[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

STUDIES ON CONDENSED PYRIMIDINE SYSTEMS. V. (1) THE PYRIMIDO[4,5-*c*][1,2,5]THIADIAZOLE RING SYSTEM

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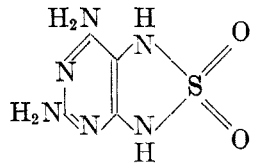
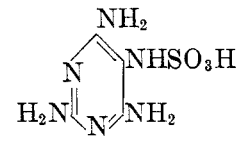
Substances containing the 2,4-diaminopyrimidine moiety have growth-inhibitory properties in a number of biological systems (2–7). This has led to the investigation of a variety of ring systems containing this structure (*cf.* 1). The structure 5,7-diamino-1,3-dihydropyrimido[4,5-*c*][1,2,5]thiadiazole-2,2-dioxide (I) was proposed as worthy of investigation. It appeared possible that this substance could be obtained by the cyclization of 2,4,6-triamino-5-pyrimidylsulfamic acid (II). The corresponding 2,4,6-trihydroxy-5-pyrimidylsulfamic acid



I



II

has long been known, having been prepared by the action of ammonium sulfite on alloxan (8) and violuric acid (9). The required triamino derivative was first encountered in this laboratory as a by-product of the reduction of 5-nitroso-2,4,6-triaminopyrimidine by hydrosulfite ion (*cf.* 10) to 2,4,5,6-tetraaminopyrimidine and later was prepared by the action of sulfuryl chloride on the tetraaminopyrimidine and by fusion of the sulfate of the latter with sulfamide.

The attempted cyclization of 2,4,6-triamino-5-pyrimidylsulfamic acid with phosphorus oxychloride or with a mixture of sulfuric acid and acetic anhydride was unsuccessful. The 5-sulfamic acid reacted with phosphorus pentachloride in phosphorus oxychloride to give a solid containing phosphorus, sulfur, and chlorine. The substance fumed in moist air and liberated hydrochloric acid on hydrolysis. The gain in weight of the product over the starting material indicated the formation of a bis- or tris-dichlorophosphamide of the type described by Johnson (11).

The failure of tetraaminopyrimidine to undergo cyclization with sulfuryl chloride to give the desired thiazolopyrimidine and the interruption of the reaction at the sulfamic acid stage was interpreted in terms of Todd's (17) statement that the 4- or the 6-amino group in a 4,5,6-triaminopyrimidine behaves as a true amino group only if the 2-position is occupied by a group incapable of partaking in a tautomeric shift (*cf.* 12–16). In an attempt to circumvent the

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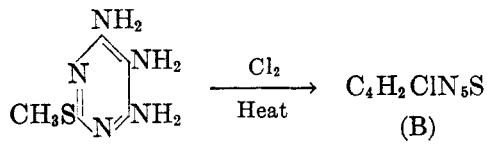
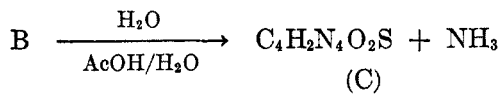
prototropic hindrance imposed by the amino-imino system, 2-methylmercapto-4,5,6-triaminopyrimidine was treated with sulfuryl chloride and, although the reaction did not yield the expected product, it did give, upon hydrolysis, two products which appear to contain the desired ring system. The major product is an alkali-soluble, acid-insoluble substance (A) which analyzes for $C_4H_2ClN_{4-5}S$ and the side product is a neutral substance (B) which analyzes for $C_4H_2ClN_5S$, the relative proportions of each depending upon the reaction conditions.

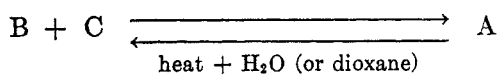
The absence of oxygen in the compounds isolated indicated that sulfuryl chloride was reacting through dissociation into sulfur dioxide and chlorine and it was found that a solution of carbon tetrachloride saturated with chlorine caused the same reaction under pressure.

Crystallization of A resulted unexpectedly in the conversion of A to B plus a third substance (C) which is amphoteric and analyzes for $C_4H_2N_4O_2S$. By dissolving B in cold 6 *N* sulfuric acid and diluting with water, conversion of this substance to A is effected. B can be completely converted to C by treatment with acetic acid.

