The Reaction of O-Benzylidene Sugars with N-Bromosuccinimide. III. Applications to the Synthesis of Aminodeoxy and Deoxy Sugars of Biological Importance[1a]

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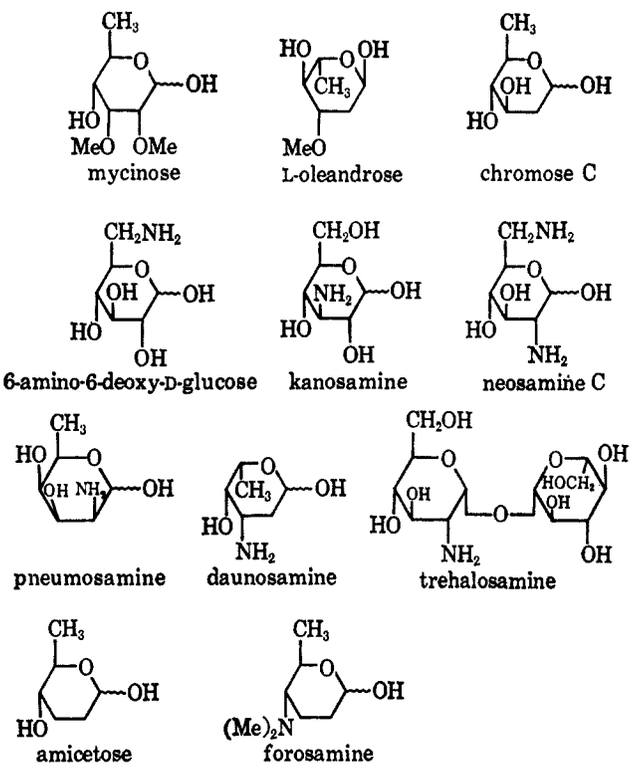
Application of the acetal ring-opening reaction of appropriately substituted methyl 4,6-*O*-benzylidene-hexopyranosides with *N*-bromosuccinimide leads to the corresponding methyl 4-*O*-benzoyl-6-bromo-6-deoxy-hexopyranosides. These products are intermediates for the synthesis of selectively benzoylated polyfunctional carbohydrate derivatives.

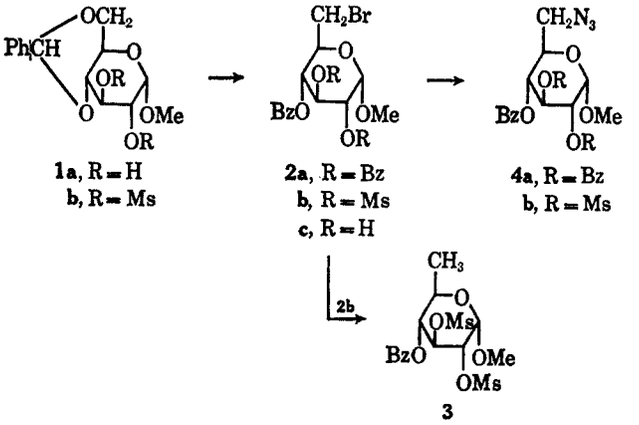
In the preceding publication[2] we described details of the reaction of various methyl 4,6-*O*-benzylidene-hexopyranosides with *N*-bromosuccinimide and showed that several of the protecting groups commonly used in carbohydrate chemistry were compatible with the reaction conditions. In this paper we wish to further demonstrate the synthetic utility of the reaction of *O*-benzylidene acetals with NBS by the synthesis of precursors to some biologically derived sugars.[3,4] Many of these are hexoses in which one, two, or more of the hydroxyl groups are replaced with an amino group or simply by hydrogen. Other types include hexoses which contain both amino and deoxy functions. Scheme I shows a list of sugars of established structure and stereochemistry which are derived from various antibiotics and other biological substances, and are pertinent to the present discussion. All of the listed sugars in Scheme I have been synthesized by conventional methods.[4] An examination of the structures will show some common pattern of substitution which interestingly enough, cannot be correlated by biogentic considerations, since closely related structural types have been found in widely different groups of antibiotics. It is apparent, however, that the majority of these uncommon sugars are 6-deoxyhexopyranoses with varied degrees of substitution in the ring, by amino (alkylamino, etc) or hydrogen (as in dideoxy sugars, etc). By the proper selection of 4,6-*O*-benzylidene intermediates containing suitably protected hydroxyl groups, it should be possible to introduce a potential amino or deoxy function at C-6 by application of the NBS reaction. The subsequent introduction of other desired functional groups in the hexopyranose ring would utilize well-established procedures. Thus, for the direct synthesis of 2,6-, 3,6-, or 2,3,6-substituted hexopyranose derivatives, a suitable choice for starting material would be the corresponding 4,6-*O*-benzylidene-glycosides.

Scheme I



The synthesis of crystalline methyl 6-azido-2,3,4-tri-*O*-benzoyl-6-deoxy-α-D-glucopyranoside **4a** was effected from **2a** by displacement with azide ion in N,N-dimethylformamide (Scheme II). Compound **4a** is a

Scheme II



(1) (a) Portions of this work were presented at the 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, D29, and the 154th National Meeting, Chicago, Ill., Sept 1967, D16. For part I, see S. Hanessian, *Carbohydrate Res.*, **2**, 86 (1966). (b) To whom correspondence should be addressed at the Department of Chemistry, University of Montreal, Montreal 3, Quebec, Canada.

(2) S. Hanessian and N. R. Plessas, *J. Org. Chem.*, **34**, 1035 (1969), preceding paper (II) in this series.

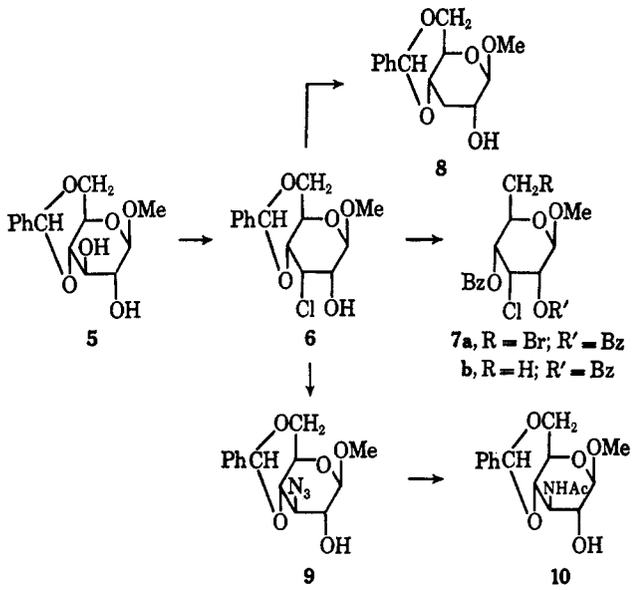
(3) J. D. Dutcher, *Advan. Carbohydrate Chem.*, **18**, 259 (1963).

(4) S. Hanessian and T. H. Haskell, "The Carbohydrates," 3rd ed, W. Pigman and D. Horton, Ed., Academic Press, New York, N. Y., in press.

precursor to 6-amino-6-deoxy-D-glucose, one of the amino sugar components of kanamycin A. The synthesis of methyl 6-amino-6-deoxy-α-D-glucopyranoside[5] can be effected by displacement reactions of the corresponding readily available tosylate. The sequence proceeding through the NBS route, however, presents the added advantage of selective esterification at C-4. This feature can be appreciated in the 6-deoxy and 6-azido derivatives **3** and **4b** which were obtained from **2b** by catalytic reduction and azide displacement, respectively. Compounds **3** and **4b** could be presumably used to advantage in further solvolytic displacement reactions *via* 3,4-benzoxonium intermediates to give 3- and/or 4-substituted derivatives.[6]

In their studies on the reaction of carbohydrates with sulfuryl chloride, Jennings and Jones[7] found that methyl 4,6-*O*-benzylidene-β-D-glucopyranoside **5** reacted with the reagent under controlled conditions to give syrupy methyl 4,6-*O*-benzylidene-3-chloro-3-deoxy-β-D-allopyranoside **6** (Scheme III). This compound possesses a

SCHEME III

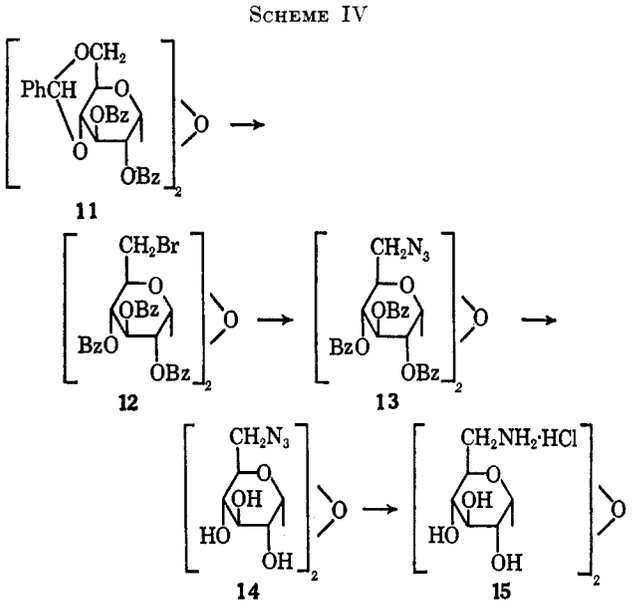


potentially reactive group at C-3 as well as the benzylidene function which could be subjected to ring opening with NBS. Accordingly, the synthesis of **6** was repeated essentially according to the published procedure and the product was obtained in crystalline condition in 47% yield. Reduction of **6** with lithium aluminum hydride in the usual way afforded crystalline methyl 4,6-*O*-benzylidene-3-deoxy-β-D-*ribo*-hexopyranoside[8] which can be considered as a convenient precursor to paratose[9] (3,6-dideoxy-D-*ribo*-hexose). Reaction of **6** with NBS, on the other hand, afforded a syrupy product which was chromatographically homogeneous. Benzoylation of this material gave the product **7a** which, when subjected to catalytic hydrogenation, underwent selective reduction of the bromo function to give syrupy methyl 2,4-di-*O*-benzoyl-3-chloro-3,6-dideoxy-β-D-allopyranoside (**7b**).

