# The Reaction of O-Benzylidene Sugars with N-Bromosuccinimide. II. Scope and Synthetic Utility in the Methyl 4,6-O-Benzylidenehexopyranoside Series[1a]

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Treatment of methyl 4,6-O-benzylidenehexopyranosides with N-bromosuccinimide in refluxing carbon tetrachloride or a suitable chlorinated hydrocarbon affords with few exceptions methyl 4-O-benzoyl-6-bromo-6-deoxyhexopyranosides as the preponderant products. Many of the groups utilized in the protection of hydroxyl groups are unaffected by the reaction conditions. Anhydro rings also remain intact. The reaction provides a convenient route to selectively C-4 benzoylated 6-substituted hexopyranose derivatives which are amenable to a variety of transformations and can serve as intermediates to 6-deoxy, 6-amino, etc. hexoses.

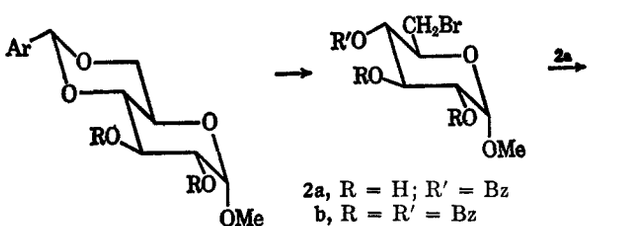
In part I of this series,[2] it was shown that the reaction of some methyl 4,6-O-benzylidene-α-D-hexopyranosides with N-bromosuccinimide (NBS) affords the corresponding methyl 4-O-benzoyl-6-bromo-6-deoxy-α-D-hexopyranosides in good yield. This reaction has considerable potential in various synthetic schemes[1-4] and is also applicable with equal success to other types of benzylidene acetals as will be discussed in the accompanying papers.[5] The present paper describes the extension of the reaction to a variety of methyl 4,6-O-benzylidenehexopyranosides and incorporates information regarding the compatibility of various common blocking groups with the experimental conditions. The scope and mechanism of the reaction are discussed.

## Results

A general procedure for this reaction involves the interaction of the benzylidene acetal with NBS in refluxing carbon tetrachloride in the presence of barium carbonate. In those cases where the starting acetals are insoluble in hot carbon tetrachloride or benzene, complete solution can be effected by the addition of dry 1,1,2,2-tetrachloroethane. The presence of excess barium carbonate as a scavenger for hydrogen bromide may be desirable, although not necessary. The reaction is invariably complete within 2–2.5 hr and is characterized in some cases by the appearance of colors ranging from orange to brick red during the initial stages of refluxing. The ring opening of the acetal and the incorporation of a benzoate function in the molecule can be readily recognized from the absence of the benzylic proton and the characteristic splitting pattern of the aromatic ring hydrogens in the nmr spectrum of the product. In several cases, the products could be crystallized directly from the crude residues.

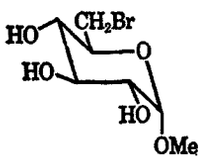
In the case of methyl 4,6-O-benzylidene-α-D-glucopyranoside[6,7] (**1a**) (Scheme I), an ether-soluble crystalline product could be isolated in about 60% yield directly from the processed syrup and was found to be methyl 4-O-benzoyl-6-bromo-6-deoxy-α-D-glucopyranoside[2] (**2a**). Thin layer chromatographic examination of the crude reaction product prior to the crystallization of **2a** showed, in addition to the latter, a slightly slower moving minor product. Benzoylation of **2a**

Scheme I




**1a**, R = H; Ar = Ph
**b**, R = Bz; Ar = Ph
**c**, R = Ms; Ar = Ph
**d**, R = H; Ar = $C_6H_4OMe$-*p*

**2a**, R = H; R′ = Bz
**b**, R = R′ = Bz
**c**, R = Ms; R′ = Bz
**d**, R = H; R′ = $COC_6H_4OMe$-*p*




**3**

afforded the crystalline tribenzoate **2b**.[8] Mesylation of **2a** gave the corresponding crystalline 2,3-dimesylate **2c**. The latter could also be obtained in about 79% yield from **1c**[9] by the NBS route. Mesylation of a crude preparation of **2a** afforded the same crystalline derivative **2c**, which was obtained from **1c** as described above. Debenzoylation of **2a** in methanol containing sodium methoxide afforded crystalline methyl 6-bromo-6-deoxy-α-D-glucopyranoside **3**.

The reaction of methyl 4,6-O-anisylidene-α-D-glucopyranoside (**1d**) with NBS afforded the product **2d** as a chromatographically homogeneous syrup, possessing the expected spectral characteristics. Treatment of the β-anomeric glycoside[6] **4** (Scheme II) with NBS

(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. (b) To whom correspondence should be addressed at the Department of Chemistry, University of Montreal, Montreal 3, Quebec, Canada.

(2) S. Hanessian, *Carbohydrate Res.*, **2**, 86 (1966).

(3) S. Hanessian, *Advan. Carbohydrate Chem.*, **21**, 146 (1966).

(4) S. Hanessian, Advances in Chemistry Series, No. 74, American Chemical Society, Washington, D. C., 1968, p 159.

(5) S. Hanessian and N. R. Plessas, *J. Org. Chem.*, **34**, 1045, 1053 (1969), papers III and IV in this series.

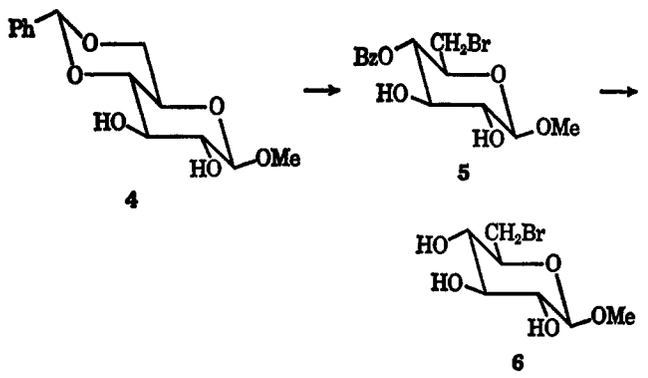
(6) K. Freudenberg, H. Toepffer, and C. C. Andersen, *Ber.*, **61**, 1750 (1928).

(7) N. K. Richtmyer, *Methods Carbohydrate Chem.*, **1**, 107 (1962).

(8) B. Helferich, W. Klein, and W. Schafer, *Ann.*, **447**, 19 (1926).

(9) J. Honeyman and J. W. W. Morgan, *J. Chem. Soc.*, 3660 (1955).

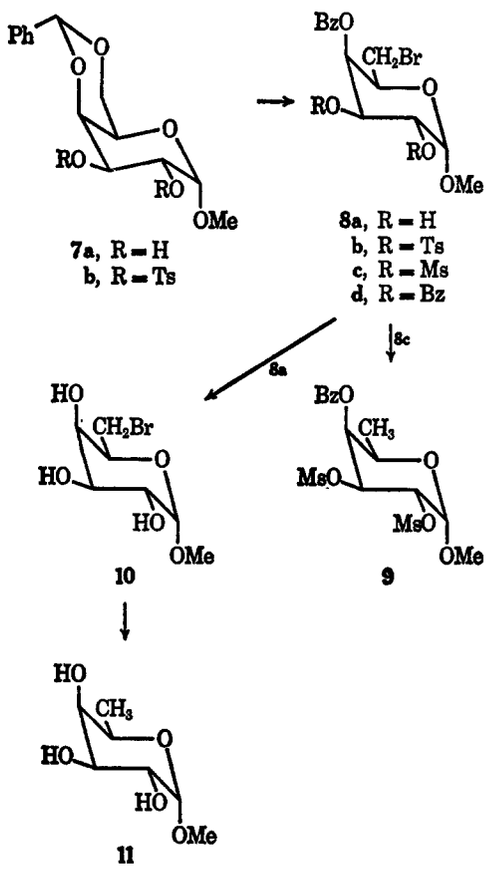
SCHEME II



gave crystalline methyl 4-*O*-benzoyl-6-bromo-6-deoxy-β-D-glucopyranoside (**5**) in 67% yield. The latter was debenzoylated to the known[10] methyl 6-bromo-6-deoxy-β-D-glucopyranoside (**6**). Thin layer chromatographic examination of the mother liquors or the crude reaction product prior to the crystallization of **5** showed no other product.