The over-all scheme of reaction and hydrolysis may be represented as follows:

1. 

2. 

3. 

The structure of compound B is the core of the problem.

The presence of chlorine in the reaction products indicated that the C—S bond had been cleaved by chlorine (*cf.* 18). The unreactivity of 4,5,6-triaminopyrimidine towards sulfuryl chloride and towards chlorine also lends support to this view. Furthermore, the triamine reacts with sulfur dichloride to give a product analyzing for $C_4H_3N_5S$, the ultraviolet spectrum of which closely resembles that of B except for the alkaline shift. It is inferred from this that the original reaction of the 2-methylmercaptopyrimidine resulted first in the cleavage of the pyrimidine—S bond and the substitution of a chlorine atom in the 2-position of the pyrimidine ring followed by the formation of sulfur dichloride, which reacted with the amino groups to form the 1,2,5-thiadiazole ring of B accompanied by partial dehydrogenation. Removal of sulfur with Raney nickel (*cf.* 19) gave a small amount of a compound analyzing for $C_4H_4ClN_5$.

The ultraviolet spectrum of A and B and its sulfur-free derivative are con-

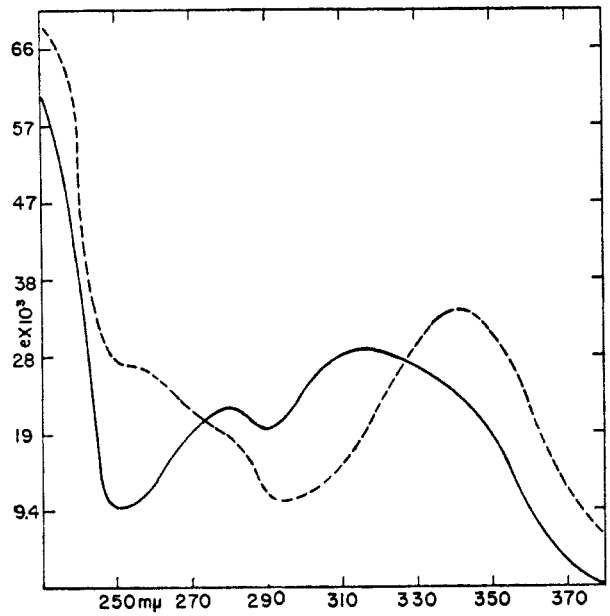


FIGURE 1. ULTRAVIOLET ABSORPTION SPECTRUM OF COMPOUND A: ———, at *p*H 1.0; ----------, at *p*H 11.0.

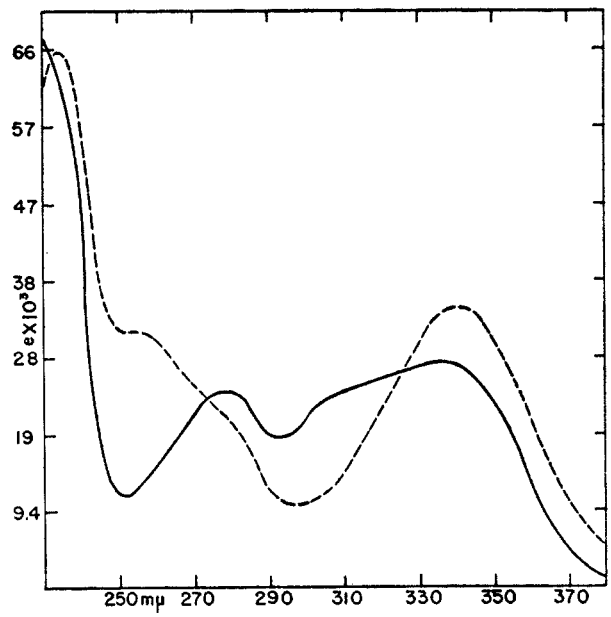
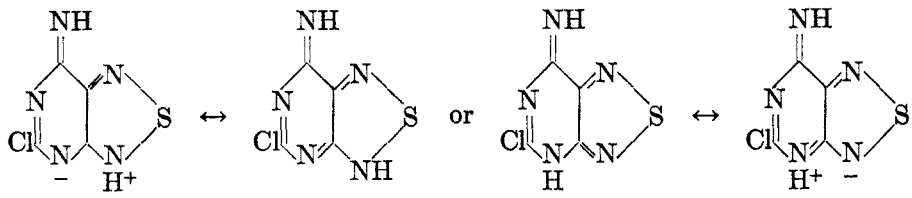


