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STUDIES OF CARBOHYDRATE DERIVATIVES HAVING THE $-CH_2F$ FUNCTION*

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ABSTRACT

The following primary sulphonates have been converted into the corresponding deoxyfluoro derivatives by reaction with potassium fluoride in ethylene glycol: 1,2:3,4-di-*O*-isopropylidene-6-*O*-tosyl-α-D-galactopyranose (**1**), methyl 2,3-*O*-isopropylidene-5-*O*-tosyl-α,β-D-ribofuranoside (**2**), 1,2:3,4-di-*O*-methylene-6-*O*-tosyl-α-D-glucofuranose (**3**), 3,5-*O*-benzylidene-1,2-*O*-isopropylidene-6-*O*-tosyl-α-D-glucofuranose (**4**), and 1,2:3,5-di-*O*-isopropylidene-6-*O*-tosyl-α-D-glucofuranose (**5**). The yields were generally poor; in the reaction of **1**, a major by-product was 6-*O*-(2-hydroxyethyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**11**). The reaction of the primary hydroxyl precursor of each of the above tosylates with *N*-(2-chloro-1,1,2-trifluoroethyl)-*N*,*N*-diethylamine generally yielded the *O*-chlorofluoroacetyl derivative; however, 1,2:3,5-di-*O*-methylene-α-D-glucofuranose (**12**) was converted into the 6-deoxy-6-fluoro derivative (**8**). The ^{19}F resonances of compounds containing the $-CH_2F$ moiety fall between ϕ_c +213 and ϕ_c +235 p.p.m. The differences between the *vicinal* ^{19}F-^1H couplings of compounds having the D-*gluco* and D-*galacto* configurations clearly reflect the influence of the C-4–O-4 substitutents on the populations of the C-5–C-6 rotamers. A novel type of noise-modulated, heteronuclear decoupling experiment is described.

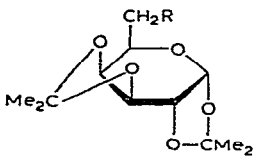
INTRODUCTION

This paper describes an evaluation of two methods, each of which involves a nucleophilic displacement reaction, which may be used for the synthesis of primary, deoxyfluoro carbohydrates, together with an appraisal of the ^{19}F-n.m.r. parameters of such compounds. This work was completed some years ago, and an excellent review article by Foster and Westwood[3] has more recently drawn attention to the use of tetrabutylammonium fluoride as a source of the fluoride anion for nucleophilic displacement reactions of sulphonates.

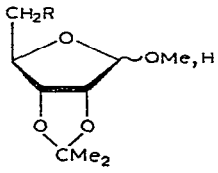
*Studies of Specifically Fluorinated Carbohydrate Derivatives: Part XVI. For Part XV, see Ref. 1. For a preliminary communication, see Ref. 2. A full account of this study was presented at the 58th Conference of the Chemical Institute of Canada, Toronto, Canada, May 25–28, 1975, Abstract 264.

RESULTS AND DISCUSSION

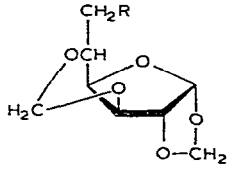
Following earlier observations by Taylor and Kent[4], the primary tosylates **1–5** were each separately subjected to reaction with anhydrous potassium fluoride in dry 1,2-dihydroxyethane. In each instance, the corresponding, primary, deoxyfluoro derivative (**6–10**) was obtained. The yields were, however, variable and low (30–70%). A more-detailed investigation of the reaction of 1,2:3,4-di-*O*-isopropylidene-6-*O*-tosyl-α-D-galactopyranose (**1**) showed that a major by-product was 6-*O*-(2-hydroxy-



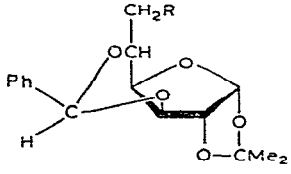
1 R = OTs
6 R = F
11 R = OCH_2CH_2OH
14 R = OH
17 R = $OCCHClF$ (O above)



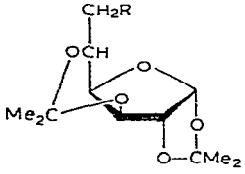
2 R = OTs
7 R = F
15 R = OH
18 R = $OCCHClF$ (O above)



3 R = OTs
8 R = F
12 R = OH



4 R = OTs
9 R = F
13 R = OH
16 R = $OCCHClF$ (O above)



5 R = OTs
10 R = F

ethyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**11**). Inspection of the crude reaction products arising from the other reactions indicated that they too contained the analogous *O*-(2-hydroxyethyl) by-product[5].

Unimpressed by the yields obtained by the above method, we next examined the so-called fluoramine reagent, *N*-(2-chloro-1,1,2-trifluoroethyl)-*N*,*N*-diethylamine, which had been used[6] for the direct conversion of alcohols into the corresponding alkyl fluoride. We were attracted to this reagent both by the high yields of fluorinated products claimed in the literature and by the simplicity of the reaction; the alcohol is mixed with an equimolar proportion of the reagent, often in dichloromethane solution, and the mixture kept at room temperature for a period which varies between several

minutes and 24 h. Our studies with model systems resulted in the conversion of 1-butanol into 1-fluorobutane (85% yield), (hydroxymethyl)cyclohexane into the corresponding fluoro derivative (77%), and the fluorination of cholesterol (72%).

