closure. The guanidinium salt has proven to be a useful derivative for the isolation of cyanonitroacetamide (fulminuric acid) (XXV) because of the rather low water solubility of this salt and the ease of regeneration of the free acid.

The base-catalyzed cyclization of *o*-nitrophenylguanidine (I, Y = NH) to form 3-amino-1,2,4-benzotriazine 1-oxide (II, Y = NH) is a well-known reaction,[1] which has been extended by several groups of workers to include various compounds substituted on the benzene nucleus.[1,2] Early work in this field[1b] also showed that *o*-nitrophenylurea (I, Y = O) and *o*-nitrophenylthiourea (I, Y = S) were converted by aqueous alkali to 3-hydroxy-1,2,4-benzotriazine 1-oxide (II, Y = O) and 3-mercapto-1,2,4-benzotriazine 1-oxide (II, Y = S) respectively.

(1) (a) F. Arndt, *Ber.*, 46, 3522 (1913); (b) F. Arndt and B. Rosenau, *Ber.*, 50, 1248 (1917); (c) J. G. Erickson, P. F. Wiley, and V. P. Wystrach, *The 1,2,3- and 1,2,4-Triazines, Tetrazines, and Pentazines*, Interscience Publishers, Inc., New York, N. Y., 1956, p. 44.

(2) F. J. Wolf and K. Pfister III, *J. Am. Chem. Soc.*, 76, 3551, 4611 (1954); J. Jiu and G. P. Mueller, *J. Org. Chem.*, 24, 813 (1959).