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.

RIDGEFIELD, N. J.

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(17) T. B. Johnson and J. M. Sprague, *J. Am. Chem. Soc.*, **60**, 1622 (1938).

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[CONTRIBUTION FROM MIDWEST RESEARCH INSTITUTE]

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

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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).

(3) H. K. Mitchell and M. B. Houlahan, *Feder. Proc.*, **6**, 506 (1947).

(4) L. H. Smith and O. Stetten, *J. Am. Chem. Soc.*, **76**, 3864 (1954).

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(8) L. K. Mokrasch and S. Grisolia, *Biochim. Biophys. Acta.*, **27**, 226 (1958); **33**, 444 (1959); **34**, 165 (1959); **39**, 361 (1960).

(9) C. Funk, A. J. Merrit, and A. Ehrlich, *Arch. Biochem. Biophys.*, **35**, 468 (1952).

(10) K. Fink, R. B. Henderson, and R. M. Fink, *J. Biol. Chem.*, **197**, 441 (1952). See also other papers published by same group of authors. *J. Biol. Chem.*, **201**, 349 (1953); **218**, 1, 9 (1956); **221**, 425 (1956).

(11) E. S. Canellakis, *J. Biol. Chem.*, **221**, 315 (1956).

(12) D. P. Wallach and S. Grisolia, *J. Biol. Chem.*, **226**, 277 (1957).

(13) P. Fritzson, *J. Biol. Chem.*, **226**, 223 (1957).

(14) P. Fritzson and A. Pihl, *J. Biol. Chem.*, **226**, 229 (1957).

(15) L. L. Campbell, Jr., *J. Bact.*, **73**, 225 (1957); *J. Biol. Chem.*, **227**, 693 (1957).

(16) I. Lieberman and A. Kornberg, *Biochim. Biophys. Acta.*, **12**, 223 (1953); *J. Biol. Chem.*, **212**, 909 (1955).

radative system are reversible except the terminal one,[17] it is reasonable to assume that other dihydropyrimidines or their derivatives might well play an important role in nucleic acid synthesis. This conception led us to investigate the synthesis of different types of dihydropyrimidines as possible antitumor agents.

Some difficulties were encountered in conducting a careful search of the literature for dihydropyrimidines due largely to the nomenclature used to designate these compounds. The naming of these compounds arbitrarily as dihydro-, tetrahydro-, and hexahydropyrimidines, depending on the number of "tautomeric" groups present in the compounds, seems unnecessarily confusing.

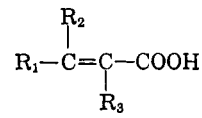
The literature revealed that relatively little attention has been focused on dihydropyrimidines. Only a few isolated reports of dihydropyrimidines, mostly in the early literature, are to be found. At present no discussion of general properties and reactions of dihydropyrimidines is available. It is evident that there is a definite need for an evaluation of the known dihydropyrimidine works as a preliminary step in the active investigation of this biologically important group of compounds.

Existing methods for the preparation of 5,6-dihydropyrimidines fall into three categories:

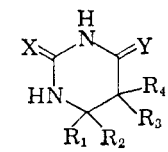
(1) The catalytic hydrogenation of pyrimidines has been reported[18-21] to yield 5,6-dihydropyrimidines. The value of this route is limited in that the yields are usually low, the reactions are difficult to control, and the structures of the products are, quite often, uncertain.

(2) The condensation of β-amino acids with isocyanates produced β-ureidopropionic acids which were then cyclized to the corresponding 5,6-dihydropyrimidines.[22-28] This method is well adapted for the preparation of *N*-substituted 5,6-dihydropyrimidines.

(3) The condensation of α,β-unsaturated acids or other α,β-unsaturated carbonyl compounds with amidine-type compounds yielded 5,6-dihydropyrimidines by direct ring closure.[22,24,25,29-33] This method has been rather widely employed. However, most of the condensations have been carried out by fusion and, as a result, the isolation procedures were quite involved and, consequently, the products were rather impure and the yields were usually low. This method has been greatly improved in our laboratories by the use of a suitable, inert solvent as a reaction medium. The condensation of urea and crotonic acid (I. $R_1 = CH_3$; R_2, R_3 = H), for instance, gave a 25% yield of 6-methyl-5,6-dihydrouracil (II. $R_1 = CH_3$; R_2, R_3, R_4 = H; X, Y = O) by the fusion process.[22] This reaction was investigated systematically under a variety of different conditions using various molar ratios of reactants, solvent systems, reaction time, and temperature. Finally the reaction product was isolated in 45% yield as analytically pure, white crystals when ethylene glycol was employed as the reaction solvent. The use of such a solvent was extended and shown to be a general method for obtaining dihydrouracils of high purity.



I



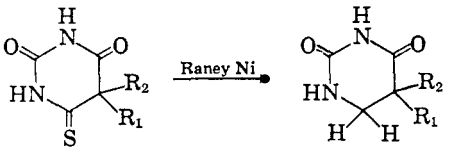
II

From a consideration of the different substituted α,β-unsaturated acids (I) studied, it would appear that the electron-donating groups on the β-carbon atom of I favor the formation of hydropyrimidines. Thus, 6-methyl-5,6-dihydrouracil[22] (II. $R_1 = CH_3$; R_2, R_3, R_4 = H; X, Y = O) and 6,6-dimethyl-5,6-dihydrouracil[34] (II. R_1, $R_2 = CH_3$; R_3, R_4 = H; X, Y = O) were obtained in 45% and 32% yield respectively, even though, in the latter case, the reaction was rather sterically hindered since both methyl groups were attached to the β-carbon atom. Electron withdrawing groups on the β-carbon atom retarded the reaction and consequently caused rather low yields. This was demonstrated by the reaction between urea and cinnamic acid (I. $R_1 = C_6H_5$; R_2, R_3 = H), which gave only 8% of the corresponding dihydrouracil. No dihydrouracil formation could be obtained when

