PROCEDURES FOR THE DIRECT REPLACEMENT OF PRIMARY HYDROXYL GROUPS IN CARBOHYDRATES BY HALOGEN*

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ABSTRACT

Efficient halogenation of carbohydrates and certain nucleosides can be effected by treatment with triphenylphosphine–*N*-halosuccinimide (bromo, chloro, or iodo) Groups commonly used in the protection of hydroxyl and amino functions are unaffected under the mild conditions of halogenation Selective halogenation of hydroxymethyl groups in polyhydroxy compounds can be effected

INTRODUCTION

The replacement of a hydroxyl group by another group that possesses functional utility, such as a halogeno group, is the basis of a large number of important synthetic transformations in carbohydrate chemistry The use of halogeno sugars[2,3] in the synthesis of aminodeoxy, deoxy, anhydro, and unsaturated sugars has been adequately outlined in the literature. Although the classical approach to halogeno sugars that involves displacement of sulfonic ester groups[4,5] with the appropriate halide is still in use, procedures have now become available that allow the direct replacement of a primary hydroxyl group by a halogen atom[2,3]. Of these, mention may be made of the Rydon-type[6] reagents[7], Vilsmeier-type† reagents[9,10], sulfuryl chloride[11], triphenylphosphine–carbon tetrachloride[12–14], and related reagents[15,16]

We report herein the details of a halogenation reaction[1] (excluding fluoro derivatives) that appears to be applicable to a variety of carbohydrate derivatives, including nucleosides The halogenation reaction involves treatment of a solution of an alcohol in *N*,*N*-dimethylformamide (DMF) with two equivalents each of tri-

$$RCH_2OH + Ph_3P + NXS \xrightarrow{DMF} RCH_2X + Ph_3P{\rightarrow}O + \text{succinimide}$$

where X = Br, Cl, or I

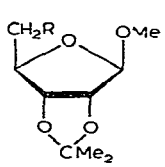
*Part of a series on Preparative and Exploratory Carbohydrate Chemistry, see also ref 1
**Post-doctoral fellow, 1970–1971
***Undergraduate research participant, 1971
†For a review, see ref 8

phenylphosphine and the appropriate *N*-halosuccinimide*. Yields are generally high, and essentially no side-products are encountered under normal operating conditions The by-products of the reaction are succinimide and triphenylphosphine oxide, which can be separated from the halogeno sugar derivatives in a variety of ways Of several solvents tried, DMF appears to be the most suitable, particularly because of its excellent solvent properties

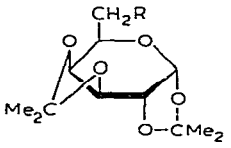
RESULTS

In our initial experiments, the halogenation reaction was tried with partially substituted carbohydrate derivatives in which a primary hydroxyl group was free With *N*-bromosuccinimide (NBS) as the source of bromine, a reaction time of 1–2 h at 50° was usually sufficient to effect the replacement of the primary hydroxyl group by a bromine atom In some cases, bromination occurred even at room temperature, but the time needed for complete reaction varied with the substrate**

In subsequent work, it was found that both chlorination and iodination could also be effected by this method Scheme 1 illustrates some of the deoxyhalogeno sugar derivatives that were prepared by the use of triphenylphosphine–*N*-halosuccinimide



R = Br, Cl or I



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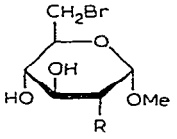

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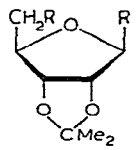
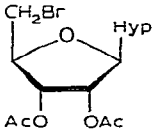
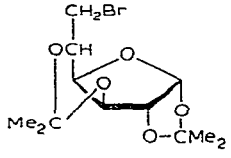
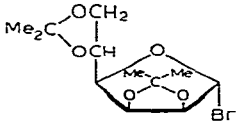


R = Br Cl or I, R = uracil-1-yl
R = Br, R' = hypoxanthin-1-yl







Scheme 1

*The mixture of NBS and PPh_3 in benzene has been used to convert ethanol and tetrahydrofurfuryl alcohol into the corresponding bromides, see ref 17

**Benzyl alcohol is converted into benzyl bromide even a. 0°

Provided that moisture is excluded from the reaction mixture, and that the acid liberated is neutralized during the subsequent processing, most acid-sensitive groups are stable under the reaction conditions Thus, glycosides, acetals, and esters are unaffected