FIGURE 2. ULTRAVIOLET ABSORPTION SPECTRUM OF MIXTURE OF 4 PARTS B AND 1 PART C: ———, at *p*H 1.0; ----------, at *p*H 11.0.

siderably more complex than those usually observed for pyrimidines and resemble those of pteridines and other fused pyrimidine systems. However, a

molecular weight determination on B by the Rast method gave the value 149.[2] We proposed for B the structure



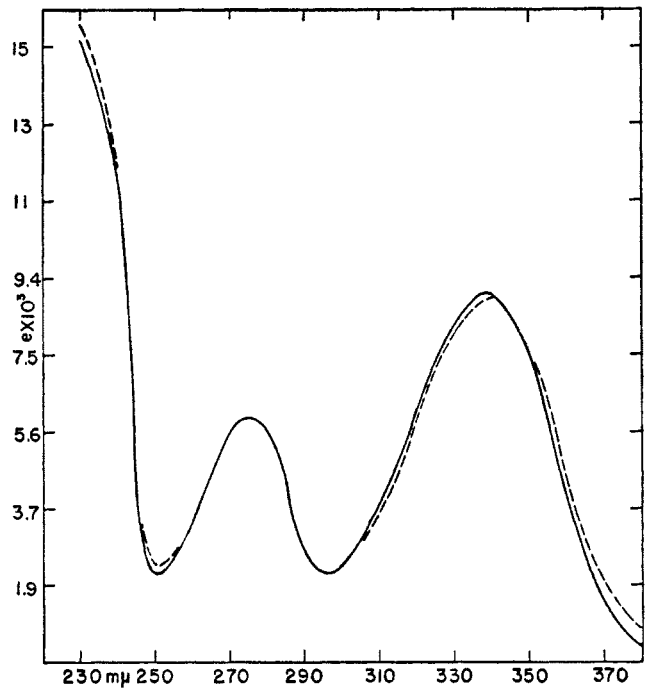
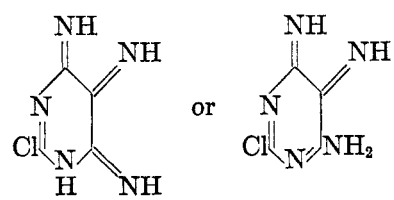


FIGURE 3. ULTRAVIOLET ABSORPTION SPECTRUM OF COMPOUND B: ———, at *p*H 1.0; ----------, at *p*H 11.0.

and an analogous structure for the compound obtained from 4,5,6-triaminopyrimidine. The compound obtained by the removal of sulfur may then be represented as



The infrared spectrum of B in Nujol shows the strongest absorption at 1655 cm.$^{-1}$ which corresponds well with the C=N frequency and weak bands at 786

[2] The mixture of camphor and compound B melted with decomposition so that the value obtained for the molecular weight is undoubtedly too low.

and 1546 cm.$^{-1}$ corresponding to the C—Cl bond and its first overtone (20). At present we are unable to assign significance to the other bands. The lack of strong absorption at the N—H frequencies at 3100–3600 cm.$^{-1}$ and the absence

