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.

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[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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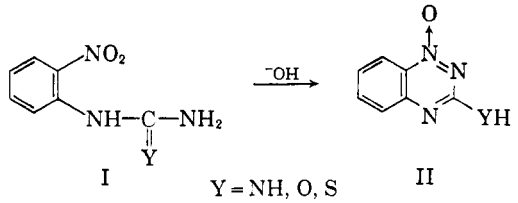
5-Guanidino-1-methyl-4-nitroimidazole (V) has been prepared by reaction of the corresponding 5-chloro compound (III) with guanidine. Treatment of V with aqueous alkali under the conditions of the Arndt benzotriazine 1-oxide synthesis[1] results only in fragmentation of the imidazole ring. Subjection 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).



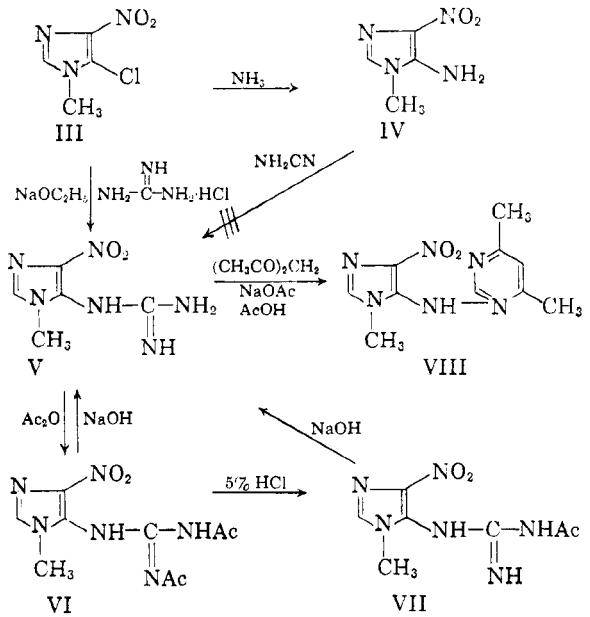

An application of the above reaction to heterocyclic compounds containing nitro groups adjacent to guanidino, ureido, or thioureido functions (such as V, XII, and XX) could conceivably give rise to hetero-condensed 1,2,4-triazines of novel ring structure and of potential value as purine or pteridine antimetabolites. This possibility has also been discussed in a recent thesis.[3] We have prepared three such compounds substituted with adjacent nitro and guanidino or urea groups, 5-guanidino-1-methyl-4-nitroimidazole (V), 4-amino-6-guanidino-5-nitropyrimidine (XII) and the corresponding urea derivative (XX), and we have investigated their behavior under the above described cyclizing conditions.

The usual conditions for the formation of *o*-nitrophenylguanidines, *i.e.*, the condensation of substituted *o*-nitroanilines with cyanamide in acidic media, were unsuccessful when applied to 5-amino-1-methyl-4-nitroimidazole (IV),[4] probably because of the very low basicity of the amino group in IV. This compound (IV) was also inert to thiocyanic acid, cyanic acid, and molten urea.

The readily available material, 5-chloro-1-methyl-4-nitroimidazole (III),[5] proved to be a suitable intermediate for the synthesis of the guanidino compound (V). Treatment of III with a solution of guanidine in ethanol (prepared by the addition of guanidine hydrochloride to ethanolic sodium ethoxide) gave an excellent yield of 5-guanidino-1-methyl-4-nitroimidazole (V).[6] This proved to be a reasonably stable substance which could be recrystallized from water to obtain the bright yellow monohydrate, and which formed a stable monohydrochloride salt. However, it soon became apparent that cyclization using aqueous alkali would be quite impractical, as the guanidino compound (V) appeared to be unstable in warm alkaline solution, decomposing to ammonia, sodium oxalate, and oxides of nitrogen. Similarly, treatment of V with either ethanolic sodium ethoxide or anhydrous sodium acetate in acetic acid under reflux resulted only in degradation of the molecule. Sodium amide in liquid ammonia or in diethylene glycol dimethyl ether at 100° were without effect on V.

With acetic anhydride in the presence of anhydrous sodium acetate, compound V was converted to the diacetyl derivative (VI), without formation of cyclized compounds. The use of anhydrous sodium acetate in this reaction was later found to be unnecessary. The diacetyl compound (VI) was hydrolyzed to a monoacetyl derivative (VII) by short treatment with 5% hydrochloric acid, while the free 5-guanidino-1-methyl-4-nitro-imidazole (V) could be regenerated in high yield simply by allowing either the mono- or diacetyl derivative to stand in dilute alkali at room temperature for a short time.

The well-known reaction of β-diketo compounds with substituted guanidines to form derivatives of 2-aminopyrimidine[7] was applicable with limited success to V. For example, reaction with 2,4-pentanedione in acetic acid containing anhydrous sodium acetate gave a moderate yield of the expected pyrimidine, 4,6-dimethyl-2-(1′-methyl-4′-nitro-5′-imidazoyl)aminopyrimidine (VIII). However, we were unable to effect a condensation of V with either ethyl malonate or ethyl acetoacetate under these conditions or in ethanolic sodium ethoxide.




