Recrystallization from petroleum ether (b.p. 60–90°) gave 1.1 g. pure α-3-methyl-4-phenyl-4-hydroxypiperidine, m.p. 132°.

Anal. Calcd. for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.12; H, 9.06; N, 7.64.

Main infrared absorptions (potassium bromide-pellet): 3.0; 3.4; 6.9; 9.9; 13.2 and 14.3 μ.

A sample of the compound was converted into the *hydrochloride*, m.p. 180° after recrystallization from ethanol-ether. This hydrochloride is only sparingly soluble in acetone.

Anal. Calcd. for $C_{12}H_{18}ClNO$: C, 63.29; H, 7.97; N, 6.15. Found: C, 63.27; H, 7.98; N, 5.85.

α-1,3-Dimethyl-4-phenyl-4-hydroxypiperidine (XVI). α-3-Methyl-4-phenyl-4-hydroxypiperidine, 570 mg., 3.0 mmoles, was dissolved in a mixture of 380 mg. (7.5 mmoles) of 90% formic acid, 330 mg. (3.3 mmoles) of 30% aqueous formaldehyde and 2.0 ml. of water. This solution was refluxed for 8 hr. An excess of hydrochloric acid was added and the mixture was evaporated at 35° under reduced pressure in a rotating evaporator. The residue was dissolved in 10 ml. of water and was made alkaline with potassium hydroxide. An oil precipitated and was extracted with three 15-ml. portions of ether. Evaporation of the dried extract furnished a crystalline residue, m.p. 98–100°, which gave upon recrystallization from 2 ml. of ligroin (b.p. 60–90°), 0.56 g. (91%) of pure α-1,3-dimethyl-4-phenyl-4-hydroxypiperidine, m.p. 100° (reported m.p. 100–101°) either alone or in mixture with an authentic sample.

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.05; H, 9.33; N, 6.82. Found: C, 76.00; H, 9.28; N, 6.86.

The main absorptions in the infrared (potassium bromide-pellet) were at 3.2; 3.45; 3.6; 6.85; 6.95; 7.3; 7.8; 8.2; 8.7; 8.9; 9.1; 9.7; 10.0; 13.2 and 14.2 μ; this spectrum was superimposable with that of an authentic sample.

Acknowledgment. We wish to acknowledge with thanks support of this research by Merck and Co., Inc. We are indebted to Geller Laboratories, Bardonia, N. Y., for the microanalyses recorded in this paper.

CHARLOTTESVILLE, VA.

[CONTRIBUTION FROM PFISTER CHEMICAL WORKS, INC., AND DEPARTMENT OF CHEMISTRY, UNIVERSITY OF COLORADO]

Pyrimidines. I. Some Halogenated Monomethylpyrimidines

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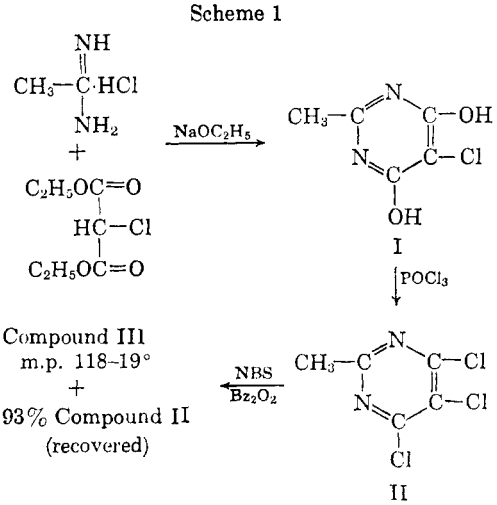
The three monomethyltrichloropyrimidines and intermediates were prepared. A study was made of the bromination of the methyl groups with *N*-bromosuccinimide.

In the course of preparing potential metabolite antagonists, the three monomethyltrichloropyrimidines and related compounds were produced. A further study was made of the bromination of the methyl groups with *N*-bromosuccinimide (NBS) in the presence of benzoyl peroxide (Bz_2O_2).

