lizations from ethanol gave crystals m.p. 112.0–113°. With ferric chloride a deep wine-red color was obtained.

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.74; H, 6.32.

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Synthesis of Analogs of Thymidine[1]

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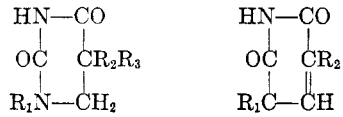
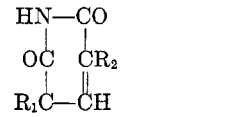
The concept of antimetabolites has been in vogue for several years and the application of this concept to cancer chemotherapy has lead to the preparation of several active compounds, *e.g.* azaguanine, 6-mercaptopurine, 2,6-diaminopurine, 6-azathymine, 5-hydroxy and 5-aminouridine, A-methopterin, etc. It has been shown that these effect thymine metabolism.[2,3] Since DNA is concerned with cell division and differs from RNA in that it contains thymine instead of uracil, it appeared that a logical approach to the problem of reducing cell division would be to prepare an antimetabolite which will block the introduction of thymine into DNA. The fact that mammalian cells incorporate the corresponding nucleosides indicates that an effective antimetabolite might be a pyrimidine substituted in the one position. Since it has been shown that 5-bromouracil inhibits the growth of several bacteria, it appeared that the 5-halogenated-1-substituted pyrimidines should also be prepared for testing.[4] We have prepared, therefore, and tested a number of 1-substituted uracils, 1-substituted-5-bromouracils, 1-substituted dihydrouracils, and 1-substituted-5-bromodihydrouracils in which the substituent was either methyl, isopropyl, or benzyl.



R_1 = benzyl, isopropyl, or methyl
R_2 = hydrogen or bromine
RR_3 = hydrogen or bromine



R_1 = benzyl, isopropyl, or methyl
R_2 = hydrogen or bromine

While several of the uracils and 5-bromouracils have previously been prepared, the following method was developed as it offered an unequivocal synthesis of the uracils and produced as intermediates the desired dihydro and 5-bromodihydrouracils.

N-Substituted-β-alanine esters, prepared by the addition of the proper primary amine to ethyl acrylate, were converted to dihydrouracils when treated with potassium cyanate and hydrochloric acid. This is an adaptation of a method employed by Johnson and Livak for the conversion of β-substituted-β-alanines to 6-substituted dihydrouracils.[5] The resulting *N*-substituted dihydrouracils were brominated to give 1-substituted-5-bromodihydrouracils, which upon dehydrohalogenation gave the corresponding substituted uracils. Since the uracils with the exception of *N*-isopropyl uracil were known, this served as a further confirmation of the structures of the previous unreported 1-substituted dihydro-and 1-substituted-5-bromodihydrouracils.

Previous bromination of substituted dihydrouracils had been carried out in sealed tubes.[6] 1-Benzyldihydrouracil and 1-methyldihydrouracil, however, gave satisfactory yields of the corresponding 5-bromo compounds when one molecular equivalent of bromine was added to a boiling acetic acid solution of the dihydrouracil. 1-Isopropyldihydrouracil, however, failed to give a pure monobrominated derivative but when treated with two molecular equivalents of bromine yielded 1-isopropyl-5,5-dibromodihydrouracil. 1-Benzyl dihydrouracil was also brominated to yield 1-benzyl-5,5-dibromodihydrouracil.

When added to boiling dimethylformamide the 1-substituted-5-bromodihydrouracils were dehydrohalogenated to give good yields of 1-substituted uracils and the 1-substituted-5,5-dihydrobromouracil gave good yields of 1-substituted-5-bromouracils (Table I).

1-Methyl-5-bromouracil was prepared by the direct bromination of 1-methyl uracil.[7]

EXPERIMENTAL[10]

The ethyl esters of *N*-methyl-β-alanine and *N*-benzyl-β-alanine were prepared by the procedure described by Adamson.[11] When 30.0 g. (0.30 mole) of ethyl acrylate was added dropwise to a cooled solution of 35.4 g. (0.60 mole of isopropylamine in 100 ml. of absolute alcohol and the product distilled, 40.5 g. (85%) of *N*-isopropyl-β-alanine ethyl ester was obtained. It boiled at 91–92° (20 mm.).

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(9) T. Johnson and Derby, *Am. Chem. J.*, **40**, 453 (1901).
(10) All melting points are uncorrected.
(11) D. Adamson, *J. Chem. Soc.*, Suppl. Issue No. 1, S144 (1949).

TABLE I

DEHYDROHALOGENATION OF 5-BROMO AND 5,5-DIBROMODIHYDROURACILS

Dihydrouracil	Uracil	Yield	M.P.	Reported M.P.
1-Methyl-5-bromo	1-Methyl	96%	232–233°	232°[7]
1-Benzyl-5-bromo	1-Benzyl	78%	171–172°	173–174°[8]
1-Isopropyl-5,5-dibromo	1-Isopropyl-5-bromo	64%	202–204°	—
1-Benzyl-5,5-dibromo	1-Benzyl-5-bromo	78%	203–205°	204°[9]

Anal. Calcd. for $C_8H_{17}O_2N$: N, 8.80. Found: N, 8.65.

