THE SYNTHESIS OF 5-CHLOROURACIL AND 5-BROMOURACIL NUCLEOSIDES*

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(Received for publication, August 16, 1947)

Kuhn and coworkers (1) found that the substitution of chlorine atoms for the methyl groups of riboflavin produced a specific metabolite antagonist for riboflavin. A similar structural change resulted in an antagonist of thymine. Hitchings and coworkers (2) reported that 5-chlorouracil and 5-bromouracil inhibited the growth of *Lactobacillus casei* and that either thymine or folic acid counteracted this inhibition. Whether 5-chlorouracil and 5-bromouracil nucleosides would be more effective thymine antagonists seemed to present an interesting problem. To solve this, 5-chloro- and 5-bromouracil nucleosides of d-ribose, d-arabinose, d-glucose, and d-galactose were prepared.

The 5-bromouracil nucleosides were prepared from the synthetic nucleosides by the method given by Hilbert and Johnson (3) for the preparation of 1-glucosyl-5-bromouracil. An alternate method in which 1-acetoglycosyl-4-ethoxyuracil, dissolved in carbon tetrachloride, was treated with bromine and then hydrolyzed was less satisfactory and gave poorer yields.

The 5-chlorouracil nucleosides were prepared from either the glycosyluracils or from the intermediate 1-acetoglycosyl-4-ethoxy nucleosides by adding anhydrous chlorine in carbon tetrachloride to the desired nucleoside dissolved in glacial acetic acid. The position of the halogeno substitution was established by hydrolysis of the 1-d-arabinosyl-5-chlorouracil to the known 5-chlorouracil. The position of the chlorine and bromine in the other compounds was assumed by analogy. The preparation from the deacetylated free nucleosides with a 5 to 10 per cent excess of chlorine, as described for the synthesis of 1-d-ribosyl-5-chlorouracil, is undoubtedly the method of choice.

The methods of syntheses of these halogenated nucleosides are reported in this paper. Results of the microbiological studies will be presented elsewhere.

EXPERIMENTAL

*Acetobromo Sugars*—These compounds were prepared according to the published methods (4–6), as modified by the present authors (7).

* This work was in part supported by a grant from the Office of Naval Research.
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2,4-Diethoxypyrimidine—The directions of Hilbert and Johnson (8) were followed for the preparation of 2,4-diethoxypyrimidine from 2,4-dichloropyrimidine.

1-d-Glucosyluracil—This compound was prepared by the method of Hilbert and Johnson (3), except that diethoxypyrimidine was substituted for dimethoxypyrimidine.

1-d-Arabinosyluracil—1-d-Arabinosyluracil, m.p. 250-252°, was synthesized following the procedure given by Hilbert (9) for the preparation of 1-L-arabinosyluracil. The specific rotation was $[\alpha]_D^{25} = -88.4^\circ$ (c = 2 in H$_2$O).

1-d-Galactosyluracil—The method of Hilbert (9) was followed for the synthesis of this nucleoside.

1-d-Ribosyluracil—A modification of the procedure of Hilbert and Rist (10) was developed for the synthesis of 1-d-ribosyluracil. After separation of 2-triacetoribosido-4-ethoxypyrimidine, as described by Hilbert and Rist, the filtrate was cooled in a CO$_2$-acetone freezing mixture. The amorphous material, m.p. 60-66°, which separated (8 gm. from 13 gm. of acetobromoribose and 16 gm. of 2,4-diethoxyuracil) was hydrolyzed in HCl-methanol. After removal of the solvents, the residue was crystallized from absolute ethanol. Yield, 27.8 per cent, m.p. 257°.

1-d-Glucosyl-5-bromouracil—This compound was prepared according to the procedure of Hilbert and Johnson (3).

1-d-Ribosyl-5-bromouracil—Ribosyl-5-bromouracil was prepared from d-ribosyluracil by the procedure of Hilbert and Johnson (3). Yield, 48.5 per cent. The specific rotation was $[\alpha]_D^{25} = -61.8^\circ$ (c = 2 in H$_2$O).

1-d-Arabinosyl-5-bromouracil—A 10 per cent excess of bromine was added to a solution of 1-acetoarabinosyl-1,2-dihydro-2-oxo-4-ethoxypyrimidine dissolved in dry carbon tetrachloride. After standing overnight at room temperature the solvent and excess bromine were removed in vacuo. The yellow residue was dissolved in absolute ethanol and the solution was concentrated to dryness by heating in an oil bath. The addition of alcohol and subsequent evaporation to dryness were repeated until the residue was white or slightly yellow. Hydrolysis of this residue in absolute methyl alcohol and the solution was concentrated to dryness by heating in an oil bath. The addition of alcohol and subsequent evaporation to dryness were repeated until the residue was white or slightly yellow. Hydrolysis of this residue in absolute methyl alcohol and HCl yielded an incompletely brominated product. After another treatment with bromine, with the procedure of Hilbert and Johnson (3), a product having the correct analysis for bromine was obtained. Yield, 86 per cent. The product was recrystallized from an alcohol and water solution, m.p. 260°. The optical rotation was $[\alpha]_D^{25} = -27.7^\circ$ (c = 2 in H$_2$O).