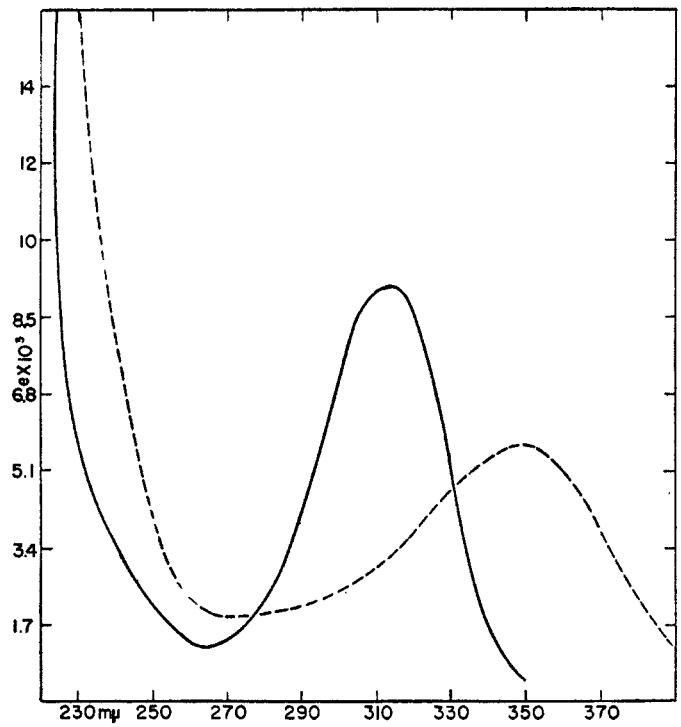


FIGURE 4. ULTRAVIOLET ABSORPTION SPECTRUM OF COMPOUND C: ————, at *p*H 1.0; ---------, at *p*H 11.0.

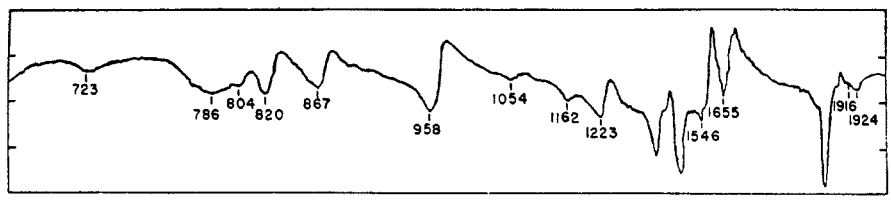
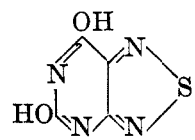


FIGURE 5. INFRARED ABSORPTION SPECTRUM OF COMPOUND B IN NUJOL.

of any alkali shift of the ultraviolet spectrum may be due to resonance contributions of the type indicated above.

The empirical formula for C, $C_4H_2N_4O_2S$, its method of synthesis, and its chemical behavior suggest the structure



This would explain the alkali and acid solubilities and the formation of C from B by hydrolysis. Johnson (18) has shown that the aqueous acid chlorination of

alkyl mercaptopyrimidines often results in a product containing oxygen rather than chlorine in the 2-position.

The ultraviolet spectrum of A resembles a summation of the spectra of B and C in the ratio of 4:1 except for the presence of an additional peak at 235 mμ. Repeated solution in alkali and subsequent precipitation by acid failed to change the characteristics of the spectrum of A. These data indicate that the precursor of component C as it exists in A has the empirical formula $C_4H_2ClN_4OS$ which is hydrolyzed to $C_4H_2N_4O_2S$. The difference in spectrum between A and the mixture of B and C may then be ascribed to the presence of a chlorine rather than a hydroxyl group at the 2-position of C. The nitrogen content of a mixture of four parts of $C_4H_2ClN_5S$ and one part of $C_4H_2ClN_4OS$ is 35.6% which corresponds well with the analytical result of 35.5%. The reaction B $\rightarrow$ C undoubtedly occurs through the intermediate $C_4H_2ClN_4OS$. Treatment of A with methyl sulfate and alkali gave a neutral substance analyzing for $C_6H_6ClN_5S$, the spectrum of which closely resembles that of B. The formula of this derivative indicates that it is the dimethyl derivative of the neutral compound B and not that of alkali-soluble compound C.

The most probable structure for A would appear to be a definite chemical combination consisting of four parts of B and one part of $C_4H_2ClN_4OS$.