Although 1,2:3,5-di-*O*-methylene-α-D-glucofuranose (**12**) was converted into the corresponding fluoro derivative (**8**), in 66% yield, 3,5-*O*-benzylidene-1,2-*O*-isopropylidene-α-D-glucofuranose (**13**), 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**14**), and methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside (**15**) were each converted into the corresponding chlorofluoroacetate (**16**, **17**, and **18**, respectively); a similar observation was made by Kent and co-workers[7].

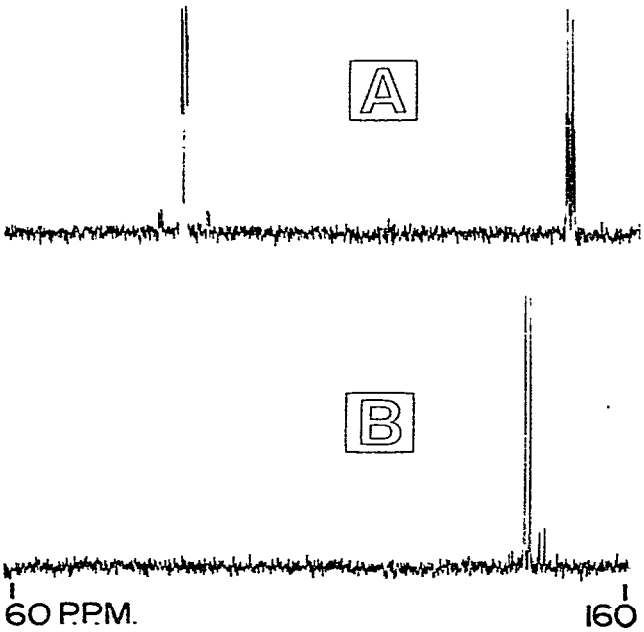


Fig. 1. ^{19}F-N.m.r. spectra (56.4 MHz) of a solution of *N*-(2-chloro-1,1,2-trifluoro)-*N*,*N*-diethylamine in dichloromethane *A*, initially; *B*, ~2 min after the addition of water. The principal resonance is that of *N*,*N*-diethyl-(1-chloro-1-fluoro)acetamide.

Evidence for the sequence of events involved in these reactions was obtained by a ^{19}F-n.m.r. study of several reaction mixtures, and these spectra are given in Figs. 1–3. A solution of the fluoramine reagent in dichloromethane gave the spectrum shown in Fig. 1A, and this solution showed no signs of decomposing during 24 h. However, addition of water caused an immediate, strongly exothermic reaction; the ^{19}F-spectrum of the resulting solution (Fig. 1B) shows the fluorine resonances of the known hydrolysis product, *N*,*N*-diethyl-(1-chloro-1-fluoro)acetamide.

Examination of a 1:1 mixture of the fluoramine reagent and 1-butanol in dichloromethane, ~2 min after mixing of the reactants, gave the ^{19}F spectrum shown in Fig. 2A. Essentially all of the fluoramine reagent had reacted, and a substantial

portion of the desired product, 1-fluorobutane, had already been formed as indicated by the complex multiplet centered at ϕ_c ~220 p.p.m. Also visible are the resonances of the other reaction products (*vide infra*), *N*,*N*-diethyl-(1-chloro-1-fluoro)acetamide (at ϕ_c ~140 p.p.m.) and fluoride ion (at ϕ_c ~174 p.p.m.). Little change occurred during the following 24 h, but addition of water immediately resulted in the spectrum shown in Fig. 2B. Since fluoride ions are water-soluble, their resonance has disappeared from the dichloromethane solution; the behaviour of the two remaining doublets is discussed below.

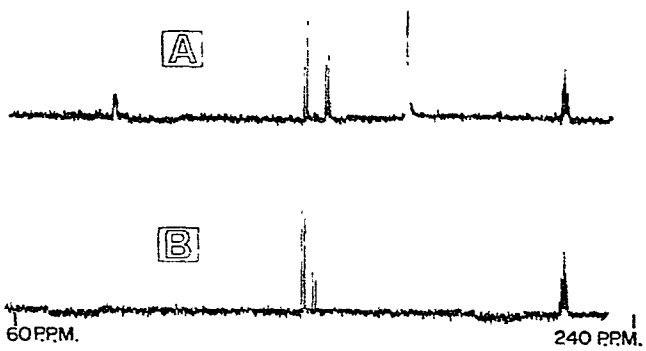


Fig. 2. ^{19}F-N.m.r. spectra (56.4 MHz) of a 1:1 mixture of 1-butanol and the fluoramine reagent in dichloromethane: *A*, within 2 min; *B*, after storage at room temperature for ~24 h followed by the addition of water.

