Note

A convenient synthesis of derivatives of 3-deoxy-3-fluoro-L-idose

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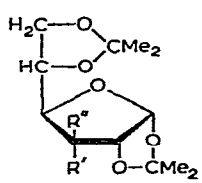
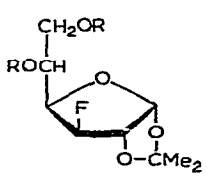
There has been a substantial increase in recent years in the number of fluorinated carbohydrates. One of the reasons for interest in these sugars is that the introduction of a fluorine atom into naturally occurring compounds involved in biochemical processes has, in several instances, produced analogues having significant biological activity and, in some instances, of therapeutic value[1].

The most successful ways for specifically introducing a fluorine atom into sugars have used[2] (*a*) nucleophilic displacement of sulphonates with fluoride ion, (*b*) opening of epoxides, and (*c*) electrophilic addition of trifluoro(fluoroxy)methane to glycals. Other methods have been applied with less success[3].

The foregoing procedures have made a number of fluoro sugar derivatives available in quantities sufficient for further transformations to be effected, thereby providing routes to other, less-accessible compounds. Such procedures have been used already in the synthesis of difluoro sugars[4], and 3-deoxy-3-fluoro-D-xylose has been prepared[5] by a sequence of reactions based on 3-deoxy-3-fluoro-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose. We now report the conversion of the latter compound into derivatives of 3-deoxy-3-fluoro-L-idose. 3-Deoxy-3-fluoro-1,2:5,6-di-*O*-isopropylidene-β-L-idofuranose (**2**) was previously obtained[6] by the reaction of tetra-*n*-butylammonium fluoride in boiling acetonitrile with 1,2:5,6-di-*O*-isopropylidene-3-*O*-toluene-*p*-sulphonyl-β-L-talofuranose (**1**), but the route to related derivatives described below is far more convenient.

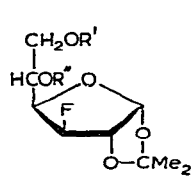


1 R′ = OTs, R″ = H
2 R′ = H, R″ = F

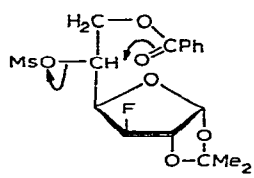


3 R = H
4 R = Ms

Partial hydrolysis[5] of 3-deoxy-3-fluoro-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose with dilute acid gave the monoacetal **3**, which was converted into the dimethanesulphonate **4** on treatment with methanesulphonyl chloride in pyridine. Treatment of **4** with sodium benzoate in hot *N*,*N*-dimethylformamide gave a mixture of three products, which was completely resolved by chromatography on silica gel. The two major crystalline products were identified as 5,6-di-*O*-benzoyl-3-deoxy-3-fluoro-1,2-*O*-isopropylidene-β-L-idofuranose (**5**) and the corresponding 6-benzoate **6** by elemental analyses, and by their conversion into the diol **7** on debenzoylation. The physical properties of **7** {m.p. 105–106°, $[\alpha]_D$ −28° (*c* 1, chloroform)} clearly distinguished it from the epimeric D-*gluco* compound **3** {m.p. 50–52°, $[\alpha]_D$ −18° (*c* 0.8, chloroform)}[5], thereby providing unequivocal evidence for the L-*ido* configuration assigned to **5** and **6**. Unimolar benzoylation of **7** reconverted it into the monobenzoate **6**, establishing C-6 as the site of esterification of the latter compound. Chromatographic separation of **5** and **6** was found to be unnecessary in subsequent preparations, since the diol **7** was obtained in crystalline form following debenzoylation of the products resulting from the displacement.