The 2-methylpyrimidine analogs were prepared by condensing acetamidine with ethyl chloromalonate in the presence of sodium ethylate to yield 5-chloro-2-methylpyrimidine-4,6-diol. This on treatment with phosphorus oxychloride yielded 2-methyl-4,5,6-trichloropyrimidine, as indicated in Scheme 1. On treatment with *N*-bromosuccinimide the expected 2-bromomethyl-4,5,6-trichloropyrimidine was not obtained; however, a small yield of a compound was gotten which contained bromine, but has not, as yet, been completely characterized.

Scheme 1



To circumvent the problem of the bromination of 2-methyl-4,5,6-trichloropyrimidine with *N*-bromosuccinimide, an alternate approach to preparing the 2-halogenomethyl-4,5,6-trichloropyrimidine was devised. As is shown in Scheme 2, benzoyl glycolamidine was condensed with ethyl chloromalonate in the presence of sodium ethylate and 5-chloro-4,6-dihydroxy-2-pyrimidinemethanol was produced. Upon treatment with phosphorus oxychloride and phosphorus pentachloride, 2-chloromethyl-4,5,6-trichloropyrimidine was obtained.

5-Methyl-2,4,6-trichloropyrimidine was prepared by the method of Gerngross[3] and on bromination with *N*-bromosuccinimide a quantitative yield of 5-bromomethyl-2,4,6-trichloropyrimidine was obtained.

Since this work was completed, it was reported by Hasegawa[4] that 5-bromomethyl-2,4,6-trichloro-

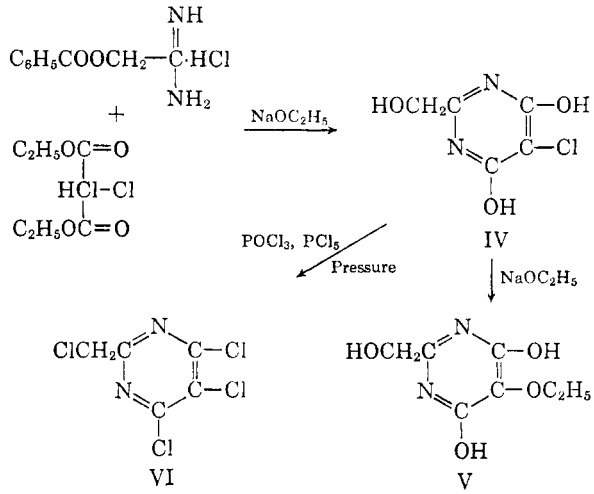
(1) Part of this work was taken from the Ph.D. thesis of of H. Gershon, University of Colorado, 1950.

(2) Present address: Division of Grants and Fellowships, American Chemical Society, Washington, D. C.

(3) O. Gerngross, *Ber.*, **38**, 3394 (1905).

(4) M. Hasegawa, *Pharm. Bull. (Japan)*, **1**, 387 (1953) [*Chem. Abstr.*, **49**, 10970 (1955)].

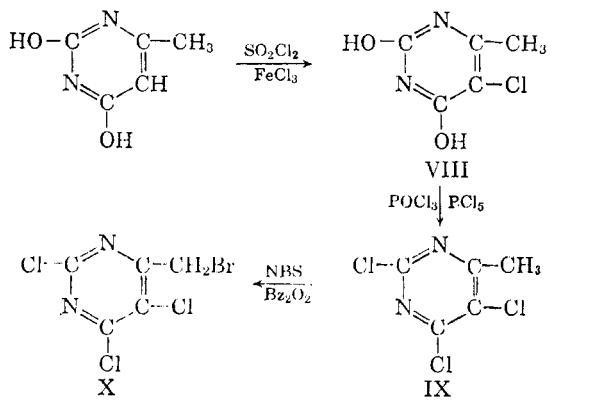
Scheme 2



pyrimidine was obtained in 77% yield by brominating the 5-methyl-2,4,6-trichloropyrimidine with *N*-bromosuccinimide in the presence of benzoyl peroxide under ultraviolet light.