Because of the nature of the intermediate involved*, cyclic acetals may in some cases rearrange, particularly when the hydroxyl group to be replaced is secondary and when the attack of the halogen is hindered Thus, in an effort to extend the halogenation to secondary alcohols, the reaction of 1,2 5,6-di-*O*-isopropylidene-α-D-glucofuranose with Ph_3P–NBS was attempted A single product was formed in high yield, and the bromine atom in it was situated on C-6, that is, the product was 6-bromo-6-deoxy-1,2 3,5-di-*O*-isopropylidene-α-D-glucofuranose Such acetal migrations had previously been observed in similar halogenation reactions[7,9,18], and a related mechanism[7,19] may be involved Except for the anomeric hydroxyl group in 2,3 5,6-di-*O*-isopropylidene-D-mannofuranose, secondary hydroxyl groups situated in five- and six-membered rings were not replaced by bromine under the mild reaction conditions** The method is thus suitable for the facile preparation of glycosyl halides from appropriately substituted sugars having the anomeric hydroxyl group free Preliminary experiments indicate that secondary hydroxyl groups situated in acyclic chains can be replaced by use of higher temperatures and longer reaction times

Nucleosides — Direct replacement of the primary and, in some cases, secondary hydroxyl groups in certain nucleosides by halogen atoms can be effected with the Rydon-type reagents[20] and by other methods[21–23] The products are valuable intermediates in the chemical modification of nucleosides, particularly for biologically or medicinally oriented objectives Moreover, halogenated nucleosides and antibiotics containing halogenated carbohydrates[24], formed by the chemical modification of the parent compound, may have significantly improved biological properties

The reagent triphenylphosphine–*N*-halogenosuccinimide in DMF was found to be a convenient and efficient combination for the bromination, chlorination, or iodination of 2′,3′-*O*-isopropylideneuridine In the purine nucleoside series, 2′,3′-*O*-isopropylideneinosine was converted into the corresponding 5′-bromo derivative in over 50% yield Treatment of 2′,3′-*O*-benzylideneuridine with triphenylphosphine–NBS in DMF at 50° afforded a 64% yield of crystalline 2′,3′-*O*-benzylidene-5′-bromo-5′-deoxyuridine[1] It is of interest that treatment of the same starting-material with NBS in a chlorinated solvent affords crystalline 3′-*O*-benzoyl-2′,5-dibromo-2′-deoxyuridine in 56% yield[25] Thus, depending on the presence or absence of triphenylphosphine in such reaction mixtures, either of two halogenation reactions*** of

*The initial formation of alkoxyphosphonium salts as intermediates is indicated in preliminary studies on the mechanism of this halogenation These studies, now in progress, will be reported at a later date

**The reagents were present in slight excess only (2 equivalents per 1 of the alcohol) The effect of higher concentrations of brominating agent is being investigated

***Clearly, two different mechanisms are operative in these two halogenation reactions, one involving the formation of alkoxyphosphonium salts with the alcohol group, and the other passing through benzoxonium ions

considerable synthetic importance in nucleoside chemistry can be achieved The sequential application of these reactions to benzylidene acetals of carbohydrates in general, and to nucleosides in particular, should provide efficient procedures for the regiospecific introduction of one or more halogen atoms in the molecules

Selectivity — Provided that the reaction conditions are compatible with the substrate, and that the yields are acceptable, an important consideration in such direct replacement reactions is the selectivity of the substitution In dealing with halogenation reactions, it is desirable to have conditions that allow the selective, and possibly sequential, replacement of primary and secondary hydroxyl groups respectively, but it appears that few such procedures are available A particularly attractive feature in the halogenation by use of triphenylphosphine–*N*-halogenosuccinimide is the selectivity observed in replacing only primary hydroxyl groups, in the presence of secondary hydroxyl groups Thus, methyl α-D-glucopyranoside was converted into methyl 2,3,4-tri-*O*-acetyl-6-bromo-6-deoxy-α-D-glucopyranoside by bromination in DMF followed by acetylation (overall yield, 66%) By the same procedure, methyl 2-acetamido-2-deoxy-α-D-glucopyranoside was converted into methyl 2-acetamido-3,4-di-*O*-acetyl-6-bromo-6-deoxy-α-D-glucopyranoside (overall yield, 55%)

