ml.) was then added and the mutarotation observed at 20°. The specific rotations and first-order rate constants are given in Table III. Based on an average rate of 0.00016, the "half-life" of the reaction was 1881 min.

When mutarotation had ceased, the solvent was removed *in vacuo* to give a sirup which was crystallized from ethyl acetate–pentane. The short, colorless needles thus obtained were recrystallized from the same solvent mixture 0.2 g. (66%), m.p. 133–135°, $[\alpha]^{20}D$ +145.4° → +102.5° (methanol, *c* 1.27). These values agree with those reported earlier in this paper for 2-*O*-benzoyl-β-L-arabinopyranose.

Acknowledgment.—We are indebted to Mr. Harry W. Diehl for the preparation of some starting materials. Analyses were performed by the Analytical Services Unit of this laboratory under the direction of Mr. H. G. McCann.

Syntheses with Partially Benzylated Sugars. III.[1] A Simple Pathway to a "*cis*-Nucleoside," 9-β-D-Arabinofuranosyladenine (Spongoadenosine)

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Condensation of 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride with methanol leads predominantly to methyl 2,3,5-tri-*O*-benzyl-β-D-arabinofuranoside. Condensation of the same halide with N-benzoyladenine and subsequent removal of the protecting groups readily gives 9-β-D-arabinofuranosyladenine, a type of glycoside which is difficultly accessible by other means.

The most generally applicable method for the synthesis of glycosides is that which Koenigs and Knorr[3] devised over sixty years ago. However, the condensation of a fully acylated glycosyl halide with a potential aglycon is normally a limited process in the sense that it leads to a product in which the aglycon is *trans* to the acyloxy group at C-2. With an acylated glycosyl halide bearing a halogen at C-1 *cis* to an acyloxy group at C-2, simple inversion predominates; with a *trans*-halide, participation of the acyloxy group at C-2 in the displacement of the halogen results either in no net inversion or formation of an ortho ester derivative.

A wide variety of special methods have been devised for the synthesis of 1,2-*cis*-glycosides. Two of these methods deserve particular attention. In the first, the configuration of C-2 in a *trans*-glycoside is inverted by one means or other. The ingenious synthesis of 9-β-D-arabinofuranosyladenine (V) from 9-β-D-xylofuranosyladenine, described by Reist, Benitez, Goodman, Baker, and Lee,[4] illustrates this approach. A second method involves the use of a glycosyl halide in which the hydroxyl group at C-2 is masked with a group which does not participate in the displacement of the halogen at C-1. The synthesis of the *cis*-linked disaccharide isomaltose (6-*O*-α-D-glucopyranosyl-D-glucose) through 3,4,6-tri-*O*-acetyl-2-*O*-nitro-β-D-glucopyranosyl chloride by Wolfrom, Pittet, and Gillam[5] is of this type.

While the two aforementioned methods are eminently successful in some sugar series, their success depends, ultimately, on selective substitutions at C-2 of aldose derivatives; such selective substitution always involves a number of steps and is not practicable with some aldoses. The concept of using a glycosyl halide, *fully* substituted with the nonparticipating benzyl group has many attractive features inasmuch as hydroxyl groups are readily masked as benzyl ethers and the benzyl groups readily cleaved by catalytic hydrogenation. Exploratory work by Barker and Fletcher[6] recently showed that 2,3,5-tri-*O*-benzyl-D-ribofuranosyl and 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl bromides could be prepared, albeit only as highly reactive sirups. We wish now to describe the preparation of the more stable 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride (III) and the studies of this substance which have led to the practicable synthesis of a 1,2-*cis*-nucleoside.

