SYNTHESIS OF ALKYL 2-DEOXY-α-D-GLYCOPYRANOSIDES AND THEIR 2-DEUTERIO DERIVATIVES[1]

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ABSTRACT

The methyl, cyclohexyl, and *t*-butyl 2-deoxy-2-iodo-α-D-manno- and β-D-glucopyranoside triacetates were formed in near quantitative yield on reaction of equimolar amounts of the corresponding alcohol, iodine, D-glucal triacetate, silver perchlorate, and 2,4,6-trimethylpyridine (collidine) in dry benzene. The proportion of the α-D-*manno* isomer in the product increased in the order, *t*-butyl > cyclohexyl > methyl. Deuterolysis of the iodide in the presence of palladium proceeded with retention of configuration when the iodine was in equatorial orientation (β-D-*gluco*-configuration) but with near complete lack of stereospecificity when axially oriented (α-D-*manno*-configuration).

2-Deoxyglycopyranosides have been prepared by reaction of *O*-acylated 2-deoxyglycopyranosyl halides with alcohols (1, 2), acid-catalyzed addition of alcohols to acylated glycals (3–6), and the acid-catalyzed alcoholysis of 2-deoxysugars (7). Also, the condensation of *O*-acyl-2-deoxy-2-halogenoglycopyranosyl halides with alcohols followed by hydrogenolysis of the 2-deoxy-2-halogenoglycoside has been employed (8–12).

The syntheses involving substituted glycosyl halides are of most general application. Since anomeric halogens are normally in axial orientation and their replacement tends to proceed with inversion of the reacting center, 2-deoxyglycopyranosides with equatorial aglycons are the expected products. This corresponds to the β-configuration for the hexoses. The formation of the α-glycoside on reaction of 2,6-dideoxy-D-ribohexopyranosyl chloride tri-*p*-nitrobenzoate with digitoxigenin (1) is undoubtedly related to the instability of the α-configuration for the chloride in the presence of the axial 3-acyloxy group. The purpose of this research was to achieve a stereochemically controlled synthetic route to the 2-deoxy-α-glycopyranosides which would proceed in high yield.

It has long been recognized that the reaction of an alkene with a halogen in the presence of a source of carboxylate ion leads to the formation of *O*-acylated halohydrin (13, 14). The halogenation of an alkene in an alcohol results in formation of *O*-alkyl halohydrin (15, 16). The yields of these substituted halohydrins are enhanced through depression of the concentrations of halide ion by addition of silver ion (13, 14, 15, 17, 18). It was observed (17) that the reaction of cyclohexene with iodine and silver perchlorate in dry ether gave a product which was hydrolyzed to cyclohexene iodohydrin on the addition of water. This observation is in keeping with the now well-recognized inability of the perchlorate ion to form covalent bonds.

D-Glucal triacetate was converted to 1-*O*-benzoyl-2-deoxy-2-iodo-D-hexose triacetates on treatment with silver benzoate and iodine (19). The product was recently found to comprise an about equimolar mixture of the isomers with the α-*manno*- and β-*gluco*-configurations (20). Evidently, it could be expected that alkyl 2-deoxy-2-iodoglycopyranoside triacetates would form on reaction of an acetylated glycal dissolved in an alcohol with iodine and a silver salt. The preparation of *trans*-2-methoxycyclohexyl iodide in

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90% yield on reaction of cyclohexene in methanol with iodine in the presence of silver perchlorate and calcium carbonate at −80° (17) would serve as a precedent. The use of silver perchlorate was found to be an unnecessary precaution in the iodomethoxylation of D-glucal triacetate when a large excess of methanol was used. Thus, the reaction in the presence of silver benzoate gave the methyl 2-deoxy-2-iodo-α-D-manno- and β-D-glucopyranoside triacetates in near quantitative yield. The isomer with the α-D-*manno*-configuration comprised about 55% of the mixture as evidenced by the relative intensities of the signals for the methoxy groups in the proton magnetic resonance (NMR) spectrum. The hydrogenolysis of these glycosides was previously shown (20) to yield the α- and β-methyl glycosides of 2-deoxy-D-glucose.

