Syntheses with Partially Benzylated Sugars. XI.[1] Studies on the Synthesis of the Anomeric 5,6-Dimethyl-1-D-ribofuranosylbenzimidazoles (Ribazoles). Comparison of the Condensation of 2,3,5-Tri-*O*-benzoyl-D-ribofuranosyl Bromide and 2,3,5-Tri-*O*-benzyl-D-ribofuranosyl Chloride with 5,6-Dimethylbenzimidazole

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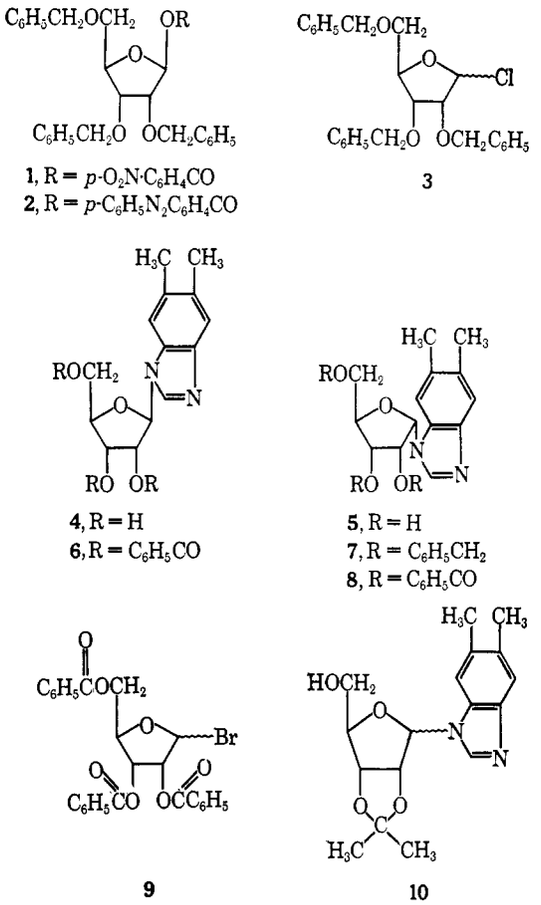
The amorphous 2,3,5-tri-*O*-benzyl-D-ribofuranosyl chloride (**3**) which is readily preparable from 2,3,5-tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl- (or *p*-phenylazobenzoyl-) β-D-ribofuranose, is a mixture of anomers in which the β form predominates. On condensation with an excess of 5,6-dimethylbenzimidazole, this halide (**3**) gives the *cis*-glycoside derivative 1-(2,3,5-tri-*O*-benzyl-α-D-ribofuranosyl)-5,6-dimethylbenzimidazole (**7**) in 66% yield; catalytic debenzylation of **7** affords 5,6-dimethyl-1-α-D-ribofuranosylbenzimidazole (**5**, α-ribazole). As usually obtained, syrupy 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**9**) is a mixture of anomers with the α form in slight excess. On condensation with an excess of 5,6-dimethylbenzimidazole, **9** gives 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-5,6-dimethylbenzimidazole (**6**, isolated as its picrate) in 51% yield and the corresponding α anomer (**8**, also isolated as its picrate) in 28% yield. The substantial quantity of **8** formed from **9** emphasizes the fact that the presence of a participating acyl group at C-2 in a glycosyl halide cannot be relied upon to ensure, even under mild conditions, the exclusive formation of glycosides which are *trans* at C-1–C-2.

In an earlier paper in this series[3] the difficulties attendant upon the synthesis of nucleosides having an aglycon in a *cis* relationship to the hydroxyl function at C-2 ("*cis* nucleosides") were described and the utility of glycosyl halides, fully substituted by the nonparticipating benzyl group, for the synthesis of such structures was demonstrated through the use of 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl chloride in the synthesis of the *cis* nucleoside 1-β-D-arabinofuranosyladenine (spongoadenosine). Subsequently, other researchers have used 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl chloride for the synthesis of 1-β-D-arabinofuranosylcytosine,[4] 1-β-D-arabinofuranosyl-5-trifluoromethyluracil,[4] 1-β-D-arabinofuranosyl-5-fluorouracil,[5] and 1-β-D-arabinofuranosylthymine.[6]

To explore further the utility of this synthetic approach, we have now turned our attention to the synthesis of the nucleosidelike substance, 5,6-dimethyl-1-α-D-ribofuranosylbenzimidazole (**5**, also called "α-ribazole")[7,8] (Chart I), which is a hydrolytic product of vitamin B_{12}. Here, as in the β-D-arabinofuranosyl nucleosides mentioned above, the aglycon is *cis* to the hydroxyl group at C-2 of the sugar moiety; the compound (**5**) has been well characterized and has been synthesized by a variety of ingenious procedures.[7,9-12]

Barker and Fletcher[13] described the preparation of 2,3,5-tri-*O*-benzyl-D-ribofuranosyl bromide through the action of hydrogen bromide on 2,3,5-tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-β-D-ribofuranose (**1**) in dichloromethane solution. Subsequent experience in the arabinofuranose series[3,14] has, however, shown that the more stable tri-*O*-benzylpentofuranosyl chlorides are to be preferred for synthetic purposes and, for this reason, 2,3,5-tri-*O*-benzyl-D-ribofuranosyl chloride (**3**) was chosen for the present work and prepared in a manner analogous to that used earlier for the corresponding bromide.[13] Like its arabinose analog, 2,3,5-tri-*O*-

