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.

Acknowledgment.—We are indebted to the staff of the Section on Microanalytical Services and Instrumentation of this Institute for spectra and elemental analyses.

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

MASANOBU HAGA,[2] ROBERT K. NESS, AND HEWITT G. FLETCHER, JR.

National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Public Health Service, U. S. Department of Health, Education and Welfare, Bethesda, Maryland 20014

Received November 22, 1967

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

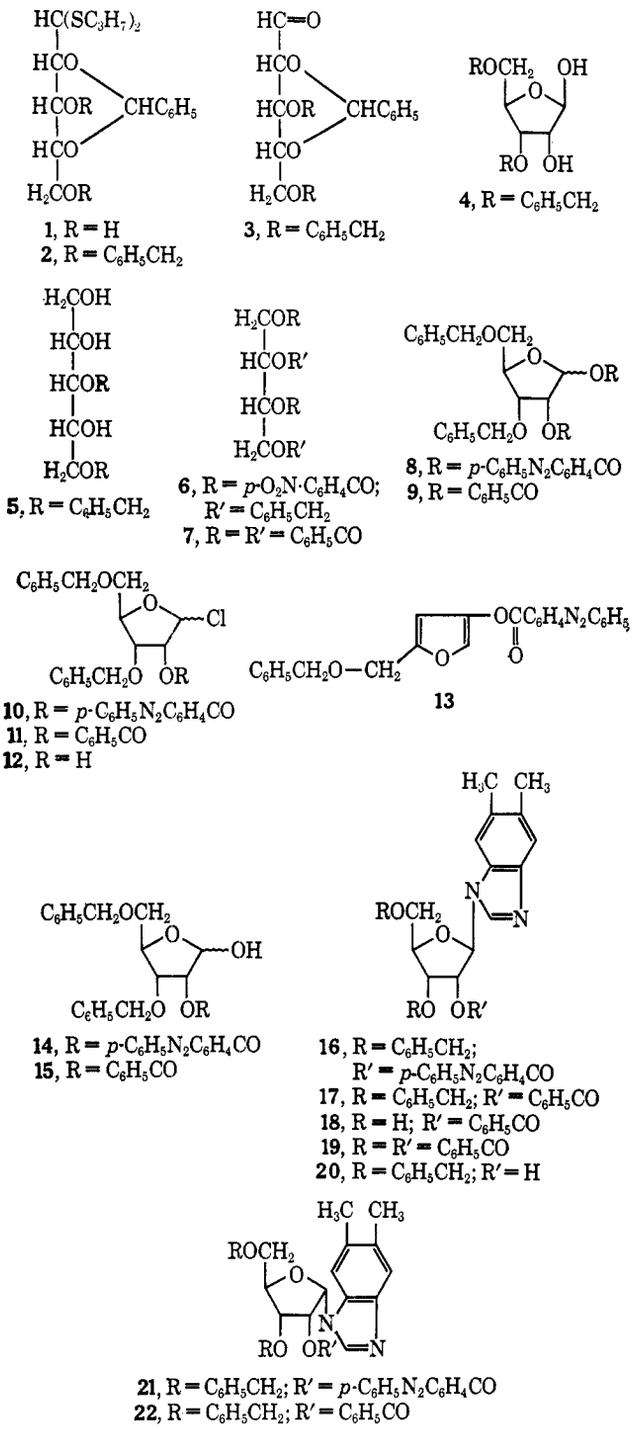
(1) Paper XI of this series: J. D. Stevens, R. K. Ness, and H. G. Fletcher, Jr., *J. Org. Chem.*, **33**, 1806 (1968).

(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).

CHART I



structure of the substance was confirmed by its conversion into erythritol derivatives. Reduction with sodium borohydride gave 1,3-di-*O*-benzyl-L-ribitol (**5** = 3,5-di-*O*-benzyl-D-ribitol) as an optically active syrup. Successive periodate oxidation, sodium borohydride reduction, and *p*-nitrobenzoylation converted **5** into 2,4-di-*O*-benzyl-1,3-di-*O*-*p*-nitrobenzoyl-D-erythritol (**6**), an optically active syrup. A sample of 3,5-di-*O*-benzyl-D-ribofuranose (**4**) was successively oxidized with periodate, reduced with sodium borohydride, debenzylated, and benzoylated to give the known erythritol tetrabenzoate[5] (**7**). Of all the various possible di-*O*-benzyl-D-riboses derivable from a D-ribose dialkyl dithioacetal, only the 3,5 isomer (**4**) could give an optically active erythritol derivative and the structure assigned to **1** by Potgieter and MacDonald[4] may be regarded as confirmed.