2,3,5-Tri-*O*-benzyl-β-D-arabinofuranose (I), readily preparable from D-arabinose by the improved procedure which Tejima and Fletcher[1] described for its enanthiomorph, was converted into 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride (III) either directly with hydrogen chloride in the presence of a desiccant or indirectly through the action of hydrogen chloride on a mixture of anomers of 2,3,5-tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-D-arabinofuranose (II).[7] The chloride III proved to be a nearly colorless sirup, markedly more stable than the corresponding bromide.[6] On condensation with methanol in the presence of sodium methoxide, it afforded a sirupy mixture of the anomeric methyl 2,3,5-tri-*O*-benzyl-D-arabinofuranosides; vapor phase chromatography showed that the β-anomer (a 1,2-*cis*-glycoside) predominated.

In order to ascertain whether other β-D-arabinofuranosides could be made by this process, a purine[8] was used as an aglycon since there is considerable current interest in the biochemical properties of nucleosides containing the β-D-arabinofuranosyl moiety,[9] and adequate special

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(2) Visiting Associate of the Public Health Service, 1962–1963.

(3) W. Koenigs and E. Knorr, *Sitzber. Math. Naturw. Kl. Bayer. Akad. Wiss. Muenchen*, **30**, 108 (1900); *Ber.*, **34**, 957 (1901).

(4) E. J. Reist, A. Benitez, L. Goodman, B. R. Baker, and W. W. Lee, *J. Org. Chem.*, **25**, 3274 (1962).

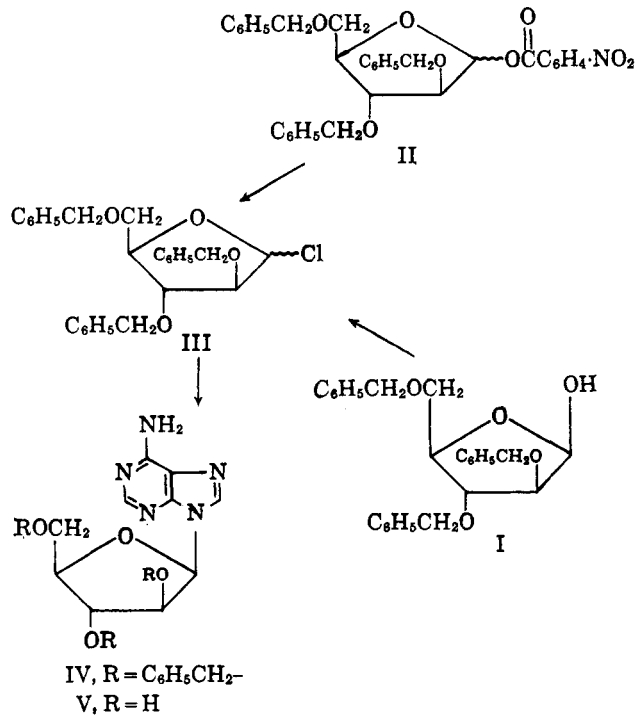
(5) M. L. Wolfrom, A. O. Pittet, and I. C. Gillam, *Proc. Natl. Acad. Sci. U. S.*, **45**, 700 (1961).

(6) R. Barker and H. G. Fletcher, Jr., *J. Org. Chem.*, **26**, 4605 (1961).

(7) It should be noted, however, that the 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride (III) differed in certain properties depending upon whether it was prepared from I or II. The available evidence appears to indicate that this difference arises from differing proportions of anomers in the two preparations of III; see the Experimental.

(8) The suggestion that adenine be used as first made to us by Professor B. R. Baker.

(9) M. Hubert-Habart and S. S. Cohen, *Biochim. Biophys. Acta*, **59**, 468 (1962); H. Tono, *J. Biol. Chem.*, **237**, 1271 (1962); M. G. Chu and G. A. Fischer, *Biochem. Pharmacol.*, **11**, 423 (1962); G. E. Underwood, *Proc. Soc. Exp. Biol. Med.*, **111**, 660 (1962); R. W. Talley and V. K. Vaitkevicius, *Blood*, **21**, 352 (1963); J. J. Brink and G. A. LePage, *Federation Proc.*, **22**, 184 (1963); G. A. LePage and I. G. Junga, *Cancer Res.*, **23**, 739 (1963); S. S. Cohen, *Perspectives Biol. Med.*, **6**, 215 (1963).



