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Synthesis and Biological Activity of 4-(β-D-Ribofuranosyl)-1,3-dihydroxybenzene ("1,3-Dideazauridine")

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In view of the marked antitumor activity of 3-deazauridine, the synthesis of 4-(β-D-ribofuranosyl)-1,3-dihydroxybenzene (1,3-dideazauridine) and its dibenzyl derivative was carried out. 4-Bromo-1,3-dihydroxybenzene was converted to its dibenzyl derivative, which, upon reaction with *n*-butyllithium followed by treatment with anhydrous cadmium chloride, gave bis(1,3-dibenzyloxyphenyl-4)cadmium. Condensation of this intermediate with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride in refluxing toluene, and subsequent removal of the protecting benzoyl groups, afforded 4-(β-D-ribofuranosyl)-1,3-dibenzyloxybenzene which, upon catalytic hydrogenation over Pd/C, furnished the desired 4-(β-D-ribofuranosyl)-1,3-dihydroxybenzene. The β configuration at the anomeric center was established by NMR and hydrogen bonding studies. 4-(β-D-Ribofuranosyl)-1,3-dibenzyloxybenzene inhibited the growth of leukemia L1210 cells by 50% at 7×10^{-6} *M*, and that of mammary carcinoma TA_3 cells at 5×10^{-5} *M*. Dideazauridine itself was less active, inhibiting the leukemia L1210 but not the TA_3 cells at 1×10^{-4} *M*, but the compound was significantly active against herpes simplex (type I) virus in vitro.

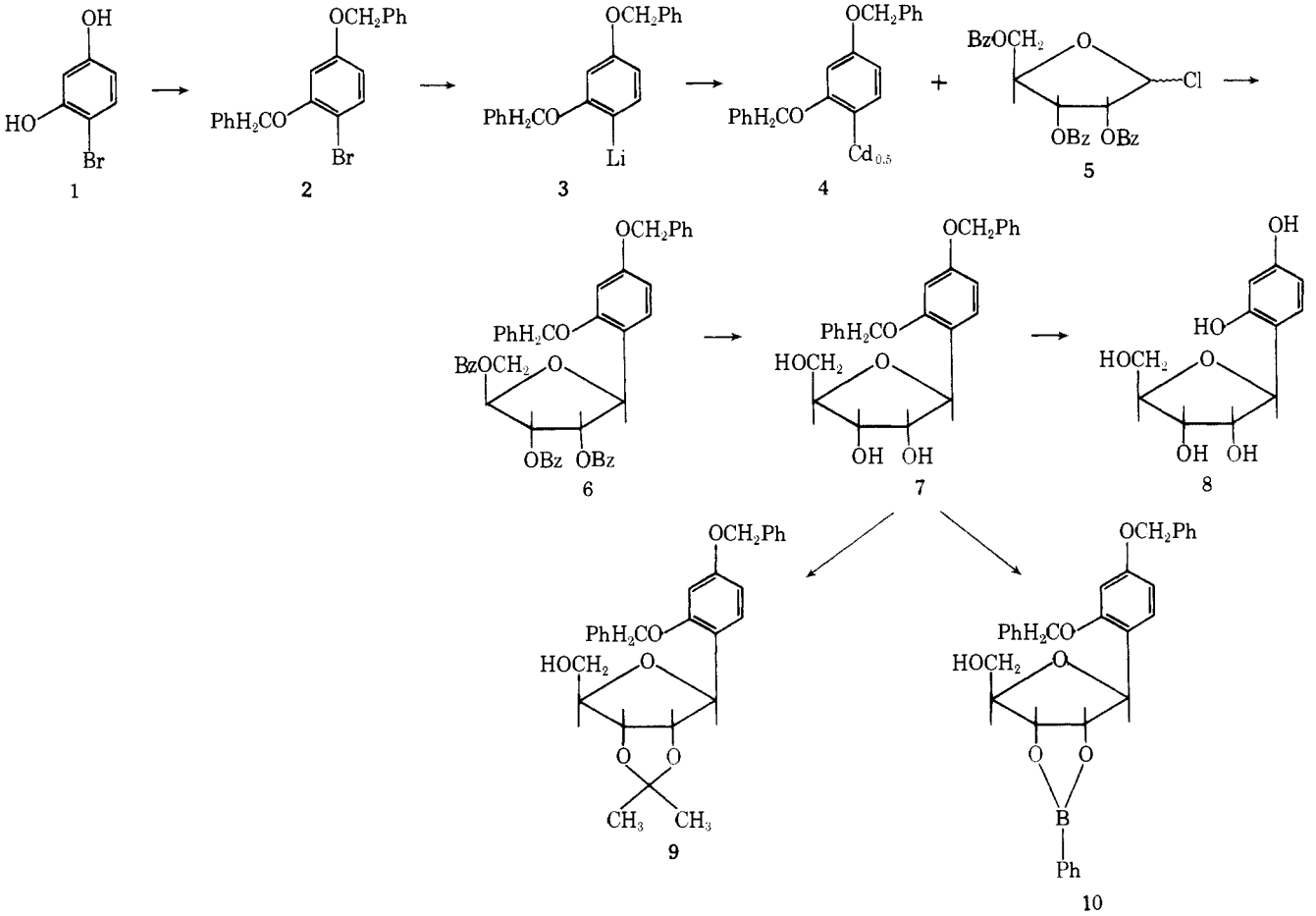
The replacement of nitrogen 3 by carbon in the heterocyclic moiety of uridine and cytidine has provided the analogs 3-deazauridine and 3-deazacytidine which have demonstrated marked antitumor activity in vitro and in vivo.[1-6] Because of this activity, we considered it worthwhile to synthesize 4-(β-D-ribofuranosyl)-1,3-dihydroxybenzene (1,3-dideazauridine, **8**). The present communication reports the synthesis and some biological effects of the compound and its 1,3-dibenzyl derivative. Part of this work has been presented in a preliminary communication.[7]