For an acyl group at C-2 in the desired 2-*O*-acyl-3,5-di-*O*-benzyl-D-ribofuranosyl halide, the initial choice was the *p*-phenylazobenzoyl group. Several practical considerations dictated this decision. In making such a halide it would be simplest to put the same acyl group at C-1 and C-2 of 3,5-di-*O*-benzyl-D-ribofuranose and recent work in this laboratory[1] has shown that the low solubility of *p*-phenylazobenzoic acid in dichloromethane makes 2,3,5-tri-*O*-benzyl-1-*O*-*p*-phenylazobenzoyl-β-D-ribofuranose, for instance, a suitable and convenient intermediate for the preparation of 2,3,5-tri-*O*-benzyl-D-ribofuranosyl chloride. In addition, it was envisaged that the presence of the colored *p*-phenylazobenzoyl group at C-2 in the nucleoside to be formed would greatly facilitate the chromatographic purification of the substance. For these reasons, 3,5-di-*O*-benzyl-β-D-ribofuranose (**4**) was *p*-phenylazobenzoylated. Two products were isolated by direct crystallization; the major one (69% yield) was levorotatory ($[\alpha]^{20}D$ −64.8° in dichloromethane) and its nmr spectrum included a singlet at τ 3.46 (H-1); this was, therefore, 3,5-di-*O*-benzyl-1,2-di-*O*-*p*-phenylazobenzoyl-β-D-ribofuranose (β **8**). The minor product (11% yield) was dextrorotatory ($[\alpha]^{20}D$ +185° in dichloromethane) and its nmr spectrum showed a doublet (4.2 Hz) centered at τ 3.19 (H-1); this, then, was α **8**. Treatment of β **8** in dichloromethane solution with hydrogen chloride caused precipitation of *p*-phenylazobenzoic acid (90% yield) and led to the isolation of a syrupy 3,5-di-*O*-benzyl-2-*O*-*p*-phenylazobenzoyl-D-ribofuranosyl chloride (**10**) with an nmr spectrum which showed it to be predominantly the β anomer.

For a base we chose 5,6-dimethylbenzimidazole since the two anomeric D-ribofuranosides of this substance (the ribazoles) are well known,[6] the two nitrogen functions are equivalent, and no other reactive groups are present. Condensation of **10** with an excess of this base in boiling dioxane solution led to the isolation of four colored products. The first of these was a crystalline, optically inactive substance; its elemental composition, molecular weight, nmr spectrum, and origin indicated it to be 2-benzyloxymethyl-4-*p*-phenylazobenzoyloxyfuran (**13**); the yield was 20%. An analogous substance, 2-benzoyloxymethyl-4-*p*-nitrophenylsulfonyloxyfuran, has been reported by Ness[7] as being formed from 3,5-di-*O*-benzoyl-2-*O*-*p*-ni-trophenylsulfonyl-D-ribofuranose on undergoing heating with benzoic acid in the presence of pyridine. The second product from the condensation was a syrup that showed hydroxyl absorption; on *p*-phenylazobenzoylation it gave β **8** in high yield and is, therefore, 3,5-di-*O*-benzyl-2-*O*-*p*-phenylazobenzoyl-D-ribofuranose (**14**).[8] The third product was 1-(3,5-

(5) A. Einhorn and F. Hollandt, *Ann. Chem.*, **301**, 95 (1898).

(6) *Cf.* ref 1 and the literature cited therein.

(7) R. K. Ness, *J. Org. Chem.*, **27**, 1155 (1962).

(8) The substance (**14**) must have arisen through the hydrolysis of **10**. While the *p*-phenylazobenzoyl group might have migrated from C-2 to C-1 during this hydrolysis [*cf.* R. K. Ness and H. G. Fletcher, Jr., *J. Amer. Chem. Soc.*, **78**, 4710 (1956)] such a migration would have given 3,5-di-*O*-benzyl-1-*O*-*p*-phenylazobenzoyl-α-D-ribofuranose. That subsequent *p*-phenylazobenzoylation yielded β **8** (rather than α **8**) indicated that a C-2 → C-1 migration did not take place or that, if it had, the reverse migration ensued during the isolation process.

di-*O*-benzyl-2-*O*-*p*-phenylazobenzoyl-β-D-ribofuranosyl)-5,6-dimethylbenzimidazole (**16**, 61%), a syrup which crystallized and was further characterized through its crystalline picrate. The fourth substance from the condensation was 1-(3,5-di-*O*-benzyl-2-*O*-*p*-phenylazobenzoyl-α-D-ribofuranosyl)-5,6-dimethylbenzimidazole (**21**, 10%); its picrate was amorphous.

A similar condensation of **10** with 5,6-dimethylbenzimidazole was carried out in dioxane solution at room temperature for 72 hr to give the following yields: **13**, 52%, **16**, 32%, and **21**, 9%. The greatly increased yield of **13** under these milder conditions may possibly be significant but speculation on the limited evidence of two experiments does not appear to be justified.

The distinction between anomers **16** and **21** was initially made on the basis of their nmr spectra. While the anomeric configuration of the majority of simple aldofuranose derivatives (such as **8**–**11**) may readily be determined from the coupling constant of H-1,[9] the coupling constants of H-1 of anomeric pairs of a number of nucleosides[9,10] do not permit such a distinction. However, as pointed out earlier,[9] the chemical shift of H-1 in aldofuranose derivatives is highly characteristic, the signal for a compound which is *cis* at C-1–C-2 appearing at lower field than that of the corresponding *trans* anomer. Thus H-1 of the *cis* glycoside **21** gives a doublet (6 Hz) centered at τ 3.50 while its *trans* anomer (**16**) gives an H-1 signal as a doublet (5 Hz) centered at τ 3.71. Later in this paper we will describe other examples of the assignment of anomeric configuration by this means as well as a direct chemical correlation which confirms the validity of this procedure for these substances.

