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THE REACTIONS OF 1-HYDROXY-HALOGENOPROPANES WITH FLUORINATING AGENTS

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SUMMARY

1-Hydroxy-2-bromopropane and the corresponding 2-iodo compounds react readily with (1,1,2-trifluoro-2-chloroethyl) diethylamine to give the rearranged 1-halogeno-2-fluoro derivatives, whereas 1-hydroxy-2-chloropropane under the same conditions affords the direct substitution product, 1-fluoro-2-chloropropane. 1-Hydroxy-2-bromopropane reacts readily with anhydrous HF to give exclusively the rearranged fluoro compound. The ^{19}F n.m.r. data of these compounds are reported and the mechanism of the rearrangement discussed.

INTRODUCTION

As part of a program directed towards the synthesis of fluoroamino acids, we became interested in the synthetic potential of the selective halide displacement from 1-fluoro-2-halogenoalkanes by suitable carbanions. Several examples of this general type of reaction had already been documented [1]. The use of (1,1,2-trifluoro-2-chloroethyl) diethylamine to convert the readily available 1-hydroxy-2-halogenoalkanes into the required fluorides seemed promising as this reagent has proved to be one of the mildest and convenient for the conversion of primary, secondary and tertiary hydroxyl groups into the corresponding fluorides [2].

This report describes the unexpected results obtained from the reaction of this and other fluorinating agents with 1-hydroxy-2-halogenopropanes.

RESULTS AND DISCUSSION

1-Hydroxy-2-bromopropane reacts smoothly with (1,1,2-trifluoro-2-chloroetnyl)diethylamine at room temperature to give in high yield a fluoro compounds which, on the basis of its physical and spectroscopic properties, was identified as 1-bromo-2-fluoropropane. Application of the same conditions to 1-hydroxy-2-iodopropane also afforded exclusively the rearranged product. The coupling constants observed in both the ^{1}H and ^{19}F n.m.r. spectra (see Table) of these products were consistent only with the attachment of the fluorine to the secondary carbon centres.

On the other hand, the reaction of 1-hydroxy-2-chloropropane with the fluoroamine proceeds more slowly and results in the formation of the required substitution product, 1-fluoro-2-chloropropane, and only trace amounts of the rearranged product. It should be noted that 1-hydroxy-3-halogenoalkanes react with the fluoroamine to give the expected substitution products [2] , as does 1-bromo-2-hydroxypropane.

As well as providing more efficient syntheses for the bromo- and iodo- compounds than those previously reported [3], this simple series of reactions offers further insight into the mechanism of the fluorination reaction. With simple alcohols two separate mechanisms appear to operate, since both inversion [4] as well as retention of configuration [5] at the reacting centre have been observed. The concerted four-centre process (1) is favoured for reactions involving retention of configuration. Whereas the S_{N_2} mechanism (2) has been proposed to account for those reactions involving inversion of configuration, in other cases, where neighbour-

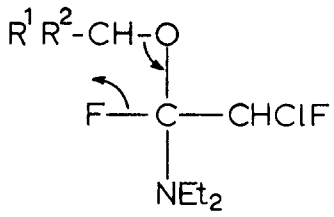
TABLE

^{19}F n.m.r. data (chemical shifts relative to internal $CFCl_3$)

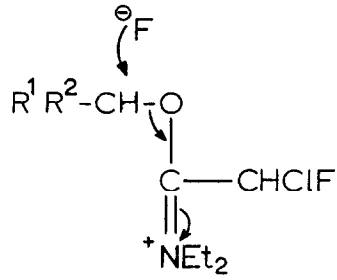
Compound (Solvent)	Chemical Shift ϕ p.p.m.	Coupling Constants (Hz) $^2J(H-F)$	$^3J(H-F)$
$BrCH_2CHFMe$			
($CFCl_3$)	170.4	47.8(d)	23.0(q), *18.2(t)
(C_4F_8)	168.8	46.4(d)	22.9(q), *15.4(t)
($CFCl_3$ + C_4F_8)	169.4	47.1(d)	22.8(q), *16.3(t)
ICH_2CHFMe			
($CFCl_3$+C_4F_8)	162.3	47.6(d)	22.7(q), *17.1(t)
$FCH_2CHClMe$			
($CDCl_3$+$CFCl_3$)	215.8	46.7(t)	14.3(d)

*the literature value for this coupling constant is a factor of ten too small [3]

ing group participation is possible, skeletal rearrangements have been observed [6].

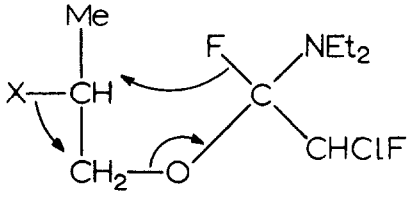


(1)

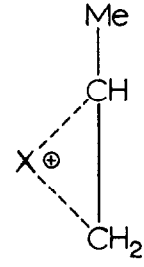


(2)

For the above rearrangements two possible mechanisms can be envisaged involving either a concerted process (3) or, alternatively, a pathway through a stabilized carbocation (4). The latter appears less likely considering the conditions



(3)



(4)

under which the reactions are conducted. This is supported by observations on reactions performed under conditions

which would be expected to favour the formation of ionic intermediates. Thus 1-hydroxy-2-bromopropane reacts with hydrogen fluoride at room temperature to give exclusively the rearranged product in excellent yield. There can be little doubt that this reaction proceeds through the halogenium ion (4). Treatment of 1-p-toluenesulphonyl-2-bromopropane with potassium fluoride in ethylene glycol at 150°C afforded a 1:1 mixture of 1-bromo-2-fluoropropane and 1-fluoro-2-bromopropane. Under the same conditions 1-p-toluene-sulphonyl-2-chloropropane yielded only 1-fluoro-2-chloropropane. It would appear that in the former reaction two independent mechanisms, involving the ionic intermediate (4) and direct substitution, are operating while in the latter, only direct S_{N_2} substitution is taking place.