Chemical. The synthesis of **8** was approached by the procedure employed for the synthesis of pseudouridine[8] (Scheme I). 4-Bromo-1,3-dihydroxybenzene (**1**) was converted to 4-bromo-1,3-dibenzyloxybenzene (**2**) by refluxing with benzyl chloride in dry acetone in the presence of anhydrous potassium carbonate. Treatment of **2** with *n*-butyllithium in absolute ether afforded 1,3-dibenzyloxyphenyl-4-lithium (**3**), which was condensed under nitrogen with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride in dry toluene. Thin-layer chromatography of the reaction mixture revealed numerous products, and no attempt was made to separate them.

This result was not completely unexpected, since numerous products and poor yields had also been obtained when 2,4-dimethoxypyrimidine-5-lithium[8] and 2,6-dibenzyloxypyridyl-3-lithium[9] were condensed with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride. We, therefore, considered the preparation of 1,3-dibenzyloxyphenylcadmium (**4**) for condensation with the chloro sugar **5**, since, as has been demonstrated,[10] diphenylcadmium does not react with the acyl-protecting groups, thus offering greater selectivity in reactions with halo sugars. By use of this method, 1-deazauridine[9] and more recently β-D-ribofuranosylbenzene have been synthesized.[11] The cadmium derivative **4** was prepared by refluxing **3** with anhydrous cadmium chloride in absolute ether (Scheme I) under nitrogen atmosphere.

Addition of the chloro sugar **5** to the cadmium compound **4** in refluxing toluene, followed by removal of the protecting benzoyl groups with methanolic sodium methoxide, furnished a mixture which, as shown by tlc, contained three products. The fastest moving product with R_f 0.95 was readily isolated and characterized as 1,3-dibenzyloxybenzene. In fact, this was the major product of the reaction, isolated in 50% yield. Although we have not fully characterized the second product which has an R_f of 0.67, preliminary evidence obtained from mass spectrometry indicates that it is presumably the sugar ketal formed by the reaction of cadmium compound **4** with the 2-*O*-benzoyl group in the

