α-conidendrin (VI) (1.0 g., 0.00264 mole) in 400 ml. of dry benzene was treated with an excess of an ether solution of lithium aluminum hydride. After one hour, the excess reagent was decomposed by the cautious addition of water and the solvent was evaporated at reduced pressure. The residue was treated with dilute sulfuric acid and the mixture extracted with chloroform. The chloroform solution was washed with water, dried, evaporated almost to dryness and methanol added. Colorless, fine needles separated and after three recrystallizations from methanol–chloroform melted at 188–189°.

Anal. Calcd. for $C_{22}H_{24}O_6$: C, 68.75; H, 6.29. Found: C, 69.02; H, 6.35.

Dimethylanhydro-β-conidendryl Alcohol (XV).—Dimethyl-β-conidendryl alcohol (XIV) (1.5 g., 3.9 millimoles) was heated (oil-bath) with potassium acid sulfate (3.0 g., 0.022 mole) for 30 minutes at 160°. The mixture was digested with 20 ml. of hot water and the solution decanted to remove the inorganic salt. The residue was extracted with three 10-ml. portions of methanol, the combined extracts concentrated to about 15 ml. and an equal volume of water added. On cooling and scratching, the anhydro compound XV separated, yield 0.92 g., m.p. 94–97°. On further dilution of the mother liquor, 0.24 g. of the material was obtained (total yield 81%). The compound is very soluble in benzene, soluble in hot cyclohexane and insoluble in low-boiling petroleum ether. Recrystallization from cyclohexane containing a small amount of benzene gave large colorless needles and long hollow rectangular pyramids, m.p. 97–98°, $[\alpha]^{26}D$ −33° (*c* 3.2, acetone), −29° (*c* 2.2, chloroform).

Anal. Calcd. for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08; OCH_3, 33.50. Found: C, 71.58; H, 7.32; OCH_3, 33.91.

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Purines. III. The Preparation of Certain Purine and Triazolopyrimidine Derivatives[1]

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The utilization of 2,6-dichloro-4-amino-5-nitropyrimidine in the preparation of a series of new purine derivatives and their azapurine analogs is described.

Since the discovery that 6-mercaptopurine possesses marked inhibitory properties[2] there has been an increasing interest in purine antagonists which has carried over into the triazolopyrimidine homologs.[3] In this Laboratory a new series of these derivatives has been prepared from 2,6-dichloro-4-amino-5-nitropyrimidine.[4]

This intermediate is readily converted to the corresponding methoxy and methylmercapto derivatives by treating it with alcoholic solutions of sodium methoxide or sodium methylmercaptide.

Both 2,6-dimethoxy-4-amino-5-nitropyrimidine and 2,6-dimethylmercapto-4-amino-5-nitropyrimidine were reduced catalytically without any difficulty to the diamine and the reduction product isolated as the rather insoluble sulfate. The sulfates were in turn cyclized to the corresponding purines.[5] 2,6-Dimethoxypurine was found to have an indefinite melting point; apparently it rearranges during fusion. This behavior has been noted in the case of 2,4-dimethoxypyrimidine.[6] The treatment of 2,6-dichloro-4-amino-5-nitropyrimidine with sodium hydrosulfide simultaneously thionated and reduced the nitropyrimidine to yield 2,6-dimercapto-4,5-diaminopyrimidine directly. This diamine was formylated and cyclized to yield 2,6-dimercaptopurine.

The preparations of the triazolopyrimidines were quite straightforward. The diamine free bases (or their sulfates) were treated with excess nitrous acid to yield the insoluble triazolo derivative.

5,7-Dimercapto-1-γ-triazolo[d]pyrimidine made by the above procedure was almost completely insoluble in all the usual solvents. With hot sodium hydroxide it is possible to solubilize the compound; however, reprecipitation with acid yields a product with different solubility characteristics; *i.e.*, solubility in ammonium hydroxide. This compound has recently been prepared by another method by Bahner and co-workers[7] who reported absorption maxima at 343 and 283 mμ at both *p*H 6.5 and 10. In this Laboratory the maximum at 343 mμ was confirmed but the other maximum was found at 273 mμ. This maximum was relatively strong at *p*H 10 and very weak at *p*H 6.5. However, the data were reproducible upon changing the *p*H back and forth so that the fading of this maximum (at 273) may be accounted for on the basis of enolization.

Experimental[8]

2,6-Dimethoxy-4-amino-5-nitropyrimidine.—2,6-Dichloro-4-amino-5-nitropyrimidine (5.0 g.) was dissolved in 110 ml. of cold absolute methanol and the mixture was slowly added over a period of 30 minutes to a solution prepared by dissolving 1.1 g. of sodium in 50 ml. of absolute methanol. The temperature was maintained between 15–20° during the reaction by means of an ice-bath. After the addition the bath was removed and the solution was stirred for three additional hours. The solution was then brought to boiling for three minutes and cooled; yield (80%) 3.85 g. of white needles, m.p. 179–179.5°; recrystallization from methanol–water gave m.p. 180–181°.