C$_9$H$_{11}$O$_4$N$_2$Br. Calculated. C 33.43, H 3.43, N 8.63, Br 24.25
323.13 Found. " 33.76, " 3.65, " 8.74, " 24.60
1-d-Galactosyl-5-bromouracil—This nucleoside derivative was prepared by the method used for the synthesis of 1-d-arabinosyl-5-bromouracil, and the product (68 per cent) was obtained by dissolving the reaction mixture in an equal weight of hot absolute alcohol followed by the addition of 3 volumes of chloroform. On cooling, the product, 1-d-galactosyl-5-bromouracil, precipitated as a white amorphous solid but was not obtained in a pure state and had an indefinite melting point.

\[ C_{12}H_{12}O_7N_2Br \]  
Calculated. N 7.94, Br 22.5  

1-d-Glucosyl-5-chlorouracil—5 gm. of 1-acetoglucosyl-1,2-dihydro-2-oxo-4-ethoxypyrimidine were dissolved in 300 cc. of dry carbon tetrachloride and 25 cc. of glacial acetic acid. A 2 per cent excess (0.767 gm.) of chlorine in 50 cc. of dry carbon tetrachloride was added to this solution at room temperature. The mixture was allowed to stand overnight and the solvents were completely removed under reduced pressure at 40°. The residue was dissolved in 50 cc. of dry methanol and 9.5 cc. of methanol containing 36 per cent by weight of HCl were added. After standing for 3 days the solvents were removed in vacuo at 35-40°. The residue was recrystallized from 95 per cent alcohol. Since the chlorine analysis of this product was low it was again treated with a 10 per cent excess of chlorine in carbon tetrachloride, yielding a product which after crystallization had the correct chlorine content. The yield was 2.0 gm. (63 per cent) of white prisms, m.p. 263-264°. The optical rotation was \([\alpha]_D^{25} = +13.9° \ (c = 2 \text{ in } H_2O)\).

\[ C_{10}H_{12}O_7N_2Cl \]  
Calculated. C 38.90, H 4.24, N 9.06, Cl 11.48  

1-d-Arabinosyl-5-chlorouracil—The procedure already described for the preparation of 1-d-glucosyl-5-chlorouracil was followed for the chlorination of 1-d-acetoarabinosyl-1,2-dihydro-2-oxo-4-ethoxypyrimidine. The product was low in chlorine and was again chlorinated as described for the glucosyl nucleoside. The yield from 4 gm. of the intermediate acetylated nucleoside was 2.5 gm. (80 per cent), m.p. 258°. The optical rotation was \([\alpha]_D^{25} = -50.4° \ (c = 2 \text{ in } H_2O)\).

\[ C_{10}H_{12}O_7N_2Cl \]  
Calculated. C 38.79, H 3.95, N 10.05, Cl 12.72  

1-d-Galactosyl-5-chlorouracil—This compound was synthesized by the procedure described for the preparation of glucosyl-5-chlorouracil. The product was isolated in the same manner as galactosylthymine (7). Analy-
sis showed that the product (53 per cent), which had an indefinite melting point, was nearly pure.

C₁₃H₁₃O₇N₄Cl. Calculated. C 38.90, H 4.24, N 9.06  
308.69  
Found. " 38.60, " 4.24, " 9.50

1-α-Ribosyl-5-chlorouracil—This compound was synthesized by the addition of a 6.5 per cent excess of chlorine in carbon tetrachloride to a glacial acetic acid solution of 1-α-ribosyluracil. After standing overnight the solvents were removed under reduced pressure at 35°, and the residue recrystallized from absolute alcohol, m.p. 245°; 0.4 gm. of 1-α-ribosyl-5-chlorouracil (40 per cent) was obtained from 0.7 gm. of α-ribosyluracil. The optical rotation was \([\alpha]_{D}^{25} = -87.3°\) (\(c = 2\) in H₂O).

C₇H₆O₃N₂Cl. Calculated. C 38.79, H 3.95, N 10.05, Cl 12.72  
278.67  
Found. " 39.68, " 4.08, " 10.15, " 12.76

5-Chlorouracil from Arabinosyl-5-chlorouracil—0.5 gm. of arabinosyl-5-chlorouracil was refluxed with 25 cc. of concentrated HCl for 12 hours. The mixture was concentrated to dryness and the 5-chlorouracil crystallized from water, m.p. 304°; mixed m.p. with 5-chlorouracil showed no depression.
Ultraviolet Absorption Spectra of Uracil Nucleosides—The ultraviolet absorption spectra of the uracil nucleosides of D-ribose, D-arabinose, and D-glucose and the corresponding 5-chloro and 5-bromo derivatives were determined with a Beckman spectrophotometer with a hydrogen discharge tube as the source of light. The maxima and minima are listed in Table I. The absorption obtained is illustrated by the curve of 5-bromoribosyluracil of Fig. 1.

The authors are indebted to Mr. Jack Fox for technical assistance and to Mr. Frank Rainwater for some of the analytical results.

| Maximum and Minimum Ultraviolet Absorption of Uracil Nucleosides and Their Bromo and Chloro Derivatives |
|---------------------------------------------------------------|-------------------------------|
| Maximum | Minimum |
| 1-d-Arabinosyluracil | 2580 | 2280 |
| 1-d-Glucosyluracil | 2580 | 2280 |
| 1-d-Ribosyluracil | 2620 | 2300 |
| Arabinosyl-5-chlorouracil | 2740 | 2380 |
| Glucosyl-5-chlorouracil | 2720 | 2360 |
| Ribosyl-5-chlorouracil | 2770 | 2360 |
| Arabinosyl-5-bromouracil | 2760 | 2410 |
| Glucosyl-5-bromouracil | 2760 | 2410 |
| Ribosyl-5-bromouracil | 2790 | 2420 |

SUMMARY

5-Chlorouracil and 5-bromouracil nucleosides of D-ribose, D-arabinose, D-glucose, and D-galactose were synthesized by direct chlorination or bromination of the corresponding synthetic nucleosides.

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