The selective bromination of primary alcohol groups was also observed in the case of some nucleosides Uridine was converted into 5′-bromo-5′-deoxyuridine, isolated in the form of its 2′,3′-*O*-isopropylidene derivative in 70% overall yield This method compares favorably with and complements others reported in the literature for effecting selective halogenations of uridine[20 21] and some of its derivatives Inosine was also selectively brominated, to give 5′-bromo-5′-deoxyinosine, isolated as its crystalline diacetate in 59% overall yield Although 2′,3′-*O*-isopropylideneinosine has been halogenated[22] at C-5′, the direct, selective bromination of inosine itself at C-5′ has not, to the best of our knowledge, hitherto been reported In connection with studies on inosine derivatives, Haga and co-workers[22] had reported that halogenation with the combinations Ph_3P–CCl_4, Ph_3P–Br_2, Ph_3P–BrCN, or Ph_3P–I_2, in the presence of triethyl phosphate, did not occur when DMF was used as the solvent, this behavior may be due to a rapid reaction of the solvent with a reactive species formed in the mixture

Preliminary experiments with adenosine, cytidine, and N^4-acetylcytidine have now revealed that the reaction with Ph_3P–NBS is not so selective as for uridine and inosine, as evidenced by studies by thin-layer chromatography Extension of this method of halogenation to these and other nucleosides is in progress In conclusion, we have shown that the reaction of polyhydroxy compounds with the combinations Ph_3P–NXS (where X = Br, Cl, or I) provides efficient and facile routes to halogeno sugars, including the glycosyl group of nucleosides These procedures will undoubtedly have important applications in synthetic work involving precursors to biologically derived deoxy[26], aminodeoxy[27], and related sugars[24], as well as in chemical modification of intact antibiotic substances containing sugar residues

EXPERIMENTAL

General — Melting points are uncorrected. N.m.r. spectra were recorded for solutions in chloroform-*d* (unless stated otherwise) at 60 or 100 MHz, with tetramethylsilane as the internal standard. I.r. spectra were recorded with a Beckman IR-8 spectrometer. Mass spectra were obtained with a Hitachi–Perkin–Elmer medium-resolution and an MS-902 high-resolution mass spectrometer. Optical rotations were measured with a Perkin–Elmer Model 141 automatic spectropolarimeter. Thin-layer chromatography (t.l.c.) was performed with plates coated with Silica Gel GF_{254}, and the spots were detected with a sulfuric acid spray. Column chromatography was conducted with short columns of the same silica gel by application of moderate suction. Conventional processing consisted in drying organic solutions with anhydrous sodium sulfate, filtration, and evaporation of the filtrate under diminished pressure.

All of the halogenated products were adequately characterized by n.m.r.-spectral and mass-spectral (halogen-isotope peaks) features.

Comments on processing — The halogenated products were separated from succinimide and triphenylphosphine oxide in a variety of ways, depending on the structure and solubility of the product.

Procedure A. For water-soluble products, the residual semi-crystalline syrups were extracted with chloroform to separate the product from Ph_3PO. A convenient method for freeing the product of succinimide consisted in evaporating the aqueous portion and acetylating the residue.

Procedure B. For products soluble in organic solvents, a preliminary extraction with water removed the succinimide. A large proportion of the Ph_3PO could be separated by triturating with cold ether and filtering. The desired halide could be isolated by passing the mixture through a short column of silica gel, by direct crystallization, or by distillation.

Procedure C. For nucleosides containing ionizable hydrogen atoms (–NH), the initial crude mixture was dissolved in dichloromethane, and the solution was extracted with cold 0.5M sodium hydroxide, the Ph_3PO was thus removed in the organic layer. Acidification of the aqueous layer liberated the halogenated nucleoside, which could then be extracted into chloroform, leaving the succinimide in the aqueous layer. Unsubstituted, halogenated nucleosides were isolated by first removing the Ph_3PO by extraction with chloroform, and converting the product into a suitable derivative (an acetal or peracetate). In some cases, traces of residual starting-material were removed by column, or preparative thin-layer, chromatography.