(17) J. Caravica and S. Grisolia, *J. Biol. Chem.*, **231**, 357 (1958).
(18) P. A. Levene and F. B. LaForge, *Ber.*, **45**, 608 (1912).
(19) E. B. Brown and T. B. Johnson, *J. Am. Chem. Soc.*, **45**, 2702 (1923); **46**, 702 (1924).
(20) J. C. Ambelang and T. B. Johnson, *J. Am. Chem. Soc.*, **61**, 74 (1939); **63**, 1934 (1941).
(21) J. J. Fox and D. V. Praag, *J. Am. Chem. Soc.*, **82**, 489 (1960).
(22) E. Fischer and G. Roeder, *Ber.*, **34**, 3751 (1901).
(23) T. Posner, *Ann.*, **389**, 1 (1912).
(24) J. Evans and T. B. Johnson, *J. Am. Chem. Soc.*, **52**, 5000 (1930).
(25) T. B. Johnson and J. E. Livak, *J. Am. Chem. Soc.*, **58**, 299 (1936).
(26) J. F. Nyc and H. K. Mitchell, *J. Am. Chem. Soc.*, **69**, 1382 (1947).
(27) A series of papers published by V. M. Rodionov and his co-workers, *Zhur. Obshcheĭ Khim.*, **3**, 628 (1933); **23**, 1794 (1953); **24**, 1971 (1954); *Akad. Nauk S.S.S.R., Otdel. Khim. Nauk*, **1952**, 103, 278; **1956**, 332.
(28)(a) J. E. Gearien and S. B. Binkley, *J. Org. Chem.*, **23**, 491 (1958); (b) N. W. Gabel and S. B. Binkley, *J. Org. Chem.*, **23**, 643 (1958); (c) R. C. Smith and S. B. Binkley, *J. Org. Chem.*, **24**, 249 (1959).
(29) P. Biginelli, *Ber.*, **24**, 1317 (1891).
(30) W. Traube and R. Schwarz, *Ber.*, **32**, 3163 (1899).
(31) M. Bachstez and G. Cavallini, *Ber.*, **66**, 681 (1933).
(32) L. Birkofer and I. Storch, *Ber.*, **86**, 529 (1953).
(33) A. P. Phillips and J. Mentha, *J. Am. Chem. Soc.*, **76**, 574 (1954).
(34) E. Philippi, F. Hendgen, and F. Hernler, *Monatsh.*, **69**, 270 (1936).

p-nitrocinnamic acid was refluxed with urea under similar conditions.

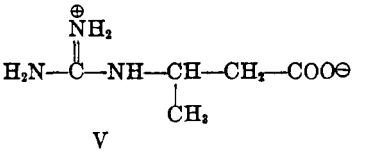
A new synthetic route to 5,5-dialkyl-substituted 5,6-dihydrouracils (IV), through the Raney nickel dethiation of 5,5-dialkyl-substituted 6-thio-5,6-dihydrouracils (III), has been devised in our laboratories. Compound III was in turn prepared from the corresponding 5,5-dialkyl-substituted 6-imino-5,6-dihydrouracils by the method of Boothe and Wilson.[35] As an example, 5-ethyl-5-propyl-5,6-dihydrouracil (IV. $R_1 = C_2H_5$, $R_2 = C_3H_7$) was obtained from 5-ethyl-5-propyl-6-thio-5,6-dihydrouracil (III. $R_1 = C_2H_5$, $R_2 = C_3H_7$) in 67% yield, or 37% over-all yield from the corresponding 6-imino compound, after purification. Some 5,5-dialkyl-substituted 5,6-dihydrouracils have been previously synthesized in unreported yield by the cyclization of α,α-disubstituted β-ureido esters.[36]



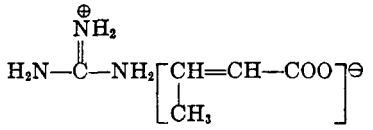
III IV

The ultraviolet spectra of 5,6-dihydrouracil and 5- and/or 6-substituted dihydrouracils do not possess absorption peaks between 220–900 mμ at *p*H 1 and 7; at *p*H 11 a low and flat peak at 223–235 mμ with a ϵ value of approximately 1000–2000 was observed. It is well known that most 5,6-dihydropyrimidines are unstable in aqueous base, hence the low peak detected in basic solution is due to some degradation product. This was verified as follows: In the ultraviolet region, 6-methyl-*2-thio*-5,6-dihydrouracil (II. $R_1 = CH_3$; R_2, R_3, R_4 = H; X = S; Y = O) exhibited two rather strong absorption maxima at 227 mμ and 271 mμ at *p*H 1 or 7. In *p*H 11, only a maximum peak at 238 mμ was observed. The position and intensity of this latter absorption peak remained the same upon reacidification, which indicated that the dihydrouracil had actually decomposed in cold base and had not undergone simply a physical change of cationic-anionic species at different *p*H.