Scheme I



halo sugar **5** as observed in other instances.[9-11] 4-(β-D-Ribofuranosyl)-1,3-dibenzyloxybenzene (**7**), with an R_f 0.37, was purified by silica gel column chromatography, using chloroform with increasing proportions of acetone as the eluent, and was obtained in 10–12% yield. Further purification of the product was carried out by recrystallization from absolute ethanol. Catalytic hydrogenation of **7**, over 5% palladium on charcoal, furnished the target compound 4-(β-D-ribofuranosyl)-1,3-dihydroxybenzene (1,3-dideazauridine, **8**) in 65% yield. The structural elucidation of **7** and **8** was based on mass, NMR, and ir spectrometry and on elemental analysis. The proposed structure of compound **8** was further substantiated by the similarity of its uv spectra with those of several 4-alkyl-1,3-dihydroxybenzene derivatives.

The anomeric configuration of **7** was established by hydrogen bonding studies using ir, and by mass and NMR spectrometry. Ir had been used by Kalvoda[12] to assign the anomeric configuration to some *C*-ribofuranosylbenzene derivatives. He demonstrated that ribofuranosyl derivatives which possess a suitably protected cis diol and form hydrogen bonds between the hydroxylic function at position 5 of the ribofuranosyl moiety and the aglycone have the β configuration. We have made the parallel observation using the phenylboronate derivative **10**.[12-14] The ir spectrum of this derivative in carbon tetrachloride showed a band at 3665 cm^{-1} for the free hydroxylic function and an intensive band at 3606 cm^{-1} attributable to hydrogen bonding involving the hydroxylic function, the furanose ring oxygen, and the π electrons of the benzene ring, supporting the β configuration of the nucleoside.

The NMR spectrum of the isopropylidene derivative **9** in DMSO-d_6 showed the 5′-hydroxyl group as a triplet [δ 4.88, $J(CH_2OH)$ = 5.5 Hz] which disappeared on D_2O exchange, demonstrating the furanose nature of the sugar moiety.[15] The anomeric proton was partly merged with the methylene signals of the benzyl groups. However, using acetone-d_6 as the solvent, the 5′-hydroxyl group appeared as a triplet [δ 4.62, $J(CH_2OH)$ = 4 Hz] and the anomeric proton as a singlet (δ 5.10), supporting the β configuration of **9**.[16-18] The NMR spectrum of the phenylboronate derivative **10** in acetone-d_6 showed also the anomeric proton as a singlet (δ 4.92) and the 5′-hydroxyl group as a triplet (δ 4.95) which collapsed to a singlet after the addition of a trace of trifluoroacetic acid. Since the $H_{1'}$–$H_{2'}$ coupling constants of the phenylboronate and alkylidene derivatives of some corresponding aldofuranoses were shown to be quite similar,[19] the use of this coupling constant for the assignment of the anomeric configuration appears justified. It has recently been shown[20-22] that the difference in the chemical shifts corresponding to the methyl groups of the 2′,3′-*O*-isopropylidene nucleoside derivatives ($\Delta\delta \leq 0.10$ for the α anomer and ≥ 0.18 for the β anomer) can be used for the assignment of the anomeric configuration. The difference in the chemical shifts of the methyl signals of compound **9** is 0.23, which is also in agreement with the proposed β configuration.

The mass spectrum of **7** showed most of the characteristics of the fragmentation pattern common to C-nucleosides possessing the ribofuranosyl ring, such as formycin, showdomycin, pseudouridine, and pyrazomycin.[23-25] Fragmentation ions appeared at *m/e* 319 (B + 30 or M − 103), 333 (M − 89), 355 (M − $2H_2O$ − CH_2OH), 386 (M − $2H_2O$), 392 (M − 30), and 404 (M − $2H_2O$). (M − 30) and (M − 89), derived from the D-ribose portion of the molecular ion, show the presence of the 5′-OH group,[26-28] supporting further the furanose nature of the sugar ring. The mechanism of fragmentation accounting for these peaks[28] not only requires the presence of a labile hydrogen at the 5′ position

but also that it should be sterically accessible to the aglycone, meaning that it should be cis to the aglycone which additionally supports the β configuration. The peak at *m/e* 355 resulted possibly from the cleavage of the $C_{4'}$–$C_{5'}$ bond with the loss of CH_2OH after the prior loss of two molecules of water, indicating a furanose form of pentose moiety, as opposed to the isomeric pyranose, since the loss of a substituent from a carbon atom bearing an ether oxygen is more favored in five-membered rings (tetrahydrofurans) than in the six-membered homologs.[28]

