TABLE II

DIELS-ALDER ADDUCTS FROM CHLORINE-CONTAINING β-NITROSTYRENES

Name	M.P.[a]	Yield, %	Calcd., % (Found, %) C	H	N
4-*p*-Chlorophenyl-5-nitrocyclohexene[b]	87	50	60.64 (60.43	5.09 4.81	5.89 5.90)
4-*o*-Chlorophenyl-5-nitrocyclohexene	78	55	60.64 (60.96	5.09 5.04	5.89 5.74)
4-(3,4-Dichlorophenyl)-5-nitrocyclohexene	95	14	52.96 (53.00	4.08 3.91	5.15 5.01)
4-(2,4-Dichlorophenyl)-5-nitrocyclohexene	75	20	52.96 (53.22	4.08 3.99	5.15 4.51)
5-*o*-Chlorophenyl-6-nitro-[2.2.1]bicyclo-2-heptene	68	85	62.53 (62.82	4.84 4.85	5.61 5.53)
5-(3,4-Dichlorophenyl)-6-nitro-[2.2.1]bicyclo-2-heptene	119–120	42	54.94 (55.13	3.90 3.87	4.93 4.74)
5-(2,4-Dichlorophenyl)-6-nitro-[2.2.1]bicyclo-2-heptene	105–106	42	54.94 (55.28	3.90 3.89	4.93 4.87)

[a] All melting points are uncorrected. [b] This adduct was reported by A. C. Huitric and W. D. Kumler, *J. Am. Chem. Soc.*, **78**, 614–622 (1956), after the paper on which this manuscript is based was presented.

was formed. The reaction mixture was allowed to stand for 15 min. after the addition of the sodium hydroxide. Enough ice water was added to dissolve the paste. The resulting solution was run into 200 ml. of a dilute hydrochloric acid solution (1 ml. of concd. hydrochloric acid to 1.5 ml. of water) with stirring, at such a rate that the stream just failed to break into drops. The resulting yellow precipitate was filtered by suction and washed with water. After recrystallization from ethanol, the yield was 27 g. (62%). 3,4-Dichloro-β-nitrostyrene was prepared by the same method.

4-o-Chlorophenyl-5-nitrocyclohexene. An iron reaction tube, made of 1/8-in.-wall pipe welded closed at one end and fitted with a threaded cap at the other end (internal dimensions: 1 × 26 in.), was charged with 37.6 g. (0.2 mole) of *o*-chloro-β-nitrostyrene and a solution of 32 g. (0.6 mole) of butadiene in 80 ml. of toluene. The tube was tightly capped and heated in a Carius tube furnace at 120° for 5 hr. The contents were removed when the tube had cooled to room temperature (12 hr.). The resulting dark brown solution was steam distilled to remove unchanged butadiene and the toluene solvent. The residue, a viscous brown liquid, solidified when cooled in an ice bath. The solid was dissolved in boiling ethanol, charcoal was added, and the hot solution was filtered. Gray-brown crystals separated upon cooling and were filtered with suction and pressed dry. The dry crystalline mass contained pieces of a black material, apparently polymeric, which were picked out and discarded. The remaining material was crystallized several times from ethanol before a white product was obtained and was finally vacuum distilled. The yield of white odorless crystals was 26 g. (55%). 4-*p*-Chlorophenyl-5-nitrocyclohexene, 4-(2,4-dichlorophenyl-5-nitrocyclohexene, and 4-(3,4-dichlorophenyl)-5-nitrocyclohexene were made by the same procedure.

5-o-Chlorophenyl-6-nitro[2.2.1]bicyclo-2-heptene. Eleven grams (0.05 mole) of 2,4-dichloro-β-nitrostyrene, 6.3 ml. (0.075 mole) of freshly distilled cyclopentadiene, and 20 ml. of toluene were mixed and placed in a tightly capped bottle. The reaction mixture was allowed to stand at room temperature for 2.5 days. After cooling, the crystals were removed by filtration and purified by several recrystallizations from ethanol with charcoal treatment to give white odorless crystals. The yield was 6 g. (42%). 5-(3,4-Dichlorophenyl-6-nitro[2.2.1]-bicyclo-2-heptene and 5-(3,4-dichlorophenyl)-6-nitro[2.2.1]bicyclo-2-heptene were made by the same procedure.