This approach to the synthesis of 2-deoxyglycopyranosides would likely not find useful application unless the acetylated glycal and the alcohol could be used in equimolar amounts to provide the 2-deoxy-2-halogenoglycoside in high yield. This goal was achieved through the anticipation that both glycosyl perchlorates and the *N*-glycosides of 2,4,6-trimethylpyridine (collidine) would prove to be unstable in the presence of an alcohol. Thus, the addition of iodine to equimolar amounts of D-glucal triacetate, silver perchlorate, collidine, and an alcohol (methanol, cyclohexanol, or *t*-butanol) provided the alkyl 2-deoxy-2-iodo-D-glycopyranoside triacetates as mixtures of α-D-*manno*- and β-D-*gluco*-configurations in near quantitative yields. The content of the isomer with the α-D-*manno*-configuration increased with increasing substitution of the α-carbon of the alcohol (methyl, 55%; cyclohexyl, about 70%; *t*-butyl, 85%). This result is reminiscent of the increased resistance displayed by 1,2-anhydro-α-D-glucopyranose triacetate with alcohols as the bulk of the group about the hydroxyl is increased (21). Thus, it seems likely that the amount of the α-D-*manno*-isomer increased because the formation of the intermediate iodonium ions is reversible and the diequatorial opening of the intermediate 1,2-α-D-*gluco* iodonium ion became less favored than the diaxial opening of the 1,2-β-D-*manno* iodonium ion with increasing size of the alkyl group.

The configurations of the iodoglycosides were established by application of NMR spectroscopy as previously described (12) and by hydrogenolysis to the corresponding α- and β-2-deoxy-D-glucopyranosides. It seemed of interest to investigate the stereochemical route of the reduction of these iodides with deuterium since it could be anticipated that the configurations of the 2-deoxy-2-deuterioglycosides could be readily interpreted from their NMR spectra. Deuterolysis of methyl 2-deoxy-2-iodo-β-D-glucopyranoside in deuterium oxide using palladium on charcoal as catalyst proceeded with apparent complete retention of configuration. The chemical shift and the triplet structure of the signal of intensity one at 1.78 p.p.m. requires the proton to be in axial orientation at the 2-position (see Fig. 1) and coupled with axial hydrogens at the 1- and 3-positions. As expected, the quartet signal (4.62 p.p.m. and spacings of 1.9 and 9.9 c.p.s.) for the anomeric hydrogen of the 2-deoxy-β-glucoside collapsed to a doublet with the larger spacing on introduction of the equatorial deuterium.

Treatment of the methyl 2-deoxy-2-deuterio-β-D-glucopyranoside with methanolic hydrogen chloride provided the α-anomer. The spectrum of this compound is shown in Fig. 2. A comparison of this spectrum with that shown in the same figure for methyl 2-deoxy-α-D-glucopyranoside clearly substantiates the configuration shown. The structure of the signal for the anomeric hydrogen allows the assignment of the larger spacing, 3.9 c.p.s., to the coupling of the anomeric hydrogen (H_1) with the axial hydrogen (H_2) at the 2-position. This result, on the basis of the Karplus relationship (22), indicates that H_1 defines a somewhat smaller dihedral angle with H_2 than with $H_{2'}$. This distortion of