Methyl 5-bromo-5-deoxy-2,3-O-isopropylidene-β-D-ribofuranoside — Method A. In dichloromethane. To a cooled solution of methyl 2,3-O-isopropylidene-β-D-ribofuranoside[28] (1.0 g, 4.9 mmoles) and NBS (1.75 g, 9.8 mmoles) in dichloromethane (50 ml) was gradually added triphenylphosphine (2.57 g, 9.8 mmoles), with stirring. The reaction was exothermic, and the color of the solution changed from pale-yellow to orange, and back to pale-yellow upon complete addition of the triphenylphosphine. Barium carbonate (0.4 g) was added to the solution, and the suspension was boiled

under reflux for 15–30 min The solids were filtered off, and the filtrate was washed with a small volume of water, and evaporated under diminished pressure at 20° to a brown syrup which was dissolved in ether (150 ml) and processed in the usual way. Triphenylphosphine oxide was removed by triturating the residue with ether and filtering, and the filtrate was evaporated *in vacuo* to a pale-yellow, partly crystalline syrup (1 68 g) T l c with 10 1 benzene–methanol revealed the presence of triphenylphosphine oxide and the title bromide (which had a higher mobility than the starting material) The yield of the bromide was calculated, from its n m r spectrum, to be ~90%

A pure sample of the title compound was obtained by passing a portion (0 6 g) of the crude product through a column of silica gel, yield 0 4 g, b p 72°/0 1 torr, $[\alpha]_D^{25}$ −80° (*c* 2 61, chloroform); n m r data τ 4 95 (s, H-1); 5 2 (d; $J_{2,3}$ 6 0 Hz; H-2), 5 35 (d, $J_{3,2}$ 6 0 Hz, H-3), 5 58 (d of d, $J_{4,5,5}$ 10 5 and 6 7 Hz, H-4), 6 54–6 73 (m, H-5,5′), 6 60 (s, OMe), and 8 47 and 8 63 (s, CMe_2)

Method B In DMF The bromination was performed in DMF (50 ml) for 15–30 min at 50° (bath temp), without the addition of barium carbonate Methanol was added to the reaction mixture to decompose the excess of reagent, and the solvents were co-distilled with butanol under diminished pressure to afford a syrup Ether (150 ml) and water (50 ml) were added, and the organic layer was processed as already described, to give the title bromide (yield 95%, by n m r) The spectral (n m r and mass) characteristics of the product were concordant with the structure assigned

When the bromination was conducted in DMF at room temperature, ~50% of the starting material had been converted into the bromide after 18 h (as revealed by t l c)

*Methyl 5-deoxy-5-iodo-2,3-*O*-isopropylidene-β-*D*-ribofuranoside* — To a cooled solution of methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside[28] (1 0 g) and *N*-iodosuccinimide (2 205 g) in DMF (50 ml) was slowly added triphenylphosphine (2 57 g), with stirring The mixture was heated for 20 min at 50° (bath temp) and cooled, methanol and then butanol were added, and the solution was evaporated *in vacuo* to a syrup Ether (150 ml) and water (50 ml) were added, and the organic layer was washed successively with aqueous sodium thiosulfate and water, dried, and processed in the usual way, affording a syrup which was purified by column chromatography to give the title compound (yield 1 10 g, 71%), b p 78–79°/0 1 torr, $[\alpha]_D^{25}$ −67 7° (*c* 2 32, chloroform) [lit [29] b p 75–80°/0 1 torr, $[\alpha]_D^{25}$ −68° (in chloroform)]; n m r data τ 4 94 (s, H-1), 5 16 (d, $J_{2,3}$ 6 0 Hz, H-2), 5 33 (d. $J_{3,2}$ 6 0 Hz, H-3), 5 53 (d of d, $J_{4,5,5}$ 9 0 and 7 5 Hz; H-4), 6 55 (s, OMe), 6 70–6 86 (m; H-5,5′); and 8 45 and 8 63 (s, CMe_2)

