tained at 40° for 2 hr. and then poured into cold water; 7.90 g. (96.5%) of phenylthiatriazole was recovered, m.p. 89–90° alone and when mixed with starting material. In a similar experiment, *p*-methoxyphenylthiatriazole was recovered in 98% yield.

Stability of 5-phenyl-1,2,3,4-thiatriazole toward methylmagnesium iodide. A stock solution of methylmagnesium iodide prepared for Zerewitinoff determinations was found to liberate 13.60 to 13.85 ml. of methane when 5-ml. portions were diluted with 4 ml. of anisole and then treated with excess water. When the Grignard solution was first treated with 0.163 g. (1 mmole) of phenylthiatriazole, 13.15 ml. (96%) of methane was liberated on subsequent hydrolysis.

Inertness of 5-phenyl-1,2,3,4-thiatriazole to methyl iodide, to picric acid, and to chlorination. A solution of 1.63 g. of phenylthiatriazole and 1.42 g. of methyl iodide in 25 ml. of Methyl Cellosolve was heated on the steam bath for 12 hr. When the mixture was diluted with water, 1.38 g. was recovered, m.p. 90–91°, not depressed by mixture with starting material. Treatment of phenylthiatriazole with picric acid in chloroform yielded no crystalline addition compound.

Chlorine was passed through a solution of 16.3 g. of phenylthiatriazole in 200 ml. of carbon tetrachloride for 1.5 hr. in the presence of 0.5 g. of amalgamated aluminum. After the solvent was removed, 14.0 g. (85.2%) of phenylthiatriazole, m.p. 90–91°, not depressed by mixture with starting material, was recovered.

Inertness of 5-p-methoxyphenyl-1,2,3,4-thiatriazole to nitration. When 1.0 g. of *p*-methoxyphenylthiatriazole was heated on a steam bath for 0.5 hr. in a mixture of 6 ml. of glacial acetic acid, 1 ml. of concd. sulfuric acid, and 0.4 ml. of yellow fuming nitric acid and then diluted with water, 0.72 g., m.p. 103–104°, undepressed by mixture with starting material, was recovered.

Reaction of N-methylbenzothionhydrazide with nitrous acid. A solution of 3 g. of sodium nitrite in cold water was added to a solution of 6.4 g. of *N*-methylbenzothionhydrazide[9] in excess dilute hydrochloric acid chilled in an ice bath; 5.4 g. (70.8%) of tan crystals, m.p. 77–78°, precipitated. Recrystallization from benzene gave nearly white *N*-methylbenzthionamide, m.p. 79–80° (reported[10] m.p. 79°). The same product was also obtained, in 62% yield, when nitrosation was carried out in glacial acetic acid instead of hydrochloric acid.

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On the Reaction of 2,4-Dichloro-5-nitropyrimidine with Amines[1]

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The reaction of 2,4-dichloro-5-nitropyrimidine (I) with amines has been studied extensively and the reaction products have been reported to be either 2,4-disubstituted derivatives[2–6] or products arising from replacement of only the 4-chloro substituent.[4–10] The fact that not a single example of selective replacement of the 2-chloro substituent has been observed has been attributed to a greater reactivity of the chlorine in the 4-position, although it should be noted that the 2-chlorine is still remarkably reactive in 2-chloro-4-amino (and substituted amino)-5-nitropyrimidines. For example, the reaction of 2,4-dichloro-5-nitropyrimidine with excess methylamine in aqueous or methanolic solution at 10° gives 2,4-bis(methylamino)-5-nitropyrimidine (II),[3,4] while the use of methanolic methylamine (1.4 moles) at 0° gives 2-methoxy-4-methylamino-5-nitropyrimidine.[3]