While 3,5-di-*O*-benzyl-2-*O*-*p*-phenylazobenzoyl-D-ribofuranosyl nucleosides are of obvious potential utility in the synthesis of a variety of specifically substituted ribo nucleoside derivatives, the presence of a reducible function at C-2 might give rise to undesirable complications in certain reactions, *e.g.*, the hydrogenolysis of the benzyl groups. For this reason, we have explored the feasibility of the synthesis of analogs with a nonreducible acyl group at C-2. Benzoylation of 3,5-di-*O*-benzyl-β-D-ribofuranose (**4**) readily gave a crystalline 1,2-di-*O*-benzoyl-3,5-di-*O*-benzyl-D-ribofuranose in 69% yield; the H-1 signal of the substance appeared as a singlet at τ 3.43, indicating that the ester was the β anomer (β **9**). This ester was treated in dichloromethane solution with hydrogen chloride; the benzoic acid liberated from C-1, being soluble in dichloromethane, was not separated. Concentration of the solution gave a syrupy 2-*O*-benzoyl-3,5-di-*O*-benzyl-D-ribofuranosyl chloride which showed a sharp singlet at τ 3.88 and was, therefore, at least predominantly, the β anomer (β **11**); the halide was condensed with 5,6-dimethylbenzimidazole in boiling dioxane solution and three products were isolated by chromatography. The first product was 1,2-di-*O*-benzoyl-3,5-di-*O*-benzyl-β-D-ribofuranose (β **9**), obtained in 45% yield. Since the nmr spectrum of **11** failed to reveal the presence of this substance, it appears that the benzoic acid contaminating the syrupy **11** recombined with the ribofuranose residue during the condensation. It is obviously desirable, therefore, to remove from glycosyl halides the carboxylic acid arising from C-1 of the ester used in their preparation and the advantage of using an ester (such as a *p*-nitrobenzoate[11] or a *p*-phenylazobenzoate) which yields a carboxylic acid relatively insoluble in dichloromethane is obvious. The second product from the condensation of **11** with 5,6-dimethylbenzimidazole was a syrup (5% yield); on benzoylation it afforded β **9** in 73% yield; the product is, therefore, probably 2-*O*-benzoyl-3,5-di-*O*-benzyl-D-ribofuranose (**15**). The third substance isolated was 1-(2-*O*-benzoyl-3,5-di-*O*-benzyl-β-D-ribofuranosyl)-5,6-dimethylbenzimidazole (**17**), obtained as a syrup in 48% yield and characterized as a crystalline picrate. The nmr spectrum of **17** included a doublet (4.6 Hz) centered at τ 3.74, signifying a β anomer. Catalytic hydrogenolysis of **17** gave 1-(2-*O*-benzoyl-β-D-ribofuranosyl)-5,6-dimethylbenzimidazole (**18**) which was benzoylated to give the known 1-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-5,6-dimethylbenzimidazole (**19**)[1] as its crystalline picrate. Deacylation of 1-(3,5-di-*O*-benzyl-2-*O*-*p*-phenylazobenzoyl-β-D-ribofuranosyl)-5,6-dimethylbenzimidazole (**16**) gave the dibenzyl ether **20**; benzoylation of **20** afforded **17**, identical with material prepared through the condensation of **11** with 5,6-dimethylbenzimidazole. These transformations provided a direct chemical correlation of the new substituted ribazoles (**16**–**21** and **22**, which is described below) and confirms anomeric assignments made through nmr spectra. An attempt to deacylate 1-(3,5-di-*O*-benzyl-2-*O*-*p*-phenylazobenzoyl-α-D-ribofuranosyl)-5,6-dimethylbenzimidazole (**21**) apparently succeeded, but the product (presumably 1-(3,5-di-*O*-benzyl-α-D-ribofuranosyl)-5,6-dimethylbenzimidazole) proved difficult to benzoylate. With benzoyl chloride in pyridine at an elevated temperature it underwent cleavage to give 1-benzoyl-5,6-dimethylbenzimidazole.

In an earlier paper in this series,[12] it was shown that 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride could be prepared through the action of hydrogen chloride on 2,3,5-tri-*O*-benzyl-D-arabinofuranose in an inert solvent and in the presence of a desiccant. We have now used a similar technique for the conversion of 3,5-di-*O*-benzyl-D-ribofuranose (**4**) into 3,5-di-*O*-benzyl-D-ribofuranosyl chloride (**12**). Condensation of this halide with 5,6-dimethylbenzimidazole in dichloromethane solution at room temperature afforded a mixture which was benzoylated with benzoic anhydride in pyridine. Preparative tlc yielded two syrupy products, one of which gave a crystalline picrate (17% yield from **12**), which proved to be identical with the picrate from **17**. The other product had an infrared spectrum and an nmr spectrum consistent with 1-(2-*O*-benzoyl-3,5-di-*O*-benzyl-α-D-ribofuranosyl)-5,6-dimethylbenzimidazole (**22**). A doublet (5.3 Hz) at τ 3.53 was attributed to H-1; this signal falls downfield of the doublet from H-1 in **17** as would be expected of an α anomer.

(9) J. D. Stevens and H. G. Fletcher, Jr., *J. Org. Chem.*, **33**, 1799 (1968).
(10) T. Nishimura, B. Shimizu, and I. Iwai, *Chem. Pharm. Bull.* (Tokyo), **12**, 1471 (1964).
(11) The use of 1-*O*-*p*-nitrobenzoylaldose derivatives for the preparation of labile aldosyl halides was introduced by W. W. Zorbach and T. A. Payne, Jr., *J. Amer. Chem. Soc.*, **80**, 5564 (1958).
(12) C. P. J. Glaudemans and H. G. Fletcher, Jr., *J. Org. Chem.*, **28**, 3004 (1963).

