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PUROMYCIN. SYNTHETIC STUDIES. VI. ANALOGS OF 6-DIMETHYLAMINOPURINE

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Degradation studies on puromycin have shown that this antibiotic is a derivative of 6-dimethylamino-9-(3′-aminoribosyl)purine (1). Synthetic studies directed towards a total synthesis of this antibiotic have led to a general method for the glycosidation of 6-dimethylaminopurine on the required 9-position (2, 3). It was observed that glycosidation of the chloromercury salts of 6-dimethylaminopurine or 2,8-bis-methylmercapto-6-dimethylaminopurine occurred on the 7-position, but that of 2-methylmercapto-6-dimethylaminopurine occurred on the 9-position. A series of N-6 substituted purines are described in this communication which should prove useful for the synthesis of puromycin analogs.

An elegant synthesis of 6-alkylaminopurines by reaction of 6-methylmercaptopurine with amines has been recently described by Elion, Burgi, and Hitchings (4). This synthesis has the definite advantage that from one intermediate a series of 6-alkylaminopurines can be made by one further reaction. Unfortunately, these 6-alkylaminopurines, particularly if the amine is tertiary, will orientate to the 7-position during glycosidation and would not be useful for synthesis of N-6 structural variants of puromycin. Since 2-methylmercapto-6-dimethylaminopurine will orientate to the 9-position, the synthesis of this compound (I → IX) described in an earlier paper of this series (5) has now been shown to be adaptable to the preparation of N-6 variants of 2-methylmercapto-6-dimethylaminopurine.

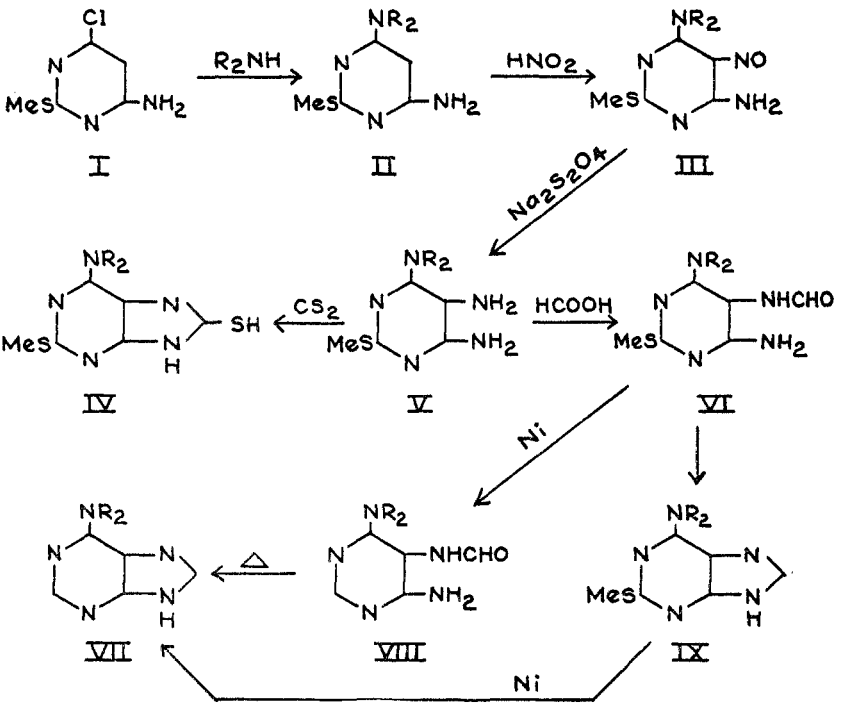
To show the wide adaptability of this synthesis, four types of amines were selected for study, (a) another symmetrical dialkylamine, diethylamine; (b) an aryl alkyl amine, N-methylaniline; (c) a cyclic secondary amine, piperidine; and (d) an unsymmetrical dialkyl amine, benzyl-*n*-butylamine. The last amine serves additional useful purposes discussed later.