In the corresponding reaction of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**14**), the spectrum obtained ~2 min after admixture of equal molar quantities of the two reactants (Fig. 3A) indicated that nearly all the fluoramine reagent had reacted, that fluoride ions had been liberated, but that none of the desired deoxyfluoro sugar had been produced. The reaction mixture did not change significantly during the subsequent 24 h (Fig. 3B), except that some minor, unassignable resonances appeared and the remaining fluoramine reagent underwent reaction. The resonance of the principal product appeared as a 1:2:1 triplet in the 56.4-MHz spectrum (inset, Fig. 3A), but re-examination at 94.1 MHz (inset, Fig. 3B) shows that this is actually due to two chemically shifted doublets, each with a characteristic, *geminal* ^{19}F,^{1}H splitting. Addition of water resulted in the immediate elimination of these resonances and the appearance of two similar doublets somewhat to lower field.

Returning briefly to Fig. 2, we note that the reaction of 1-butanol resulted in a similar doublet with the same chemical shift, which also shifted slightly to low field when water was added. This implies that both reactions form a common "product". In the reaction of **14**, the observation of *two* doublets for the –CFHCl moiety is to be expected; the –CFHCl moiety constitutes an asymmetric centre which, when attached to an optically active substrate, can give rise to diastereoisomeric products. This behaviour is observed throughout the compounds studied here.

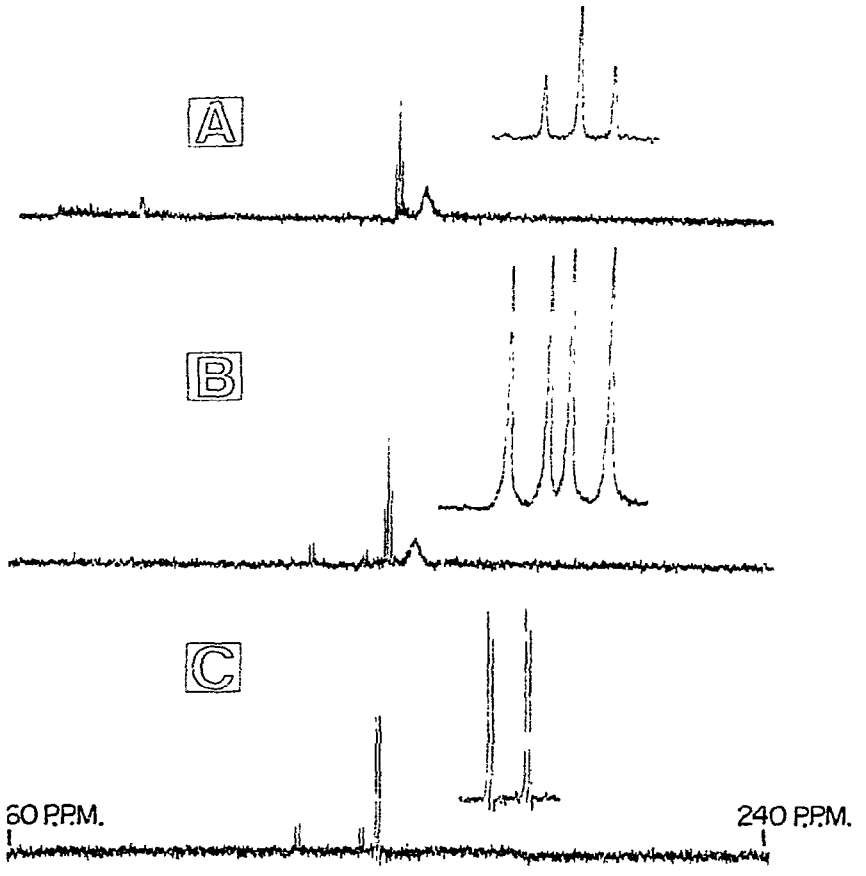
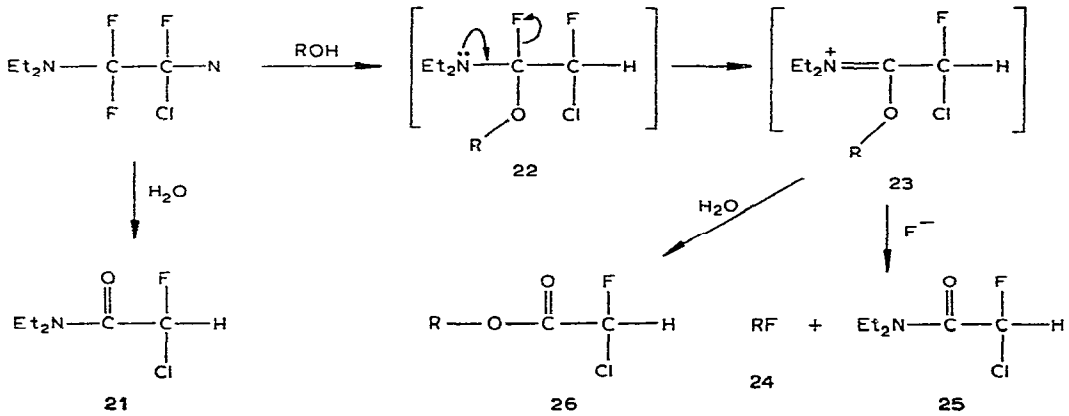


Fig. 3. ^{19}F-N.m.r. spectra (56.4 MHz) of a mixture of the fluoramine reagent and 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**14**) in dichloromethane: *A*, after ~2 min (the insert shows an expansion of the region near ϕ_c 150); *B*, after ~24 h (the insert shows an expansion of the "triplet" *located near* ϕ_c *150, measured at 94.1 MHz*); *C*, after ~2 min, followed by the addition of water, and storage for 24 h.

