2-Methylsulfonyladenine. A.—2-Methylmercaptoadenine (0.5 g.) in *N* sodium hydroxide (20 ml.) was treated with 30% hydrogen peroxide (5 ml.), left at room temperature for 24 hr., and made just acid with acetic acid; a white precipitate was collected and combined with a second crop obtained by addition of ethanol and ether to the filtrate. The combined solids were recrystallized from water to fine white needles (0.41 g., 67%) of 2-methylsulfonyladenine, m.p. above 300°. Todd, *et al.*,[9] gave m.p. above 350°.

B.—2-Methylmercaptoadenine (1 g.) was suspended in methanol (30 ml.) and the slurry was stirred at room temperature while chlorine gas was bubbled into it. After less than 1 min., all the starting material had dissolved; about 2 min. later a crystalline product began to precipitate. The reaction was stopped after an additional 5 min. and the product, collected by filtration (1.15 g., 97%), was identical in its ultraviolet absorption spectra and in its paper chromatographic behavior with 2-methylsulfonyladenine from procedure A.

Action of Concentrated Hydrochloric Acid on 2-Methylsulfinyladenine 1-N-Oxide.—2-Methylsulfinyladenine 1-N-oxide (0.1 g.) in concentrated hydrochloric acid (2 ml.) was heated at 90° for 2 to 3 min. The reaction mixture was cooled and 0.07 g. of white needles of the hydrochloride of 2-methylmercaptoadenine 1-N-oxide was collected. The mother liquor contained more of this product, isoguanine N-oxide, and trace amounts of a third compound which was ferric chloride positive and ultraviolet absorbing.

Action of Concentrated Hydrochloric Acid on 2-Methylsulfinyladenine.—2-Methylsulfinyladenine (0.1 g.) in concentrated hydrochloric acid (2 ml.) was heated at 90° for 2 to 3 min. The reaction was cooled and 0.1 g. of white microcrystals of the hydrochloride of 2-methylmercaptoadenine was collected. The mother liquor of this reaction contained a trace of this same product and a second unidentified ultraviolet-absorbing substance.

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Displacement of the 2-Methylmercapto Group in Pyrimidines Bearing a 5-Nitroso Substituent[1]

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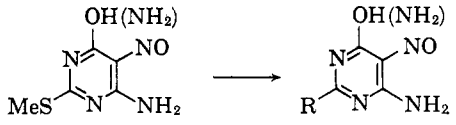
The 5-nitroso group has been shown to have an activating effect on the nucleophilic displacement of the 2-methylmercapto substituent in 2-methylmercapto-5-nitrosopyrimidines.

The synthesis of 2-substituted amino-6-hydroxypurines by the displacement of a 2-methylmercapto group by alkylamines was reported a number of years ago.[2a] Attempts[2a,b] to synthesize 2-substituted amino-6-aminopurines in a similar manner were unsuccessful. The lack of reactivity of the 2-methylmercapto group in 6-amino-2-methylmercaptopurine is in keeping with the poor reactivity observed for the 2-chloro substituent in the corresponding 2-chloro-6-aminopurine,[3-5] and the 2-methylmercapto substituent in certain pyrimidines and purines.[2b,6-9]

The most surprising report on the lack of reactivity of the methylmercapto grouping was the observation[2b] that this group could not be replaced by an amino group in 4-amino-2-methylmercapto-6-hydroxy-5-nitropyrimidine, where activation of the substituent in the 2-position by the 5-nitro group would be expected. As pyrimidines of type II would be convenient intermediates not only for the synthesis of purines, but also for 8-aza or 8-mercapto analogs, we decided to reinvestigate the displacement of the 2-methylmercapto group from pyrimidines suitably activated by substitution in the 5-position. The choice of the 5-nitroso grouping as such an activator was particularly fortunate, as the 5-nitroso derivatives of the 2-methylmercaptopyrimidines (I) are blue or blue-green, and the 5-nitroso derivatives of the products (II) are red. Any reaction could, therefore, be followed by looking for a color change.



Ia = 6-OH
Ib = 6-NH_2

Ia, b

When either 4-amino-6-hydroxy-2-methylmercapto-5-nitrosopyrimidine (Ia) or 4,6-diamino-2-methylmercapto-5-nitrosopyrimidine (Ib) is refluxed in aqueous solution with four equivalents of amine, a rapid evolution of methylmercaptan takes place; in ten to twenty minutes the color change is complete. The yields vary from 70 to 90%. The reactions also proceed, although more slowly, at room temperature, and initial solution of the starting material is unnecessary.