Reaction of methyl 4,6-*O*-benzylidene-α-D-galactopyranoside[11] (**7a**) (Scheme III) with NBS in a mixture of

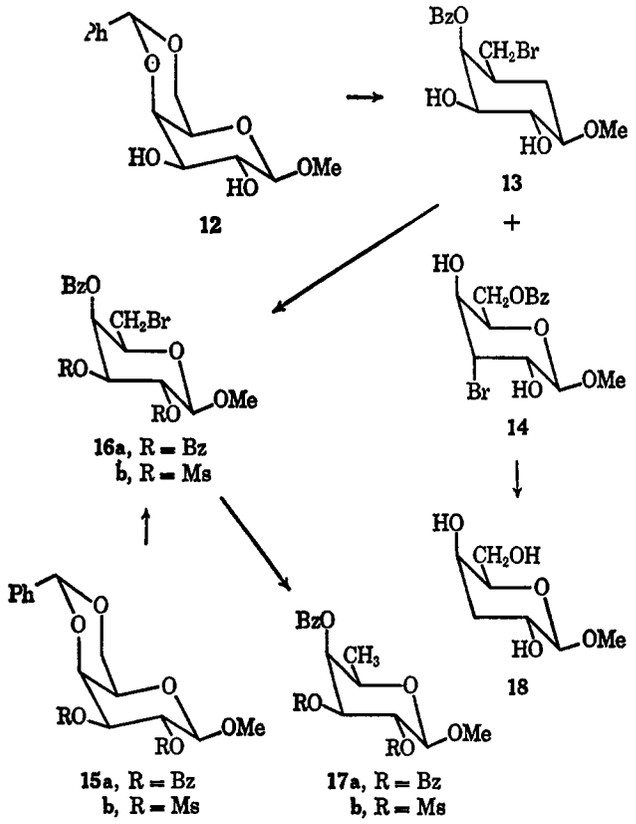
SCHEME III



carbon tetrachloride and tetrachloroethane containing excess barium carbonate afforded the corresponding 6-bromo-4-benzoate derivative[2] **8a** in over 90% yield. The ether-soluble product was obtained as a chromatographically homogeneous colorless syrup (or a brittle solid). The crystalline tribenzoate **8d** and dimesylate **8c** derivatives could be prepared from **8a** in the usual manner. Catalytic reduction of **8c** gave crystalline methyl 4-*O*-benzoyl-6-deoxy-2,3-di-*O*-methylsulfonyl-α-D-galactopyranoside (**9**). Catalytic debenzoylation of **8a** afforded crystalline methyl 6-bromo-6-deoxy-α-D-galactopyranoside (**10**) which was further transformed into crystalline methyl 6-deoxy-α-D-galactopyranoside (**11**) by catalytic hydrogenation.

In the case of methyl 4,6-*O*-benzylidene-β-D-galactopyranoside[11] (**12**) (Scheme IV), two products were

SCHEME IV



formed in the NBS reaction. These were separated by chromatography and were obtained as homogeneous syrups (about 1:1 ratio) which had the properties expected of isomeric bromo benzoate derivatives. The componentent with lower chromatographic mobility was oxidized in aqueous sodium metaperiodate solution. On benzoylation, this product afforded a crystalline tribenzoate **16a** which when catalytically reduced gave crystalline methyl 2,3,4-tri-*O*-benzoyl-6-deoxy-β-D-galactopyranoside (**17a**). The identity of the latter derivative was clearly evident from its nmr spectrum. The isomer having a lower chromatographic mobility is therefore methyl 4-*O*-benzoyl-6-bromo-6-deoxy-β-D-galactopyranoside (**13**). The isomer having a higher chromatographic mobility was unaffected by periodate. When subjected to catalytic reduction and debenzoylation a crystalline product was obtained which, rather surprisingly, proved to be methyl 3-deoxy-β-D-*xylo*-hexopyranoside[12] (**18**). The initial reaction product

(10) B. A. Lewis, F. Smith, and A. M. Stephen, *Methods Carbohydrate Chem.*, **2**, 172 (1963).

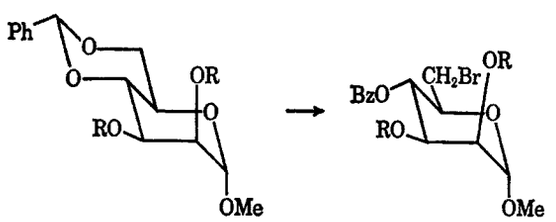
(11) E. Sorkin and T. Reichstein, *Helv. Chim. Acta*, **28**, 1 (1945), and references cited therein.

(12) M. Dahlgard, B. H. Chastain, and Ru-Jen Lee Han, *J. Org. Chem.*, **27**, 929 (1962). We thank Dr. Dahlgard for an authentic specimen.

is therefore most likely methyl 6-*O*-benzoyl-3-bromo-3-deoxy-β-D-gulopyranoside (**14**). When the benzoylated analog[13] of **12**, namely **15a**, was used as substrate, the NBS reaction afforded a single product which was identical with **16a** derived from **13**. The reaction, however, was incomplete even after 3 hr as evidenced by the presence of starting material in tlc-monitored experiments. The identity of **16a** obtained by this route was further substantiated by its conversion into crystalline **17a**. The mesylated analog **15b** also afforded a single product **16b** in the NBS reaction. In this case, however, no starting material could be detected chromatographically after the normal reaction period of 2.5 hr. The product **16b** was converted into methyl 4-*O*-benzoyl-6-deoxy-2,3-di-*O*-methylsulfonyl-β-D-galactopyranoside (**17b**), thereby locating the position of the bromine atom in **16b**. The latter substance could also be obtained by mesylation of **13**.

In the mannose series (Scheme V), methyl 4,6-*O*-

SCHEME V



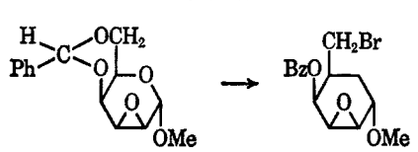

**19a**, R = H
**b**, R = Bz
**c**, R = Ac

**20a**, R = H
**b**, R = Bz
**c**, R = Ac

benzylidene-α-D-mannopyranoside[14] (**19a**) was treated with NBS in refluxing carbon tetrachloride containing 10% by volume of tetrachloroethane. The major component in the ether-soluble syrupy product (79%) was the expected methyl 4-*O*-benzoyl-6-bromo-6-deoxy-α-D-mannopyranoside (**20a**). Conventional benzoylation afforded the crystalline tribenzoate **20b**. The latter product was also obtained in over 70% yield by the NBS procedure starting with the dibenzoate **19b**. It is noteworthy that whereas both **19b** and **20b** have strongly negative optical rotations the corresponding diacetates **19c**[15] and **20c** have positive rotations.

The NBS reaction was also applied successfully in the case of benzylidene acetals of anhydro sugar derivatives. Thus, methyl 2,3-anhydro-4,6-*O*-benzylidene-α-D-talopyranoside[16] (**21**) (Scheme VI) afforded crystalline

SCHEME VI

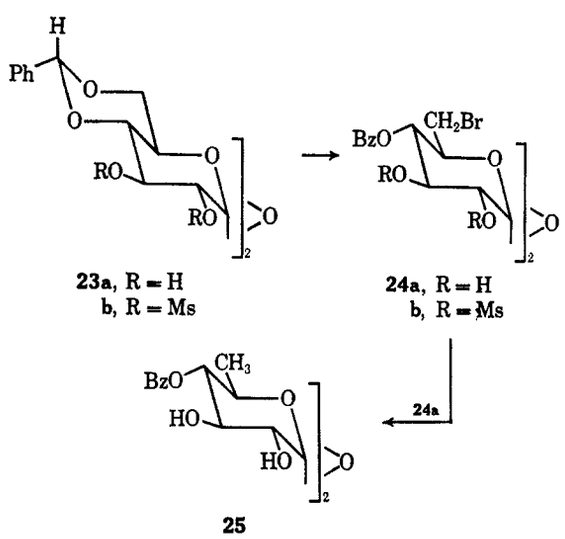



**21** **22**

methyl 2,3-anhydro-4-*O*-benzoyl-6-bromo-6-deoxy-α-D-talopyranoside (**22**) in 81% yield. Under reaction conditions which do not utilize an excess of NBS, no side products resulting from the cleavage of the susceptible anhydro ring could be detected by thin layer chromatography. The structure assigned to **22** is based on previous analogies and on certain transformations of related products into 6-substituted derivatives.[5]

The adaptability of the NBS reaction to benzylidene acetals of some disaccharides was also established. Crystalline α,α-trehalose dihydrate was converted into its 4,6:4′,6′-di-*O*-benzylidene derivative **23a** by conventional reaction with benzaldehyde in the presence of zinc chloride. The crystalline product contained 2.4% moisture (Karl Fischer titration) but was suitable for use as such. The NBS reaction in a mixture of carbon tetrachloride and tetrachloroethane afforded the anticipated 4,4′-di-*O*-benzoyl-6,6′-dibromo-6,6′-dideoxy-α,α-trehalose (**24a**) in 60% crude yield (Scheme VII).

SCHEME VII




**23a**, R = H
**b**, R = Ms

**24a**, R = H
**b**, R = Ms

**25**

This material was contaminated with some minor impurities of low mobility as evidenced on thin layer chromatograms and could be purified by column chromatography. The yield of crystalline **24a** could be improved and the chromatographic step could be obviated by utilizing anhydrous starting material which can be conveniently obtained by dehydration with pyridine as described for α,α-trehalose.[17] Mesylation of **24a** afforded the tetramesylate derivative **24b**. Alternatively, an NBS reaction utilizing **23b** afforded the same product obtained by mesylation of **24a**. Catalytic reduction of **24a** afforded crystalline 4,4′-di-*O*-benzoyl-6,6′-dideoxy-α,α-trehalose (**25**), the structure of which was confirmed from its nmr spectrum.

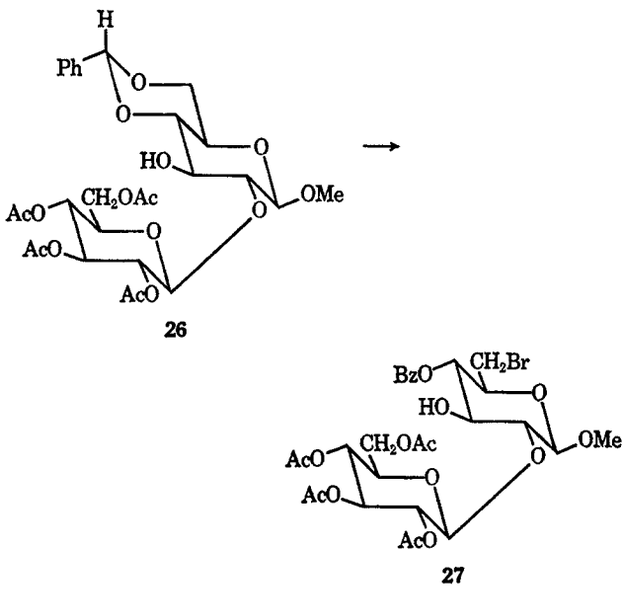
Finally another disaccharide derivative, methyl 2-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-4,6-*O*-benzylidene-α-D-glucopyranoside[18] (**26**) (Scheme VIII), was converted into the corresponding 4-*O*-benzoyl-6-bromo-6-deoxy derivative **27** *via* the NBS reaction.