Acknowledgment. Analyses were made by the Clark Microanalytical Laboratory, Urbana, Ill. Special thanks are due the Research Corp. for support of this research through a Frank Gardner Cottrell fellowship.

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Some Properties of Aryl and Alkyl Thiatriazoles[1]

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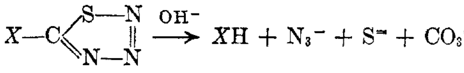
Received June 16, 1961

The thiatriazole ring system, first reported in 1896 by Freund, Schander, and Schwartz,[2] has received almost no attention until recently, when the studies of Lieber and co-workers[3] put the earlier structural assignments on a firmer basis. At the inception of the present work, all reported studies dealt only with 5-mercapto- or 5-aminothiatriazoles (I), whose characteristic behavior is alkaline hydrolysis to azide, sulfide, and carbonate, and thermal decomposition to cyano compounds, sulfur, and



$$\mathrm{I} \longrightarrow X\text{—CN} + \mathrm{S} + \mathrm{N_2}$$

nitrogen. The reported conversion of chlorodifluorothioacetyl fluoride to chlorodifluoroacetonitrile by heating with sodium azide is also probably an example of the formation and decomposition of a thiatriazole.[4]

When most of the present work had been completed, Bacchetti and Alemagna[5a] described 5-

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[1] From the doctoral dissertation of D. H. K., 1960. Supported in part by the Office of Ordnance Research, DA Project No. 299-01-004, Contract No. DA-20-018-ORD-13283 and a grant from the Michigan Division, American Cancer Society.

(2) M. Freund and A. Schander, *Ber.*, **29**, 2500 (1896); M. Freund and H. P. Schwartz, *Ber.*, **29**, 2506 (1896).

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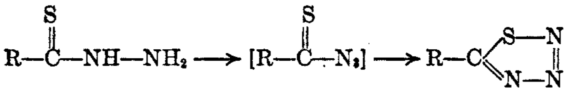
phenylthiatrazole, and Kirmse[5b] reported the preparation of 5-phenyl-, 5-α- and -β-naphthyl-, and 5-benzylthiatriazoles. They decompose on heating into nitriles, sulfur, and nitrogen, but on ultraviolet irradiation show up to 10% rearrangement to isothiocyanate. The thiatriazole ring is inert to attack by peroxyacetic acid, and shows a deactivating and *ortho-para* directing influence on nitration of the attached aryl group. In our work, we have prepared some additional 5-substituted thiatriazoles and have investigated other aspects of their behavior.

We prepared phenyl-, *p*-anisyl-, and *p*-chlorophenylthiatriazoles by treating the corresponding thionhydrazides, prepared by the method of Holmberg,[6] with nitrous acid. Their infrared spectra showed, by the absence of absorption in the 2100–2200-cm.$^{-1}$ region, that the thiatriazole ring had indeed closed, and that the substances were not the isomeric thioacyl azides (II).


II

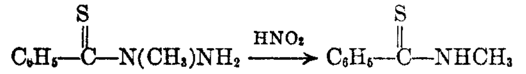
Heating these substances above their melting points in solution in decalin or nitriles brought about smooth decomposition into nitriles, sulfur, and nitrogen, parallel with the reported behavior of related compounds. Limited decomposition of this sort also occurred on prolonged storage. Attempts were also made to prepare an alkylthiatriazole by treating cyclohexanethiocarbonyl hydrazide with nitrous acid; in many attempts, only an unstable oil was obtained, which decomposed on standing and during attempted purification, depositing sulfur and developing infrared absorption in the region characteristic of nitriles. This is very similar to the behavior of 5-benzylthiatriazole, which, however, Kirmse obtained crystalline.

Because of its easy preparation, 5-phenylthiatriazole was principally used for investigations of other chemical behavior. It was found to withstand both warm alcoholic alkali and Grignard reagents. It showed only feeble basic properties, dissolving in concentrated hydrochloric or nitric acid. Concentrated sulfuric acid, however, brought about decomposition to the same products as heating. A picrate could not be obtained, even in anhydrous medium, and no evidence for reaction with methyl iodide or maleic anhydride was observed.