Reaction of 2,4-dichloro-5-nitropyrimidine with methylammonium acetate in dioxane solution at 15–20° has been reported[4] to give 2-chloro-4-methylamino-5-nitropyrimidine (III) in 14% yield, and "considerable amounts of 2,4-bis(methylamino)-5-nitropyrimidine from the mother liquors." As we had observed in the course of a reinvestigation of this reaction that the latter compound (II) is only slightly soluble in ethanol, while the former compound (III) is by contrast extremely soluble, it is obvious that something is amiss in the published experimental work. We now wish to report that a repetition of the published procedure at 0–5° failed to give any 2,4-bis(methylamino)-5-nitropyrimidine (II), while at 15–20° only a small amount was formed. At *both* temperatures, however, two other products were formed. The major reaction product, which separated as heavy yellow needles, m.p. 85–86°, was shown to be the previously reported[4] 2-chloro-4-methylamino-5-nitropyrimidine (III). The second product, which separated as colorless, fine needles, m.p. 122°, is the previously unreported 2-methylamino-4-chloro-5-nitropyrimidine (IV). Lower solubility of IV in the reaction mixture and in ethanol as compared with the 4-methylamino isomer III facilitated its isolation, in spite of the fact that it is formed in small amounts. In a typical experiment at 15–20°, the over-all yield of product was 67%, of which 5.5% was shown by isolation to be the bis(methylamino) derivative II, and the remainder was shown by examination of its infrared spectrum to contain 70–80% of III and 30–20% of IV. When the reaction was carried out at 0°, the over-all yield was

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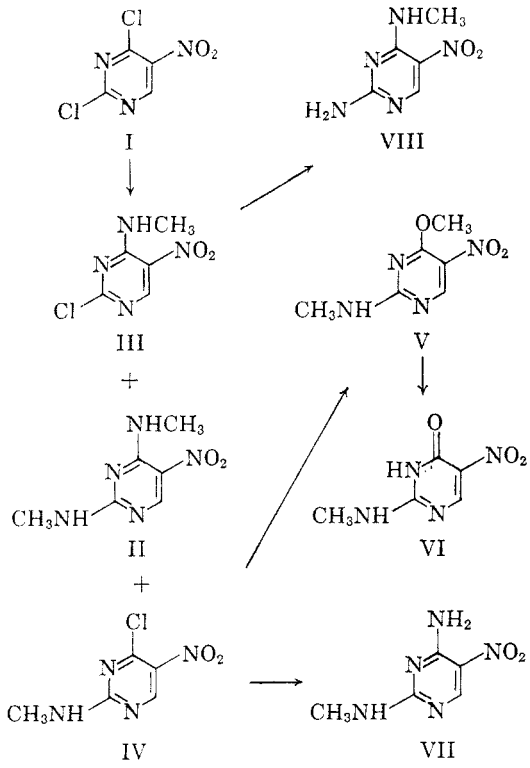
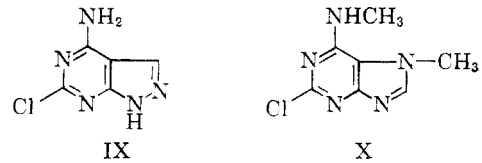


lowered to 57% but the isomer distribution remained unchanged.