The reaction of the chloropyrimidine, I, with these amines was run in refluxing Methyl Cellosolve[1] in the case of diethylamine and piperidine, whereas direct fusion was employed for the higher-boiling benzyl-*n*-butylamine and N-methylaniline. In all cases the yields of diamines, II, were good. The nitrosation reaction to III was varied in concentration of acetic acid in water depending upon the solubility of the diamines. Reduction to the non-crystalline triamines, V, was efficient with sodium hydrosulfite in 50% acetone. The crude triamines were immediately reacted with 90% formic acid giving the 5-formamidopyrimidines, VI, as crystalline solids.[2] Cyclization to the desired 2-methylmercapto-6-dialkyl-

[1] Trade name for the monomethyl ether of ethylene glycol.

[2] The triamines could also be reacted with carbon disulfide in pyridine to give the crystalline 8-mercaptopurines (IV) (5) in quite variable yields.

aminopurines, IX, was nearly quantitative when the amides, VI, were fused at 230–250° except in the case of 2-methylmercapto-6-N-methylanilinopurine (IXb).



a Series, $R_2N = Et_2N-$

b Series, $R_2N = C_6H_5\underset{|}{N}CH_3$

c Series, R_2N = piperidino

d Series, $R_2N = C_6H_5CH_2\underset{|}{N}C_4H_9(n)$

The N-benzyl group on IXd served two other purposes besides being an example of a mixed amine type. The N-benzyl group can be removed by hydrogenolysis or sodium-ammonia reduction at any desired stage, preferably after glycosidation, to give structural variants with an N-6 monoalkyl substituent. Without the N-benzyl group cyclization of VI would proceed to a 6-amino-9-alkylpurine (6). Secondly, a *tert*-amine at position-6 in IX would be expected to orientate an incoming glycosyl group to the 9-position, whereas the orientating effect of a secondary amine at position-6 could not necessarily be predicted with certainty.

The four model 6-dialkylaminopurines (VII) were also prepared either by desulfurization of IX or, preferably, by desulfurization of the 5-formamidopurines, VI, to VIII followed by ring closure.

The general synthesis is not limited to a 2-methylmercapto group, since a 2-benzylmercapto derivative was used successfully with a 6-piperidino group.

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EXPERIMENTAL

2-Benzylmercapto-4-amino-6-pyrimidol. To a hot solution of 2.6 g. of sodium hydroxide in 20 cc. of water and 100 cc. of alcohol was added 10 g. of 2-mercapto-4-amino-6-pyrimidol (7). The mixture was heated for a few minutes when the mercapto pyrimidine dissolved and the sodium salt separated. After the addition of 8.1 cc. of benzyl chloride, the mixture was refluxed for 15 minutes when the mixture had dropped to *p*H 8. During this time the sodium salt dissolved and the product separated. The mixture was cooled in an ice-bath, the solid was collected and washed with cold alcohol, then water; yield, 12.1 g. (75%), m.p. 239–241°. Recrystallization of a sample from Methyl Cellosolve[1]-water gave white crystals, m.p. 243–243.5°.

Anal. Calc'd for $C_{11}H_{11}N_3OS$: C, 56.8; H, 4.75; N, 18.0.
Found: C, 56.6; H, 4.95; N, 18.0.

2-Benzylmercapto-4-amino-6-chloropyrimidine. Reaction of 11.3 g. of the preceding pyrimidol with 57 cc. of phosphorus oxychloride and 3 cc. of dimethylaniline at the b.p. for eight hours, then work-up as described for 2-methylmercapto-4-amino-6-chloropyrimidine (5) gave 6.4 g. (53%) of product, m.p. 93–95°. Recrystallization from heptane afforded white needles, m.p. 103–104°.

Anal. Calc'd for $C_{11}H_{10}ClN_3S$: C, 52.4; H, 3.98; N, 16.7.
Found: C, 52.2; H, 4.55; N, 16.4.

2-Methylmercapto-4-amino-6-piperidinopyrimidine (IIc). A solution of 5.0 g. of I and 6 g. of piperidine in 18 g. of Methyl Cellosolve was refluxed for 4 hours, then evaporated to dryness *in vacuo*. Trituration of the residue with 50 cc. of water gave 6.6 g. (103%) of crude product, m.p. 137–141°, suitable for the next step. Recrystallization of a sample from 50% alcohol gave white crystals of constant m.p. 151–153°.

Anal. Calc'd for $C_{10}H_{16}N_4S$: C, 53.6; H, 7.20; N, 25.0.
Found: C, 53.8; H, 7.52; N, 23.3, 23.7.