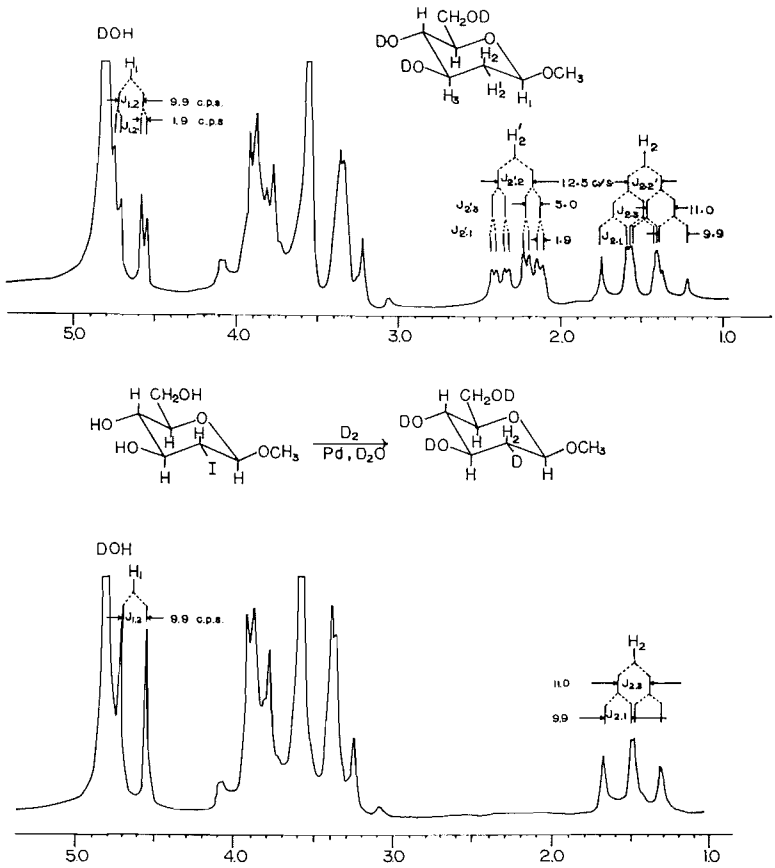

FIG. 1. NMR spectra at 60 Mc.p.s. in deuterium oxide of methyl 2-deoxy-β-D-arabohexopyranoside and methyl 2-deoxy-2-deuterio-β-D-glucopyranoside. The spacings are in c.p.s. and the chemical shifts in p.p.m. from tetramethylsilane used as an external reference.

the pyranose ring would be in the direction expected on the basis that the non-bonded interactions between the axial oxygen and the opposing axial hydrogens do not allow the oxygen to assume an exactly axial orientation. The spacings of 5.0 and 11.4 c.p.s. observed in the signals for the 2′- and 2-hydrogens, respectively, which arise from coupling with the 3-hydrogen, together with the above-mentioned spacings for the anomeric hydrogen obviously require the compound to possess the chair conformation.

The deuterolyses of both the methyl and *t*-butyl 2-deoxy-2-iodo-α-D-mannopyranosides both proceeded with extensive inversion (about 40%) of the reacting center. That the deuterium replaced the iodine is evident from the structures of the signals for hydrogens at the 2-position (see Fig. 3). The relative intensities of these signals provided the relative amounts of the two epimers in the mixture. Since the spacings found in the signals for these hydrogens are virtually the same for both the methyl and the *t*-butyl 2-deoxy-2-deuterio-α-D-glucopyranosides, it is clear that the size of the alkyl group of the aglycon has little if any influence on the conformation of the pyranose ring. The extent of racemization of the 2-position in the deuterolysis of the axially oriented iodine requires the reaction in this case to proceed by way of a configurationally labile intermediate such as a free radical or carbanion.