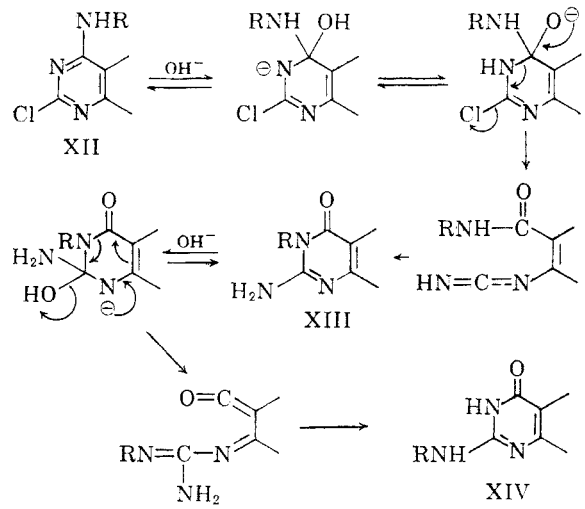
The identity of 2-methylamino-4-chloro-5-nitropyrimidine (IV) was established as follows: (a) Reaction with sodium methoxide gave a methoxy derivative V which was hydrolyzed with acid to 2-methylamino-5-nitro-4(3*H*)-pyrimidone (VI). Although the melting point of VI was identical with the melting point of the isomeric 4-methylamino-5-nitro-2(1*H*)-pyrimidone,[11,12] the two compounds were readily distinguishable by comparison of ultraviolet spectra (both in neutral and alkaline solution), and by the close similarity of their spectra with the spectra of nitroisocytosine[13] and nitrocytosine respectively. (b) Reaction of IV with ammonia gave the known 2-methylamino-4-amino-5-nitropyrimidine (VII), identical with an authentic sample.[14] Reaction of the isomeric 2-chloro-4-methylamino-5-nitropyrimidine (III) with ethanolic ammonia at room temperature gave 2-amino-4-methylamino-5-nitropyrimidine (VIII).

The facility with which both of these amination reactions proceeded suggested that conditions previously employed for the bisamination of 2,4-dichloro-5-nitropyrimidine (I) (reaction with alcoholic ammonia at elevated temperatures in a sealed tube,[10] or passage of a vigorous stream of ammonia through a solution of I in boiling phenol[15]) were unnecessarily severe. We have now shown that 2,4-diamino-5-nitropyrimidine may be prepared in quantitative yield by allowing a solution of I in ethanolic ammonia to stand at room temperature overnight, or in greater than 95% yield in thirty minutes.

2-Chloro-4-methylamino-5-nitropyrimidine (III) is closely related structurally to 4-amino-6-chloropyrazolo(3,4-d)pyrimidine (IX) and to 2-chloro-6-methylamino-7-methylpurine (X), both of which are known to undergo a remarkable sequence of ring-opening, ring-closure reactions upon treatment with alkali to give hydrolysis products in which the



positions of substituents are essentially reversed (XII → XIII).[16,17] It appeared feasible that a similar rearrangement might take place with III, with the additional attractive possibility that a rearrangement of the intermediate corresponding to XIII to 2-methylamino-5-nitro-4(3*H*)-pyrimidone (VI, corresponding to XIV) might be anticipated because of stabilization of the necessary anionic intermediate in the rearrangement by the 5-nitro group.[18] However, it was found that treatment of 2-chloro-4-methylamino-5-nitropyrimidine (III) with aqueous base led predominately to 4-methyl-



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(13) $\lambda_{max}^{H_2O}$ 254, 339 mμ; ε 5314, 14,134. $\lambda_{max}^{0.1N\ NaOH}$ 217, 246, 353 mμ; ε 9989, 5951, 12,965.

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amino-5-nitro-2(1*H*)-pyrimidone by direct hydrolysis of the 2-chloro substituent. A similar result was obtained upon alkaline hydrolysis of 2-methylamino-4-chloro-5-nitropyrimidine (IV). A small amount of a base-insoluble product was formed in each case which was shown to be 2,4-bis(methylamino)-5-nitropyrimidine (II) and must have arisen by reaction of methylamine, formed in a secondary hydrolysis, with unchanged IV. The isolation of this product from aqueous base illustrates in a striking way the much greater nucleophilicity of methylamine as compared with hydroxide ion. Hydrolysis of 2-chloro-4-amino-5-nitropyrimidine, which might have been expected to give 5-nitroisocytosine had the postulated rearrangement taken place, in fact gave 5-nitrocytosine in a high state of purity.