CHART I



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benzyl-D-ribofuranosyl chloride (**3**) proved to be amorphous; its nmr spectrum showed it to be a mixture of anomers with the β anomer predominating. Condensation of **3** in dioxane solution with slightly more than 2 molar equiv of 5,6-dimethylbenzimidazole gave, after chromatography, 1-(2,3,5-tri-*O*-benzyl-α-D-ribofuranosyl)-5,6-dimethylbenzimidazole (**7**) in 66% yield. This yield may be compared with the 46% yield of 9-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)adenine isolated subsequent to the condensation of 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl chloride with *N*-benzoyladenine.[8] Although amorphous, the product here (**7**) appeared to be homogeneous, its nmr spectrum showing a doublet (4.8 Hz) at τ 3.87. The substance was identified by conversion into the picrate of 5,6-dimethyl-1-α-D-ribofuranosylbenzimidazole (**5**)[9] and into 1-(2,3-*O*-isopropylidene-α-D-ribofuranosyl)-5,6-dimethylbenzimidazole (α **10**).[9]

Minor variations in the condensation were studied. The use of acetonitrile as a solvent in place of dioxane gave, in one experiment, a lower yield (46%) of **7**; when the silver salt of 5,6-dimethylbenzimidazole[15] was used in suspension in acetonitrile, the yield dropped to 25%.

The major advantage in the use of **1** for the preparation of 2,3,5-tri-*O*-benzyl-D-ribofuranosyl chloride (**3**) depends, of course, on the relative insolubility of *p*-nitrobenzoic acid in dichloromethane. Although the yield of this acid in the conversion of **1** into **3** is nearly quantitative, a small amount of **1** was recovered in chromatographing the crude **7**. From several points of view, the use of a colored acyl group in place of the *p*-nitrobenzoyl group would seem to offer advantages. Not only might the purification of the starting material (analogous to **1**) be facilitated but the progress of its conversion into the colorless **3** would be plainly visible and, finally, the removal of unchanged starting material from the crude product would be simplified. Since *p*-phenylazobenzoic acid is even less soluble in dichloromethane than is *p*-nitrobenzoic acid (*ca.* 0.48 mg/ml *vs. ca.* 1.52 mg/ml at 23°), we acylated 2,3,5-tri-*O*-benzyl-D-ribofuranose with *p*-phenylazobenzoyl chloride and obtained a readily crystallizable product; its nmr spectrum clearly showed it to be the β anomer **2**. Treatment of this ester in dichloromethane solution with hydrogen chloride precipitated *p*-phenylazobenzoic acid in virtually quantitative yield; the halide **3** remaining in the still slightly colored solution was condensed with 5,6-dimethylbenzimidazole as before and gave **7** in 62% yield. It is evident, therefore, that *p*-phenylazobenzoates such as **2** are as suitable as the corresponding *p*-nitrobenzoates for the preparation of fully benzylated glycosyl halides.

One of the initial objectives of the researches reported in this series of papers was the development of a straightforward and general pathway for the synthesis of aldose derivatives which are *cis* at C-1–C-2. This effort was undertaken because of the unsuitability of acylated aldosyl halides for such syntheses; we wish now to reconsider certain aspects of the chemistry of this class of halides.

As early as 1939, Tipson[16] noted that, regardless of anomeric configuration, acylated glycosyl halides underwent reaction with the silver salts of carboxylic acids to give aldose esters which are *trans* at C-1–C-2; this generalization was first rationalized on mechanistic grounds by Isbell[17] and further clarified by the work of Winstein and his coworkers[18] on the role of neighboring acyloxy groups in nucleophilic displacements. Extensive researches in this laboratory[19,20] showed that poly-*O*-benzoylaldosyl halides are normally methanolyzed in the absence of an acid acceptor to give the *trans* glycoside exclusively. Baker[21] summarized experiences in the synthesis of nucleosides by stating that "condensation of a heavy metal salt of a purine or pyrimidine with an acylated glycosyl halide will form a nucleoside with C-1–C-2 *trans* configuration in the sugar moiety regardless of the original configuration at C-1–C-2;" this statement is now widely termed "Baker's *trans* rule."