In contrast to the results obtained above, the reaction of 4,6-dichloro-5-nitropyrimidine (IX)[8] with guanidine in ethanol (guanidine hydrochloride in ethanolic sodium ethoxide) gave only the ether, 4,6-diethoxy-5-nitropyrimidine (X).[9] However, the substitution of the chlorine atom in 4-amino-6-

(3) H. M. Taylor, Ph.D. Thesis, Univ. of N. Carolina, 1958, University Microfilms Mic 59-5587, Ann Arbor, Mich.

(4) I. E. Balaban, *J. Chem. Soc.*, 268 (1930).

(5) J. Sarasin and E. Wegmann, *Helv. Chim. Acta*, **7**, 713 (1924).

(6) It is of interest that the isomeric compound, 4-chloro-1-methyl-5-nitroimidazole (ref. 5), could not be converted to the corresponding 4-guanidino derivative using this method.

(7) G. W. Kenner and Sir A. Todd, "Pyrimidine and its Derivatives," in R. C. Elderfield, *Heterocyclic Compounds*, John Wiley and Sons, New York, N. Y., Vol. 6, p. 234 (1957).

(8) W. R. Boon, W. G. M. Jones, and G. R. Ramage, *J. Chem. Soc.*, 96 (1951).

(9) Similar results have recently been described (see Ref. 3) for the reaction of IX with guanidine hydrochloride in the presence of methanolic sodium methoxide.

chloro-5-nitropyrimidine (XI)[8,10] by the guanidino group proceeded normally under the same conditions to give a 78% yield of the desired 4-amino-6-guanidino-5-nitropyrimidine (XII), along with a very small quantity of the ether, 4-amino-6-ethoxy-5-nitro-pyrimidine (XIII).

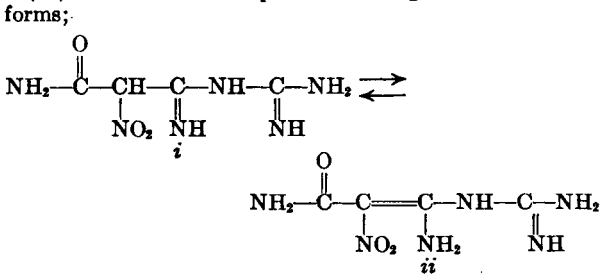
The chemistry of this guanidino pyrimidine (XII) has proved to be fairly complex. For example, simple treatment with refluxing aqueous hydrochloric acid gives at least three compounds, which arise by ring opening and loss of the carbon atom at position 2, followed by ring closure onto the guanidino group to form another pyrimidine. The first of these compounds, a base-soluble crystalline solid which precipitated from the hot acid solution of XII, gave a satisfactory elemental analysis for $C_4H_5N_5O_3$. This material, which appeared to be a diaminohydroxynitro-pyrimidine, was subsequently identified as 2,4-diamino-6-hydroxy-5-nitropyrimidine (XVIII) by comparison with a known sample. A second compound ($C_4H_9ClN_6O_3$), which precipitated from the cooled reaction mixture, was undoubtedly a hydrochloride salt (XV), as treatment with aqueous ammonia converted it to $C_4H_8N_6O_3$. The structure of the latter material is most likely 3-guanidino-3-imino-2-nitropropionamide (XVII) or its tautomer.[11] Although this material (XVII) was stable and insoluble in aqueous ammonia, it quickly dissolved in aqueous sodium hydroxide. Acidification of the solution thus obtained gave a precipitate of 2,4-diamino-6-hydroxy-5-nitropyrimidine (XVIII), identical in all respects with a known sample. A third, acid-soluble compound ($C_4H_6N_6O_2$) was subsequently identified as 5-nitro-2,4,6-triaminopyrimidine (XVI)[12] by comparison of the infrared spectrum with that of an authentic sample. Ring-closure of the hypothetical intermediate, XIV, could easily account for the presence of XVI in the reaction mixture.

The various 5-nitropyrimidines required for comparison purposes in the course of this work were synthesized by the direct nitration of the appropriate pyrimidine in concentrated sulfuric acid at 30–35°. The best results were obtained by dissolving the pyrimidine compound in concentrated sulfuric acid at room temperature, followed by a slow addition of fuming nitric acid (sp. gr. 1.49–1.50) with careful temperature control. The use of the reverse procedure as recommended by Gabriel[12] for the nitration of 2,4,6-triaminopyrimidine,[13] *i.e.*, addition of the compound to nitric acid followed by addition of sulfuric acid, gave highly colored products which were difficult to purify. In fact, the nitration of 2,4,6-triaminopyrimidine by the latter procedure gave 4,6-diamino-2-hydroxy-5-nitro-pyrimidine (XXI) as the sole product.

The products obtained from aqueous alkali treatment of the guanidino compound (XII) were found to depend markedly on the strength of the alkali employed. Treatment with 35% aqueous sodium hydroxide at 100° for only five minutes resulted in complete destruction of the starting material, along with formation of the rearranged product, 2,4,6-triamino-5-nitropyrimidine (XVI). A long period of heating (thirty-five minutes) re-

(10) S. M. Greenberg, L. O. Ross, and R. K. Robins, *J. Org. Chem.*, **24**, 1314 (1959); H. Segal and D. Shapiro, *J. Med. Pharm. Chem.*, **1**, 371 (1959).