2-Methylmercapto-4-amino-6-diethylaminopyrimidine (IIa) *and picrate.* A solution of 3.0 g. of I and 5.5 cc. of diethylamine in 11 g. of Methyl Cellosolve was refluxed for 20 hours, then evaporated to dryness *in vacuo*. The residue was dissolved in acetone and filtered from diethylamine hydrochloride. Evaporation to dryness *in vacuo* left 3.47 g. (96%) of product as an oil which failed to crystallize, but was suitable for the next step.

To a solution of 0.6 g. of crude product in 10 cc. of 10% acetic acid was added 70 cc. of 1% aqueous picric acid. The *picrate* was collected and washed with water; yield, 1.25 g. (75%), m.p. 188–190° dec. Recrystallization from 50% alcohol gave yellow needles, m.p. 210–212° dec.

Anal. Calc'd for $C_9H_{16}N_4S \cdot C_6H_3N_3O_7$: C, 40.7; H, 4.34; N, 22.2.
Found: C, 40.8; H, 4.68; N, 22.0.

2-Benzylmercapto-4-amino-6-piperidinopyrimidine and picrate. A solution of 5.8 g. of 2-benzylmercapto-4-amino-6-chloropyrimidine and 6 cc. of piperidine in 16 g. of Methyl Cellosolve was refluxed for 4 hours, then evaporated to dryness *in vacuo*. Addition of water gave an oil which was extracted with chloroform. The chloroform solution, dried with magnesium sulfate, was evaporated to dryness *in vacuo*; yield, 5.7 g. (83%) of an oil suitable for the next step. A sample of this oil gave a 76% yield of *picrate*, m.p. 192–193°, when prepared in alcohol. Recrystallization from 50% alcohol afforded yellow crystals, m.p. 194–195°.

Anal. Calc'd for $C_{16}H_{20}N_9S \cdot C_6H_3N_3O_7$: C, 50.0; H, 4.37; N, 18.5.
Found: C, 50.3; H, 4.70; N, 18.5.

2-Methylmercapto-4-amino-6-N-methylanilinopyrimidine (IIb) *and hydrochloride.* A mixture of 25 g. of I and 38 cc. of N-methylaniline was heated in a bath at 125° for 22 hours during which the hydrochloride crystallized. The cooled mixture was triturated with acetone and the product was washed with acetone until the washings were colorless; yield, 36.7 g. (92%), m.p. 255–257° dec. Recrystallization from 25% alcohol gave white crystals, m.p. 253–254° dec.

Anal. Calc'd for $C_{12}H_{14}N_4S \cdot HCl$: C, 50.8; H, 5.30; N, 19.8.
Found: C, 50.6; H, 5.35; N, 19.7.

A sample of the *hydrochloride* was dissolved in hot alcohol and poured into four volumes of water containing excess alkali. The free base, m.p. 123–125°, was collected and washed with water. Recrystallization from 50% alcohol gave white crystals, m.p. 122–124°.

Anal. Calc'd for $C_{12}H_{14}N_4S$: C, 58.5; H, 5.70; N, 22.8.
Found: C, 58.1; H, 5.84; N, 22.9.

2-Methylmercapto-4-amino-6-benzyl-n-butylaminopyrimidine (IId) *hydrochloride.* Benzyl-*n*-butylamine was prepared in 96% yield, b.p. 122–125° (12 mm.) by catalytic reduction of 40 g. of benzaldehyde and 37 cc. of *n*-butylamine in 100 cc. of alcohol in the presence of 200 mg. of Adams platinum oxide catalyst.

A mixture of 12 g. of this amine and 5.0 g. of I was heated in a bath at 125° for 22 hours. Some benzyl-*n*-butylamine hydrochloride crystallized. The mixture was dissolved in 100 cc. of ethyl acetate and washed with three 100-cc. portions of 1 *N* hydrochloric acid. The ethyl acetate layer, on standing (or concentration), deposited 4.9 g. of the hydrochloride, m.p. 149–151°. An additional 0.8 g. with the same m.p. was obtained by dilution of the filtrate with heptane; total yield, 5.7 g. (60%). Recrystallization from chloroform by addition of some absolute alcoholic hydrogen chloride followed by ether to turbidity gave white crystals, m.p. 149–150°.

Anal. Calc'd for $C_{16}H_{22}N_4S \cdot HCl$: C, 56.6; H, 6.80; N, 16.5.
Found: C, 56.9; H, 7.10; N, 16.8.