## Discussion

Three aspects of the reaction of methyl 4,6-*O*-benzylidene-α-D-hexopyranosides (and the correspond-

(13) J. S. D. Bacon, D. J. Bell, and H. W. Kosterlitz, *J. Chem. Soc.*, 1248 (1939).
(14) J. G. Buchanan and J. C. P. Schwartz, *ibid.*, 4770 (1962).
(15) B. Coxon, *Tetrahedron*, **21**, 3481 (1965).
(16) M. Gyr and T. Reichstein, *Helv. Chim. Acta*, **28**, 226 (1945).
(17) G. G. Birch, *J. Chem. Soc.*, 3489 (1965).
(18) We are indebted to Dr. I. J. Goldstein, The University of Michigan, for a sample of this compound.

SCHEME VIII

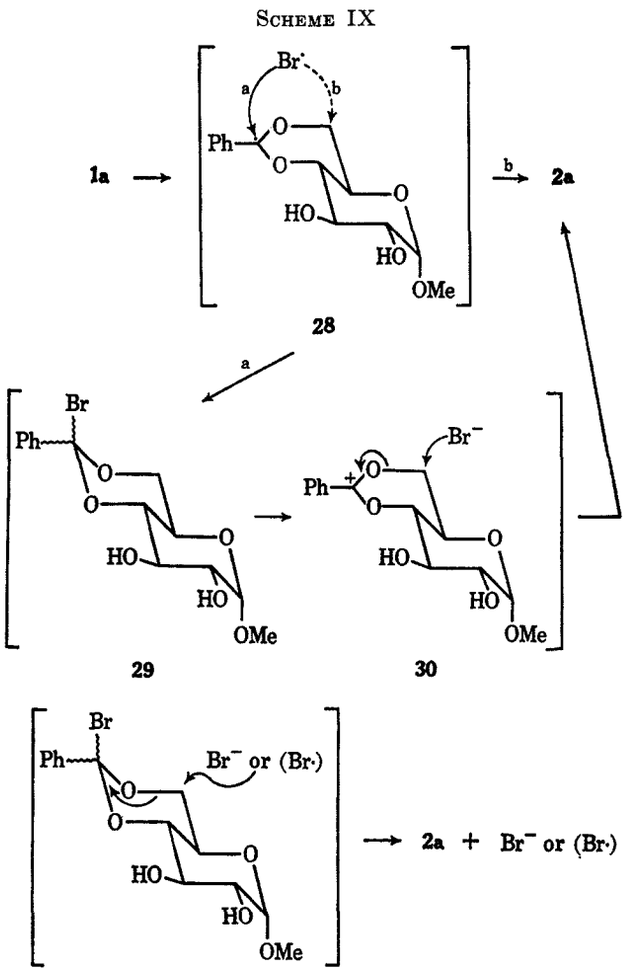



ing 2-, 3-, or 2,3-substituted analogs) with NBS are particularly important. First, the major reaction products are invariably methyl 4-*O*-benzoyl-6-bromo-6-deoxy-α-D-hexopyranosides which lend themselves to a variety of chemical transformations.[1-5] For example, the synthesis of 6-deoxy, 6-amino, 6-fluoro, and other 6-substituted sugars can be effected in two steps from the readily available acetals, by subjecting the intermediate bromo benzoates to reduction or nucleophilic displacement reactions, respectively. Second, the reaction provides an indirect method for the selective benzoylation of the C-4 hydroxyl group in the hexopyranosyl moieties, irrespective of the configuration of that carbon atom. The situation of a benzoate group at C-4 could be of considerable value in stereochemical and conformational assignments, since the C-4 proton appears in a downfield position in the nmr spectra of such derivatives, and the splitting pattern can be suitably analyzed. Furthermore, the removal of the ester function from suitably substituted (at C-2 and C-3) glycosides, or starting with 2-substituted methyl 4,6-*O*-benzylidenehexopyranosides, provides derivatives which are fully protected except at C-4 and C-3, respectively. Such derivatives are ideally suited for saccharide synthesis. Third, except for an isolated example, the nature of the reaction products in the series reported in this paper seems to be unaffected by steric hindrance and stereochemical factors.

The compatibility of such functional groups as anhydro, ester, methylsulfonyloxy, amide, azide, methoxy, and other commonly used protecting groups in carbohydrate chemistry with the reaction conditions broadens the scope of the reaction considerably. The products derived from acetal derivatives containing benzyl or *p*-tolylsulfonyl functions should be carefully examined, since according to mechanistic considerations these groups could be susceptible to attack by the reagent. For example, reaction of methyl 4,6-*O*-benzylidene-2,3-di-*O*-*p*-tolylsulfonyl-α-D-galactopyranoside (**7b**), with 1.14 molar equiv of NBS afforded a crystalline product which, when examined on thin layer chromatograms, consisted of a major component and a minor component having a slightly faster mobility. An elementary analysis showed a higher percentage of bromine than that calculated for the expected product **8b**. Repeated recrystallizations failed to provide satisfactory figures. The major component was therefore separated by preparative thin layer chromatography and was obtained crystalline. Analytical and other data proved it to be the expected product **8b**. It is most likely therefore, that the faster moving component is a product in which some of the benzylic hydrogen(s) on the tosyloxy functions are replaced by bromine atoms. The proportion of this by-product was not significant enough to allow its recognition from the integrated area of the tosyloxy methyl groups in the nmr spectrum of the mixed product.

We can envisage two general pathways (Scheme IX)

SCHEME IX




for the reaction of *O*-benzylidene acetals with NBS under the present conditions: an over-all free-radical mechanism and a radical hydrogen abstraction step followed by a concerted-type or ionic termination reaction. While it is difficult to exclude experimentally one or the other, there is evidence indicating that, at least in some cases, the latter mechanism may prevail.[19]

(19) 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.

With **1a** as a model, initial hydrogen abstraction could lead to the radical-like intermediate **28**[20] which could then react by pathways a or b. The former pathway could give a bromo acetal intermediate **29** which could disproportionate into the benzoxonium ion **30** and bromide ion. Attack of the latter ion at the least hindered C-6 position in **30** would give **2a**. The product could also be formed by a direct attack of a bromine atom *via* pathway b or by a concerted attack (ionic or radical) *via* **29**. The preponderance of the 4-*O*-benzoyl-6-bromo-6-deoxy isomer, in this and other cases, even when the configuration and bulk of substituents at C-2 and C-3 were altered, indicates a high degree of selectivity in the ring-opening step.

Subsequent to the preliminary announcement of our work,[2] a communication by Hullar and coworkers[21] described the ring opening of three substituted methyl 4,6-*O*-benzylidenehexopyranosides with NBS in the presence of a free-radical initiator. The preponderant formation of 6-bromo-6-deoxy derivatives was also noted by these workers who suggested a "radical displacement" type of reaction to explain the results (pathway b, Scheme IX).

Two examples involving the reaction of *O*-benzylidene acetals with NBS in the absence of added catalysts are pertinent to the present discussion. In the first example[22] the light-catalyzed reaction of benzaldehyde diethyl acetal with NBS in refluxing carbon tetrachloride was shown to give ethyl benzoate, but no ethyl bromide could be detected. Several years later, the benzylidene acetal from *cis*-cyclohexane-1,2-diol was treated with NBS in refluxing carbon tetrachloride, presumably under normal laboratory lighting conditions.[23] A product obtained in 82% yield was identified as *trans*-2-bromocyclohexyl benzoate. Current views[24-26] on the mechanism of bromination by NBS imply that the function of the latter is to provide molecular bromine and hence bromine atoms in very low concentrations, which act as the hydrogen-abstracting species. Bromine atoms can be generated in the present case by reactions of NBS with traces of peroxides or simply by its thermal homolysis. A low concentration of molecular bromine can be subsequently maintained in the reaction mixture by various processes including the ionic reaction of NBS with hydrogen bromide. Although the reactions are performed in the presence of agents capable of sequestering the acid as it is formed (barium carbonate, pyridine), it is not unlikely that traces of hydrogen bromide are always present under these heterogeneous and homogeneous conditions, respectively. Model experiments were carried out with compound **1c** and it was found that yields of the product **2c** were essentially unchanged when the reaction was performed for the same period of time, either in the absence of barium carbonate or in the presence of an organic peroxide. Moreover, the presence of modifiers[27] such as pyridine (an accelerator) or 1,3,5-trinitrobenzene (a retarder) seemed to have no appreciable effect on the yield of **2c**. When excess pyridine was incorporated in the reaction mixture, a gummy substance separated on the walls of the flask during the refluxing period. This material was insoluble in carbon tetrachloride, but was soluble in alcohols and water and could conceivably be a pyridinium salt resulting from the reaction of the intermediate (*e.g.*, **29** or **30**) with pyridine. When the NBS reaction was performed in the presence of 1 equiv of water, lower yields of product were isolated at the expense of the formation of some components which had slower mobility on thin layer chromatograms. These substances were not examined further; however, it was established that at least one of these contained a benzoate group and could conceivably be a product derived from ring opening of the intermediate **29** or **30** by the competing hydroxyl ion. Direct proof was obtained to demonstrate that *bromine* itself is actually involved in the reaction of *O*-benzylidene acetals as in the bromination of allylic and related systems.[24-26] A solution of **1c** in refluxing carbon tetrachloride containing excess barium carbonate was treated with 1.1 equiv of bromine in carbon tetrachloride solution, dropwise over a period of 1 hr. The reaction mixture was then refluxed for an additional 1 hr and was processed as usual. A crystalline substance was isolated directly in 47% yield from the crude product and proved to be **2c**. The decreased yield (compared to the NBS route 70%) is to be expected since no physical method of sustained bromine introduction into the reaction medium could approach the role of NBS itself. When the experiment was repeated with bromine in the presence of benzoyl peroxide for the same period of time, the yield of crystalline **2c** was 68%. The improvement in yield indicates that in this case, at least the first stage of the reaction is favored in the presence of free-radical initiators. In addition, when the reaction of **1c** with NBS was carried out in nonaqueous polar solvents such as N,N-dimethylformamide or acetonitrile, only traces of product **2c** were formed and starting material could be recovered in good yield. This observation lends support for an initial radical-type rather than ionic hydrogen abstraction step. Brominations by NBS are also known to be affected by such environmental conditions as light, heat, the presence of peroxides, etc.[27] Since our experiments were performed under ordinary laboratory lighting conditions, it was of interest to next study the effect, if any, of the remotely installed neon lights on the reaction. Accordingly, compound **1c** was allowed to react with NBS in refluxing carbon tetrachloride in the absence of light. Although starting material was recovered, the product **2c** was still formed in 40% yield. The lower yield compared to that under normal conditions is probably due to the slower rate of reaction in the bromine-deficient medium and accentuates the role of diffuse light even from a distance. Although it is possible that the NBS reaction is catalyzed by traces of peroxides present in the solvents used, the need for heat is evident from the fact that no