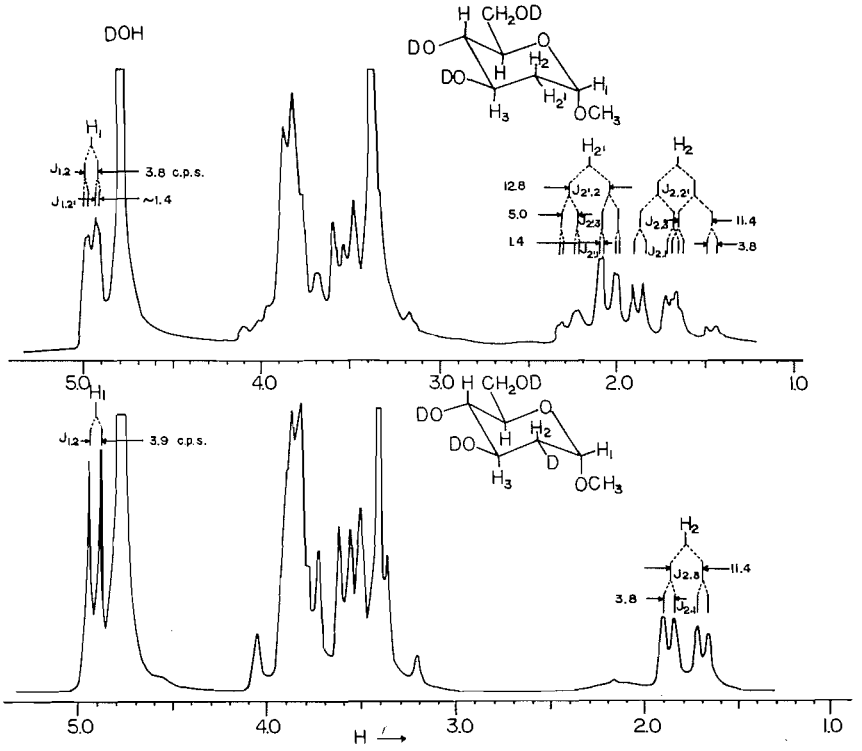

FIG. 2. NMR spectra at 60 Mc.p.s. in deuterium oxide of methyl 2-deoxy-α-D-arabohexopyranoside and methyl 2-deoxy-2-deuterio-α-D-glucopyranoside. The spacings are in c.p.s. and the chemical shifts in p.p.m. from tetramethylsilane used as an external standard.

Incidental to this research, the NMR spectrum of the methyl 2-deoxy-α-D-ribopyranoside was determined both in chloroform and deuterium oxide (see Fig. 4). It is of interest to note that the structures of the signals for the anomeric hydrogen changed from a triplet to a quartet on changing the solvent from chloroform to deuterium oxide. In view of the dependence of the coupling constant for hydrogens on vicinal carbons on the dihedral angles defined by the hydrogens (22), it is clearly apparent that the 1-axial conformation wherein the anomeric hydrogen is *gauche* to both the 2-hydrogens is much more favored in the non-hydroxylic solvent. It seems most probable that this conformation is favored in chloroform since it allows an intramolecular hydrogen bond between the 3-hydroxyl and the methoxyl. In the deuterium oxide solution, hydrogen bonding of the hydroxyl groups with the solvent is favored over intramolecular hydrogen bonding and therefore, the 1-equatorial conformation is preferred since it avoids non-bonded interaction between the 1- and 3-substituents.

EXPERIMENTAL

All melting points were determined on a heating stage and are uncorrected. The proton magnetic resonance spectra were determined in chloroform with a Varian Associates HR-60 spectrometer and the chemical shifts are reported in p.p.m. from tetramethylsilane.

Methyl 2-deoxy-2-iodo-β-D-gluco- and -α-D-mannopyranosides

(*a*) To a stirred suspension of 1.15 g (5 mmoles) of dry silver benzoate in a solution of 1.36 g (5 mmoles) of D-glucal triacetate (23) in 150 ml of dry methanol, 1.27 g (5 mmoles) of iodine were added over a period