(11) This material is capable of existing in two tautomeric forms;



*i* *ii*

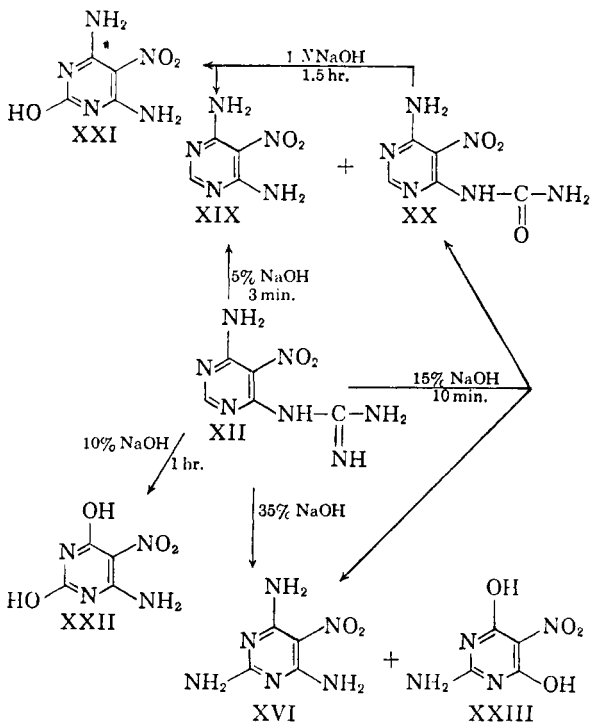
however we have not determined which of these is the correct structure. The carbonyl absorption in the infrared falls exactly on 6.0 $\mu$, a fact which seems to favor structure *i*, since the conjugated carbonyl in *ii* might be expected to absorb at slightly higher wave lengths.

(12) S. Gabriel, *Ber.*, **34**, 3362 (1901).

(13) W. Traube, *Ber.*, **37**, 4544 (1904).

sulted in partial hydrolysis of the amino groups[14] in XVI to form 2-amino-4,6-dihydroxy-5-nitropyrimidine (XXIII).[15] On the other hand, the action of more dilute alkali (5% sodium hydroxide) on XII gives only the normal hydrolysis products, 4-amino-5-nitro-6-ureidopyrimidine (XX) and 4,6-diamino-5-nitropyrimidine (XIX).

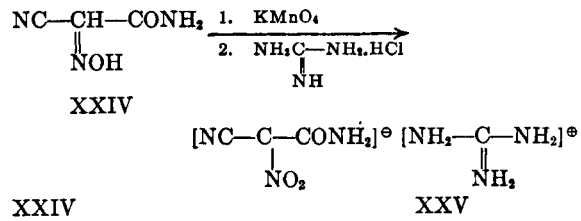
A careful examination of the mixture obtained by the treatment of XII with 15% aqueous sodium hydroxide (100° for ten minutes) revealed at least three compounds. Only one of these was alkali insoluble, and was shown to be the rearranged product, 5-nitro-2,4,6-triaminopyrimidine (XVI). The alkali soluble material proved to be a mixture of at least two compounds. One of these was identified as the urea derivative (XX) (insoluble in *N*,*N*-dimethylformamide), while the other fraction (soluble) has not been identified. 4-Amino-5-nitro-6-ureidopyrimidine (XX), when subjected to further alkali treatment (1*N* sodium hydroxide for an hour and a half), partially rearranges to form 4,6-diamino-2-hydroxy-5-nitropyrimidine (XXI), while the remainder is simply hydrolyzed to form 4,6-diamino-5-nitropyrimidine (XIX).




No compounds containing the pyrimido[4,5-e]-*as*-triazine nucleus could be isolated from the alkaline treatment of XII or XX. Apparently the extremely facile ring opening of these compounds occurs before the slower intramolecular reaction to form the triazine ring can take place.

As it was noticed that 4-amino-6-guanidino-5-nitropyrimidine (XII) decomposed at approximately 220° with gas evolution and formation of a solid sublimate, the possibility of thermal cyclization of XII was investigated. However, the thermal decomposition of a sample of XII gave only a 40% yield of 4,6-diamino-5-nitropyrimidine (XIX).

The ring opened intermediate, 3-guanidino-3-imino-2-nitropropionamide (XVII), could conceivably be prepared by the addition of guanidine to the nitrile group in fulminuric acid (cyanonitroacetamide).[16] Although we were not successful in carrying out this conversion, we have discovered that the introduction of guanidine hydrochloride into the aqueous solution of potassium fulminurate obtained by permanganate oxidation of cyanoisonitrosoacetamide (XXIV),[16] results in the separation of the sparingly soluble salt, guanidinium fulminurate (XXV). Furthermore, free fulminuric acid, normally obtained by rather tedious methods,[17] is easily isolated merely by adding the guanidinium salt to concentrated hydrochloric acid, in which the free acid is quite insoluble, although it is extremely soluble in water.