(20) Such a radical could presumably be stabilized by electron donation of the acetal ring oxygens to give polar and nonpolar resonating hybrids.

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

(22) E. N. Marvell and M. J. Joncich, *J. Am. Chem. Soc.*, **73**, 973 (1951).

(23) A. Rieche, E. Schmitz, W. Schade, and E. Beyer, *Chem. Ber.*, **94**, 2926 (1961).

(24) P. S. Skell, D. L. Tuleen, and P. D. Readio, *J. Am. Chem. Soc.*, **85**, 2849 (1963); B. P. McGrath and J. M. Tedder, *Proc. Chem. Soc.*, 80 (1961).

(25) G. A. Russell, C. DeBoer, and K. M. Desmond, *J. Amer. Chem. Soc.*, **85**, 365 (1963).

(26) C. J. M. Stirling, "Radicals in Organic Chemistry," Oldbourne Press, London, 1965, p 53.

(27) H. J. Dauben, Jr., and L. L. McCoy, *J. Am. Chem. Soc.*, **81**, 4863 (1959).

reaction occurred for prolonged periods at room temperature.

The literature records[28,29] some examples of the incorporation of chlorine in the reaction products when NBS reactions were conducted in chlorinated solvents. Although such a process appeared unlikely in our system, the NBS reaction was performed in benzene as solvent with the model acetal, **1c**. The product was identical in all respects with that obtained using the chlorinated hydrocarbons.

Attention was also given to the study of peroxide-induced NBS reactions in order to establish such criteria as product distribution, optimum yields, and compatibility with certain blocking groups. As in the noninduced reactions, the 4-*O*-benzoyl-6-bromo-6-deoxy derivatives were once again formed in preponderance. It was also found that at least on a small scale, the presence of free hydroxyl functions in the molecule is compatible with the reaction conditions.

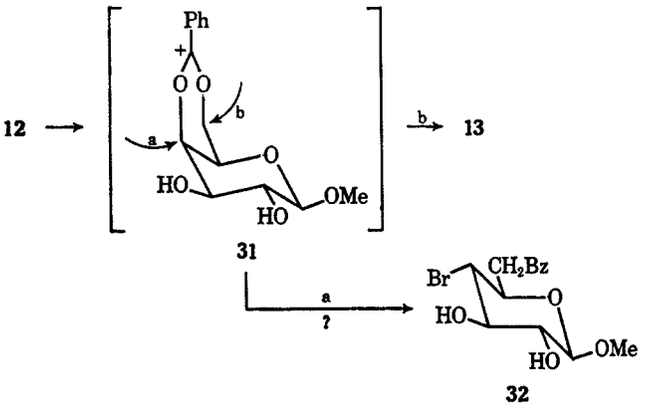
The NBS reaction with methyl 4,6-*O*-benzylidene-α-D-galactopyranoside and its derivatives provides easy access to the corresponding methyl 4-*O*-benzoyl-6-bromo-6-deoxy-α-D-galactoside (**8**) and hence to 6-deoxy- and 6-substituted D-galactose derivatives. This feature is noteworthy because the commonly used methods[4] for the introduction of halogen atoms at C-6 in the galactose structure, such as the displacement of tosylates, usually result in low yields and are often unpredictable. It has been recognized[30] for some time that the displacement of sulfonyloxy groups at the 6 position in various galactose derivatives[31-33] is a comparatively slow reaction. The situation is quite pronounced in the β-D-anomeric series. A direct route to 6-deoxyhexoses is available by the lithium aluminum hydride reduction of terminal sulfonates.[34] The relatively vigorous reaction conditions in the presence of the powerful hydride reagent are oftentimes incompatible with other protecting groups such as esters, etc., in the molecule. The alternate two-step route to 6-deoxyhexoses *via* the replacement of 6-sulfonates and subsequent reduction of the corresponding 6-halides has been known for many years and continues to be the method of choice in many laboratories. The inherent problems concerned with the decreased reactivity of the 6-sulfonates in the galactopyranose series are, however, still unsolved.

The application of the NBS reaction to various substituted methyl 4,6-*O*-benzylidene-α-D-galactopyranoside derivatives averts the necessity for sulfonate displacement reactions and presents a practical procedure for the preparation of methyl 6-bromo-6-deoxy-α-D-galactoside and other 6-substituted derivatives such as **8a, 8b,** etc.

Another unique feature of the NBS reaction in this series is the indirect benzoylation of the C-4 axial hydroxyl group in the presence of two equatorial groups at C-2 and C-3, **7a** → **8a.**

Because of the success of the NBS reaction in the methyl α-D-galactoside series, it was of interest to extend this application to the β anomeric series where the introduction of halogen atoms at C-6 using established methods[4] has met with limited success. It was anticipated that attack of bromide ion on the intermediate benzoxonium ion[19] **31** (Scheme X) might occur

SCHEME X




at C-4 (pathway a) in addition to that expected at C-6 (pathway b), because of the relative inertness of the latter position toward nucleophilic agents. The reaction did indeed afford two products, of which one was identified as methyl 4-*O*-benzoyl-6-bromo-6-dexoy-β-D-galactopyranoside (**13**). The other product was not the expected methyl 6-*O*-benzoyl-4-bromo-4-deoxy-β-D-glucoside (**32**), but presumably methyl 6-*O*-benzoyl-3-bromo-3-deoxy-β-D-guloside (**14**). Although the actual stereochemistry of **14** was not established, the D-*gulo* configuration can be assigned from its transformation into crystalline methyl 3-deoxy-β-D-*xylo*-hexopyranoside (**18**), which requires the presence of the bromine atom at C-3. The same results were obtained when the NBS reaction was performed in the presence of benzoyl peroxide.

In order to ascertain that **14** was not formed from the isomeric methyl 3,4-*O*-benzylidene-β-D-galactoside which could have presumably been present in the original **12,** the purity of the latter compound was checked. Thus the crystalline di-*O*-benzoate[13] and di-*O*-methyl[35] derivatives of **12** were prepared and found to have physical constants in agreement with the reported values. Furthermore, in the case of the dimethyl ether, the *crude* methylation product as well as a recrystallized specimen showed a purity of >99% by vapor phase chromatographic analysis and had identical retention times. At the present time we have no satisfactory explanation for the formation of compound **14,** except to speculate that a charged cyclic intermediate could be involved at some stage which would have to be attacked stereoselectively at C-3 (and/or at C-6). That the C-3 hydroxyl group plays a role in diverting the reaction from its normal course is relevant from the observation that the reaction of the dibenzoate **15a** with NBS gave only **16a** with no trace of an isomeric product. However, even after a 3-hr reaction period a noticeable amount of starting material was still present.

(28) J. D. Prugh and W. C. McCarthy, *Tetrahedron Letters*, 1351 (1966).
(29) F. W. Baker, H. D. Holtz, and L. M. Stock, *J. Org. Chem.*, **28**, 514 (1963).
(30) R. S. Tipson, *Advan. Carbohydrate Chem.*, **8**, 107 (1953).
(31) S. Nadkarni and N. R. Williams, *J. Chem. Soc.*, 3496 (1965).
(32) J. M. Sugihara and W. J. Teerlink, *J. Org. Chem.*, **29**, 550 (1964).
(33) M. Akazi, S. Tejima, and M. Haza, *Chem. Pharm. Bull.* (Tokyo), **11**, 559 (1963).
(34) H. Schmid and P. Karrer, *Helv. Chim. Acta*, **32**, 1371 (1949).
(35) J. W. H. Oldham and D. J. Bell, *J. Am. Chem. Soc.*, **60**, 323 (1938).