Oxidation by peroxides was ineffective toward phenylthiatriazole, but reduction by lithium aluminum hydride occurred readily. All nitrogen was removed, and benzyl mercaptan (isolated and identified as dibenzyl disulfide) was formed.

Attempts to substitute the benzene ring of 5-phenylthiatriazole were made with both chlorine and bromine under various conditions. Even the most vigorous treatment was without effect, either on the phenyl group or the thiatriazole system. Attempted nitration of phenyl- or *p*-methoxyphenylthiatriazole with mixed acid in acetic acid, or sulfonation, led only to disruption of the thiatriazole ring or recovery unchanged.

When treatment of 5-phenylthiatriazole with methyl iodide failed to give a thiatriazolium compound, we sought another route to such a structure, by treating *N*-methylbenzthionhydrazide (III) with nitrous acid. Reaction occurred in both strongly and weakly acidic solution, but only *N*-methylbenzthionamide could be isolated, and no evidence for the formation of a cationic organic compound could be obtained. Similar behavior has been reported for *N*-benzylbenzthionhydrazide.[7]



$$C_6H_5-\overset{\overset{\displaystyle S}{\|}}{C}-N(CH_3)NH_2 \xrightarrow{HNO_2} C_6H_5-\overset{\overset{\displaystyle S}{\|}}{C}-NHCH_3$$

III

The insensitivity of phenylthiatriazole to base and Grignard reagent indicates that there is no significant equilibration with the thioacyl azide structure, even in solution and in the warm. Such a structure would be expected to hydrolyze readily and to react vigorously with the Grignard reagent. This lends additional support to the contention of Lieber, Pillai, and Hites[3] that the alkaline hydrolysis observed with 5-aminothiatriazoles results from initial proton removal rather than simple ring-chain tautomerism.

The low basicity and nucleophilicity, the inertness to oxidizing agents, and the deactivating influence on the benzene ring all indicate a low electron availability at the thiatriazole ring and relate it closely to triazoles and tetrazoles.

The decompositions in nitrile solvents had been carried out in order to see if a thioacyl azene, R—CH(—N:), could be trapped by addition to the C≡N triple bond to form the stable 1,3,4-thiadiazole system. Such compounds are known to be formed readily by oxidation of thionhydrazides and sometimes occur as side products in the preparation of thiatriazoles by treatment of thionhydrazides with nitrous acid at room temperature or below; it appeared in principle possible that their occurrence might be the result of an addition of a thioacyl azene to a nitrile. The absence of thiadiazoles from the products when thiatriazoles were heated in nitrile solvents is presumptive evidence against such a reaction path, although it could also be explained by the less likely hypothesis that an increase of temperature accelerates the loss of sulfur from a thioacyl azene to form a nitrile very much more than it accelerates the presumed addition reaction.

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TABLE I

PROPERTIES AND YIELDS OF *S*-THIOACYLMERCAPTOACETIC ACIDS, R—CSSCH$_2$COOH, THIONHYDRAZIDES, *p*-NITROBENZYLIDENE DERIVATIVES, AND THIATRIAZOLES

	R = Phenyl	R = *p*-Chlorophenyl	R = *p*-Anisyl	R = Cyclohexyl
S-Thioacylmercaptoacetic acid, m.p.	122–123[a]	118–119[d]	124–125[h]	78–79[l]
S-Thioacylmercaptoacetic acid, yield, %	40	1	10	3
Thionhydrazide, RCSNHNH$_2$, m.p.	80–82[b]	123–124[e]	123.5–124[i]	106–107[m]
Thionhydrazide, RCSNHNH$_2$, yield, %	40	79	85.5	77
Thionhydrazide, *p*-nitrobenzylidene derivative, m.p.	—	168–170[f]	164–165[j]	125–126[n]
Thiatriazole, RCSN$_3$, m.p.	94–94.5[c]	97–98[g]	103–104[k]	Oil
Thiatriazole, RCSN$_3$, yield, %	87	65	48	