5 R′= R″= Bz
6 R′= Bz, R″= H
7 R′= R″= H



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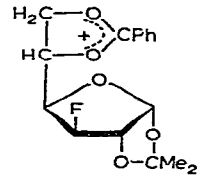

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The monobenzoate **6**, formed in the displacement reaction, presumably results from attack of adventitious water on an intermediate benzoxonium ion **9**. The formation of **9** can be rationalised by assuming that the more reactive, primary sulphonate group of **4** is first displaced to give 6-*O*-benzoyl-3-deoxy-3-fluoro-1,2-*O*-isopropylidene-5-*O*-methanesulphonyl-α-D-glucofuranose (**8**), which can undergo a benzoyloxy-assisted displacement of the secondary sulphonate group at C-5. However, recent findings[7,8] with related systems have indicated that the extent of C-6 acyloxy-group participation in the displacement of a 5-sulphonate is strongly solvent dependent, and it appears that direct displacement is favoured[7] in such solvents as *N*,*N*-dimethylformamide. We presume, therefore, that the dibenzoate **5** is formed mainly by a competing S_N2 displacement on the intermediate sulphonate **8**, rather than by attack of benzoate ion at the primary carbon atom of the benzoxonium ion **9**. However, the latter pathway is followed exclusively[7,9] in displacements on related systems with acetate and chloride ions in such solvents as acetic anhydride and acetonitrile.

EXPERIMENTAL

Thin-layer chromatography (t.l.c.) was performed on Kieselgel G (Merck) with detection by vanillin–sulphuric acid[10]. Infrared spectra were routinely recorded

on Nujol mulls with a Perkin–Elmer Infracord spectrometer, and ^{1}H and ^{19}F n.m.r. spectra were recorded with a Bruker Spectrospin spectrometer operating at 90 MHz; the spectra were entirely consistent with the structures assigned.

3-Deoxy-3-fluoro-1,2-O-isopropylidene-5,6-di-O-methanesulphonyl-α-D-glucofuranose (**4**). — Methanesulphonyl chloride (0.6 ml) was added to a cooled (0°) solution of 3-deoxy-3-fluoro-1,2-*O*-isopropylidene-α-D-glucofuranose[5] (**3**, 0.5 g) in dry pyridine (5 ml), and, after standing for 1 h at 0°, the solution was left for 3 h at room temperature. Methanol was then added to destroy the excess of reagent, and the solvents were removed. The residue was extracted with chloroform (150 ml), and the extract was washed with water (3 × 150 ml) and dried ($MgSO_4$). After removal of the solvent, the residue was recrystallised from ethyl acetate–hexane to give **4** (0.73 g, 86%), m.p. 113–114°, $[\alpha]_D$ −12° (*c* 1, chloroform) (Found: C, 35.3; H, 4.9; F, 4.9; S, 16.9. $C_{11}H_{19}FO_9S_2$ calc.: C, 34.9; H, 5.0; F, 5.0; S, 16.9%).

Reaction of 3-deoxy-3-fluoro-1,2-O-isopropylidene-5,6-di-O-methanesulphonyl-α-D-glucofuranose (**4**) *with sodium benzoate.* — A solution of the disulphonate **4** (1 g) in *N*,*N*-dimethylformamide (30 ml) containing sodium benzoate (5 g) was heated at 170–175° for 20 h, after which time ethyl acetate (50 ml) was added to the cooled reaction mixture which was then filtered with the aid of a Celite pad. The filtrate was concentrated to dryness, and a solution of the residue in chloroform (150 ml) was decolourized (charcoal), dried ($MgSO_4$), and concentrated. The residue was subjected to chromatography on silica gel, and elution with ether–hexane (1:2) gave an unidentified syrup (60 mg). Subsequent elution with ether–hexane (1:1) gave 5,6-di-*O*-benzoyl-3-deoxy-3-fluoro-1,2-*O*-isopropylidene-β-L-idofuranose (**5**) (0.55 g, 48%), m.p. 114–115° (from ethanol), $[\alpha]_D$ −9° (*c* 1, chloroform) (Found: C, 64.3; H, 5.5; F, 4.8. $C_{23}H_{23}FO_7$ calc.: C, 64.1; H, 5.3; F, 4.4%). Continued elution with the same solvent gave 6-*O*-benzoyl-3-deoxy-3-fluoro-1,2-*O*-isopropylidene-β-L-idofuranose (**6**; 0.29 g, 34%), m.p. 111–112° (from hexane–ether), $[\alpha]_D$ −8.5° (*c* 1, chloroform) (Found: C, 58.6; H, 5.9; F, 5.4. $C_{16}H_{19}FO_6$ calc.: C, 58.9, H, 5.8; F, 5.8%).

