(0.5 cc.) for 4 hr. The solid obtained on working up as usual was ground with alcohol (10 cc.) and filtered. The residue was crystallized from a mixture of alcohol and acetic acid. They gave negative ferric reaction.

The following acetoxyflavones were thus obtained: 5-acetoxy-8-nitroflavone, m.p. 155–156°.

Anal. Calcd. for $C_{17}H_{11}NO_6$: N, 4.3. Found: N, 4.2.

5-Acetoxy-8-nitro-4′-methoxyflavone m.p. 163–165°.

Anal. Calcd. for $C_{18}H_{13}NO_7$: N, 3.94. Found: N, 4.00.

5-Acetoxy-8-nitro-3′-4′-methylenedioxyflavone, m.p. 215–217°.

Anal. Calcd. for $C_{18}H_{11}NO_8$: N, 3.79. Found: N, 3.80.

Acknowledgments. The authors wish to express their gratitude to Dr. C. V. Jadhav for his keen interest in the work.

BOMBAY, INDIA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PENNSYLVANIA]

Some Analogs of Toxopyrimidine and Methioprim[1]

TAKUO OKUDA AND CHARLES C. PRICE

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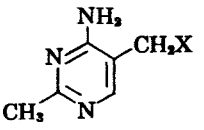
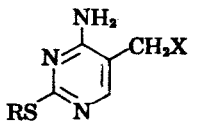
A number of new pyrimidines, related to 2-methyl-4-amino-5-hydroxymethylpyrimidine (I, toxopyrimidine) and 2-methylthio-4-amino-5-hydroxymethylpyrimidine (VIII, methioprim) have been prepared and characterized.

The antimetabolite properties of toxopyrimidine[2] (I) stimulated our earlier work leading to the discovery of interesting antimetabolite and antitumor activity in "methioprim" (VIII).[3–6] We now wish to report the syntheses and characterization of a number of additional compounds related to these substances.

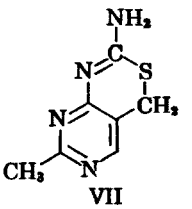
The analogs of toxopyrimidine were made by appropriate substitution reactions with the bromomethyl compound (X).[7] Reaction of X with thiourea, followed by neutralization of the crude isothiuronium salt, produced not only the disulfide III (presumably through the mercaptan) but led also to the isolation of the thiazinopyrimidine (VII), shown to be different from the isomeric thiocyanate (VI). XII, however, reacted normally with thiourea to produce the isothiuronium salt, XVII, which



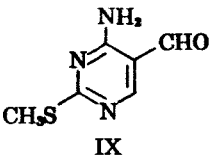
I, X = OH
II, X = SH
III, X =)$_2$S$_2$
IV, X =)$_2$S
V, X = SCH_3
VI, X = SCN
X, X = Br



VIII, R = CH_3, X = OH
XI, R = H, X = OH
XII, R = CH_3, X = Br
XIII, R = CH_3, X = OCH_3
XIV, R = CH_3, X = SCH_3
XV, R = CH_3, X = $SCOCH_3$
XVI, R = CH_3, X = SH
XVII, R = CH_3, X = $SC(NH_2)_2^+Br^-$
XVIII, R = CH_3, X =)$_2$S$_2$
XIX, R = C_2H_5, X = OH



VII

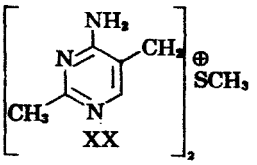


IX

was converted to disulfide, but did not give the analogous thiazinopyrimidine.

Oxidation of VIII by dichromate proceeded surprisingly smoothly to the aldehyde IX, which was also readily converted to the oxime.

When X was heated with sodium methyl mercaptide in ether, and then in dioxane, the sulfide IV instead of V was formed. This reaction may have proceeded through formation of a sulfonium salt (XX) as an intermediate.



XX

The replacement of the bromine atom of XII by methoxyl proceeded readily by solvolysis.

