Tetrahedron. Vol. 27, pp. 3457 to 3463. Pergamon Press 1971. Printed in Great Britain

FLUOROCARBOHYDRATES—XX

2-DEOXY-2-FLUORO-D-LYXOPYRANOSE AND RELATED SUGARS SYNTHESIZED BY ADDITION OF CF_3OF TO 3,4-DI-O-ACETYL-D-XYLAL

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(*Received in the UK* 18 *January* 1971; *Accepted for publication* 1 *April* 1971)

Abstract—Experimental details are described of the addition of CF_3OF to diacetyl-D-xylal, which proceeds smoothly at $-70°$ in $CFCl_3$. Four products characterized were trifluoromethyl 3,4-di-O-acetyl-2-deoxy-2-fluoro-α-D-xylopyranoside; trifluoromethyl 3,4-di-O-acetyl-2-deoxy-2-fluoro-β-D-lyxopyranoside; 3,4-di-O-acetyl-2-deoxy-2-fluoro-α-D-xylopyranosyl fluoride and 3,4-di-O-acetyl-2-deoxy-2-fluoro-β-D-lyxopyranosyl fluoride.

The structures were assigned on the basis of ^1H–^1H and ^1H–^{19}F NMR spectra. The *lyxo* derivatives were in the 1-C conformation whereas the *xylo* products were C-1. Corresponding products found in addition to triacetylglucal had C-1 conformation. Measurements of chemical shifts for F (with reference to $CFCl_3$) at 30° in a variety of positions showed that fluorine in $—OCF_3$ was located at +60 ppm, F(1a) at +157 ppm and F(2e) at +212 ppm.

INTRODUCTION

RELATIVELY few examples have been reported of selective addition of electrophilic fluoride to unactivated olefinic bonds.[2,3] Fluorinating agents so far investigated in this connexion include lead tetrafluoride,[4,5] xenon fluorides[6] and, for highly nucleophilic olefins such as enol ethers[7] and enamines,[8] perchloryl fluoride[9,10] has provided a useful route to monofluorides especially in the steroid series.[7,8,11]

The discovery and application of fluoroxy compounds[12–14] and especially of fluoroxy-trifluoromethane[15] (CF_3OF) has shown them to possess the tractability and selectivity of the milder fluorinating agents while retaining a high level of reactivity towards unsaturated bonds. As with $FClO_3$, addition occurs with fluorine becoming linked to the more nucleophilic C atom. Unsaturated ketones and simple vinylic esters which react slowly, if at all, with $FClO_3$, react smoothly with CF_3OF giving the predicted products. Addition of CF_3OF to a 2,3 enol ester in the steroid series[16] leads to a 2α-fluoro derivative with F or CF_3O substitution in the 3α position.

Fluoroxy compounds would appear to offer an interesting means for the introduction of fluorine via unsaturated sugars into secondary positions of carbohydrates. While the ensuing work was in progress a preliminary communication by Adamson *et al.*[17] provided some evidence in line with this view. Other routes for the synthesis of fluorocarbohydrates have been reviewed recently.[18]

DISCUSSION

Previous investigation of addition reactions of interhalogens such as BrF to acetylated glycals, results in the formation of all four possible 2-deoxy-2-haloglycosyl

fluorides.[19–21] The predominant products are found to be those predicted by the operation of the anomeric effect as in halomethoxylation[22,23] and other additions. Extensive use has been made of ^1H and ^{19}F NMR parameters in assigning these configurations of fluorinated sugars,[24–26] and in one case independent establishment of configuration has been made by X-ray crystal structure analysis.[1]

