608. *Fluorocarbohydrates. Part VII.* Epimeric 2-Bromo-2-deoxyhexosyl Fluorides Derived from Triacetylglucal.*

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Two crystalline isomeric addition products result when 3,4,6-tri-*O*-acetyl-D-glucal reacts with *N*-bromosuccinimide and hydrogen fluoride in ether at −60°. The less soluble isomer has been identified as 3,4,6-tri-*O*-acetyl-2-bromo-2-deoxy-β-D-mannosyl fluoride, by defluorination in methanolic hydrogen chloride and conversion of the resulting methyl bromo-glycoside into an alkali-resistant benzylidene-bromo-glycoside. Hydrogenation and hydrolysis of the bromo-glycoside lead to 2-deoxy-D-glucose. The more soluble isomer, 3,4,6-tri-*O*-acetyl-2-bromo-2-deoxy-α-D-glucosyl fluoride, undergoes conversion by analogous reactions into a benzylidene derivative, which with sodium methoxide gives methyl 2,3 anhydro-4,6-benzylidene-β-D-mannoside.

CONSIDERABLE success has been achieved in introducing fluorine into steroid nuclei [1,2] by mixed addition at a double bond, reagents being *N*-bromoacetamide or *N*-bromosuccinimide and anhydrous hydrogen fluoride in a suitable Lewis base such as diethyl ether or tetrahydrofuran. The reaction, first demonstrated with cyclohexene, appears to take the course of a *trans*-addition since 3β-hydroxy-Δ^5-steroids led to the 6β-fluoro-5α-bromo-products.[3]. By similar means, 5-, 6-, 11-, and 16-fluoro-steroids have been synthesised. The analogous reaction [2] with *N*-iodosuccinimide, however, gave unexpectedly the 5α-fluoro-6β-iodo-derivative, suggesting that steric factors were significant in directing its course. The present work is concerned with the study of these effects in the carbohydrate field.

* Part VI, *J.*, 1963, 2743.

[1] Bowers, Ibanez, Denot, and Becarra, *J. Amer. Chem. Soc.*, 2960, **82**, 4001.
[2] Bowers, Denot, and Becarra, *J. Amer. Chem. Soc.*, 1960, **82**, 4007.
[3] Bowers, *J. Amer. Chem. Soc.*, 1959, **81**, 4107.

Triacetyl-D-glucal reacted smoothly with *N*-bromosuccinimide and anhydrous hydrogen fluoride in ether at −60°, to give two crystalline isomeric bromo-fluoro-sugars. The less soluble isomer (I), $[\alpha]_D^{20}$ −32°, m. p. 139°, was a remarkably stable compound which did not reduce Fehling's solution except on prolonged boiling. The more soluble isomer (II), $[\alpha]_D^{20}$ +67°, m. p. 113°, obtained from the mother-liquor, had similar stability but was dextrorotatory.

Isomer (I) was considered to be a β-D-hexosyl fluoride on account of its negative optical rotation and non-reducing properties. Methanolysis selectively and quantitatively removed fluorine from the anomeric carbon atom with accompanying inversion of rotation and deacetylation. The resulting methyl α-glycoside (III) carried a bromine atom at position 2 and was in the pyranose form, as shown by periodate oxidation, 1 mol. being consumed. This assignment was confirmed by catalytic hydrogenation of the bromo-glycoside (III) to crystalline methyl 2-deoxy-α-D-glucoside [4] which after acidic hydrolysis gave 2-deoxy-D-glucose benzylphenylhydrazone, identical with the known compound.[5] The deoxy-sugar obtained from the reduction product reacted in the same fashion as 2-deoxyglucose in the Dische diphenylamine reaction.