While of unquestionable utility, these generalizations, emphasizing the *trans* products from acylated glycosyl halides, have tended to obscure the fact that *cis* anomers are also often encountered, even in the synthesis of simple glycosides.[20] The stereochemistry of these displacements is obviously influenced by many factors—solvent, temperature, acid acceptor, nature and state of potential aglycon, etc.—and it is likely that more than one mechanism is involved. The Hilbert–Johnson synthesis (for which, incidentally, Baker's *trans* rule is not applicable) has been found to give mixtures of anomeric nucleosides.[22] Of more immediate relevance, it is of particular interest to note that *cis* glycosides of benzimidazole and of 5,6-dimethylbenzimidazole have been isolated in syntheses involving acylated glycosyl halides. Thus, Johnson, *et al.*,[10] condensed 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide with benzimidazole in dioxane solution at 100° and subsequently isolated 1-α-D-glucopyranosylbenzimidazole in 3.7% yield as well as its β anomer in 21% yield; with 5,6-dimethylbenzimidazole, the yield of the α glucoside was 5.1% and that of the β glucoside 20%.[23] These authors also condensed amorphous 2,3,5-tri-*O*-acetyl-D-ribofuranosyl chloride with 5,6-dimethylbenzimidazole and obtained the *cis* anomer (**5**, as its picrate) in 3.9% yield and the *trans* anomer (**4**) in 10% yield. More recently, Bräuniger and Koine[24] have heated acylated glycosyl halides with 1-trimethylsilylbenzimidazole *in vacuo* at 110–130°

(15) A. J. Cleaver, A. B. Foster, and W. G. Overend, *J. Chem. Soc.*, 409 (1959).

(16) R. S. Tipson, *J. Biol. Chem.*, **130**, 55 (1939).

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(19) R. K. Ness, H. G. Fletcher, Jr., and C. S. Hudson, *ibid.*, **73**, 959 (1951).

(20) L. J. Haynes and F. H. Newth, *Advan. Carbohyd. Chem.*, **10**, 207 (1955).

(21) B. R. Baker in "Ciba Foundation Symposium on the Chemistry and Biology of Purines," G. E. W. Wolstenholme and C. M. O'Connor, Ed., Little, Brown and Co., Boston, Mass., 1957, p 120. The precise wording of the statement has been ignored by various authors who have thereby given it a greater generality than the original author probably intended; *cf.* E. Walton, F. W. Holly, G. E. Boxer, and R. F. Nutt, *J. Org. Chem.*, **31**, 1163 (1966).

(22) T. Naito and T. Kawakami, *Chem. Pharm. Bull.* (Tokyo), **10**, 627 (1962); J. Farkaš, L. Kaplan, and J. J. Fox, *J. Org. Chem.*, **29**, 1469 (1964); T. Nishimura and B. Shimizu, *Chem. Pharm. Bull.* (Tokyo), **13**, 803 (1965); M. Prystaš and F. Šorm, *Collect. Czech. Chem. Commun.*, **31**, 1035, 1053 (1966).

(23) Subsequent to completion of the research described here, one of us (J. D. S.) restudied the condensation of 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide with benzimidazole; careful chromatography of the product led to isolation of 1-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)benzimidazole in 31% yield and of its β anomer in 45% yield.

(24) H. Bräuniger and A. Koine, *Arch. Pharm.* (Weinheim), **296**, 668 (1963).

and, in each of three sugar series, obtained anomeric products in approximately equal yields which varied from 22 to 35%. In view of these facts, we deemed it desirable to supplement our study of the use of a fully benzylated glycosyl halide with a careful reexamination of the use of a more conventional acylated glycosyl halide, namely 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**9**). This amorphous bromide, prepared from 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose,[25-27] gave nmr signals which showed it to be an anomeric mixture with the α anomer slightly predominating. Condensation of the halide with an excess of 5,6-dimethylbenzimidazole in dry dioxane solution at 100° led, after extensive chromatography, to the isolation of the crystalline picrate of 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-5,6-dimethylbenzimidazole (**6**) in 51% yield and of the amorphous picrate of its α anomer (**8**) in 28% yield. The identities of these picrates were established through their conversion into the respective ribazoles and known derivatives thereof. Their yields are markedly higher than those obtained earlier by other workers who used similar methods.[28] From the results described here, it appears that 2,3,5-tri-*O*-benzyl-D-ribofuranosyl chloride (**3**) is the intermediate of choice for the synthesis of α-D-ribofuranosyl nucleosides while 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**9**) is preferable for the synthesis of β-D-ribofuranosyl nucleosides. The substantial yield of the α anomer (**8**) from **9** should serve as an additional warning that mechanistic considerations alone should never be relied upon in assigning anomeric configurations to glycosides derived from acylated glycosyl halides.

Experimental Section[29]

2,3,5-Tri-*O*-benzyl-1-*O*-*p*-phenylazobenzoyl-β-D-ribofuranose (2).—*p*-Phenylazobenzoyl chloride (15 g) was added to dry pyridine (50 ml) and to the stirred suspension was added 2,3,5-tri-*O*-benzyl-D-ribofuranose (20 g).[30] Stirring was continued for 40 hr and then 6 drops of water was added. After being stirred for a further 2 hr, the reaction mixture was diluted with dichloromethane and washed successively with 3 *N* sulfuric acid and aqueous sodium bicarbonate solution. Moisture was removed with sodium sulfate and the solution was concentrated *in vacuo* to a solid mass which contained some *p*-phenylazobenzoic acid. The desired product was extracted with dichloromethane (100 ml) at room temperature and the extract was concentrated *in vacuo*. From its solution in cyclohexane (100 ml), the product (29.9 g, 71%) crystallized as fine orange needles, mp 118–119°. After recrystallization from boiling ethanol and then from cyclohexane, the product (19.3 g) was homogeneous (tlc, silica gel G, cyclohexane–ethyl acetate, 4:1, v/v): mp 120–121°; $[\alpha]^{20}D$ +12° (*c* 0.38, chloroform). The nmr spectrum of the substance included a singlet at τ 3.47 (H-1), signifying that **2** is a β anomer.