The reduction of 2-mercapto-4-amino-5-carbeth-

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(1) Supported in part by the U. S. Public Health Service Grant CY-2714.

(2) K. Makino, T. Kinoshita, T. Sasaki, and T. Shiei, *Nature*, 173, 34 (1954); K. Makino, T. Kinoshita, Y. Aramaki, and S. Shintani, *Nature*, 174, 275 (1954); K. Makino and M. Koike, *Nature*, 174, 1056 (1954); K. Makino and T. Kinoshita, *J. Vitaminol.*, 1, 14 (1955); S. Shintani, *J. Vitaminol.*, 8, 185 (1956).

(3) T. L. V. Ulbricht and C. C. Price, *J. Org. Chem.*, 21, 567 (1956); *Chem. & Ind. (London)*, 1221 (1955).

(4) T. L. V. Ulbricht and J. S. Gots, *Nature*, 178, 913 (1956); D. B. McNair-Scott, T. L. V. Ulbricht, M. L. Rogers, E. Chu and C. Rose, *Cancer Research*, in press; D. F. Dunning, T. L. V. Ulbricht, C. C. Price, and R. Jones, Jr., unpublished results; R. Guthrie, M. E. Loebeck, and M. J. Hillman, *Proc. Soc. Exptl. Biol. Med.*, 94, 792 (1957); R. Guthrie, J. F. Holland, E. A. Hyatt, M. Hillman, and D. T. Mount, *Proc. Am. Assoc. Cancer Research*, 2, 113 (1956); I. J. Slotnick, R. Guthrie, J. F. Holland, and M. J. Hillman, *Proc. Am. Assoc. Cancer Research*, 3, 251 (1957).

(5) F. Rosen, J. F. Holland, and C. A. Nichol, *Proc. Am. Assoc. Cancer Research*, 3, 243 (1957).

(6) This name has been suggested to us by Dr. Joseph S. Gots, Univ. of Pa., and Dr. Robert Guthrie, Roswell Park Memorial Institute.

(7) Kindly supplied by Dr. Max Tishler, Merck & Co., Rahway, N. J.

thoxypyrimidine (XXI) to XI with lithium aluminum hydride was successfully carried out in *N*-ethylmorpholine.

Dr. Joseph S. Gots has found that compounds VIII, IX, XII, and XVI are antagonists for I in microorganisms requiring I for growth. Details will be reported elsewhere.

EXPERIMENTAL[8]

2-Methyl-4-amino-5-mercaptomethylpyrimidine (II) *and bis-(2-methyl-4-amino-5-pyrimidylmethyl) disulfide* (III). (I) *2-Methyl-4-amino-5-mercaptomethylpyrimidine.* 2-Methyl-4-amino-5-bromomethylpyrimidine dihydrobromide[7] (30 g., 0.082 mole) was slowly added to a solution of 6.3 g. (0.083 mole) of thioacetic acid in 150 ml. of pyridine. After the evolution of heat stopped, the mixture was stirred and refluxed gently for 7 hr. After cooling, a white precipitate was filtered and washed with ether. The precipitate was dissolved in 35 ml. of 5% hydrochloric acid and the solution was washed with ether, and then made weakly alkaline with sodium carbonate solution. The solution was quickly extracted ten times with 100-ml. portions of ether. The combined ether solutions were dried over magnesium sulfate for 1 hr. The ether was distilled *in vacuo* leaving 3.0 g. of white plates. This product was recrystallized three times from acetone, m.p. 161–163° (in vacuo). The sample was kept in a sealed tube containing nitrogen.

Anal. Calcd. for $C_6H_9N_3S$: C, 46.43; H, 5.84; S, 20.66. Found: C, 46.60; H, 5.52; S, 20.44.

(II) *Bis(2-methyl-4-amino-5-pyrimidylmethyl) disulfide.* The aqueous alkaline solution from which the 2-methyl-4-amino-5-mercaptomethylpyrimidine above was extracted was kept at room temperature for four days. A white crystalline precipitate which weighed 1.6 g. was obtained and was recrystallized from ethanol, m.p. 242–245° (dec.).