When the reaction time was 6 hours, the yield was only 36%. Both benzyl-*n*-butylamine hydrochloride and IId hydrochlorides are soluble in a number of organic solvents. The separation is based on the insolubility of IId hydrochloride in water compared to the starting amine hydrochloride.

2-Methylmercapto-4-amino-5-nitroso-6-diethylaminopyrimidine (IIIa). To a solution of 6.4 g. of crude IIa (obtained in 106% yield) in 100 cc. of 50% acetic acid cooled in an ice-bath was added a solution of 2.3 g. of sodium nitrite in 20 cc. of water. The product soon began to crystallize. After 2 hours at 0°, the mixture was filtered and the solid washed with 50% acetic acid, then water; yield, 4.7 g. (82% from I), of blue-green solid, m.p. 129–131° dec. When the reaction was run in 10% acetic acid (5), the yield was only 27% and the quality was poorer. Several recrystallizations from absolute alcohol gave deep blue plates of constant m.p. 133–134° dec., which were still not pure.

Anal. Calc'd for $C_9H_{15}N_5OS$: C, 44.8; H, 6.26; N, 29.0.
Found: (sample 1), C, 45.6; H, 6.56; N, 28.5.
(sample 2), C, 45.7; H, 6.46; N, 28.5.

2-Benzylmercapto-4-amino-5-nitroso-6-piperidinopyrimidine. A filtered solution of 5.6 g. of crude 2-benzylmercapto-4-amino-6-piperidinopyrimidine in 100 cc. of 50% acetic acid was cooled in an ice-bath and treated with a solution of 1.4 g. of sodium nitrite in 10 cc. of water. After 2 hours at 0°, the mixture was diluted with 150 cc. of water, filtered, and the solid was washed with water; yield, 4.9 g. (80%), m.p. 135–137° dec., suitable for the next step. Several recrystallizations from heptane gave dark green crystals, m.p. 152–153° dec.

Anal. Calc'd for $C_{16}H_{19}N_5OS$: C, 58.3; H, 5.79; N, 21.2.
Found: C, 58.6; H, 6.23; N, 21.0.

2-Methylmercapto-4-amino-5-nitroso-6-piperidinopyrimidine (IIIc). By treatment of 5.8 g. of IIc in 125 cc. of 13% acetic acid with 1.9 g. of sodium nitrite as described for IIIa there was obtained 5.7 g. (87%), m.p. 168–169° dec. Recrystallization from absolute alcohol with the aid of Norit gave light blue crystals, m.p. 169–170° dec.

Anal. Calc'd for $C_{10}H_{15}N_5OS$: C, 47.5; H, 5.95; N, 27.7.
Found: C, 47.8; H, 6.38; N, 28.0.

2-Methylmercapto-4-amino-5-nitroso-6-benzyl-n-butylaminopyrimidine (IIId). To a solution of 5.7 g. of IId hydrochloride in 120 cc. of 50% acetic acid cooled to 0° was added 1.26 g. of sodium nitrite in 12 cc. of water. A dark green oil separated. After 2 hours at 0°, the mixture was diluted with about 300 cc. of water and extracted with chloroform. The combined extracts, dried with magnesium sulfate, were evaporated to dryness *in vacuo*. The residue was extracted with hot heptane. The solution was decanted from the insoluble oil and cooled; yield, 3.9 g. (70%), m.p. 115–116°. Recrystallization from heptane with the aid of Norit gave pale blue crystals, m.p. 118–119°.

Anal. Calc'd for $C_{16}H_{21}N_5OS$: C, 58.0; H, 6.42; N, 21.2.
Found: C, 58.3; H, 6.36; N, 21.0.

2-Methylmercapto-4-amino-5-nitroso-6-N-methylanilinopyrimidine (IIIb). To a solution of 36.5 g. of IIb hydrochloride in 600 cc. of 50% acetic acid cooled in an ice-bath was added 9.8 g. of sodium nitrite in 60 cc. of water. After 5 hours at 0°, the solution had deposited some solid and some gum. The slurried mixture was filtered, decanting from the gum. The remaining gum was triturated with cold alcohol giving a solid which was collected. The combined solids were washed with cold alcohol; yield, 5.0 g. (14%), m.p. 180–182° dec. Recrystallization from absolute alcohol with the aid of Norit gave green needles, m.p. 197–197.5°.