The reaction of **6** with various nucleophilic agents should, under favorable conditions afford the epimeric 3-substituted derivative having the D-*gluco* configuration. Displacement with sodium azide in *N,N*-dimethylformamide proceeded as anticipated but the reaction was very slow. Thus, even after 4 days at reflux temperature, the presence of a small amount of starting material could be demonstrated by tlc. Processing the reaction mixture gave the crystalline product which was contaminated with some **6**. This product was reduced and N-acetylated by stirring in methanol solution containing acetic anhydride in the presence of excess Raney nickel. Since the solubility characteristics of the product **10** are greatly different from that of **6** (which remained intact during the reduction), a separation could be easily effected by ether extraction with little or no loss of **10**. In this way methyl 3-acetamido-4,6-*O*-benzylidene-3-deoxy-β-D-glucopyranoside (**10**) was obtained from **6** in an over-all yield of 28% and was identical with an authentic specimen.[10] It should be pointed out that this sequence provides an alternate route to kanosamine[11] (3-amino-3-deoxy-D-glucose), one of the amino sugar components in kanamycins A and C.[12]

That the NBS reaction was adaptable to *O*-benzylidene acetals of disaccharides was demonstrated in the case of α,α-trehalose and sophorose derivatives.[2] The ring opening of 4,6:4′,6′-*O*-benzylidene-2,2′:3,3′-tetra-*O*-benzoyl-α,α-trehalose (**11**) with NBS gave the crystalline 6,6′-dibromo-6,6′-dideoxy derivative **12** in 78% yield (see Scheme IV). Reaction of this product with

SCHEME IV



sodium azide in *N,N*-dimethylformamide at 95° overnight afforded after processing a 67% yield of the

(5) F. Cramer, H. Otterbach, and H. Springmann, *Chem. Ber.*, **92**, 384 (1949).

(6) C. L. Stevens, J. P. Dickerson, and K. G. Taylor, Abstracts of Papers, 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, D17.

(7) H. J. Jennings and J. K. N. Jones, *Can. J. Chem.*, **43**, 2372 (1965).

(8) E. J. Hedgley, W. G. Overend, and R. A. C. Rennie, *J. Chem. Soc.*, 4701 (1963).

(9) C. Fouquey, J. Polonsky, E. Lederer, O. Westphal, and O. Lüderitz, *Nature*, **182**, 944 (1958).

(10) H. H. Baer and F. Kienzle, *J. Org. Chem.*, **32**, 3169 (1967). We thank Dr. Baer for providing us with an authentic specimen of **10** prepared by a different route.

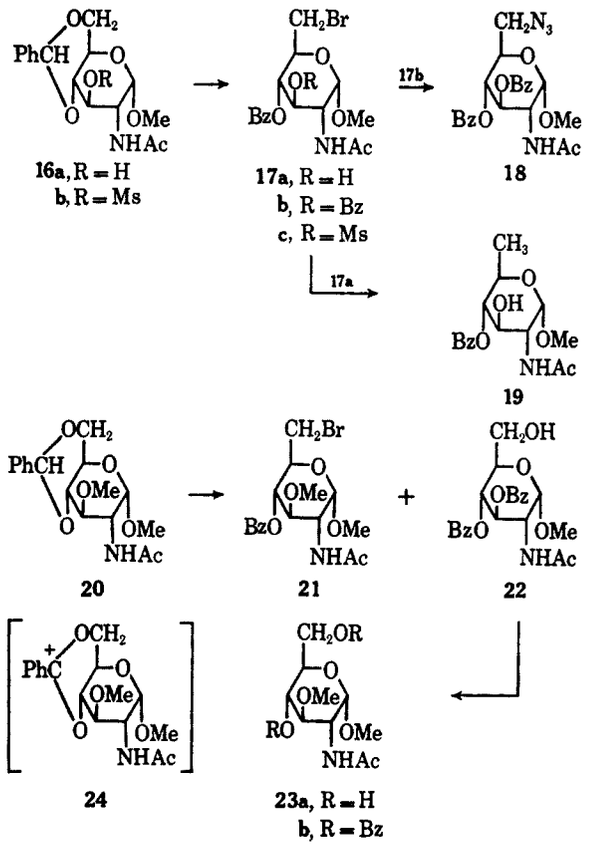
(11) H. H. Baer, *J. Am. Chem. Soc.*, **83**, 1882 (1961).

(12) H. Umezawa, M. Ueda, K. Maeda, K. Yagishita, S. Kondo, Y. Okami, R. Utahara, Y. Osato, K. Nitta, and T. Takeuchi, *J. Antibiotics* (Tokyo), **10A**, 181 (1957).

corresponding crystalline 6,6′-diazido-6,6′-dideoxy derivative **13**. Debenzoylation of **13** in the usual manner afforded **14** as a solid which was catalytically reduced to the 6,6′-diamino-6,6′-dideoxy-α,α-trehalose (**15**). This product has been recently obtained from the conventional reaction of the 6,6′-di-*O*-tosyl derivative of α,α-trehalose with ammonia.[13] Compound **15** is an amino analog of the antibiotic substance trehalosamine[14] which has been recently synthesized.[15]

It has been established[2] that the presence of unsubstituted hydroxyl groups does not present any difficulties during the ring opening of methyl 4,6-*O*-benzylidenehexopyranosides. The compatibility of the acetamido group with the NBS reaction was therefore investigated with the expectation that the successful ring opening reaction of benzylidene acetals of amino sugar glycosides might provide useful and facile routes to diaminohexoses and aminodideoxyhexoses. Methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside[16] (**16a**) was treated with NBS in a mixture of carbon tetrachloride and tetrachloroethane to give the anticipated 6-bromo-6-deoxy derivative **17a** in 77% yield (Scheme V); although the product was chromato-

SCHEME V



graphically homogeneous and exhibited the correct spectral properties, it was difficult to crystallize and had a tendency to form a gel. Benzoylation afforded the crystalline dibenzoate **17b** which was treated with sodium azide in the usual manner to give crystalline methyl 2-acetamido-6-azido-3,4-di-*O*-benzoyl-2,6-dideoxy-α-D-glucopyranoside (**18**) in 72% yield. The sequence **16** → **18** provides a facile route to a precursor to neosamine C[17] (2,6-diamino-2,6-dideoxy-D-glucose),[18] a constituent of the aminoglycoside antibiotics[4,19,20] neomycin C, paromomycin II, and kanamycin B.

Another significant feature is that **17a** contains an unsubstituted hydroxyl group at C-3 which makes it a potentially good candidate for oligosaccharide synthesis. The same situation exists in the reduction product of **17a**, namely **19** which in addition, provides a convenient model compound for the class of 2-amino-2,6-dideoxyhexoses such as pneumosamine (2-amino-2,6-dideoxy-L-talose) and its C-2 epimer which are found in certain types of pneumococcal polysaccharides.[21] Reaction of **16b** with NBS afforded an 84% yield of methyl 2-acetamido-4-*O*-benzoyl-6-bromo-2,6-dideoxy-3-*O*-methylsulfonyl-α-D-glucopyranoside (**17c**). An unexpected product was formed when methyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-methyl-α-D-glucopyranoside (**20**)[16] was treated with NBS. Thus, in addition to the expected 6-bromo-6-deoxy derivative **21**, a second product was obtained which proved to be methyl 2-acetamido-4-*O*-benzoyl-2-deoxy-3-*O*-methyl-α-D-glucopyranoside[22] (**22**). The identity of the latter was confirmed from spectral data and by its conversion into the known[22] crystalline derivatives **23a** and **b**. A logical explanation for the formation of **22** should take into account the incorporation of a hydroxyl group into the molecule. Since the reaction conditions were essentially anhydrous, the possibility of hydration was investigated. Actually our sample of **20**, prepared by a published procedure,[16] did indeed contain moisture (calcd for 1 H_2O, 5.32; found 4.97). The formation of **22** could be rationalized[2] on the basis of a competitive attack of hydroxyl ion from the water, in addition to that of the existing bromide ion, upon the initially formed benzoxonium ion **24**.[2,23] Attack of hydroxyl ion could occur directly at C-6 as with bromide ion or more likely at the benzylic center to give an ortho ester intermediate which would collapse, in what appears to be a stereoselective manner, to give **22**. When a sample of **20** was dried in a vacuum oven at about 80° prior to use, the yield of **21** was increased at the expense of **22**;

(13) S. Umezawa, T. Tsuchiya, S. Nakada, and K. Tatsuta, *Bull. Chem. Soc. Japan*, **40**, 395 (1967).