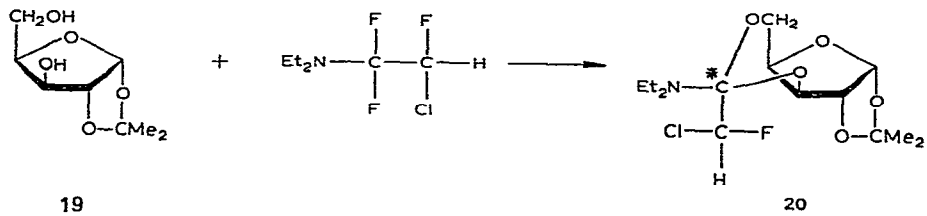
The above evidence is consistent with the sequence of events summarised in Scheme 1. In the absence of an alcohol, or other hydroxylic material, the fluoramine reagent is stable. Addition of water results in immediate hydrolysis to the amide derivative **21**. In the presence of an alcohol, the fluoramine reagent is rapidly converted into an intermediate which, on the basis of its ^{19}F-resonance (doublet* at ϕ_c ~150 p.p.m.), is better described by formula **23** than by **22**. This same intermediate occurs in both the reaction mixtures studied. For 1-butanol, C-1 is evidently susceptible to nucleophilic attack by fluoride ion, as the intermediate reacts within minutes to give 1-fluorobutane (**24**) and the diethylamide (**25**). For the reaction of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**14**), C-6 is apparently not attacked by fluoride ion under the reaction conditions employed, and the intermediate **23** remains intact indefinitely; when water is added, hydrolysis immediately occurs to



Scheme 1.

give the chlorofluoroacetate **26**. It should be noted that some of the same intermediate **23** also remains in the reaction of 1-butanol, even after 24 h.

Further, indirect evidence which supports the above general reaction scheme came from the reaction of the fluoramine reagent with 1,2-*O*-isopropylidene-α-D-xylofuranose (**19**). The sole product was the cyclic acetal **20**; presumably, the reagent was first attacked by HO-5, and the intermediate **22** was trapped as the cyclic acetal **20** by further reaction with HO-3.



Besides providing useful information concerning the mechanism of the fluoramine reaction, ^{19}F- and ^{1}H-n.m.r. studies provide much information on structure and conformation. The complexity of the normal ^{1}H-spectra is typified by Fig. 4A. Fortunately, ^{1}H-spectral assignments were invariably facilitated by ^{1}H-{^{19}F}heteronuclear decoupling experiments[8] (*vide infra*), as shown in Fig. 4B. For monitoring the progress of a reaction, ^{19}F-n.m.r. spectroscopy provided an invaluable probe. However, the ^{19}F-spectra often showed more transitions than the "doubletted-triplet" anticipated on the basis of first-order theory. This is due to the fact that strong coupling within the proton spectrum, by virtue of small chemical shifts between the protons, results in the fluorine substituent's being the "X" of an "ABCX" spin-system, and hence giving many more transitions than predicted on a first-order basis. This point is illustrated in Fig. 5, which shows the ^{19}F-resonances of the two anomers of methyl 5-deoxy-5-fluoro-2,3-*O*-isopropylidene-D-ribofuranoside.