In experiments with 3,4-di-O-acetyl-D-xylal, near-quantitative addition with CF_3OF was found to occur smoothly in an inert solvent at low temperatures. Of the four products detected by gas liquid chromatography, three were separated in pure form by column chromatography on silica. The products obtained, in order of elution, were identified as trifluoromethyl 3,4-di-O-acetyl-2-deoxy-2-fluoro-α-D-xylopyranoside (**2**, 5% yield; m.p. 150° $[\alpha]_D^{24}$ +130°), trifluoromethyl 3,4-di-O-acetyl-2-deoxy-2-fluoro-β-D-lyxopyranoside (**3**, 26%, $[\alpha]_D^{24}$ −120°, pure but not crystallized); 3,4-di-O-acetyl-2-deoxy-2-fluoro-α-D-xylopyranosyl fluoride (about 5%, tentative identification by NMR, not fully free from other isomers), and 3,4-di-O-acetyl-2-deoxy-2-fluoro-β-D-lyxopyranosyl fluoride (**4**, 42%, m.p. 109–111°, $[\alpha]_D^{24}$ −114°).

The structures of these derivatives were established in the first instance by ^1H and ^{19}F NMR spectrometry the results of which are given in Table 1. The *lyxo* configurations of **3** and **4** are fully supported by the magnitude of the ^1H–^1H coupling constants as well as the ^1H–^{19}F couplings. In the ^1H spectrum of **3** J[H(5e)–H(5a)] was 13·1 Hz consistent with an axial acetoxy group at C-4 and indicates that the compound exists in the 1-C conformation.[27–29] All the ring protons exhibited a number of long range couplings, as reported between protons in 1,3-diequatorial configurations. Similarly, the fluorolyxosyl fluoride **4** shows couplings consistent with the existence of the 1-C conformation J[H(5e)–H(5a), 12·5 Hz] (Fig 1). The presence of this conformational form in **3** and **4** supports the observations of Hall and Manville[25,26] that in pentose, anomeric fluorine (and it appears, $-OCF_3$) takes up preferentially the axial configuration. The ^{19}F–^1H interactions in the trifluoromethyl lyxoside **3** give values for J[H(2)–F(2)] of 44·2 Hz and for J[H(3)–F(2)] and J[H(1)–F(2)] of 3·8 Hz consistent[31] with the *gem* fluorine–hydrogen at C_2 and equatorial protons at C-1 and C-3. In the fluorolyxosyl fluoride **4**, two *gem* H-F interactions were observed, J[H(1)–F(1)] 55 Hz and J[H(2)–F(2)] 43·5 Hz. The J values for H(2) and H(3) interactions with fluorine at C-1 and C-2 respectively are in agreement with the 1-C *lyxo* conformation proposed and with the β-anomeric configuration for F(1).

In the course of a detailed survey of ^{19}F–^{19}F shifts and couplings which has been carried out in this laboratory, a modified wide-sweep ^{19}F NMR technique showed for the first time that in **3** the chemical shift (ϕ_c) for F(2) was +214 ppm (with respect to $CFCl_3$, 33°C) and for the trifluoromethyl F, +60 ppm (ϕ_c values accurate to ±5 ppm). In **4**, ϕ_c F(1) was +156 ppm and, in agreement with the previous compound, ϕ_c F(2) was at +215 ppm. Chemical shifts for F(1) in glycosyl fluorides have been reported[31] but it is highly probable that values for F atoms sited in different positions may be strongly influenced by neighbouring electronegative environment in addition to the influence of the ring oxygen, and may be also notably sensitive to solvent changes.

The diacetate **4** was readily de-esterified to give crystalline 2-deoxy-2-fluoro-β-D-lyxosyl fluoride **5**. This derivative also appeared to occur in the 1-C conformation as indicated by NMR data, J[H(1)–H(2)] 3·0 Hz, J[H(1)–F(2)] 4·5 Hz and J[H(2)–F(1)] 22 Hz whilst the expected *gem* couplings for F–H at C-1 and C-2 respectively were 53·0 Hz and 45·5 Hz (measured in D_2O). The compound[8] was non-reducing to

TABLE 1. COUPLING CONSTANT (J — Hz) FOR PRODUCTS DERIVED FROM CF_3OF ADDITION TO 3,4-DI-O-ACETYL-D-XYLAL (IN $CDCl_3$, 100 MHz, 34°)