3-Deoxy-3-fluoro-1,2-O-isopropylidene-β-L-idofuranose (**7**). — A small piece of sodium was added to a solution of the dibenzoate **5** (0.62 g) in dry methanol (30 ml), and the solution was set aside for 3 h at room temperature; t.l.c. (ethyl acetate–hexane, 1:1) then showed that no starting material remained. The solution was neutralised with solid carbon dioxide and, after filtration, was concentrated to dryness. Chromatography of the residue on silica gel (ethyl acetate–ether, 1:2) gave the diol **7** (0.3 g, 93%), m.p. 105–106° (from ether–hexane), $[\alpha]_D$ −28.5° (*c* 1, chloroform) (Found: C, 48.7; H, 6.6; F, 8.4. $C_9H_{15}FO_5$ calc.: C, 48.65; H, 6.75; F, 8.55%).

Similar treatment of the monobenzoate **6** gave **7**, m.p. and mixed m.p. 105–106°, $[\alpha]_D$ −28° (*c* 1, chloroform).

Preparation of 6-O-benzoyl-3-deoxy-3-fluoro-1,2-O-isopropylidene-β-L-idofuranose (**6**) *from the diol* **7**. — A solution of **7** (0.1 g) in dry pyridine (3 ml) was treated at 0° with benzoyl chloride (70 mg, *ca.* 1 mol.) for 1 h, and then left for 2 h at room temperature. Work-up in the usual way, with chromatography on silica gel (elution with hexane–ether, 1:1), gave the monobenzoate **6** (80 mg, 54%), m.p. 111–112°,

$[\alpha]_D$ −8° (*c* 1, chloroform), which showed no depression of melting point on admixture with the material obtained in the benzoate displacement reaction.

ACKNOWLEDGMENTS

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REFERENCES

1 P. GOLDMAN, *Science*, 164 (1969) 1123.
2 For general reviews, see J. E. G. BARNETT, *Advan. Carbohyd. Chem.*, 22 (1967) 177; P. W. KENT, *Chem. Ind. (London)*, (1969) 1128; A. B. FOSTER AND J. H. WESTWOOD, *Angew. Chem. Int. Ed. Engl.*, 11 (1972) in press.
3 L. D. HALL AND L. EVELYN, *Chem. Ind. (London)*, (1968) 183; K. R. WOOD, D. FISHER, AND P. W. KENT, *J. Chem. Soc., C*, (1966) 1994.
4 A. B. FOSTER AND R. HEMS, *Carbohyd. Res.*, 10 (1969) 168.
5 A. B. FOSTER, R. HEMS, AND J. M. WEBBER, *Carbohyd. Res.*, 5 (1967) 292.
6 J. S. BRIMACOMBE, P. A. GENT, AND J. H. WESTWOOD, *J. Chem. Soc., C*, (1970) 1632.
7 M. MILJKOVIĆ, A. JOKIĆ, AND E. A. DAVIDSON, *Carbohyd. Res.*, 17 (1971) 155.
8 J. S. BRIMACOMBE, A. M. MOFTI, AND L. C. N. TUCKER, *J. Chem. Soc., C*, (1971) 2911.
9 R. C. CHALK, D. H. BALL, M. A. LINTNER, AND L. LONG, JR., *Chem. Commun.*, (1970) 245.
10 *Chromatography*, E. Merck A.G., Darmstadt, 2nd edn., p. 30.