Novel Reagent System for converting a Hydroxy-group into an Iodo-group in Carbohydrates with Inversion of Configuration. Part 2 †

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Isolated primary and secondary hydroxy-groups in carbohydrate derivatives are transformed into iodo-groups with inversion of configuration on treatment with either triphenylphosphine, iodine, and imidazole or triphenylphosphine and 2,4,5-tri-iodoimidazole at elevated temperatures. At lower temperatures, primary hydroxy-groups may be selectively replaced by iodo-groups.

THE conversion of hydroxy-groups into iodo-groups has attracted considerable attention in carbohydrate chemistry. Deoxyiodo-sugars are themselves of biochemical interest, for example as contrast agents in urography, and their reduction [1] produces deoxy-sugars such as occur in natural compounds of biological significance, *e.g.* in antibiotic substances, cardiac glycosides, and bacterial antigens. Iodide is a good leaving group, and deoxyiodo-sugars are amenable to further transformations, such as substitution and elimination.

The classical approach to deoxyiodo-sugars involves the displacement of a sulphonic ester group with iodide.[2] In the 1950's Rydon and his co-workers [3] introduced iodination of alcohols using various phosphorus-based reagents, the most important being methyltriphenoxyphosphonium iodide and iodotriphenoxyphosphonium iodide. Kochetkov and his co-workers [4] have studied the use of these reagents in carbohydrate chemistry. In 1972, Hanessian and his co-workers [5] published procedures for the direct replacement of primary hydroxy-groups by halogen using triphenylphosphine and *N*-halogenosuccinimides in dimethylformamide, and in 1978, Binkley and Heheman [6] reported the synthesis of iodides from alcohols by converting single hydroxy-groups in protected carbohydrates into the triflate esters followed by treatment with tetrabutylammonium iodide in refluxing benzene. Various other methods have also been described.[7]

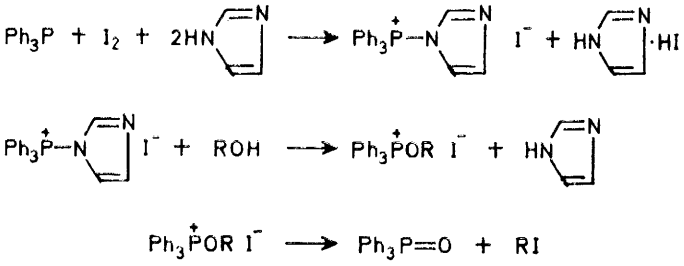
We have previously reported [8] the transformation of pyranosidic vicinal diols into the corresponding dideoxy-enoside derivatives, using either triphenylphosphine, iodine, and imidazole or a modification of this reagent [9] in which iodine is replaced by 2,4,5-tri-iodoimidazole. These reagents are also useful for the conversion of single hydroxy-groups into the corresponding iodides, with inversion of configuration in the case of unsymmetrical alcohols. This has been the subject of a preliminary account [10] and we now report the full experimental details of the transformation.

Triphenylphosphine, imidazole, and iodine in toluene at reflux temperature furnishes a two-phase system which appears to be most efficient in transforming alcohols into iodides, with inversion at the reaction centre. The alcohol does not have to be soluble in the reaction medium. Mechanistic studies have not been carried out, but a plausible rationalization is outlined in Scheme 1.

† Part 1 is ref. 10.

In the absence of imidazole, triphenylphosphine and iodine in toluene form an adduct which is virtually insoluble and of limited use for the present purpose. If, however, imidazole is added, a partially soluble complex is formed which rapidly combines with the alcohol. Toluene acts essentially as an inert heat-transfer medium, and it also dissolves the product as it is formed.

More detailed considerations of possible intermediates in the above reaction led us to add 2,4,5-tri-iodoimidazole rather than iodine to the reaction mixture. This modified reagent system, thus containing triphenylphosphine and tri-iodoimidazole [11] (see Experimental



SCHEME 1

section) in toluene at elevated temperature in general gave higher yields than did the original system, particularly for sterically hindered, secondary alcohols.