A study was made of the condensation of guanidine and α,β-unsaturated acids to form dihydroisocytosine and related compounds (II. X = NH, Y = O). Paquin[37] refluxed a mixture of guanidine nitrate, crotonic acid, and dilute hydrochloric acid to give a product of unreported yield, m.p. 179–180°; Radionov and Urbanskaya,[38] apparently unaware of the work of Paquin,[37] obtained a product (m.p. 294–295°) from β-methylalanine and *O*-methylurea in 47% yield. Both of these investigators[37,38] claimed their products to be 6-methyl-5,6-dihydroisocytosine (II. X = NH; Y = O; $R_1 = CH_3$; R_2, R_3, R_4 = H). Paquin's method was repeated in our laboratories and only starting materials, instead of the claimed product, were isolated. When guanidine carbonate was used instead of guanidine nitrate, a product was obtained in 60–30% yield which did melt at 179–180°. However, our analysis indicated the presence of one molecule of water in addition to the proposed structure. Our product gave a positive Baeyer's test with permanganate, and decolorized bromine readily without evolution of hydrogen bromide. It was very soluble in cold water, and *completely* transparent in ultraviolet light. All these facts ruled out the possibility that the structure of the product was either a hydrated 6-methyl-5,6-dihydroisocytosine or the addition product, β-guanidinobutyric acid (V), and suggested that it was simply guanidine crotonate (VI). Cyclization of this salt to the desired 6-methyl-5,6-dihydroisocytosine, m.p. 292–294°, was finally achieved by refluxing VI in dimethylsulfoxide. The structure



V



VI

of the latter compound was confirmed by the fact that it was also prepared in our laboratories by an adaptation of the method of Phillips and Mentha[38] for the preparation of 6-phenyl-5,6-dihydroisocytosine. The two products were found to be identical by comparison of their melting points and ultraviolet and infrared spectral measurements.

In the course of utilizing the general method of Fischer and Roeder[22] for the bromination and dehydrobromination of the 5,6-dihydrouracils (II. X, Y = O) to give the corresponding uracils, a number of interesting observations were made.

(1) When R_1, R_2, R_3, and R_4 = H, bromination took place readily with the formation of 5-bromo-5,6-dihydrouracil (II. X, Y = O; R_1, R_2, and R_3 = H; R_4 = Br). Although the brominated product was rather stable, dehydrobromination was effected by boiling it in basic or high boiling solvent.

(2) When R_1, R_3, and R_4 = H, $R_2 = CH_3$, the resulting brominated product was also stable, but dehydrobromination was achieved under less severe conditions.

(35) J. H. Boothe and C. O. Wilson, *J. Am. Chem. Soc.*, 68, 448 (1946).

(36) O. Dalmer, C. Diehl, and H. Pieper, Ger. Patent, 606,349 (Nov. 30, 1934).

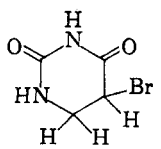
(37) A. M. Paquin, *Kunststoffe*, 37, 170 (1947).

(38) V. M. Rodionov and O. S. Urbanskaya, *Zhur. Obshchei Khim.*, 18, 2023 (1948).

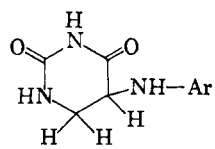
(3) When R_1, R_2, and R_3 = H, R_4 = CH_3, the resulting 5-bromo derivative dehydrobrominated very readily to yield thymine. Fischer and Roeder[22] have reported the preparation of 5-bromo-5,6-dihydrothymine by the bromination of 5,6-dihydrothymine. However, the elementary analysis for this brominated compound was not reported. When this bromination was repeated in our laboratories, although a variety of carefully controlled conditions were studied, the brominated product could not be isolated in pure form (see Experimental). This is readily explained when the steric and electron-donating effects of the 5-methyl group are considered.

(4) When R_1, R_2 = CH_3 and R_3, R_4 = H, the rate of bromination was much slower, and a longer reaction time and a higher temperature were required. The resulting 5-bromo derivative was very stable since dehydrobromination to the uracil is theoretically impossible.

When substituted alkyl- and arylamines were heated with 5-bromo-5,6-dihydrouracil(VII), various results were obtained depending on the nature of the amine used. Compound VII and aliphatic amines in refluxing ethanolic solution resulted in dehydrobromination and produced uracil in quantitative yield. Aromatic amines, on the other hand, replaced the bromine atom to give the corresponding 5-substituted anilino-5,6-dihydrouracils (VIII): Aniline and VII gave 5-anilino-5,6-dihydrouracil (VIII. Ar = C_6H_5)[39] either when refluxed in ethanol or when heated in the absence of a solvent. Substituted anilines did not react with VII satisfactorily in refluxing ethanol; however, a slow



VII



VIII

fusion at a comparatively low temperature, depending on the basicity and steric effect of the substituted anilines (see Table I), produced VIII in 60–80% yield. Rapid heating of the reaction mixture to higher temperatures (>200°) caused dehydrobromination of VII to give uracil. Attempts to prepare 5-anilino-6-methyl-5,6-dihydrouracil from 5-bromo-6-methyl-5,6-dihydrouracil and aniline were unsuccessful. Dehydrobromination occurred exclusively under a variety of conditions to give 6-methyluracil in good yield.

The aromatization of 5,6-dihydrothymine (II. R_1, R_2, R_3 = H; R_4 = CH_3; X, Y = O) to thymine was achieved in the presence of palladium on charcoal[40] in boiling quinoline. Attempts to aromatize 5-anilino-5,6-dihydrouracil (VIII. Ar = C_6H_5) by the bromination procedure gave, instead of 5-anilino-5-bromo-5,6-dihydrouracil, exclusively 5-(*p*-bromoanilino)-5,6-dihydrouracil (VIII. Ar = *p*-Br—C_6H_4). The structure of this brominated product was established as follows: VII and *p*-bromoaniline gave a 5-*p*-bromoanilino derivative which exhibited an identical melting point, ultraviolet and infrared absorption spectra and paper chromatographic behavior with those of the above brominated product. The corresponding 5-(*o*-bromoanilino)isomer (see Table I) was not isolated from the bromination reaction mixture.