Anal. Calcd. for $C_{12}H_{14}N_6S_2$: C, 46.73; H, 5.23; N, 27.25; S, 20.79. Found: C, 47.01; H, 5.38; N, 27.00; S, 20.57.

Bis(2-methyl-4-amino-5-pyrimidylmethyl) disulfide (III), *bis(2-methyl-4-amino-5-pyrimidylmethyl) sulfide* (IV) *and 2-methyl-7-aminothiazino(6,5-e)pyrimidine* (VII). (I) *Bis-(2-methyl-4-amino-5-pyrimidylmethyl) disulfide.* 2-Methyl-4-amino-5-bromomethylpyrimidine dihydrobromide (10 g., 0.27 mole) was added to a solution of 2.08 g. (0.027 mole) of thiourea in 150 ml. of tetrahydrofuran. The mixture was refluxed with stirring for 50 min. A solid precipitate which weighed 11.6 g. was collected after cooling. The material slowly decomposed between 200° and 235°. A solution of 5 g. of this material in 50 ml. of 10% sodium hydroxide was neutralized with hydrochloric acid after standing 30 min. and then extracted five times with 100-ml. portions of ether. After the combined ether solutions were dried over magnesium sulfate for 1 hr., the ether was distilled giving *ca.* 100 mg. of pale yellow crystalline residue contaminated with viscous material. The residue was recrystallized twice from 20-ml. portions of ethanol giving colorless crystals which melted at 245°. On admixture with bis-(2-methyl-4-amino-5-pyrimidylmethyl) disulfide, no melting point depression was observed.

(II) *7-Amino-2-methyl-5(H)-metathiazino[4,5-d]pyrimidine* (VII). The neutralized solution from which ether-soluble materials were extracted in (I) was concentrated to 10 ml. *in vacuo* and cooled. A colorless precipitate was collected and recrystallized three times from ethanol, m.p. 256–258°.

Anal. Calcd. for $C_7H_8N_4S$: C, 46.65; H, 4.47; N, 31.09; S, 17.74. Found: C, 46.90; H, 4.55; N, 31.14; S, 17.76.

The condensation product (5 g.) from 2-methyl-4-amino-5-bromomethylpyrimidine dihydrobromide and thiourea was dissolved in 30 ml. of water and the solution was made weakly alkaline with sodium carbonate. The white precipitate which immediately appeared was collected, washed three times with 10-ml. portions of water, and then heated with 500 ml. of ethanol. The material slowly dissolved in ethanol with evolution of ammonia. After all the solid was dissolved in the ethanol, the solution was concentrated to 50 ml. and cooled. Colorless crystals which weighed 1.78 g. separated and were recrystallized from 80 ml. of ethanol, giving crystals which melted at 256–258°. No melting point depression was observed on admixture with the earlier sample of VII.

(III) *Bis(2-methyl-4-amino-5-pyrimidylmethyl) sulfide* (IV). The condensation product (11.6 g.) from 10 g. of 2-methyl-4-amino-5-bromomethylpyrimidine dihydrobromide and 2.08 g. of thiourea was dissolved in 15 ml. of water. The white precipitate which appeared immediately on neutralization with sodium hydroxide was collected and washed with 10 ml. of water. The material weighed 5.4 g. and melted at 154–158°. This material was dissolved in 30 ml. of boiling 10% sodium hydroxide and the solution was refluxed for 1 hr. After cooling, the precipitated crystals were recrystallized from ethanol giving 1.3 g. of colorless crystals, m.p. 284–286° (dec.).

Anal. Calcd. for $C_{12}H_{16}N_6S$: C, 52.12; H, 5.85; N, 30.42; S, 11.61. Found: C, 52.15; H, 6.07; N, 30.16; S, 11.51.