methods are available for the synthesis of pyrimidine β-D-arabinofuranosides.[10]

Condensation of 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride (III) with a twofold excess of N-benzoyladenine, followed by alkaline N-debenzoylation, led to the isolation in 46% yield of a crystalline tri-*O*-benzylpentosyladenine which was further characterized as its crystalline picrate. Reductive hydrogenolysis of the tri-*O*-benzylpentosyladenine over palladium black afforded 9-β-D-arabinofuranosyladenine (V), identical with a sample kindly provided by Dr. Leon Goodman.[4] Investigation of the mother liquor afforded chromatographic evidence for the formation of the anomeric nucleoside, 9-α-D-arabinofuranosyladenine, in very low yield. The mother liquor also yielded a substantial quantity of methyl 2,3,5-tri-*O*-benzyl-D-arabinofuranoside. Although the initial condensation had been conducted for one week at room temperature in the presence of a solid acid acceptor (molecular sieve) and of an excess of N-benzoyladenine, the isolation of the methyl glycoside may indicate that some 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride had survived to react with the barium methoxide used for the N-debenzoylation.

Discussion

While all benzylated glycosyl halides thus far prepared have been amorphous, it seems reasonable to assume that the proportions of anomeric forms in any one case are roughly those which are encountered with the corresponding acylated glycosyl halide. With both the 2,3,5-tri-*O*-benzoyl-D-arabinofuranosyl bromides[11] and 2,3,5-tri-*O*-benzoyl-L-arabinofuranosyl chlorides[12] the α-anomer greatly predominates. We might expect, therefore, that III is largely 2,3,5-tri-*O*-benzyl-α-D-arabinofuranosyl chloride and hence methyl 2,3,5-tri-*O*-benzyl-β-D-arabinofuranoside and IV are formed *via* Walden inversion at C-1. If this view were correct, one might predict that the synthetic pathway described here would be especially suitable for the synthesis of *cis*-glycosides from those sugars in which the dominant halide is *trans*. Furthermore, exploratory experiments appear to show that the proportion of anomeric products obtained from a given halide (lacking participating groups) may be modified through the use of appropriate reaction conditions,[13] suggesting the possibility that any desired anomer may be preparable from a given halide. A study of the mechanism of the displacement of halogens in glycosyl halides lacking participating groups is currently being pursued in this laboratory.

(10) J. J. Fox and I. Wempen, *Advan. Carbohydrate Chem.*, **14**, 238 (1959).

(11) R. K. Ness and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, **80**, 2007 (1958).

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Experimental[14]

2,3,5-Tri-*O*-benzyl-D-arabinofuranosyl Chloride (III). (A) From the 2,3,5-Tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-D-arabinofuranoses (II).—A mixture of the anomeric forms of 2,3,5-tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-D-arabinofuranoses[6] ($[\alpha]^{20}D$ +6° in CH_2Cl_2, m.p. 70–79°, 0.3038 g.) which had been dried *in vacuo* at 50° was added to 7 ml. of a solution of hydrogen chloride in dichloromethane (0.31 *N*) which had been cooled to 0°. After standing at 0° for 2 hr., the reaction mixture was filtered, a nearly quantitative yield of *p*-nitrobenzoic acid being consistently recovered (the infrared spectrum being identical with authentic *p*-nitrobenzoic acid). On concentration *in vacuo* at room temperature, the filtrate gave a nearly colorless oil which was held in high vacuum over solid sodium hydroxide for 40 min.; the specific rotation of III, prepared in this fashion, varied from $[\alpha]^{20}D$ +91.1 to +96° (CH_2Cl_2, *c* 1.25). A portion (0.149 g.) of this chloride was dissolved in 5 ml. of benzene and the solution treated with a mixture of 3 ml. of benzene and 2 ml. of sodium methoxide in methanol (0.86 *N*). A white precipitate became visible after 15 sec.; after 5 hr. the reaction mixture was washed with four portions of water, dried over magnesium sulfate, filtered, and concentrated to a sirup which showed $[\alpha]^{20}D$ −52.6° (CH_2Cl_2, *c* 2.0).