Decomposition of the nitroso pyrimidines can be followed by the weakening of their distinctive colors. The displacement of the methylmercapto group from the 4-amino-6-hydroxy-2-methylmercapto-5-nitrosopyrimidine in aqueous ammonia at 100° was a slow reaction; considerable decomposition of the starting material occurred, and only a 26% yield of the product was obtained. With the 6-amino compound, no aminated product was obtained, and decomposition was extensive.

A simpler method of making the 2-amino analog consists of treating the 2-methylmercaptopyrimidine with an excess of hydroxylamine at room temperature. In

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this way the corresponding 2-hydroxylaminopyrimidines (IIa,b, R = NHOH) were obtained in good yield and were used directly for the next step, namely, the simultaneous reduction of both the nitroso and hydroxylamino groups with sodium dithonite. For example, an over-all yield of more than 90% could be obtained in the conversion of 4-amino-6-hydroxy-2-methylmercapto-5-nitrosopyrimidine to 2,4,5-triamino-6-hydroxypyrimidine sulfate.[10] The ready reduction of a hydroxylamino substituent on the pyrimidine ring of a purine has already been observed.[11] An interesting comparison of the reactivity of the methylmercapto substituents in these two nitroso pyrimidines is afforded by the respective reactions with hydroxylamine. With 4-amino-6-hydroxy-2-methylmercapto-5-nitrosopyrimidine, the reaction is complete in two to three hours, but needs five days and four times as much amine with the corresponding 6-aminopyrimidine.

Reduction of all the 5-nitrosopyrimidines to the corresponding 5-amino derivatives was accomplished with sodium dithionite. The 5-amino compounds have been used without further purification for several ring closures to purines and azapurines.

Experimental

Reaction of Amines with 4-Amino-6-hydroxy-2-methylmercapto-5-nitrosopyrimidine. A.—The nitrosopyrimidine[12] (0.5 g.) was dissolved in water (10 ml.) containing morpholine (0.94 g.), and the solution was either left at room temperature for 90 min. or refluxed for 10 min. The pH was then adjusted to 5 with glacial acetic acid; the solid that formed was collected and washed with water. Recrystallization from water gave 4-amino-6-hydroxy-2-morpholino-5-nitrosopyrimidine as red needles (0.525 g., 87%), m.p. 245° dec.

Anal. Calcd. for $C_8H_{11}N_5O_3$: C, 42.7; H, 4.9; N, 31.1. Found: C, 43.1; H, 5.4; N, 31.4.

B.—With piperidine (0.92 g.) as described in the previous method and a 10-min. reflux, the 2-piperidinopyrimidine was obtained as light red needles (0.45 g., 75%), m.p. 243°.

Anal. Calcd. for $C_9H_{13}N_5O_2$: C, 48.4; H, 5.9; N, 31.4. Found: C, 48.4; H, 6.0; N, 31.1.

C.—The reaction with pyrrolidine (0.76 g.) gave, after recrystallization from water, with the addition of sufficient ethanol to effect solution, red needles (0.48 g., 85%) of the pyrrolidino derivative, m.p. 270°.

Anal. Calcd. for $C_8H_{11}N_5O_2 \cdot {}^1/_4H_2O$: C, 45.0; H, 5.3; N, 32.8. Found: C, 45.0; H, 5.4; N, 32.8.

D.—The reaction was repeated with β-hydroxyethylamine (0.65 g.). The refluxing was continued until the starting material all had gone into solution. After acidification to pH 5 an orange solid separated. Recrystallization from about 500 ml. of water gave light orange microcrystals (0.4 g., 75%) of the 2-β-hydroxyethylamino derivative, m.p. 262°.

Anal. Calcd. for $C_6H_9N_5O_3$: C, 36.2; H, 4.6. Found: C, 35.9; H, 4.4.

E.—The nitrosopyrimidine (0.5 g.) was suspended in a solution of hydroxylamine hydrochloride (0.76 g.) in water (10 cc.) containing sodium hydroxide (0.38 g.). The reaction mixture was stirred at room temperature for 3 hr. The orange precipitate, which gave a dark green color in the test with ferric chloride, was collected by filtration and washed with water, ethanol, and ether. Recrystallization from water gave a bright orange solid (0.45 g., 98%), m.p. above 300°.

Anal. Calcd. for $C_4H_5N_5O_3$: C, 28.1; H, 2.9; N, 40.9. Found: C, 27.6; H, 3.5; N, 40.8.