2-Methyl-4-amino-5-methylthiomethylpyrimidine (V). Methyl mercaptan (10 g., 0.208 mole) was added to a solution of 3.8 g. (0.165 mole) of sodium in 150 ml. of absolute ethanol. Then 20 g. (0.055 mole) of 2-methyl-4-amino-5-bromomethylpyrimidine dihydrobromide was added, and the mixture was stirred and refluxed for 30 min. After cooling, the precipitate (23 g.) was recrystallized from 100 ml. of 50% ethanol. A second recrystallization from 50 ml. of 50% ethanol gave 4.0 g. of colorless prisms, m.p. 176–178°. By concentration of the mother liquors, 2.5 g. more of the product was obtained.

Anal. Calcd. for $C_7H_{11}N_3S$: C, 49.68; H, 6.55; N, 24.83; S, 18.95. Found: C, 49.89; H, 6.49; N, 24.71; S, 18.76.

Bis(2-methyl-4-amino-5-pyrimidylmethyl) sulfide (IV). Sodium (2 g., 0.087 mole) was added to a solution of 5 g. (0.105 mole) of methyl mercaptan in 100 ml. of ether which was cooled in an ice salt bath. After stirring 4 hr., 10 g. (0.28 mole) of 2-methyl-4-amino-5-bromomethylpyrimidine dihydrobromide was added. Because no heat was evolved, the ether and the excess of methyl mercaptan were distilled off, and the residue was heated with 50 ml. of dioxane on a steam bath. The color of the reaction mixture suddenly changed from dark gray to pale brown when it was heated to 100°. The mixture was heated with stirring for 1 hr., and the solid was filtered off. After cooling, 10 ml. of ethanol was added to convert the remaining sodium to sodium ethoxide, and then the solvent was removed by distillation. Addition of 50 ml. of water precipitated 0.4 g. of solid which was recrystallized from 50 ml. of ethanol giving colorless crystals which melted at 277–280° (dec.). On admixture with the authentic bis(2-methyl-4-amino-5-pyrimidylmethyl) sulfide, no melting point depression was observed. The infrared spectrum was also identical with that of the sulfide.

2-Methyl-4-amino-5-thiocyanomethylpyrimidine (VI). 2-Methyl-4-amino-5-bromomethylpyrimidine dihydrobromide (5 g., 0.014 mole) was added to a solution of 1.35 g. (0.014 mole) of potassium thiocyanate in 150 ml. of tetrahydrofuran. The mixture was refluxed with stirring for 2 hr., and, after cooling, the solid precipitate (3 g.) was collected. It was dissolved in 25 ml. of water and the solution was neutralized with sodium bicarbonate giving 0.9 g. of crystalline precipitate. The precipitate was recrystallized three times from benzene. The resulting white crystals showed no definite melting point, but slowly decomposed at 150–198°.

Anal. Calcd. for $C_7H_8N_4S$: C, 46.65; H, 4.47; N, 31.09. Found: C, 47.15; H, 4.68; N, 31.07.

(8) Melting points are uncorrected. Analyses are by Microtech Inc., Skokie, Ill., and Midwest Microlab, Inc., Indianapolis, Ind.

The infrared spectra clearly distinguished this material from the isomeric thiazinopyrimidine.

The filtrate from the free thiocyanate was concentrated to 10 ml. and 0.3 g. of precipitate was obtained after standing overnight. It was recrystallized from ethanol giving colorless crystals, m.p. 248–252° (dec.). On admixture with bis(2-methyl-4-amino-5-pyrimidylmethyl) disulfide, no melting point depression was observed.