EXPERIMENTAL

Preparation of 2,4,6-triamino-5-pyrimidylsulfamic acid. (a) *By reduction of 5-nitroso-2,4,6-triaminopyrimidine with sodium bisulfite.* A mixture of 10 g. of 5-nitroso-2,4,6-triaminopyrimidine, 13 g. of sodium bisulfite, and 20 g. of ammonium chloride in 300 ml. of water was boiled for 90 minutes, during which time the deep rose color turned to a light pink. The mixture was then made alkaline and filtered. Acidification of the filtrate caused the precipitation of 5.8 g. (42%) of the 5-sulfamic acid. 2,4,6-Triamino-5-pyrimidylsulfamic acid was identified by elementary analysis and by hydrolysis with 2 *N* hydrochloric acid for one hour at 100° to give the tetraaminopyrimidine sulfate in 80% yield.

Anal. Calc'd for $C_4H_8N_6O_3S$: C, 21.85; H, 3.64; N, 38.15.
Found: C, 22.20; H, 3.30; N, 37.60.

(b) *By reaction of tetraaminopyrimidine with sulfuryl chloride.* Amorphous tetraaminopyrimidine (5.0 g., prepared from the sulfite salt by neutralization with barium hydroxide or by the platinum-catalyzed reduction of 2,4,6-triamino-5-nitrosopyrimidine in absolute ethanol at a hydrogen pressure of 25 lbs. at room temperature) was suspended in 300 ml. of anhydrous ether containing 4.8 g. of sulfuryl chloride. The mixture was stirred under reflux for 24 hours, cooled, filtered, and washed with 1 *N* sodium hydroxide. Acidification of the alkaline filtrate with 10% acetic acid caused the precipitation of a light yellow solid which was redissolved in alkali and precipitated by pouring the alkaline solution into hot dilute acetic acid. The white solid was dried.

Anal. Calc'd for $C_4H_8N_6O_3S$: N, 38.15. Found: N, 38.0.

(c) *By reaction of tetraaminopyrimidine with sulfamide.* A mixture of 0.5 g. of tetraaminopyrimidine sulfate and 1.5 g. of sulfamide was heated at 150–160° for one hour. The mixture was cooled and triturated with 5 ml. of 1 *N* sodium hydroxide and filtered. Acidification of the alkaline filtrate gave 0.1 g. of the 5-sulfamic acid identified by its spectrum.

Reaction of 2-methylmercapto-4,5,6-triaminopyrimidine with sulfuryl chloride. 2-Methylmercapto-4,5,6-triaminopyrimidine (10 g.) was refluxed in 250 ml. of sulfuryl chloride for eight hours, cooled, filtered, and decanted. The total weight of solids represented about 40% of the starting material and considerable amounts of ammonia and methyl mercaptan

were detected in working up the reaction mixture. The residue was washed with ether and hydrolyzed with 1 *N* sodium hydroxide under ether. The ether was evaporated off and the remaining mixture was filtered. The residue (0.7 g.) was crystallized three times from water and three times from alcohol to give white needles (B), m.p. 220–225° (d); molecular weight, 149 (Rast).

Anal. Calc'd for $C_4H_2ClN_5S$: C, 25.6; H, 1.06; Cl, 18.9; N, 37.2; S, 17.1.
Found: C, 25.8; H, 1.08; Cl, 18.7; N, 37.6; S, 17.1.

The alkaline filtrate from the hydrolysis was acidified with 10% acetic acid to give 2.0 g. of a light yellow solid which was filtered off, dissolved in alkali, and precipitated by the addition of acid. The last step was repeated three times, cooling the alkaline solution in an ice-bath in order to crystallize out any amount of B present. A white solid A was obtained which gave only B on crystallization from water.

Anal. Calc'd for $C_4H_2ClN_5S$: C, 25.6; H, 1.06; Cl, 18.9; N, 37.2.
Found: C, 26.1; H, 1.01; Cl, 18.4; N, 35.5.

When the reaction with sulfuryl chloride was carried out in a bomb at 100° the ratio of products, as compared with the reflux reaction, was reversed, and in both instances varied between 5:1 and 3:1.

2-Methylmercapto-4,5,6-triaminopyrimidine (10 g.) gave approximately equal weights of A and B upon treatment with carbon tetrachloride saturated with chlorine in a sealed bomb at 100° for six hours.

Concentration of all the aqueous liquors from A and B resulted in the crystallization of 0.1 g. of hard yellow prisms.

