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SYNTHESIS AND PROPERTIES OF BORON AND SILICON SUBSTITUTED URACIL OR 2'-DEOXYURIDINE

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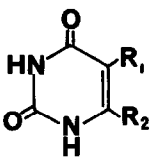
Numerous modifications of nucleosides have been made in an attempt to find effective antiviral and anticancer agents[1]. Stable organo-boron derivatives of pyrimidines[2] and purines[3] have been synthesized for use in cancer therapy[4] based on the ability of the ^{10}B-isotope to absorb thermal neutrons thereby producing a cell destroying nuclear reaction. More recently various amino acids containing boron also have been prepared[5], and recently two naturally occuring boron-containing antibiotics were isolated[6].

Several boron-compounds have been reported to be excellent enzyme inhibitors. 2-Phenylethane boronic acid[7] [$PhCH_2CH_2B(OH)_2$] is an effective competitive inhibitor of the hydrolysis of methyl hippurate by α-chymotrypsin and a boronic analogue of acetylcholine[8] [$CH_3B(OH)CH_2CH_2CH_2N(CH_3)_2$] is a potent inhibitor of acetylcholinesterase with a binding affinity of 10^4 times greater than the association constant for acetylcholine. These findings stimulated our attempts to synthesize boron analogues of nucleosides.

Liao *et al.*[2] first synthesized 5-dihydroxyboryluracil (*1*), however since free pyrimidines with substituents having a van der Waal radius similar to chlorine or larger are poorly utilized by mammalian systems, the corresponding deoxyribonucleoside was synthesized. Various 6-substituted uracils[9] have been prepared as analogues of orotic acid, hence the synthesis of 6-dihydroxyboryluracil (*2*) was carried out since this boron analogue is approximately isoelectronic and isostructural with orotic acid. The procedure[2] for the synthesis of compound *1* was



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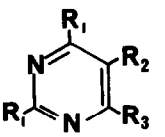

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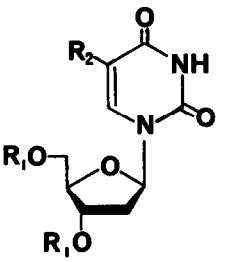

10 - 13

1. R_1=B(OH)$_2$, R_2=H

2. R_1=H, R_2=B(OH)$_2$

3. R_1=OBn, R_2=Br, R_3=H

4. R_1=OBn, R_2=B(OH)$_2$, R_3=H

5. R_1=OBn, R_2=B(OCH$_2$CH$_2$)$_2$NH, R_3=H

6. R_1=OH, R_2=B(OCH$_2$CH$_2$)$_2$NH, R_3=H

7. R_1=OBn, R_2=H, R_3=Br

8. R_1=OBn, R_2=H, R_3=B(OH)$_2$

9. R_1=OH, R_2=H, R_3=B(OCH$_2$CH$_2$)$_2$NH

10. R_1=SiMe$_3$, R_2=Br

11. R_1=SiMe$_3$, R_2=B(OBu)$_2$

12. R_1=H, R_2=B(OH)$_2$

13. R_1=H, R_2=SiMe$_3$

modified thereby affording the isolation and characterization of the intermediate reaction products as well as providing an effective synthesis for 6-dihydroxyboryluracil (*2*).