2-Methylthio-4-amino-5-formylpyrimidine (IX). A solution of 2-methylthio-4-amino-5-hydroxymethylpyrimidine (5 g., 0.027 mole) in 13 ml. of acetic acid was added with stirring to a solution of 2.9 g. (0.1 mole) of sodium dichromate dihydrate in 15 ml. of acetic acid. Colorless crystals slowly precipitated and, after 2 hr., were collected and washed with 30 ml. of water. The precipitate weighed 3.4 g. The cooled filtrate was neutralized with ammonia, and then kept at 0° overnight. An additional 0.7 g. of white precipitate was combined with the first crop. The combined product was dissolved in 300 ml. of chloroform and the green solution was washed twice with 20-ml. portions of water, which removed the color. The decolorized chloroform solution was dried with magnesium sulfate and concentrated to 100 ml. On cooling and filtering, 2.50 g. of colorless crystals, m.p. 183–184°, were obtained. The filtrate was further concentrated to 20 ml. giving another 0.50 g. of crystals, m.p. 182–183°.

Anal. Calcd. for $C_6H_7N_3OS$: C, 42.59; H, 4.17; N, 24.84; S, 18.95. Found: C, 42.53; H, 4.23; N, 24.89; S, 18.92.

2-Methylthio-4-amino-5-pyrimidylaldoxime. A solution of 1.5 g. of 2-methylthio-4-amino-5-formylpyrimidine in 50 ml. of hot ethanol was added to a solution of 5 g. of hydroxylamine hydrochloride in 10 ml. of water made basic with 20 ml. of 10% sodium hydroxide. The mixed solution was heated on a steam bath for 30 min. and concentrated to 40 ml. A crystalline precipitate, which weighed 1.5 g., was recrystallized twice from a mixture of benzene and ethanol (10:1) to yield colorless crystals, m.p. 201–202°.

Anal. Calcd. for $C_6H_8N_4OS$: C, 39.12; H, 4.37; N, 30.42; S, 17.41. Found: C, 39.19; H, 4.50; N, 30.60; S, 17.50.

2-Mercapto-4-amino-5-hydroxymethylpyrimidine (XI). To a solution of lithium aluminum hydride (5 g., 0.132 mole) in 50 ml. of anhydrous ether and 300 ml. of *N*-ethylmorpholine, 10 g. (0.050 mole) of 2-mercapto-4-amino-5-carbethoxypyrimidine was slowly added as a fine powder. After the evolution of heat ceased, the reaction mixture was stirred and heated at 80° for 2.5 hr. After cooling, 20 ml. of ethyl acetate was added with stirring, and then 10 ml. of water. The precipitate was filtered after standing overnight. The filtrate gave no crystalline residue when the solvent was distilled. The solid was extracted (Soxhlet) with boiling ethanol. The extract was concentrated to 20 ml. and neutralized with acetic acid, giving 3.8 g. of crystalline precipitate. Further extractions with methanol gave no solid product. The combined extracts were recrystallized four times from ethanol, giving pale yellow crystals, m.p. 229–232° (dec.).

Anal. Calcd. for $C_5H_7N_3OS$: C, 38.20; H, 4.49; S, 20.40. Found: C, 38.42; H, 4.69; S, 20.22.

2-Methylthio-4-amino-5-bromomethylpyrimidine hydrobromide (XII). Glacial acetic acid (175 ml.) was saturated with anhydrous hydrogen bromide at 0°, and added to a solution of 12 g. of 2-methylthio-4-amino-5-hydroxymethylpyrimidine in 100 ml. of acetic acid. After heating on a steam bath for 2 hr. and cooling, 27.5 g. of white precipitate was collected. The product was recrystallized from 650 ml. of acetic acid, giving 18.5 g. of colorless needles which began to decompose above 280°.

Anal. Calcd. for $C_6H_9Br_2N_3S$: C, 22.87; H, 2.88; Br, 50.74; N, 13.34; S, 10.18. Found: C, 23.39; H, 3.08; Br, 50.81; N, 13.11; S, 9.84.

2-Methylthio-4-amino-5-methoxymethylpyrimidine (XIII). 2-Methylthio-4-amino-5-bromomethylpyrimidine hydrobromide (2 g.) was refluxed with 20 ml. of methanol for 1 hr., and then the solvent was distilled leaving an oily residue. Aqueous ammonia was added to the residue until the solution became weakly alkaline, and after cooling, 0.7 g. of colorless crystals precipitated. Recrystallization from water followed by recrystallization from a mixture of benzene and ligroin gave colorless prisms, m.p. 104–106°.