Anal. Calc'd for C, $C_4H_2N_4O_2S$: C, 27.7; H, 1.16; N, 32.2.
Found: C, 28.4; H, 1.14; N, 32.2

Cleavage of compound A *in dioxane.* Compound A was treated with boiling dioxane for one hour leaving a residue identified as C. The first finely divided crystals deposited were unreacted A. Filtration and continued cooling of the dioxane resulted in the crystallization of B as large orange solvated crystals which melted at room temperature to deposit amorphous B. The ratio of B to C isolated was 2.4:1.

Acid hydrolysis of compound B. Compound B was dissolved in cold 6 *N* sulfuric acid which gave on dilution an equal weight (approx.) of A. When compound B was evaporated to dryness from a boiling 50% acetic acid solution the spectrum and solubility of the residue were those of C.

Reaction of compound A *with methyl sulfate.* Compound A (0.5 g.) was dissolved in 1 *N* sodium hydroxide and the solution was shaken with 1.0 g. of methyl sulfate for 15 minutes at which time yellow crystals separated out. The product was filtered off and recrystallized from alcohol.

Anal. Calc'd for $C_6H_6ClN_5S$: C, 33.4; H, 2.79; N, 32.2.
Found: C, 33.8; H, 2.82; N, 32.1.

Reaction of 4,5,6-triaminopyrimidine with sulfur dichloride. 4,5,6-Triaminopyrimidine (1.8 g.) was treated with 50 ml. of "sulfur dichloride" (sulfur monochloride was saturated with chlorine gas at 0° and swept with nitrogen to remove excess chlorine) (21) at 100° for six hours in a bomb. The reaction mixture was diluted with petroleum ether and the red solid was filtered off and dissolved in hot dilute sodium hydroxide which was filtered, concentrated under reduced pressure, and acidified to give a yellow solid. This was crystallized three times from dioxane to give 0.3 g. of material of m.p. 248–250° (d.) which was soluble in alkali but insoluble in acid.

Anal. Calc'd for $C_4H_3N_5S$: C, 31.4; H, 1.96; N, 45.7; S, 20.9.
Found: C, 32.9; H, 1.91; N, 43.6; S, 20.1.

Ultraviolet absorption spectrum: ϵ = 4,300, 11,000 (*p*H 1.0) at 265 mμ and 328 mμ; minima at 245 mμ and 283 mμ; ϵ = 5,400, 8,100 (*p*H 11.0) at 275 mμ and 332 mμ; minima at 250 mμ and 295 mμ.

4,5,6-Triaminopyrimidine (0.2 g.) was refluxed with sulfuryl chloride for 45 hours but

was recovered unchanged. The same reaction conducted at 100° in a bomb also gave only starting material.

Dethiolation of B. A mixture of 6 g. of B, 60 g. of Raney nickel, and 2 g. of sodium carbonate in 400 ml. of 95% alcohol was refluxed for six hours and filtered hot. The Raney nickel was extracted in a Soxhlet apparatus for 12 hours with 95% alcohol. The combined alcohol extract was treated with Darco, concentrated to 30 ml., and diluted with ether, causing the formation of a precipitate. The mixture was cooled overnight at 5° and filtered. The residue was dissolved in 1 *N* sodium hydroxide, filtered through Filter Cel, and the filtrate was acidified with 10% acetic acid. The solution was concentrated until an orange solid precipitated.

Anal. Calc'd for $C_4H_4ClN_5$: C, 30.48; H, 2.54.

Found: C, 30.34; H, 2.56.

Ultraviolet absorption spectrum: ϵ = 9,200 (*p*H 1.0) at 269 mμ; ϵ = 9,300 (pH 11.0) at 274 mμ.

Treatment of B with hydrogen at 45 lbs. pressure in the presence of Adams platinum catalyst in ethanol at 75° was without effect.

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SUMMARY

The reaction between 2-methylmercapto-4,5,6-triaminopyrimidine and sulfuryl chloride or chlorine in carbon tetrachloride gives rise to two products which appear to have the pyrimido[4,5-*c*][1,2,5]thiadiazole structure. One of these is monomeric but the other appears to be more complex, containing at least five pyrimidine nuclei.

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