(14) F. Arcamone, G. Canevazzi, and M. Ghione, *Giorn. Microbiol.*, **2**, 205 (1956); F. Arcamone and F. Bizioli, *Gazz. Chim. Ital.*, **87**, 896 (1957).

(15) S. Umezawa, K. Tatsuta, and R. Muto, *J. Antibiotics* (Tokyo), **A20**, 388 (1967).

(16) A. Neuberger, *J. Chem. Soc.*, 50 (1941); R. Jeanloz, *J. Am. Chem. Soc.*, **78**, 555 (1954).

(17) K. L. Rinehart, Jr., M. Hichens, K. Striegler, K. R. Rover, T. P. Culbertson, S. Tatsuoka, S. Horii, T. Yamaguchi, H. Hitomi, and A. Miyake, *J. Am. Chem. Soc.*, **83**, 2964 (1961).

(18) H. Weidmann and H. K. Zimmerman, Jr., *Ann.*, **644**, 127 (1961).

(19) K. L. Rinehart, Jr., "The Neomycins and Related Antibiotics," John Wiley and Sons, Inc., New York, N. Y., 1964.

(20) H. Umezawa, "Recent Advances in Chemistry and Biochemistry of Antibiotics," Microbial Chemistry Research Foundation, Tokyo, 1964.

(21) S. A. Barker, J. S. Brimacombe, M. J. How, M. Stacey, and J. M. Williams, *Nature*, **189**, 303 (1961); J. S. Brimacombe and M. J. How, *J. Chem. Soc.*, 5037 (1962).

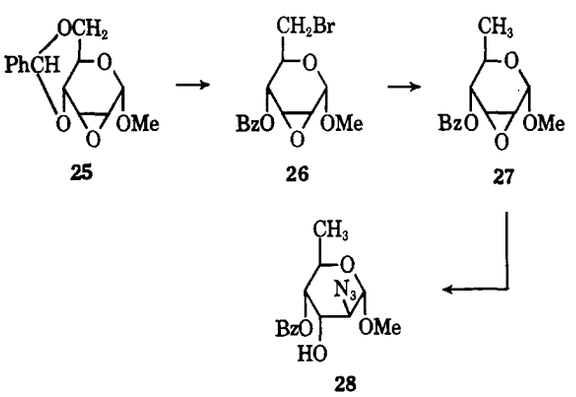
(22) R. W. Jeanloz, *J. Am. Chem. Soc.*, **79**, 2591 (1957); *J. Org. Chem.*, **26**, 905 (1961).

(23) Since there are no data available as yet to support the over-all free-radical or concerted-type mechanisms, the intermediates involved in these reactions will be provisionally depicted in their ionic form, that is, as benzoxonium ions. Support for an ionic termination process is provided in subsequent work involving the reaction of internal *O*-benzylidene acetals, *i.e.*, spanning two secondary hydroxyl groups, with NBS. The product distribution and several unique features, such as the induced rearrangement caused by participating groups in the molecule, can be best interpreted in terms of ionic intermediates based on our present knowledge of carboxonium ions and their reactions; see S. Hanessian and N. R. Plessas, *J. Org. Chem.*, **34**, 1053 (1969), paper IV of this series.

however the latter was still formed, presumably due to the presence of small amounts of moisture. It was shown, at least qualitatively, in part II[2] that the addition of small amounts of water to the NBS reaction mixtures resulted in a lower yield of the expected 4-*O*-benzoyl-6-bromo-6-deoxy derivatives. Although our experinence with the NBS reaction with compound **20** represents an isolated case, care should be taken to avoid the use of hydrated or solvated samples to minimize side reactions.

The successful application of the NBS reaction to methyl 2,3-anhydro-4,6-*O*-benzylidenehexopyranosides provides polyfunctional derivatives which are of great synthetic utility. Advantage can be taken of the well-known epoxide-opening reactions before or after the NBS step. In this manner facile syntheses of sugars containing substituents at positions 2, 3, and 6 in various combinations can be effected. The readily available methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-allopyranoside[24] (**25**) was treated with NBS in the presence of a free-radical initiator (benzoyl peroxide) to give crystalline methyl 2,3-anhydro-4-*O*-benzoyl-6-bromo-6-deoxy-α-D-allopyranoside (**26**) in 53% yield (Scheme VI).

SCHEME VI

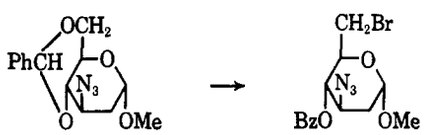


The syrupy mother liquors contained additional product which could not be induced to crystallize because of the presence of traces of impurities (tlc), but could be used as such in subsequent steps.

The conversion into **26** was also possible in the absence of benzoyl peroxide. Catalytic reduction of **26** gave the corresponding 6-deoxy derivative **27** in an over-all yield of 62% after purification by column chromatography. Reaction of **27** with sodium azide in 2-methoxyethanol containing 1 molecular equiv of ammonium chloride afforded a syrupy product which consisted of three components on tlc, all of which were of slower mobility than **27** itself. Partial crystallization of this syrup could be effected, and a product tentatively designed as **28** was thus obtained. Examination of the mother liquors showed the presence of more of this substance, in addition to the other two components. The crystalline product had the slowest mobility on tlc among the three components. Its structure is assigned based on the analogies of ring-opening reactions of 2,3-epoxides in the D-*allo* series. The nature of the other two components is not known at the moment, although one of them could conceivably be an isomer resulting from attack of azide ion at C-3. Ring-opening reactions of compounds of the type of **26** and **27** (nucleophilic displacements, reduction, etc) are under investigation.

Extension of the NBS reaction to methyl 3-azido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-*arabino*-hexopyranoside[25] (**29**) gave a syrupy product which had the properties expected of the ring-opening product **30** (Scheme VII).

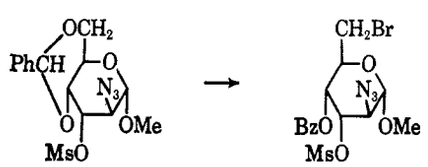
SCHEME VII



It can be recognized that the reduction of **30** would provide an isomer of the sugar daunosamine[26] (3-amino-2,3,6-trideoxy-L-*lyxo*-hexose) which has been recently synthesized.[27] The N,N-dimethylamino analog of daunosamine, namely, rhodosamine, is a constituent of the rhodomycin and pyrromycin complex of antibiotics.[28]

A useful synthetic intermediate **32** is obtained in 84% yield from the reaction of methyl 2-azido 4,6-*O*-benzylidene-2-deoxy-3-*O*-methylsulfonyl-α-D-altropyranoside[29] (**31**) with NBS (Scheme VIII). Compound **32** is a

SCHEME VIII



unique type of polyfunctional sugar derivative which can be subjected to selective reactions at each of the sites.

The ready availability of 2-deoxy-D-*arabino*-hexose prompted us to investigate the ring-opening reaction of methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*arabino*-hexopyranoside[30] (**33a**) with NBS. The product **34a**, initially obtained as a syrup (Scheme IX), crystallized upon purification by chromatography. Catalytic reduction of **34a** afforded crystalline methyl 4-*O*-benzoyl-2,6-dideoxy-α-D-*arabino*-hexopyranoside (**35a**), which is the immediate precursor of the recently synthesized[31] 2,6-dideoxy-D-*arabino*-hexose (chromose C).[32] Appli-

(24) N. K. Richtmyer and C. S. Hudson, *J. Am. Chem. Soc.*, **63**, 1730 (1941); N. K. Richtmyer, *Methods Carbohydrate Chem.*, **1**, 109 (1962).

(25) (a) R. D. Guthrie and D. Murphy, *J. Chem. Soc.*, 6956 (1965); (b) J. Kovář, V. Dienstbierová, and J. Jarý, *Collection Czech. Chem. Commun.*, **32**, 2498 (1967).

(26) F. Arcamone, G. Cassinelli, P. Orezzi, G. Franceschi, and R. Mondelli, *J. Am. Chem. Soc.*, **86**, 5335 (1964).

(27) J. P. Marsh, C. W. Mosher, E. M. Acton, and L. Goodman, *Chem. Commun.*, 573 (1967).

(28) H. Brockmann and E. Spohler, *Naturwissenschaften*, **48**, 716 (1961); H. Brockmann, E. Spohler and T. Wahneldt, *Chem. Ber.*, **96**, 2925 (1963).