Product	Conformation	H(5e)–H(5a)	H(4)–H(5e)	H(4)–H(5a)	H(3)–H(4)	H(2)–H(3)	H(1)–H(2)	F(2)–H(3)	F(2)–H(2)	F(2)–H(1)	F(1)–H(2)	F(1)–H(1)
2	C-1	10·0	6·5	9·5	9·5	9·8	3·8	1	48	0·5		
	·	·	·	·	·	·	·	·	·	·	·	·
3	1-C	13·1	2·8	3·8	·	3·8	3·8	8·5	44·2	*ca* 3	·	·
4	1-C	12·5	*ca* 2	·	·	3·6	3·6	·	43·5	*ca* 1	24·2	55
5	1-C	12·2	2·5	3·5	·	3·0	3·0	·	45·5	4·5	22·0	53·0

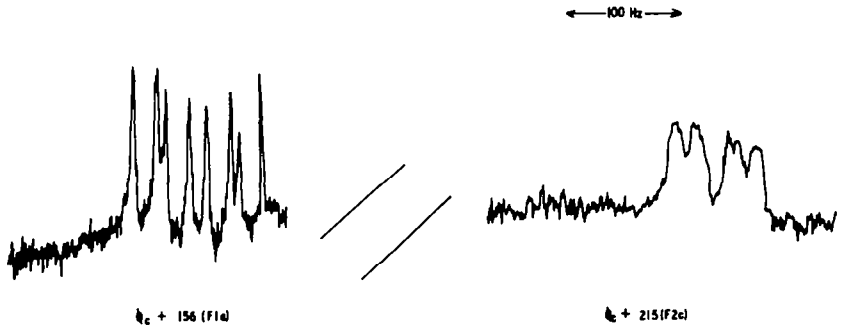
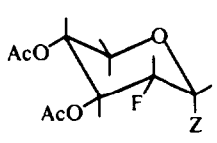


FIG 1. ^{19}F-NMR (high resolution) responses of 3,4-di-O-acetyl-2-deoxy-2-fluoro-p-D-lyxosyl fluoride **4** ($CHCl_3$, 94 MHz, 33°)

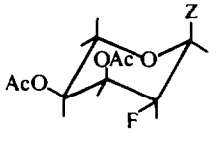
copper reagents but was oxidisable by sodium metaperiodate, consistent with the presence of the α-glycol group at C(3) and C(4).

In strongly acidic conditions, fluorine was hydrolyzed from C-1 at room temperature giving crystalline 2-deoxy-2-fluoro-D-lyxose **6**. The NMR spectra of this compound in D_2O were complex, indicative of the presence in solution of both furanose and pyranose forms.

The additions of CF_3OF to diacetylxylal provided also two minor products, of which trifluoromethyl 3,4-di-O-acetyl-2-deoxy-2-fluoro-α-D-xylopyranoside was isolated crystalline. The ^{1}H–^{1}H couplings (Table 1) unequivocally support the *xylo* configuration in the C-1 conformation with the —OCF_3 axially disposed at C(1) and fluorine equatorially disposed at C(2). Measurement of the ^{19}F chemical shift gave values of ϕ_c + 60 ppm for OCF_3 fluorine and +212 ppm for F(2). The other minor product, 3,4-di-O-acetyl-2-deoxy-2-fluoro-α-D-xylosyl fluoride though not entirely free from 3, gave clear evidence of the presence of two fluorine atoms ϕ_c + 152, +220 for F(1) and F(2) and allows a tentative assignment of structure to be made.

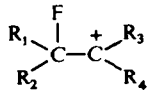


2: Z = OCF_3



3: Z = OCF_3; **4**: Z = F

The mechanism of these additions with CF_3OF is not considered to involve homolytic scission of the O—F bond prior to attack of the olefinic bond. The formation of products bearing —OCF_3 or —F groups suggests the possibility of a cationic intermediate



the stability of which is governed by the electron-donating contributions of R_3 and R_4. The origin of F may be attributed[32–33] to the ambifunctional nucleophilic character of CF_3O^- or to the reaction $CF_3O^- \rightleftharpoons COF_2 + F^-$. The isolation of β-*lyxo* and α-*xylo* products supports the concept of *cis* addition, as in the hexose series.[17] In the pentose series, however, greater ease of conformational interchange results in the 1-C form of the lyxose derivatives predominating (in contrast to C-1 for xylose, as well as glucose and mannose analogues) such that F and —OCF_3 at C(1) are disposed axially. Further details of F–F shifts and couplings in carbohydrates bearing more than one F atom will be published elsewhere.