Anal. Calc'd for $C_{12}H_{13}N_5OS$: C, 52.4; H, 4.76; N, 25.4.
Found: C, 52.7; H, 5.03; N, 25.2.

That the product had the nitroso group on the pyrimidine ring and not on the benzene ring is conclusively proven by subsequent reduction, formylation and formation of a purine ring.

2-Methylmercapto-4-amino-5-formamido-6-diethylaminopyrimidine (VIa). To a solution of 1.9 g. of IIIa in 25 cc. of warm acetone was added a solution of 3 g. of sodium hydrosulfite in 25 cc. of water. The green solution immediately became light orange with the separation of inorganic solids. The mixture was diluted with several volumes of water and extracted with three 10-cc. portions of chloroform. The combined, magnesium sulfate dried extracts were evaporated *in vacuo* leaving 1.7 g. of crude triamine, Va, as a gum.

The gum was immediately dissolved in 17 cc. of 90% formic acid and heated on the steam-bath for 1 hour. The solution was concentrated to a thin syrup *in vacuo*, then dissolved in 10 cc. of water and poured into excess ammonia water and ice. The product was collected and washed with water; yield, 0.82 g. (52%), m.p. 137–138°. Recrystallization from water with the aid of Norit gave white crystals, m.p. 154–155°.

Anal. Calc'd for $C_{10}H_{17}N_5OS$: C, 47.0; H, 6.70; N, 27.4.
Found: C, 47.2; H, 7.02; N, 27.7.

2-Methylmercapto-4-amino-5-formamido-6-N-methylanilinopyrimidine (VIb). By reduction and formylation of 5 g. of IIIb as described for VIa there was obtained 4.6 g. (87%) of product, m.p. 203–205°. Recrystallization from alcohol with the aid of Norit gave white crystals, m.p. 212–213°.

Anal. Calc'd for $C_{13}H_{15}N_5OS$: C, 53.8; H, 5.21; N, 24.2.
Found: C, 54.0; H, 5.49; N, 24.1.

2-Methylmercapto-4-amino-5-formamido-6-piperidinopyrimidine (VIc). Reduction of 5.0 g. of IIIc as described for IIIa gave a gummy triamine, Vc, which when triturated with cold alcohol formed 2.8 g. (60%) of crystals, m.p. 162–165° dec. This material could not be readily purified and was therefore formylated as described for VIa; yield, 1.9 g. (74%), m.p. 182–184°. Recrystallization from chloroform-heptane afforded white crystals, m.p. 185–187°.

Anal. Calc'd for $C_{11}H_{17}N_5OS$: C, 49.1; H, 6.40; N, 26.2.
Found: C, 49.5; H, 6.62; N, 26.2.

2-Methylmercapto-4-amino-5-formamido-6-benzyl-n-butylaminopyrimidine (VId). Reduction of 3.0 g. of IIId as described for IIIa gave a quantitative yield of triamine, Vd, as a

gum which in turn gave a quantitative yield of *picrate* from alcohol, m.p. 159–160°. Recrystallization from 50% alcohol afforded bronze crystals, m.p. 159–160°.

Anal. Calc'd for $C_{16}H_{23}N_5S \cdot C_6H_3N_3O_7$: C, 48.5; H, 4.82; N, 20.5.
Found: C, 48.9; H, 5.12; N, 20.6.

Formylation of the crude triamine as described for VIa gave a 62% yield of VId from chloroform-heptane, m.p. 148–150°. Recrystallization from the same solvents with the aid of Norit afforded white crystals, m.p. 150–151°.

Anal. Calc'd for $C_{17}H_{23}N_5OS$: C, 59.4; H, 6.70; N, 20.4.
Found: C, 59.3; H, 6.95; N, 20.6.

2-Benzylmercapto-4-amino-5-formamido-6-piperidinopyrimidine. Reduction of 4.6 g. of 2-benzylmercapto-4-amino-5-nitroso-6-piperidinopyrimidine in 75 cc. of acetone with 10.3 g. of sodium hydrosulfite in 50 cc. of water followed by formylation as described for VIa gave, after recrystallization from chloroform-heptane, 2.7 g. (56%) of product, m.p. 143–147°. Recrystallization from dilute alcohol gave nearly white crystals, m.p. 153–154°.