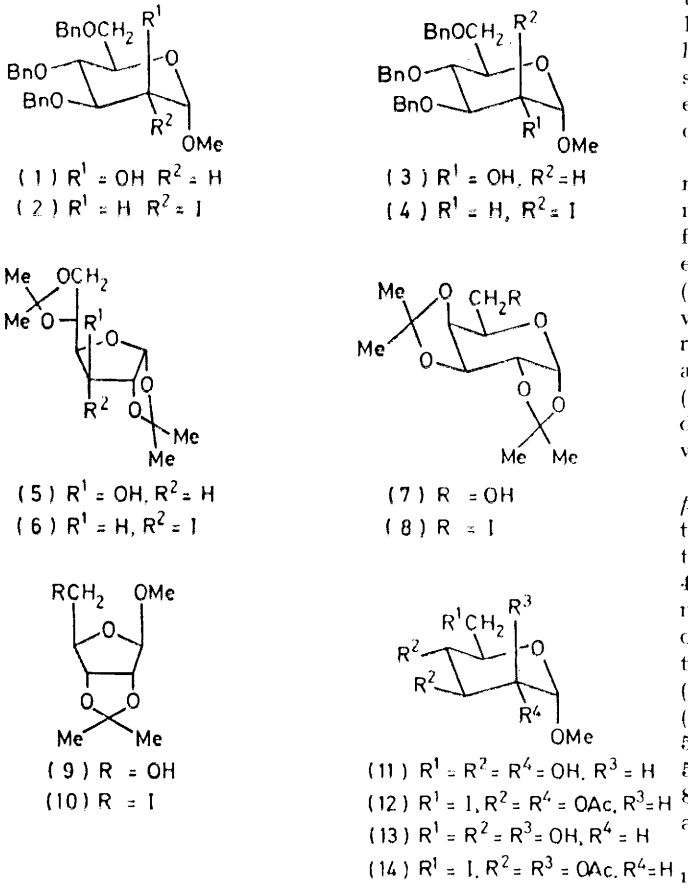
The various protected carbohydrates (1) to (10) (Scheme 2), each with a single free hydroxy-group, all gave the corresponding iodides, with inverted configuration at secondary positions, in good yield. The conversion of the hydroxy-groups in the 2-positions in the pyranosides (1) and (3) to the 2-deoxy-2-iodoglycosides (2) and (4) in yields of 82—87% is particularly noteworthy.

Both reagent systems show steric selectivity in that primary hydroxy-groups in the unprotected methyl pyranosides (11) and (13) were converted into the corresponding 6-deoxyiodoglycosides in 70--80% yield by reaction at 70 °C. Further regioselectivity in iodination as well as brominations using this type of reaction is currently being investigated.

EXPERIMENTAL

General Methods.—Melting points are corrected. Concentrations were performed in a vacuum at a bath temperature below 40 °C Optical rotations were recorded using a Perkin-Elmer 241 polarimeter, 99.55-MHz ^{1}H and 25.05-

MHz ^{13}C n.m.r. spectra (in $CDCl_3$) were recorded in the Fourier-transform mode using a JEOL JNM FX 100 instrument. Chemical shifts are given in p.p.m. downfield from tetramethylsilane. N.m.r. spectra, recorded for new compounds, were invariably in accordance with postulated structures; only selected n.m.r. data are presented below. T.l.c. was performed using pre-coated silica-gel plates (F_{254}, Merck) and the spots were detected by charring with 8% aqueous H_2SO_4. Column chromatography was performed on silica gel 60 (0.040—0.063 mm, Merck).



SCHEME 2

If tri-iodoimidazole, as described in the literature is used,[11] imidazole (about 3 equivalents per hydroxy-group) must be added to the reaction mixture to effect dissolution of the reagent. The following modification of existing procedures for making tri-iodoimidazole was used throughout this work.