The mass spectrum of the trimethylsilyl derivative of **8** also supported the above conclusions. In the mass spectrum, the lower mass ions of *m/e* 73, 103, 147, 217, and 230 derived principally from the sugar moiety, demonstrating that the sugar is a pentofuranose.[29-34]

Biological. The effect which the newly synthesized analogs exert on the in vitro growth of various cell systems is shown in Table I. Neither dideazauridine (**8**) nor its dibenzyl derivative **7** inhibited the growth of *Streptococcus faecium* and *Escherichia coli*. In contrast, the dibenzyl derivative inhibited the growth of leukemia L1210 cells by 50% at 7×10^{-6} *M* and that of mammary carcinoma TA_3 cells at 5×10^{-5} *M*. Dideazauridine (**8**) itself was less active, inhibiting the L1210 but not the TA_3 cells at 1×10^{-4} *M*. The reason for this difference in activity is, as yet, unclear. In contrast, the inhibition of L1210 cell growth by the dibenzyl derivative was reversed competitively by uracil, uridine, and 2′-deoxyuridine, the inhibition indices ([I]/[S] 50%) being 20, 50, and 8, respectively. Cytosine and its nucleosides and thymidine prevented the inhibition only to a slight extent. At 3×10^{-5} *M*, 1,3-dideazauridine decreased the plaque diameter of herpes simplex virus (type I) in the CP-1 monolayer by approximately 50%. At 1×10^{-4} *M*, the plague formation was reduced by over 90%.†

Table I. Effect of 1,3-Dideazauridine and Its Dibenzyl Derivative on Cell Growth in Vitro

Compound	Molar concn for 50% inhibn of growth of: Leukemia L1210	Mammary carcinoma TA_3	*S. faecium*	*E. coli*
1,3-Dideazauridine	1×10^{-4}	$>10^{-4}$	$>10^{-4}$	$>10^{-3}$
Dibenzyl-1,3-dideazauridine	7×10^{-6}	5×10^{-5}	$>10^{-3}$	$>10^{-3}$

Experimental Section

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Uv spectra were recorded on a Cary Model 14 spectrophotometer. Optical rotations were determined with a Perkin-Elmer 141 polarimeter with a 1-dm path length and NMR spectra on Varian A-60, Joel MH-100, and Varian XL-100 spectrometers using TMS as internal standard. The mass spectra were recorded on a CEC 21-491 double-focusing mass spectrometer using an ionization voltage of 70 eV. Ir spectra were recorded on Perkin-Elmer 457 spectrophotometer. Thin-layer chromatography was performed on silica gel N-HR/UV precoated plastic sheets (Brinkman); the products were detected by uv absorbance or by spraying with 20% v/v sulfuric acid–ethanol and heating. Column chromatography was performed on Bio-Sil A (100–200 mesh, Bio-Rad). Satisfactory analyses (C, H, and Br, within ±0.4% of the theoretical values) were obtained from the Galbraith Laboratories Inc. Knoxville, Tenn.

4-Bromo-1,3-dibenzyloxybenzene (2). Benzyl chloride (35.5 g, 0.28 mol) was added dropwise, over a period of 45 min, to a mixture of anhydrous K_2CO_3 (16.5 g, 0.12 mol), dry acetone (500 ml), and 4-bromo-1,3-dihydroxybenzene (24.57 g, 0.13 mol) refluxing under nitrogen. Refluxing was continued for 65 hr under anhydrous conditions. After cooling, the solid was removed by filtration and washed several times with acetone, and the combined filtrates were concentrated to a light brown syrup. The syrup was partitioned between benzene and 1 *N* NaOH, and the organic layer was further washed with saturated NaCl solution. The benzene layer was dried over anhydrous Na_2SO_4 and was then evaporated to dryness. The brown-colored oil thus obtained was dissolved in a minimum amount of MeOH and, after standing in the refrigerator overnight, colorless needle-shaped crystals were obtained. Recrystallization from the same solvent furnished 31.2 g (65% yield) of **2**: mp 38–39°; λ_{max}^{MeOH} 282 nm (ε 4428); NMR (DMSO-d_6) δ 5.18, 5.28 (2 s, 4 H, $2CH_2$), 6.5–7.7 (m, 13 H, aromatic); mass spectrum *m/e* 371, 369 (M^+). Anal. ($C_{20}H_{17}BrO_2$) C, H, Br.

