The Synthesis of 1-(2-Deoxy-D-arabinohexopyranosyl)-5-bromo-6-azauracil (1)

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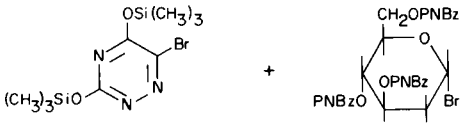
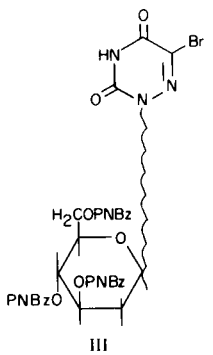
Interest in "fradulent" pyrimidine nucleosides has developed in several related areas: (a) 1-(2′-deoxy-β-D-arabinohexopyranosyl)thymine ("2-deoxyglucoxylthymine") (2) is a specific inhibitor of the enzyme pyrimidine nucleoside phosphorylase (3); (b) some 5-substituted pyrimidine nucleosides have antiviral activity (4); and (c) several nucleosides are used as anticancer agents (5). The above considerations prompted us to synthesize the nucleoside 1-(2′-deoxy-D-arabinohexopyranosyl)-5-bromo-6-azauracil 2-(2′-deoxy-D-arabinohexopyranosyl)-6-bromo-*as*-triazine-3,5-(2*H*,4*H*)-dione (IV). The structure of IV incorporates: (a) the 2′-deoxy-D-arabinohexopyranosyl moiety which is found in the pyrimidine nucleoside phosphorylase inhibitor "2-deoxyglucosylthymine" (3); (b) the halogen substituent at the 5-position of the pyrimidine ring as is found in some antiviral agents (4); and (c) the 6-azapyrimidine aglycone found in the anticancer agent, 6-azauridine (5).

The synthesis of IV was accomplished by the method of Nishimura and Iwai (6). The coupling of 3,5-bis-(trimethylsilyloxy)-6-bromo-*as*-triazine (I) (7) and 2-deoxy-3,4,6-tri-*O*-*p*-nitrobenzoyl-α-D-arabinohexosyl bromide (II) (8) gave the protected nucleoside (III). Ammination of III with methanoic ammonia resulted in the desired product (IV).

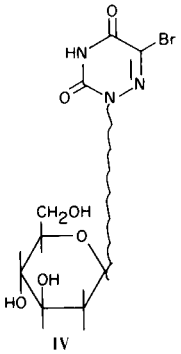


I

II



III



IV

PNBz = *p*-NO_2-C_6H_4-C(=O)-

The assignment of the carbohydrate moiety to the *N*-1 position of the 5-bromo-6-azauracil ring is based on the fact that the nucleoside (IV) exhibits a hypochromatic shift of the absorption maximum in the ultraviolet spectrum on the change from acidic to basic conditions. This is typical of *N*-1 substituted 6-azauracils (9).

The anomeric proton appears in the n.m.r. spectra of IV in dimethylsulfoxide$_{d6}$ (after deuterium oxide exchange) at τ, 4.3 as a partly coalescing pair of doublets, J 7-8 cps and J 5-6 cps (figure 1). This indicates that the conformation is not the supposed C-1 form but a more flattened, twisted or distorted one. Examination of models show that there might be little difference between the multiplet patterns for the anomeric proton for the α- and β-anomers if the true conformation were considerably distorted. In such a conformation, the 1,3-diaxial interaction normally occurring in the 1-C form would be alleviated and the sterically crowded axial position normally occupied by the base at the anomeric center in the C-1 form for the α-anomer would be relieved. These possibilities could be realized because of the symmetrical nature of the Karplus Equation so that a large coupling constant, J_{HH}, of the order of 7-8 cps, need not necessarily be generated from a near diaxial proton proton relationship (dihedral angle near 180°), but could arise from an dihedral angle of near 180° or one near 20° (10). Also the C-2′ protons of the sugar moiety appearing at τ = 8.0 (J 15 cps) do not have the expected coupling of *ca.* 27 cps which would be expected to result from the C-1 conformation due to the gem hydrogens (J *ca.* 12 cps), axial 2′H, axial 1′H (J 6-10 cps) and axial 2′H, axial 3′H (J 6-10 cps). Thus the conformation of the sugar moiety is not known and the n.m.r. coupling constants cannot be used to determine the anomeric configuration of the nucleoside (IV). The position of the signal from the anomeric proton indicates that IV may be the β-anomer by comparison with the n.m.r. spectra of other nucleosides of this type (11) and with the work of Lemieux *et al.*, on glucopyranosyl derivatives (12). The spectra verified the presence of only one anomer. A Varian A-60 n.m.r. spectrometer was used. The proton chemical shift (ppm τ) was measured from tetramethylsilance as internal standard.