Anal. Calcd. for $C_{27}H_{30}O_5$ (434.51): OCH_3, 7.14. Found: Found: OCH_3, 7.01.

Gas chromatography[15] showed the mixture to contain two components. The minor one cochromatographed with an authentic sample of methyl 2,3,5-tri-*O*-benzyl-α-L-arabinofuranoside[6]; it is assumed that the major peak is the β-anomer. Based on the heights of the peaks, the mixture consisted of 98.3% of the β-anomer of 1.7% of the α-anomer.

(B) From 2,3,5-Tri-*O*-benzyl-β-D-arabinofuranose (I).—2,3,5-Tri-*O*-benzyl-β-D-arabinofuranose (1.00 g.), prepared by the improved procedure for its enantiomorph described by Tejima and Fletcher,[1] was dissolved in 60 ml. of benzene which had been saturated with hydrogen chloride at room temperature. Anhydrous magnesium sulfate (5 g.) was added and the reaction mixture left at room temperature (with occasional shaking) for 2.5 hr., when the rotation had become constant. After filtration the solution was concentrated *in vacuo* and the residual sirup held briefly in high vacuum over solid sodium hydroxide; $[\alpha]^{20}D$ +72.5° (CH_2Cl_2, *c* 1.25).[16] The infrared spectrum of the sirup showed no hydroxyl absorption. A sample of the chloride (0.184 g.) was dissolved in 7.5 ml. of benzene and the solution treated with a mixture of 3 ml. of 1 *N* sodium methoxide in methanol and

(13) For instance, condensation of 2,3,5-tri-*O*-benzyl-D-arabinofuranosyl chloride (III) with chloromercuri-N-benzoyladenine in dimethyl sulfoxide solution yields (after deblocking) a product which, on the basis of paper chromatographic behavior in acetone–water (95:5), appears to consist of the two anomeric 9-D-arabinofuranosyl-adenines in approximately equal quantities.

(14) Melting points are corrected.

(15) SE 30 (1.5%) on 100–400 Chromosorb W, silanized, was used at 260°, together with a flame ionization detector.

(16) When prepared by this method, III was uniformly found to have a lower specific rotation than when made from II. In another preparation dichloromethane was used in place of benzene, giving III with a rotation of $[\alpha]^{20}D$ +73° (CH_2Cl_2) and, thence, methyl 2,3,5-tri-*O*-benzyl-D-arabinofuranoside with a methoxyl content of 7.18% and $[\alpha]^{20}D$ −41.3° (CH_2Cl_2). Use of III made from I gave poor yields of IV and the product thus obtained proved difficult to purify.

4 ml. of benzene. There was thus obtained a sirup which showed $[\alpha]^{20}D$ −39.3° (CH_2Cl_2, *c* 3.05).

Anal. Calcd. for $C_{27}H_{30}O_5$ (434.51): OCH_3, 7.14. Found: OCH_3, 7.36.

Gas chromatography[15] showed the sirup to consist of methyl 2,3,5-tri-*O*-benzyl-α-D-arabinofuranoside (15.6%) and its β-anomer (84.4%).[17] Using the previous numerical data and the specific rotation (with changed sign) which Barker and Fletcher[6] reported for methyl 2,3,5-tri-*O*-benzyl-α-L-arabinofuranoside ($[\alpha]^{20}D$ −44.6° in CH_2Cl_2), one may calculate the specific rotation of methyl 2,3,5-tri-*O*-benzyl-β-D-arabinofuranoside. Based on the mixture obtained in A, this value is $[\alpha]^{20}D$ −54.3°; the data obtained from B give a value of $[\alpha]^{20}D$ −54.9°.