The reaction between 5,6-dihydrothymine (II. R_1, R_2, R_3 = H; R_4 = CH_3; X, Y = O) and phosphorus pentasulfide was studied. At lower temperature one oxygen atom was replaced by sulfur to yield 2-thio-5,6-dihydrothymine (II. R_1, R_2, R_3 = H; R_4 = CH_3; X = S; Y = O). The structure of the thiated product was assigned on the basis of elementary analyses and by comparison of its ultraviolet absorption spectra with those of 2-thio-6-methyl-5,6-dihydrouracil. The attempted synthesis of 2-thio-5,6-dihydrothymine from methacrylate ester and thiourea was unsuccessful. When the thiation of 5,6-dihydrothymine was carried out at higher temperature, both oxygen atoms were replaced, accompanied by simultaneous dehydrogenation to yield 2,4-dithiothymine. This compound was found to be identical with an authentic sample prepared from thiourea and 2,4-dichloro-5-methylpyrimidine.[41,42]

EXPERIMENTAL[43]

5,6-Dihydrouracil.[44] A mixture consisting of 504 g. (7 moles) of acrylic acid, 840 g. (14 moles) of urea, 6 g. of hydroquinone, and 200 ml. of ethylene glycol was heated slowly to 130°, with vigorous stirring, in an open beaker. The heating was discontinued and the temperature of the stirred mixture spontaneously rose to 180°. After the violent reaction had subsided, the mixture was heated at 200–210° for 1 hr. and then cooled to 150°. The reaction mixture was added cautiously to 1.5 l. of water. The solution was boiled, decolorized with charcoal, and filtered. On cooling, 192 g. (24%) of white crystals, m.p. 268–270°, were obtained. Recrystallization from ethanol raised the melting point to 276–278° (lit. m.p. 275°). No ultraviolet absorption was observed at *p*H 1 and 7. $\lambda_{max}^{pH\ 11}$ 234 mμ (ε 820).

Anal. Calcd. for $C_4H_6N_2O_2$: N, 24.5. Found: N, 24.5.

6-Methyl-5,6-dihydrouracil.[22] A mixture of 86 g. (1 mole) of crotonic acid and 150 g. (2.5 moles) of urea in 300 ml. of ethylene glycol was heated slowly with stirring to 190°. The temperature was then maintained at 185–195° for 1 hr. The reaction mixture was refrigerated overnight. White crystals

(39) S. Gabriel, *Ber.*, **38**, 637 (1905).

(40) This catalyst is frequently used in the aromatization of benzenoid hydrocarbons, see, for example: (a) M. S. Newman and H. V. Zahm, *J. Am. Chem. Soc.*, **65**, 1097 (1943); (b) M. S. Newman and F. T. J. O'Leary, *J. Am. Chem. Soc.*, **68**, 258 (1946).

(41) H. L. Wheeler and D. McFarland, *Am. Chem. J.*, **43**, 25 (1910).

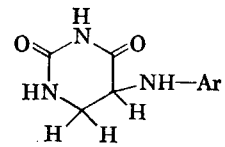
(42) G. B. Elion, W. S. Ide, and G. H. Hitchings, *J. Am. Chem. Soc.*, **68**, 2138 (1946).

(43) All melting points were taken on a Thomas-Hoover melting point apparatus. The infrared spectra were taken with a Perkin-Elmer infracord and the ultraviolet absorption spectra were determined with a Beckman DK-2.

(44) H. Weidel and E. Roithner, *Monatsh*, **17**, 174 (1896).

TABLE I

5-(SUBSTITUTED ANILINO)-5,6-DIHYDROURACILS



Ar	Reaction Temp.	Yield, %	M.P.	UV Absorption ($M\mu$) Ethanol λ_{max}	Ethanol ϵ	pH 1 λ_{max}	pH 1 ϵ	pH 7 λ_{max}	pH 7 ϵ	pH 11 λ_{max}	pH 11 ϵ	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
C_6H_5	115	78	241–242	241	14,100	236	7,600	237	11,500	238	15,300			20.5			20.7
				290	2,300												
o-Cl—C_6H_4	167–173	57	253–255	242	12,900	238	10,000	238	10,000	240	10,800	50.1	4.2	17.5	49.9	4.5	17.6
				294	2,950	291	2,200	291	2,200	291	2,300						
o-Br—C_6H_4	164–170	24	250–251	240	9,700	238	9,400	238	9,700	240	10,000	42.2	3.5	14.8	42.0	3.6	14.6
				295	2,430	292	2,250	292	2,250	292	2,300						
m-CH_3—C_6H_4	114–117	72	240–242	243	10,700	237	8,300	239	7,800	241	5,700	60.3	6.0	19.1	60.0	6.1	18.7
				291	2,100	285	1,750	286	1,750	287	1,750						
p-Cl—C_6H_4	150–155	73	260–262	250	18,400	248	12,700	247	14,100	246	14,600	50.1	4.2	17.5	49.9	4.2	17.6
				300	2,800	295	1,900	295	2,200	295	2,400						
p-Br—C_6H_4	130–140	71	265–266	249	17,300	247	12,500	248	12,500	248	13,000	42.2	3.5	14.8	42.5	3.8	14.7
				300	2,400	295	1,700	295	1,700	295	2,000						
p-CH_3—C_6H_4	95–105	78	265–266	243	13,400	—	—	238	11,000	239	12,800	60.3	6.0	19.1	60.1	6.1	19.2
				297	2,420			290	2,000	290	2,000						
p-C_2H_5O—C_6H_4	100–105	80	253–254	242	11,700	225	13,200	237	13,100	240	13,400	57.8	6.1	16.9	58.0	6.2	16.7
				307	2,250	271	1,740	299	2,490	299	2,480						
2-Cl-4-Br—C_6H_3	[a]	78	260–261	248	20,400	246	5,600	246	5,100	246	6,700	37.7	2.9	13.2	37.6	2.9	13.2
				306	3,500	303	1,200	303	1,200	303	1,200						
3,4-$(CH_3)_2$—C_6H_3	105–110	75	265–267	243	12,800	—	—	248	10,600	249	11,400	61.8	6.5	18.0	62.1	6.5	18.2
				295	2,740			291	2,200	291	2,200						