5-Dihydroxyboryluracil (*1*) was originally prepared[2] *via* a halogen-metal exchange reaction on 5-bromo-2,4-dibenzyloxypyrimidine[10] (*3*) followed by boronation. However, the product could not be isolated and it was converted directly to *1* by hydrogenation. We repeated their experiment and found that it is necessary to operate at -85° to -95°C during the whole reaction sequence in order to obtain 5-dihydroxyboryl-2,4-dibenzyloxypyrimidine (*4*) as a crystalline solid[11]; mp 99-102°C NMR ($CDCl_3$) δ 8.74 (6-H). Maximum yield was achieved when 4-5 min had elapsed between the addition of *n*-butyllithium and tri-*n*-butyl borate. The product was further characterized as the iminodiethanol derivative *5*; mp 167-170°C NMR ($CDCl_3$) δ 8.41 (6-H); precision MS *m/e* 405.1863 (M^+, Calcd for $C_{22}H_{24}BN_3O_4$: 405.1860). Catalytic hydrogenation of *5* furnished the deblocked compound *6*; mp 230°C dec; NMR [$(CD_3)_2SO$] δ 6.96 (6-H). 5-Dihydroxyboryluracil (*1*) was obtained by hydrogenation of *4* in an overall 65% yield; mp 330°C dec; NMR [$(CD_3)_2SO$] δ 7.73 (s, 1, 6-H), 8.11 (bs, 2, OH), 11.41 (bs, 2, NH).

6-Dihydroxyboryluracil (*2*), mp 303°C dec; NMR (D_2O) δ 5.52 (5-H) and compounds *8* and *9* were obtained by the same reaction sequence as for *1*, from 6-bromo-2,4-dibenzyloxypyrimidine[12] (*7*) in an overall 20% yield[11]. Although this boron analogue *2* was stable in acid and only fairly stable in base ($t_{1/2}$ = 4 days) it decomposed to uracil when dissolved in dimethyl sulfoxide containing traces of water[13].

No attempt was made to obtain 5-dihydroxyboryl-2'-deoxyuridine (*12*) by direct glycosylation of *1*. However, the nucleoside was prepared *via* a metal-halogen exchange at -50°C in tetrahydrofuran on 5-bromo-3',5'-bis-*O*-trimethylsilyl-2'-deoxyuridine (*10*)[14], using 2 equivalents of *n*-butyllithium followed, after 8 min had elapsed, by boronation at -65°C with excess tri-*n*-butyl borate in the presence of 8% hexamethylphosphoric triamide or diglyme. After acid hydrolysis of *11* the product was purified by column chromatography on silica, eluting with $CHCl_3$-EtOH, 2:1, and repeated fractional crystallization in methanol. The absence of 2'-deoxyuridine and 5-bromo-2'-deoxyuridine was ascertained using a high-pressure liquid-chromatographic method. Pure compound *12* was obtained as hydrolytically stable white prisms[11] in an overall 12% yield; mp 226-227°C dec; NMR [$(CD_3)_2SO$] δ 2.12 (m, 2, 2'-H), 3.54 (m, 2, 5'-CH_2), 3.80 (m, 1, 4'-H), 4.22 (bs, 1, 3'-H), 4.95 (t, J = 5.3 Hz, 1, 5'-OH), 5.28 (d, J = 3.5 Hz, 1, 3'-OH), 6.14 (t, J = 6.6 Hz, 1, 1'-H), 8.12 [s, 2, $B(OH)_2$], 8.13 (s, 1, 6-H), 11.67 (s, 1, NH).

Substituting trimethylchlorosilane for tri-*n*-butyl borate in the above experiment afforded 5-trimethylsilyl-2'-deoxyuridine (*13*) as an amorphous white solid; NMR [$(CD_3)_2SO$] δ 7.73 (6-H); MS *m/e* 300 (M^+), 184 (base).

Whereas compounds *1*, *2* and *12* showed no activity against murine Sarcoma 180 cells, the nucleoside *12* inhibited the replication of Herpes simplex type I in cell culture.

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11. All compounds described gave analytical results (C,H,N,B) with $\pm$ 0.4%.

12. Prepared from barbituric acid by a method analogous to that described by J.D. Bryant and N.J. Leonard, *J. Org. Chem.*, 43, 511 (1978); NMR ($CDCl_3$) δ 5.34 and 5.37 (2 s, 4, CH_2), 6.58 (1, s, 5-H), 7.43-7.26 (m, 10, C_6H_5).

13. The mechanism for this decomposition is at present being investigated.

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