Anal. Calcd for $C_{39}H_{36}N_2O_6$ (628.74): C, 74.50; H, 5.77. N, 4.46. Found: C, 74.57; H, 5.48; N, 4.60.

Condensation of 2,3,5-Tri-*O*-benzyl-D-ribofuranosyl Chloride (3) with 5,6-Dimethylbenzimidazole.—A stream of dry hydrogen chloride was passed for 10 min into a solution of 2,3,5-tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-β-D-ribofuranose[13] (**1**, 5.932 g, 10.4 mmol) in dichloromethane (60 ml). After 20 min, the precipitated *p*-nitrobenzoic acid was removed by filtration and washed with dichloromethane; the combined filtrate and washings were then concentrated *in vacuo* to a syrup from which a fresh batch of dichloromethane was evaporated. The nmr spectrum of the 2,3,5-tri-*O*-benzyl-D-ribofuranosyl chloride thus made included a sharp singlet at τ 3.93 (H-1 of β **3**) and a doublet centered at 3.8 (4.1 Hz, H-1 of α **3**); the intensities of the signals indicated that the halide was approximately 80% of the β anomer and 20% of the α anomer. Finely powdered 5,6-dimethylbenzimidazole[31] (3.36 g, 23.0 mmol) and anhydrous dioxane (30 ml) were added to the syrupy halide and the reaction mixture was stirred at 100° for 1.5 hr. After cooling, the reaction mixture was diluted with benzene (70 ml) and stored at room temperature for 3 hr. The solid was removed by filtration and the solution was concentrated to a syrup which was adsorbed on a column of silicic acid (70 g, Mallinckrodt).

Initial elution with chloroform led to the recovery of 2,3,5-tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-β-D-ribofuranose (615 mg). A mixture of acetone and chloroform (1:50, v/v) was then used as eluent to give **1-(2,3,5-tri-*O*-benzyl-α-D-ribofuranosyl)-5,6-dimethylbenzimidazole** (**7**, 3.78 g, 66%) as a brown syrup, $[\alpha]^{20}D$ +56.7° (*c* 2.08, chloroform). The nmr spectrum of the product showed only one signal in the region of τ 3.3–5.0 and that was a doublet (4.8 Hz) centered at 3.87.

A portion of **7** (2.00 g) was dissolved in methanol (30 ml) and the solution, to which palladium on charcoal (10%, 2 g) and palladium chloride (2 g) were added, was shaken with hydrogen until absorption of the gas had ceased. The solution was filtered, neutralized with Amberlite IR-45, and concentrated to yield crude 5,6-dimethyl-1-α-D-ribofuranosylbenzimidazole (**5**, 949 mg, 94%). The product thus obtained was partially dissolved in pyridine and the resulting solution was filtered; concentration of the filtrate afforded a residue which was heated on a steam bath with saturated aqueous picric acid solution (60 ml). On cooling, the solution deposited 1.085 g (63% from **5**) of **5,6-dimethyl-1-α-D-ribofuranosylbenzimidazole picrate**: mp 211° (darkening at 205°); $[\alpha]^{20}D$ +13.5° (*c* 3.14, pyridine). Recrystallization from ethanol gave the pure picrate as needles: mp 209–212° (Pyrex capillary), 217–219° (hot stage); $[\alpha]^{20}D$ +12.8° (*c* 2.71, pyridine). For this compound the following constants have been reported: mp 201–202°,[11] 210°,[10] 213–214°,[8] and 218–220°;[9] $[\alpha]^{25}D$ +12 ± 2° (*c* 1.6, pyridine),[11] $[\alpha]^{19}D$ +9° (*c* 1, pyridine),[10] $[\alpha]^{23}D$ +9.9 ± 1.6° (*c* 2.4, pyridine),[8] and $[\alpha]^{23}D$ +9° (*c* 4, pyridine).[9]

In a similar condensation, acetonitrile was used in place of dioxane; the yield of chromatographed but crude **7** was lowered (46%) but its specific rotation, $[\alpha]^{20}D$ +55.2° (*c* 1.20, chloroform), was essentially identical with that obtained when dioxane was used. In a wholly parallel experiment, **3**, prepared from 2,3,5-tri-*O*-benzyl-1-*O*-*p*-phenylazobenzoyl-β-D-ribofuranose (**2**), was used in dioxane solution; the yield of **7** obtained was 62%.

1-(2,3-*O*-Isopropylidene-α-D-ribofuranosyl)-5,6-dimethylbenzimidazole (α 10).—In order to confirm the identity of the crude **5** obtained through the hydrogenolysis of its tribenzyl ether (**7**), a sample (1.65 g) was converted into α **10** by the procedure described later for the preparation of β **10**: 772 mg (41%); mp 177–179°; $[\alpha]^{20}D$ −82.3° (*c* 0.91, chloroform). Melting points of 181–181.5°[9] and 176°[12] and a specific rotation of $[\alpha]^{23}D$ −76° (chloroform)[9] have been reported for this substance. Its nmr spectrum showed a doublet (3.5 Hz) centered at τ 3.66.