The above observations are instructive in that they provide evidence that the displacement of hydroxyl groups by fluoride using various fluorinating agents is subject to neighbouring group participation. The possiblity of similar rearrangements should be considered when devising reaction sequences. However, in some cases, it is envisaged that it could be synthetically advantageous to employ the associated re-arrangement process. In order to distinguish definitively between the alternative rearrangement mechanisms (3) and (4) it will be necessary to prepare an optically active 1-hydroxy-2-halogenopropane and this objective is currently under investigation.

EXPERIMENTAL

Materials

Hydrogen fluoride (I.S.C. Chemicals Ltd., anhydrous grade) was purified by vacuum transference in a fluorocarbon vacuum line. (1,1,2-Trifluoro-2-chloroethyl)diethylamine was prepared from chlorotrifluoroethene and diethylamine [2].

Analysis

The ^{19}F n.m.r. spectra were recorded on a Varian HA100 spectrometer which had been modified to enable wide-sweeps to be carried out in the locked mode: $CFCl_3$ were used as the internal reference material. The ^{1}H n.m.r. spectra were measured on a Jeol MH-100 spectrometer operating at 99.8 MHz.

Fluorination of 1-hydroxy-2-halogenopropanes

(1,1,2-Trifluoro-2-chloroethyl)diethylamine (0.03M) was added dropwise to a stirred solution of the 1-hydroxy-2-halogeno-propane (0.03M) in dry ether (10ml) over a period of 1h. After standing for 18h the reaction mixture was washed with water and potassium carbonate (10%), dried ($MgSO_4$), and distilled to afford the pure 1-halogeno-2-fluoropropane.

1-Bromo-2-fluoropropane (71%) b.p. 72-75°.
^{1}H n.m.r.τ(98.5MHz; $CDCl_3$) 5.16 (1H, m, J(H-F) 44.6Hz), 6.53 (2H, doublet of doublets, J(H-F) 18.4, J(H-H) 5.3 Hz), and 8.53 (3H, doublet of doublets, J(H-F) 23.7, J(H-H) 6.5Hz).

1-Iodo-2-fluoropropane (65%) b.p. 50°/20mm
^{1}H n.m.r.τ($CDCl_3$) 5.30 (1H m, J(H-F) 47.1 Hz), 6.66 (2H, d.d., J(H-F) 19.16, J(H-H) 5.4 Hz), and 8.54 (3H, d.d., J(H-F) 22.1, J(H-H) 6.6Hz).

1-Fluoro-2-chloropropane (40%) b.p. 61-63°
^{1}H n.m.r.τ($CDCl_3$) 5.5 (2H, d.d J(H-F) 42.4, J(H-H) 5.1Hz), 5.54-5.92 (1H, m.), and 8.45 (3H, d, J(H-H) 5.8Hz).

Fluorination of 1-bromo-2-hydroxypropane

Under similar conditions to those described above, 1-bromo-2-hydroxypropane yielded 1-bromo-2-fluoropropane (55%) b.p. 72-75° identical with the above described sample.

Reaction of 1-hydroxy-2-bromopropane with HF

1-Hydroxy-2-bromopropane (0.01M) was treated with excess anhydrous HF in vacuo and the yellow solution left at room temperature for 2 h. Some of the HF was removed from the now

red-brown solution and the residue was poured onto ice. The product was extracted and distilled as described above to yield 1-bromo-2- fluoropropane (70%)

Reaction of 1-p-toluenesulphonyl-2-bromopropane with potassium fluoride

Dry potassium fluoride (8.8g, 0.15M) was added to a stirred solution of 1-p-toluenesulphonyl-2-bromopropane (20g, 0.07M) in diethylene glycol (40 ml). The reaction mixture was heated in an oil bath to 150° and the distillate boiling between 65-73° collected. ^{1}H n.m.r. showed this to be a 1:1 mixture of 1-fluoro-2-bromopropane and 1-bromo-2-fluoropropane (6.25g., 65%). Fractional distillation of this product afforded 1-bromo-2-fluoropropane b.p. 72 75° identical with an authentic sample and 1-fluoro-2-bromopropane b.p. 74-78°. ^{1}H n.m.r. τ ($CDCl_3$) 5.6-5.9 (1H,m), 6.32 (2H, d.d., J(H-F) 27.5, J(H-H) 5.1Hz), and 8.20 (3H, d, J(H-H) 7.5Hz).

Reaction of 1-p-toluenesulphonyl-2-chloropropane with potassium fluoride

Reaction of 1-p-toluenesulphonyl-2-chloropropane with dry potassium fluoride under the same conditions as described above afforded only 1-fluoro-2-chloropropane (75%) identical with an authentic sample.

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