The investigation of other heterocyclic systems substituted with adjacent nitro and guanidino functions is now in progress and will be reported at a later date.

## EXPERIMENTAL[18]

*5-Guanidino-1-methyl-4-nitroimidazole* (V). To a solution of sodium ethoxide, prepared by dissolving 2.42 g. (0.105 g.-atom) of sodium in 200 ml. of absolute ethanol, was added 10.0 g. (0.105 mole) of guanidine hydrochloride. After stirring for 5 min., 5-chloro-1-methyl-4-nitroimidazole (III)[5] (8.08 g., 0.050 mole) was added, and the bright yellow mixture was refluxed with stirring for 5 hr. The product was filtered with suction and recrystallized from water to obtain

(14) The ready hydrolysis of amino groups in the 2-, 4-, or 6-positions of 5-nitropyrimidines has been observed previously. For examples, see W. J. Hale and H. C. Brill, *J. Am. Chem. Soc.*, **34**, 82 (1912), and R. O. Roblin, Jr., P. S. Winnek, and J. P. English, *J. Am. Chem. Soc.*, **64**, 567 (1942).

In another experiment, in which XII was heated with 10% aqueous sodium hydroxide on the steam bath for 1.25 hr., the only isolable product was identified as 6-amino-5-nitrouracil (XXII), which probably was formed by hydrolysis of either compound XVI or XXI. This compound was identified by comparison with a known sample [P. Bitterli and H. Erlenmeyer, *Helv. Chim. Acta.*, **34**, 835 (1951)].

(15) W. Traube, *Ber.*, **26**, 2551 (1893).

(16) M. Conrad and A. Schulze, *Ber.*, **42**, 735 (1909).

(17) J. Liebig, *Ann.*, **95**, 282 (1855); L. Schischkoff, *Ann.*, **97**, 53 (1856); H. B. Hill and W. J. Hale, *Am. Chem. J.*, **29**, 253 (1903).

(18) The melting points are uncorrected and were taken on a Fisher-Johns melting point apparatus unless stated otherwise in the Experimental.

8.6 g. (85%) of the *monohydrate* of V as bright yellow needles, m.p. 240–241.5° dec. An analytical sample, prepared by recrystallization from water, was obtained as yellow needles, m.p. 244–245° dec.

*Anal.* Calcd. for $C_5H_8N_6O_2.H_2O$: C, 29.70; H, 4.99; N, 41.57. Found: C, 29.67; H, 5.17; N, 41.93.

The anhydrous material could be obtained by heating overnight in a vacuum oven at 100°, or by heating to 150–160° for 15 min.

*Anal.* Calcd. for $C_5H_8N_6O_2$: C, 32.60; H, 4.38; N, 45.63. Found: C, 32.68; H, 4.54; N, 45.76.

This compound was insoluble in cold aqueous alkali, but dissolved instantly in dilute hydrochloric acid to form a colorless solution, from which the bright yellow base was precipitated unchanged upon neutralization. The *monohydrochloride* salt was prepared by suspending in ethanol and adding an excess of concd. hydrochloric acid. The clear solution thus formed deposited colorless crystals on cooling, which were purified for analysis by recrystallization from ethanol containing a few drops of hydrochloric acid. The colorless prisms thus obtained decomposed slowly above 210°.

*Anal.* Calcd. for $C_5H_9ClN_6O_2$: C, 27.22; H, 4.11; Cl, 16.07; N, 38.10. Found: C, 27.35; H, 4.17; Cl, 15.91; N, 38.06.

*Diacetyl 5-guanidino-1-methyl-4-nitroimidazole* (VI). One gram (0.005 mole) of 5-guanidino-1-methyl-4-nitroimidazole (V) was mixed with 15 ml. of acetic anhydride and refluxed for 1 hr. The resulting pale yellow solution was evaporated to dryness *in vacuo* to leave a syrup which crystallized when triturated with ethanol. The crude product weighed 0.87 g. (65%), m.p. 210–211°. An analytical sample was obtained as bright yellow prisms from water, m.p. 212–213°.

*Anal.* Calcd. for $C_9H_{12}N_6O_4$: C, 40.30; H, 4.51; N, 31.34. Found: C, 39.98; H, 4.64; N, 31.15.

The *monoacetyl derivative* of V was readily obtained by heating the above diacetate in 5% aqueous hydrochloric acid on the steam bath for 15 min. Upon neutralizing to *p*H 7 and cooling, the *monoacetate* was obtained as a cream-colored powder, m.p. 270–272° dec.

*Anal.* Calcd. for $C_7H_{10}N_6O_3$: C, 37.17; H, 4.46; N, 37.16; O, 21.21. Found: C, 37.76; H, 5.12; N, 36.73; O, 21.08.

Compound V was regenerated with ease when either the mono- or diacetyl derivative was allowed to stand at room temperature in dilute alkaline solution for 0.5 hr.