[a] Prepared by direct bromination of 5-(o-chloroanilino)-5,6-dihydrouracil.

separated slowly from the viscous solution. The product was filtered and washed with cooled ethanol and a small amount of ice water. The yield was 52 g., m.p. 216–218°. An additional yield of 6 g. was obtained from the filtrate by concentration. Total yield was 58 g. (45%). After recrystallization from ethanol, the melting point was 217–218°. No ultraviolet absorption was observed at *p*H 1 and 7. $\lambda_{max}^{pH\ 11}$ 233 mμ (ε 1,430). The product was found to be identical to a sample prepared according to Fischer and Roeder.[22]

Anal. Calcd. for $C_5H_8N_2O_2$: N, 21.9. Found: N, 21.7, 22.0.

6-Methyl-2-thio-5,6-dihydrouracil.[45] The product was obtained in 23% yield (3.3 g.), m.p. 218–220°, from 8.6 g. of crotonic acid, 19 g. of thiourea, and 25 ml. of ethylene glycol as pale yellow crystals. Recrystallization from dilute ethanol gave white needles, m.p. 220–221° (lit. m.p. 221°). When quinoline was used as the solvent, the product was isolated as light brown crystals in 26% yield, m.p. 218–220°. $\lambda_{max}^{pH\ 1}$ 227 mμ (ε 10,100), 271 mμ (ε 15,900); $\lambda_{max}^{pH\ 7}$ 227 mμ (ε 9,500), 271 mμ (ε 14,900); $\lambda_{max}^{pH\ 11}$ 238 mμ (ε 10,500); $\lambda_{max}^{ethanol}$ 276 mμ (ε 18,300).

Anal. Calcd. for $C_5H_8N_2O_2S$: N, 19.5. Found: N, 19.5.

6,6-Dimethyl-5,6-dihydrouracil.[34] The product was obtained in 32% yield (22.1 g.), m.p. 203–204° from 50 g. of β,β-dimethylacrylic acid and 75 g. of urea in 120 ml. of ethylene glycol. A sample recrystallized from ethanol melted at 204° (lit. m.p. 202°). No ultraviolet absorption at *p*H 1 and 7. $\lambda_{max}^{pH\ 11}$ 234 mμ (ε 1,780).

Anal. Calcd. for $C_6H_{10}N_2O_2$: N, 19.7. Found: N, 19.8.

Dethiation of 5,5-diethyl-6-thio-5,6-dihydrouracil. Twenty-five grams of 5,5-diethyl-6-thio-5,6-dihydrouracil,[35] [m.p. 195–197°; $\lambda_{max}^{pH\ 1}$ 287 mμ (ε 14,600); $\lambda_{max}^{pH\ 7}$ 289 mμ (ε 12,400) and $\lambda_{max}^{pH\ 11}$ 239 mμ (ε 5,200), 310 mμ (ε 13,200)] was refluxed with vigorous stirring with 250 g. of Raney nickel in 1300 ml. of ethanol for 2 hr. The catalyst was then filtered and the solvent was removed under reduced pressure. The residue was recrystallized from isopropyl alcohol to give 6.5 g. (31%) of 5,5-diethyl-5,6-dihydrouracil, m.p. 192–194° (lit. m.p. 198–199°).

Anal. Calcd. for $C_8H_{14}N_2O_2$: C, 56.5; H, 8.3; N, 16.4. Found: C, 56.1; H, 8.0; N, 16.3.

5-Ethyl-5-propyl-6-thio-5,6-dihydrouracil. A mixture of 16 g. (0.081 mole) of 5-ethyl-5-propyl-6-imino-5,6-dihydrouracil[46] and 1 l. of a saturated solution of ethanolic hydrogen sulfide was heated at 145° in a bomb for 12 hr. The yellow solution was evaporated under reduced pressure. The residue was disolved in 300 ml. of 5% sodium hydroxide and a trace of insoluble material was removed by filtration. The filtrate was acidified with dilute hydrochloric acid and the precipitate, which was free of unchanged imino compound, was filtered. The crude product was recrystallized from a mixture of water and ethanol to give 9.6 g. (55%) of light yellow needles, m.p. 137–138°. $\lambda_{max}^{pH\ 1}$ 289 mμ (ε 15,100); $\lambda_{max}^{pH\ 7}$ 290 mμ (ε 12,800); $\lambda_{max}^{pH\ 11}$ 310 mμ (ε 14,500).

Anal. Calcd. for $C_9H_{14}N_2O_2S$: C, 50.6; H, 6.6; N, 13.1. Found: C, 51.0; H, 6.7; N, 13.0.

Dethiation of 5-ethyl-5-propyl-6-thio-5,6-dihydrouracil. 5-Ethyl-5-propyl-5,6-dihydrouracil was obtained after recrystallization from water in 67% yield as white needles, m.p. 180–181°, from 5-ethyl-5-propyl-6-thio-5,6-dihydrouracil, Raney nickel, and ethanol by the method described previously for the preparation of 5,5-diethyl-5,6-dihydrouracil.

Anal. Calcd. for $C_9H_{16}N_2O_2$: C, 58.7; H, 8.8; N, 15.2. Found: C, 58.9; H, 8.9; N, 15.2.