9-(2,3,5-Tri-*O*-benzyl-β-D-arabinofuranosyl)adenine (IV).—Ten grams of a thoroughly dried mixture of the two anomeric forms of 2,3,5-tri-*O*-benzyl-1-*O*-*p*-nitrobenzoyl-D-arabinofuranose was added to 165 ml. of dichloromethane which had been saturated with anhydrous hydrogen chloride at 0°. After 2 hr. at 0°, the precipitate of *p*-nitrobenzoic acid (2.845 g., 97%) was removed by filtration and the solution concentrated *in vacuo* to a nearly colorless sirup which was held at 0.08 mm. and room temperature for 2 hr., $[\alpha]^{20}D$ +91.1° (CH_2Cl_2, *c* 2.27). The chloride was then dissolved in 100 ml. of dry dichloromethane and the solution added to a mixture of dried N-benzoyladenine (9 g., 2.14 moles/mole of II) and molecular sieve (29 g.).[18] The reaction mixture was stirred at room temperature in a glass-stoppered flask for 1 week, filtered through a layer of Celite, and concentrated *in vacuo* to a sirup (10.2 g.) which was dissolved in 100 ml. of methanol. Barium methoxide (0.9 *N*, 85 ml.) was added and the solution boiled under reflux for 5 hr. to give a dark solution which was neutralized with carbon dioxide and filtered. Solvent was removed from the filtrate and the semisolid mass was extracted with dichloromethane, the insoluble material being removed by centrifugation and then thoroughly washed. The combined extract and washings (350 ml.) were diluted with cyclohexane (450 ml.), filtered through Celite, and boiled in an open flask until the vapor temperature had risen to 70° when crystallization began spontaneously. The solution was allowed to cool slowly to give a mass of fine needles (5.20 g.). One recrystallization from 5.2 parts of warm isopropyl alcohol gave nearly pure 9-(2,3,5-tri-*O*-benzyl-β-D-arabinofuranosyl)-adenine, 4.38 g., 46%, m.p. 125–128°, $[\alpha]^{20}D$ +21.8° (CH_2Cl_2, *c* 2.0). Two further recrystallizations from isopropyl alcohol raised the melting point to 128–129° but did not change the specific rotation.

Anal. Calcd. for $C_{31}H_{31}N_5O_4$ (537.60): C, 69.25; H, 5.81; N, 13.03. Found: C, 69.40; H, 6.03; N, 12.85.

A sample of IV (50 mg.) was dissolved in 1 ml. of ethanol and to this solution was added 4 ml. of a 4% ethanolic solution of picric acid. The precipitate (73 mg.) was recrystallized from boiling ethanol–acetone (3:2, 30 ml.) to give flat yellow needles of **IV picrate**, 64.1 mg. (90%), m.p. 196–199°, $[\alpha]^{20}D$ +29 7° (CH_2Cl_2, *c* 0.45).

Anal. Calcd. for $C_{37}H_{34}N_8O_{11}$ (766.70): C, 57.95; H, 4.47; N, 14.61. Found: C, 58.06; H, 4.63; N, 14.89.

The original mother liquor from the preparation of IV was concentrated to a sirup which was chromatographed on 100 g. of Mallinckrodt 100-mesh silicic acid. Succesive elution with benzene–ether (95:5), benzene–ether (70:30), ether, and acetone led to the recovery of a total of 2.06 g. of material. One fraction (eluted with benzene–ether, 95:5) (976 mg.) showed the infrared spectrum and gas chromatographic behavior[15] expected of a mixture of the anomeric methyl 2,3,5-tri-*O*-benzyl-D-arabinofuranosides; the yield was 13%.

Anal. Calcd. for $C_{27}H_{30}O_5$ (434.51): OCH_3, 7.14. Found: OCH_3, 7.21.