2,4,5-Tri-iodoimidazole.[11]—Iodine (76.1 g, 0.30 mol) and imidazole (6.81 g, 0.10 mmol) in alkaline water–hexane were allowed to react and worked up as previously described.[9] The crude precipitated product was dissolved in hot methanol (100—150 ml) containing small amounts of imidazole. The product was allowed to crystallize first at room temperature and then at −20 °C. A second crop of crystals was obtained by concentration of the filtrate from the first crop. Large, compact, heavy crystals were obtained (*ca.* 35 g).

Work-up, procedure A: for products insoluble in water. The reaction mixture was cooled, an equal volume of saturated aqueous sodium hydrogencarbonate was added, and the mixture was stirred for 5 min. Iodine was added in portions. When the toluene phase remained iodine-coloured it was stirred for an additional 10 min. Excess of iodine was removed by the addition of aqueous sodium thiosulphate. The mixture was transferred to a separating funnel and material remaining in the reaction vessel was dissolved in a small amount of acetone and added to the main bulk of material. The organic layer was diluted with toluene, and after separation, the toluene layer was extracted with water, dried ($MgSO_4$), filtered, and concentrated. For small-scale operations the residue was dissolved *in a* little of the eluant before chromatography; on a larger scale, triphenylphosphine oxide was precipitated in diethyl ether and the filtrate concentrated and then subjected to column chromatography (toluene–ethyl acetate, 4 : 1).

Work-up, procedure B: for products soluble in water. The reaction mixture was cooled, water was added, and the mixture was stirred vigorously for 15 min and then transferred to a separating funnel. The toluene phase was extracted with water until no product remained there (t.l.c.). The combined aqueous phase was shaken once with a small amount of toluene and then concentrated. The residue was acetylated with acetic anhydride and pyridine at room temperature. When the acetylation was complete (t.l.c.), the reaction mixture was concentrated and the residue dissolved in toluene. The toluene solution was extracted with water, concentrated, and the residue crystallized.

Methyl 3,4,6-Tri-O-benzyl-2-deoxy-2-iodo-α-D-glucopyranoside (2). *Method A.* A mixture of methyl 3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (1) (0.50 g, 1.08 mmol),[12] triphenylphosphine (1.13 g, 4.32 mmol), imidazole (0.29 g, 4.32 mmol), and iodine (0.82 g, 3.24 mmol) in toluene (50 ml) was stirred under reflux at a bath temperature of 120 °C overnight; the mixture was then worked up (procedure A) to yield the title compound (0.413 g, 67%), m.p. 67—68 °C (crystallized once from ligroin), $[\alpha]_D^{22}$ +102° (*c* 1, $CHCl_3$) (Found: C, 58.6; H, 5.47; I, 22.2. $C_{28}H_{31}O_5I$ requires C, 58.5; H, 5.44; I, 22.1), δ_C (25 MHz, $CDCl_3$): 29.75 (C-2), 55.70 (OCH_3), 68.32 (C-6), 71.10, 73.54, 75.02, 75.43, 79.47, 82.01 (C-3, C-4, C-5, 3 × CH_2Ph), and 100.7 (C-1). The anomeric proton showed almost no coupling on ^1H n.m.r.

Method B. A mixture of methyl 3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (1) (0.50 g, 1.08 mmol),[12] triphenylphosphine (0.56 g, 2.16 mmol), and tri-iodoimidazole (0.48 g, 1.08 mmol) in toluene (50 ml) was stirred under reflux at a bath temperature of 120 °C for 3 h, after which additional triphenylphosphine (0.56 g, 2.16 mmol) and tri-iodoimidazole (0.48 g, 1.08 mmol) were added. The mixture was stirred at 120 °C overnight. The yield of title compound, indistinguishable from the above product, after work-up (procedure A), was 0.51 g (82%).