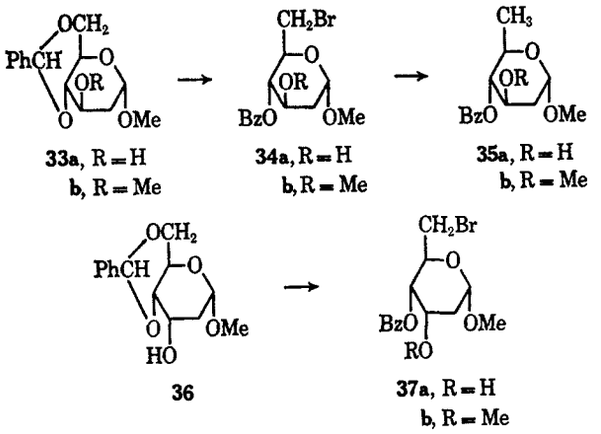
(29) R. D. Guthrie and D. Murphy, *J. Chem. Soc.*, 5288 (1963); Y. Ali and A. C. Richardson, *Carbohydrate Res.*, **5**, 441 (1967).

(30) B. Flaherty, W. G. Overend, and N. R. Williams, *J. Chem. Soc.*, 398 (1966).

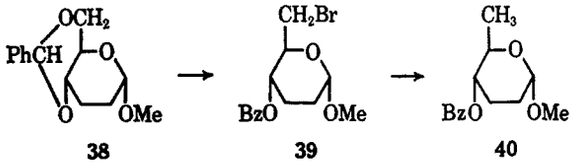
(31) W. W. Zorbach and J. P. Ciaudelli, *J. Org. Chem.*, **30**, 451 (1965).

(32) M. Miyamoto, Y. Kawamatsu, M. Shinohara, Y. Nakadaira, and K. Nakanishi, *Tetrahedron*, **22**, 2785 (1966); M. Miyamoto, Y. Kawamatsu, M. Shinohara, K. Nakanishi, Y. Nakadaira, and N. S. Bhacca, *Tetrahedron Letters*, 2371 (1964).

SCHEME IX



SCHEME X



cation of the NBS reaction to methyl 4,6-*O*-benzylidene-2-deoxy-α-D-*ribo*-hexopyranoside (**36**) afforded syrupy methyl 4-*O*-benzoyl-6-bromo-2,6-dideoxy-α-D-*ribo*-hexopyranoside (**37a**) which afforded a crystalline dibenzoate **37b** (Scheme X). These and other isomeric 2,6-dideoxyhexoses are constituents of the chromomycin[33] and olivomycin[34] group of antibiotics, and of other biologically derived substances[3,4,20,35]

Treatment of methyl 4,6-*O*-benzylidene-2-deoxy-3-*O*-methyl-α-D-*arabino*-hexopyranoside (**33b**) with NBS gave a syrupy product which was homogenous by tlc. Catalytic reduction afforded methyl 4-*O*-benzoyl-2,6-dideoxy-3-*O*-methyl-α-D-*arabino*-hexopyranoside (**35b**) as a chromatographically homogeneous syrup. This product is a derivative of D-oleandrose (2,6-dideoxy-3-*O*-methyl-D-*arabino*-hexose),[36] which is enantiomeric with one of the sugar components in the antibiotic oleandomycin.[37] In this connection it is noteworthy to mention a recent note by Jones and coworkers[38] who also made use of the presently described NBS reaction to introduce the potential 6-deoxy group in their synthesis of the branched-chain sugar arcanose (2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-D-*xylo*-hexose).[39]

Finally, the usefulness of the NBS reaction is demonstrated in a simplified synthesis of a derivative of amicetose[40] (2,3,6-trideoxy-D-*erythro*-hexose), the trideoxy sugar component of the antibiotic amicetin.[41,42]

Treatment of methyl 4,6-*O*-benzylidene-2,3-dideoxy-α-D-*erythro*-hexopyranoside[43] (**38**) with NBS gave the expected methyl 4-*O*-benzoyl-6-bromo-2,3,6-trideoxy-α-D-*erythro*-hexopyranoside (**39**) as a homogeneous syrup (Scheme XI). The latter was catalytically reduced to methyl 4-*O*-benzoyl-2,3,6-trideoxy-α-D-*erythro*-hexopyranoside (**40**), which was obtained a a pure syrup having the expected spectral properties. It should be pointed out that compound **40** could be a suitable intermediate for the synthesis of derivatives of amicetose directly, as well as of the aminodeoxy sugar forosamine[44,45] indirectly, through well-established nucleophilic displacement reactions and double-inversion procedures[44] on appropriate intermediates.

Experimental Section

Melting points are uncorrected. Nmr spectra were obtained on a 60-Mc spectrometer using tetramethylsilane as reference in chloroform-*d* unless otherwise stated. Optical rotations were measured with a Perkin-Elmer photoelectric polarimeter at 25°. Thin layer chromatography (tlc) was performed on silica gel-HF plates and the spots were detected with a spray containing 5% each of ammonium molybdate, sulfuric acid, and phosphoric acid, after heating the plate for 10 min at 110°, and with a 1% potassium permanganate solution in 0.1 *N* sulfuric acid. Solvent systems and mobilities are given. Carbon tetrachloride and 1,1,2,2-tetrachloroethane were dried by passage over neutral alumina (Woelm) prior to use. Processed solutions of chloroform, ether, etc., were dried over anhydrous sodium sulfate. Vapor phase chromatography was done on columns containing 5% SE-30 (Analabs, Inc.), or 3% OV-17 (Applied Science Labs, Inc.) depending on the derivative.

Methyl 6-Azido-2,3,4-tri-*O*-benzoyl-6-deoxy-α-D-glucopyranoside (4a).—A solution of **2a**[2] (1 g) in 30 ml of DMF containing 1 g of sodium azide was heated at 90° for 12 hr. The solution was evaporated to dryness in the presence of butyl alcohol, the residue was suspended in ether, and the solution was washed with water. The ethereal solution was dried and processed to a syrup that crystallized from a small volume of cold methanol; yield 0.65 g (70%), mp 134–135°. Recrystallization of a portion afforded an analytical sample: mp 137–138°; $[\alpha]_D$ 75.3° (*c* 1.03, chloroform); ir data (KBr), 2100 (azide), 1730 cm^{-1} (ester), no OH absorption. The product had the same chromatographic mobility (tlc, chloroform–2,2,4-trimethylpentane–methanol, 100:30:1) as the starting material.

Anal. Calcd for $C_{28}H_{25}N_3O_8$: C, 63.26; H, 4.74; N, 7.90. Found: C, 63.37; H, 4.76; N, 7.85.

Methyl 6-Azido-4-*O*-benzoyl-6-deoxy-2,3-di-*O*-methylsulfonyl-α-D-glucopyranoside (4b).—A solution of **2b**[2] (0.5 g) in 30 ml of DMF containing 0.1 g of sodium azide was stirred at 95° for 6 hr. Evaporation of the solvent by codistillation with butyl alcohol gave a solid residue which was dissolved in ether and washed with water. Drying and evaporation of the ether solution afforded a syrup which crystallized. The crystals were triturated with a mixture of ether and pentane and filtered; yield 0.295 g (64%) of the product showing a single spot on tlc (chloroform–2,2,4-trimethylpentane–methanol, 100:30:2, medium). A portion was recrystallized from methanol to give an analytical sample: mp 130–132°; $[\alpha]_D$ 59.2° (*c* 1.05, chloroform); ir data (KBr), 2100 (azide), 1730 (ester), 1180 cm^{-1} (sulfonate).

Anal. Calcd for $C_{16}H_{21}N_3O_{10}S_2$: C, 40.10; H, 4.30; N, 8.70; S, 13.40. Found: C, 39.99; H, 4.54; N, 8.97; S, 13.40.

Methyl 4-*O*-Benzoyl-6-deoxy-2,3-di-*O*-methylsulfonyl-α-D-glucopyranoside (3). (a) From 2c.—An amount of **2c**[2] (0.4 g) in 80 ml of methanol containing 0.1 g of 20% palladium on carbon and 0.1 ml of triethylamine was hydrogenated at room temperature and atmospheric pressure during 2 hr. Filtration

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of the catalyst and evaporation of the solvent afforded a chromatographically homogeneous colorless syrup (tlc, chloroform–methanol, 100:7), yield 0.273 g (88%). Mesylation of this product with methanesulfonyl chloride in pyridine at 5° (dark) afforded after processing the crude dimesylate **3** as a crystalline solid, yield 0.32 g, mp 120–122°. Two recrystallizations from a small volume of acetone gave pure material, mp 129–130°, $[\alpha]_D$ 54.4° (*c* 0.258, chloroform).

Anal. Calcd for $C_{16}H_{22}O_{10}S_2$: S, 14.42. Found: 14.05.

(b) **From 2b.**—A mixture of methanol (100 ml), 2 g of **2b**,[2] 1 g of 20% palladium on carbon, and 1 g of barium carbonate was hydrogenated with stirring during 3 hr. Filtration and evaporation afforded a foamy solid which crystallized upon trituration with a small volume of cold methanol, yield 1.25 g, mp 122–125°. A further 0.1 g was recovered from the mother liquors, total yield 80%. The product was identical with that obtained from **2c**.