Guanidine crotonate. A solution of 143 g. (1.65 moles) of crotonic acid in 200 ml. of water was added slowly, with stirring, to a suspension of 145 g. (1.5 moles) of guanidine carbonate in 100 ml. of water. Carbon dioxide was liberated during the mixing. The clear solution was then refluxed for 1 hr. The solvent was removed under reduced pressure. The residue was triturated with 300 ml. of dry acetone and filtered. The solid was washed thoroughly with dry acetone to remove the excess crotonic acid. The crude product, m.p. 175–177°, weighed 161 g. (74%). Recrystallization from a mixture of isopropyl alcohol and isopropyl ether raised the melting point to 179–180°. The product was extremely soluble in water, very soluble in ethanol, insoluble in chloroform and acetone, decolorized bromine readily, and gave a positive Baeyer's test for unsaturation. Based on this information and the elementary analyses, the structure of the product was assigned as guanidine crotonate (VI).

Anal. Calcd. for $C_5H_{11}N_3O_2$: C, 41.4; H, 7.6; N, 28.9. Found: C, 41.7; H, 7.3; N, 28.8.

6-Methyl-5,6-dihydroisocytosine.[38] A solution of 50 g. of guanidine crotonate in 100 ml. of dimethyl sulfoxide was heated at 180–200° for 2 hr. with stirring. The solvent was then distilled under reduced pressure and the residue was triturated with 200 ml. of ethanol. After overnight refrigeration the product was filtered and recrystallized from methanol to yield 6.6 g. (15%) of 6-methyl-5,6-dihydroisocytosine, m.p. 292–294° (lit. 294–295°). $\lambda_{max}^{pH\ 7}$ 232 mμ (ε 6,500); $\lambda_{max}^{pH\ 11}$ 235 mμ (ε 10,500); $\lambda_{max}^{ethanol}$ 236 mμ (ε 14,500).

Anal. Calcd. for $C_5H_9N_3O$: N, 33.1. Found: N, 32.8.

This compound was also obtained in 18% yield by refluxing a mixture of 22.8 g. (0.2 mole) of ethyl crotonate, 25.8 g. (0.27 mole) of guanidine hydrochloride and 13.0 g. (0.24 mole) of sodium methoxide in 500 ml. of absolute ethanol for 20 hr. The product, m.p. 292–294°, was found to be identical with the product obtained by the above procedure by comparison of their ultraviolet and infrared absorption spectra.

5,6-Dihydroisocytosine. A mixture of 40 g. (0.4 mole) of ethyl acrylate and 28.4 g. (0.48 mole) of guanidine was refluxed in 1 l. of absolute ethanol for 20 hr. The solution was evaporated to *ca.* 150 ml. A white solid product separated on cooling. It was filtered and recrystallized from methanol. The product was then boiled with benzene, the benzene layer was decanted, and the residue was recrystallized from *n*-butyl alcohol to yield 5,6-dihydroisocytosine, m.p. 253–254°. The yield after purification was 6.8 g. (15%). $\lambda_{max}^{pH\ 11}$ 235 mμ (ε 9,800); $\lambda_{max}^{ethanol}$ 236 mμ (ε 18,000).

Anal. Calcd. for $C_4H_7N_3O$: C, 42.5; H, 6.2; N, 37.1. Found: C, 42.8; H, 6.4; N, 37.0.

By the same procedure, guanidine and methyl methacrylate gave 5-methyl-5,6-dihydroisocytosine, m.p. 266–268°, in 18% yield after purification from methanol. $\lambda_{max}^{pH\ 11}$ 235 mμ (ε 9,900); $\lambda_{max}^{ethanol}$ 236 mμ (ε 11,600).

Anal. Calcd. for $C_5H_9N_3O$: C, 47.2; H, 7.1; N, 33.1. Found: C, 47.5; H, 7.2; N, 33.2.

Similarly, 6-carbethoxy-5,6-dihydroisocytosine, m.p. 218–220°, was obtained in 11% yield, after recrystallization from *n*-butyl alcohol, from guanidine and diethyl maleate. $\lambda_{max}^{pH\ 7}$ 226 mμ (ε 9,200); $\lambda_{max}^{pH\ 11}$ 229 mμ (ε 7,500); $\lambda_{max}^{ethanol}$ 229 mμ (ε 11,900).

Anal. Calcd. for $C_7H_{11}N_3O_3$: C, 45.5; H, 6.0; N, 22.7. Found: C, 45.3; H, 6.1; N, 22.6.

5-Bromo-5,6-dihydrouracil. This compound has previously been prepared by Gabriel[39] in a sealed tube. A practical scale bromination of 5,6-dihydrouracil was carried out as follows.

A solution of 160 g. (1 mole) of bromine in 200 ml. of glacial acetic acid was added dropwise to a well-stirred and refluxed solution of 114 g. (1 mole) of 5,6-dihydrouracil in 450 ml. of glacial acetic acid. Approximately 1 hr. was required for the addition. The heating was discontinued as soon as all the free bromine had disappeared. The reaction mixture was then neutralized carefully with 10% sodium hydroxide to *p*H 5. On cooling, white crystals of 5-bromo-5,6-dihydrouracil separated. The product was filtered and washed several times with small amounts of water to give 130 g. of crude product, m.p. 185–190°. An additional amount (32 g.) of the product of the same purity was obtained from the concentrated filtrate. Total yield = 84%.

(45) E. Billet and C. Mentzer, *Compt. rend.*, **224**, 1164 (1947).

(46) von M.-Conrad, *Ann.*, **340**, 318 (1905).

The product was recrystallized from a mixture of water and dimethylformamide (boiling in dimethylformamide alone should be avoided), followed by recrystallization from ethanol, resulting in 100 g. (52%) of analytically pure white needles. The product melted at 207–208° (lit. m.p. 195°) to a clear liquid, with the simultaneous liberation of hydrogen bromide, followed by immediate solidification, which was remelted at 315–317°. No ultraviolet absorption maxima were observed at *p*H 1 and 7. $\lambda_{max}^{pH\ 11}$ 240 mμ (ε 600).