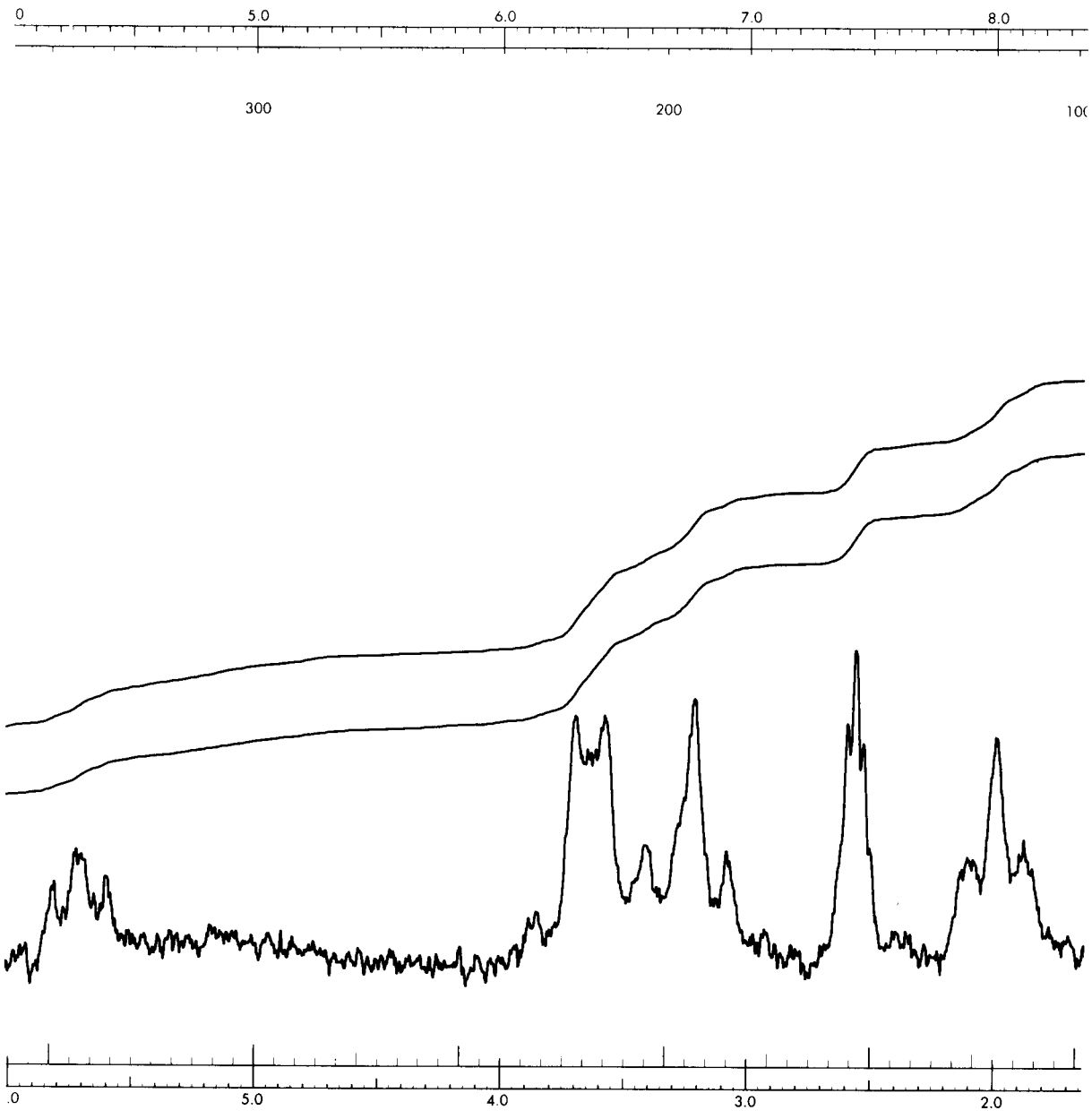


Figure 1

EXPERIMENTAL (13)

3,5-Bis-(trimethylsilyloxy)-6-bromo-*as*-triazine (I) (14).

A mixture of 24 g. (0.125 mole) of 5-bromo-6-azauracil (15) and 150 ml. hexamethyldisilazane was refluxed 2.5 hours. The excess solvent was removed under vacuum at 20 mm. and the product distilled, b.p. 98-99° at 0.2 mm., giving 39.4 g., (85.5%) of I, m.p. *ca.*, 44°. Due to the high reactivity of this intermediate, analysis was not attempted. The infrared spectrum showed a strong band at 9.75μ (film), indicating the presence of the $[(CH_3)_3SiO-]$ group (6a).

1-(2′-Deoxy-3,4,6-tri-*O*-*p*-nitrobenzoyl-D-arabinohexosyl)-5-bromo-6-azauracil (III).