For the preparation of the 6-methylpyrimidine derivatives, 6-methyluracil[5] was the starting material. It was chlorinated in the 5-position with sulfuryl chloride according to Barrett, Goodman, and Dittmer.[6] 6-Methyl-2,4,5-trichloropyrimidine was produced by treating successively with phosphorus oxychloride and phosphorus pentachloride. On bromination with *N*-bromosuccinimide, 38% of 6-bromomethyl-2,4,5-trichloropyrimidine was obtained. These reactions are illustrated in Scheme 3.

Scheme 3



It was demonstrated by Bailey and Bello[7] that an electron-withdrawing group attached to the *alpha* carbon inhibits allylic bromination. Shelton[8] and Cialdella have shown that an electron-releasing group next to the double bond increases the tendency to react by a polar mechanism. Polarization favors the heterolytic reaction, whereas lack of polarization favors the homolytic mechanism. Electron[9] deficiencies at positions 2, 4, and 6 of the pyrimidine ring are attributable to resonance of the entire ring. In the competition between the 2, 4 (or 6) positions, although there is a statistical factor of two favoring the latter, electronic effects might favor greater electron deficiency in the 2 position. Since position 5 is insulated from the ring nitrogens, it is considerably less electron deficient. This is borne out by the data obtained on the bromination of the three methyl trichloropyrimidines with *N*-bromosuccinimide in the presence of benzoyl peroxide. The methyl group on carbon atom 2 appears to have been sufficiently polarized to resist bromination completely, whereas the methyl group on carbon atom 4 was 38% brominated and the methyl group on carbon atom 5 was quantitatively brominated.

West[10] and Barrett reported the preparation of 5-chloromethyluracil by chlorinating thymine with *N*-chlorosuccinimide. This work was subjected to criticism by Burckhalter,[11] Seiwald and Scarborough and by Skinner,[12] Schelstraete and Baker who demonstrated that the compound thus prepared did not possess the assigned structure. Among the qualitative tests which this compound failed to give were: a positive test with alcoholic silver nitrate, instability toward boiling water and lack of absorption in the ultraviolet. The three halogenomethyltrichloropyrimidines herein reported could be recrystallized from aqueous alcohol with no decomposition, and the 2-chloromethyl-4,5,6-trichloropyrimidine failed to give a test with alcoholic silver nitrate. Ultraviolet spectra were obtained on the three halogenomethyltrichloropyrimidines and compared with the corresponding methyltrichloropyrimidines.

Table I contains a summary of the ultraviolet spectral data obtained on the methyl- and halogenomethyltrichloropyrimidines.

TABLE I

ULTRAVIOLET DATA FOR METHYLTRICHLOROPYRIMIDINES

Substance	Spectral Data in CH_3OH λ_{max} (mμ)	log ε
2-Methyl-4,5,6-trichloropyrimidine	270	3.68
2-Chloromethyl-4,5,6-trichloropyrimidines	270	3.71
5-Methyl-2,4,6-trichloropyrimidine	269	3.74
5-Bromomethyl-2,4,6-trichloropyrimidine	269	3.69
6-Methyl-2,4,5-trichloropyrimidine	271	3.63
6-Bromomethyl-2,4,5-trichloropyrimidine	283	3.70

(5) A. W. Dox, *Org. Syntheses*, **Coll. Vol. II**, 422 (1943).
(6) H. W. Barrett, I. Goodman, and K. Dittmer, *J. Am. Chem. Soc.*, **70**, 1753 (1948).
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(10) R. A. West and H. W. Barrett, *J. Am. Chem. Soc.*, **76**, 3146 (1954).
(11) J. H. Burckhalter, R. J. Seiwald, and H. C. Scarborough, *J. Am. Chem. Soc.*, **82**, 991 (1960).

These data show that the introduction of the fourth halogen atom was accompanied by retention of absorption in the ultraviolet and consequently the halogen atom must be on the side chain and not on the ring.

These compounds have been submitted to Cancer Chemotherapy National Service Center, National Institutes of Health for anticancer screening.