Anal. Calcd. for $C_6H_8N_4O_4$: N, 28.0. Found: N, 27.9.

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2,6-Dimethylmercapto-4-amino-5-nitropyrimidine.—2,6-Chloro-4-amino-5-nitropyrimidine (5.0 g.) was dissolved in 110 ml. of cold methanol and added slowly with stirring to a cooled solution (0–10°) of the sodium salt of methyl mercaptan prepared by adding 4 ml. of methyl mercaptan to a cooled solution of 1.21 g. of sodium in 50 ml. of methyl alcohol. The solution was then treated as described for the 2,6-dimethoxy analog; yield 5.2 g. (94%) yellow powder, m.p. 218–220°. A small amount was recrystallized from methanol–water mixture for analysis, m.p. 220–221°.

Anal. Calcd. for $C_6H_8N_4O_2S_2$: C, 31.08; H, 3.45. Found: C, 31.3; H, 3.30.

2,6-Dimethoxy-4,5-diaminopyrimidine.—To 160 ml. of methanol containing 2 g. of Raney nickel was added 1.78 g. of 2,6-dimethoxy-4,5-diaminopyrimidine. This mixture was hydrogenated at approximately 1 atmosphere of hydrogen until the theoretical amount of hydrogen had been absorbed (1–10 hours). The catalyst was then removed and the filtrate evaporated to yield 1.5 g. of a brown residue which was redissolved in 100 ml. of boiling water, decolorized with Norite and cooled; yield 0.7 g. of white crystals (46%), m.p. 178–179°. On standing the crystals become discolored. Recrystallization from water gave a product with m.p. 177.5–178.5°.

Anal. Calcd. for $C_6H_{10}N_4O_2$: N, 32.98. Found: N, 33.0.

2,6-Dimethylmercapto-4,5-diaminopyrimidine.—Two grams of 2,6-dimethylmercapto-4-amino-5-nitropyrimidine was dissolved in 150 ml. of methanol and hydrogenated using Raney nickel at 24 p.s.i. until the theoretical hydrogen was absorbed. The suspension was then heated to boiling, the catalyst was removed and the filtrate was evaporated to dryness to yield 1.5 g. (86%) of crude diamine, m.p. 189–190°. Recrystallization from methanol gave white, shiny flakes, m.p. 192–193°.

Anal. Calcd. for $C_6H_{10}N_4S_2$: C, 35.63; H, 4.95. Found: C, 35.6; H, 4.8.

2,6-Dimethoxypurine.—2,6-Dimethoxy-4-amino-5-nitropyrimidine (1.55 g.) was suspended in 80 ml. of methanol together with 2 g. of Raney nickel catalyst. After reduction at slightly more than 1 atmosphere the catalyst was removed and the *p*H was adjusted to 1 with concentrated sulfuric acid. Upon cooling, 1.5 g. of white crystalline salt separated.

This sulfate was dissolved in 20 ml. of formamide and heated for 20 minutes. Upon cooling and diluting with 10 ml. of water the *p*H was adjusted to 7–8 and the mixture then placed in a refrigerator overnight; yield 0.5 g. of crude purine. This was recrystallized from 120 ml. of water to yield 0.3 g. (21%) of product; 0.2 g. more of product was recovered from the filtrate. The 2,6-dimethoxypurine starts to melt at 233° forming a solid–liquid phase up to 300°; decomposes above 300°.

Anal. Calcd. for $C_7H_8N_4O_2$: C, 46.67; H, 4.44. Found: C, 46.8; H, 4.38.

2,6-Dimethylmercaptopurine.—2,6-Dimethylmercapto-4,5-diaminopyrimidine (1.5 g.) was dissolved in 45 ml. of 5% sulfuric acid. This solution upon cooling yielded 1.72 g. of the sulfate salt. The sulfate was then dissolved in 18 ml. of hot formamide and gently boiled for 20–25 minutes, cooled and then diluted with 10 ml. of water. After standing overnight the precipitate was removed; yield 1.13 g. (72%) of a greenish powder which softens 217° and melts 253–254°. When dissolved in 100 ml. of methanol and decolorized with Norite, it crystallized upon cooling to yield 0.75 g. which melts at the same temperature.

Anal. Calcd. for $C_7H_8N_4S_2$: C, 39.62; H, 3.77. Found: C, 39.6; H, 3.64.