[a] Reported[6b] m.p. 127–128°. [b] Reported[6] m.p. 81–82°. [c] Reported[5] m.p. 94–95°. [d] *Anal.* Calcd. for $C_9H_7ClO_2S_2$: C, 43.80; H, 2.86. Found: C, 43.82; H, 2.88. [e] *Anal.* Calcd. for $C_7H_7ClN_2S$: C, 45.04; H, 3.78; N, 15.01. Found: C, 45.30; H, 3.99; N, 15.32. [f] *Anal.* Calcd. for $C_{14}H_{10}ClN_3O_2S$: C, 52.58; H, 3.15; N, 13.14. Found: C, 52.65; H, 3.22; N, 13.30. [g] *Anal.* Calcd. for $C_7H_4ClN_3S$: C, 42.34; H, 2.04; N, 21.26. Found: C, 42.49; H, 2.21; N, 21.37. [h] *Anal.* Calcd. for $C_{10}H_{10}O_3S_2$: C, 49.56; H, 4.16. Found: C, 49.62; H, 4.29. [i] *Anal.* Calcd. for $C_8H_{10}N_2O_2S$: C, 52.72; H, 5.53; N, 15.40. Found: C, 52.78; H, 5.57; N, 15.52. [j] *Anal.* Calcd. for $C_{15}H_{13}N_3O_3S$: C, 57.13; H, 4.15; N, 13.33. Found: C, 57.17; H, 4.11; N, 13.29. [k] *Anal.* Calcd. for $C_8H_7N_3OS$: C, 49.73; H, 3.65; N, 21.75. Found: C, 49.83; H, 3.89; N, 21.84. [l] *Anal.* Calcd. for $C_9H_{14}O_2S_2$: C, 49.51; H, 6.56. Found: C, 49.65; H, 6.48. [m] *Anal.* Calcd. for $C_7H_{14}N_2S$: C, 53.12; H, 8.91; N, 17.71. Found: C, 53.29; H, 8.94; N, 17.45. [n] *Anal.* Calcd. for $C_{14}H_{18}N_3O_2S$: C, 57.71; H, 5.88; N, 14.42. Found: C, 57.44; H, 6.09; N, 14.72.

EXPERIMENTAL[8]

S-Thioacylmercaptoacetic acids, thionhydrazides, their p-nitrobenzylidene derivatives, and thiatriazoles. The yields and properties of these substances are summarized in Table I. The experimental procedures were closely similar to those of the *p*-methoxyphenyl series, described below.

S-p-Methoxythiobenzoylmercaptoacetic acid. A solution of 63 g. (50 ml.) of carbon disulfide in 100 ml. of absolute ether was added dropwise to a well stirred, ice-cold solution of Grignard reagent prepared from 100 g. of *p*-anisyl bromide and 14.5 g. of magnesium. After 12 hr., 300 g. of ice was added. The aqueous layer containing magnesium dithioanisate was separated, washed with ether, filtered, and treated with a solution of 50 g. of chloroacetic acid and 76 g. of sodium carbonate. After standing for 12 hr. at room temperature, the mixture was acidified with sulfuric acid, precipitating yellow crystals of *S*-*p*-methoxythiobenzoylmercaptoacetic acid, 11.3 g. (10%), m.p. 95–100°, raised to 124–125° after three recrystallizations from benzene.

p-Anisothionhydrazide. To a solution of 4.5 g. of *S*-*p*-methoxythiobenzoylmercaptoacetic acid in 20 ml. of 1*N* sodium hydroxide, 4 ml. of hydrazine hydrate was added. After the addition of 6 ml. of glacial acetic acid, 3.05 g. (85.5%) of a yellow solid, m.p. 122–123°, precipitated. Two recrystallizations from benzene gave a colorless product, m.p. 123.5–124°.

p-Nitrobenzaldehyde p-methoxythiobenzoylhydrazone. A solution of 80 mg. of *p*-anisothionhydrazide and 65 mg. of *p*-nitrobenzaldehyde in 10 ml. of methanol was warmed and then diluted with water to precipitate 115 mg. of crude product, m.p. 162.5–163.5°. Recrystallization from aqueous methanol gave an analytical sample, m.p. 164–165°.