EXPERIMENTAL

2-Chloro-4-methylamino-5-nitropyrimidine (III). Eighty milliliters of a 25% aqueous solution of methylamine was adjusted to *p*H 7 with 60 ml. of glacial acetic acid and this solution was added with stirring over a period of 20 min. to 31.5 g. of 2,4-dichloro-5-nitropyrimidine in 120 ml. of dioxane at 0–5°. The reaction solution was stirred for 3 hr. and then diluted gradually with 350 ml. of an ice-water mixture. After 2 hr. at 0°, the mixture was filtered and the solid washed with cold water and dried; yield of crude product, 17.5 g. (57%), m.p. 80–115°. Comparison of the infrared spectrum of this mixture in chloroform solution with the spectra of known mixtures of 2-chloro-4-methylamino-5-nitropyrimidine (III) and 4-chloro-2-methylamino-5-nitropyrimidine (IV) showed it to be 70–80% III and 30–20% IV. Careful fractional crystallization of the crude product from aqueous ethanol gave, as the more soluble product, 9 g. of heavy yellow needles, m.p. 85–86°. 2-Chloro-4-methylamino-5-nitropyrimidine is reported to melt at 80–82°.[4] Extraction of the mother liquor with chloroform and evaporation of the extract gave an additional 3–4 g. of product which proved to be almost pure III by examination of its infrared spectrum. In contrast to the published comment that this compound turns orange upon exposure to light, we have found that the pure material is completely stable to light. $\lambda_{max}^{C_2H_5OH}$ 225, 256, 356 mμ: ε 21,185, 9,452, 5,975. The principal infrared absorption maxima in chloroform solution are at 2.95, 6.17, 6.35, 6.60, 6.70, 7.08, 7.30, 7.46, 7.96, 8.11, 8.41, 9.21, 9.60, and 10.70 μ.

4-Chloro-2-methylamino-5-nitropyrimidine (IV). Fractional crystallization of the less soluble of the two products obtained in the above reaction yielded 2–3 g. of fine white needles, m.p. 122°, which gradually turned a reddish color when exposed to air and light.

Anal. Calcd. for $C_5H_5N_4O_2Cl$: C, 31.8; H, 2.7; N, 29.7; Cl, 18.8. Found: C, 32.5; H, 2.9; N, 30.4; Cl, 18.6.

$\lambda_{max}^{C_2H_5OH}$ 223, 256, 330 mμ; ε 16,246, 5,894, 8,303. The principal infrared absorption maxima in chloroform solution were at 2.90, 2.95, 6.17, 6.26, 6.45, 6.60, 7.10, 7.30, 7.46, 7.51, 7.60, 7.96, 8.11, 8.40, 9.21, and 10.70 μ.

Repetition of the reaction of 2,4-dichloro-5-nitropyrimidine with methylamine acetate under the same conditions as specified above, but at 15–20°, gave 20.2 g. (67%) of crude product which was carefully extracted with warm ethanol. The extract contained a mixture of II and IV in approximately the same ratio as was found above as determined by an examination of its infrared spectrum. The ethanol-insoluble residue (1.1 g.) was shown to be 2,4-bis(methylamino)-5-nitropyrimidine (II), m.p. 261–263°. This compound is reported to melt at 253–255°.[3]

2-Amino-4-methylamino-5-nitropyrimidine (VIII). A mixture of 2.0 g. of 2-chloro-4-methylamino-5-nitropyrimidine and 50 ml. of 10% ethanolic ammonia was allowed to stand at room temperature for 4 hr. Filtration gave 1.63 g. (91%) of crude product which was recrystallized from aqueous acetic acid to give long, yellow needles, m.p. 249–250°.

Anal. Calcd. for $C_5H_7N_5O_2$: C, 35.5; H, 4.2; N, 41.4. Found: C, 35.4; H, 4.2; N, 42.1.