Methyl 4,6-*O*-Benzylidene-3-chloro-3-deoxy-β-D-allopyranoside (6).—Methyl 4,6-*O*-benzylidene-β-D-glucopyranoside[46] **5** was recrystallized from hot water and the crystalline product, mp 195°, was dried at 120° for 3 hr. A solution containing 7 g of this material in 70 ml of chloroform and 28 ml of pyridine was cooled to −70° and 18.2 ml of sulfuryl chloride was added dropwise with stirring over a period of 30 min. The temperature was allowed to rise to about −20° gradually and finally to room temperature over a period of 2 hr. After the solution had stirred at room temperature for 10 min a slightly exothermic reaction was observed with the color of the solution changing from pale yellow to orange. The solution was immediately cooled and poured into cold 10% aqueous sulfuric acid (120 ml) which was washed with chloroform and the latter layer was processed as usual to give a reddish syrup. This was dissolved in 50 ml of methanol containing 25 g of barium carbonate and a solution of sodium iodide (12 g) in 30 ml of methanol–water (1:1) was added with swirling. Iodine was formed and a temperature rise was observed. The solution was cooled briefly, treated with another portion of sodium iodide in aqueous methanol, and filtered. Evaporation of the neutral filtrate gave a reddish solid which was extracted with excess benzene, the solution was filtered, and the filtrate was treated with charcoal and evaporated to a pale yellow syrup, 5 g (64%), which was homogeneous on tlc (chloroform–2,2,4-trimethylpentane–methanol, 100:30:5, medium). The syrup crystallized at 5° overnight and trituration with ether–petroleum ether (bp 30–60°) gave 3.5 g (47%) of crystalline product. Recrystallization from ether–pentane with the addition of a few drops of acetone gave an analytical sample: mp 129–131°; $[\alpha]_D$ −24° (*c* 1.0, chloroform); nmr data, τ 7.22 (*J* = 6 cps, hydroxyl proton), 6.75 (C-1 methoxyl protons), 5.3 (C-1 proton, apparent triplet, *J* = 7 cps), 4.5 (benzylic proton), etc.

Anal. Calcd for $C_{14}H_{17}ClO_5$: C, 56.00; H, 5.72; Cl, 11.82. Found: C, 55.71; H, 5.69; Cl, 11.88.

Methyl 2,4-*O*-Dibenzoyl-3-chloro-3,6-dideoxy-β-D-allopyranoside (7b).—A suspension of **6** (0.15 g), NBS (0.1 g), and barium carbonate (0.5 g) in 10 ml of carbon tetrachloride was refluxed with stirring for 2 hr. The salts were filtered and the filtrate was processed to give a syrup which was dissolved in ether and filtered through decolorizing carbon. Evaporation of the filtrate gave the product as a colorless syrup which was chromatographically homogeneous and had a mobility slightly faster than **6** (chloroform–2,2,4-trimethylpentane–methanol, 100:30:5); yield 0.16 g (89%).

The syrup was benzoylated in pyridine solution in the usual way to give a syrupy dibenzoate derivative **7a**. The latter (0.23 g) was dissolved in methanol and hydrogenated in the presence of 20% palladium on charcoal and barium carbonate during 4 hr. Filtration and evaporation gave the product **7b** as a colorless chromatographically homogeneous syrup: yield 0.1 g; nmr data, τ 8.65 (center of a doublet, C-6 protons); $[\alpha]_D$ −43° (*c* 1.25, chloroform).

Anal. Calcd for $C_{21}H_{21}ClO_6$: C, 62.29; H, 5.22; Cl, 8.75. Found: C, 62.25; H, 5.53; Cl, 8.70.

Methyl 4,6-*O*-Benzylidene-3-deoxy-β-D-*ribo*-hexopyranoside (8).—A solution of **6** (0.5 g) in 10 ml of ether was added dropwise to a stirring suspension of 0.2 g of lithium aluminum hydride in 50 ml of ether. The suspension was refluxed with stirring during 20 hr, and the excess reagent was decomposed by the addition of dilute hydrochloric acid until the aqueous layer was weakly acidic. The ethereal layer was separated, washed with water, and processed in the usual way to give a crystalline solid. Trituration with cold ether gave the product in two crops, 0.225 g (51%), mp 168–169° (softening at 165°), $[\alpha]_D$ −60.5° (*c* 1.05, chloroform); lit.[8] mp 165°, $[\alpha]_D$ 59.5° (chloroform).

Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.10; H, 6.80. Found: C, 63.23; H, 6.81.

Methyl 3-Acetamido-4,6-*O*-benzylidene-3-deoxy-β-D-glucopyranoside (10).—A suspension of **6** (0.5 g) and 2 g of sodium azide in 20 ml of dry DMF was stirred under reflux for 4 days. The tan solution was cooled, diluted with excess ether, filtered, and evaporated to dryness by codistillation with butyl alcohol. The residual solid was suspended in ether and the latter was washed with a small volume of water. Drying and evaporation of the solvent afforded a residue which crystallized from ether–pentane, yield 0.47 g. This product showed two spots on tlc (chloroform–2,2,4-trimethylpentane–methanol, 100:30:5), the slower moving one (minor) being starting material and the slightly faster spot being **9**. The mixture was dissolved in 50 ml of methanol containing 2 ml of acetic anhydride and the suspension was stirred with an excess of Raney nickel for 2 days. Filtration and evaporation gave 0.682 g of a pale greenish solid which was washed well with ether to remove unreacted **6**. The solid was then washed with cold 1 *N* acetic acid by decantation, whereupon the product remained as a colorless crystalline solid. Drying the solid gave 0.15 g (28% over-all from **6**) of crystalline product, mp 292–294°; $[\alpha]_D$ −82° (*c* 1.02, pyridine); lit.[10] mp 294°, $[\alpha]_D$ −78° (pyridine) for the monohydrate.

4,6:4′,6′-Di-*O*-benzylidene-2,2′,3,3′-tetra-*O*-benzoyl-α,α-trehalose (11).—A solution containing 3.42 g of 4,6:4′,6′-di-*O*-benzylidene-α,α-trehalose[2] in 70 ml of dry pyridine was treated dropwise with 10 ml of benzoyl chloride at 0°. The solution was left at room temperature overnight, then poured into ice–water. The resulting gum crystallized after successive washings with cold water and finally with cold pentane, yield 5.7 g. Recrystallization from a mixture of methanol and acetone gave 5.2 g of pure product: mp 240–241°; $[\alpha]^{25}_D$ 239° (*c* 1.01, chloroform); ir data (KBr), 1730 cm^{-1} (ester). The mother liquors contained some additional product as evidenced by tlc (benzene–methanol, 10:1, fast), but they were not processed.

Anal. Calcd for $C_{54}H_{46}O_{15}$: C, 69.37: H, 4.90. Found: C, 69.33; H, 5.14.

2,2′,3,3′,4,4′-Hexa-*O*-benzoyl-6,6′-dibromo-6,6′-dideoxy-α,α-trehalose (12).—A suspension containing 4 g of **11**, 1.86 g of NBS, and 10 g of barium carbonate in 400 ml of dry carbon tetrachloride was refluxed with vigorous stirring for 2 hr. Filtration and evaporation gave a syrup that was dissolved in chloroform and washed with water. The organic phase was dried and evaporated to a syrup which crystallized on standing. Recrystallization from a mixture of acetone, ether, and pentane gave 3.65 g (78%) of pure product in two crops: mp 112–114°; $[\alpha]^{25}_D$ 214° (*c* 1.07, chloroform); ir data (KBr), 1728 cm^{-1} (ester).

Anal. Calcd for $C_{54}H_{44}Br_2O_{15}$: C, 59.34; H, 4.03; Br, 14.60. Found: C, 59.12; H, 4.04; Br, 14.77.

6,6′-Diazido-2,2′,3,3′,4,4′-hexa-*O*-benzoyl-6,6′-dideoxy-α,α-trehalose (13).—A solution of **12** (0.1 g) in 20 ml of DMF containing 0.30 g of sodium azide was heated with stirring at 90° for 16 hr. The solvent was removed by codistillation with butyl alcohol. Successive evaporations from toluene, methanol, and ether afforded a pale yellow syrup which was suspended in ether and the solution was washed with a small volume of water. Drying the ethereal solution and evaporation gave a syrup which crystallized from a mixture of ether and pentane; yield 62.6 mg (67%) of a white solid. Investigation of the mother liquors by tlc (chloroform–2,2,4-trimethylpentane–methanol, 100:30:0.2, medium) revealed the presence of more product and two slower moving minor components which were not investigated further. Recrystallization of the product from hot ethanol afforded an analytical sample: mp 180–182°; $[\alpha]^{25}_D$ 212° (*c* 0.37, chloroform); ir data (KBr), 2100 (azide), 1730 cm^{-1} (ester). When the reaction was repeated on a larger scale (1 mmole or more) the yield of initial crystalline product was lower, 30–40%.

Anal. Calcd for $C_{54}H_{44}N_6O_{15}$: C, 63.77; H, 4.34; N, 8.20. Found: C, 63.75; H, 4.41; N, 8.21.

6,6′-Diazido-6,6′-dideoxy-α,α-trehalose (14).—To a meth-

(46) K. Freudenberg, H. Toepffer, and C. C. Andersen, *Ber.*, **61**, 1750 (1928).

anolic solution containing 0.44 g of **13** was added a small piece of sodium metal at 0°. The solution was allowed to stand at room temperature overnight and was then neutralized with Dowex-50 (H^+). Filtration and evaporation afforded a solid which was suspended in a mixture of ether and pentane (containing a few drops of methanol) and filtered to give the product: yield 0.15 g; mp 195–198°; ir data (KBr), 2100 cm^{-1} (azide). The product displayed a single spot on tlc (ethyl acetate–isopropyl alcohol–water, 195:70:35, medium) and was used as such in the next step.