This feature, which has not been encountered heretofore in our experiences, could be a reflection of the relative retardation in the first step of the reaction, namely the abstraction of the benzylic proton. The fate of the benzoxonium ion[19] which is formed must be decided by the relative susceptibilities of C-4 and C-6 to nucleophilic attack and by the nature of the C-3 substituent. Contrary to this case, the dimesylate derivative **15b** reacted with NBS in a normal fashion to give the 4-*O*-benzoyl-6-bromo-6-deoxy derivative **16b**. No trace of either starting material or other isomers of **16b** could be found. It can be concluded therefore that the bulk and the nature of the substituents at C-3 in the β-D-galactoside series (**12, 15a, 15b**) play dominant roles in determining the yield and type of product. It is noteworthy that the NBS reaction in the case of the β-D-glucoside derivative **4** proceeded normally to give the 6-bromo-4-benzoate **5** as the sole product. Previous experiences[30] have shown that displacement reactions at C-6 in β-D-glucoside derivatives are also sluggish, although not to the extent of the displacement reactions at C-6 of the β-D-galactosides.

An important feature in the NBS reaction with methyl 2,3-anhydro-4,6-*O*-benzylidene hexopyranosides is that the epoxide function remains intact. The resulting polyfunctional products are versatile synthetic intermediates since use could be made of ring-opening reactions as well as various modifications at C-6.[1,5] These substances can provide facile routes to 2,6- or 3,6-disubstituted sugar derivatives, depending on the orientation of the epoxide function.

The synthesis of a 6,6′-dideoxy derivative of α,α-trehalose from the readily available 4,6:4′,6′-di-*O*-benzylidene derivative can be realized in essentially two steps from α,α-trehalose. A previous synthesis[36] of 6,6′-dideoxy-α,α-trehalose is based on a sequence which necessitates at least six steps.

## Experimental Section

Melting points are uncorrected. Nmr spectra were obtained in chloroform-*d* unless otherwise stated, on a 60-Mc spectrometer using tetramethylsilane as reference. Optical rotations were measured with a Perkin-Elmer photoelectric polarimeter at 25°. Thin layer chromatography 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 (slow, medium, fast) 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 and ether 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 4-*O*-Benzoyl-6-bromo-6-deoxy-α-D-glucopyranoside (2a).**[2]—To a suspension of **1a** (10 g) in 500 ml of carbon tetrachloride and 30 ml of tetrachloroethane were added 7.5 g of NBS and 4 g of barium carbonate. The suspension was heated at reflux with efficient stirring for 2.5 hr and filtered while hot. The cake was washed with hot carbon tetrachloride (120 ml) and the filtrate and washings were evaporated to dryness. The resulting syrup was dissolved in ether (300 ml), and the solution was washed with three 30-ml portions of water and dried. Evaporation of the solution afforded a colorless syrup which readily crystallized upon trituration with cold ether, yield 6.08 g. The mother liquors afforded an additional 0.9 g of product: combined yield 56%; ir data (KBr), 1722 $cm^{-1}$ (ester). The colorless product had mp 121–122° and was chromatographically homogeneous (chloroform–methanol, 100:5, medium). An analytical sample was obtained by recrystallization from a mixture of acetone, ether, and pentane; mp 130–131°, $[\alpha]_D$ 118° (*c* 1.01, chloroform).[37]

*Anal.* Calcd for $C_{14}H_{17}BrO_6$: C, 46.55; H, 4.74; Br, 22.12. Found: C, 46.38; H, 4.69; Br, 22.10.

The reaction was repeated under the same conditions but without adding barium carbonate. The product **2a** was obtained in 43% yield, mp 130–131°. The mother liquors were processed to give a syrup, which was chromatographically identical with the crystalline product, except for contamination with some minor slower moving components; total crude yield, 90–93%.

The reaction was repeated (3.6-mmol scale) under the same conditions in the presence of 0.01 mmol of benzoyl peroxide. The product **2a** was obtained in 60% over-all yield, mp 130–131°, unchanged when cocrystallized with the product obtained in the absence of the catalyst.

Mesylation of crude **2a** prior to crystallization with methanesulfonyl chloride in pyridine at 0° overnight followed by conventional processing afforded the crystalline dimesylate **2c**, mp 130–132°, yield 40%.

Benzoylation of **2a** with benzoyl chloride in pyridine at room temperature overnight, followed by conventional processing, afforded the tribenzoate **2b** in 82% yield, mp 118–120°, lit.[8] mp 122°.

**Methyl 4-*O*-Benzoyl-6-bromo-6-deoxy-2,3-di-*O*-methylsulfonyl-α-D-glucopyranoside (2c).** (a) **NBS Method.**—A suspension containing 11.5 g of **1c**, 6.4 g of NBS, and 6.0 g of barium carbonate in 390 ml of carbon tetrachloride and 50 ml of tetrachloroethane was refluxed with stirring for 2 hr. The filtered solution was evaporated to dryness and the resulting syrup was dissolved in ether and washed with water twice. The ethereal extracts were dried and evaporated to a colorless syrup which crystallized within a few minutes from a small volume of cold methanol; yield 8.5 g, mp 130–132°. An additional crop (0.5 g) was obtained from the mother liquors, total yield 68–70%. The product was chromatographically homogeneous (chloroform–2,2,4-trimethylpentane–methanol, 100:30:2, medium). Recrystallization from cold methanol afforded an analytical sample: mp 134–135°; $[\alpha]_D$ +53.5° (*c* 1.01, chloroform); ir data (KBr), 1730 $cm^{-1}$ (ester).

*Anal.* Calcd for $C_{16}H_{21}BrO_{10}S_2$: C, 37.14; H, 4.09; Br, 15.44; S, 12.39. Found: C, 37.31; H, 4.32; Br, 15.38; S, 12.43.

The reaction was repeated on a 1-mmol scale without the addition of barium carbonate. The product **2c** was isolated in about 75% crude yield as described above, mp 128–130°.

The reaction was repeated on a 1-mmol scale with the exclusion of light. The yield of crystalline **2c** was 40%. In the absence of heat (overnight, room temperature), no product was formed and starting material was isolated.

The reaction was repeated on a 1-mmol scale in the presence of benzoyl peroxide (0.01 mmol/mmol of **1c**) and the product **2c** was isolated in the usual way; yield 68%.

The reaction was repeated on a 1-mmol scale in the presence of pyridine (1 mmol/mmol of **1c**) without the addition of barium carbonate, and also in the presence of 1,3,5-trinitrobenzene (0.1 mmol/mmol of **1c**). The yields of **2c** were 71 and 77%, respectively.

When excess pyridine was present (4 mmol/mmol of **1c**), a brown gummy substance was formed on the walls of the flask during refluxing. At the end of the reaction period, the solution was decanted and the gum was washed with excess carbon tetrachloride, then with ether. It was soluble in methanol, water, methyl sulfoxide, etc. Thin layer chromatography (chloroform–2,2,4-trimethylpentane–methanol, 100:30:2) of an aliquot revealed the presence of a trace of **1c** or **2c** in addition to a slower moving uv absorbing spot. An infrared spectrum (liquid film) showed the presence of pyridine hydrobromide (≃2600 $cm^{-1}$, broad), succinimide (1780, 1710 $cm^{-1}$), aromatic absorption, and sulfonate absorption (1180 $cm^{-1}$). An nmr spectrum in a mixture of deuterium oxide and DMSO-$d_6$ confirmed the presence of the methylsulfonyl group, the methoxyl group, and aromatic protons in the product.

(b) **Bromine Method.**—A solution of bromine (0.04 ml, 0.078 mmol) in 2 ml of carbon tetrachloride was added dropwise over

(36) G. G. Birch, *J. Chem. Soc.*, 1072 (1966).

(37) This product was previously reported[2] to have mp 115–116°.

a period of 1 hr to a stirred refluxing solution of **1c** (0.22 g, 0.05 mmole) in 10 ml of carbon tetrachloride. The slightly colored solution was refluxed an additional 2.5 hr, cooled, and filtered from a trace of unreacted **1c**. The filtrate was evaporated to a colorless syrup which crystallized from cold methanol to give 0.122 g (47.2%) of **2c**, mp 130–131°.

The reaction was repeated in the presence of benzoyl peroxide (0.01 mmol/mmol of **1c**). Processing the reaction mixture afforded a 68% yield of **2c**, mp 130–132°.

**Methyl 6-Bromo-6-deoxy-α-D-glucopyranoside (3).**[2]—To a solution containing 70 mg of **2a** in 20 ml of methanol was added a small amount of sodium methoxide. After 16 hr at room temperature the colorless solution was neutralized with Dowex-50 ($H^+$), filtered, and evaporated to dryness. The crystalline residue was recrystallized from ether to give pure material, mp 126–127°, $[\alpha]_D$ 137° (*c* 0.54, methanol).

*Anal.* Calcd for $C_7H_{13}BrO_5$: Br, 31.1. Found: Br, 30.7.

**Methyl 4-*O*-Benzoyl-6-bromo-6-deoxy-β-D-glucopyranoside (5).**—A suspension containing 2.82 g of methyl 4,6-*O*-benzylidene-β-D-glucopyranoside (**4**), 4 g of barium carbonate, and 2 g of NBS in 150 ml of carbon tetrachloride and 70 ml of tetrachloroethane was heated under reflux for 2 hr. The inorganic salts were removed by filtration and the filtrate was evaporated to a syrup. The latter was dissolved in ether and the solution was washed with water and processed to give a colorless syrup, 3.7 g. Crystallization was effected from ether–pentane to give 2.42 g (67%) of colorless crystals, mp 105–107°, which migrated as a single spot on tlc (chloroform–methanol, 100:5, medium). The mother liquors showed essentially the same component. Recrystallization of the solid product from a mixture of acetone, ether, and pentane gave an analytical sample: mp 120–121°; $[\alpha]_D$ −9° (*c* 1.05, chloroform); ir data (KBr), 1720 $cm^{-1}$ (ester).