*Methyl 5-chloro-5-deoxy-2,3-*O*-isopropylidene-β-*D*-ribofuranoside* —Triphenylphosphine (2 57 g) was gradually added to a cooled solution of methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside[28] (1 0 g) and *N*-chlorosuccinimide (1 31 g) in DMF (50 ml), and the mixture was heated for 20 min at 50° (bath temp), and cooled The solution was processed in the usual way, to give the title compound (95% yield,

estimated by n m r spectroscopy) A portion was purified by preparative t l c with 10 1 benzene–methanol as the developer, to afford the title compound as a colorless liquid, $[\alpha]_D^{25}$ −93° (*c* 2 04, chloroform), n m r data τ 4 95 (s, H-1), 5 2 (d, $J_{2,3}$ 6 0 Hz, H-2), 5 35 (d, $J_{3,2}$ 6 0 Hz, H-3), 5 70 (d of d, $J_{4,5,5'}$ 9 0 and 7 5 Hz, H-4), 6 43–6 60 (m, H-5,5'), 6 73 (s, OMe), and 8 5 and 8 65 (s, CMe_2)

6-Bromo-6-deoxy-1,2 3,4-di-O-*isopropylidene-α*-D-*galactopyranose* — Triphenylphosphine (1 97 g, 7 5 mmoles) was gradually added to a cooled solution of 1,2 3,4-di-*O*-isopropylidene-α-D-galactopyranose[30] (2 0 g, 7 5 mmoles) and NBS (1 34 g, 7 5 mmoles) in DMF (50 ml), and the mixture was heated, with stirring, for 2 h at 50° (bath temp) Methanol and then butanol were added, and the solution was evaporated to a syrup that was dissolved in ether The solution was washed with water, and the water was extracted with ether The ether extract and solution were combined (300 ml), and processed in the usual way, to give a chromatographically homogeneous, pale-yellow syrup (yield 2 3 g, 70%) A pure sample of the title compound was obtained by column chromatography on silica gel, followed by crystallization from hexane, m p 56°, b p 101–102°/0 1 torr, lit [31] m p 48–49°

Reduction of the product with lithium aluminum hydride in ether, or catalytically (Pd–C), gave the corresponding 6-deoxy-1,2 3,4-di-*O*-isopropylidene-α-D-galactopyranose, which gave a characteristic green color[9] with the molybdate spray[32] A portion was purified by preparative t l c (using 10 1 benzene–methanol) to give a pure liquid, $[\alpha]_D^{25}$ −48° (*c* 2 55, chloroform), lit [9,33,34] $[\alpha]_D^{25}$ −47 1° (chloroform)

6-Chloro-6-deoxy-1,2 3,4-di-O-*isopropylidene-α*-D-*galactopyranose* — To a cooled solution of 1,2 3,4-di-*O*-isopropylidene-α-D-galactopyranose[30] (1 0 g, 3 76 mmoles) and *N*-chlorosuccinimide (1 0 g, 7 5 mmoles) in DMF (50 ml) was gradually added triphenylphosphine (1 97 g, 7 5 mmoles), with stirring The mixture was heated for 2 h at 50° (bath temp) and cooled After the usual processing (procedure B), the title compound was obtained in 68% yield (n m r spectroscopy) A portion was purified by column chromatography on silica gel, and then had physical constants identical with those of an authentic specimen[9 31,35 36], b p 100–101°/0 1 torr, $[\alpha]_D^{25}$ −64° (*c* 1 0, chloroform)

Methyl 2,3,4-tri-O-*acetyl-6-bromo-6-deoxy-α*-D-*glucopyranoside* — To a cooled solution of methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside[37] (0 47 g, 1 46 mmoles) and NBS (0 52 g, 2 92 mmoles) in DMF (25 ml) was gradually added triphenylphosphine (0 77 g, 2 92 mmoles), with stirring The mixture was heated for 1 h at 50°, cooled, and processed according to procedure B, to give a pale-yellow, partly crystalline syrup Recrystallization from 95% ethanol gave 0 43 g (77% yield) of the title compound, m p. 110–115° A second recrystallization from the same solvent afforded pure material, m p 116–117°, $[\alpha]_D^{25}$ +123° (*c* 1 0, pyridine), lit [38] m p 117°, $[\alpha]_D^{25}$ +125 8° (in pyridine)

6-Bromo-6-deoxy-1,2 3,5-di-O-*isopropylidene-α*-D-*glucofuranose* — Triphenyl phosphine (2 02 g, 7 7 mmoles) was added in small portions to a cooled solution of 1,2 5,6-di-*O*-isopropylidene-α-D-glucofuranose[39] (1 0 g, 3 84 mmoles) and NBS (1 37 g, 7 7 mmoles) in DMF (50 ml) The mixture was stirred for 1 h at 50°, cooled,

and processed as described in procedure B, to give a pale-yellow, partly crystalline syrup (1 86 g) T l c with 10 1 benzene–methanol indicated the presence of triphenylphosphine oxide and the title compound (85% yield by n m r spectroscopy) A pure sample of the latter was obtained by column chromatography, b p 106°/0 1 torr, $[\alpha]_D$ +19 2° (*c* 1 83, chloroform), reported[31] to be an oil