5-p-Methoxyphenyl-1,2,3,4-thiatriazole. A solution of 10 g. of sodium nitrite in cold water was added to a solution of 10 g. of *p*-anisothionhydrazide dissolved in 100 ml. of 6% hydrochloric acid chilled in an ice bath. There was an immediate precipitate of solid, weight 5 g. (47.8%), m.p. 92–95°. Two recrystallizations from benzene gave a pale yellow product, m.p. 103–104°. After about 1 year of storage, the sample had turned tan and had m.p. 95–100° with prior softening.

Reaction of cyclohexanethiocarbonyl hydrazide with nitrous acid. An aqueous solution of 0.75 g. of sodium nitrite was added to an ice-cold solution of 1.18 g. of cyclohexanethiocarbonyl hydrazide dissolved in excess 6% hydrochloric acid. A yellow oil with a pleasant odor formed and was separated. It decomposed slowly on standing, precipitating a solid identified as sulfur by mixed melting point. The amount of sulfur produced increased with time. The infrared spectrum of the freshly prepared oil showed only a weak absorption near 2100 cm.$^{-1}$; in subsequent spectra its intensity became progressively greater. The oil, believed to be cyclohexylthiatriazole, could not be crystallized or distilled.

Decomposition of 5-phenyl-1,2,3,4-thiatriazole in sulfuric acid. A solution of 4.25 g. of phenylthiatriazole in 50 ml. of concd. sulfuric acid was allowed to stand for 12 hr. and was then poured over ice; 0.80 g. (96%) of sulfur, m.p. 120–121°, was removed by filtration. The filtrate was extracted with benzene, and the extracts dried over magnesium sulfate and evaporated, leaving a residue of 0.2 g. (8%) of benzoic acid, identified by mixed melting point.

Thermal decomposition of 5-methoxyphenyl-1,2,3,4-thiatriazole. A solution of 2.83 g. of 5-*p*-methoxyphenyl-1,2,3,4-thiatriazole in 28 ml. of tetralin was heated to just below its boiling point; 339 ml. of gas (S.T.P.) was collected (calculated 328 ml.). The mixture was filtered from a trace of tar and washed four times with 35 ml. of saturated sodium sulfide solution to remove sulfur. The tetralin solution, whose infrared spectrum showed absorption at 2130 cm.$^{-1}$, was heated with 75% sulfuric acid to hydrolyze benzonitrile, separated, washed with a little water, and extracted with 10% sodium hydroxide solution. Acidification produced 1.40 g. (62.5%) of impure *p*-anisic acid, m.p. 182–183°, undepressed when mixed with an authentic sample.

In another experiment, 4.65 g. of 5-*p*-methoxyphenylthiatriazole produced 515 ml. of gas (calculated, 531 ml.). The solvent was then removed by steam distillation, leaving 0.42 g. (54%) of sulfur, m.p. 120–121°. Similar results were obtained in experiments with phenylthiatriazole.

Reduction of 5-phenyl-1,2,3,4-thiatriazole by lithium aluminum hydride. A solution 7.48 g. of phenylthiatriazole in 50 ml. of anhydrous ether was added to 2.1 g. of lithium hydride, stirred for 10 min., and then 2.1 ml. of water was added followed by 8.5 ml. of 4% sodium hydroxide. The filtered and dried ether layer was evaporated, leaving a residue of 4.77 g. (83.9%) of brown oil, which solidified on standing in air to give dibenzyl disulfide, m.p. 72°, undepressed by mixture with a known sample.

Attempted oxidation of 5-phenyl-1,2,3,4-thiatriazole and 5-p-methoxyphenyl-1,2,3,4-thiatriazole with peroxyformic acid. A mixture of 8.15 g. of phenylthiatriazole, 6.90 g. of 25% hydrogen peroxide, and 84.5 g. of 90% formic acid was main-

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[8] Melting points are uncorrected. Analyses by Spang Microanalytical Laboratory, Ann Arbor, Mich.

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]

EDWARD C. TAYLOR AND MALCOLM J. THOMPSON

Received June 19, 1961

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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(1) This work was supported by a research grant (CY-2551) to Princeton University from the National Cancer Institute, National Institutes of Health, Public Health Service.

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