EXPERIMENTAL

5-Chloro-2-methylpyrimidine-4,6-diol (I). To 500 ml. of absolute ethanol containing 12.5 g. (0.5 g.-atom) of sodium were added 50 g. (0.5 mole) of acetamidine hydrochloride[13] and 98 g. (0.5 mole) of ethyl chloromalonate.[14] The mixture was shaken thoroughly for 30 min. and allowed to stand at room temperature for 24 hr. Water was added until a clear solution was obtained, and then the mixture was acidified to Congo Red with concentrated hydrochloric acid. After cooling for 3 days in the refrigerator, 22.5 g. of crystalline precipitate was filtered off. The yield was 35%. An analytical sample was obtained from water, and it did not melt below 305°.

Anal. Calcd. for $C_5H_5ClN_2O_2$: N, 17.44; Cl, 23.59. Found: N, 17.35; Cl, 23.45.

2-Methyl-4,5,6-trichloropyrimidine (II). Eight and one-tenth grams (0.05 mole) of 5-chloro-2-methylpyrimidine-4,6-diol was refluxed with 81 ml. of phosphorus oxychloride for 12 hr. with mechanical stirring. A clear solution resulted. Fifty milliliters of phosphorus oxychloride was distilled, and the residue was cautiously poured onto ice. The solid produced was taken up in isopropyl ether, and upon evaporation of the ether a crystalline mass remained which was then sublimed. Nine and one-tenth grams of 2-methyl-4,5,6-trichloropyrimidine was obtained, m.p. 68°. The yield was 92%.

Anal. Calcd. for $C_5H_3Cl_3N_2$: N, 14.14; Cl, 53.92. Found: N, 14.12; Cl 53.70.

Bromination of 2-methyl-4,5,6-trichloropyrimidine with N-bromosuccinimide (III). Ten grams (0.05 mole) of 2-methyl-4,5,6-trichloropyrimidine was dissolved in 100 ml. of dry carbon tetrachloride, and 8.9 g. (0.05 mole) of *N*-bromosuccinimide and 1.2 g. (10 mole %) of benzoyl peroxide were added. The mixture was refluxed with mechanical stirring for 77 hr. One and four-tenths grams of a compound was obtained as the residue of the sublimation which on recrystallization from absolute ethanol and decolorization with Darco G-60 melted at 112–115°. The presence of bromine was determined by sodium fusion. An analytical sample was prepared by repeated recrystallization from absolute ethanol, m.p. 118–119°. Found: C, 17.34; H, 0.87; N, 7.93.

4,6-Dihydroxy-2-pyrimidinemethanol. To 60 ml. of absolute ethanol containing 1.3 g. (0.05 g.-atom) of sodium were added 10.8 g. (0.05 mole) of benzoyl glycolamidine hydrochloride (as prepared by W. Klarer and E. Urech[15]), and 8.0 g. (0.05 mole) of freshly distilled ethyl malonate. The mixture was shaken well for 30 min. and allowed to stand at room temperature for 24 hr. Sufficient water was added to dissolve all the material, and then the solution was acidified with concentrated hydrochloric acid to Congo Red, and cooled overnight. Six grams of crystalline product was filtered off, and the yield was 50%. An analytical sample was prepared by dissolving the product in a large volume of water and decolorization with Darco G-60. The product did not melt below 305°.

Anal. Calcd. for $C_5H_6N_2O_3$: C, 42.25; H, 4.23; N, 19.71. Found C, 41.79; H, 4.59; N, 19.34.

5-Chloro-4,6-dihydroxy-2-pyrimidinemethanol (IV). Two and six-tenths grams (0.11 g.-atom) of sodium was dissolved in 120 ml. of absolute ethanol and to the mixture were added 19.5 g. (0.1 mole) of ethyl chloromalonate[14] and 21.5 g. (0.1 mole) of benzoylglycolamidine hydrochloride.[15] After thorough shaking, the mixture was allowed to stand at room temperature for 24 hr. Enough water was added to dissolve all the material. The solution was then acidified with concentrated hydrochloric acid to Congo Red and allowed to cool overnight. The product was filtered and recrystallized from 95% ethanol using Darco G-60 to decolorize it. A yield of 6.5 g. or 37% of the theoretical was obtained. It did not melt below 360°.

Anal. Calcd. for $C_5H_5ClN_2O_3$: C, 33.99; H, 2.83; N, 15.82. Found: C, 34.25; H, 2.76; N, 15.32.