*4,6-Dimethyl-2-(1'-methyl-4'-nitro-5'-imidazoyl)aminopyrimidine* (*VIII*). A mixture of 9.2 g. (0.050 mole) of anhydrous 5-guanidino-1-methyl-4-nitroimidazole (V), 5.5 g. (0.055 mole) of 2,4-pentanedione, 4.5 g. (0.055 mole) of anhydrous sodium acetate, and 80 ml. glacial acetic acid was heated under reflux for 1 hr. The brown solution was evaporated to dryness *in vacuo*, 100 ml. water added, and the yellow solid isolated by suction filtration. Recrystallization from ethanol gave 6.0 g. (48%) of yellow needles, m.p., 230–231°.

*Anal.* Calcd. for $C_{10}H_{12}N_6O_2$: C, 48.38; H, 4.87; N, 33.85. Found: C, 48.16; H, 5.03; N, 34.00.

The aqueous filtrate from the above reaction was made basic with aqueous sodium hydroxide to give 2.6 g. (26% recovery) of the starting material monohydrate (V), identified by mixed melting point and infrared spectra.

*Attempted base-catalyzed ring closure of* V. One gram of 5-guanidino-1-methyl-4-nitroimidazole (V) was added to a solution of 5.0 g. of sodium hydroxide in 10 ml. of water, and heated on the steam bath for 10 min. Ammonia was copiously evolved during this period. The reaction mixture, containing a white solid, was treated with 15 ml. of ethanol, cooled, and filtered with suction. The colorless powder thus obtained was purified by dissolving in a little warm water and adding three volumes of ethanol to obtain a finely divided colorless solid, m.p. >400°. This material was identified as *sodium oxalate* by comparison of the infrared spectra with that of an authentic sample.

Attempts to carry out the desired ring closure using more dilute solutions of sodium hydroxide gave similar results. The treatment of V with sodium amide in liquid ammonia or in diethylene glycol dimethyl ether at 100° gave only recovered starting material.

*4,6-Diethoxy-5-nitropyrimidine* (X). To a solution prepared by dissolving 0.92 g. (0.040 g.-atom) of sodium in 80 ml. of absolute ethanol was added 3.82 g. (0.040 mole) of guanidine hydrochloride. The mixture was stirred at room temperature for 5 min. and, finally, 3.88 g. (0.020 mole) of 4,6-dichloro-5-nitropyrimidine (IX)[8] was added in one portion. The temperature rose spontaneously to 50–55°. Stirring was continued until the mixture had returned to room temperature (about 0.5 hr.). The ethanol was removed *in vacuo*, and the brown residue stirred with 40 ml. of water. The brown solid thus obtained was recrystallized first from 60% ethanol, and, finally, from petroleum ether (b.p. 60–70°) to obtain 1.5 g. (35%) of colorless, flattened needles, m.p. 61.5–62.0°.

*Anal.* Calcd. for $C_8H_{11}N_3O_4$: C, 45.07; H, 5.20; N, 19.71. Found: C, 45.42; H, 5.44; N, 19.70.

*4-Amino-6-guanidino-5-nitropyrimidine* (XII). Sodium metal (1.15 g., 0.050 g.-atom) was dissolved in 100 ml. of absolute ethanol, and 4.78 g. (0.050 mole) of guanidine hydrochloride was added. The mixture was stirred for about 5 min., 4.32 g. (0.0248 mole) of 4-amino-6-chloro-5-nitropyrimidine (XI)[8,10] added, and the resulting mixture was refluxed for 1 hr. The bright yellow suspension was filtered with suction, and the solid washed by suspension in 60 ml. of warm water and filtering. The bright yellow solid thus obtained weighed 3.8 g. (78%), m.p., 221–222° dec. The melting point was unchanged by recrystallization of the product from methyl cellosolve–water. Analysis of material dried in a vacuum desiccator for 24 hr. indicated the product to be a hemihydrate.

*Anal.* Calcd. for $C_5H_7N_7O_2.{}^1/_2\ H_2O$: C, 29.12; H, 3.91; N, 47.55. Found: C, 29.29; H, 4.25; N, 47.42.

The anhydrous material was obtained by drying a sample overnight at 100° *in vacuo*.

*Anal.* Calcd. for $C_5H_7N_7O_2$: C, 30.45; H, 3.58; N, 49.72. Found: C, 30.75; H, 3.83; N, 49.70.

The ethanolic mother liquor from the above reaction was evaporated to dryness *in vacuo*, 50 ml. water added to the residue, and the insoluble material isolated by filtration. This substance (0.5 g.) was purified by sublimation at 160–170° and 0.2 mm., to obtain 0.2 g. of colorless crystals, m.p. 178.5–180°. One recrystallization from ethanol gave colorless needles, m.p. 180.0–180.5°. Analysis indicated this material to be *4-amino-6-ethoxy-5-nitropyrimidine* (XIII).

*Anal.* Calcd. for $C_6H_8N_4O_3$: C, 39.12; H, 4.38; N, 30.42. Found: C, 39.00; H, 4.39; N, 30.49.

The *monohydrochloride salt* of XII was prepared by suspending 0.50 g. of 4-amino-6-guanidino-5-nitropyrimidine (XII) in 15 ml. of water and adding 10% hydrochloric acid until the mixture was acidic to Congo Red. The bright yellow starting material changed immediately to a colorless solid of different crystal form. The suspension was heated to dissolve the solid, filtered while hot, and cooled to give colorless prismatic needles of the monohydrochloride sesquihydrate, m.p. >300°. The anhydrous material was readily obtained by drying overnight at 75° *in vacuo*.