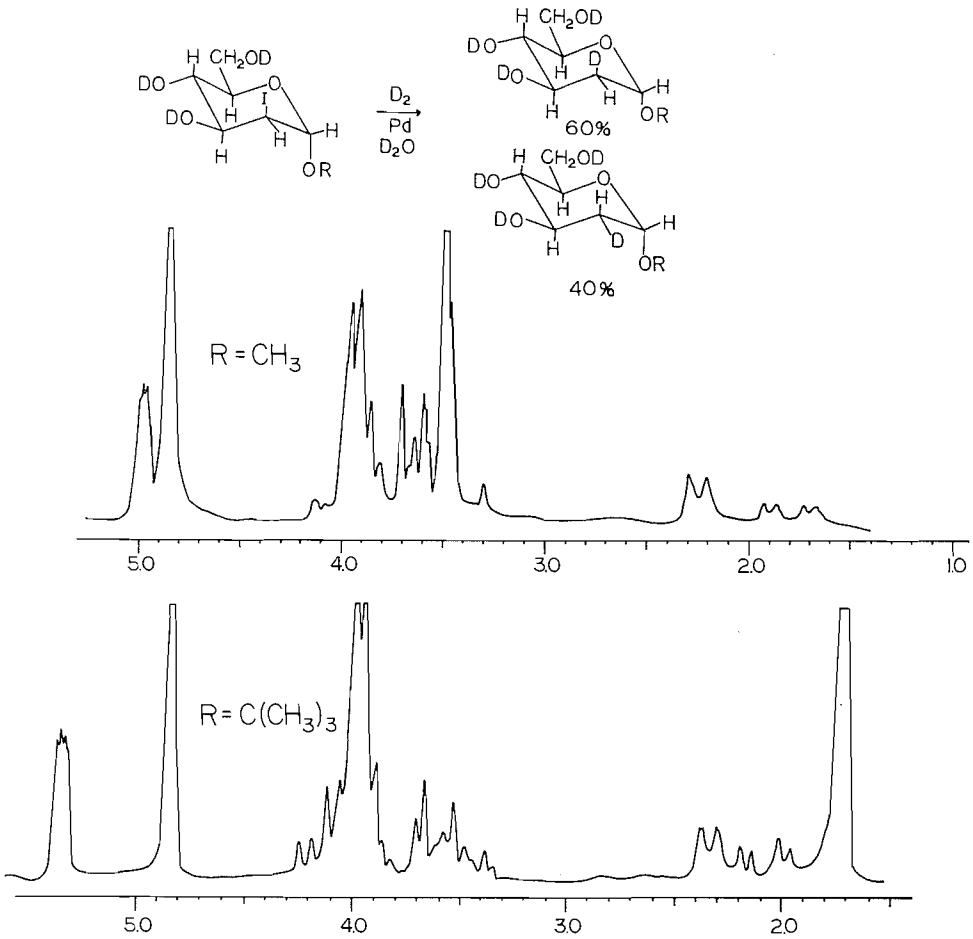

FIG. 3. The NMR spectra at 60 Mc.p.s. in deuterium oxide of the mixtures obtained on deuterolysis of the methyl and *t*-butyl 2-deoxy-2-iodo-α-D-mannopyranosides. The chemical shifts are in p.p.m. from tetramethylsilane used as an external standard. The doublets at 2.25 and 2.33 p.p.m. in the upper and lower spectra, respectively, are assigned to the equatorial 2-protons of the component with the *manno*-configuration. The lower intensity quartets to higher field centered at 1.8 and 2.1 p.p.m., respectively, are assigned to the axial 2-protons of the *gluco*-isomers.

of 5 minutes. Except for the last addition when slight coloration remained, the iodine coloration rapidly disappeared after each addition. After the suspension was stirred at room temperature for 30 minutes, the silver salts were removed by filtration, the filtrate was evaporated to near dryness, and the residue was dissolved in chloroform. The solution was washed with aqueous sodium thiosulphate, then with aqueous bicarbonate, and finally with water before drying. Removal of the chloroform left a viscous oil, 2.01 g (93.5% yield). The NMR spectrum showed two signals for methoxyl-group protons of relative intensities 10:13. The sirup was dissolved in 50 ml of dry methanol saturated with ammonia. After 1 day at room temperature, the solution was evaporated to dryness. The residue was freed of acetamide by chromatography on silicic acid using 5% methanolic chloroform as eluant. The acetamide-free sirup was dissolved in ethyl acetate. On seeding of the solution with methyl 2-deoxy-2-iodo-β-D-glucopyranoside (20), crystals of this material were deposited. The yield (based on the D-glucal triacetate) after one recrystallization from ethyl acetate was 21%. The sirup obtained on evaporation of the mother liquor was seeded with methyl 2-deoxy-2-iodo-α-D-mannopyranoside. After crystallization was complete, the crystals were washed with ethyl acetate and recrystallized from this solvent to provide a 30% yield of the mannoside. The identifications were based on melting points and mixed melting points with authentic samples (20).

(*b*) Anhydrous silver perchlorate, 0.451 g (2.19 mmoles) was added to a solution of 0.590 g (2.19 mmoles)