In passing, it should be noted that the relative rotations of two pairs of anomeric ribazole derivatives encountered in this research (Table I) violate Hud-

TABLE I

DERIVATIVES OF THE ANOMERIC 1-(D-RIBOFURANOSYL)-5,6-DIMETHYLBENZIMIDAZOLES

	$[\alpha]^{20}D$ (CH_2Cl_2), deg	$[M]^{20}D$
21 (α anomer)	−138.4	−92,300
16 (β anomer)	−83.6	−55,400
22 (α anomer)	−26.7	−15,000
17 (β anomer)	−9.1	−5,100

son's rule,[13] the α anomers, **21** and **22**, each being more levorotatory than the corresponding β anomers, **16** and **17**. A similar reversal of the normal relationship between the rotations of anomers has been observed with the 1-(2,3-*O*-isopropylidene-D-ribofuranosyl)-5,6-dimethylbenzimidazoles.[14]

Experimental Section[15]

3,5-Di-*O*-benzyl-2,4-*O*-benzylidene-*aldehydo*-D-ribose (3).—2,4-*O*-Benzylidene-D-ribose dipropyl dithioacetal[4] (**1**, 51.54 g) was added to a stirred suspension of powdered potassium hydroxide[16] (*ca.* 90 g) in benzyl chloride (230 ml) which was cooled in an ice bath. The stirred reaction mixture was held in an ice bath for 2 hr and then at room temperature. After 21 hr, the mixture was diluted with dichloromethane, water was added, and the aqueous layer was separated and washed with dichloromethane. The washings were added to the main dichloromethane solution which was then washed successively with water, 3 *N* sulfuric acid, and saturated aqueous sodium bicarbonate solution. Moisture was removed with magnesium sulfate and the solution was concentrated *in vacuo* (finally at 0.2 mm and 100°) to afford a light yellow syrup (**2**) which was dissolved in acetone (600 ml). Yellow mercuric oxide (110 g) and then a solution of mercuric chloride (110 g) in a mixture of acetone (300 ml) and water (250 ml) were added and the mixture was stirred at room temperature for 2 days. The insoluble material was removed by filtration and the filtrate was concentrated *in vacuo* to a syrup which was dissolved in dichloromethane and the resulting solution was washed twice with water. Moisture was removed with magnesium sulfate and the solution was concentrated *in vacuo* to give a crystalline product which was washed with ether and dried: yield 35.07 g; mp 95–98°. A further quantity of material (3.33 g, 94–97°) was recovered from the mother liquor to give a total yield of 75%. Recrystallized from dichloromethane–ether, the pure 3,5-di-*O*-benzyl-2,4-*O*-benzylidene-*aldehydo*-D-ribose (**3**) had mp 96–97° and $[\alpha]^{20}D$ +26.0° (*c* 2.29, dichloromethane).

Anal. Calcd for $C_{26}H_{26}O_5$ (418.50): C, 74.62; H, 6.26. Found: C, 74.69; H, 6.53.

3,5-Di-*O*-benzyl-β-D-ribofuranose (4).—A solution of **3** (30.0 g) in dioxane (300 ml) was diluted with water (300 ml), heated to boiling, and treated with 3 *N* sulfuric acid (12 ml). The reaction mixture was boiled under reflux for 2.3 hr and then neutralized with barium carbonate (15 g). The filtered solution was steam distilled to remove the dioxane and benzaldehyde; on cooling in ice–water, the product crystallized. After recrystallization from carbon tetrachloride (*ca.* 40 ml), the pure 3,5-di-*O*-benzyl-β-D-ribofuranose (**4**, 16.98 g, 72%) had mp 84–86°, $[\alpha]^{20}D$ +47.3° (*c* 0.55, dichloromethane), and $[\alpha]^{20}D$ +48° (2.5 min) → + 55° (4 hr, constant, *c* 1.61, 18:7 dioxane–water, v/v).

Anal. Calcd for $C_{19}H_{22}O_5$ (330.39) C, 69.07; H, 6.71. Found. C, 69.19; H, 6.76.

A small sample of **4** was dissolved in ethyl acetate; palladium black was added; and the suspension was shaken with hydrogen until absorption of the gas had ceased. After removal of the catalyst and the solvent, the residual syrupy material was examined by tlc (propyl alcohol–ethyl acetate–water, 3:2:1, and propyl alcohol–ammonia–water, 6:2:1) and also (after trimethylsilylation) by glpc; the material was indistinguishable from an authentic specimen of D-ribose.

1,3-Di-*O*-benzyl-L-ribitol (5 = 3,5-Di-*O*-benzyl-D-ribitol).—A solution of sodium borohydride (0.50 g) in water (12.5 ml) was added dropwise to a cold solution of **4** (2.13 g) in dioxane (6.5 ml) and the reaction mixture, diluted with an additional 7 ml of dioxane, stirred at room temperature overnight. Amberlite IR-120 (H^+) (20 ml) was added to the pasty mass and stirring continued for 2 hr, the mixture then being filtered and the resin washed with water. The combined filtrate and washings were concentrated *in vacuo* to a volume of *ca.* 30 ml and this aqueous solution was extracted with dichloromethane. On concentration, the extract afforded a syrup which was dissolved in benzene and placed on a column of silica gel (85 g). The column was successively eluted with benzene–ethyl acetate (1:1, 500 ml), ethyl acetate (250 ml), and methanol (200 ml), and the composition of the eluate was monitored by tlc (ethyl acetate). The ethyl acetate eluate and an early part of the methanol eluate yielded a single substance (2.01 g, 94%). The most concentrated 40-ml fraction in the ethyl acetate eluate gave a syrup: $[\alpha]^{20}D$ +15.8° (*c* 1.61, chloroform).

Anal. Calcd for $C_{19}H_{24}O_5$ (332.40): C, 68.65; H, 7.28. Found: C, 68.71; H, 7.54.