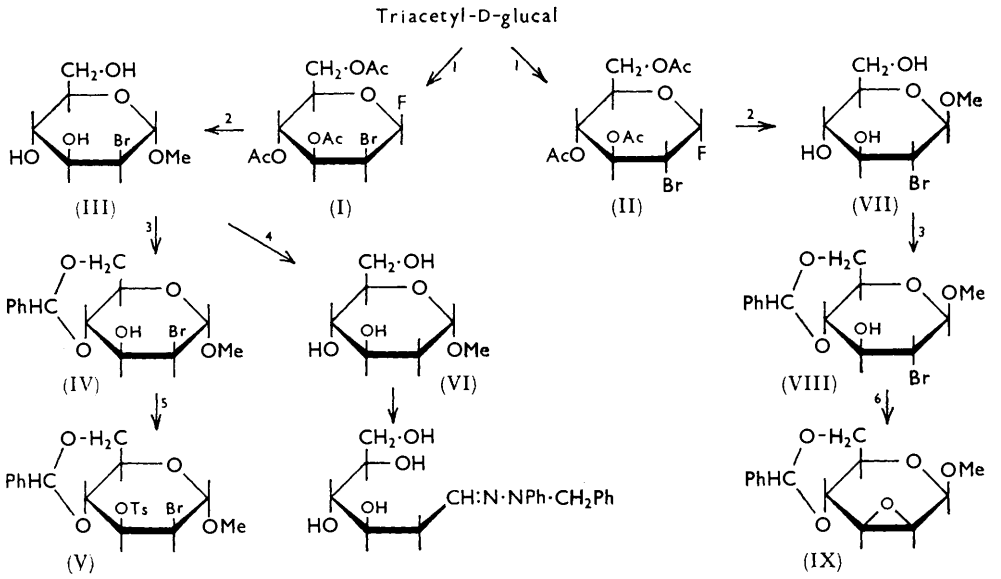
However, the crystalline benzylidene derivative (IV) formed from the bromo-glycoside (III) gave no infrared evidence for the presence of a hydroxyl group, whose presence was nevertheless demonstrated by the preparation of a toluene-*p*-sulphonate (V) that did not undergo exchange with sodium iodide in acetone under the conditions of Oldham and Rutherford.[6] This provides confirmation that the hydroxy-group was located in a secondary position (*e.g.*, 3) and that the benzylidene group thus occupied the 4,6-positions. The distinction between the *gluco*- and *manno*-configuration was made by investigation of the action of sodium methoxide on the 4,6-benzylidene-2-bromo-2-deoxyhexoside (IV). In the *gluco*-configuration, where the 2-bromine atom lies *trans* to the 3-hydroxyl group, ready elimination may be expected, giving a 2,3-anhydro-D-mannoside. With the *manno*-isomer no such reaction can be expected. Though this reaction with compound (IV) was investigated under a variety of conditions, no evidence was obtained of the formation of an anhydro-sugar, or of the liberation of more than trace amounts of bromide ion. It was therefore concluded that the sugar was of the mannose series and that isomer (I) was 2-bromo-2-deoxy-3,4,6-tri-*O*-acetyl-β-D-mannosyl fluoride.

Isomer (II) was submitted to a similar examination. In this case, methanolysis was accompanied by decrease in optical rotation consistent with the initial presence of an α-anomer, and by release of fluoride ion. As in the preceding case, the resulting bromo-glycoside (VII) was oxidised by sodium metaperiodate and readily gave a crystalline benzylidene derivative (VIII). The latter compound reacted readily with hot sodium methoxide in methanol, giving methyl 2,3-anhydro-4,6-benzylidene-β-D-mannoside (IX), having properties identical with those described by Peat and Wiggins.[7] It was concluded therefore that in isomer (II) the bromine atom lies *trans* to the 3-hydroxyl group and that the sugar thus possesses the *gluco*-configuration. Isomer (II) is considered to be 3,4,6-tri-*O*-acetyl-2-bromo-2-deoxy-α-D-glucosyl fluoride.

It is of interest that, in contrast to the *trans*-additions reported [1,2] for this reaction with unsaturated steroids, in the present case both products arise by *cis*-addition. Unlike the reactions of bromofluoro-steroids, it was possible to retain the bromine atom while selectively expelling the fluorine. Location of fluorine at position 1 is in keeping with the expected electronic effect of the ring-oxygen atom and the known behaviour of normal hexosyl fluorides. Since both α- and β-isomers have been isolated it is unlikely that anomeric rearrangements occur after addition. No evidence of ring contraction has been

[4] Hughes, Overend, and Stacey, *J.*, 1949, 2846.
[5] Bergmann and Schotte, *Ber.*, 1921, **54**, 440.
[6] Oldham and Rutherford, *J. Amer. Chem. Soc.*, 1932, **54**, 366.
[7] Peat and Wiggins, *J.*, 1938, 1088.

found, as in the reaction of pentose acetates with hydrogen fluoride.[8] As other additions,[9] *e.g.*, of halogen in alcoholic solvents, by triacetylglucal are reported to afford *trans*-products, we conclude that the present results in some way denote a peculiarity of fluorine or that a concerted mechanism intervenes in the addition. A *cis*-configuration for " 1,2-dichloroglucose " has been suggested by Newth and Phillips.[10]



Reagents: 1, HF–*N*-bromosuccinimide. 2, H^+–MeOH. 3, Ph·CHO–$ZnCl_2$. 4, H_2–Ni. 5, *p*-$C_6H_4Me·SO_2Cl$–pyridine. 6, NaOMe.