EXPERIMENTAL

Paper partition chromatography was performed by downward elution on Whatman No. 1 paper using butan-1-ol/ethanol/water (4:1:5 v/v). Compounds were detected by alkaline potassium permanganate or KOH–silver nitrate. *Thin layer chromatography.* Plates (20 × 5 cm) were prepared with Keiselgel PF254 (0·25 mm) as support and compounds (*ca* 100 μg) separated by elution in ethyl acetate or EtOAc–light petroleum (1:1, v/v) were detected by spraying with H_2SO_4 in EtOH (1:1). *Column chromatography.* Columns (usually 3 × 40 or 50 cm) were prepared from silica gel for chromatographic absorptions, 60–120 mesh (British Drug Houses). Fractions (5 ml or 10 ml) were collected and eluted components were detected by GLC. *Gas liquid chromatography.* Analyses were carried out using a Pye series 104 chromatograph model 24, and dual circular columns 6½ ft of diataport —S(80–100 mesh) (Hewlett Packard Inc) 3% S.E. 30 (Applied Science Laboratories Inc), with an argon flow of 40 ml min. The temp gradient was programmed at 2° min except where otherwise stated. Quantitative responses were calibrated by reference to solutions of known concentration. *Fluorine analyses* were performed by the method of Belcher Leonard & West.[34] *Optical rotations* were measured using a Bendex Erricson Automatic polarimeter type 143 A arranged with a Sunvic potentiometer Recorder type 10S, with 1 cm cell. Sucrose solutions were used for cailibration. *IR spectra* were determined using a Grating Infra-red Spectrometer model 257 (Perkin–Elmer Ltd). *NMR spectral data.* PMR spectra were measured through the kindness of Mrs. E. Richards on a Perkin–Elmer R-14 spectrometer operating at 100 mc/sec and 34°. Tetramethylsilane was used as standard. With the kind collaboration of Dr. R. A. Dwek ^{19}FMR spectra were run on a Japan Electron Optics Lab. (JEOL) spectrometer, model JNM-4H-100 operating at 94 MHz and at 33°. Spin–spin couplings were measured by the normal high resolution technique but chemical shifts were obtained by using a wide-sweep unit attachment, which enabled the total field sweep to be up to about 4500 ppm. Calibration of the appropriate field sweep range, usually 450 ppm in these experiments, was carried out using 4 KHz modulation sidebands. Problems occur with field drift, since the required range is too large to use the super-stabilizer. The shift values thus have a slight error estimated to be ±5 ppm. The results quoted are the averages of several runs.

Reaction of fluoroxy-trifluoromethane with 3,4-di-O-acetyl-D-xylal (**1**). The acetylated **1** (1 g), dissolved in $CFCl_3$ (40 ml) containing dry chloroform (2 ml) was cooled to −70° and CF_3OF (2 g) was introduced as a slow stream over a period of 3 hr (approx one bubble per sec). No starting material was then detectable by TLC. After standing for a further 30 min dry N_2 was passed through the soln for 2 min and the soln was allowed to reach room temp. Chloroform (20 ml) was added and the remaining fluorinating agent was removed under reduced pressure. After addition of more chloroform (150 ml), the soln was washed successively with water, $NaHCO_3$ aq and again with water, and was finally dried ($CaCl_2$). Removal of the solvent gave syrupy mixed products (1·6 g; 19·5% F, no.F^- detectable). GLC showed components T_m 15·0 and 16·5 min (starting temp 110, gradient 2°/min) with two minor components T_m 12·9 and 13·9 min in approximate ratio 0·18:0·2:0·2, respectively.