2-Methylamino-4-methoxy-5-nitropyrimidine (V). A solution of 0.5 g. of 4-chloro-2-methylamino-5-nitropyrimidine in 10 ml. of methanol containing 0.1 g. of sodium was heated under reflux for 30 min. and then cooled. Filtration gave 0.22 g. (45%) of crude product, m.p. 206–207°, which was recrystallized from aqueous methanol to give pale yellow needles, m.p. 207–208°.

Anal. Calcd. for $C_6H_8N_4O_3$: C, 39.1; H, 4.4; N, 30.4. Found: C, 39.1; H, 4.5; N, 30.3.

2-Methylamino-5-nitro-4(3H)-pyrimidone (VI). A mixture of 0.35 g. of 4-chloro-2-methylamino-5-nitropyrimidine and 20 ml. of 1*N* sodium hydroxide was heated on a steam bath for 1 hr. Cooling and filtering removed a small amount (0.045 g.) of a yellow solid, m.p. 260–263°, which was identified as 2,4-bis(methylamino)-5-nitropyrimidine by comparison with an authentic sample. Acidification of the filtrate with concentrated hydrochloric acid gave 0.1 g. (31%) of a white solid, m.p. 321° dec. Recrystallization from water raised the decomposition point to 326°.

Anal. Calcd. for $C_5H_6N_4O_3$: C, 35.3; H, 3.6; N, 32.9. Found: C, 35.0; H, 3.9; N, 32.8.

This product was identical with that prepared by hydrolysis of 2-methylamino-4-methoxy-5-nitropyrimidine with concentrated hydrochloric acid on a steam bath for 2 hr. $\lambda_{max}^{H_2O}$ 258, 345 mμ; ε 5,160, 16,645. $\lambda_{max}^{0.1NNaOH}$ 217, 257, 362 mμ; ε 12,428, 4,550, 16,645.

4-Methylamino-5-nitro-2(1H)-pyrimidone. A mixture of 0.5 g. of 2-chloro-4-methylamino-5-nitropyrimidine and 20 ml. of 1*N* sodium hydroxide was heated on a steam bath for 1 hr. and then filtered to remove 0.026 g. of yellow crystals, m.p. 261–262°, identified as 2,4-bis(methylamino)-5-nitropyrimidine by comparison with an authentic sample.[3] Careful acidification of the filtrate with hydrochloric acid precipitated 0.21 g. (47%) of white crystals, m.p. 325° dec. This product was identical with that prepared by hydrolysis of 2-methoxy-4-methylamino-5-nitropyrimidine with concentrated hydrochloric acid on a steam bath for 2 hr. $\lambda_{max}^{H_2O}$ 230, 328 mμ; ε 16,500, 6,700. $\lambda_{max}^{0.1NNaOH}$ 219, 255, 367 mμ; ε 12,500, 2,960, 14,250.

5-Nitrocytosine. A mixture of 0.5 g. of 2-chloro-4-amino-5-nitropyrimidine[7] and 40 ml. of 0.5*N* sodium hydroxide was heated for 45 min. on a steam bath and then cooled and acidified with hydrochloric acid. Filtration gave 0.2 g. (45%) of a bright yellow solid, m.p. > 360°, which was identical with an authentic sample of 5-nitrocytosine prepared by nitration of cytosine.[19] $\lambda_{max}^{H_2O}$ 223, 320, 250 (inflex.) mμ; ε 13,540, 7,863, 6,770. $\lambda_{max}^{0.1NNaOH}$ 219, 253, 353 mμ; ε 9,540, 5,724, 14,500.

2,4-Diamino-5-nitropyrimidine. A solution of 10 g. of 2,4-dichloro-5-nitropyrimidine in 50 ml. of ethanol was added rapidly to 200 ml. of alcoholic ammonia. After the initial reaction had subsided, the mixture was heated to boiling and then allowed to stand for 30 min. Filtration gave 7.65 g. (95.5%) of product, m.p. > 350°. An additional 0.25 g. separated from the filtrate on standing to give a total yield of 7.90 g. (99%).

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