*Anal.* Calcd for $C_{14}H_{17}BrO_6$: C, 46.55; H, 4.74; Br, 22.12. Found: C, 46.85; H, 5.04; Br, 21.95.

**Methyl 6-Bromo-6-deoxy-β-D-glucopyranoside (6).**—A solution containing 0.5 g of **5** in 30 ml of methanol was treated with a few drops of sodium methoxide solution and left at room temperature for 18 hr. Neutralization of the solution with Dowex-50 ($H^+$) and processing afforded a syrup which crystallized from ethyl acetate. Two recrystallizations from the same solvent gave the pure product, mp 150–152°, $[\alpha]_D$ −15.9° (*c* 0.647, methanol), lit.[10] mp. 154°

**Methyl 4,6-*O*-*p*-Anisylidene-α-D-glucopyranoside (1d).**—A suspension of D-glucose (50 g) and 35 g of zinc chloride in 150 ml of *p*-anisaldehyde was stirred at room temperature for 3 days. The reaction mixture was poured into ice–water and the resulting oil was repeatedly washed by decantation first with water and then with petroleum ether (bp 30–60°). The oily residue was then covered with a small volume of ether and diluted with excess petroleum ether and the partially crystalline mixture was left at 0° overnight. The crystalline product was collected and washed with cold ether–petroleum ether; yield 3.5–5 g. Recrystallization from a mixture of chloroform and ether gave colorless crystals, mp 195–196°, $[\alpha]_D$ 107° (*c* 1.05, chloroform). The mother liquors of crystallization were not investigated further.

*Anal.* Calcd for $C_{15}H_{20}O_7$: C, 57.68; H, 6.45. Found: C, 57.39; H, 6.29.

**Methyl 4-*O*-*p*-Anisoyl-6-bromo-6-deoxy-α-D-glucopyranoside (2d).**—A suspension containing 0.312 g of **1d**, 0.2 g of NBS, and 0.5 g of barium carbonate in 20 ml of carbon tetrachloride and 7 ml of tetrachloroethane was stirred under reflux for 2.5 hr. The formation of the product was monitored by tlc. In the system chloroform–methanol (100:6 medium) the product had a slightly faster and discernible mobility than the starting material. The suspension was filtered and the filtrate was evaporated to a syrup which was dissolved in ether and the solution was washed with a little water. Processing of the ethereal phase afforded a colorless syrup which was homogeneous on tlc; $[\alpha]_D$ 104° (*c* 1.11, chloroform). A portion was purified by preparative tlc.

*Anal.* Calcd for $C_{15}H_{19}BrO_7$: C, 46.04; H, 4.89; Br, 20.42. Found: C, 45.84; H, 5.13; Br, 19.84.

**Methyl 4-*O*-Benzoyl-6-bromo-6-deoxy-α-D-galactopyranoside (8a).**[2]—A suspension containing 4.0 g of **7a**, 2.7 g of NBS, and 3.0 g of barium carbonate in 180 ml of carbon tetrachloride and 27 ml of tetrachloroethane was stirred under reflux for 2.5 hr. The colorless suspension was filtered and the filtrate was evaporated to dryness. The residue was dissolved in ether, washed with a small volume of water to eliminate succinimide, dried, and evaporated to a colorless syrup which showed essentially one spot on tlc (chloroform–methanol, 100:5, medium). Repeated evaporation from ether produced a white brittle foam: yield 5.17 g (approximately quantitative); $[\alpha]_D$ 156° (*c* 0.558, methanol); ir data (liquid film), 1720 $cm^{-1}$ (ester).

Conventional benzoylation of **8a** with benzoyl chloride in pyridine afforded the crystalline **methyl 2,3,4-tri-*O*-benzoyl-6-bromo-6-deoxy-α-D-galactopyranoside (8d)** in 30% yield, mp 122–123°, $[\alpha]_D$ 229° (*c* 1.06, chloroform). Vpc analysis showed a single peak.

*Anal.* Calcd for $C_{28}H_{25}BrO_8$: C, 59.05; H, 4.42; Br, 14.03. Found: C, 58.91; H, 4.35; Br, 14.44.

The mother liquors showed a major spot on tlc (chloroform–2,2,4-trimethylpentane–methanol, 100:30:1, fast), which had the same mobility as the crystalline product, together with a minor spot having much slower mobility.

Mesylation of **8a** with methanesulfonyl chloride in pyridine at 5° overnight and processing in the usual manner gave a syrup which solidified when triturated with cold water, to give a 78% yield of the homogeneous product **methyl 4-*O*-benzoyl-6-bromo-6-deoxy-2,3-di-*O*-methylsulfonyl-α-D-galactopyranoside (8c)** (chloroform–2,2,4-trimethylpentane–methanol, 100:30:1, medium), $[\alpha]^{25}_D$ 95° (*c* 0.164, chloroform).

*Anal.* Calcd for $C_{16}H_{21}BrO_{10}S_2$: C, 37.14; H, 4.09; S, 12.39; Br, 15.44. Found: C, 37.20; H, 4.20; S, 12.07; Br, 15.78.

**Methyl 4-*O*-Benzoyl-6-deoxy-2,3-di-*O*-methylsulfonyl-α-D-galactopyranoside (9).**—A methanolic solution of **8c** (4.5 g) containing 2 g of 20% palladium on carbon and 4 g of barium carbonate was hydrogenated with stirring during 3 hr. Thin layer chromatography showed the presence of some starting material (higher mobility). The hydrogenation was repeated for 6 hr after which the suspension was filtered and the filtrate was processed as usual to give a crystalline solid. Recrystallization from ethanol afforded the product in two crops, yield 2.43 g (64%), mp 135–136°, $[\alpha]_D$ 121° (*c* 0.68, chloroform).

*Anal.* Calcd for $C_{16}H_{22}O_{10}S_2$: C, 43.82; H, 5.05; S, 14.62. Found: C, 43.66; H, 4.91; S, 14.1.

**Methyl 6-Bromo-6-deoxy-α-D-galactopyranoside (10).**[2]—To a solution containing 70 mg of **8a** in 20 ml of methanol was added a catalytic amount of sodium methoxide. After standing overnight at room temperature, the solution was neutralized with Dowex-50 ($H^+$) and evaporated to a syrup. Extraction of this with ether and evaporation to a small volume gave the crystalline product **10** in 82% yield, mp 174–175°, $[\alpha]^{26}_D$ 157° (*c* 0.5, water).

*Anal.* Calcd for $C_7H_{13}BrO_5$: Br, 31.0. Found: Br, 31.22.

**Methyl 6-Deoxy-α-D-galactopyranoside (11).**[2]—An excess of Raney nickel was added to a solution containing 0.1 g of **10** and 0.1 ml of triethylamine in 60 ml of methanol, and the mixture was hydrogenated at room temperature and atmospheric pressure during 2 hr. Filtration and evaporation afforded a crystalline residue containing triethylamine hydrobromide and the product **11**. The latter was purified by passage of its aqueous solution through a chilled column containing Dowex-50 ($H^+$) and evaporating the effluent, yield 0.45 g (64%). Physical constants and an infrared spectrum were identical with those of an authentic sample.

**Methyl 4-*O*-Benzoyl-6-bromo-6-deoxy-2,3-di-*O*-*p*-tolylsulfonyl-α-D-galactopyranoside (8b).**—To a solution containing 0.6 g of methyl 4,6-*O*-benzylidene-2,3-di-*O*-*p*-tolylsulfonyl-α-D-galactopyranoside in 20 ml of carbon tetrachloride and 1 ml of tetrachloroethane were added 0.2 g of NBS and 1 g of barium carbonate. The suspension was refluxed with stirring for 2 hr. Filtration and evaporation of the filtrate gave a syrup which was dissolved in ether and the ethereal solution was washed with water. Evaporation of the ether gave a syrup which solidified under cold methanol, yield 0.6 g. Two recrystallizations from methanol gave colorless crystals, mp 128–129°, unchanged on further recrystallizations. This material showed a major spot and a slightly faster moving minor spot on tlc (chloroform–2,2,4-trimethylpentane–methanol, 100:30:1.5). A portion (0.1 g) of this material was purified by preparative thin layer chromatography to give the desired pure product (63 mg), mp 126–127°.

*Anal.* Calcd for $C_{28}H_{29}BrO_{10}S_2$: C, 50.22; H, 4.36; S, 9.57; Br, 11.93. Found: C, 50.30; H, 4.39; S, 9.78; Br, 12.04.

**Methyl 4-*O*-Benzoyl-6-bromo-6-deoxy-β-D-galactopyranoside (13).**—A suspension containing 0.7 g of **12**, 0.5 g of NBS, and

1.0 g of barium carbonate in 40 ml of carbon tetrachloride and 12 ml of tetrachloroethane was refluxed with stirring for 2.5 hr. The filtered solution was evaporated to dryness and processed as described above. A colorless syrup was obtained (0.75 g) which showed two spots of medium mobility on tlc (chloroform–methanol, 100:5). The two components were separated by preparative thin layer chromatography (or column chromatography on neutral alumina with chloroform as eluent, in case of larger runs) and were obtained as homogeneous colorless syrups. The slower-moving component (0.135 g) was identified as **13** and had $[\alpha]_D$ +25.5° (*c* 1.57, chloroform); ir data (liquid film), 1718 $cm^{-1}$ (ester); nmr data, $\tau$ 4.27 (center of a doublet, $J_{12}$ = 5 cps, C-1 proton), 6.38 (methoxyl protons). The compound was degraded in an aqueous solution of sodium metaperiodate (the disappearance of **13** was observed chromatographically). In one case, the NBS reaction was stopped after refluxing for 30 min. Thin layer chromatography showed the absence of starting material and the presence of the two products obtained above. The same results were obtained when the NBS reaction was done in the presence of a catalytic amount of benzoyl peroxide.