4-(β-D-Ribofuranosyl)-1,3-dibenzyloxybenzene (7). A solution of **2** (14.76 g, 0.04 mol) in 150 ml of Et_2O was added in one portion to a rapidly stirring solution of *n*-BuLi (5.3 g, 0.08 mol) in 100 ml of Et_2O under N_2 atmosphere. After 50–60 min of stirring at room temperature, a yellow-colored solution of the lithium derivative **3** was obtained. Anhydrous $CdCl_2$ (11.40 g, 0.05 mol) was added to the solution, and the suspension thus obtained was refluxed under N_2 for 2.5–3 hr, yielding a gray-colored cadmium salt **4**. From this mixture approximately 100 ml of Et_2O was distilled off and 150 ml of a solution of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride[35] (prepared from 15.0 g, 0.03 mol, of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose in 300 ml of anhydrous toluene) was added. The remaining Et_2O was then distilled off, and the remaining half of the chloro sugar solution was added. The reaction mixture was refluxed under N_2 for 3.5 hr.

After cooling in ice, ice-cold H_2O was added to the reaction mixture, and the mixture was acidified with enough glacial AcOH to completely dissolve the solid. The toluene fraction was removed, and the remaining aqueous solution was extracted four times with toluene. The toluene fractions were combined and washed with a saturated solution of $NaHCO_3$ and then with H_2O and dried over anhydrous Na_2SO_4. After filtration the solution was evaporated to dryness to give a dark red syrup. The syrup was dissolved in 300 ml of anhydrous C_6H_6–MeOH (1:1) and treated with MeONa in MeOH (2.0 g of Na in 50 ml of MeOH) and stirred at room temperature overnight. The pH of the solution, which was alkaline, was adjusted to almost neutral with Dowex 50W-X2 (200–400 mesh, H^+ form). The mixture was filtered and evaporated to a deep brown oil. Tlc of this mixture showed three major products with R_f values of 0.95, 0.67, and 0.37 in $CHCl_3$–Me_2CO (7:3). The crude mixture was taken up in a minimal amount of $CHCl_3$ and a few drops of MeOH and was poured on a dry silica gel column (112 × 13 cm). The column was washed with 800 ml of $CHCl_3$ and the desired 4-(β-D-ribofuranosyl)-1,3-dibenzyloxybenzene (R_f 0.37) was eluted with a mixture of $CHCl_3$–Me_2CO (80:20, v/v). It was repurified on a dry silica gel column using the same eluent and was obtained in a 2.02-g (12%) yield. Recrystallization from EtOH gave **7** as a colorless, crystalline, analytically pure sample: mp 115–116°; $[\alpha]^{26}D$ −8.0° (*c* 0.3, MeOH); λ_{max}^{MeOH} 278 nm (ε 2911); NMR (DMSO-d_6) δ 6.56–7.60 (m, 13 H, aromatic), 5.12, 5.18 (2 s, 4 H, $2CH_2$), 5.03 (d, 1 H, 1′-H, $J_{1'-2'}$ = 4 Hz), 4.72–4.84 (m, 3 H, OH's), 3.56–4.08 (m, 5 H, 2′-H, 3′-H, 4′-H, and 5′-H); mass spectrum *m/e* 422 (M^+). Anal. ($C_{25}H_{26}O_6$) C, H.