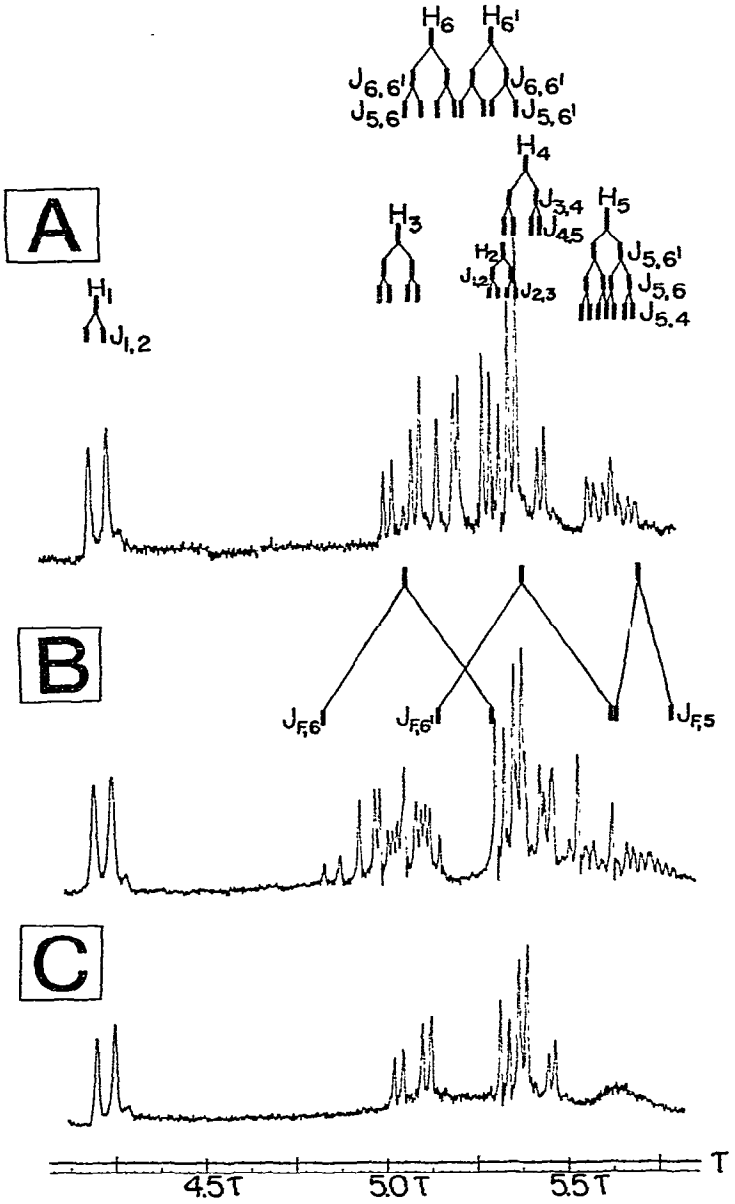


Fig. 4. Partial ^{1}H-n.m.r. spectra (100 MHz) of a solution of 6-deoxy-6-fluoro-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**6**) in deuterioacetone: *A*, with 200-Hz, noise-modulated irradiation at the ^{19}F-resonance frequency; *B*, normal spectrum; *C*, irradiation as in *A* but with the noise-bandwidth substantially increased and the radiofrequency power-level decreased.

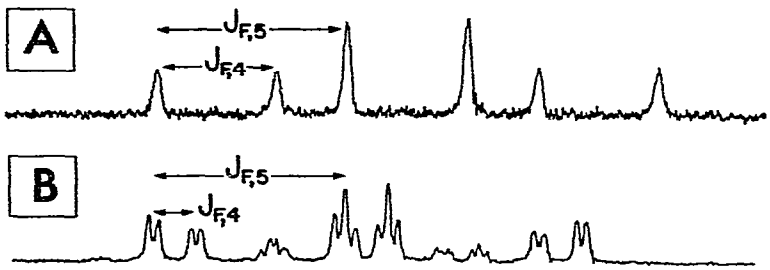


Fig. 5. ^{19}F-N.m.r. spectra (94.1 MHz) of solutions of methyl 5-deoxy-5-fluoro-2,3-*O*-isopropylidene-α-D-ribofuranoside (*A*) and methyl 5-deoxy-5-fluoro-2,3-*O*-isopropylidene-β-D-ribofuranoside (*B*) in benzene.

TABLE I

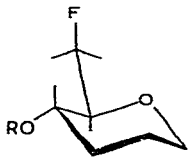
^{19}F-N.M.R. DATA FOR PRIMARY DEOXYFLUORO COMPOUNDS

Compound	*Chemical shift*	*Geminal ^{19}F-^{1}H coupling*	*Vicinal ^{19}F-^{1}H coupling*
6-Deoxy-6-fluoro derivatives			
α-D-Galactopyranose	229.0[a]	46.7	15.8
	229.2[a]	46.6	18.5
1,2:3,4-Di-*O*-isopropylidene-α-D-galactopyranose (6)	231.4[b]	47.0	13.9
Methyl α-D-galactopyranoside	230.0[a]	46.4	16.9
1,2,3,4-Tetra-*O*-acetyl-α-D-galactopyranose	230.6[b]	48.0	11.8
D-Glucopyranose	234.5[a]	48.0	26.8
	234.6[a]	48.0	28.5
1,2:3,5-Di-*O*-methylene-α-D-glucofuranose (8)	225.8[b]	48.1	35.0
3,5-*O*-Benzylidene-1,2-*O*-isopropylidene-α-D-glucofuranose (9)	213.7[b]	47.5	36.5
1,2:3,5-Di-*O*-isopropylidene-α-D-glucofuranose (10)	229.2[b]	48.0	22.2
5-Deoxy-5-fluoro derivatives			
D-Ribofuranose	227.3[a]	50.0	23.5
Methyl 2,3-*O*-isopropylidene-α-D-ribofuranoside (7)	232.1[b]	47.5	30.0
Methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside (7)	224.8[b]	47.5	10.5
Methyl 2,3,4-tri-*O*-acetyl-β-D-ribopyranoside	232.5[b]	47.5	29.5

[a]Value determined in D_2O with $CFCl_3$ in an external capillary. [b]Value determined in $CDCl_3$:$CFCl_3$ (ϕ_c value).