Anal. Calc'd for $C_{17}H_{21}N_5OS$: C, 59.6; H, 6.15; N, 20.4.
Found: C, 59.8; H, 6.26; N, 20.6.

2-Methylmercapto-6-diethylaminopurine (IXa). Fusion of 1.00 g. of VIa at 230° until water evolution was complete (10 minutes) gave 0.85 g. (92%) of solid on cooling, m.p. 192–193°. Recrystallization from absolute alcohol afforded nearly white crystals, m.p. 198–200°.

Anal. Calc'd for $C_{10}H_{15}N_5S$: C, 50.6; H, 6.36; N, 29.5.
Found: C, 51.0; H, 6.59; N, 29.5.

2-Methylmercapto-6-N-methylanilinopurine (IXb). When 1.00 g. of VIb was fused in a bath at 250–260° for 20 minutes, water evolution was complete. The cooled melt was dissolved in 10 cc. of Methyl Cellosolve and poured into 200 cc. of water to give 0.78 g. (83%) of crude product, m.p. 190–192° dec. A sample was dissolved in warm 1 *N* sodium hydroxide. The solution was clarified with Norit and acidified with acetic acid to give white crystals, m.p. 218–220°. Recrystallization from absolute alcohol raised the m.p. to 220–221°.

Anal. Calc'd for $C_{13}H_{13}N_5S$: C, 57.7; H, 4.82; N, 25.9.
Found: C, 57.6; H, 4.83; N, 26.2.

In another run the yield of material purified through an alkaline solution was 40% (0.37 g.), m.p. 218–220°.

2-Methylmercapto-6-piperidinopurine (IXc). Fusion of VIc at 230° until water evolution was complete gave a quantitative yield of product, m.p. 218–220°. Recrystallization from absolute alcohol afforded nearly white crystals, m.p. 226–228°.

Anal. Calc'd for $C_{10}H_{15}N_5S$: C, 53.0; H, 6.03; N, 28.1.
Found: C, 53.1; H, 6.23; N, 28.1.

2-Methylmercapto-6-benzyl-n-butylaminopurine (IXd). Fusion of VId at 250° gave a quantitative yield, m.p. 146–148°. Recrystallization from 50% alcohol gave white crystals, m.p. 149–151°.

Anal. Calc'd for $C_{17}H_{21}N_5S$: C, 62.5; H, 6.44; N, 21.4.
Found: C, 62.7; H, 6.59; N, 21.7.

2-Benzylmercapto-6-piperidinopurine. By fusion of 1.3 g. of 2-benzylmercapto-4-amino-5-formamido-6-piperidinopyrimidine in a bath at 250° for 10 minutes was obtained, on cooling, a solid. This was dissolved in 10 cc. of Methyl Cellosolve and poured into 100 cc. of water; yield, 1.0 g. (81%), m.p. 198–203° dec. Several recrystallizations from absolute alcohol with the aid of Norit gave white crystals, m.p. 216–217°.

Anal. Calc'd for $C_{17}H_{19}N_5S$: C, 62.9; H, 5.87; N, 21.6.
Found: C, 63.0; H, 6.12; N, 21.8.

4-Amino-5-formamido-6-diethylaminopyrimidine (VIIIa). A solution of 0.67 g. of VIa in 67 cc. of absolute alcohol was refluxed with 1 teaspoon of desulfurizing Raney nickel (8) for ½ hour. The hot mixture was filtered through Celite. The combined filtrate and washings were evaporated to dryness *in vacuo* leaving 0.47 g. (86%) of crude product, m.p. 136–142°.

Several recrystallizations from chloroform gave white crystals, m.p. 155–157°. Admixture with VIa gave a m.p. of 126–128°.

Anal. Calc'd for $C_9H_{15}N_5O$: C, 51.5; H, 7.18; N, 33.3.
Found: C, 51.8; H, 7.30; N, 33.4.

4-Amino-5-formamido-6-N-methylanilinopyrimidine (VIIIb). Desulfurization of 1.00 g. of VIb as described for VIIIa gave 0.57 g. (68%) of crude product, m.p. 148–150°. Recrystallization from chloroform-heptane afforded white crystals, m.p. 157–158°. This material appears to be contaminated with some VIb.