4-(β-D-Ribofuranosyl)-1,3-dihydroxybenzene (8). To a solution of 4-(β-D-ribofuranosyl)-1,3-dibenzyloxybenzene (844 mg, 0.002 mol) in 150 ml of EtOH was added 75 mg of 5% palladium on charcoal and a slow stream of H_2 gas was bubbled into the solution for 1 hr at room temperature and atmospheric pressure. The catalyst was removed by filtration with the aid of a Celite pad, and after washing with EtOH the combined filtrate and washings were evaporated to yield 313 mg (65%) of **8** as a syrup. The syrup was dissolved in a minimum amount of absolute EtOH, and C_6H_6 was added until the solution became turbid and kept at room temperature overnight to yield colorless crystals: 288 mg (60%); mp 131–132°; $[\alpha]^{26}D$ −10.6° (*c* 0.3, MeOH); λ_{max}^{MeOH} 280 nm (ε 2722); NMR (DMSO-d_6–D_2O) δ 6.18, 7.0 (2 d, 2 H, 5-H, 6-H), 6.33 (s, 1 H, 2-H), pattern of the sugar protons poorly resolved. Mass spectrum *m/e* 244 (M + 2),[36,37] mass spectrum of the trimethylsilyl derivative 602 (M^+). Anal. ($C_{11}H_{14}O_6$) C, H.

4-(β-D-Ribofuranosyl)-1,3-dibenzyloxybenzene 2′,3′-*O*-Cyclophenylboronate (10). Phenylboronic anhydride (21.6 mg,

† Personal communication, Drs. R. E. Hughes, W. M. Munyon, J. A. O'Malley, and W. A. Carter, Department of Medical Oncology, RPMI.

0.204 mmol) was added to the glycosyl derivative **7** (71.8 mg, 0.170 mmol) suspended in 10 ml of dry ethyl acetate containing 100 mg of anhydrous magnesium sulfate, the mixture was stirred at room temperature for 2 hr and filtered, and the filtrate was evaporated under reduced pressure. The product thus obtained was characterized as cyclic boronate by NMR spectroscopy and also by mass spectrometry which showed the characteristic fragmentation pattern at *m/e* 146 derived from the elimination of $C_8H_7BO_2^+$ similar to a number of cyclic boronates of sugars possessing the vicinol *cis*-amino alcohol group.[13] The infrared spectrum of the product in carbon tetrachloride exhibited a band of free hydroxylic function at 3665 cm^{-1} and an intensive band at 3606 cm^{-1} due to the hydrogen bonding involving the free hydroxylic function, the furanose ring oxygen atom, and the π electrons of the benzene ring; NMR (acetone-d_6) δ 6.54–8.02 (m, 18 H, aromatic), 5.10, 5.14 (2 s, 4 H, $2CH_2$), 4.95 (t, 1 H, 5′-OH), 4.92 (s, 1 H, 1′-H), 3.74–4.46 (m, 5 H, 2′-H, 3′-H, 4′-H, and 5′-H).

4-(2′,3′-*O*-Isopropylidene-β-D-ribofuranosyl)-1,3-dibenzyloxybenzene (9). A mixture of **7** (100 mg), *p*-toluenesulfonic acid (20 mg), acetone (10 ml) and 2,2-dimethoxypropane (1 ml) was stirred at room temperature for 10–12 hr. It was then neutralized with aqueous sodium bicarbonate, filtered, and evaporated to dryness. The purification was done by dry silica gel column chromatography using benzene–acetone (9:1). The product was characterized by mass spectrometry which showed an intense molecular ion peak at *m/e* 462; NMR (DMSO-d_6) δ 6.36–7.76 (m, 13 H, aromatic), 5.14 (br s, 5 H, $2CH_2$ overlapping with 1′-H), 4.88 (t, 1 H, 5′-OH), 3.48–4.68 (m, 5 H, 2′-H, 3′-H, 4′-H, and 5′-H), 1.28, 1.51 (2 s, 6 H, $2CH_3$); NMR (acetone-d_6) δ 5.12, 5.17 (2 s, 4 H, $2CH_2$), 5.10 (s, 1 H, 1′-H), 4.62 (t, 1 H, 5′-OH).

Biological Procedures. The techniques used for the biological evaluation of the compounds have been reported previously.[5]

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