2,4-Di-O-benzyl-1,3-di-*O*-*p*-nitrobenzoyl-D-erythritol (6) from 1,3-Di-*O*-benzyl-L-ribitol (5).—A sample (345.8 mg) of **5** was oxidized with sodium metaperiodate in aqueous dioxane solution, the substance consuming 1.08 mol equiv of oxidant over the course of 3.7 hr. The product was extracted with dichloromethane and chromatographed on a column of silica gel (50 g) using dichloromethane (260 ml) and then ether (200 ml) for elution. Concentration of the ether eluate afforded a product (100 mg) which showed $[\alpha]^{20}D$ + 45.8° (*c* 0.48, chloroform). This material was reduced in aqueous dioxane solution with sodium borohydride and the product was chromatographed on a column of silica gel using dichloromethane and then ethyl acetate for elution. The major fraction obtained was *p*-nitrobenzoylated and then chromatographed on silica gel using benzene to give 2,4-di-*O*-benzyl-1,3-di-*O*-*p*-nitrobenzoyl-D-erythritol (**6**) as a syrup: yield 71 mg (11%); $[\alpha]^{20}D$ −51.2° (*c* 0.60, chloroform).

Anal. Calcd for $C_{32}H_{28}N_2O_{10}$ (600.59): C, 63.99; H, 4.70; N, 4.66. Found: C, 64.07; H, 4.74; N, 4.48.

Erythritol Tetrabenzoate (7) from 3,5-Di-*O*-benzyl-β-D-ribofuranose (4).—A sample (192.6 mg) of **4** was dissolved in dioxane (20 ml) and the solution was treated with 0.02 *M* sodium metaperiodate (20 ml). The mixture was stored at 20° for 16 hr and a further quantity (20 ml) of 0.02 *M* sodium metaperiodate solution was added. After 2 hr, the product was extracted with dichloromethane and the extract was washed with water and concentrated to yield a syrup (195.8 mg) which was deformylated by treatment (overnight) with 0.1 *N* barium methoxide in methanol (0.5 ml). The alkali was neutralized with carbon dioxide and the solution was concentrated to a residue which was dissolved in dioxane and treated with a solution of sodium borohydride (200 mg) in water (10 ml). The product was worked up in conventional fashion to yield a syrup (149 ml) which was dissolved in methanol and reduced with hydrogen in the presence of 10% palladium on charcoal. The catalyst and solvent were removed to give a residue which was benzoylated with benzoyl chloride in pyridine to give, after work-up, a crystalline mass. Recrystallized from ethanol, the product (100 mg, 32%) had mp 188–189° and mixture melting point with authentic erythritol tetrabenzoate, 188–190°. The infrared spectrum of the product was identical with that of authentic material.[5]

The Anomeric 3,5-Di-*O*-benzyl-1,2-di-*O*-*p*-phenylazobenzoyl-D-ribofuranoses (8).—A solution of *p*-phenylazobenzoyl chloride (2.53 g) in dry pyridine (25 ml) was added with stirring to **4** (1.55 g). After 16 hr at room temperature, the reaction mixture was treated with a few chips of ice and stirring continued for 0.5 hr. Dichloromethane was added and the resulting solution washed successively with water, 10% sulfuric acid, saturated aqueous sodium bicarbonate solution, and water. Moisture was removed with magnesium sulfate and the solution was concen-

(13) C. S. Hudson, *J. Amer. Chem. Soc.*, **31**, 66 (1909).

(14) F. W. Holly, C. H. Shunk, E. W. Peel, J. J. Cahill, J. B. Lavigne, and K. Folkers, *ibid.*, **74**, 4521 (1952).

(15) Melting points are corrected. Thin layer chromatography was conducted on silica gel GF_{254} (E. Merck AG, Darmstadt) using the solvent systems specified, components being detected under ultraviolet light and by charring after spraying with 10% sulfuric acid. Silica gel no. 7734 (0.05–0.20 mm) of E. Merck was used for column chromatography. Nmr spectra were obtained in $CDCl_3$ solution using a Varian A-60 spectrometer and tetramethylsilane as an internal standard.

(16) Hooker Chemical Corp., Niagara Falls, N. Y.

trated *in vacuo* to a syrup (3.43 g) which, from its solution in absolute ethanol (20 ml), afforded **β 8**: yield 3.08 g; mp 134–138°. One recrystallization from chloroform–ethanol gave the pure compound as needles (2.43 g, 69%), mp 145–147°; a second recrystallization did not alter the melting point: $[\alpha]^{20}D$ −64.8° and $[\alpha]^{20}_{6438}$ −48.1° (both *c* 1.6, dichloromethane), nmr singlet at τ 3.46 (H-1).

Anal. Calcd for $C_{45}H_{38}N_4O_7$ (746.84): C, 72.37; H, 5.13; N, 7.50. Found: C, 72.35; H, 5.01; N, 7.49.

On storage at +5° for 3 days, the chloroform–ethanol mother liquor from the first recrystallization of **β 8** deposited **α 8** as needles: yield 0.38 g (11%); mp 101–102° (the melting point of the substance was unchanged on recrystallization); $[\alpha]^{20}D$ +185° and $[\alpha]^{20}_{6438}$ +156° (both *c* 2.2 in dichloromethane); nmr doublet (4.2 Hz) centered at τ 3.19 (H-1).

Anal. Calcd for $C_{45}H_{38}N_4O_7$ (746.84): C, 72.37; H, 5.13; N, 7.50. Found: C, 72.31; H, 5.04; N, 7.20.