Anal. Calcd. for $C_7H_{11}N_3OS$: C, 45.39; H, 5.98; S, 17.31. Found: C, 45.60; H, 5.70; S, 17.91.

2-Methylthio-4-amino-5-methylthiomethylpyrimidine (XIV). Methyl mercaptan (1 g., 0.02 mole) was added to a solution of 0.5 g. (0.02 mole) of sodium in 100 ml. of absolute ethanol and 3 g. (0.01 mole) of 2-methylthio-4-amino-5-bromomethylpyrimidine hydrobromide was added with stirring. After the evolution of heat stopped, the mixture was heated on a steam bath for 30 min. with stirring. The solvent was distilled off, 40 ml. of water was added to the residue and the mixture stirred and heated for 10 min. The crystalline precipitate was filtered after cooling and recrystallized twice from 30% ethanol, giving 1.4 g. of colorless prisms, m.p. 139–140°.

Anal. Calcd. for $C_7H_{11}N_3S_2$: C, 41.76; H, 5.51; N, 20.88; S, 31.86. Found: C, 41.87; H, 5.49; N, 20.62; S, 31.74.

2-Methylthio-4-amino-5-acetylthiomethylpyrimidine (XV). 2-Methylthio-4-amino-5-bromomethylpyrimidine hydrobromide (4 g., 0.013 mole) was added to a solution of 2 g. (0.026 mole) of thioacetic acid in 25 ml. of pyridine. The mixture was stirred and heated on a steam bath for 1 hr., and the solvent was distilled *in vacuo*. The hygroscopic crystalline residue was dissolved in 20 ml. of water and then 2% sodium hydroxide was added making the solution weakly alkaline. Brown viscous material separated from the solution and slowly solidified. The solid was filtered and recrystallized from ethanol, giving 1.8 g. of pale yellow crystals which melted at 148–151°. Recrystallizing once more from ethanol and then from a mixture of ligroin and benzene (2:1), yielded almost colorless crystals, m.p. 161–163°.

Anal. Calcd. for $C_8H_{11}N_3OS_2$: C, 41.92; H, 4.84; N, 18.34; S, 27.98. Found: C, 41.95; H, 4.74; N, 18.25; S, 28.15.

2-Methylthio-4-amino-5-mercaptomethylpyrimidine (XVI). 2-Methylthio-4-amino-5-bromomethylpyrimidine hydrobromide (5.4 g., 0.017 mole) was added to a solution of 2.7 g. (0.035 mole) of thioacetic acid in 25 ml. of pyridine. The mixture was heated on a steam bath for 1 hr. After cooling, crystals of pyridine hydrobromide were filtered off, and the solvent was distilled from the filtrate *in vacuo*, leaving a brown viscous residue. The residue was heated on a steam bath with 30 ml. of 2% hydrochloric acid for 1 hr. The resulting solution was neutralized with sodium carbonate after cooling, giving a brown viscous precipitate which slowly solidified. The solid gave no crystalline product after repeated attempts of recrystallization from ethanol, acetone, and benzene. The filtrate was extracted six times with 50-ml. portions of ether. The combined extracts were dried over magnesium sulfate for 1.5 hr. After the ether was distilled at atmospheric pressure, pyridine was removed *in vacuo*, leaving 99.6 mg. of white plates. These were recrystallized from benzene, m.p. 138–139° (*in vacuo*).

Anal. Calcd. for $C_6H_9N_3S_2$: C, 38.47; H, 4.84; S, 34.24. Found: C, 37.96; H, 4.89; S, 34.05.