4,6-Dihydroxy-5-ethoxy-2-pyrimidinemethanol (V). To a solution of 2.8 g. (0.12 g.-atom) of sodium in 50 ml. of absolute ethanol was added 5.3 g. (0.03 mole) of 5-chloro-4,6-dihydroxy-2-pyrimidinemethanol and the mixture was refluxed for 12 hr. The material, completely dissolved in 250 ml. of hot water, was acidified to Congo Red with concentrated hydrochloric acid. The crystals obtained on cooling were filtered off and washed free of chloride with cold water. The yield was 4.5 g. or 80%. An analytical sample was obtained from water, m.p. 209–210° dec.

Anal. Calcd. for $C_7H_{10}N_2O_4$: C, 45.16; H, 5.38; N, 15.05. Found: C, 45.46; H, 5.24; N, 14.56.

2-Chloromethyl-4,5,6-trichloropyrimidine (VI). A mixture of 36.0 g. (0.2 mole) of 5-chloro-4,6-dihydroxy-2-pyrimidinemethanol and 360 ml. of phosphorus oxychloride was refluxed with mechanical agitation overnight. The mixture was then transferred to a bomb and 130 g. (0.6 mole) of phosphorus pentachloride was added. The bomb was heated to 130° for 3 hr. Two hundred and fifty milliliters of phosphorus oxychloride was distilled, and the residue was poured onto ice. The product was extracted with isopropyl ether and upon evaporation of the ether, was distilled. The fraction boiling at 120–125° (6 mm.) was collected. A yield of 42.1 g. or 91% was obtained. A sample recrystallized from aqueous ethanol melted at 28.5–29.0°.

Anal. Calcd. for $C_5H_2Cl_4N_2$: C, 25.86; H, 0.86; N, 12.07. Found: C, 26.26; H, 0.69; N, 12.05.

5-Bromomethyl-2,4,6-trichloropyrimidine. Five grams (0.025 mole) of 5-methyl-2,4,6-trichloropyrimidine[1] was dissolved in 50 ml. of dry carbon tetrachloride and 4.45 g. (0.025 mole) of *N*-bromosuccinimide was added. To the mixture was added 600 mg. (10 mole %) of benzoyl peroxide. The material was refluxed with mechanical agitation for 30 hr. The succinimide was extracted with water, and on evaporation of the carbon tetrachloride, 6.8 g. of crude product remained. Upon recrystallization from absolute ethanol, 5-bromomethyl-2,4,6-trichloropyrimidine was obtained in 95% yield, m.p. 133–134°.

Anal. Calcd. for $C_5H_2BrCl_3N_2$: C, 21.66; H, 0.72; N, 10.11. Found: C, 21.66; H, 1.00; N, 10.16.

5-Chloro-6-methyluracil (VIII). 6-Methyluracil[3] was chlorinated in the 5-position by the method of Barrett, Goodman, and Dittmer.[4] In 600 ml. of a 5% mixture of acetic anhydride in glacial acetic acid 63.0 g. (0.5 mole) of 6-methyluracil was dissolved, and a catalytic quantity of ferric chloride was added. Seventy-four grams (0.55 mole) of sulfuryl chloride was added in small portions to the solution. A white precipitate formed upon the completion of addition of the sulfuryl chloride, and the mixture was refluxed for an additional 2 hr. until no more hydrogen chloride came off. The material was cooled to room temperature and the solids filtered off. The yield was 75 g., and the mother liquor yielded an additional 3.0 g. making a total of 97.5%. An analytical sample was prepared from water which did not

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(13) J. J. Donleavy and M. A. Kise, *Org. Syntheses*, **Coll. Vol. I**, 5 (1944).

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melt below 300°. Johnson and Sprague[16,17] claimed to have prepared this compound by another method, but listed no melting point or analytical data.

Anal. Calcd. for $C_5H_5ClN_2O_2$: N, 17.44; Cl, 23.59. Found: N, 17.24; Cl, 23.33.