1,2-Di-*O*-benzoyl-3,5-di-*O*-benzyl-β-D-ribofuranose (β 9).—3,5-Di-*O*-benzyl-β-D-ribofuranose (**4**, 3.26 g) was added with stirring to a cold mixture of benzoyl chloride (5.6 g) and pyridine (30 ml). The resulting mixture was stored at 0° for 30 min and then at room temperature for 18 hr. It was worked up in the usual fashion to give a syrup which was dissolved in ether–ligroin (bp 100–115°) to give (at +5°) a crystalline product: yield 3.69 g (69%); mp 78–86°. Recrystallized from ether–ligroin, the pure product (3.02 g) had mp 87–89° (further recrystallization did not alter this value); $[\alpha]^{20}D$ +15.8° (*c* 1.7, dichloromethane) nmr singlet at τ 3.43 (H-1).

Anal. Calcd for $C_{33}H_{30}O_7$ (538.60): C, 73.59; H, 5.61. Found: C, 73.47; H, 5.78.

Condensation of 3,5-Di-*O*-benzyl-2-*O*-*p*-phenylazobenzoyl-D-ribofuranosyl Chloride (10) with 5,6-Dimethylbenzimidazole.—A stream of dry hydrogen chloride was passed for a period of 5 min into a solution of **β 8** (4.50 g) in dry dichloromethane (30 ml). The *p*-phenylazobenzoic acid which precipitated (1.23 g, 90%, mp 247–248°) was removed by filtration and the filtrate was concentrated *in vacuo* to a syrup from which benzene was distilled *in vacuo*. The **10** thus prepared was predominantly the β anomer as shown by a sharp singlet in its nmr spectrum at τ 3.78 (H-1); a barely discernible doublet (5 Hz), centered at τ 3.16 was attributed to the presence of a minor quantity of **α 10**. The syrupy halide was dissolved in dioxane (30 ml) which had been dried over Molecular Sieve 5A[17] and the solution was treated with powdered 5,6-dimethylbenzimidazole[18] (2.11 g). The reaction mixture was boiled under reflux for 2 hr, cooled, and filtered and the filtrate was concentrated *in vacuo* to a syrup. The crude product was dissolved in benzene (10 ml) and the solution was filtered and placed on a column of silica gel (720 g); elution with benzene–ether (9:1) yielded four fractions. Fraction 1, **2-benzyloxymethyl-4-*p*-phenylazobenzoyloxyfuran (13)**, was obtained as red needles from ligroin (bp 100–115°): 498 mg (20%); mp 94–96°; nmr signals at τ 5.52 and 5.41 (singlets, each 2 H, CH_2), 3.50 (singlet, 1 H, H-5), and 1.6–2.58 (10 H). The substance was optically inactive.

Anal. Calcd for $C_{25}H_{20}N_2O_4$: C, 72.80; H, 4.89; N, 6.79; mol wt, 412.46. Found: C, 73.03; H, 5.11; N, 6.71; mol wt, 413.[19]

Fraction 2 consisted of a red syrup, **3,5-di-*O*-benzyl-2-*O*-*p*-phenylazobenzoyl-D-ribofuranose (14**, 363 mg, 11%), which showed infrared absorption at 3400–3450 cm^{-1} (OH). *p*-Phenylazobenzoylation of a sample (100.4 mg) of this fraction led to the isolation of **β 8**, 124 mg (89%), mp and mmp 147–149°.

Fraction 3 was **1-(3,5-di-*O*-benzyl-2-*O*-*p*-phenylazobenzoyl-β-D-ribofuranosyl)-5,6-dimethylbenzimidazole (16)**, a red syrup: yield 2.44 g (61%), $[\alpha]^{20}D$ −83.6° (*c* 1.5, dichloromethane), nmr doublet (5 Hz) centered at τ 3.71 (H-1). From ether–pentane solution the syrup crystallized: mp 103–106°; $[\alpha]^{20}D$ −93.5° (*c* 1.5, dichloromethane).

Anal. Calcd for $C_{41}H_{38}N_4O_5$ (666.79): C, 73.85; H, 5.74; N, 8.40. Found: C, 73.56; H, 5.67; N, 8.45.

A portion of the syrupy **16** (198.4 mg) was converted into a crystalline picrate: yield 245.1 mg (92%); mp 196–198° (from chloroform–ethanol); $[\alpha]^{20}D$ −47.5° and $[\alpha]^{20}_{6438}$ −40.9° (both *c* 1.2, dichloromethane).

Anal. Calcd for $C_{47}H_{41}N_7O_{12}$ (895.90): C, 63.01; H, 4.61; N, 10.94. Found: C, 63.24; H, 4.46; N, 11.13.

Fraction 4 was **1-(3,5-di-*O*-benzyl-2-*O*-*p*-phenylazobenzoyl-α-D-ribofuranosyl)-5,6-dimethylbenzimidazole (21)**, a red syrup: yield 397.1 mg (10%); $[\alpha]^{20}D$ −138.4° and $[\alpha]^{20}_{6438}$ −111.9° (both *c* 2.65, dichloromethane). From ether solution this material crystallized. It was recrystallized from ether–pentane and from ethanol–pentane: mp 113–114°, $[\alpha]^{20}D$ −164° (*c* 1.26, dichloromethane); nmr doublet (6 Hz) centered at τ 3.55 (H-1).

Anal. Calcd for $C_{41}H_{38}N_4O_5$ (666.79): C, 73.85; H, 5.74. Found: C, 73.90; H, 5.95.