Methyl 3,4,6-Tri-O-benzyl-2-deoxy-2-iodo-α-D-mannopyranoside (4).* *Method A.* A mixture of methyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (3) (0.50 g, 1.08 mmol),[13] triphenylphosphine (0.85 g, 3.23 mmol), imidazole (0.29 g, 4.30 mmol), and iodine (0.68 g, 2.69 mmol) in toluene (50 ml) was stirred under reflux at a bath temperature of 120 °C for 6 h and then worked up (procedure A) to yield the title compound (0.467 g, 75%), $[\alpha]_D^{22}$ +5° (*c* 1, $CHCl_3$) (Found: C, 58.8; H, 5.57; I, 22.3. $C_{28}H_{31}IO_5$ requires C, 58.5; H, 5.44; I, 22.1), δ_C (25 MHz, $CDCl_3$): 33.14 (C-2), 54.89

* In the preliminary communication[10] this was erroneously reported as the β-anomer. In this reaction (method B), methyl 3,4,6-tri-*O*-benzyl-β-D-glucopyranoside gives a yield of only 50% of methyl 3,4,6-tri-*O*-benzyl-2-deoxy-2-iodo-β-D-mannopyranoside.

(OCH_3), 68.93 (C-6), 70.83, 72.07, 73.36, 75.12, 76.92 (C-3, C-4, C-5, 3 × CH_2Ph), and 102.40 (C-1). The anomeric proton showed almost no coupling on ^1H n.m.r.

Method B. A mixture of methyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranoside (3) (0.50 g, 1.08 mmol),[13] triphenylphosphine (0.56 g, 2.16 mmol), and tri-iodoimidazole (0.48 g, 1.08 mmol) in toluene (50 ml) was stirred under reflux at a bath temperature of 120 °C for 3 h, after which additional triphenylphosphine (0.28 g, 1.08 mmol) and tri-iodoimidazole (0.24 g, 0.54 mmol) were added. The mixture was stirred at 120 °C for 3 h. The yield of title compound, indistinguishable from the above product, after work-up (procedure A), was 0.54 g (87%).

3-Deoxy-3-iodo-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (6).[6,14]—*Method A.* A mixture of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (5) (0.50 g, 1.92 mmol), triphenylphosphine (1.51 g, 5.76 mmol), imidazole (0.39 g, 5.76 mmol), and iodine (0.97 g, 3.84 mmol) in toluene (40 ml) was stirred under reflux at a bath temperature of 120 °C overnight and then worked up (procedure A) to yield the title compound (0.426 g, 60%), $[\alpha]_D^{22}$ +63° (*c* 1, $CHCl_3$), (lit. $[\alpha]$,[6,14] ^1H n.m.r. shifts and coupling constants were in agreement with those published). Catalytic reduction of the product with 10% palladium on carbon yielded 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose identical to an authentic sample on t.l.c. and ^1H n.m.r.

Method B. A mixture of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (0.50 g, 1.92 mmol), triphenylphosphine (0.76 g, 2.88 mmol), and tri-iodoimidazole (0.64 g, 1.44 mmol) in toluene (40 ml) was stirred under reflux at a bath temperature of 120 °C for 3 h, after which additional triphenylphosphine (0.50 g, 1.92 mmol) and tri-iodoimidazole (0.43 g, 0.96 mmol) were added. The mixture was stirred at 120 °C overnight. The yield of title compound, indistinguishable from the above product, after work-up (procedure A), was 0.56 g (78%).

6-Deoxy-6-iodo-1,2:3,4-di-O-isopropylidene-α-D-galactopyranose (8).[15]—*Method A.* A mixture of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (7) (0.5 g, 1.92 mmol), triphenylphosphine (1.51 g, 5.76 mmol), imidazole (0.39 g, 5.76 mmol), and iodine (0.97 g, 3.84 mmol) in toluene (50 ml) was stirred under reflux at a bath temperature of 120 °C for 4 h and worked up (procedure A) to yield the title compound (0.668 g, 94%), m.p. 58 °C (crystallized once from ligroin), $[\alpha]_D^{22}$ −49° (*c* 1, $CHCl_3$) {lit.,[15] m.p. 70 °C, $[\alpha]_D^{18}$ −50° (1,1,2,2-tetrachloroethane)}.