2-Methylthio-4-amino-5-pyrimidylmethylisothiourea dihydrobromide (XVII). 2-Methylthio-4-amino-5-bromomethylpyrimidine hydrobromide (5 g., 0.016 mole) was added to a solution of 1.3 g. (0.017 mole) of thiourea in 100 ml. of acetone. The mixture was refluxed with stirring for 2 hr. After cooling, a white solid which weighed 4.5 g. was collected and recrystallized from ethanol, m.p. 240–241°.

Anal. Calcd. for $C_7H_{13}Br_2N_5S_2$: C, 21.49; H, 3.35; N, 17.90; S, 16.39. Found: C, 21.80; H, 3.37; N, 17.76; S, 16.86.

Bis(2-methylthio-4-amino-5-pyrimidylmethyl) disulfide (XVIII). 2-Methylthio-4-amino-5-pyrimidylmethylisothiourea dihydrobromide (3 g.) was dissolved in 40 ml. of water, and to this solution ammonium hydroxide was added until the solution was shown to be weakly alkaline (*p*H 8). White crystals immediately precipitated and were collected. The precipitate weighed 1.25 g. and melted at 103–105°. A 0.2-g. sample of the precipitate was dissolved in 20 ml. of boiling ethanol and the solution was concentrated to 2 ml. and

cooled overnight. The resulting precipitate was recrystallized from ethanol giving colorless crystals which melted at 213–215°, indicating formation of disulfide.

Anal. Calcd. for $C_{12}H_{16}N_6S_4$: C, 38.69; H, 4.29; N, 22.57; S, 34.43. Found: C, 39.01; H, 4.60; N, 22.47; S, 34.13.

The alkaline filtrate gave a further 0.15 g. of white precipitate after standing five days at room temperature. The precipitate was recrystallized from ethanol giving a crystalline product which was found identical with the disulfide from ethanol recrystallization of the main crop.

2-Ethylthio-4-amino-5-hydroxymethylpyrimidine (XIX) was prepared from 2-mercapto-4-amino-5-carbethoxypyrimidine *via* 2-ethylthio-4-amino-5-carbethoxypyrimidine. 2-Mercapto-4-amino-5-carbethoxypyrimidine was synthesized by condensation of ethyl ethoxymethylenecyanoacetate with thiourea by the method of Ulbricht and Price,[3] and the yield of 2-ethylthio-4-amino-5-hydroxymethylpyrimidine from ethyl ethoxymethylenecyanoacetate was 48%. This was a considerable improvement over the yields obtained by other workers.[9]

2-Mercapto-4-amino-5-carbethoxypyrimidine (10 g., 0.05 mole) was dissolved in a solution of 3.1 g. (0.055 mole) of potassium hydroxide in 50 ml. of water and 8 g. (0.052 mole) of diethyl sulfate was gradually added with shaking. After stirring 3 hr., the crystals were collected, washed and dried to yield 9.4 g. (83%) of 2-ethylthio-4-amino-5-carbethoxypyrimidine. This may be recrystallized from ethanol to give pale yellow plates, m.p. 100–102°.

This material was placed in a Soxhlet extractor mounted on a flask containing a solution of 3 g. (0.079 mole) of lithium aluminum hydride in 350 ml. of dry ether. The ether was refluxed with stirring for 3 hr. After cooling, 20 ml. of ethyl acetate was added with stirring, and then 10 ml. of water. The solid precipitate was filtered after standing overnight, and then extracted three times with 100-ml. portions of boiling acetone. The acetone solutions were combined and the solvent was distilled yielding white crystalline residue. The ether was distilled from the filtrate giving pale yellow crystalline residue which was combined with the acetone extracts. The crude products were washed with acetone and benzene leaving 7.5 g. of white crystals. After recrystallizing from ethanol, 5.9 g. (74%) of crystals which melted at 154–155.5° (lit.[8] m.p. 170° and 151–152° were obtained.

Anal. Calcd. for $C_7H_{11}N_3OS$: C, 45.38; H, 5.99; N, 22.68; S, 17.31. Found: C, 45.56; H, 6.15; N, 22.59; S, 17.49.