Routine analysis of the various spectra gave the data summarised in Table I; these data require little discussion. The ^{19}F-chemical shifts lie in the range ϕ_c +213 to +235 p.p.m., which accords well with data previously published[9] for derivatives of 6-deoxy-6-fluoro-D-glucopyranose (ϕ_c +232 to +235 p.p.m.). The large *geminal* ^{19}F-^{1}H couplings are as anticipated, as also are the *vicinal* ^{19}F-^{1}H couplings.

The large difference between the *vicinal* ^{19}F-^{1}H coupling constants of the D-galactose and D-glucose derivatives gives a clear indication of the dependence[10] of the rotamer population about the C-5–C-6 bond of D-hexopyranoses on the configuration at C-4. Clearly, the D-glucopyranose derivatives have a substantial population of the rotamer **27**, whereas this rotamer is destabilized by interaction with the axially oriented oxygen function at C-4 in the D-galactopyranose systems **28**.



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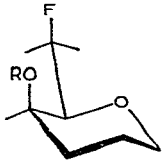

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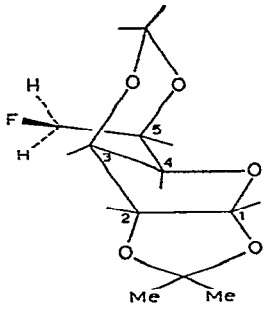

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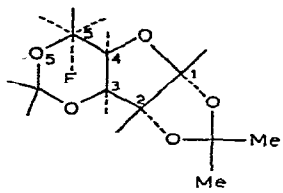
A similar dependence appears to exist in the furanose series, since some of the ribofuranose derivatives also have high values for the F–H-5 coupling. However, the large difference between the couplings of the α and β anomers of **7** indicates that, for these derivatives, the balance is a fine one that can be controlled by other influences, in this case the methoxyl group at C-1.

The variations of the F–H-5 coupling of derivatives **8**, **9**, and **10** clearly illustrate the dependence of rotamer populations on steric interactions of a fluorine substituent. The large coupling (~35 Hz) of **8** and **9** indicates that, for these two compounds, the *preferred* rotamer about the C-5–C-6 bond has the fluorine substituent oriented towards the axial hydrogen of the acetal group, as in **29**. Replacement of this hydrogen by a methyl group, as in **10**, would be expected to substantially destabilize this rotamer and the decrease in the coupling of this derivative (to ~22 Hz) clearly indicates that this is so. It is only surprising that the coupling is not even smaller: insufficient data are available to decide whether it is appropriate to invoke here the so-called[11] "gauche-effect", although the representation in **30** could be consistent with that particular rationale. If this is so, it is not obvious why rotamer **30** is favoured over rotamer **31**.

The ^{19}F-n.m.r. spectra of the chlorofluoroacetates obtained with the fluoramine reagent indicated that some of the products were mixtures of diastereoisomers. Thus,



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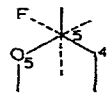

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the ^{19}F-chemical shift of these derivatives was far-removed (ϕ_c ~146 p.p.m.) from that characteristic for the $-CH_2F$ moiety. Furthermore, two such resonances were observed for the products **16–18**, indicating the presence of diastereoisomers at the chlorofluoroacetate carbon. Although two ^{19}F-resonances were observed for **20**, it is not known whether these reflect two isomers at the chlorofluoromethyl carbon or isomerism at the "acetal" carbon (C* in formula **20**).

During the course of one n.m.r. experiment, we "rediscovered" one of the several variants on the noise-modulated, heteronuclear decoupling experiment first invented by Ernst[8a]. In a "conventional" noise-modulated decoupling experiment, the noise-bandwidth and the field-strength of the radiofrequency field to be used for the decoupling experiment are set such that all points in the spectrum to be irradiated receive a radiofrequency component the magnitude of which, in frequency units, exceeds the magnitude of the couplings to be collapsed. The results of such an experiment are shown in Fig. 4A. A useful variant on this experiment occurs when the spectral density of the noise-modulated, decoupling field is barely sufficient to cause spin-decoupling. Under these conditions, the noise modulation applies a time-dependent perturbation to the resonance being irradiated which is transferred to any spin-coupled nuclei, causing their resonances to be broadened. The amount of broadening depends on the spectral density, which can be controlled by altering either the modulation bandwidth, or the radiofrequency intensity, and by the magnitude of the spin-coupling involved. Thus, the larger the coupling constant, the larger the broadening. The utility of such an experiment is clearly seen in Fig. 4C, where the resonances of H-6 and H-6′ have become so broadened that they have effectively disappeared and the H-5 resonance has also broadened. The transitions which have no coupling to the fluorine substituent are now clearly resolved and their assignment is trivial. We find this type of experiment to be very convenient to perform and to have substantial diagnostic potential.

EXPERIMENTAL

All solutions were concentrated under reduced pressure. T.l.c. was performed on silica gel G, using methanol–chloroform (1:19) and detection by charring with sulphuric acid. Column chromatography was performed with Fischer silica gel (60–200 mesh), using methanol–chloroform mixtures.

N.m.r. spectra were measured on either Varian T-60 or HA-100 instruments; tetramethylsilane and chlorotrifluoromethane (Freon 11) were used as internal

references. All proton shifts are given on the τ scale, and the ^{19}F-resonances on the ϕ_c scale.