*Anal.* Calcd. for $C_5H_8ClN_7O_2$: C, 25.71; H, 3.45; Cl, 15.18; N, 41.97. Found: C, 25.54; H, 4.04; Cl, 15.25; N, 41.87.

Calcd. for $C_5H_8ClN_7O_2.1{}^1/_2H_2O$: $H_2O$, 10.37. Found: $H_2O$, 10.07, 10.30.

*Thermal decomposition of* XII. One gram (4.9 mmoles) of 4-amino-6-guanidino-5-nitropyrimidine (XII) was placed in a 50-ml. round bottomed flask covered with a watch glass, and slowly heated in an oil bath. At 223–225° a vigorous reaction occurred; a colorless solid sublimed onto the watch glass and the reaction mass turned to a dark brown solid. The latter material was sublimed at 210–220° at 0.1 mm. to give 0.3 g. (40%) of a colorless solid, m.p. >400°.

This compound was identified as 4,6-diamino-5-nitropyrimidine (XIX)[8,19] by analysis and comparison of the infrared spectrum with that of an authentic sample.

*Anal.* Calcd. for $C_4H_5N_5O_2$: C, 30.97; H, 3.25; N, 45.16; O, 20.64. Found: C, 31.40; H, 3.37; N, 45.08; O, 20.42.

The residue from the sublimation (0.4 g.) was a dark brown, high-melting solid, which could not be purified.

*Acid-catalyzed rearrangement of* XII. Five grams (0.025 mole) of 4-amino-6-guanidino-5-nitropyrimidine (XII) was added to a solution of 2.5 ml. of concd. hydrochloric acid in 50 ml. of water and refluxed for 0.75 hr. The clear solution was treated with an additional 2.5 ml. of concd. hydrochloric acid and the refluxing was continued for 1 hr., during which time a colorless precipitate slowly separated. This material (0.51 g., 12%) was filtered, and purified for analysis by dissolving in warm aqueous sodium hydroxide, filtering, and neutralizing the warm solution with acetic acid to obtain colorless, fine needles, m.p. >350°. The elemental analysis and infrared spectra (see below) identified this compound as *2,4-diamino-6-hydroxy-5-nitropyrimidine* (XVIII).

*Anal.* Calcd. for $C_4H_5N_5O_3$: C, 28.07; H, 2.95; N, 40.94; O, 28.05. Found: C, 29.29; H, 3.00; N, 39.82; O, 28.27.

The hydrochloric acid filtrate from XVIII was chilled in an ice bath and the colorless precipitate filtered with suction, m.p. 205–207° dec. when heated fairly rapidly. This material, subsequently identified as *3-guanidino-3-imino-2-nitropropionamide hydrochloride* (XV), was recrystallized from water containing a little hydrochloric acid, to obtain 2.1 g. (37%) of colorless needles, m.p. 207–209° dec. when heated fairly rapidly. Analysis indicated the material to be the hemihydrate.

*Anal.* Calcd. for $C_4H_9ClN_6O_3 \cdot {}^1/_2H_2O$: C, 20.57; H, 4.32; Cl, 15.18; N, 35.98. Found: C, 20.75; H, 4.02; Cl, 14.71; N, 35.74.

The free base, *3-guanidino-3-imino-2-nitropropionamide* (XVII), was obtained as yellow needles by neutralizing a solution of the above hydrochloride salt in water with ammonium hydroxide.[20] This material (XVII) was purified by dissolving in warm aqueous hydrochloric acid, and precipitating as yellow needles by the addition of ammonium hydroxide, m.p. >380°.

*Anal.* Calcd. for $C_4H_8N_6O_3$: C, 25.52; H, 4.29; N, 44.66; O, 25.50. Found: C, 25.68; H, 4.69; N, 44.89; O, 25.77.

The original hydrochloric acid filtrate from the isolation of XV was evaporated to dryness *in vacuo*, and the residual solid stirred with 25 ml. of ethanol and filtered to give 1.3 g. of a colorless crystalline solid, m.p. >300°, identified as ammonium chloride by comparison of its infrared spectrum with that of a known sample.

The ethanol filtrate from the ammonium chloride was evaporated to dryness *in vacuo*, the residual syrup dissolved in 15 ml. of water, clarified by filtration, and neutralized to *p*H 8 with aqueous sodium hydroxide. The pale yellow precipitate which formed, 0.2 g. (5%), had m.p. >350°, and was identified as *5-nitro-2,4,6-triaminopyrimidine* (XVI)[12] by comparison of its infrared spectrum with that of a known sample.

*2,4-Diamino-6-hydroxy-5-nitropyrimidine* (XVIII). *A. By ring closure of* XVII. 3-Guanidino-3-imino-2-nitropropionamide (XVII) (0.4 g.) was added to 5 ml. of 2*N* sodium hydroxide and heated on the steam bath for 4–5 min. A clear yellow solution was formed which gave a finely divided colorless precipitate when acidified with acetic acid. The product was purified by dissolving in warm aqueous alkali, filtering, and precipitating with acetic acid to obtain fine colorless needles, m.p. >350°. The infrared spectrum of this material was identical with that of an authentic sample of 2,4-diamino-6-hydroxy-5-nitropyrimidine (XVIII) (see below).