Anal. Calc'd for $C_{12}H_{13}N_5O$: C, 59.3; H, 5.38; N, 28.8.
Found: C, 58.9; H, 5.57; N, 28.0.

6-Diethylaminopurine (VIIa). (*A*). A mixture of 670 mg. of IXa and 54 cc. of 1 *N* sodium hydroxide was stirred on the steam-bath until solution was complete. Then 4 cc. of centrifuged desulfurizing Raney nickel (8) was added and stirring on the steam-bath was continued for 30 minutes. The filtered solution was acidified with acetic acid, filtered from alumina, then concentrated to about ⅓ in volume when crystals separated; yield, 170 mg. (32%), m.p. 212–214°. No additional material could be isolated from the filtrate. Recrystallization from water gave white crystals, m.p. 212–214° (uncorr.).

Anal. Calc'd for $C_9H_{13}N_5$: C, 56.6; H, 6.82; N, 36.7.
Found: C, 56.9; H, 6.75; N, 36.8.

The *picrate* was prepared in alcohol and formed yellow crystals, m.p. 202–203° dec. The synthesis of VIIa by another path has recently been described by Robins and Christensen (9). They record a m.p. of 222–223° (corr.).

(*B*). When crude VIIIa was fused at 250° for ten minutes, water evolution was complete. The residue was dissolved in warm water and filtered from a little insoluble IXa. The filtrate was evaporated to dryness *in vacuo* leaving white crystals, m.p. 206–208°. A mixture with preparation *A* gave no depression in m.p.

6-N-Methylanilinopurine (VIIb) (*A*). Fusion of 150 mg. of VIIIb at 240° for 10 minutes gave 140 mg. (100%) of product, m.p. 218–220°. Recrystallization from chloroform-heptane afforded white crystals, m.p. 224–225°.

Anal. Calc'd for $C_{12}H_{11}N_5$: C, 64.0; H, 4.88; N, 31.1.
Found: C, 64.2; H, 5.08; N, 30.7.

(*B*). A solution of 370 mg. of IXb in 37 cc. of Methyl Cellosolve and 1.37 cc. of 1 *N* methanolic sodium methoxide was stirred on the steam-bath with 1.3 teaspoons of desulfurizing Raney nickel (8) for ½ hour. The solution was filtered through Celite and evaporated to dryness *in vacuo*. The residual gum was dissolved in 10 cc. of water and the solution was clarified by filtration through Celite. The filtrate was acidified with acetic acid and extracted twice with chloroform. Dried with magnesium sulfate, the combined extracts were evaporated to dryness *in vacuo*. Recrystallization from benzene-heptane gave 70 mg. (23%) of product, m.p. 225–226°. Admixture with preparation *A* gave no depression in m.p.

6-Piperidinopurine (VIIc). A solution of 0.90 g. of IXc in 77 cc. of 1 *N* sodium hydroxide was stirred on the steam-bath with 6 cc. of centrifuged desulfurizing Raney nickel (8) for 30 minutes. The filtered solution was acidified with acetic acid. The precipitate was collected and was a mixture of product and alumina. No additional product could be isolated from the filtrate. The precipitate was dissolved in 0.5 *N* hydrochloric acid. Clarified by filtration, the solution was treated with excess 1% aqueous picric acid. The *picrate* was collected and washed with water; yield, 430 mg. (28%), m.p. 194–195°.

The Raney nickel was digested on the steam-bath with 200 cc. of 1 *N* hydrochloric acid, then the mixture was filtered. To the filtrate was added 125 cc. of 1% aqueous picric acid. The *picrate* was collected and washed well with water; yield, 450 mg. (total 57%), m.p. 192–194°. Recrystallization from absolute alcohol with the aid of Norit gave yellow crystals, m.p. 193–194°.

Anal. Calc'd for $C_{10}H_{13}N_5 \cdot C_6H_3N_3O_7$: C, 44.3; H, 3.72; N, 25.9.
Found: C, 44.7; H, 3.86; N, 25.7.

6-Benzyl-n-butylaminopurine (VIId). Desulfurization of 500 mg. of IXd in 70 cc. of 1 *N* sodium hydroxide with 3 cc. of desulfurizing Raney nickel (8) as described for VIIc gave, on acidification a precipitate which was a mixture of product and alumina. The dried solid was extracted with hot chloroform. Evaporation of the extracts to dryness *in vacuo* left 60 mg. (14%) of product, m.p. 155–157°. Recrystallization from dilute alcohol gave white crystals, m.p. 157–158°.