Infrared spectra (in potassium bromide, wavelength, and % absorption): IV; 2.98 (66), 3.15 (71), 6.06 (82), 6.29 (83), 6.43 (79), 6.76 (62), 7.02 (78), 7.33 (52), 7.78 (48), 8.12 (53), 10.00 (35), 10.30 (57), 12.64 (45), 12.89 (46).

VI; 2.90 (82), 3.22 (85), 4.61 (79), 6.00 (90), 6.29 (88), 6.38 (90), 6.75 (83), 7.01 (88), 7.80 (75), 8.13 (80), 9.63 (63), 10.35 (72), 11.38 (58), 12.65 (78), 12.97 (84), 13.27 (77), 14.50 (60).

VII; 2.90 (39), 3.34 (53), 6.57 (72), 7.04 (78), 7.31 (58), 7.60 (64), 8.33 (34), 8.70 (36), 8.82 (34), 10.41 (36), 12.27 (39), 12.47 (44), 12.85 (41), 14.54 (29).

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[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Steroidal Sapogenins. XLIX. C-Ring Oxygenated Derivatives of Correllogenin[2]

EDWARD S. ROTHMAN AND MONROE E. WALL

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In the course of conversion of natural mixtures of the 25D and 25L isomeric sapogenins gentrogenin (25D) and correllogenin (25L) to 11-keto diosgenin and 11-keto yamogenin, it was found possible to separate and characterize several intermediates which were sterically pure 25L compounds, *viz.* 3β,12β-dihydroxy-20α,22β,25L-spirost-5-en-11-one, Ia, and its diacetate, Ib; 20α,22β,25L-spirost-5-en-3β,11α-diol, IIa, and its diacetate, IIb. These new correllogenin derivatives have previously evaded isolation because of the difficulties in separating the pure parent compound. It was found that 3β,12β-diacetoxy-20α,22β,25D-spirost-5-en-11-one on treatment with calcium in liquid ammonia solution gave, in the presence of water, a high yield of 20α,22β,25D-spirost-5-en-3β,11α-diol (11α-hydroxy diosgenin).

In earlier papers of this series[3,4] we have described the isolation of gentrogenin[5] (3β-hydroxy-20α,22β,25D-spirost-5-en-12-one[5]), its 25L-diastereoisomer, correllogenin,[3] and the conversion of the former to 11-keto diosgenin.[4] In the latter paper were described the properties and reactions of a number of C-11 and C-12 oxygenated derivatives of gentrogenin. Because of the unavailability of pure correllogenin,[6] we were unable to prepare the corresponding 25L- derivatives. During the large scale conversion of a gentrogenin-correllogenin mixture to 3β-hydroxy-5,16-pregnadiene-11,20-dione,[7] we were able to isolate and characterize

(1) Eastern Utilization Research and Development Division, Agricultural Research Service, United States Department of Agriculture.

(2) Paper XLVIII, E. S. Rothman and M. E. Wall, submitted to *J. Am. Chem. Soc.*

(3) H. A. Walens, S. Serota, and M. E. Wall, *J. Org. Chem.*, **22**, 182 (1957).

(4) E. S. Rothman and M. E. Wall, *J. Am. Chem. Soc.*, **79**, 3228 (1957).

(5) For basis of formal nomenclature, particularly at C_{22}, *cf. Tentative Rules for Steroid Nomenclature*, Comptes Rendus de la Dix-Huitieme Conference, Zurich, 20–28 July, 1955, pp. 190–198.

(6) Although correllogenin may constitute twenty per cent of the total ketonic fraction isolated from *D. spiculiflora*, it is difficult to separate this sapogenin from the isomeric gentrogenin[5] and consequently only minute quantities of the sterically pure 25L- form have ever been obtained.

(7) Since pseudomerization followed by oxidative cleavage and alkaline hydrolysis converts the 25D- and 25L-sapogenins to the same 16-dehydro-20-keto-pregnene it is often convenient to work directly with the mixture.