*Anal.* Calcd for $C_{14}H_{17}BrO_6$: C, 46.55; H, 4.74. Found: C, 46.25; H, 5.03.

Benzoylation with benzoyl chloride in pyridine in the usual way afforded the tribenzoate **16a**, mp 158–195°.

Mesylation with methanesulfonyl chloride in pyridine gave the dimesylate **16b**, identical with the derivative obtained from **15b**.

**Methyl 6-*O*-Benzoyl-3-bromo-3-deoxy-β-D-gulopyranoside (14) and Methyl 3-Deoxy-β-D-*xylo*-hexopyranoside (18).**—The faster moving component from the above experiment (0.166 g) was tentatively assigned structure **14**. It had $[\alpha]^{25}_D$ −6° (*c* 1.65, chloroform) and was resistant to oxidation by aqueous periodate; ir data (liquid film), 1720 $cm^{-1}$ (ester); nmr data, $\tau$ 4.46 (C-1 anomeric proton, doublet, $J_{12}$ = 5 cps), 6.38 (C-1 methoxyl protons).

An amount of **14** (0.12 g) was dissolved in 80 ml of methanol and hydrogenated in the presence of 20% palladium on carbon and excess barium carbonate. After 4 hr at room temperature, the hydrogenation was stopped and the filtered solution was evaporated to a syrup which showed essentially one spot on tlc; $[\alpha]_D$ −65.5° (*c* 2.6, chloroform). Catalytic debenzoylation of a portion (31 mg) afforded crystalline methyl 3-deoxy-β-D-*xylo*-hexopyranoside (**18**), mp 174–175°, $[\alpha]_D$ −75.8° (*c* 0.18, water); lit.[12] mp 173–174°, $[\alpha]_D$ −69.4° (water). A mixture melting point with an authentic sample showed no depression and the infrared spectra were identical.

**Methyl 2,3,4-Tri-*O*-benzoyl-6-bromo-6-deoxy-β-D-galactopyranoside (16a).**—An amount of **15a**[14] (0.245 g) in 15 ml of carbon tetrachloride containing 0.1 g of NBS and excess barium carbonate was stirred at reflux temperature. Thin layer chromatography of an aliquot, after 3.5 hr of reaction time, showed the presence of starting material together with the expected product (chloroform–2,2,4-trimethylpentane–methanol, 100:30:0.8). The suspension was then filtered and evaporated to dryness, yield 0.29 g (quantitative). The desired product was separated by chromatography over a column containing neutral alumina with chloroform as eluent. The fractions containing the product were combined and evaporated to a syrup which crystallized from pentane–ether to give pure **16a**, 0.18 g, 65%, mp 158–159°, $[\alpha]_D$ +179° (*c* 0.91, chloroform).

*Anal.* Calcd for $C_{28}H_{25}BrO_8$: C, 59.05; H, 4.42; Br, 14.03. Found: C, 58.59; H, 4.58; Br, 14.37.

**Methyl 2,3,6-Tri-*O*-benzoyl-6-deoxy-β-D-galactopyranoside (17a).**—A solution of **16a** (0.17 g) in 70 ml of methanol containing 0.25 g of 20% palladium on charcoal and excess barium carbonate was hydrogenated during 5 hr. Filtration of the mixture and evaporation gave a residue which crystallized from ether–pentane, yield 90 mg (62%). Recrystallization from ether–pentane afforded pure material: mp 163–164°; $[\alpha]_D$ 190° (*c* 0.92, chloroform); nmr data, $\tau$ 8.65 (C-6 protons, three proton doublet).

*Anal.* Calcd for $C_{28}H_{26}O_8$: C, 68.56; H, 5.34. Found: C, 68.70; H, 5.34.

**Methyl 4-*O*-Benzoyl-6-bromo-6-deoxy-2,3-di-*O*-methylsulfonyl-β-D-galactopyranoside (16b).**—Mesylation of **12** (0.5 g) with methanesulfonyl chloride in pyridine during 18 hr at 5° afforded **methyl 4,6-*O*-benzylidene-2,3-di-*O*-methylsulfonyl-β-D-galactopyranoside (15b)** as a pale tan crystalline substance, 0.62 g. Recrystallization from methanol gave **15b** as colorless crystals, mp 207–208°.

*Anal.* Calcd for $C_{16}H_{22}O_{10}S_2$: C, 43.82; H, 5.05; S, 14.62. Found: C, 43.56; H, 5.21; S, 14.73.

An amount of **15b** (0.22 g) was subjected to the NBS reaction in the presence of barium carbonate in refluxing carbon tetrachloride (15 ml). After 2.5 hr the suspension was filtered and processed to a colorless syrup (0.22 g, 84%) which showed one spot on tlc (chloroform–2,2,4-trimethylpentane–methanol, 100:30:4). The syrup solidified from a mixture of ether and pentane but a definite melting point could not be obtained, mp 70–80° (foaming). The same product could be obtained by mesylation of **13**.

*Anal.* Calcd for $C_{16}H_{21}BrO_{10}S_2$: C, 37.14; H, 4.09; S, 12.4; Br, 15.44. Found: C, 37.45; H, 4.16; S, 12.25; Br, 15.47.

**Methyl 4-*O*-Benzoyl-6-deoxy-2,3-di-*O*-methylsulfonyl-β-D-galactopyranoside (17b).**—To a solution containing 60 mg of **16b** in 90 ml of methanol were added 0.2 g of 20% palladium on carbon and 1 g of barium carbonate. The stirred mixture was hydrogenated during 2.5 hr at room temperature. The mixture was then filtered, and the filtrate was processed to give a syrup (43.7 mg) which showed essentially one spot on thin layer chromatograms (chloroform–2,2,4-trimethylpentane–methanol, 100:30:4); $[\alpha]_D$ 10.4° (*c* 1.98, chloroform); nmr data, $\tau$ 4.28 (C-1 anomeric proton, doublet, $J_{12}$ = 4 cps), 5.06 (C-4 proton, multiplet), 6.36 (C-1 methoxyl protons), 6.83, 6.88 (methylsulfonyl protons), 8.72 (C-6 protons).

**Methyl 4-*O*-Benzoyl-6-bromo-6-deoxy-α-D-mannopyranoside (20a).**—NBS (0.44 g) was added to a suspension of **19a** (0.565 g) and barium carbonate (1.5 g) in 40 ml of carbon tetrachloride and 2 ml of tetrachloroethane. The mixture was refluxed with stirring for 2 hr and filtered hot, and the filtrate was evaporated to a syrup. The latter was dissolved in ether, and the solution was washed with water, dried, and evaporated to a colorless syrup, 0.572 g (79%). Thin layer chromatography (chloroform–methanol, 100:5, medium) showed one major spot, a minor fast-moving substance (solvent front), and a trace of a slower moving component. This syrupy product was suitable for further use. The major component could be separated from the minor components by chromatography on a silicic acid column using the solvent system chloroform–2,2,4-trimethylpentane–methanol (100:30:5) as developer. A portion purified by preparative thin layer chromatography (same solvent) gave a colorless syrup, $[\alpha]_D$ −124° (*c* 2.39, chloroform). Addition of pentane to an ethereal solution gave **20a** as a colorless amorphous solid.

Benzoylation of the crude reaction product **20a** in the usual manner gave the tribenzoate **20b** in 50% yield, mp 181–182°, $[\alpha]_D$ −115° (*c* 0.4, chloroform). The mother liquors of recrystallization were examined by tlc and consisted predominantly of **20b** together with a slightly slower moving component (chloroform–2,2,4-trimethylpentane–methanol, 100:30:0.7).

*Anal.* Calcd for $C_{28}H_{25}BrO_8$: C, 59.06; H, 4.43; Br, 14.03. Found: C, 59.11; H, 4.47; Br, 13.96.

**Methyl 2,3,4-Tri-*O*-benzoyl-6-bromo-6-deoxy-α-D-mannopyranoside (20b).**—An amount of **19a** (0.14 g) was benzoylated with benzoyl chloride in pyridine in the usual way and the product was isolated as a chromatographically homogeneous syrup, 0.186 g (**19b**). This material had the expected spectral properties and was used directly in the NBS reaction.

To a solution of **19b** (0.18 g) in 10 ml of carbon tetrachloride were added 75 mg of NBS and 0.2 g of barium carbonate, and the resulting suspension was refluxed with stirring for 2 hr. Processing of the reaction mixture in the usual way afforded a syrup which was dissolved in ether and the solution was washed with a small amount of water. Drying, filtration, and evaporation of the etheral extracts afforded a colorless syrup (0.2 g, 92%) showing essentially one spot on tlc (chloroform–2,2,4-trimethylpentane–methanol, 100:30:0.3, fast). The syrup solidified upon trituration with cold methanol and was recrystallized from the same solvent; yield 0.145 g, 70%. This product was identical in all respects with that obtained from the benzoylation of **20a**.

**Methyl 2,3-Di-*O*-acetyl-4-*O*-benzoyl-6-bromo-6-deoxy-α-D-mannopyranoside (20c).**—NBS (0.2 g) and barium carbonate (1 g) were added to a solution of **19c**[15] (0.3 g), $[\alpha]_D$ 21° (*c* 0.975, chloroform), in 15 ml of carbon tetrachloride. After stirring under reflux for 2 hr the suspension was filtered and the filtrate was processed as usual to give a syrup which was crystallized

from a mixture of ether and petroleum ether; yield 0.25 g (68%), mp 120–121°, $[\alpha]_D$ 21° (*c* 1.09, chloroform); lit.[38] mp 119–120°, $[\alpha]_D$ 21.1° (chloroform).