2,6-Dimercapto-4,5-diaminopyrimidine.—To a solution saturated with hydrogen sulfide and containing 50 ml. of water, and 4.6 g. of sodium hydrosulfide was added 1.0 g. of 2,6-dichloro-4-amino-5-nitropyrimidine. This mixture was heated for 2.5 hours on a steam-bath, then filtered while hot to remove a small amount of insoluble residue. The filtrate was acidified with glacial acetic acid which precipitated the product along with considerable free sulfur. The precipitate was recrystallized from 400 ml. of water to yield 0.6 g. (73%) of golden crystals; recrystallization from water gave 0.35 g. (42%).

Anal. Calcd. for $C_4H_6N_4S_2$: N, 32.2. Found: N, 32.3.

2,6-Dimercaptopurine.—2,6-Dimercapto-4,5-diaminopyrimidine (3.5 g.) was refluxed in 100 ml. of 90% formic acid for 15 minutes. The suspension was cooled, filtered and washed with water; yield 3.1 g. (77%) of crude product.

The formyl derivative (2.85 g.) was suspended in 29 ml. of formamide and gently boiled for 15 minutes and filtered while hot. The filtrate then was diluted with 10 ml. of water and acidified with glacial acetic acid to complete the precipitation of the purine; yield 2.52 g. of a yellow product. This was twice dissolved in 90 ml. of aqueous ammonia, treated with Norite and reprecipitated with glacial acetic acid; yield 2.22 g. (86%) of a yellow powder.

Anal. Calcd. for $C_5H_4N_4S_2$: C, 32.61; H, 2.17. Found: C, 32.6; H, 2.23.

5,7-Dimercapto-1-γ-triazolo[d]pyrimidine.—2,6-Dimercapto-4,5-diaminopyrimidine (0.8 g.) was dissolved in 500 ml. of water containing 0.3 ml. of concd. sulfuric acid. The solution was decolorized with Norite and cooled to 10°. While stirring 0.4 g. of sodium nitrite was added (positive starch–iodide) and soon a fine white precipitate began to form. After stirring for one hour the mixture was filtered and the product washed with water; yield 0.58 g. (67%) of a tan powder. This compound was insoluble in cold base while the starting compound was soluble. An analytical sample was prepared by washing the product with cold 5% ammonium hydroxide and water and then drying under reduced pressure. The compound gradually turns brown on heating up to 300°; on rapid heating it explodes.

Anal. Calcd. for $C_4H_3N_5S_2$: C, 25.95; H, 1.62. Found: C, 26.1; H, 1.36.

5,7-Dimethylmercapto-1-γ-triazolo[d]pyrimidine.—2,6-Dimethylmercapto-4,5-diaminopyrimidine (0.6 g.) was dissolved in 350 ml. of hot water containing 0.2 ml. of concentrated sulfuric acid, cooled to 15° and filtered. To the cooled solution was added with stirring 0.3 g. of sodium nitrite. After a few minutes a precipitate began to form; the stirring was continued for 30 minutes longer and the mixture was then cooled for two hours. The precipitate was removed by filtration, washed with water and dried; yield 0.59 g. (93%) of a white water-insoluble powder, m.p. 226.5–227°. The product was decolorized with Norite and recrystallized from 30 ml. of methanol to yield 0.45 g. (71%), m.p. 228–229°.

Anal. Calcd. for $C_6H_7N_5S_2$: C, 33.80; H, 3.28. Found: C, 33.8; H, 3.22.

5,7-Dimethoxy-1-γ-triazolo[d]pyrimidine.—2,6-Dimethoxy-4,5-diaminopyrimidine sulfate (1.5 g.) was dissolved in 100 ml. of boiling water and the solution then cooled to 10°. To this solution was added 0.42 g. of sodium nitrite (positive starch–iodide) and the mixture then stirred until a fine precipitate began to form. After standing three hours in a refrigerator the product was separated by filtration; yield 0.88 g. (82%) of a white powder, m.p. 215–216°. Recrystallization from methanol did not improve the melting point.

Anal. Calcd. for $C_6H_7N_5O_2$: C, 39.78; H, 3.87. Found: C, 39.9; H, 3.83.

5-Mercapto-1-γ-triazolo[d]pyrimidine.—2-Mercapto-4,5-diaminopyrimidine[9] (2.0 g.) was dissolved in 1200 ml. of water containing 2.0 g. of sodium nitrite; the solution was decolorized with Norite and filtered. The solution was cooled to 30° and acidified by the dropwise addition of acetic acid. The *p*H was then adjusted to 5–6 and the solution was set aside overnight at room temperature to precipitate, yield (1.6 g.). The crude product was dissolved in 50 ml. of dilute ammonium hydroxide and reprecipitated with acetic acid. The product was soluble in acetone in contrast to the starting material. It explodes on a melting point block.

Anal. Calcd. for $C_4H_3N_5S$: C, 31.37; H, 1.96. Found: C, 31.1; H, 1.78.

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