A mixture of 7.0 g. (19 mmoles) of 3,5-bis-(trimethylsilyloxy)-6-bromo-*as*-triazine (I) and 3.5 g. (5.2 mmoles) of 2-deoxy-3,4,6-tri-*O*-*p*-nitrobenzoyl-α-D-arabinohexosyl bromide (II) (8) was heated at 105°; on stirring the mixture a gas (trimethylsily bromide ?) was evolved. After heating for 2 days the solid mixture was stirred 4 hours with a mixture of 200 ml. of dichloromethane and 4 ml. of absolute ethanol. The residue (mainly 5-bromo-6-azauracil) was removed by filtration and the dichloromethane extract evaporated to an oil *in vacuo* at 50°. This oil on digestion with 100 ml. of absolute ethanol slowly solidified and the crude

protected nucleoside (III) was removed by filtration of the hot mixture. The crude material was recrystallized from glacial acetic acid, yielding 1.2 g. of product, m.p. 258-263°. An additional 0.8 g. (m.p. 257-263°) was obtained from the mother liquors, giving a yield of 43%. In several instances this compound was obtained in a solvated form (m.p. 158-159° recrystallizing and melting at 257-263°). Recrystallization from glacial acetic acid gave an analytical sample, m.p. 263-265°.

Anal. Calcd. for $C_{30}H_{21}BrN_6O_{15}$: C, 45.87; H, 2.70; Br, 10.18; N, 10.70. Found: C, 45.72; H, 2.72; Br, 10.16; N, 10.41.

1-(2′-Deoxy-D-arabinohexopyranosyl)-5-bromo-6-azauracil (IV).

A mixture of 4.5 g. (5.73 mmoles) of the protected nucleoside (III) and 230 ml. of anhydrous methanol saturated with ammonia was stirred 3 hours at room temperature. The solvent was evaporated *in vacuo* at 50°; the resulting oil was treated with 100 ml. of water and extracted with three portions of ethyl acetate-ether (50 ml.-25 ml.). The aqueous layer was treated with 30 g. of Dowex 50W-X4 strongly acidic cation exchange resin, filtered and evaporated under diminished pressure at 65°. The residue was crystallized from absolute ethanol yielding 500 mg. of product (IV), m.p. 236-239° dec. An additional 910 mg. of product was recovered from the mother liquors (identical infrared spectra), giving a 73% yield of IV. Recrystallization from absolute ethanol gave an analytical sample, m.p. 239-241° dec., $[\alpha]_D^{27}$ -16.2° (c 1.03 water), λ max (0.1 *N* hydrochloric acid), 275 mμ (log ε 3.86), λ min. (0.1 *N* hydrochloric acid), 241 mμ, λ max (*p*H 7 buffer), 264 mμ (log ε 3.79), λ min. (*p*H 7 buffer), 230 mμ, λ max (0.1 *N* sodium hydroxide), 263 mμ (log ε 3.75), λ max (Nujol), 5.89μ (C=O).

Anal. Calcd. for $C_9H_{12}BrN_3O_6$: C, 31.97; H, 3.58; Br, 23.64; N, 12.43. Found: C, 32.14; H, 3.61; Br, 23.38; N, 12.31.

REFERENCES

(1) This work was supported by a Leukemia Society of America, Inc. Grant-in-Aid.

(2) W. W. Zorbach and G. J. Durr, *J. Org. Chem.*, 27, 1474 (1962).

(3) G. Etzold and P. Langen, *Chem. Ber.*, 98, 1988 (1965); M. Zimmerman, *Biochem. Biophys. Res. Commun.*, 16, 600 (1964); J. W. Mellors and R. K. Barclay, *J. Biol. Chem.*, 240, 1281 (1965); W. W. Zorbach, H. R. Munson and K. V. Bhat, *J. Org. Chem.*, 30, 3955 (1965).

(4) C. H. Stuart-Harris and L. Dickinson, "The Background to Chemotherapy of Virus Diseases," Charles C. Thomas, Springfield, Ill., 1964.

(5) G. B. Elion and G. H. Hitching, *Advan. Chemotherapy*, 2, 91, (1965).

(6a) T. Nishimura and I. Iwai, *Chem. Pharm. Bull. (Tokyo)*, 12, 353 (1963); (b) for a review of this method see, B. Shimizu, *Ann. Sankyo Res. Lab.*, 19, 1 (1967).

(7) T. Y. Shen, W. V. Rugle and R. L. Bugianesi, *J. Heterocyclic Chem.*, 2, 495 (1965).

(8) W. W. Zorbach and H. R. Munson, *Synthetic Procedures in Nucleic Acid Chem.*, 1, 379 (1968).

(9) K. Y. Zee-Cheng and C. C. Cheng, *J. Org. Chem.*, 27, 976 (1962); J. Jonas and J. Gut, *Collect. Czech. Chem. Commun.*, 26, 2155 (1961).

(10) The authors wish to thank the referee for the above comments.

(11) G. J. Durr, J. F. Keiser and P. A. Ierardi, *J. Heterocyclic Chem.*, 4, 291 (1967).

(12) R. U. Lemieux, R. K. Kullnig, H. J. Berstein and W. G. Schneider, *J. Am. Chem. Soc.*, 80, 6098 (1958).

(13) All melting points were determined using a Kofler hot stage. Ultraviolet absorption spectra were recorded by a Bausch and Lomb Spectronic 505 spectrophotometer. Infrared spectra were determined on a Perkin Elmer Infracord spectrophotometer. Analyses were performed by Micro-Tech Laboratories, Skokie, Ill.

(14) The synthesis of this compound (I) without purification is reported in reference 7.

(15) P. K. Chang, *J. Org. Chem.*, 26, 1118 (1961).

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