The components (1 g) were separated chromatographically on a silica column (3 × 50 cm) by elution with 80–100° light petroleum/diethyl ether (2:1 v/v) at a rate of 60 ml/hr. Eluted compounds were detected by GLC analysis of fractions.

Trifluoromethyl 3,4-di-O-acetyl-2-deoxy-2-fluoro-α-D-xylopyranoside (**2**). This was obtained after passage of between 300 and 400 ml of elutant. After recrystallization from the same solvent, the xyloside **2** (94 mg) had m.p. 150° $[\alpha]_D^{24}$ +130° (*c*, 0·37. $CHCl_3$) and corresponded to the fraction T_m 12·9 min in the initial GLC analysis. (Found: C, 40·5; H, 4·55; F, 26·9. Calc. for $C_{10}H_{12}O_6F_4$: C, 39·5; H, 3·95; F, 24·8%).

Trifluoromethyl 3,4-di-O-acetyl-2-deoxy-2-fluoro-β-D-lyxopyranoside (**3**). This product was located in the eluted fractions when 400 to 600 ml had passed through the column. Removal of the solvent gave a syrup, homogeneous by TLC and GLC which did not crystallize, yield *ca* 0·4 g $[\alpha]_D^{24}$ −120° (*c* 0·4, $CHCl_3$) T_m 15·0. (Found: C, 39·8; H, 4·02; F, 24·9. Calc. for $C_{10}H_{12}O_6F_4$: C, 39·5; F, 24·8%).

3,4-Di-O-acetyl-2-deoxy-2-fluoro-β-D-lyxopyranosyl fluoride (**4**). The compound, present in 650 to 850 ml of elutant from the column, was obtained crystalline on evaporation of the solvents. After recrystallization from 80–100° light petroleum, the fluoride **4** (0·42 g; 39%) had m.p. 109–111°, $[\alpha]_D^{24}$ −114° (*c*, 0·4 $CHCl_3$) R_F (TLC) 0·55 (EtOAc) T_m 16·5. (Found C, 45·9; H, 4·95; F, 18·3. Calc. for $C_9H_{12}O_5F_2$: C, 45·4; H, 5·05; F, 16·0%).

2-Deoxy-2-fluoro-β-D-lyxopyranosyl fluoride (**5**). Catalytic deacetylation of **4** (100 mg) in dry methanolic NaOMe (10 ml; 0·01M; 30 min), removal of the inorganic salts (Amberlite IR 120 H^+ 0·5 ml washed in MeOH) and evaporation of the solvent gave **5**. The product, recrystallized from dry EtOH–diethyl ether had m.p. 114°, yield 52 mg (81%); $[\alpha]_D^{24}$ −142° (*c*, 0·22 EtOH) trimethyl-silyl derivative, T_m 26 min (100° at 1°/min), R_F (TLC) 0·32 (EtOAc). (Found: C, 40·2; H, 5·88; F, 26·5. Calc. for $C_5H_8O_3F_2$: C, 38·9; H, 5·2; F, 24·7%).

2-Deoxy-2-fluoro-D-lyxose (**6**). The fluoride **5** (80 mg) was dissolved in H_2SO_4 (0·5M; 10 ml) and the course of hydrolysis was followed polarimetrically (α − 0·040° → −0·0058°). When completed (after 3½ hr), the mixture was neutralized using Amberlite MB-3 (20 ml). Evaporation of the solvent gave a syrup which crystallized on standing. After recrystallization from dry EtOH, the 2-deoxy-2-fluoro-lyxose (20 mg) had m.p. 124–126° $[\alpha]_D^{24}$ −11·5° (*c*, 0·56, H_2O) R_F (TLC) 0·13 (EtOAc), R_F (paper) 0·46. (Found: C, 39·2; H, 5·75; F, 12·4. Calc. for $C_5H_9O_4F$: C, 39·5; H, 5·90; F, 12·5%).

Acknowledgements—The authors thank Professor W. K. R. Musgrave for advice, Dr. R. A. Dwek, Mr. P. F. Daniel and Mr. A. Harrison for their cooperation and Imperial Smelting Corp. for the gift of $CFCl_3$.

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