Reduction of a portion with lithium aluminum hydride in ether or catalytically, as previously described[9], afforded the known[9,14] 6-deoxy-1,2 3,5-di-*O*-isopropylidene-α-D-glucofuranose as a mobile liquid, $[\alpha]_D$ +36° (*c* 1 3, chloroform)

2,3 5,6-Di-O-isopropylidene-α-D-mannofuranosyl bromide — Triphenylphosphine (26 0 g, 0 1 mole) was added in small portions to a cooled solution of 2,3 5,6-di-*O*-isopropylidene-α-D-mannofuranose[39] (10 g, 38 4 mmoles) and NBS (17 0 g, 0 1 mole) in DMF (200 ml) The mixture was heated for 4–5 h at 50°, and cooled, and ether (600 ml) was added The solution was washed three times with cold water, dried, and evaporated under diminished pressure to give a syrup which crystallized Trituration with petroleum ether (b p 30–60°) and filtration removed most of the triphenylphosphine oxide (recovered in 95% yield) The filtrate was evaporated to a colorless syrup (12 g) that contained less than 5% of triphenylphosphine oxide, and had n m r spectral features that were those expected of the title compound, n m r data τ 3 58 (s, H-1), 4 83 (d; $J_{2,3}$ 6 0 Hz, H-2), 5 16 (d of d; $J_{3,2}$ 6 0 Hz and $J_{3,4}$ 3.75 Hz, H-3); 5 5–6 2 (m, H-4–H-6), 8 55 (m, CMe_2) A freshly prepared solution of the product in chloroform showed a single spot on t l c in 50 25.1 chloroform–2,2,4-trimethylpentane–methanol On standing in aqueous acetone containing sodium hydrogen carbonate, the product was transformed into the starting material, m p 122–123°, lit[39,40] m p 122–123°

Bromination of methyl α-D-glucopyranoside — To a cooled solution of methyl α-D-glucopyranoside (1 0 g, 5 15 mmoles) and NBS (1 83 g, 10 3 mmoles) in DMF (50 ml) was gradually added triphenylphosphine (2 7 g, 10 3 mmoles), with stirring The mixture was heated for 2 h at 50°, and cooled, methanol and then butanol were added, and the solution was evaporated *in vacuo* to a syrup Dichloromethane (20 ml) was added, the solution was extracted with water (3 × 50 ml), and the extracts were combined, made neutral with IR-45 (OH^-) ion-exchange resin, the suspension filtered, and the filtrate evaporated to a pale-yellow syrup The syrup was treated with acetic anhydride in pyridine, and the mixture was poured into ice–water to give 1 3 g (66% yield, calculated on methyl α-D-glucopyranoside) of methyl 2,3,4-tri-*O*-acetyl-6-bromo-6-deoxy-α-D-glucopyranoside, m p 115–117°, lit[38] m p 117°

Bromination of methyl 2-acetamido-2-deoxy-α-D-glucopyranoside — Triphenylphosphine (2 23 g, 8 5 mmoles) was added in small portions to a cooled solution of methyl 2-acetamido-2-deoxy-α-D-glucopyranoside (1 0 g, 4 25 mmoles) and NBS (1 52 g, 8 5 mmoles) in DMF (50 ml) The mixture was heated for 2 h at 50° (bath temp), cooled, and processed according to procedure A, to give a pale-yellow syrup which contained mainly the 6-bromo compound and some succinimide The syrup was acetylated with acetic anhydride in pyridine–dichloromethane overnight at 3°, and the mixture was poured into ice–water, and extracted with dichloromethane.