*Anal.* Calcd for $C_{18}H_{21}BrO_8$: C, 48.55; H, 4.75; Br, 17.94. Found: C, 48.72; H, 4.72; Br, 17.58.

**Methyl 2,3-Anhydro-4-*O*-benzoyl-6-bromo-6-deoxy-α-D-talopyranoside (22).**—The anhydro derivative **21** (0.18 g), NBS (0.15 g), and barium carbonate (1 g) were suspended in 25 ml of carbon tetrachloride containing 2 ml of tetrachloroethane and the mixture was stirred under reflux for 2 hr. The colorless suspension was filtered and washed with carbon tetrachloride and the filtrate was evaporated to dryness. The resulting solid residue was washed with a little cold water by decantation and the residue was dissolved in ether and dried. Filtration, followed by addition of pentane at 0° gave 42 mg of the product **22**. An additional 60 mg was obtained from the mother liquors, total yield 80%. The combined crops showed essentially one spot on tlc (chloroform–2,2,4-trimethylpentane–methanol, 100:30:0.3). An analytical sample was obtained by recrystallization from ether–pentane; mp 134–135°; $[\alpha]_D$ −63.6° (*c* 0.3, chloroform); ir data (KBr), 1732 $cm^{-1}$ (ester).

*Anal.* Calcd for $C_{14}H_{15}BrO_5$: C, 49.15; H, 4.42; Br, 23.15. Found: C, 48.97; H, 4.50; Br, 22.93.

**4,6:4′,6′-Di-*O*-benzylidene-α,α-trehalose (23a).**—A suspension of crystalline α,α-trehalose dihydrate (60 g) and 300 g of anhydrous zinc chloride in 450 ml of benzaldehyde was stirred at room temperature for 18 hr. The solution was poured into ice–water and petroleum ether and the resulting precipitate was filtered and washed with cold water then with cold ether, yield 45.57 g. Recrystallization from hot ethanol gave the product as a hydrate (found $H_2O$, 2.4%), yield 37.4 g, mp 195°. A portion of this product was dehydrated by evaporation from pyridine according to the procedure described by Birch[17] for the dehydration of α,α-trehalose dihydrate. The crystalline residue was washed with ether and dried, mp 195°, $[\alpha]^{25}_D$ 80.3° (*c* 0.424, methanol).

*Anal.* Calcd for $C_{26}H_{30}O_{11}$: C, 60.22; H, 5.83. Found: C, 60.16; H, 6.11.

**4,4′-Di-*O*-benzoyl-6,6′-dibromo-6,6′-dideoxy-α,α-trehalose (24a).**—An amount of dry **23a** (0.5 g) was suspended in 40 ml of carbon tetrachloride and 35 ml of tetrachloroethane (soluble when hot) containing 0.5 g of NBS and 2 g of barium carbonate. The mixture was then heated under reflux for 2.5 hr and filtered, and the filtrate was evaporated to dryness. The resulting syrup was dissolved in chloroform, washed with a small volume of water to remove succinimide, and the organic phase was dried and evaporated. The syrup solidified upon trituration with cold water, yield 0.27 g (60%) of a white crystalline solid, that showed essentially one spot on tlc (chloroform–methanol, 100:12, fast). A portion of the product was dissolved in ether containing a few drops of acetone and excess pentane was added. After being stored at 0° for several hours the product was filtered and dried; mp 198° dec; $[\alpha]^{25}_D$ 67.5° (*c* 0.304, methanol); ir data (KBr), 1720 $cm^{-1}$ (ester).

*Anal.* Calcd for $C_{26}H_{28}Br_2O_{11}\cdot H_2O$: C, 44.97; H, 4.06; Br, 23.00. Found: C, 45.44; H, 4.26; Br, 22.32.

The experiment was repeated using starting material that had not been dried and contained 2.4% water as determined by a Karl Fischer titration. The crude syrupy product was passed through a column (2.5 × 25 cm) containing silicic acid and eluted with a chloroform–methanol mixture (10:0.1 initially to remove fast-moving contaminants). The same mixture in a ratio of 10:1.5 eluted the product which crystallized when the solvent was evaporated. The residue was triturated with water and gave after filtration and drying 0.7 g (60%) of product.

Mesylation of a portion (0.24 g) with methanesulfonyl chloride in pyridine at 0° overnight and precipitation of the product from ice–water gave 0.25 g of crude tetramesylate **24b**. An analytical sample was obtained by recrystallization from a mixture of acetone, ether, and pentane; mp 132–133°, $[\alpha]^{25}_D$ 79.8° (*c* 0.74, chloroform). The product was identical with the material obtained from **23b** by the NBS route.

**4,4′-Di-*O*-benzoyl-6,6′-dideoxy-α,α-trehalose (25).**—To a solution of **24a** (1.1 g) in 150 ml of methanol were added 0.13 g of 20% palladium on charcoal and excess barium carbonate and the mixture was hydrogenated during 4 hr. The suspension was filtered, and the filtrate was evaporated to dryness. The crystalline residue was extracted with ether, and the soluble portion was evaporated to dryness. The solid residue showed essentially one spot on tlc (chloroform–methanol, 100:5, medium) which had the same mobility as **24a** but which produced a green color (for 6-deoxyhexoses) with the molybdate spray reagent. A portion was purified by preparative thin layer chromatography to give the product as a hydrate: mp 135–138° (foaming); $[\alpha]_D$ 77.2° (*c* 0.48, MeOH); ir data, 1720 $cm^{-1}$ (ester); nmr data, τ 8.83 (C-6, C-6′ protons, six proton doublet).

*Anal.* Calcd for $C_{26}H_{30}O_{11}\cdot H_2O$: C, 58.20; H, 5.63. Found: C, 58.78; H, 5.93. The weight loss at 80° was 2.1%.

**4,6:4′,6′-Di-*O*-benzylidene-2,3,2′,3′-tetra-*O*-methylsulfonyl-α,α-trehalose (23b).**—To 3.4 g of **23a** in 50 ml of dry pyridine was added 10 ml of methanesulfonyl chloride at 0°. The solution was kept at 0° overnight, then poured into ice–water, where upon the product precipitated. Filtration and recrystallization of the crystalline product from hot methanol gave the tetramesylate **23b** as colorless needles, yield 3.96 g, mp 242° dec, $[\alpha]_D$ 57° (*c* 1.02, chloroform).

*Anal.* Calcd for $C_{30}H_{38}O_{19}S_4$: S, 15.4. Found: S, 15.33.

**4,4′-Di-*O*-benzoyl-6,6′-dibromo-6,6′-dideoxy-2,3,2′,3′-tetra-*O*-methylsulfonyl-α,α-trehalose (24b).**—A suspension of **23b** (3.96 g) in 435 ml of carbon tetrachloride containing 1.7 g of NBS and 10 g of barium carbonate was refluxed for 2 hr. The mixture was filtered, the filtrate was evaporated to dryness, the residue was dissolved in ether, and the resulting solution was washed once with water. Drying and evaporation of the ethereal solution gave a crystalline residue which was recrystallized from a mixture of ether and pentane; yield 1 g, mp 132–134°, $[\alpha]_D$ 77.1° (*c* 0.654, chloroform).

*Anal.* Calcd for $C_{30}H_{36}Br_2O_{19}S_4$: C, 36.44; H, 3.67; Br, 16.16; S, 12.97. Found: C, 36.42; H, 3.73; Br, 16.57; S, 13.36.

**Methyl 2-*O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-4-*O*-benzoyl-6-bromo-6-deoxy-α-D-glucopyranoside (27).**—To a suspension of **26** (0.218 g) in 25 ml of carbon tetrachloride were added 0.2 g of NBS and 1 g of barium carbonate and the mixture refluxed for 2 hr. The slightly colored mixture was filtered, the filtrate was evaporated to dryness, the residue was dissolved in ether, and the solution was washed with water. Processing of the ethereal phase gave 0.1 g of a solid product in two crops, which showed a single spot on tlc (chloroform–2,2,4-trimethylpentane–methanol, 100:30:2); $[\alpha]_D$ 41.4° (*c* 0.133, chloroform); ir data, 1750 $cm^{-1}$ (ester). A portion was recrystallized from a mixture of acetone, ether, and pentane; mp 108–110°.

*Anal.* Calcd for $C_{28}H_{35}BrO_{15}$: C, 48.62; H, 5.10; Br, 11.56. Found: C, 48.54; H, 5.10; Br, 11.80.

**Registry No.**—*N*-Bromosuccinimide, 128-08-5; **1d**, 18929-63-0; **2a**, 10368-81-7; **2c**, 18944-91-7; **2d**, 18929-65-2; **8a**, 10368-78-2; **8b**, 18929-67-4; **8c**, 18929-68-5; **8d**, 18929-69-6; **9**, 18929-70-9; **13**, 18929-71-0; **15b**, 18929-72-1; **16a**, 18929-73-2; **16b**, 18929-74-3; **17a**, 18929-75-4; **17b**, 18929-76-5; **18**, 6198-74-9; **20a**, 18929-78-7; **20b**, 18929-79-8; **20c**, 18929-80-1; **22**, 18929-81-2; **23a**, 18929-82-3; **23b**, 18968-33-7; **24a**, 18929-83-4; **24b**, 18929-84-5; **25**, 18929-85-6; **27**, 18929-86-7; **3**, 7465-44-3; **5**, 18929-88-9.

(38) D. Horton and A. E. Luetzow, *Carbohydrate Res.*, **7**, 101 (1968).