Experimental

Chromatography.—This was performed on Whatman paper No. 1 or No. 4 by downward elution with the water-poor phase of butan-1-ol–ethanol–water (4 : 1 : 5). Hydroxylic compounds were detected with a 1% solution of potassium permanganate in 2% aqueous sodium carbonate,[11] and glycols with 0·01M-sodium metaperiodate followed after 6 min. by 5% methanolic benzidine.[12] Esters were detected by means of the hydroxamic acid–ferric chloride colour,[13] and aldehydes by means of aniline hydrogen phthalate or silver nitrate–ethanolic sodium hydroxide.[14]

Fluorine Analyses.—These were performed by the method of Belcher, Leonard, and West.[15]

Reaction of Tri-O-acetyl-D-glucal with Hydrogen Fluoride and N-Bromosuccinimide.—Anhydrous ether (18·3 g.) was added to anhydrous hydrogen fluoride (10·0 g.) in a Polythene bottle cooled by acetone–carbon dioxide. *N*-Bromosuccinimide (4·0 g.) and triacetylglucal (5·0 g.) were added, portionwise, to the stirred solution during 10 min. After 2 hr. at −60°, the temperature was raised to 0° for a further 2 hr. After dilution with ether (175 ml.), the solution was poured into an ice-cold saturated solution of sodium hydrogen carbonate (750 ml.). The ethereal layer was washed with water, dried ($MgSO_4$), and concentrated. The crystals (isomer I) which separated were recrystallised from 1 : 5 v/v chloroform–light petroleum (b. p. 60—80°). This product was identified as 3,4,6-*tri*-O-*acetyl*-2-*bromo*-2-*deoxy*-β-D-*mannosyl fluoride* (1·8 g.), m. p.

[8] Peterson and Fletcher, *J. Amer. Chem. Soc.*, 1960, **82**, 946.
[9] Lemieux, personal communication.
[10] Newth and Phillips, *J.*, 1953, 2900.
[11] Pacsu, Mora, and Kent, *Science*, 1949, **110**, 446.
[12] Cifonelli and Smith, *Analyt. Chem.*, 1954, **26**, 1132.
[13] Abdel-Akher and Smith, *J. Amer. Chem. Soc.*, 1951, **73**, 5869.
[14] Trevelyan, Proctor, and Harrison, *Nature*, 1950, **166**, 444.
[15] Belcher, Leonard, and West, *J.*, 1959, 3577.

139°, R_F 0·6, $[\alpha]_D^{20}$ −32° (*c*, 0·9 in $CHCl_3$) (Found: C, 38·7; H, 4·3; Br, 21·3; F, 5·0. $C_{12}H_{16}BrFO_7$ requires C, 38·8; H, 4·3; Br, 21·5; F, 5·1%).

Concentration of the mother-liquors gave isomer (II), 3,4,6-*tri*-O-*acetyl*-2-*bromo*-2-*deoxy*-α-D-*glucosyl fluoride*, which after recrystallisation from ethanol had m. p. 113° (0·91 g.), $[\alpha]_D^{20}$ +67·3° (*c* 0·73 in $CHCl_3$) (Found: C, 39·1; H, 4·3; Br, 21·6; F, 5·1%).

Methanolysis of 2-*Bromo*-2-*deoxy*-3,4,6-*tri*-O-*acetyl*-β-D-*mannosyl Fluoride* (I).—The bromofluoro-compound (I) (1 g.) was refluxed with 1% methanolic hydrogen chloride (10 ml.) for 5½ hr. (α, −1·6° ⟶ +1·59°). Neutralisation with lead carbonate and evaporation gave *methyl* 2-*bromo*-2-*deoxy*-α-D-*mannoside* (III) (0·53 g.), n_D^{18} 1·5190, $[\alpha]_D^{20}$ +47·5° (*c* 0·7 in $CHCl_3$) (Found: C, 32·9; H, 5·4; Br, 29·7; OMe, 11·5. $C_7H_{13}BrO_5$ requires C, 32·7; H, 5·1; Br, 31·1; OMe, 12·0%).