6-Methyl-2,4,5-Trichloropyrimidine (IX). Ninety-six grams (0.6 mole) of 5-chloro-2,4-dihydroxy-6-methylpyrimidine was refluxed with stirring with 960 ml. of phosphorus oxychloride for 11 hr., and then 250 g. (1.2 moles) of phosphorus pentachloride was added, and the mixture was further refluxed for 4 hr. till very little hydrogen chloride was produced. Six hundred milliliters of phosphorus oxychloride was distilled, and the residue was poured onto ice. After extracting with isopropyl ether and evaporating, 104 g. of residue remained. The product was distilled and the fraction boiling at 115–120° (12 mm.) was collected, f.p. 20–21°. The yield was 95 g. or 80%. The preparation of this compound was previously described by Behrend[18] in a yield of 38%, b.p. 245–247°, and Elderfield[19] and Prasad reported a quantitative yield, b.p. 55–56° (0.2 mm.).

6-Bromomethyl-2,4,5-trichloropyrimidine (X). A mixture of 60 g. (0.3 mole) of 6-methyl-2,4,5-trichloropyrimidine, 54 g. (0.3 mole) of *N*-bromosuccinimide and 6.0 g. (10 mole %) of benzoyl peroxide in 400 ml. of dry carbon tetrachloride was refluxed with stirring for 40–50 hr. After filtering off the succinimide and evaporating the solvent, the residue was fractionated. Thirty-four grams of 6-methyl-2,4,5-trichloropyrimidine was recovered, or 56% of the starting material and 27.7 g. of a fraction (38% yield), boiling at 154–160° (14 mm.) which on recrystallization from isopropyl alcohol melted at 56–57°.

Anal. Calcd. for $C_5H_2BrCl_3N_2$: C, 21.66; H, 0.72; N, 10.11. Found: C, 21.92; H, 0.81; N, 10.00.

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[CONTRIBUTION FROM MIDWEST RESEARCH INSTITUTE]

Pyrimidines. III. 5,6-Dihydropyrimidines[1]

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Received October 10, 1960

The direct ring closure of α,β-unsaturated acids with urea, thiourea, and guanidine to 5,6-dihydropyrimidines was improved to make this preparation a practical method. A new synthesis of 5,5-dialkyl-substituted 5,6-dihydrouracils from the corresponding 6-imino-5,6-dihydrouracils is described. A theoretical consideration of the ease of formation of 5,6-dihydrouracils and the characterization of their ultraviolet absorption at different *p*H units are discussed. Bromination and dehydrobromination of 5,6-dihydrouracils were studied in detail. The reactions between 5-bromo-5,6-dihydrouracil and aliphatic and aromatic amines were investigated. It was found that aliphatic amines dehydrobrominated 5-bromo-5,6-dihydrouracil readily under all the conditions studied, while aromatic amines replaced the bromine atom under certain conditions to form 5-substituted anilino-5,6-dihydrouracils in good yield. The catalytic aromatization of 5,6-dihydrothymine to thymine was achieved in the presence of palladium on charcoal in boiling quinoline. Thiation studies of dihydrothymine were conducted and the products isolated at higher and lower temperature were identified.

The conversion of ureidosuccinic acid to orotic acid through dihydroorotic acid in pyrimidine biosynthesis has been well established.[2] Since biological intermediates are very rarely generated from a single precursor or through one single reaction route, other possible pathways in biogenesis of the nucleic acids and pyrimidines have been actively studied by a number of investigators.[3–6] Recent reports have indicated that dihydrouracil, which is believed to be unrelated to the orotate system, was incorporated in the *anabolism* of pyrimidines by certain biological systems.[7,8] It has long been recognized that dihydropyrimidines are important intermediates in the *catabolism* of pyrimidines.[9–16] Since all reactions in the deg-

(1) This investigation was supported by research contract SA-43-ph-3025 from the Cancer Chemotherapy National Service Center, National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) See, for example: (a) I. Liberman and A. Kornberg, *J. Biol. Chem.*, **207**, 911 (1954); (b) C. Cooper, R. Wu, and D. W. Wilson, *J. Biol. Chem.*, **216**, 37 (1955); (c) R. A. Yates and A. B. Pardee, *J. Biol. Chem.*, **221**, 743 (1956).

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