*Anal.* Calcd. for $C_4H_5N_5O_3$: C, 28.07; H, 2.95; N, 40.94. Found: C, 27.88; H, 2.73; N, 40.78.

*B. By nitration of 2,4-diamino-6-hydroxypyrimidine.*[21] A solution of 2,4-diamino-6-hydroxypyrimidine[21] (12.6 g., 0.10 mole) in 75 ml. of concd. sulfuric acid was prepared with occasional cooling to keep the temperature below 35°. Twenty-five milliliters of fuming nitric acid (sp. gr. 1.49–1.50) was carefully added with stirring in very small portions, keeping the temperature at 30–35°. The clear, yellow solution was allowed to stand at room temperature for 15 min., and then poured with stirring into about 1 l. of ice water. The resulting mixture, containing a colorless precipitate, was stirred and cooled in an ice bath while concd. aqueous ammonia was dropped in until the *p*H reached 8–9. The product was isolated by suction filtration, washed with water, and purified by dissolving in aqueous alkali and precipitating with acid. There were thus obtained 13.3 g. (77.8%) of fine colorless needles, m.p. >350°.

*Anal.* Calcd. for $C_4H_5N_5O_3$: C, 28.07; H, 2.95; N, 40.94. Found: C, 28.07; H, 2.77; N, 41.14.

The infrared spectrum of this compound was identical in all respects with that of the compound obtained from the ring-closure of XVII.

*4,6-Diamino-2-hydroxy-5-nitropyrimidine* (XXI). This compound was prepared by direct nitration of 6-aminocytosine[22] using a procedure analogous to that described above. The nitration also could be carried out by adding the 6-aminocytosine to fuming nitric acid at 20–25°, followed by the addition of concd. sulfuric acid at the same temperature; however, the product was colored violet and was difficult to purify. Using the recommended procedure, a colorless product was obtained, m.p. >350°, 79% yield.

*Anal.* Calcd. for $C_4H_5N_5O_3$: C, 28.07; H, 2.95; N, 40.94. Found: C, 28.38; H, 2.98; N, 40.78.

*5-Nitro-2,4,6-triaminopyrimidine* (XVI).[12] A similar nitration of 14.8 g. (0.118 mole) of 2,4,6-triaminopyrimidine[12] using 75 ml. of concd. sulfuric acid and 25 ml. of fuming nitric acid (sp. gr. 1.49–1.50) gave 16.2 g. (80.7%) of colorless needles from *N,N*-dimethylformamide-water, m.p. >350°.

*Anal.* Calcd. for $C_4H_6N_6O_2$: C, 28.24; H, 3.56; N, 49.41. Found: C, 28.33; H, 3.79; N, 49.81.

An attempt to prepare the above compound by the method of Gabriel[12] (red fuming nitric acid at 45–50°) gave, as the sole product, a 77% yield of 4,6-diamino-2-hydroxy-5-nitropyrimidine (XXI), identified by comparison of the infrared spectrum with that of a known sample (see above).

*Anal.* Calcd. for $C_4H_5N_5O_3$: C, 28.07; H, 2.95; N, 40.94; O, 28.05. Found: C, 28.16; H, 3.26; N, 41.00; O, 28.05.

*Base-catalyzed reactions of* XII. *A. In 35% sodium hydroxide solution.* One gram (4.86 mmoles) of XII was added to 15 ml. of 35% aqueous sodium hydroxide and heated on the steam bath with stirring for 5 min. The bright yellow starting material disappeared during this period, and was replaced by a white solid. The mixture was cooled and the product filtered with suction and washed with water. This compound was recrystallized from *N,N*-dimethylformamide-water (2:3) to obtain 0.10 g. (12%) of colorless feathery needles, m.p. >400°. This compound was found to be *5-nitro-2,4,6-triaminopyrimidine* (XVI) by comparison of infrared spectra.

*Anal.* Calcd. for $C_4H_6N_6O_2$: C, 28.24; H, 3.56; N, 49.41. Found: C, 28.50; H, 3.89; N, 49.23.

In a similar experiment in which 5.0 g. of XII was heated with 50 ml. of 35% aqueous sodium hydroxide on the steam bath for a longer period of time (35 min.), a much smaller quantity of 5-nitro-2,4,6-triaminopyrimidine (XVI) was

(19) R. K. Robins, K. J. Dille, C. H. Willits, and B. E. Christensen, *J. Am. Chem. Soc.*, **75**, 263 (1953).

(20) It is essential that a weak base such as ammonium hydroxide be used to convert the hydrochloride (XV) to the free base (XVII), since compound XVII is cyclized to 2,4-diamino-6-hydroxy-5-nitropyrimidine (XVIII) with extreme ease in the presence of strong alkali.

(21) J. A. Van Allan, *Org. Syntheses*, **32**, 45 (1952).