F.—The nitrosopyrimidine (0.5 g.) was suspended in ammonium hydroxide (25 ml.; *d*, 0.88) and boiled, without a reflux condenser, for 2 hr.; the volume was kept more or less constant by additions of ammonium hydroxide. The starting material gradually went into solution, and the pink solid that separated was collected and washed with water, ethanol, and ether. It proved to be identical with an authentic sample of 2,4-diamino-6-hydroxy-5-nitrosopyrimidine obtained from the nitrosation of 2,4-diamino-6-hydroxypryimidine[10]; yield, 0.11 g., 26%.

Reaction of Amines with 4,6-Diamino-2-methylmercapto-5-nitrosopyrimidine. A.—The nitrosopyrimidine (0.5 g.), prepared by nitrosation of 4,6-diamino-2-methylmercaptopyrimidine,[13] was dissolved in a solution of morpholine (0.94 g.) in water (10 ml.), and the mixture was refluxed for 20 min. The crystals, formed as the solution cooled, were collected by filtration and recrystallized from water to give the purple needles of the 2-morpholinopyrimidine (0.43 g., 71%), m.p. 237–238°.

Anal. Calcd. for $C_8H_{12}N_6O_2$: C, 42.8; H, 5.4; N, 37.5. Found: C, 42.8; H, 5.8; N, 37.4.

B.—A solution of the starting material (0.5 g.) in a 25% aqueous solution of dimethylamine (20 ml.) was heated to reflux and then allowed to cool to room temperature. The crystalline precipitate was purified by recrystallization from water to give the 2-dimethylamino analog (0.42 g., 85%) identical with the known[2] compound.

C.—Under similar conditions with piperidine (0.92 g.) and a 10-min. reflux, red crystals (0.5 g., 83%) were obtained after neutralization with glacial acetic acid, m.p. 195–197°.

Anal. Calcd. for $C_9H_{14}N_6O$: C, 48.6; H, 6.3; N, 37.8. Found: C, 48.6; H, 6.6; N, 38.3.

D.—With pyrrolidine (0.76 g.) and a procedure identical to that in C, the purple crystalline 2-pyrrolidino derivative (0.51 g., 89%) was obtained, b.p. 294–295°.

Anal. Calcd. for $C_8H_{21}N_6O$: C, 46.1; H, 5.8; N, 40.4. Found: C, 46.1; H, 5.9; N, 39.8.

E.—Reflux for 10 min. with β-hydroxyethylamine (0.65 g.) and subsequent cooling gave the 2-β-hydroxyethylaminopyrimidine as orange needles (0.4 g., 75%), m.p. 240°.

Anal. Calcd. for $C_6H_{10}N_6O_2$: C, 36.4; H, 5.1; N, 42.4. Found: C, 36.6; H, 5.4; N, 42.4.

F.—The nitrosopyrimidine (0.5 g.) in water (10 ml.) containing sodium hydroxide (0.38 g.) was treated with hydroxylamine hydrochloride (0.76 g.). The suspension was stirred at room temperature for 5 days and, at intervals, a total of an additional 1.14 g. of hydroxylamine hydrochloride and 0.57 g. of sodium hydroxide were added. After 5 days, the suspension had changed from the original blue color to bright orange, and the crude solid 2-hydroxylamino analog was collected and washed with cold water; yield, 0.36 g., 78%; m.p. above 300°. It gave a deep orange color with ferric chloride.

Anal. Calcd. for $C_4H_6N_6O_2$: C, 28.2; H, 3.6; N, 49.4. Found: C, 28.9; H, 3.7; N, 49.2.

Reduction of Nitrosopyrimidines.—The nitrosopyrimidine was suspended in about 5 times its weight of 0.1 *N* sodium hydroxide and treated at 90° with just enough sodium dithionite to destroy the color of the nitroso starting material. The reaction mixture was cooled; the 4,5-diaminopyrimidine was collected, washed with water and ether, and used directly for subsequent syntheses. By this method the following 5-aminopyrimidines were obtained in the yields specified; 4,5,6-triamino-2-morpholinopyrimidine (90%), 4,5,6-triamino-2-piperidinopyrimidine (98%), 4,5,6-triamino-2-pyrrolidinopyrimidine (65%), 4,5-diamino-6-hydroxy-2-morpholinopyrimidine (92%), 4,5-diamino-6-hydroxy-2-piperidinopyrimidine (67%), and 4,5-diamino-6-hydroxy-2-pyrrolidinopyrimidine (87%).

The same reaction on 4-amino-6-hydroxy-2-hydroxylamino-5-nitrosopyrimidine and 4,6-diamino-2-hydroxylamino-5-nitrosopyrimidine gave 2,4,5-triamino-6-hydroxypyrimidine and 2,4,5,6-tetraaminopyrimidine, respectively. They were isolated as their sulfates and were identical with authentic samples.[9,14]

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