The extract was successively washed with aqueous sodium hydrogen carbonate and water, and evaporated under diminished pressure to a syrup Water was added, and the solution was evaporated *in vacuo*, this process was repeated a few times, to give a crystalline mass which was then triturated with cold ethanol, giving 0 8 g of crystals An additional amount of product (80 mg) was obtained from the mother liquors, giving 0 88 g (55% overall yield) of methyl 2-acetamido-3,4-di-*O*-acetyl-6-bromo-2,6-dideoxy-α-D-glucopyranoside, m p 160–163° Recrystallization from ether afforded pure material, m p 164–165°, $[\alpha]_D^{25}$ +89 5° (*c* 1 47, chloroform)

Anal Calc for $C_{13}H_{20}BrNO_7$ C, 40 83, H, 5 26, Br, 20 90, N, 3 67 Found C, 41 05, H, 5 80, Br, 20 63; N, 3 88

5'-Bromo-5'-deoxy-2',3'-O-isopropylideneuridine — Triphenylphosphine (0 36 g, 1 75 mmoles) was added in small portions to a cooled solution of 2',3'-*O*-isopropylideneuridine[41] (0 142 g, 0 5 mmole) and NBS (0 223 g, 1 25 mmoles) in DMF (10 ml)* The mixture was heated for 3 5 h at 50° (bath temp), and the excess of the reagents was decomposed by adding methanol Processing according to procedure C gave a solid that was recrystallized from chloroform–hexane to yield 0 136 g (79%) of the title compound, m p 183–185° Recrystallization from the same solvent-mixture afforded pure material, m p 184–186° [lit m p 179–181° (ref 21), 184–186° (ref 42)], mass spectral data *m/e* 346, 348 (M^+), 331, 333 ($M-CH_3$); 288, 290 (M—acetone), etc

5'-Deoxy-5'-iodo-2',3'-O-isopropylideneuridine — To a cooled solution of 2',3'-*O*-isopropylideneuridine[41] (0 142 g, 0 5 mmole) and triphenylphosphine (0 458 g, 1 75 mmoles) in DMF (10 ml) was gradually added *N*-iodosuccinimide (0 281 g, 1.25 mmoles), with stirring The solution was heated for 2 5 h at 50° (bath temp), cooled, and processed as usual (Procedure C) The crude nucleoside derivative was obtained as a solid Recrystallization from chloroform–hexane afforded 0 132 g (67%) of the title compound, m p 164–166° (lit [20,43] m p 165–166°), mass spectral data *m/e* 394 (M^+), 379 ($M-CH_3$), 336 (M—acetone), etc

5'-Chloro-5'-deoxy-2',3'-O-isopropylideneuridine — To a cooled solution of 2',3'-*O*-isopropylideneuridine (0 142 g, 0 5 mmole) and triphenylphosphine (0 458 g, 1 75 mmoles) in DMF (10 ml) was slowly added *N*-chlorosuccinimide (0 167 g, 1 25 mmoles), with stirring The mixture was stirred for 2 5 h at 50° (bath temp), cooled, and processed by procedure C, giving a syrup which crystallized from chloroform–hexane to yield 0 134 g (89%) of the title compound, m p 175–178° (lit [21] m p 174–178°), mass spectral data *m/e* 304, 302 (M^+), 289, 287 ($M-CH_3$), 246–244 (M—acetone), etc

2',3'-O-Benzylidene-5'-bromo-5'-deoxyuridine — To a cooled solution of 2',3'-*O*-benzylideneuridine[44] (0 166 g, 0 5 mmole) and triphenylphosphine (0 786 g, 3 0 mmoles**) in DMF (10 ml) was gradually added NBS (0 134 g, 0 75 mmole), with stirring The mixture was heated for 4 h at 50°, cooled, and processed by procedure

*In the halogenation of uridine derivatives, a slight excess of triphenylphosphine was used, in order to minimize bromination at C-5 of the uracil residue by NBS

**A slight excess of triphenylphosphine was used, in order to minimize bromination at C-5 of the uracil residue by NBS

C, to give a syrup which was purified by column chromatography on silicic acid to afford the product Recrystallization from chloroform–hexane gave 0 126 g (64%) of the title compound, m p 139–141° Recrystallization from the same solvent-mixture yielded pure material, m p 140–142°, $[\alpha]_D^{25}$ −31 2° (*c* 3 4, chloroform); n m r data τ 2 6 (aromatic protons), 2 80 (d, $J_{6\,5}$ 8 0 Hz; H-6); 4 03, 4 16 (s, PhCH, diastereoisomers), 4 32 (d, $J_{5,6}$ 8 0 Hz, H-5), 4 40 (d, $J_{1\,2}$ 2 5 Hz, H-1'), 5 0 (m, H-2', H-3'), 5 52 (m, H-4'), 6 25 (m; H-5,5'), mass spectral data *m/e* 397, 395 (M^+)