Anal. Calcd. for $C_4H_5BrN_2O_2$: N, 14.5. Found: N, 14.5.

5-Bromo-6-methyl-5,6-dihydrouracil,[22] m.p. 313–315° (dec.,) was similarly prepared. $\lambda_{max}^{pH\ 11}$ 243 mμ (ε 3,760).

5-Bromo-6,6-dimethyl-5,6-dihydrouracil. The product, m.p. 241–243° (dec.,) was obtained in 89% yield (11.7 g) by a similar bromination procedure from 8.5 g. (0.06 mole) of 6,6-dimethyl-5,6-dihydrouracil, 9.6 g. (0.06 mole) of bromine and 70 ml. of glacial acetic acid. No ultraviolet absorption at *p*H 1 and 7. $\lambda_{max}^{pH\ 11}$ 240 mμ (ε 6,200).

Anal. Calcd. for $C_6H_9BrN_2O_2$: C, 32.6; H, 4.1; N, 12.7. Found: C, 32.8; H, 4.0; N, 12.8.

Bromination of 5,6-dihydrothymine. To a reflux solution of 25.6 g. (0.2 mole) of 5,6-dihydrothymine in 200 ml. of glacial acetic acid was added dropwise with stirring a solution of 32 g. (0.2 mole) of bromine in 50 ml. of glacial acetic acid. As soon as the addition was complete and the bromine had disappeared, the reaction mixture was quickly cooled and the *p*H was adjusted by the addition of 100 ml. of 10% cold sodium hydroxide. The product was collected after overnight refrigeration and recrystallized from ethanol to yield 20 g. of white crystals, m.p. 313–315°. A study of the extinction coefficient of the ultraviolet absorption spectra has indicated the presence of 46% of thymine, and the nitrogen analysis (Found: N, 17%) has also shown the presence of 45% thymine, in the brominated product, 5-bromo-5,6-dihydrothymine.

5-Anilino-5,6-dihydrouracil.[39] A solution of 10 g. (0.05 mole) of 5-bromo-5,6-dihydrouracil, 20 ml. (0.2 mole) of aniline in 500 ml. of ethanol was refluxed for 6 hr. The volume of the reaction mixture was then reduced to 150 ml. to give 8.7 g. of white crystals. Recrystallization from water gave 7 g. (66%) of analytically pure 5-anilino-5,6-dihydrouracil, m.p. 241–242° (lit. m.p. 239°). The product was also obtained by fusion (see Table I).

5-(Substituted anilino)-5,6-dihydrouracils (see Table I). A mixture of 0.01 mole of 5-bromo-5,6-dihydrouracil and 0.05 mole of the substituted aniline was well mixed and heated *slowly*, with stirring, in an oil bath until a spontaneous reaction commenced. The temperature of the reaction was then maintained at 150° for 20 min. and cooled. To the reaction mixture was added 10–20 ml. of ethanol. The mixture was boiled for 5 min. and the solid product was collected by filtration and purified by recrystallization from a mixture of dimethylformamide and water (see Table I) as small white needles.

Only pure 5-bromo-5,6-dihydrouracil (m.p. >200°) was used for the preparation of 5-(substituted anilino)-5,6-dihydrouracils. Furthermore, the reaction temperature should be carefully controlled. Under no circumstances should the spontaneous reaction temperature be allowed to exceed 180°. Above this temperature dehydrobromination occurs and the main product is uracil.

Bromination of 5-anilino-5,6-dihydrouracil. To a solution of 3 g. (0.015 mole) of 5-anilino-5,6-dihydrouracil in 50 ml. of pyridine at 50–60° was added dropwise 2.4 g. (0.015 mole) of bromine. The reaction mixture was stirred for 1 hr. at that temperature and then was refluxed for 2 hr. The solvent was removed under reduced pressure. To the residue was added 50 ml. of water and the solid product was filtered and washed with water. The yield was 3.5 g. (85%), m.p. 245–246°. Recrystallization from dimethylformamide and water gave 2.1 g. (50%), m.p. 261–263°. The product was found to be identical with an authentic sample of 5-(*p*-bromoanilino)-5,6-dihydouracil (see Table I) by the comparison of their ultraviolet, infrared absorption spectra, paper chromatograms, and mixed melting point determinations. No 5-(*o*-bromoanilino) isomer was detected.

Thiation of 5,6-dihydrothymine. A. *At refluxing temperature of pyridine.* A mixture of 15 g. of 5,6-dihydrothymine, 75 g. of purified phosphorus pentasulfide[47] in 200 ml. of dry pyridine was refluxed for 4 hr. The excess solvent was removed and to the residue was added 400 ml. of water. Enough aqueous ammonia was added to dissolve all the solid. The aqueous solution was boiled, decolorized with charcoal, and filtered. A brown solid, which separated upon acidification of the filtrate with hydrochloric acid, was recrystallized twice from ethanol-water to give 2.5 g. (13.5%) of fine yellow needles, m.p. 280–281° dec. The product was identified as 2,4-dithiothymine by comparing the melting point, elementary analyses, paper chromatograms, ultraviolet and infrared spectra with an authentic sample prepared according to Wheeler and McFarland.[41] $\lambda_{max}^{pH\ 1}$ 285 mμ (ε 22,600), 349 mμ (ε 9,500); $\lambda_{max}^{pH\ 7}$ 261 mμ (ε 10,800), 280 mμ (ε 18,400); $\lambda_{max}^{pH\ 11}$ 253 mμ (ε 13,900), 262 mμ (ε 10,500), 278 mμ (ε 17,100). R_f = 0.73 (pink fluorescence, in *n*-butyl alcohol saturated with 10% urea, 25°, descending), 0.85 (pink fluorescence, in *n*-butyl alcohol saturated with 0.2 N hydrochloric acid, 25°, descending).

