Preliminary communication

A method for the selective bromination of primary alcohol groups*

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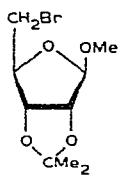
(Received March 20th, 1971)

Halogenodeoxy sugars[1,2] are versatile precursors to a number of chemically and biologically important sugars, many of which are vital constituents of medicinally important antibiotics[3]. Moreover, halogenated antibiotics[4,5], and especially nucleosides[6,7], formed by chemical modification of the parent compounds, have in many cases shown significantly enhanced antibacterial activity and distinctly improved chemotherapeutic effects. The exploration of newer methods of halogenation in the carbohydrate series therefore continues to be an area of particular interest.

We now describe an efficient and selective method for the replacement of the primary hydroxyl group in carbohydrates by a bromine atom. The reaction consists in treatment of the alcohol with two equivalents each of *N*-bromosuccinimide (NBS) and triphenylphosphine[8] in anhydrous *N,N*-dimethylformamide (DMF) for 0.5–1.3 h at 50°. Bromination also occurs in DMF during 1–2 days at room temperature and in boiling dichloromethane under reflux in 30 min. Compounds **1**–**5** are typical products (yield, 70–85%) prepared by this procedure from the corresponding alcohols, and characterized† by conversion into the corresponding deoxy sugars[9].



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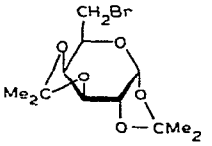

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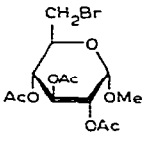

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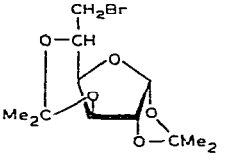

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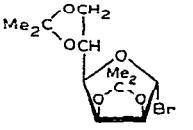

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A variety of functional groups (ester, amide, aglycon, hydroxyl, acetal, *etc.*) are compatible with the reaction conditions, although acetal migration can occur, as with

*Part of a series on "Preparative and Exploratory Carbohydrate Chemistry".

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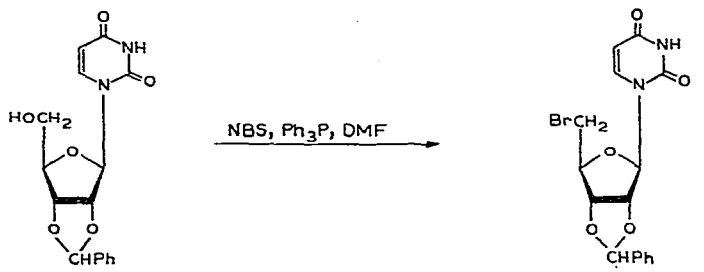
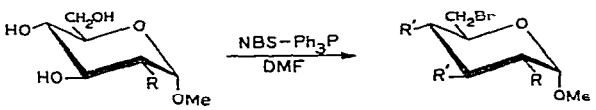
† Compounds reported in this work afforded i.r., n.m.r.,and mass spectra that were in accord with their structures. Melting points are uncorrected and analyses were acceptable.

1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose, which affords the rearranged product **4** in high yield. The method appears to be the simplest devised to date[2,10] for the incorporation of a halogen atom at C-6 in the D-glucofuranose structure. Application of the bromination reaction to nucleosides is exemplified by the formation of 5′-bromo-5′-deoxy-2′,3′-*O*-isopropylideneinosine (50%), m.p. 190° (dec.) (*cf.* Ref. 11) and 5′-bromo-5′-deoxy-2′,3′-*O*-isopropylideneuridine (70%), m.p. 176–178° (*cf.* Ref. 12). From 2′,3′-*O*-benzylideneuridine (**6**) was obtained the crystalline 5′-bromo derivative **7** (yield 72%), m.p. 130–132°. We recently reported[13] that treatment of **6** with NBS in a chlorinated solvent gives 3′-*O*-benzoyl-2′,5-dibromo-2′-deoxyuridine in good yield. It is evident that either of two different reactions of considerable preparative significance in nucleoside chemistry can be achieved, simply by *including* triphenylphosphine in,or *excluding* it from, the reaction mixture containing **6** and NBS.



6 **7**

A particularly attractive feature of the bromination reaction is the selectivity observed in the case of polyhydroxy compounds that contain a primary hydroxyl group. Replacement occurs with methyl α-D-glucopyranoside (**8**) (DMF, 1 h at 50°) to give, after acetylation, methyl 2,3,4-tri-*O*-acetyl-6-bromo-6-deoxy-α-D-glucopyranoside (**9**) (overall yield 66%), m.p. 116–117° (*cf.* Ref. 14). The 2-acetamido analog **10** is brominated to give, after acetylation, the 6-bromo derivative **11** (overall yield 55%), m.p. 164–165°, thus providing a simple and efficient procedure for the preparation of sugar derivatives that are brominated in the terminal position. Uridine is brominated in high yield to give 5′-bromo-5′-deoxyuridine, isolated as the crystalline 2′,3′-*O*-isopropylidene derivative.



8, R = OH
10, R = NHAc

9, R′ = OAc = R
11, R = NHAc ; R′ = OAc

It should be pointed out that there are very few procedures of preparative value for effecting such direct and selective bromination in the carbohydrate series[1,2,10], particularly in nucleosides[12,15,16].

Our studies on the mechanism of bromination with[17] NBS–Ph_3P indicate that the reaction most probably proceeds by the initial formation of an alkoxyphosphonium ion, and that this undergoes attack by bromide ion to give the product obtained★. After due

★The existence of a pentacovalent intermediate and an internal attack of the S_Ni type by bromine cannot be excluded, especially in nonpolar media.

consideration of the nature of the intermediate, the product, and the medium, we have successfully effected nucleophilic displacement reactions by incorporating a nucleophile in the medium, either at the outset (iodide ion) or after formation of the bromide (azide ion), the net outcome being the replacement of a primary hydroxyl group by a substituent X (X = I, N_3, SCN, *etc.*), without the necessity of preparing sulfonate intermediates. For example, sequential bromination and displacement with azide ion could be achieved with compound **1** without the isolation of intermediates. Reaction of 2′,3′-*O*-isopropylideneuridine with NBS–Ph_3P in DMF containing an excess of $Bu_4N^+I^-$ afforded the desired 5′-iodo analog[15] (*m/e* 379, $M^+ - 15$), presumably via initial formation of a 5′-oxyphosphonium ion and displacement by iodide ion.

Compared to other methods used in carbohydrate chemistry for converting alcohols into bromides, *e.g.*, the applications[15,18] of Rydon-type reagents[19], the method now reported, although complementary, offers the features of simplicity of operation and use of readily available reagents. The wide range of substrates studied, as well as the selectivity and newer implications in replacement reactions that use alkoxyphosphonium intermediates[20], provides a versatile approach to halogeno and other substituted sugars.

ACKNOWLEDGMENTS

Generous financial support from the National Research Council of Canada is gratefully acknowledged. The skilful technical assistance of M. Savaria (undergraduate research participant, Summer 1970) is also acknowledged.

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