Anal Calc for $C_{16}H_{15}BrN_2O_5$ C, 48 58, H, 3 79; Br, 20 24, N, 7 10 Found, C, 48 35, H, 3 85, Br, 20 20; N, 6.78

5'-Bromo-5'-deoxy-2',3'-O-isopropylideneinosine — To a cooled solution of 2',3'-*O*-isopropylideneinosine[45] (0 5 g, 1 02 mmoles) and NBS (0 578 g, 3 24 mmoles) in DMF (25 ml) was slowly added triphenylphosphine (0 916 g, 3 50 mmoles), with stirring, and the solution was kept for 1 5 h at 50° (bath temp) Methanol and then butanol were added, and the solution was evaporated *in vacuo* to a syrup Dichloromethane (50 ml) and water (30 ml) were added, and the mixture was processed according to procedure C Processing of the final dichloromethane extract gave a solid which was triturated with ethanol, and the suspension filtered Recrystallization from methanol gave pure title-compound (0 3 g, 50%), m p 198° (dec), lit [22] m p 194° (dec) Because of the difference in melting point, the compound was analyzed

Anal Calc for $C_{13}H_{14}BrN_4O_4$ C, 42 05, H, 4 10, Br, 21 60, N, 15 10 Found C, 42 20, H, 3 66, Br, 21 80, N, 15 34

Bromination of uridine — To a cooled solution of uridine (0 122 g, 0 5 mmole) and triphenylphosphine (0 46 g, 1 75 mmoles) in DMF (10 ml) was gradually added NBS (0 223 g, 1 25 mmoles), with stirring, and the mixture was heated for 3 h at 50° (bath temp) Methanol and then butanol were added to the yellow solution, and the solution was evaporated *in vacuo* to a syrup Dichloromethane (30 ml) was added, and the solution was extracted with water (4 × 40 ml) The extracts were combined, and neutralized with IR-45 (OH^-) ion-exchange resin, and the suspension was filtered The filtrate was evaporated to a syrup which contained a trace of uridine (t l c with 10 4 1 chloroform–hexane–methanol) 5'-Bromo-5'-deoxyuridine was isolated by preparative t l c and obtained as a syrup that did not crystallize

The product was treated with a solution of 2,2-dimethoxypropane in DMF (4 ml), and *p*-toluenesulfonic acid monohydrate (5 mg) was added After being kept overnight at room temperature, the mixture was made neutral with aqueous sodium hydrogen carbonate, and the solution was extracted with dichloromethane Processing of the extract gave 0 12 g (70%, overall) of 5'-bromo-5-'deoxy-2',3'-*O*-isopropylideneuridine, m p 184–185°, lit [42] m.p 184–186°

Bromination of inosine isolation of 2',3'-di-O-acetyl-5'-bromo-5'-deoxyinosine — To a cooled solution of inosine (0 268 g, 1 mmole) and triphenylphosphine (0 92 g, 3 5 mmoles) in DMF (10 ml) was slowly added NBS (0 445 g, 2 5 mmoles), with stirring, and the mixture was heated for 2 5 h at 50° Methanol and then butanol were added, and the solution was evaporated *in vacuo* to a syrup Dichloromethane (30 ml) was added, and the solution was extracted with water (3 × 40 ml) The extracts

were combined, neutralized with IR-45 (OH^-) ion-exchange resin, the suspension was filtered, and the filtrate was evaporated under diminished pressure to a pale-yellow syrup, traces of water were removed by co-evaporation with benzene

Acetylation of the resulting syrup with acetic anhydride in pyridine gave the title compound, which crystallized from ethanol (0.243 g, 59%), m.p. 175–180°. Recrystallization from ethanol gave pure material, m.p. 182–185°; $[\alpha]_D^{25}$ +48.1° (*c* 1, chloroform)

Anal. Calc. for $C_{14}H_{14}BrN_4O_6$: C, 40.60; H, 3.41; Br, 19.30; N, 13.50. Found: C, 40.89; H, 3.70; Br, 19.62; N, 13.15.

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