All tosyl derivatives were made from the partially blocked precursor by dissolution in dry pyridine followed by dropwise addition, at 0°, of a cold solution of toluene-*p*-sulphonyl chloride (1.1 mol.) in pyridine. The solution was left at room temperature for ~24 h, then poured into water, and extracted with chloroform. The extract was washed successively with 2M HCl, aqueous $NaHCO_3$, and water, then dried (Na_2SO_4), and concentrated. The residue was crystallized and recrystallized from 95% ethanol.

Nucleophilic displacement reactions. — Reaction[4] of the primary sulphonates **1**[12], **2**[13], **3**[14], **4**[15], and **5**[16] with anhydrous potassium fluoride in dry ethane-1,2-diol afforded the corresponding deoxyfluoro derivatives **6**, **7**, **8**, **9**, and **10**.

The conversion of **1**→**6** gave a syrupy mixture of products which was separated by fractional distillation at 0.02 mmHg to give **6** (30%), b.p. 78°, and a second major product (~20%), b.p. 85°, which was shown by n.m.r. spectroscopy to be 6-*O*-(2-hydroxyethyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**11**). N.m.r. data ($CDCl_3$): H-1, 4.56; H-2, 5.78; H-3, 5.47; H-4, 5.8; H-5, 6.10; H-6, ~6.4; $-OCH_2CH_2O-$, ~6.4; OH, 6.97; Me, ~8.5; $J_{1,2}$ 5.1, $J_{2,3}$ 2.5, $J_{3,4}$ 7.7, $J_{4,5}$ 2.0, $J_{5,6}$ 5.5, $J_{5,6'}$ 7.0 Hz.

Anal. Calc. for $C_{14}H_{24}O_7$: C, 55.25; H, 7.95. Found: C, 54.47; H, 7.55.

Each of the products **6**, **7**, and **8** was converted by standard procedures to give additional derivatives containing the $-CH_2F$ function. These were studied by ^{1}H- and ^{19}F-n.m.r. spectroscopy, and the ^{19}F-n.m.r. data are summarized in Table I.

N-(*2-Chloro-1,1,2-trifluoroethyl*)-N,N-*diethylamine*[6]. — A slow stream of 2-chloro-1,1,2-trifluoroethane was passed through diethylamine (50 g) at ~ −5° for 6 h. The resulting liquid was distilled at 30–40°/15 mmHg to give the fluoramine reagent (70%), which was stable when stored at low temperatures in the absence of water.

N.m.r. data (neat liquid): H-2, 3.85; CH_2, 7.2; CH_3, 8.87; F-2, +150; F-1, +87.2; F-1′, +90.5; J_{2,F_2} 48.2, J_{2,F_1} 4.0, $J_{2,F_1'}$ 5.2, $J_{F_2,F_1} = J_{F_2,F_1'} = 11.7$, $J_{F_1,F_1'}$ 123.5 Hz.

Hydrolysis of the reagent with water, followed by extraction with CH_2Cl_2, work-up in the usual fashion, and distillation, gave a quantitative yield of *N,N*-diethyl-(1-chloro-1-fluoro)acetamide, b.p. ~80°/15 mmHg. The same material was isolated in good yield from all subsequent reactions that led to a fluorinated product.

N.m.r. data (neat liquid): H-1, 3.35; CH_2, 6.55 and 6.60; CH_3, 8.80 and 8.90; ^{19}F, +143.2; $J_{1,F}$ 50.0 Hz.

Reactions with the fluoramine reagent. — (*a*) 1-Butanol was added dropwise to the fluoramine reagent (4 g) until no further heat was evolved. Distillation at atmospheric pressure gave 1-fluorobutane (1.3 g, 85% based on fluoramine), b.p. 31°.

N.m.r. data (neat liquid): H-1, 5.71; ^{19}F, +219.3; $J_{1,F}$ 48.0, $J_{1,2}$ 6.0, $J_{F,2}$ 24 Hz.

(*b*) An excess of cyclohexylmethanol was added to the fluoramine reagent, and

the required cyclohexylmethyl fluoride was isolated in 77% yield, b.p. 30°/15 mmHg.

N.m.r. data (neat liquid); H-1, 5.93; ^{19}F, +223.8; $J_{1,F}$ 47.8, $J_{1,2}$ 5.8, $J_{2,F}$ 16.6 Hz.

(*c*) A solution of cholesterol (2.5 g) and the fluoramine reagent (2 g) in dry CH_2Cl_2 (25 ml) was kept at ~5° overnight, and then worked-up in the usual manner to give cholesteryl fluoride (1.8 g, 72%), m.p. 102°; lit.[17] m.p. 95°.

N.m.r. data ($CHCl_3$): H-3, 5.7; H-6, 4.66; $J_{F,3}$ 51 Hz; the remaining protons gave a series of resonances between 7.5 and 9.4.