Anal. Calcd. for $C_5H_6N_2S_2$: C, 38.1; H, 3.8; N, 17.6. Found: C, 38.3; H, 3.6; N, 17.3.

B. *At 100°.* A mixture of 15 g. of 5,6-dihydrothymine, 75 g. of purified phosphorus pentasulfide in 250 ml. of pyridine was heated at 100° for 2 hr. with stirring. The excess solvent was removed and the residue was boiled with 250 ml. of water, decolorized with charcoal, and filtered. On cooling, a yellow solid separated which was recrystallized from ethanol to give 0.8 g. (4%) of 2,4-dithiothymine, m.p. 280–281° dec. The filtrate was concentrated to about 50 ml. to yield a white solid. Recrystallization from methanol gave 6.1 g. (36%) of 2-thio-5,6-dihydrothymine as white crystals, m.p. 165–168°. For analysis, the compound was recrystallized again from water and ethanol to give a melting point of 171–173°. $\lambda_{max}^{pH\ 1}$ 226 mμ (ε 11,500) 269 mμ (ε 24,700); $\lambda_{max}^{pH\ 7}$ 226 mμ (ε 11,000), 269 mμ (ε 24,800); $\lambda_{max}^{pH\ 11}$ 269 mμ (ε 3,900), 238 mμ (ε 13,700), and $\lambda_{max}^{ethanol}$ 226 mμ (ε 9,500), 275 mμ (ε 23,800). By comparing the ultraviolet absorption spectra with those of 2-thio-6-methyl-5,6-dihydrothymine, which are completely identical, and also from the fact that paper chromatographic data indicated the presence of only one absorption spot (R_f = 0.67 in *n*-butyl alcohol saturated with 0.2*N* of hydrochloric acid, 25°, descending; *Rf* = 0.65 in *n*-butyl alcohol saturated with 10% urea, 25°, descending), the structure of the product was assigned as 2-thio-5-methyl-5,6-dihydrouracil.

Anal. Calcd. for $C_5H_8N_2OS$: C, 41.6, H, 5.6; N, 19.5. Found: C, 41.6; H, 5.9; N, 19.2.

When the thiation of 5,6-dihydrothymine was carried out at 60–80° for 60 hr., only a small amount of 2-thio-5-methyl-5,6-dihydrouracil was formed, together with unchanged starting material, which was identified by ultraviolet and infrared spectra.

Dehydrogenation of 5,6-dihydrothymine to thymine. A mixture of 5 g. of 5,6-dihydrothymine, 0.5 g. of 10% palladium on charcoal in 50 ml. of redistilled quinoline was heated under reflux for 60 hr. with stirring. The catalyst was filtered and washed with hot quinoline. The combined filtrate and washings were evaporated to dryness under reduced pressure. The residue was triturated with 10 ml. of absolute ethanol. The portion that was insoluble in ethanol was collected by filtration and recrystallized from water. The product, 0.8 g (15%), m.p. 310–312°, was identified as thymine by comparing the ultraviolet, infrared absorption spectra, and paper chromatograms with an authentic sample of thymine.

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[CONTRIBUTION FROM MIDWEST RESEARCH INSTITUTE]

Pyrimidines. IV. Aziridinylpyrimidines[1]

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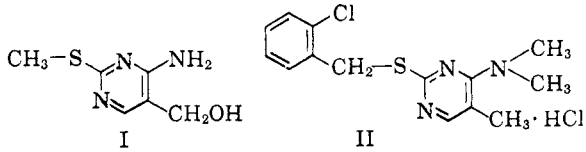
Syntheses of the aziridinylpyrimidine analogs of methioprim, DG-428 and DG-935 were accomplished. The activating effect of a 5-bromo group on the nucleophilic substitution of chloropyrimidines and methylsulfonylpyrimidines by ethylenimine was investigated. A new bromination method was reported.

The structures of 2-(1′-aziridinyl)-4,6-dichloropyrimidine and 4-(1′-aziridinyl)-2,6-dichloropyrimidine were definitely established by unambiguous syntheses and their chemical behavior was studied.

A number of alkylating agents of the ethylenimine type have been found to possess tumor inhibitory and cytotoxic activity,[2] especially in the treatment of the chronic leukemias, ovarian cancer, carcinoma of the breast, and the Hodgkin's disease.[2] Several of these compounds are being used clinically.[3] However, these compounds are, in general, quite toxic. It seems probable that a higher degree of selectivity might be attained by attaching the aziridinyl moiety to a "carrier" which could be transported *in vivo* to a particular site of action.[4]

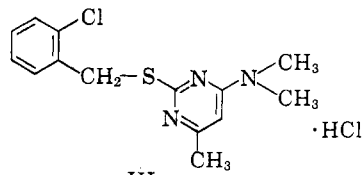
Early investigators[5] utilized the extremely reactive chloro-1,3,5-triazines to prepare numerous aziridinyl derivatives of considerable antitumor activity.[6] This would suggest that the pyrimidine ring, which is of more biological importance than the 1,3,5-triazine ring, might be advantageously utilized to design compounds with a more favorable therapeutic index. The pioneering study by Hendry and co-workers[7] has already indicated that in all cases where a comparison was possible, the pyrimidine derivatives proved to be more active than their triazine analogs. This apparent success strongly suggests that the specificity of action and, therefore, the antitumor activity might be further enhanced by utilizing, as carriers, pyrimidine derivatives more closely related to some known antimetabolites.

In an effort to enhance the known antimetabolic activity of methioprim (I),[8] DG-428 (II)[9] and DG-



I

II



III

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