Condensation of 2,3,5-Tri-*O*-benzyl-D-ribofuranosyl Chloride (3) with Silver 5,6-Dimethylbenzimidazole.—2,3,5-Tri-*O*-benzyl-D-ribofuranosyl chloride (**3**), prepared from **2** (1.08 g), was dissolved in acetonitrile (15 ml) and the solution was treated with silver 5,6-dimethylbenzimidazole.[15] The reaction mixture was stirred at room temperature for 6 days and then filtered. Chromatography on silica gel as described earlier afforded **7**: 235 mg (25%); $[\alpha]^{20}D$ +52.4° (*c* 0.86, chloroform).

(25) F. Weygand and F. Wirth, *Ber.*, **85**, 1000 (1952).

(26) R. K. Ness and H. G. Fletcher, Jr., *J. Amer. Chem. Soc.*, **75**, 3289 (1953).

(27) R. K. Ness, H. W. Diehl, and H. G. Fletcher, Jr., *ibid.*, **76**, 763 (1954).

(28) The procedure used by Bräuniger and Koine[24] cannot be regarded as strictly comparable. The yields obtained by Johnson, *et al.*,[10] have already been cited. Weygand and Wirth[25] obtained **4** in 3.7% yield after condensing **9** with the silver salt of 5,6-dimethylbenzimidazole; with the chloromercuri derivative of the base, the yield of **4** was 8%. Davoll and Brown [*ibid.*, **73**, 5781 (1951)] condensed 2,3,5-tri-*O*-acetyl-D-ribofuranosyl chloride with the chloromercuri derivative of the base and obtained **4** in 43% yield.

(29) Melting points are corrected. Chloroform used for chromatography was rendered alcohol free immediately prior to use by passage through a column of silica gel. Nmr spectra were obtained in $CDCl_3$ solution using a Varian A-60 spectrometer and tetramethylsilane as an internal standard.

(30) This substance was originally prepared in amorphous form by Barker and Fletcher[13] and subsequently obtained in crystalline form by N. A. Hughes and P. R. H. Speakman [*J. Chem. Soc., Sect. C*, 1182 (1967)]; we are indebted to Dr. Hughes for seed crystals of the compound.

(31) 5,6-Dimethylbenzimidazole (Aldrich Chemical Co., Milwaukee, Wis.) was sublimed *in vacuo* (0.3 mm and 190° bath) and then recrystallized from ethanol.

2,3,5-Tri-*O*-benzoyl-D-ribofuranosyl Bromide (9).—Hydrogen bromide was bubbled into an ice-cold solution of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose[32] (25.2 g, 50 mmol) in dichloromethane (150 ml) for 15 min. After the reaction mixture had been stored at 0° for 1 hr and room temperature for 15 min, it was concentrated *in vacuo* to a thin syrup. Dry dichloromethane (25 ml) and dry toluene (25 ml) were successively distilled *in vacuo* from the syrup which was then used immediately for the condensation described below. The nmr spectrum of the syrup included a singlet at τ 3.5 (H-1 of β **9**) and a doublet centered at 3.10 (4.4 Hz, H-1 of α **9**). By one method of integration, the relative intensities of these signals indicated α:β = 60:40; another method gave α:β = 55:45.

Condensation of 2,3,5-Tri-*O*-benzoyl-D-ribofuranosyl Bromide (9) with 5,6-Dimethylbenzimidazole.—To the syrupy 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**9**), prepared as described above, was added powdered 5,6-dimethylbenzimidazole[31] (18 g, 123 mmol), followed by dry dioxane (100 ml). The mixture was stirred in a boiling water bath for 2.5 hr, cooled, diluted with benzene (200 ml), and stored at 0° for 3 hr. The solid was removed by filtration and washed with a benzene–dioxane mixture; concentration of the combined filtrate and washings afforded a light brown syrup which was dissolved in chloroform (25 ml) and adsorbed on a column (5.8 × 17.5 cm) of silicic acid (Mallinckrodt, 100 mesh, 240 g, packed in chloroform). Chloroform (1200 ml) was passed through the column, followed by acetone–chloroform (1:19, v/v). The leading uv-fluorescent band was collected in the first 1500 ml of eluate (fraction 1); two further fractions, fraction 2 (350 ml) and fraction 3 (1300 ml), were also collected. Removal of solvent from the fractions yielded, respectively, 14.11 g, 10.53 g, and 3.03 g of material as foamed syrups.

The material from fraction 1 was dissolved in hot alcohol (250 ml) and a hot solution of picric acid (7.16 g) in alcohol (150 ml) was added. Ethyl acetate (25 ml) was added to the solution in order to dissolve some syrupy picrate which precipitated and the mixture was heated on a steam bath for 15 min, a crystalline picrate precipitating. The mixture was cooled slowly to *ca.* 30° and the crystalline picrate of **1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-5,6-dimethylbenzimidazole (6)** was removed by filtration, washed with alcohol, and dried to give 12.72 g, $[\alpha]^{20}D$ −84.8° (*c* 2.16, chloroform). Recrystallized from a mixture of ethyl acetate (170 ml) and ethanol (200 ml), the substance was obtained in pure form: mp 160–161°; $[\alpha]^{20}D$ −85.8° (*c* 2.06, chloroform). Further recrystallization failed to change these values significantly.