(*d*) To a solution of 1,2:3,5-di-*O*-methylene-α-D-glucofuranose[14] (**12**, 2 g) in a minimum volume of dichloromethane was added the fluoramine reagent (2 g). A ^{19}F-n.m.r. spectrum of this solution showed that the desired fluoride **8** was formed immediately. Sufficient solid sodium hydrogen carbonate was added to decompose the excess of reagent and to neutralize the hydrogen fluoride. The solution was then filtered and concentrated to a syrup.

The product was isolated either by column chromatography on silica gel, using methanol–dichloromethane (1:99) (yield 66%), or by fractional distillation under reduced pressure. *N,N*-Diethyl-(1-chloro-1-fluoro)acetamide distilled first, followed by 6-deoxy-6-fluoro-1,2:3,5-di-*O*-methylene-α-D-glucofuranose (**8**, 30%), $[\alpha]_D^{25}$ +33° (*c* 5.8, chloroform). N.m.r. data ($CDCl_3$): ^{19}F, +225.8; $J_{5,F}$ 35.0, $J_{6,F}$ 48.1 Hz.

Anal. Calc. for $C_8H_{11}FO_5$: C, 46.60; H, 5.38; F, 9.22. Found: C, 46.82; H, 5.5; F, 9.01.

(*e*) The fluoramine reagent (1 g) was added to a solution of 3,5-*O*-benzylidene-1,2-*O*-isopropylidene-α-D-glucofuranose[15] (**13**, 1 g) in dichloromethane (15 ml). The mixture was left at ~5° for 2 days. Solid sodium hydrogen carbonate was then added, the mixture was filtered, and the filtrate was concentrated. The syrupy residue was eluted from silica gel, using methanol–dichloromethane (1:99), to give 3,5-*O*-benzylidene-6-*O*-(chlorofluoroacetyl)-1,2-*O*-isopropylidene-α-D-glucofuranose (**16**, 60%), $[\alpha]_D^{25}$ +21° (*c* 1.0, chloroform). N.m.r. data ($CDCl_3$): ^{19}F, +146.5 and +146.6; $J_{H,F}$ 49.5 Hz.

Anal. Calc. for $C_{18}H_{20}ClFO_7$: C, 53.67; H, 5.01; F, 4.72. Found: C, 53.83; H, 4.82; F, 4.59.

(*f*) A similar reaction sequence to that described in (*e*) resulted in the conversion of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose[12] (**14**) into 6-*O*-(chlorofluoroacetyl)-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**17**, ~63%), $[\alpha]_D^{25}$ −52° (*c* 1.5, chloroform). N.m.r. data ($CDCl_3$): H-1, 4.51; H-2, 5.69; H-3, 5.38; H-4, 5.78; H-5, 5.94; H-6, ~5.6; ClFC*H*, 3.63; ^{19}F, +146.5 and +146.6; $J_{1,2}$ 5.0, $J_{2,3}$ 2.5, $J_{3,4}$ 7.5, $J_{4,5}$ 2.0, $J_{H,F}$ 49.5 Hz.

Anal. Calc. for $C_{14}H_{20}ClFO_7$: C, 47.37; H, 5.73; F, 5.35. Found: C, 47.53; H, 5.81; F, 5.61.

(*g*) Reaction of methyl 2,3-*O*-isopropylidene-β-D-ribofuranoside[13] (**15**) with the fluoramine reagent, as in (*e*), yielded methyl 5-*O*-(chlorofluoroacetyl)-2,3-*O*-isopropylidene-β-D-ribofuranoside (**18**, 45%), $[\alpha]_D^{25}$ −43° (*c* 0.8, chloroform).

N.m.r. data ($CDCl_3$): H-1, 5.09; H-2, 5.37; H-3, 5.49; ClFC*H*, 3.72; Cl*F*CH, +146.3 and +146.4; $J_{1,2}$ 0, $J_{2,3}$ 6, $J_{H,F}$ 49.5 Hz.

Anal. Calc. for $C_{11}H_{16}ClFO_6$: C, 44.2; H, 5.4. Found: C, 44.6; H, 5.3.

(*h*) Reaction of 1,2-*O*-isopropylidene-α-D-xylofuranose[18] (**19**) with the fluoramine reagent, as in (*e*), afforded 3,5-*O*-[2(*R*,*S*)-chloro-1(*R*,*S*)-diethylamino-2-fluoroethylidene]-1,2-*O*-isopropylidene-α-D-xylofuranose (**20**, 74%; isomer ratio ~3:2 by ^{1}H-n.m.r.), $[\alpha]_D^{25}$ +7.5° (*c* 0.8, chloroform). N.m.r. data ($CDCl_3$): H-1, 4.12 and 4.16; H-2, 5.48 and 5.52; H-3, 5.82; H-4, 6.02; H-5, 6.16; H-5′, 5.95; ClFC*H*, 4.15; Cl*F*CH, +146.2 and +146.3; $J_{1,2}$ 3.5, $J_{2,3}$ 0, $J_{3,4}$ 2.0, $J_{H,F}$ 48.2 Hz.

Anal. Calc. for $C_{14}H_{23}ClFNO_5$: C, 49.48; H, 6.82; N, 4.12; F, 5.59. Found: C, 49.43; H, 6.68; N, 4.23; F, 5.42.

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