A similar condensation of **10** with 5,6-dimethylbenzimidazole in dioxane solution which was not heated but allowed to proceed at room temperature for 72 hr, gave the following yields: **13**, 52%, **16**, 32%, and **21**, 9%.

Condensation of 2-*O*-Benzoyl-3,5-di-*O*-benzyl-D-ribofuranosyl Chloride (11) with 5,6-Dimethylbenzimidazole.—A stream of hydrogen chloride was passed into a solution of **β 9** (1.05 g) in dry dichloromethane (25 ml) for a period of 5 min and the reaction mixture was then stored at room temperature for 30 min. The solution was concentrated *in vacuo* and benzene was distilled *in vacuo* several times from the residual syrup in order to remove the excess of hydrogen chloride. The nmr spectrum of the chloride included a sharp singlet at τ 3.88 (H-1 of **β 11**); no signal attributable to **α 11** was detected. The syrupy chloride (**11**) was dissolved in dioxane (30 ml), 5,6-dimethylbenzimidazole[18] (1.14 g) was added, and the solution was boiled under reflux for 2 hr. The cooled solution was filtered, the residue being washed with benzene; solvent was removed *in vacuo* from the combined filtrate and washings and the residue was largely dissolved in benzene. After filtration, the benzene solution was applied to a column of silica gel (250 g) which was then eluted with benzene–ether (5:1).

Fraction 1 consisted of **β 9** (469 mg, 45%); its infrared spectrum and behavior on tlc (ether–pentane, 2:3) served for identification. Fraction 2 was obtained as a syrup (46.3 mg, 5%); on benzoylation, the material afforded **β 9** in 73% yield and it was, therefore, probably **2-*O*-benzoyl-3,5-di-*O*-benzyl-D-ribofuranose (15)**. Fraction 3 consisted of **1-(2-*O*-benzoyl-3,5-di-*O*-benzyl-β-D-ribofuranosyl)-5,6-dimethylbenzimidazole (17)**, a syrup (530 mg, 48%). Some of this (292 mg) was converted into the crystalline picrate: yield 364 mg (89%); mp 165–167°; $[\alpha]^{20}D$ −8.9° (*c* 0.84, dichloromethane).

Anal. Calcd for $C_{41}H_{37}N_5O_{12}$ (791.79): C, 62.19; H, 4.71; N, 8.85. Found: C, 62.15; H, 4.50; N, 8.75.

In order to obtain pure **17**, its picrate (427 mg) was dissolved in chloroform (100 ml) and the solution was twice shaken with saturated aqueous sodium bicarbonate solution. Moisture was removed from the chloroform solution with magnesium sulfate and the solution was concentrated *in vacuo* to give pure **17**: yield 306 mg; $[\alpha]^{20}D$ −9.0° (*c* 1.2, dichloromethane); nmr signal (doublet, 4.6 Hz) centered at τ 3.74 (H-1).

1-(2-*O*-Benzoyl-β-D-ribofuranosyl)-5,6-dimethylbenzimidazole (18).—Palladium black, freshly prepared from palladium oxide (120 mg), was added to a solution of **17** (512 mg) in methanol (20 ml) and the suspension was shaken with hydrogen until absorption of the gas ceased. After removal of the catalyst, the solution was chilled to give **18** (147 mg, 42%) as needles, mp 225–227°. Recrystallization from ethyl acetate afforded pure **18**: yield 140 mg; mp 228–230°; $[\alpha]^{20}D$ −76.4° (*c* 0.61, methanol).

Anal. Calcd for $C_{21}H_{22}N_2O_5$ (382.41): C, 65.95; H, 5.80; N, 7.33. Found: C, 66.22; H, 5.55; N, 7.45.

Benzoylation of **18** (22.8 mg), using benzoyl chloride in pyridine, gave β-ribazole tribenzoate (**19**) which was separated as its picrate: yield 32.5 mg (67%); mp 162–163°; mixture melting point with authentic material,[1] 161–162°. The infrared spectrum of the product was identical with that of an authentic specimen.

1-(3,5-Di-*O*-benzyl-β-D-ribofuranosyl)-5,6-dimethylbenzimidazole (20) and 1-(2-*O*-Benzoyl-3,5-di-*O*-benzyl-β-D-ribofuranosyl)-5,6-dimethylbenzimidazole (17) from 1-(3,5-Di-*O*-benzyl-2-*O*-*p*-phenylazobenzoyl-β-D-ribofuranosyl)-5,6-dimethylbenzimidazole (16).—A specimen (493 mg) of **16** was deacylated at room temperature with methanolic barium methoxide in normal fashion. After neutralization of the reaction mixture with carbon dioxide and removal of the methanol, the product was chromatographed on a column of silica gel (100 g). Elution with ether removed the methyl *p*-phenylazobenzoate; elution with methanol gave the desired product (**20**, 333 mg, 98%). A portion of this (110

(17) Fisher Scientific Co.

(18) 5,6-Dimethylbenzimidazole (Aldrich Chemical Co., Milwaukee, Wis.) was sublimed *in vacuo* (0.3 mm and 190° bath) and then recrystallized from ethanol.

(19) Determined with a vapor pressure osmometer, model 301A, Mechrolab, Inc., Mountain View, Calif.

mg) was converted into a crystalline picrate: yield 139 mg (84%); mp 142–143°; $[\alpha]^{20}D$ −5.4° (*c* 1.75, dichloromethane).

Anal. Calcd for $C_{34}H_{33}N_5O_{11}$ (687.67): C, 59.38; H, 4.84; N, 10.18. Found: C, 59.61; H, 4.94; N, 10.27.