Anal. Calcd for $C_{41}H_{33}N_5O_{14}$ (819.75): C, 60.07; H, 4.06; N, 8.54. Found: C, 59.99; H, 4.20; N, 8.38.

Concentration of the filtrate *in vacuo* yielded a syrupy picrate which was collected by decantation and then washed with alcohol.

A similar treatment of fraction 2 gave a further 10.8 g of the crystalline picrate of **6**, $[\alpha]^{20}D$ −72.9°, which was recrystallized from a mixture of ethanol (300 ml) and ethyl acetate (70 ml) to give 7.99 g, mp 165–166°. The total yield of **6** picrate obtained (20.71 g) corresponds to 51%, based on **9**.

Fraction 3 yielded a syrupy picrate which was combined with the syrupy picrate obtained from fraction 1 and from the mother liquor remaining after the crystallization and recrystallization of **6** picrate from fraction 2. The total yield of the **picrate of 1-(2,3,5-tri-*O*-benzoyl-α-D-riborfuranosyl)-5,6-dimethylbenzimidazole (8,** *ca.* 11.45 g) was 28%, based on **9**. A portion (9.93 g) of the syrupy picrate was dissolved in chloroform (150 ml) and the solution was washed with a solution of lithium hydroxide (0.6 g) in water (150 ml) and then with water. The solution was concentrated to a syrup which was redissolved in chloroform and chromatographed on a column of alumina (Woelm, neutral, grade 1, 45 g). Elution was made with chloroform, the last of the product being removed with 20% acetone in chloroform (v/v). Removal of the solvent from the eluate afforded crude syrupy **1-(2,3,5-tri-*O*-benzoyl-α-D-ribofuranosyl)-5,6-dimethylbenzimidazole (8,** 5.85 g, 82% from the picrate). The optical rotation of such preparations varied from $[\alpha]^{20}D$ −52° to −64° (chloroform). Further purification was effected by chromatographing a sample (1.10 g, $[\alpha]^{20}D$ −53.2°, *c* 1.9, chloroform) on a column (2.8 × 39 cm) of silicic acid (Mallinckrodt, 100 mesh) using acetone–chloroform (1:39, v/v), the progress of the material being monitored through the use of a short-wavelength uv lamp.[33] After 590 ml of eluate had been collected, a narrow band emerged in the next 125 ml; this contained 185 mg of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose, identified through its nmr spectrum. After a total of 815 ml of eluate had been collected, the eluent was changed to 1:29 (v/v) acetone–chloroform and 100-ml fractions were collected until the total eluate was 1515 ml; thereafter, fractions of 40 ml were collected. Nucleoside emerged in fraction 16 and later fractions. The composition of the material in each fraction was ascertained through the different chemical shifts in the nmr spectrum of **6** and **8**, the α anomer (**8**) having signals at τ 7.72 and 7.77 and the β anomer (**6**) having signals at 7.71 and 7.91. Fractions **26** to 34 contained almost pure **6** (318 mg) while fraction 42 and succeeding fractions contained **8**; the last traces of **8** were removed from the column using acetone–chloroform (1:9, v/v) to give a total of 537 mg of pure **8**. Intermediate fractions (35 to 41) contained 464 mg of material which was predominantly **8**. The pure **1-(2,3,5-tri-*O*-benzoyl-α-D-ribofuranosyl)-5,6-dimethylbenzimidazole (8)** was obtained as a friable foam: $[\alpha]^{20}D$ −53.8° (*c* 1.26, chloroform), $[\alpha]^{20}D$ −73.8° (*c* 1.12, ethanol).

Anal. Calcd for $C_{35}H_{30}N_2O_7$ (590.61): C, 71.17; H, 5.12; N, 4.74. Found: C, 71.36; H, 5.29; N, 4.71.

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-5,6-dimethylbenzimidazole (6).—A chloroform solution of the picrate of **6** (8.2 g) was extracted with an aqueous solution of lithium hydroxide (630 mg) and then washed with water. The solution was then passed through a short column of alumina and concentrated to a syrup which was dissolved in warm benzene (15 ml) and to the warm solution petroleum ether (25 ml, bp 60–70°) was added. The solution was seeded and crystallization was allowed to proceed at room temperature, a further 25 ml of petroleum ether being added after several days to give 5.56 g, mp 135–137°. A second crop (0.25 g, mp 134–136°) raised the total yield of **6** to 98%. Recrystallized from ethanol, pure **6** had mp 136–137° and specific rotations of $[\alpha]^{20}D$ −121.0° (*c* 1.02, chloroform) and $[\alpha]^{20}D$ −152.7° (*c* 1.09, methanol).