(22) H. L. Wheeler and G. S. Jamieson, *Am. Chem. J.*, **32**, 342 (1904).

obtained (50 mg.). Acidification of the alkaline filtrate from XVI gave a finely divided white solid, which was purified by dissolving in aqueous alkali and precipitating with hydrochloric acid.[23] This material, m.p. >400°, was identified as *2-amino-4,6-dihydroxy-5-nitropyrimidine* (XXIII) by comparison with an authentic sample (infrared), prepared as directed by Traube.[15]

*B. In 15% sodium hydroxide solution.* Five grams (0.024 mole) of XII was heated with 25 ml. of 15% sodium hydroxide solution on the steam bath for 10 min. The mixture was cooled and filtered to obtain 0.70 g. (17%) of white tiny needles, identified as 5-nitro-2,4,6-triaminopyrimidine (XVI) by its infrared spectrum. The alkaline filtrate was acidified to *p*H 3 with concd. hydrochloric acid and the pale yellowish precipitate was air-dried (3.4 g.). This alkaline soluble fraction proved to be a mixture of two compounds, which were readily separable by extracting with warm *N,N*-dimethylformamide. A sample of the alkaline-soluble material (2.3 g.) was stirred for 10 min. with 15 ml. of *N,N*-dimethylformamide at 50° and filtered to obtain 1.65 g. (51%) of *4-amino-5-nitro-6-ureidopyrimidine* (XX), m.p. >400°. This material (XX) was extremely difficult to obtain analytically pure because of its high insolubility in organic solvents, coupled with its tendency to decompose in alkaline solution (see below). The best sample was obtained by dissolving in warm aqueous ammonia, filtering, and neutralizing with acetic acid to obtain a finely divided white powder, m.p. >400°.

*Anal.* Calcd. for $C_5H_6N_6O_3$: C, 30.30; H, 3.05; N, 42.41. Found: C, 29.75; H, 3.24; N, 41.93.

The *N,N*-dimethylformamide soluble fraction could be obtained as a pale yellow powder by dilution with water, m.p. 201–203° dec. (cap.). This substance remains unidentified.

*C. In 5% sodium hydroxide solution.* Two grams (9.7 mmoles) of XII was heated with 30 ml. of 5% sodium hydroxide solution at 100° for 3 min. The pale yellowish suspension was cooled and filtered to give 0.3 g. (20%) of *4,6-diamino-5-nitropyrimidine* (XIX).[8,19] This compound was purified by sublimation at 250° at 0.1 mm., m.p. >350°. The infrared spectrum was identical with that of an authentic sample of XIX.[8,19]

The alkaline filtrate from XIX was acidified with hydrochloric acid and the finely divided solid isolated by filtration. This material (0.9 g., 47%) had m.p. >400°, and was identical in all respects with *4-amino-5-nitro-6-ureidopyrimidine* (XX) (see above).

*Base-catalyzed hydrolysis and rearrangement of 4-amino-5-nitro-6-ureidopyrimidine* (XX). A solution of 0.30 g. (1.5 mmoles) of XX in 5 ml. of 1*N* sodium hydroxide was heated on the steam bath for 1.5 hr. The resulting suspension was filtered with suction and the pale yellow solid washed with water, m.p. >350°. This material gave an infrared spectrum identical in all respects with that of *4,6-diamino-5-nitropyrimidine* (XIX).[8,19]

The combined filtrates from XIX were acidified with hydrochloric acid and the white solid thus obtained purified by dissolving in aqueous alkali and precipitating with acid. *4,6-Diamino-2-hydroxy-5-nitropyrimidine* (XXI) was thus obtained as a colorless, finely divided solid, m.p. >400°. The infrared spectrum was identical with that of an authentic sample prepared by direct nitration of 6-aminocytosine (see above).

*Cyanonitroacetamide guanidine salt* (*Guanidinium fulminurate*) (XXV). Cyanoisonitrosoacetamide (desoxyfulminuric acid) (XXIV)[16] (18.5 g., 0.164 mole) was dissolved in 165 ml. of water, and a solution of 17.4 g. (0.11 mole) of potassium permanganate in 225 ml. of water slowly added with stirring. The manganese dioxide was removed by suction filtration and the filter cake washed with water. The colorless filtrates were combined and treated with 20 g. (0.21 mole) of guanidine hydrochloride. The product separated almost immediately as colorless needles, m.p. 207–209° dec. An additional quantity was obtained by evaporation of the mother liquors to half volume, total yield 18.2 g. (59.2%). An analytical sample was obtained as long colorless needles from water, m.p., 221–223° dec.

*Anal.* Calcd. for $C_4H_8N_6O_3$: C, 25.52; H, 4.29; N, 44.66. Found: C, 25.54; H, 4.16; N, 44.49.

Free fulminuric acid[17] could be readily obtained from the guanidine salt merely by treatment with a threefold quantity of concentrated hydrochloric acid and filtering. Although fulminuric acid is extremely soluble in water, it appears to be quite insoluble in concentrated hydrochloric acid.

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(23) It is necessary to use strong hydrochloric acid to free completely the 2-amino-4,6-dihydroxy-5-nitropyrimidine (XXIII) from sodium ion. This compound forms a sparingly soluble sodium salt which is not completely destroyed by acetic acid.