Methyl 4,6-O-*Benzylidene*-2-*bromo*-2-*deoxy*-α-D-*mannoside* (IV).—The bromo-mannoside (III) (0·4 g.) was shaken with zinc chloride (0·3 g.) and redistilled benzaldehyde (3 ml.) for 12 hr., then neutralised with sodium carbonate, and the excess of benzaldehyde was removed in steam.[16] Chloroform-extraction afforded a *benzylidene derivative* (IV) (0·2 g.) which after recrystallisation from chloroform–light petroleum (b. p. 60—80°) had m. p. 83—85°, $[\alpha]_D^{20}$ +15·3° (*c* 0·8 in $CHCl_3$) (Found: C, 47·7; H, 4·9; Br, 23·1; OMe, 8·9. $C_{14}H_{17}BrO_5$ requires C, 48·7; H, 4·9; Br, 23·2; OMe, 8·8%).

This derivative (50 mg.) was treated with toluene-*p*-sulphonyl chloride (100 mg.) in anhydrous pyridine (4·5 ml.) at 20° for 24 hr. The resulting 3-*toluene*-p-*sulphonate* (V) (44 mg.) when recrystallised from ethanol, had m. p. 153° (Found: C, 50·4; H, 4·6; Br, 16·1; S, 6·4. $C_{21}H_{23}BrO_7S$ requires C, 50·5; H, 4·6; Br, 16·0; S, 6·4%).

The bromo-mannoside (IV) (30 mg.) was treated with 0·1N-methanolic sodium methoxide (1·3 ml.) at 0° for 4 hr., then for 12 hr. at 4°, and for 2 hr. each at 20°, 40°, and 60°. In each case the starting material was recovered. Only at 60° was the liberation of bromide ion detected and this was accompanied by some breakdown of the sugar; nevertheless starting material (27 mg.) was the only recognisable compound isolated.

2-*Deoxy*-D-*glucose Benzylphenylhydrazone*.—The methyl bromo-mannoside (III) (100 mg.) and Raney nickel (0·5 g.) in methanol (20 ml.) was shaken with hydrogen at 1 atm. (uptake 8 ml., 1 mol., in 4 hr.). A product (VI) was obtained which crystallised (53 mg.; m. p. 89°; cf. methyl 2-deoxy-α-D-glucoside,[4] m. p. 91°). This compound (50 mg.) was hydrolysed with 0·04N-hydrochloric acid (10 ml.) at 75° (α, +0·21° ⟶ +0·12°, constant in 40 min.), giving after neutralisation by silver carbonate 2-deoxy-D-glucose (R_F 0·36), identical with the authentic sugar.

The deoxy-sugar, dissolved in 75% aqueous ethanol (1·5 ml.) containing *N*-benzyl-*N*-phenylhydrazine (65 mg.), was treated for 1 hr. at 70°. The solid (41 mg.), recrystallised from ethyl acetate (Found: C, 66·2; H, 7·3; N, 8·3. Calc. for $C_{19}H_{24}N_2O_5$: C, 66·2; H, 7·0; N, 8·1%), had m. p. 155° alone or in admixture with 2-deoxy-D-glucose benzylphenylhydrazone.[5]

Methanolysis of 3,4,6-*Tri*-O-*acetyl*-2-*bromo*-2-*deoxy*-α-D-*glucosyl Fluoride* (III).—The bromofluoro-sugar (II) (0·9 g.) was refluxed with 0·3% methanolic hydrogen chloride for 6 hr. (α, +0·73° ⟶ +0·10°, constant). The product (VII), isolated as above, was a syrup (0·6 g.), R_F 0·52 (Found: C, 32·1; H, 4·9; Br, 29·9; OMe, 11·3%).

This bromo-glucoside (0·5 g.) was treated with benzaldehyde and zinc chloride as described above. Methyl 4,6-*O*-benzylidene-2-bromo-2-deoxy-β-D-glucoside recrystallised from ethanol as needles, m. p. 174°, $[\alpha]_D^{20}$ +1° (*c* 2 in $CHCl_3$) (Found: C, 48·4; H, 5·0; Br, 20·9%).

This benzylidene derivative (0·3 g.) was heated at 60° for 2 hr. with 0·1N-methanolic sodium methoxide. The solution was neutralised and evaporated and the product was extracted with ether. After drying ($MgSO_4$) and removal of the solvent, methyl 2,3-anhydro-4,6-*O*-benzylidene-β-D-mannoside (IX) was isolated which, when recrystallised from methanol, had m. p. 182°, $[\alpha]_D^{20}$ −30·4° (*c* 0·2 in $CHCl_3$) (Found: C, 63·3; H, 6·1. Calc. for $C_{14}H_{16}O_5$: C, 63·6; H, 6·1%) (lit.,[7] m. p. 183°, $[\alpha]_D$ −30° in $CHCl_3$).

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[16] Newth and Homer, *J.*, 1953, 989.