Anal. Calcd for $C_{35}H_{30}N_2O_7$ (590.61): C, 71.17; H, 5.12; N, 4.74. Found: C, 71.35; H, 4.92; N, 4.52.

5,6-Dimethyl-1-β-D-ribofuranosylbenzimidazole (4).—A solution of **6** (4.98 g) in anhydrous methanol (100 ml) was treated with 1 *N* sodium methoxide in methanol (2 ml) and then heated at 50° for 2.5 hr. After cooling, the solution was neutralized with Amberlite IRC-50 (H^+) and concentrated to a solid which was freed of methyl benzoate by repeated extraction with cyclohexane. The residue was dissolved in ethanol, water was added, and the solution was cooled to yield 1.18 g of crystalline 5,6-dimethyl-1-β-D-ribofuranosylbenzimidazole (**4**), mp 191–193°. A second crop (0.40 g, mp 191–192°) raised the yield to 67%. Recrystallization of the first crop from a mixture of ethanol (7 ml) and water (1.5 ml) gave the pure glycoside (**4**): mp 190–192°; $[\alpha]^{20}D$ −51.9° (*c* 2.01, pyridine), $[\alpha]^{20}D$ −30.2 (*c* 1.95, methanol). For this substance Weygand and Wirth[25] cited mp 201–202° and $[\alpha]^{20}D$ −47.2 ± 2° (*c* 1.1, pyridine), Johnson, *et al.*,[10] cited mp 197–200° and $[\alpha]^{19}D$ −44° (*c* 1, pyridine), and Holly, *et al.*,[9] cited mp 190–192° and $[\alpha]^{23}D$ −44° (*c* 3, pyridine). A sample of our **4** gave a picrate of mp 174–175°; melting points of 172–174° (Davoll and Brown[26]), 192°,[24] and 175–177°[9] have been reported for this substance.

1-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)-5,6-dimethylbenzimidazole (β 10).—To an ice-cold solution of crude **4** (0.7 g) in a mixture of acetone (50 ml) and 2,2-dimethoxypropane (2 ml) was added concentrated sulfuric acid (2 ml). After 2 hr, the solution was neutralized by the addition of a solution of sodium hydroxide (2.9 g) in water (10 ml). The filtered solution was concentrated and the residue, dissolved in chloroform, was washed with water. After removal of the chloroform, the material was dissolved in acetone (*ca.* 10 ml) to yield colorless crystals (0.33 g), mp 190°; a second crop (0.205 g) raised the yield to 67%. Recrystallization from acetone gave pure **β 10**: mp 189–190°; $[\alpha]^{20}D$ −29.8° (*c* 1.30, chloroform). Holly, *et al.*,[9] reported mp 191–192° and $[\alpha]^{23}D$ −28° (chloroform) for this substance. The nmr spectrum of the product included a doublet (2.5 Hz) centered at τ 3.94 (H-1).

5,6-Dimethyl-1-α-D-ribofuranosylbenzimidazole (5).—Crude, syrupy **8** (612 mg, $[\alpha]^{20}D$ −52° in chloroform) was debenzoylated

(32) Calbiochem, Los Angeles, Calif.

(33) "Mineralite" Model SL 2537, Black Light Eastern Corp., New York, N. Y.

by heating its solution in 0.03 *N* methanolic sodium methoxide at 50° for 1.5 hr. The cooled solution was deionized with Amberlite IRC-50 (H^+) and concentrated, the residue being freed of methyl benzoate by extraction with cyclohexane. Dilution of an ethanol–acetone solution of the product with hexane afforded a flocculent precipitate which was discarded. The addition of more hexane to the clear filtrate gave a crystalline product (128 mg, 44%), mp 190–191°. Recrystallization from ethanol–acetone–hexane afforded 81 mg of pure **5**, 192–196° (Pyrex capillary), 195–197° (hot stage). The ir spectrum of the product was identical with that of a sample prepared by the hydrolysis of α **10**.

Registry No.—**2**, 16205-52-0; **3** α-chloride, 16205-53-1; **3** β-chloride, 16205-54-2; **6**, 16205-55-3; **6** picrate, 16205-56-4; **7**, 16205-57-5; **8**, 16205-58-6; **9** α-bromide, 16205-59-7; **9** β-bromide, 16205-60-0; 5,6-dimethylbenzimidazole, 582-60-5.

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Syntheses with Partially Benzylated Sugars. XII.[1] 3,5-Di-*O*-benzyl-β-D-ribofuranose and Its Use as an Intermediate in the Synthesis of Partially Substituted Ribo Nucleosides