6,6′-Diamino-6,6′-dideoxy-α,α-trehalose (15).—A solution of **14** (0.15 g) in 80 ml of methanol containing 80 mg of 20% palladium on carbon was hydrogenated during 1 hr at room temperature. Filtration of the catalyst and evaporation of the solution afforded a residue which solidified from methanol–ether; yield 71 mg. This material was chromatographically homogeneous in the following solvent systems using plates coated with avicel,[47] *t*-butyl alcohol–acetic acid–water (2:2:1, medium), and propyl alcohol–water–ammonium hydroxide (70:30:1, medium). It migrated slightly slower than trehalosamine. A hygroscopic dihydrochloride, mp ~80°, lit.[12] 82–83°, was obtained by dissolution in methanol, adding a drop of methanolic hydrogen chloride followed by ether to the turbid point.

Methyl 2-Acetamido-4-*O*-benzoyl-6-bromo-2,6-dideoxy-α-D-glucopyranoside (17a).—A suspension of **16a**[16] (0.322 g) and barium carbonate (1.0 g) in a mixture of carbon tetrachloride (20 ml) and tetrachloroethane (7 ml) was treated with NBS (0.2 g) and the whole was stirred under reflux for 2 hr. The colorless suspension was filtered and the filtrate was evaporated to a syrup which was reconstituted in dichloromethane and washed with a small volume of water. Drying and evaporation of the organic solution gave the product **17a** as a colorless solid, 0.312 g (77%), which showed essentially one spot on tlc (chloroform–methanol, 100:5, medium). The product was difficult to crystallize, easily forming a gel. A portion was applied on thick-layer silica gel plates and developed in chloroform–methanol (100:10). Elution of the zone corresponding to the product and evaporation gave a solid from ether–pentane; mp 94–98°; $[\alpha]^{25}D$ 29.4° (*c* 0.306, chloroform); ir data (KBr), 1728 (ester), 1660 (amide I), 1540 cm^{-1} (amide II).

Anal. Calcd for $C_{16}H_{20}BrNO_6$: N, 3.5. Found: N, 3.63.

Methyl 2-Acetamido-3,4-di-*O*-benzoyl-6-bromo-2,6-dideoxy-α-D-glucopyranoside (17b).—An amount of **17a** (0.4 g) in 5 ml of dry pyridine was treated dropwise at −10° with 0.2 ml of benzoyl chloride. The mixture was left at 0° overnight, then it was poured into ice–water whereupon the product precipitated as a cream-colored solid. Filtration, followed by washing with cold water, then pentane, afforded the crude product, yield 0.418 g, which was homogeneous on tlc (chloroform–methanol, 100:1, medium). Recrystallization from hot methanol containing a few drops of acetone afforded an analytical sample, mp 231–231°, $[\alpha]D$ −17.8° (*c* 0.98, chloroform).

Anal. Calcd for $C_{23}H_{24}BrNO_7$: C, 54.55; H, 4.77; N, 2.76; Br, 15.78. Found: C, 54.50; H, 4.77; N, 2.83; Br, 15.61.

Methyl 2-Acetamido-4-*O*-benzoyl-6-bromo-2,6-dideoxy-3-*O*-methylsulfonyl-α-D-glucopyranoside (17c).—A suspension of **16b** (0.2 g), 0.5 g of barium carbonate, and 0.1 g of NBS in 20 ml of carbon tetrachloride and 3 ml of tetrachloroethane was stirred under reflux for 2.5 hr. The colorless suspension was filtered while hot and the filtrate was evaporated to dryness. The colorless residue was dissolved in ether, and the solution was extracted with cold water, dried, and evaporated to a syrup which solidified when triturated with cold water; yield 0.194 g (84%), mp 135–137°. Pure product was obtained by dissolving in ethanol, adding water, and allowing the solution to evaporate slowly; mp 146–148° (softens at *ca.* 135°), $[\alpha]D$ 22° (*c* 0.173, chloroform).

Anal. Calcd for $C_{17}H_{22}BrNO_8S$: C, 42.50; H, 4.61; N, 2.9; Br, 16.64; S, 6.67. Found: C, 42.14; H, 4.53; N, 2.97; Br, 16.35; S, 6.49.

Methyl 2-Acetamido-4-*O*-benzoyl-2,6-dideoxy-α-D-glucopyranoside (19).—To a solution of **17a** (0.28 g) in 70 ml of methanol was added 0.2 g of 20% palladium on charcoal and 0.1 ml of triethylamine. Hydrogen was bubbled through the suspension during 2 hr. Filtration and evaporation gave a syrup which solidified under ether; yield 0.1 g (44%). This material showed essentially one major spot on tlc (chloroform–methanol, 100:5, medium). A portion was purified by preparative tlc; mp 92–94° (from ether–pentane); nmr data, τ 8.8 (center of a doublet, C-6 protons), 8.05 (N-acetyl protons, singlet), etc.

Anal. Calcd for $C_{16}H_{21}NO_6$: N, 4.33. Found: N, 3.95.

Reaction of Methyl 2-Acetamido-4,6-*O*-benzylidene-2-deoxy-3-*O*-methyl-α-D-glucopyranoside Hydrate with NBS.—Compound **20** hydrate (H_2O: calcd, 5.32; found, 4.97) (0.135 g), barium carbonate (1 g), and NBS (0.08 g) were suspended in 10 ml of dry tetrachloroethane, and the mixture was stirred at 85° for 2 hr. Filtration and evaporation gave a colorless syrup which showed two spots on tlc (chloroform–methanol, 10:5, fast and slow) as detected with the permanganate spray. Although the faster spot could be extracted with ether from the original syrup, a more efficient separation could be achieved by chromatography on silicic acid. Evaporation of the fractions containing the fast component afforded about 30 mg of crystalline **methyl 2-acetamido-4-*O*-benzoyl-6-bromo-2,6-dideoxy-3-*O*-methyl-α-D-glucopyranoside (21)**, which could be recrystallized with difficulty (tendency to form a gel) from a mixture of acetone, ether, and pentane. The melting point was rather indefinite, *ca.* 95°, even though the sample was pure; $[\alpha]D$ 38° (*c* 0.523, chloroform); ir data (KBr), 1720 (ester), 1660 (amide I), 1550 cm^{-1} (amide II), no OH (solution spectrum in chloroform.)

Anal. Calcd for $C_{17}H_{22}BrNO_6$: N, 3.36; Br, 19.19. Found: N, 3.19; Br, 18.87.

Processing the fractions containing the slower moving component afforded 70 mg of a crystalline product which was identified as **methyl 2-acetamido-4-*O*-benzoyl-2-deoxy-3-*O*-methyl-α-D-glucopyranoside (22)**: mp 155–157°; $[\alpha]D$ 23° (*c* 0.516, chloroform); ir data (KBr), 1725 (ester), 1660 (amide I), 1540 cm^{-1} (amide II).

Anal. Calcd for $C_{17}H_{23}NO_7$: C, 57.77; H, 6.55; N, 3.94. Found: C, 57.21; H, 7.12; N, 4.12.

Debenzoylation of a portion of **22** in methanolic sodium methoxide and processing in the usual manner gave the known[16] **methyl 2-acetamido-2-deoxy-3-*O*-methyl-α-D-glucopyranoside (23a)** as the only product, mp 208–210° (tlc, chloroform–methanol, 100:3, medium).

Benzoylation of a portion of **22** with benzoyl chloride in pyridine in the usual way afforded the known **methyl 2-acetamido-4,6-di-*O*-benzoyl-2-deoxy-3-*O*-methyl-α-D-glucopyranoside (23b)**, mp 120–122° (tlc, chloroform–methanol, 10:1.5, medium).

The proportion of the slower moving by-product could be considerably minimized by rigorously drying the starting material. An amount of **20** (0.33 g) was suspended in 30 ml of carbon tetrachloride and 20 ml of tetrachloroethane, and the solution was heated until about 20 ml of solvent had been collected in a side arm. Fresh carbon tetrachloride was added and the azeotroping process was repeated. The solution was allowed to cool, 0.25 g of NBS and 2 g of barium carbonate were added, and the suspension was heated at 85° with stirring for 2.5 hr. Filtration and evaporation in the presence of butyl alcohol gave a syrup which was dissolved in ether, and the solution was filtered from a trace of insoluble material and evaporated to dryness. The resulting cream-colored solid was triturated with ether and pentane and filtered. This material showed essentially one spot on tlc but a trace of the slower moving component was also present. The latter could be removed by washing an ethereal solution of the product with a small volume of cold water. The final yield of the product **21** was only 23–25% (about 0.1 g).