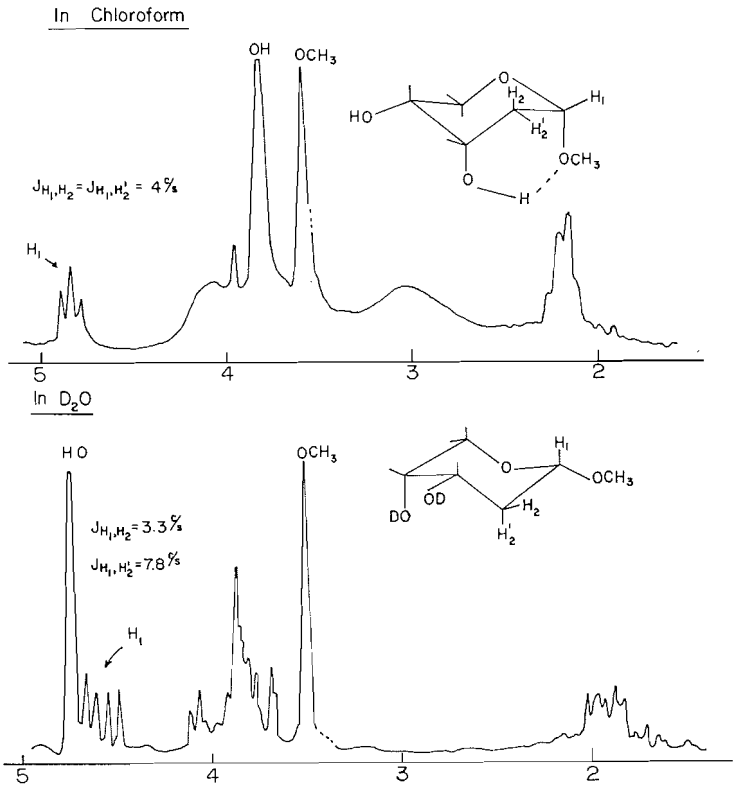

FIG. 4. The effect of solvent on the NMR spectrum at 60 Mc.p.s. of methyl 2-deoxy-α-D-ribopyranoside

of D-glucal triacetate, 0.071 g (2.23 mmoles) of anhydrous methanol, and 0.497 g (2.25 mmoles) of 2,4,6-trimethylpyridine (collidine) in 50 ml of dry benzene. A white precipitate was formed. Iodine, 0.55 g (2.19 mmoles) was added and the mixture was stirred at room temperature for 20 minutes. The reaction product was isolated in a manner similar to that described above. The yield was 0.895 g (95%) of a viscous oil which gave NMR and IR spectra almost identical with those obtained in the reaction described above using methanol as the solvent. The NMR spectrum indicated the product to contain 43% and 57% of the compounds with β-D-*gluco* and α-D-*manno* configurations, respectively. The mixture was deacetylated and the methyl 2-deoxy-2-iodoglycosides were isolated as described in the above preparation in pure condition for positive identification.

Cyclohexyl 2-deoxy-2-iodo-β-D-gluco- and -α-D-mannopyranosides

Reaction of 1.28 g (4.71 mmoles) of D-glucal triacetate, 0.480 g (4.80 mmoles) of dry cyclohexanol, 1.02 g (4.71 mmoles) of silver percholate, 1.20 g (4.71 mmoles) of iodine, and 0.431 (4.77 mmoles) of collidine in 50 ml of dry benzene for 20 minutes, followed by the isolation procedure described above, gave 2.28 g (97% yield). The NMR spectrum of the product required it to be free of D-glucal triacetate. The substance was deacetylated in methanol saturated with ammonia and chromatographed on silicic acid using chloroform as the developing phase. The faster moving of the components was isolated as an amorphous powder, in 50% overall yield, which resisted crystallization. The specific rotation was +68.7° (*c*, 1.9 in methanol). The slower moving component was eluted from the chromatographic column using 5% methanolic chloroform. This compound was obtained in crystalline condition on evaporation of the solvent in 23% overall yield. After purification by recrystallization from benzene, the melting point was 151–152.5° with $[\alpha]_D$ +16.0° (*c*, 2.1 in methanol).

Anal. Calc. for $C_{12}H_{21}O_5I$: C, 38.72; H, 5.69; I, 34.10. Found: C, 38.50; H, 5.83; I, 33.61%.

Cyclohexyl 2-Deoxy-α-D-glucopyranoside

The above-described cyclohexyl 2-deoxy-2-iodo-α-D-mannopyranoside, $[\alpha]_D$ +68.7°, 372 mg, was dissolved in 15 ml of methanol with 138 mg of diethylamine, and 40 mg of 5% palladium on charcoal was added to catalyze a hydrogenolysis. The theoretical amount of hydrogen was consumed within 30 minutes. After

filtration to remove the catalyst, silver carbonate was added to remove the iodide ion. The silver salts were removed and the filtrate was treated with hydrogen sulphide. Treatment with charcoal, filtration, and evaporation gave viscous oil, 206 mg (84% yield), which completely crystallized on trituration with benzene. Recrystallization from benzene gave white crystals, m.p. 123–124°, $[\alpha]_D$ +129.3° (*c*, 1.1 in methanol).