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A procedure for the synthesis of D-ribofuranosides having a substituent of one type at C-2 and one of another type at C-3 and at C-5 was studied. Benzylation of the known 2,4-*O*-benzylidene-D-ribose dipropyl dithioacetal (**1**), followed by demercaptalation, gave 3,5-di-*O*-benzyl-2,4-*O*-benzylidene-*aldehydo*-D-ribose (**3**); hydrolysis of the latter substance afforded crystalline 3,5-di-*O*-benzyl-β-D-ribofuranose (**4**). The structure of this ether was confirmed by degradation to the erythritol derivatives **6** and **7**. From **4**, both of the anomeric 1,2-di-*O*-*p*-phenylazobenzoyl esters (**8**) and the β form of the 1,2-di-*O*-benzoyl derivative (**9**) were obtained in crystalline form. Treatment of β **8** in dichloromethane solution with hydrogen chloride precipitated *p*-phenylazobenzoic acid and gave amorphous 3,5-di-*O*-benzyl-2-*O*-*p*-phenylazobenzoyl-D-ribofuranosyl chloride (**10**). The reaction of **10** with 5,6-dimethylbenzimidazole afforded 2-benzyloxymethyl-4-*p*-phenylazobenzoyloxyfuran (**13**), 3,5-di-*O*-benzyl-2-*O*-*p*-phenylazobenzoyl-D-ribofuranose (**14**), and the two anomeric 1-(3,5-di-*O*-benzyl-2-*O*-*p*-phenylazobenzoyl-D-ribofuranosyl)-5,6-dimethylbenzimidazoles (**16** and **21**), with the β anomer (**16**) predominating. The dibenzoate, β **9**, was also treated in dichloromethane solution with hydrogen chloride and the resulting 2-*O*-benzoyl-3,5-di-*O*-benzyl-D-ribofuranosyl chloride (**11**, predominantly the β anomer) was treated (without removal of the benzoic acid) with 5,6-dimethylbenzimidazole. The following products were isolated: β **9**, 2-*O*-benzoyl-3,5-di-*O*-benzyl-D-ribofuranose (**15**), and 1-(2-*O*-benzoyl-3,5-di-*O*-benzyl-β-D-ribofuranosyl)-5,6-dimethylbenzimidazole (**17**). While the anomeric configurations of **16**, **17**, and **21** are apparent from the chemical shifts of the signals from H-1, independent chemical evidence was obtained through hydrogenolysis of **17** to 1-(2-*O*-benzoyl-β-D-ribofuranosyl)-5,6-dimethylbenzimidazole (**18**) and conversion of **18** into the picrate of the known 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-5,6-dimethylbenzimidazole (**19**). The anomeric configuration of **16** was confirmed by conversion into **17**. Direct treatment of 3,5-di-*O*-benzyl-β-D-ribose (**4**) with hydrogen chloride in an inert solvent and in the presence of a desiccant gave 3,5-di-*O*-benzyl-D-ribofuranosyl chloride (**12**); condensation of this halide with 5,6-dimethylbenzimidazole, followed by benzoylation with benzoic anhydride–pyridine, led to the isolation of **17** (as its picrate) and of 1-(2-*O*-benzoyl-3,5-di-*O*-benzyl-α-D-ribofuranosyl)-5,6-dimethylbenzimidazole (**22**). The relationship of the optical rotations of **21** and **16** and of **22** and **17** is the reverse of that expected from Hudson's rule.

Selective substitution of one or more of the hydroxyl groups in the sugar moiety of ribo nucleosides and of other ribofuranosides has been the subject of a variety of researches and has involved synthetic problems which have been met in various ways.[3] In the investigation to be described here, we have explored the possibility of avoiding these problems through the expedient of introducing appropriate substituents into the ribofuranose moiety prior to establishment of the glycosidic bond of the nucleoside. In particular, we have sought a route for the synthesis of ribo nucleosides in which C-2′ bears one type of substituent and C-3′ and C-5′ another type. For this purpose, a 2-*O*-acyl-3,5-di-*O*-benzyl-D-ribofuranosyl halide appeared to be a logical intermediate since acyl and benzyl groups have sharply contrasting reactivities and an acyl group at C-2 should assure the predominant formation of a β-D-ribo nucleoside on condensation of the halide with a base. The synthesis of 3,5-di-*O*-benzyl-D-ribofuranose (**4**) will be discussed first.

Potgieter and MacDonald[4] found conditions under which D-ribose dipropyl dithioacetal could be converted in high yield into a monobenzylidene derivative and they showed that this acetal was 2,4-*O*-benzylidene-D-ribose dipropyl dithioacetal (**1**) (Chart I). As might be expected, this substance is well suited for the synthesis of 3,5-disubstituted D-ribofuranose derivatives. In the present research it was benzylated and then demercaptalated to give crystalline 3,5-di-*O*-benzyl-2,4-*O*-benzylidene-*aldehydo*-D-ribose (**3**) in 75% yield; acidic cleavage of the cyclic acetal gave 3,5-di-*O*-benzyl-D-ribofuranose as a crystalline material which showed a dextromutarotation in aqueous dioxane and is, therefore, the β anomer (**4**). The

(1) Paper XI of this series: J. D. Stevens, R. K. Ness, and H. G. Fletcher, Jr., *J. Org. Chem.*, **33**, 1806 (1968).

(2) Chemical Foundation Fellow, 1963–1966.

(3) This topic, as such, does not appear to have been reviewed but is dealt with in a limited and incidental fashion in accounts of the synthesis of nucleotides; *cf.* A. M. Michelson, "Chemistry of Nucleosides and Nucleotides," Academic Press Inc., London, 1963, p 110 ff.

(4) D. J. J. Potgieter and D. L. MacDonald, *J. Org. Chem.*, **26**, 3934 (1961).