Anal. Calc'd for $C_{16}H_{19}N_5$: C, 68.4; H, 6.84; N, 24.9.
Found: C, 68.7; H, 7.16; N, 25.1.

No additional product could be isolated from the catalyst or aqueous filtrate.

2-Methylmercapto-6-diethylamino-8-mercaptopurine (IVa). The crude triamine (Va) from 3.0 g. of IIIa was refluxed with 7 cc. of carbon disulfide in 37 cc. of pyridine (5) for 90 minutes. The solution was evaporated to dryness *in vacuo*. Trituration of the residue with warm chloroform gave 0.77 g. (23%) of product, m.p. 254–257°. Recrystallization from absolute alcohol afforded white crystals, m.p. 264–265°.

Anal. Calc'd for $C_{10}H_{15}N_5S_2$: C, 44.6; H, 5.62; N, 26.0.
Found: C, 44.3; H, 5.75; N, 25.9.

2-Methylmercapto-6-N-methylanilino-8-mercaptopurine (IVb). A solution of the triamine (Vb) from 1.00 g. of IIIb in 10-cc. of pyridine and 2 cc. of carbon disulfide (5) was refluxed for 30 minutes, then evaporated to dryness *in vacuo*. Trituration of the residue with hot absolute alcohol gave 0.70 g. (64%) of product, m.p. 295–298° dec. Recrystallization from Methyl Cellosolve-water afforded white crystals, m.p. 302–303° dec.

Anal. Calc'd for $C_{13}H_{13}N_5S_2$: C, 51.5; H, 4.30; N, 23.1.
Found: C, 51.7; H, 4.54; N, 23.2.

2-Methylmercapto-6-benzyl-n-butylamino-8-mercaptopurine (IVd). The triamine (Vd) from 1.00 g. of IIId was dissolved in 11 cc. of pyridine and treated with 2 cc. of carbon disulfide (5). After 24 hours the solution was evaporated to a syrup *in vacuo*. The residue was diluted with 0.5 *N* sodium hydroxide. The solution was clarified by filtration through Celite, then treatment with Norit. Acidification gave 0.14 g. (8.5%) of product, m.p. 168–170°. Recrystallization from chloroform-heptane gave nearly white crystals, m.p. 199–201°.

Anal. Calc'd for $C_{17}H_{21}N_5S_2$: C, 56.8; H, 5.90; N, 19.5.
Found: C, 57.1; H, 6.24; N, 19.2.

No product could be isolated when the pyridine solution was refluxed in the usual manner.

2-Benzylmercapto-6-piperidino-8-mercaptopurine. Treatment of the triamine from 1.00 g. of 2-benzylmercapto-4-amino-5-nitroso-6-piperidinopyrimidine with carbon disulfide in pyridine as described for IVa (R = H), except that the product was isolated by trituration of the reaction residue with alcohol, gave a 58% yield, m.p. 272–273° dec. Recrystallization from Methyl Cellosolve-water gave cream-colored crystals, m.p. 273–274° dec.

Anal. Calc'd for $C_{17}H_{19}N_5S_2$: C, 57.2; H, 5.35; N, 19.6.
Found: C, 57.1; H, 5.55; N, 19.6.

2-Methylmercapto-6-N-methylanilino-8-benzylmercaptopurine. To a hot solution of 100 mg. of IVb in 10 cc. of methanol and 0.33 cc. of 1 *N* sodium methoxide was added 0.31 cc. of benzyl chloride. After being refluxed for 15 minutes, the solution had *p*H 8. Dilution with 25 cc. of water gave 80 mg. (61%) of white solid, m.p. 192–194°. Recrystallization from absolute alcohol raised the m.p. to 197–199°.

Anal. Calc'd for $C_{20}H_{19}N_5S_2$: C, 61.2; H, 4.88; N, 17.9.
Found: C, 61.5; H, 5.17; N, 18.2.

An attempt to S-methylate IVb in the usual manner (5) gave an oil which could not be crystallized.

SUMMARY

The synthesis of N-6 variants of 2-methylmercapto-6-dimethylaminopurine by a general method suitable for preparation of analogs of puromycin has been described.

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