Anal. Calc. for $C_{12}H_{22}O_5$: C, 58.52; H, 9.00. Found: C, 58.71; H, 8.98%.

Cyclohexyl 2-Deoxy-β-D-glucopyranoside

The above-described cyclohexyl 2-iodo-2-deoxy-β-D-glucopyranoside, $[\alpha]_D$ +16.0°, 185 mg, was hydrogenolyzed and the product, 117 mg (95% yield), was isolated as described for the α-anomer. The crystalline compound melted at 126–127° with $[\alpha]_D$ + 46.3° (*c*, 0.9 in methanol) after recrystallization from benzene.

t-Butyl 2-Deoxy-2-iodo-β-D-glucopyranoside and -α-D-mannopyranosides

A mixture of the triacetates of these two compounds was obtained in 97% yield using the reaction conditions described above for the preparation of the cyclohexyl 2-deoxy-2-iodoglycoside triacetates except that dry *t*-butanol was used instead of the cyclohexanol. The product was deacetylated and chromatographed as reported for the corresponding cyclohexyl glycosides. The band eluted with chloroform provided a 59% yield of a crystalline product which, after one recrystallization from benzene, melted at 146–147° with $[\alpha]_D$ +65.2° (*c*, 2.1 in methanol).

Anal. Calc. for $C_{10}H_{19}O_5I$: C, 34.69; H, 5.53; I, 36.67. Found: C, 34.55; H, 5.30; I, 36.02%.

Elution of the chromatographic column with 5% methanolic chloroform gave a sirup from which a 4% yield of compound, m.p. 153–154°, $[\alpha]_D$ +13.2° (*c*, 0.08 in methanol), was obtained.

Anal. Calc. for $C_{10}H_{19}O_5I$: C, 34.69; H, 5.53; I, 36.67. Found: C, 35.02; H, 5.56; I, 36.20%.

A sample of the reaction mixture was deacetylated and its NMR spectrum in deuterium oxide showed a chemical shift for the *t*-butyl groups of the two components. The relative intensities of the signals required the mixture to comprise 85% of the α-D-mannoside and 15% of the β-D-glucoside.

t-Butyl 2-Deoxy-α-D-glucopyranoside

The above-described *t*-butyl 2-deoxy-2-iodo-α-D-mannopyranoside, $[\alpha]_D$ +65.2°, was hydrogenolyzed under the same conditions as described for the cyclohexyl mannoside except that water was used as solvent. The yield was 84% of a crystalline product which was recrystallized from benzene. On heating, the compound, $[\alpha]_D$ +123.0° (*c*, 0.7 in methanol), first melted at 136–138° then solidified to a crystal form which melted at 144–145°.

Anal. Calc. for $C_{10}H_{20}O_5$: C, 54.53; H, 9.15. Found: C, 54.42; H, 9.01%.

Deuterolysis of the Iodoglycosides

Methyl 2-deoxy-2-iodo-β-D-glucopyranoside and the methyl and *t*-butyl 2-deoxy-2-iodo-α-D-mannopyranosides after exchange of the active hydrogens using deuterium oxide, were treated with deuterium at atmospheric pressure and room temperature in the presence of 5% palladium on charcoal and diethylamine using deuterium oxide as solvent. The product in each case was isolated by first precipitating the iodide ion with silver carbonate as described above in similar preparations. The yields in each case were near quantitative. The NMR spectra of the 2-deoxy-2-deuterioglycosides are reproduced in Figs. 1 and 3. Methyl 2-deoxy-2-deuterio-α-D-glucopyranoside was obtained by allowing a solution of the β-anomer in 5% methanolic hydrogen chloride to achieve constant rotation. The α-glucoside was readily isolated in crystalline condition using the usual isolation procedure. Its NMR spectrum is reproduced in Fig. 2.

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