Method B. A mixture of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (7) (0.5 g, 1.92 mmol), triphenylphosphine (0.76 g, 2.88 mmol), and tri-iodoimidazole (0.64 g, 1.44 mmol) in toluene (50 ml) was stirred under reflux at a bath temperature of 120 °C for 4 h. The yield of title compound, indistinguishable from the above product, after work-up (procedure A), was 0.670 g (94%).

Methyl 5-Deoxy-5-iodo-2,3-O-isopropylidene-β-D-ribofuranoside (10).[16]—*Method A.* A mixture of methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside (9) (0.5 g, 2.45 mmol),[17] triphenylphosphine (1.60 g, 6.10 mmol), imidazole (0.42 g, 6.17 mmol), and iodine (1.24 g, 4.89 mmol) was stirred under reflux at a bath temperature of 120 °C for 2.5 h and worked up (procedure A) to yield the title compound (0.71 g, 92%), $[\alpha]_D^{22}$ −72° (*c* 1, $CHCl_3$) {lit.,[16] $[\alpha]_D^{25}$ −68° ($CHCl_3$)}. ^1H N.m.r. shifts and coupling constants were in agreement with those published.[5]

Method B. A mixture of methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside (9),[17] (0.50 g, 2.45 mmol), triphenylphosphine (0.96 g, 3.67 mmol), and tri-iodoimidazole (0.82 g, 1.83 mmol) in toluene (50 ml) was stirred at 120 °C for 2.5 h. The yield of title compound, indistinguishable from the above product, after work-up (procedure A), was 0.75 g (97%).

Methyl 2,3,4-Tri-O-acetyl-6-deoxy-6-iodo-α-D-glucopyranoside (12).[18]—*Method A.* A mixture of methyl α-D-glucopyranoside (11) (0.50 g, 2.57 mmol, finely ground), triphenylphosphine (1.01 g, 3.86 mmol), imidazole (0.53 g, 7.72 mmol), and iodine (0.91 g, 3.60 mmol) in toluene (50 ml) was vigorously stirred at 70 °C for 2.5 h and then worked up (procedure B) to yield the title compound (0.89 g, 80%), m.p. 148—149 °C (crystallized once from ethanol), $[\alpha]_D^{22}$ +114° (*c* 1, $CHCl_3$) {lit.,[18] m.p. 150—151 °C, $[\alpha]_D^{24}$ +116° ($CHCl_3$)}.

Method B. A mixture of methyl α-D-glucopyranoside (11) (0.50 g, 2.57 mmol, finely ground), triphenylphosphine (1.01 g, 3.85 mmol), and tri-iodoimidazole (0.86 g, 1.93 mmol) was vigorously stirred at 120 °C for 2.5 h. The yield of title compound, indistinguishable from the above product, after work-up (procedure B), was 0.84 g (76%).

Methyl 2,3,4-Tri-O-acetyl-6-deoxy-6-iodo-α-D-mannopyranoside (14).[19]—A mixture of methyl α-D-mannopyranoside (13) (0.50 g, 2.57 mmol, finely ground), triphenylphosphine (1.01 g, 3.86 mmol), imidazole (0.53 g, 7.72 mmol), and iodine (0.91 g, 3.60 mmol) in toluene (50 ml) was vigorously stirred at 70 °C for 5 h and then worked up (procedure B) to yield the title compound (0.78 g, 70%), m.p. 91—92 °C (crystallized once from ethanol), $[\alpha]_D^{22}$ +45° (*c* 1, $CHCl_3$) {lit.,[19] m.p. 91—92 °C, $[\alpha]_D^{25}$ +37° (*c* 0.6 $CHCl_3$)}.

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