Another portion (100.2 mg) of **20** was benzoylated with benzoyl chloride and pyridine to give a colorless syrup (122 mg, 99%) which was converted into the picrate (160 mg, 93%): mp 165–167°. A mixture melting point with the picrate of **17**, prepared through the condensation of **11** with 5,6-dimethylbenzimidazole, was undepressed.

Condensation of 3,5-Di-*O*-benzyl-D-ribofuranosyl Chloride (12) with 5,6-Dimethylbenzimidazole.—To a solution of 3,5-di-*O*-benzyl-β-D-ribofuranose (**4**, 1.056 g) in dichloromethane (10 ml) was added anhydrous magnesium sulfate and a solution of hydrogen chloride (82 mg) in dichloromethane (10 ml). After storage at room temperature for 6 min, the reaction mixture was filtered and the filtrate was concentrated *in vacuo* to a syrup which was dissolved in dichloromethane (20 ml). 5,6-Dimethylbenzimidazole[18] (1.084 g) was added and the mixture was stirred at room temperature for 2 hr. After filtration, the solution was washed successively with 3 *N* sulfuric acid, saturated aqueous sodium bicarbonate solution, and water. Moisture was removed with sodium sulfate and the solution concentrated *in vacuo*. The resulting product was treated with benzoic anhydride (1.8 g) and pyridine (10 ml) and the solution was held at 70–75° for 16 hr. A little ice was added and the mixture was stored at room temperature for 1 hr to decompose the excess of benzoic anhydride. The reaction mixture was worked up in conventional fashion to yield a syrup which was chromatographed on an 8 in. × 8 in. plate of silica gel using ether. Inspection of the chromatogram under ultraviolet light showed a major component of R_f *ca.* 0.5; this material was extracted with alcohol and the extract treated with picric acid (1.5 g) to give the picrate of **17**: yield 439 mg (17%); mp 164–165°; mmp 165–166°. The alcoholic filtrate was concentrated *in vacuo* to a syrup which was dissolved in chloroform and the solution was washed with aqueous sodium bicarbonate solution until the picric acid had been removed. After drying with sodium sulfate, the solution was concentrated *in vacuo* to give a pale yellow syrup (167 mg) which was chromatographed on six 8 in. × 8 in. plates of silica gel using ether. The slower moving component was extracted with alcohol and the solvent removed to give **1-(2-*O*-benzoyl-3,5-di-*O*-benzyl-α-D-ribofuranosyl)-5,6-dimethylbenzimidazole** (**22**) as a syrup: yield 108 mg (6%); $[\alpha]^{20}D$ −26.7° (*c* 1.0, dichloromethane); infrared absorption at 1724 (C=O) but none between 3125 and 4000 cm^{-1} (OH); the nmr spectrum included a singlet at τ 7.67 (6 H, 2 CH_3), a triplet at 6.37 (2 H, H-3 and H-4), a multiplet at 5.3 (6 H, CH_2 of benzyl groups, H-5 and H-5′), a triplet at 4.12 (1 H, H-2), and a doublet at 3.53 (1 H, 5.3 Hz, H-1).

Attempt to Convert 21 into 22.—The syrupy **21** (397 mg) was deacylated in normal fashion using methanolic barium methoxide (0.1 *N*, 3 ml) diluted with methanol (20 ml) at room temperature. Thin layer chromatography (ether) after 18 hr showed that the methanolysis was complete. The base was neutralized with carbon dioxide and the mixture concentrated *in vacuo* to dryness. The methyl *p*-phenylazobenzoate was removed by chromatography on a column of silica gel using ether and the colorless product was dissolved in a mixture of benzoyl chloride (0.8 ml) and pyridine (5 ml). The mixture was held at 70° for 16 hr and then worked up in normal fashion to give a crude product which was chromatographed on a column of silica gel to yield **1-benzoyl-5,6-dimethylbenzimidazole**: yield 137 mg (92%); mp and mmp 132–134°. An authentic specimen of the compound was prepared as follows. A solution of 5,6-dimethylbenzimidazole (121.8 mg) in pyridine (2 ml) was treated with benzoyl chloride and stored at room temperature for 16 hr. The cautious addition of water then precipitated a crystalline product: yield 170.9 mg (85%); mp 128–132°. One recrystallization from ethanol afforded needles, mp 132–134°; a second recrystallization did not alter this value.

Anal. Calcd for $C_{16}H_{14}N_2O$ (250.31): C, 76.78; H, 5.64; N, 11.19. Found: C, 77.01; H, 5.48; N, 11.13.

Registry No.—**3**, 16054-76-5; **4**, 16504-77-6; **5**, 16054-78-7; **6**, 16054-79-8; **7**, 16054-80-1; **8α**, 16054-81-2; **8β**, 16054-82-3; **9β**, 16054-83-4; **10β**, 16109-41-4; **13**, 16054-84-5; **14**, 16109-42-5; **16**, 16054-99-2; **16** picrate, 16109-43-6; **17**, 16109-44-7; **17** picrate, 16054-85-6; **18**, 16054-86-7; **20** picrate, 16054-87-8; **21**, 16109-45-8; **22**, 16054-88-9; 1-benzoyl-5,6-dimethylbenzimidazole, 16109-46-9.

Acknowledgment.—We are indebted to the staff of the Section on Microanalytical Services and Instrumentation of this institute for elemental analyses and nmr spectra. We also wish to thank Dr. D. Jerina of this institute for assistance in obtaining the nmr spectrum of **21**.