Methyl 2-Acetamido-6-azido-3,4-di-*O*-benzoyl-2,6-dideoxy-α-D-glucopyranoside (18).—A solution of **17b** (90.6 mg) in 10 ml of dry DMF containing 0.1 g of sodium azide was heated with stirring at 90–100° for 20 hr. The solution was evaporated to dryness by codistillation with butyl alcohol. The residue was suspended in ether and the solution was filtered. The filtrate was washed with a small volume of water, dried, and evaporated to a crystalline residue. Trituration with pentane and filtration gave 61 mg (72%) of the product **18** which was homogeneous on tlc (chloroform–methanol, 100:1, medium). Recrystallization was effected from ether–pentane; mp 188–190°; $[\alpha]D$ 21.4° (*c* 0.99, chloroform); ir data (KBr), 2100 (azide), 1720 (ester), 1660 (amide I), 1540 cm^{-1} (amide II).

Anal. Calcd for $C_{23}H_{24}N_4O_7$: C, 58.96; H, 5.16; N, 11.96. Found: C, 58.31; H, 5.36; N, 11.76.

Methyl 2,3-Anhydro-4-*O*-benzoyl-6-bromo-6-deoxy-α-D-allopyranoside (26).—A benzene solution (90 ml) containing 3.96 g

(47) A product of the FMC Corp., Marcus Hook, Pa.

of **25**, 3 g of NBS, and 0.12 g of benzoyl peroxide was refluxed with stirring (overhead stirrer) during 2 hr. A red color was observed within the first few minutes of refluxing, but it faded after 5 min. The solution was evaporated to dryness and the residue was suspended in ether and filtered. The ethereal filtrate was washed three times with small volumes of water, dried, and evaporated to a syrup. Crystallization was effected from ether–pentane; yield 2.7 g (53%) of colorless crystals, mp 60–62°, showing a single spot on tlc (chloroform–2,2,4-trimethylpentane–methanol, 100:30:0.5, medium). A portion of the crystalline product was recrystallized from the minimum volume of ether after the addition of pentane and cooling; mp 60–61°; $[\alpha]^{25}D$ 177° (*c* 1.03, chloroform); ir data (KBr), 1720 cm^{-1} (ester), no hydroxyl absorption.

Anal. Calcd for $C_{14}H_{15}BrO_5$: C, 48.99; H, 4.40; Br, 23.28. Found: C, 48.85; H, 4.39; Br, 23.58.

The mother liquors were treated with charcoal and evaporated to a syrup which showed a major spot corresponding to the product in addition to some slower moving spots, yield 2.16 g. Although the syrup could not be induced to crystallize, it was satisfactory for further synthetic transformations as such.

When the above reaction was repeated using 1 g of **25** in 100 ml of carbon tetrachloride containing 1 g of NBS and 5 g of barium carbonate in the usual way, the product was obtained as a chromatographically homogeneous syrup, 0.85 g (61.5%), which could be used directly as such.

Methyl 2,3-Anhydro-4-*O*-benzoyl-6-deoxy-α-D-allopyranoside (27).—Hydrogen was bubbled during 7 hr through a stirring methanolic suspension (80 ml) containing 0.5 g of **26**, 0.5 g of 20% palladium on carbon, and 2 g of barium carbonate. The mixture was filtered, and the filtrate was evaporated to a colorless syrup which showed a major spot (green color with the molybdate spray) in addition to two slower moving spots of minor intensity on tlc (chloroform–2,2,4-trimethylpentane–methanol, 100:30:0.5, medium), yield 0.32 g (80–82%).

Purification could be effected by alumina column chromatography using chloroform as solvent. The fractions containing the product were combined and evaporated to a colorless syrup: yield 0.238 g (62% over-all); $[\alpha]^{25}D$ 225° (*c* 1.37, chloroform); ir data (liquid film), 1720 cm^{-1} (ester), no hydroxyl absorption; nmr data, τ 8.8 (center of a doublet, C-6 protons), 4.92, (C-4 proton, multiplet), 5.12, (center of a doublet, J_{12} = 3 cps, C-1 proton). A few of the subsequent fractions contained, in addition to the product, a substance of slower mobility and were discarded.

Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.62; H, 6.10. Found: C, 63.92; H, 6.03.

Hydrogenation of the syrupy mother liquors from the preparation of **26** followed by chromatography over alumina afforded **27** in an over-all yield of 50–60%.

Methyl 2-Azido-4-*O*-benzoyl-2,6-dideoxy-α-D-altropyranoside (28).—An amount of **27** (0.33 g) was dissolved in 10 ml of 2-methoxyethanol containing 1.3 ml of water. Sodium azide (0.33 g) and ammonium chloride (0.13 g) were added and the solution was stirred at reflux temperature for 4 hr. The solution was cooled, diluted with water, and extracted with chloroform. Processing of the organic phase in the usual way afforded a syrup which showed three distinct spots of approximately equal intensity on tlc (benzene–methanol, 100:3, medium-fast) all of which were of slower mobility than the starting material. The syrup was dissolved in ether and petroleum ether was added. On cooling, a small amount of crystalline product was formed which was filtered and washed with cold ether–pentane; yield 42 mg, mp 123–124°. This product to which structure **28** is assigned was homogeneous on tlc and had the same mobility as that corresponding to the slowest spot in the original syrup. Chromatographic examination of the mother liquors revealed the presence of all three components as before. The crystalline material was recrystallized from ether–petroleum ether; mp 124–125°; $[\alpha]^{25}D$ 119° (*c* 0.285, chloroform); ir data (KBr), 2100 (azide), 1728 cm^{-1} (ester).

Anal. Calcd for $C_{14}H_{17}N_3O_5$: C, 54.71; H, 5.57; N, 13.67. Found: C, 54.57; H, 5.53; N, 13.58.

Methyl 3-Azido-4-*O*-benzoyl-6-bromo-2,3,6-trideoxy-α-D-*arabino*-hexopyranoside (30).—An amount (100 mg) of **29**[25] and NBS (75 mg) was suspended in 10 ml of carbon tetrachloride and 0.1 g of barium carbonate was added. The suspension was stirred under reflux for 2.5 hr, cooled, and filtered, and the filtrate was evaporated to dryness. The residual syrup was dissolved in ether and the solution was washed with a small volume of cold water, dried, charcoaled, and evaporated to a colorless syrup (70 mg). This product was essentially homogeneous on tlc (benzene–methanol, 10:1, medium) and had a mobility comparable to that of the starting material. A portion was purified by preparative tlc to give the product as a colorless syrup, $[\alpha]^{25}D$ 52.7° (*c* 0.53, chloroform).

Methyl 2-Azido-4-*O*-benzoyl-6-bromo-2,6-dideoxy-3-*O*-methylsulfonyl-α-D-altropyranoside (32).—To a solution containing 0.39 g of **31**[29] in 20 ml of carbon tetrachloride were added 0.2 g of NBS and 1 g of barium carbonate. After refluxing for 2 hr, the suspension was filtered, and the filtrate was processed as usual to a colorless syrup which was essentially homogeneous on tlc (chloroform–2,2,4-trimethylpentane–methanol, 100:40:0.7); yield 0.335 g (84%); ir data (liquid film), 2100 (azide), 1728 (ester), 1180 cm^{-1} (sulfonate). A portion was purified by preparative tlc and the product was isolated as a syrup which solidified on standing; $[\alpha]D$ 40° (*c* 0.625, chloroform).

Anal. Calcd for $C_{15}H_{18}BrN_3O_7S$: N, 9.05. Found: 9.26.

Methyl 4-*O*-Benzoyl-6-bromo-2,6-dideoxy-α-D-*arabino*-hexopyranoside (34a).—To a solution of **33a**[30] (0.72 g) in 50 ml of carbon tetrachloride were added 0.54 g of NBS and 2 g of barium carbonate. The suspension was stirred under reflux for 2 hr, and processed in the usual way to give a pale yellow syrup after evaporation. The syrup was dissolved in ether and the solution was washed with water, dried, and evaporated to a pale yellow syrup, yield 0.913 g (98%). This product showed one major spot on tlc (chloroform–2,2,4-trimethylpentane–methanol, 100:30:1.5, medium) in addition to two minor components of slow mobility. The syrup was kept at 0° and used within a few days; ir data (liquid film), 1720 cm^{-1} (ester). A portion was purified by preparative tlc, and the product crystallized after a few days (60%) and was recrystallized from ether–pentane; mp 85–86°, $[\alpha]^{25}D$ 71.5° (*c* 3.85, methanol).

Anal. Calcd for $C_{14}H_{17}BrO_5$: C, 48.70; H, 4.96; Br, 23.15. Found: C, 48.77; H, 5.33; Br, 22.84.

Methyl 4-*O*-Benzoyl-2,6-dideoxy-α-D-*arabino*-hexopyranoside (35a).—Hydrogen was bubbled through a stirred methanolic suspension (50 ml) containing 0.7 g of **34a**, 0.5 g of 20% palladium on carbon, and 2 g of barium carbonate. After 3 hr the suspension was filtered and the filtrate was evaporated to a colorless syrup (0.7 g) which was incompletely reduced as indicated from an nmr spectrum. The hydrogenation was repeated during 5 hr and the product was isolated in the usual manner to give 0.4 g (72%) of a syrup which contained traces of starting material (tlc, chloroform–2,2,4-trimethylpentane–methanol, 100:30:1.5). The syrup was purified by preparative tlc for analytical purposes. The eluted zone was processed to a syrup (0.27 g, 49%) which solidified under cold pentane. Recrystallization from ether–pentane gave colorless crystals: mp 61–62°; $[\alpha]^{25}D$ 128° (*c* 1.07, chloroform); ir data (KBr), 1720 cm^{-1} (ester); nmr data, τ 8.76 (center of a doublet, C-6 protons).

Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: 63.06; H, 7.10.

Methyl 4-*O*-Benzoyl-6-bromo-2,6-dideoxy-3-*O*-methyl-α-D-*arabino*-hexopyranoside (34b).—To a solution of **33b** (0.47 g) in 30 ml of carbon tetrachloride were added 0.34 g of NBS and 2 g of barium carbonate. The suspension was stirred under reflux for 2 hr and worked up in the usual way to give a colorless syrup, yield 0.52 g (87%). The product showed essentially one spot on tlc (chloroform–methanol, 100:0.2, medium). A portion purified by preparative tlc showed $[\alpha]D$ 57° (*c* 7.89, chloroform); ir data (liquid film), 1720 cm^{-1} (ester).

Anal. Calcd for $C_{15}H_{19}O_5Br$: C, 50.15; H, 5.33; Br, 22.24. Found: C, 50.16; H, 5.34; Br, 22.35.

Methyl 4-*O*-Benzoyl-2,6-dideoxy-3-*O*-methyl-α-D-*arabino*-hexopyranoside (35b).—A stirred methanolic suspension (150 ml) containing 0.52 g of **34b**, 0.5 g of 20% palladium on carbon, and 3 g of barium carbonate was hydrogenated during 4 hr. The suspension was filtered, the filtrate was evaporated to dryness, the residue was dissolved in ether, and the solution was filtered. Evaporation gave a colorless syrup, yield 0.32 g (78%), exhibiting a major spot on tlc (chloroform–methanol, 100:0.2, medium). A portion was separated by preparative tlc to give the pure product as a syrup, $[\alpha]D$ 87° (*c* 12.3, chloroform).

Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.26; H, 7.19. Found: C, 63.92; H, 7.24.

Methyl 3,4-Di-*O*-benzoyl-6-bromo-2,6-dideoxy-α-D-*ribo*-hexopyranoside (37b).—NBS (0.4 g) was added to a suspension of

barium carbonate (2 g) and **36**[25b] (0.53 g) in 30 ml of dry carbon tetrachloride. After refluxing for 2 hr the suspension was filtered and the filtrate was processed to a colorless syrup, yield 0.68 g (quantitative), which was kept at 0°. Benzoylation of a portion at 0° in the usual way gave the product **37b** as a syrup showing a single spot on tlc with a higher mobility than **36** (chloroform–methanol, 100:1). Infrared data revealed some contamination with benzoic anhydride. A portion of this syrup was purified by preparative tlc to give the crystalline product **37b**, mp 95–96°.

Anal. Calcd for $C_{21}H_{21}BrO_6$: C, 56.13; H, 4.71; Br, 17.78. Found: C, 56.13; H, 4.64; Br, 17.98.

Methyl 4-*O*-Benzoyl-6-bromo-2,3,6-trideoxy-α-D-*erythro*-hexopyranoside (39).—Methyl 4,6-*O*-benzylidene-2,3-dideoxy-α-D-*erythro*-hexopyranoside (**38**)[43] was prepared by the catalytic hydrogenation of the corresponding 2,3-unsaturated glycoside.[48] To 1 g of **38** in 30 ml of carbon tetrachloride were added 0.8 g of NBS and 2 g of barium carbonate. The suspension was stirred under reflux for 2 hr. The reaction mixture was filtered, the filtrate was evaporated to a syrup which was dissolved in ether, and the solution was evaporated to a colorless syrup, yield 1.2 g (92%), which showed a major spot on tlc (chloroform–methanol, 100:0.5, medium); $[\alpha]_D$ 119° (*c* 1.946, chloroform); ir data (liquid film), 1724 cm^{-1} (ester); nmr data, τ 8.08 (C-2, C-3 protons, four-proton multiplet), 5.0 (C-4 proton, multiplet), 5.2 (C-1 proton, apparent doublet, J = 3.5 cps). A portion was purified by short-path distillation.

(48) E. Albano, D. Horton, and T. Tsuchiya, *Carbohydrate Res.*, **2**, 349 (1966), and references cited therein; R. U. Lemieux, E. Fraga, and K. A. Watanabe, *Can. J. Chem.*, **46**, 61 (1968).

Anal. Calcd for $C_{14}H_{17}BrO_4$: C, 51.07; H, 5.21; Br, 24.27. Found: C, 51.20; H, 5.21; Br, 24.67.

Methyl 4-*O*-Benzoyl-2,3,6-trideoxy-α-D-*erythro*-hexopyranoside (40).—Hydrogen was bubbled through a stirred methanolic suspension (80 ml) containing 0.3 g of **39**, 0.2 g of 20% palladium on charcoal, and 1 g of barium carbonate. After 6–7 hr, the suspension was filtered and the filtrate was processed to give the product as a colorless syrup, yield 0.175 g (78%), which showed a major spot on tlc (chloroform–methanol, 100:0.3, medium) in addition to traces of two slower moving spots. A portion was purified by preparative tlc to give the product as a pure syrup: $[\alpha]_D$ 182° (*c* 3.01, chloroform); nmr data, τ 8.78 (center of a doublet, C-6 protons), 8.10 (C-2, C-3 protons, four-proton multiplet).

Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.24. Found: C, 66.88; H, 7.26.

Registry No.—**3**, 18933-80-7; **4a**, 18933-81-8; **4b**, 18933-82-9; **6**, 4990-99-2; **7b**, 18933-84-1; **11**, 18933-85-2; **12**, 18933-86-3; **13**, 18933-87-4; **14**, 18933-88-5; **17a**, 18933-78-3; **17b**, 18933-79-4; **17c**, 18933-53-4; **18**, 18933-54-5; **19**, 18933-55-6; **21**, 10368-84-0; **22**, 10368-83-9; **23a**, 10427-79-9; **23b**, 18944-95-1; **26**, 18933-59-0; **27**, 18933-60-3; **28**, 18933-61-4; **30**, 18933-62-5; **32**, 18933-63-6; **34a**, 18933-64-7; **34b**, 18933-65-8; **35a**, 18944-96-2; **35b**, 18933-66-9; **37b**, 18933-67-0; **39**, 18933-68-1; **40**, 18933-69-2.

The Reaction of *O*-Benzylidene Sugars with *N*-Bromosuccinimide. IV. Neighboring-Group Effects and Rearrangements[1a]

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Reaction of various *O*-benzylidene acetals of sugars in which the acetal ring spans two secondary hydroxyl groups, with NBS, affords, in general, isomeric bromodeoxy sugar benzoates. In the presence of a nearby participating function (hydroxyl, ester) the acetal ring opening may be accompanied by rearrangement leading to the incorporation of bromine at a carbon atom other than those involved in the acetal ring.

We have shown in previous papers in this series[2,3] that 4,6-*O*-benzylidene acetals of various methyl hexopyranosides and disaccharides undergo smooth ring opening by the action of N-bromosuccinimide. With the exception[2] of methyl 4,6-*O*-benzylidene-β-D-galactopyranoside, the acetals under study gave the corresponding methyl 4-*O*-benzoyl-6-bromo-6-deoxyhexopyranosides as the preponderant, if not the exclusive, products. It was also demonstrated[1-3] that these products which possess the combined advantages of a displaceable group at C-6, as well as a selectively benzoylated site at C-4, are versatile synthetic intermediates in carbohydrate chemistry. The examples reported so far have dealt with acetals of the 2-aryl-1,3-dioxane type which are fused *cis* or *trans* to C-4 and C-6 of a hexopyranoside moiety. This paper describes the extension of the NBS reaction to other less common *O*-benzylidene sugars in which the acetal ring spans two *secondary* hydroxyl groups. In the simplest case of a 2-aryl-1,3-dioxolane type the reaction leads to isomeric bromo benzoate derivatives as a result of incorporation of a bromine atom at either carbon atom involved in the 1,3-dioxolane ring. When the molecule contains ester or hydroxyl functions which are in favorable spatial disposition with respect to the acetal ring, the reaction may lead to products other than those expected, due to rearrangements.

In a preceding paper[2] we elaborated on three possible mechanisms for the reaction of *O*-benzylidene sugars with NBS: a "radical-displacement"[4,5] type reaction, an initial hydrogen-abstraction step involving free radicals followed by an ionic termination reaction, and

(1) (a) Portions of this work were presented at the 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966, D29, and the 154th National Meeting, Chicago, Ill., Sept 1967, D16. For part I, see S. Hanessian, *Carbohydrate Res.*, **2**, 86 (1966). (b) To whom correspondence should be addressed at the Department of Chemistry, University of Montreal, Montreal 3, Quebec, Canada.

(2) S. Hanessian and N. R. Plessas, *J. Org. Chem.*, **34**, 1035 (1969), part II of this series.

(3) S. Hanessian and N. R. Plessas, *ibid.*, **34**, 1045 (1969), preceding paper (III) in this series.

(4) D. L. Failla, T. L. Hullar, and S. B. Siskin, *Chem. Commun.*, 710 (1966).

(5) J. D. Prugh and W. C. McCarthy, *Tetrahedron Letters*, 1351 (1966).