1-Methyldihydrouracil. A solution of 30.0 g. (0.23 mole) of the ethyl ester of *N*-methyl-β-alanine in 30 ml. of water and 23.5 ml. of hydrochloric acid was added dropwise to a cooled solution of 24.3 g. (0.30 mole) of potassium cyanate in 30 ml. of water. This reaction mixture was allowed to stand overnight, the water removed by distillation under vacuum, and the semisolid residue heated at 100–110° (25 mm.) for 1 hr. The solid residue was extracted with boiling absolute alcohol. Upon evaporation of the alcohol a white crystalline solid was obtained. Recrystallization from ethanol yielded 13.0 g. (50%) of 1-methyldihydrouracil, which melted at 173–174°. (Lit. 174–175°).[12]

1-Isopropyldihydrouracil. When 31.8 g. (0.20 mole) of the ethyl ester of *N*-isopropyl-β-alanine was allowed to react with 21.0 g. (0.26 mole) of potassium cyanate and 20.0 ml. of hydrochloric acid according to the procedure described for the preparation of 1-methyldihydrouracil, 20.0 g. (61%) of 1-isopropyldihydrouracil was obtained. The compound after recrystallization from water melted at 140–141°.

Anal. Calcd. for $C_7H_{12}O_2N_2$: N, 17.93. Found: N, 17.68.

1-Benzyldihydrouracil. When 22.0 g. (0.11 mole) of the ethyl ester of *N*-benzyl-β-alanine was allowed to react with 9.7 g. (0.12 mole) potassium cyanate and 10.7 ml. of hydrochloric acid according to the procedure described for the preparation of 1-methyldihydrouracil a water insoluble oil formed. After shaking the mixture overnight, the oil was separated and heated at 110° for 2 hr. Upon cooling the oil solidified and was recrystallized from isopropyl alcohol to yield 15.0 g. (67%) of a white crystalline solid melting at 125–127°.

Anal. Calcd. for $C_{11}H_{12}O_2N_2$: N, 13.72. Found: N, 13.56.

Bromination of 1-substituted dihydrouracils. A well-stirred solution of the 1-substituted dihydrouracil in ten times its weight in acetic acid was heated to boiling. To this boiling solution one or two molecular equivalents of bromine in 3 times its volume of acetic acid was added dropwise. When the bromine color was discharged, most of the acetic acid was removed by distillation, the residue diluted with 20 ml. of water and neutralized with 10% sodium hydroxide solution. A solid precipitated from the neutral solution and was purified by recrystallization.

1-Methyl-5-bromodihydrouracil. When 1-methyldihydrouracil was treated with one molecular equivalent of bromine a 59% yield of 1-methyl-5-bromodihydrouracil was obtained. After recrystallization from ethanol it melted at 132–135°.

Anal. Calcd. for $C_5H_7O_2N_2Br$: N, 13.53; Br, 38 60. Found: N, 13.58; Br, 38.42.

1-Benzyl-5-bromodihydrouracil. 1-1-Benzyldihydrouracil when treated with one molecular equivalent of bromine gave 1-benzyl-5-bromodihydrouracil in 51% yield. After several recrystallizations from ethanol it melted at 150–152°.

Anal. Calcd. for $C_{11}H_{11}O_2N_2Br_2$: N, 9.90; Br, 28.22. Found: N, 9.76, Br, 28.36.

1-Isopropyl-5,5-dibromodihydrouracil. 1-Isopropyldihydrouracil when treated with one equivalent of bromine yielded a mixture of brominated compounds which could not be separated. When treated with two molecular equivalents of bromine, a 52% yield of 1-isopropyl-5,5-dibromodihydrouracil was obtained. After several recrystallizations from ethanol it melted at 129–132°.

Anal. Calcd. for $C_7H_{10}O_2N_2Br_2$: N, 8.92; Br, 50.89. Found: N, 8.88; Br, 50.46.

1-Benzyl-5,5-dibromodihydrouracil. 1-Benzyldihydrouracil when treated with two molecular equivalents of bromine gave 1-benzyl-5,5-dibromouracil in 51% yield. After recrystallization from alcohol it melted at 157–159°.

Anal. Calcd. for $C_{11}H_{10}O_2N_2Br_2$: N, 7.74; Br, 44.14. Found: N, 7.52; Br, 43.79.

Dehydrohalogenation of 5-bromo and 5,5-dibromodihydrouracils. The brominated uracil was added in small portions to ten times its weight of boiling dimethylformamide, and the resulting solution refluxed for one hour. The dimethylformamide was removed by distillation under reduced pressure, and the residue treated with a small quantity of water. The resulting solid was filtered and recrystallized from alcohol (see Table I).

When 4.4 g. (0.014 mole) of 1-isopropyl-5,5-dibromodihydrouracil was dehydrogenated according to the above procedure, 2.3 g. (70%) of 1-isopropyl-5-bromouracil was obtained. It melted at 202–204°.

Anal. Calcd. for $C_7H_9O_2N_2Br$: N, 12.02; Br, 34.28. Found: N, 12.10; Br, 33.99.

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Reduction of Trimethylacetonitrile with Grignard Reagents. II. The Reaction of Trimethylacetonitrile with *t*-Butylmagnesium Chloride at Elevated Temperatures[1]

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It has been shown that *t*-butylmagnesium chloride reacts readily with trimethylacetonitrile at high temperature (150°) and pressure to yield the reduction products, trimethylacetaldehyde, 2,2 - dimethylpropylidene - 2′,2′ - dimethylpropylamine (I), and higher boiling material of unknown structure. These findings have been interpreted in terms of the six-membered ring transition state mechanism for the "abnormal" Grignard reaction.

In the reaction of Grignard reagents with trimethylacetonitrile it was found[2] that as the

(1) Abstracted from the thesis submitted by Erwin J. Blanz, Jr., to Stanford University in partial fulfillment of the requirements for the M.S. degree, April 1957.

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