A sample was hydrolyzed using the technique of Tejima and Fletcher[1] to give, from a mixture of isopropyl and ethyl ethers, needles, m.p. 75–79°, $[\alpha]^{20}D$ +12.7° (final, *c* 1.1, dioxane–water, 9:1, containing a trace of ammonia). An equilibrium value of $[\alpha]^{20}D$ −11.6° has been recorded[1] for 2,3,5-tri-*O*-benzyl-L-arabinofuranose under these conditions.

Another fraction (281 mg.), eluted from the silicic acid column with acetone, was hydrogenated over palladium black and then chromatographed on paper using acetone–water (95:5); two components were observed (under ultraviolet light), migrating at the same rates as authentic samples of the two anomeric 9-D-arabinofuranosyladenines.

9-β-D-Arabinofuranosyladenine (V).—Palladium chloride (300 mg.) was suspended in 150 ml. of methanol and reduced by shaking with hydrogen at room temperature. To the acidic suspension was then added a solution of 300 mg. of 9-(2,3,5-tri-*O*-benzyl β-D-arabinofuranosyl)adenine in 50 ml. of methanol. The reaction mixture was shaken with hydrogen until absorption of the gas was complete (100 min.). After the catalyst had been removed, the solution was passed through a column of Dowex 2-X8 (HCO_3^-) and concentrated *in vacuo* to a sirup (159 mg.) which crystallized on rubbing with water. Recrystallization from 12 ml. of hot water afforded the pure nucleoside, 148 mg. (93%, anhydrous basis), m.p. 258–260°, $[\alpha]^{20}D$ −1.7° (pyridine, *c* 0.54), λ_{max}^{EtOH} 258 mμ. The product did not depress the melting point of a sample of 9-β-D-arabinofuranosyladenine synthesized from 9-β-D-xylofuranosyladenine[4]; the infrared spectra and chromatographic behavior of the two samples were identical. The analytical sample was dried *in vacuo* at 100° overnight, losing 5.6% of its weight.

Anal. Calcd. for $C_{10}H_{13}N_5O_4$ (267.24): C, 44.94; H, 4.90; N, 26.21. Found: C, 45.06; H, 4.98; N, 26.09.

The nucleoside (26.1 mg., the analytical sample) was dissolved in hot water (2.50 ml.) and, after cooling (with partial crystallization), was treated with 0.60 ml. of 0.245 *M* sodium metaperiodate. It was left in the dark 4 days with intermittent shaking. Excess periodate was removed by the addition of barium chloride (24.5 mg.) followed by filtration. Ten milligrams of sodium borohydride was added to the filtrate, followed after 2 hr. by 3 drops of glacial acetic acid. The specific rotation of the solution of 2-*O*-[1-(9-adenyl)-2-(hydroxy)ethyl]glycerol (based on weight of the starting material) was $[\alpha]^{20}D$ +66°. When adenosine was oxidized and reduced in identical fashion, the resulting solution had $[\alpha]^{20}D$ +61°.

Oxidation and reduction of 9-α-D-ribofuranosyladenine, leading to a product with $[\alpha]^{20}D$ −66°, has been reported.[19]

Acknowledgment.—We are indebted to Dr. John A. Montgomery for the gift of a sample of authentic 9-α-D-arabinofuranosyladenine, to Mr. Harry W. Diehl for assistance in the preparation of 2,3,5-tri-O-benzyl-β-D-arabinofuranose, and to the Analytical Services Unit of this laboratory, under the direction of Mr. H. G. McCann, for analyses.

(17) The higher proportion of α-anomer found here suggests that III, prepared from I as described previously, contains a higher proportion of the β-anomer than is the case when it is prepared from II. This conclusion is supported by the fact that III is less dextrorotatory when prepared from I than when prepared from II.

(18) Type 4A, 1/16-in. pellets, Fisher Scientific Co.

(19) R. S. Wright, G. M. Tener, and H. G. Khorana, *J. Am. Chem. Soc.* **80**, 2006 (1958).