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HIGHLY FLUORINATED HETEROCYCLES.
IX.* THE FLUORINATIONS OF 2-METHYLTETRAHYDROFURAN AND 2,5-DIMETHYLTETRAHYDROFURAN OVER POTASSIUM TETRAFLUOROCOBALTATE(III)

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SUMMARY

2-Methyltetrahydrofuran and 2,5-dimethyltetrahydrofuran have been fluorinated with potassium tetrafluorocobaltate(III). The major product in the former case was 2-difluoromethyl-2,5,5-trifluoro-3-oxolen, and in the latter a mixture of the *cis* and *trans* isomers of 2,5-bis-(difluoromethyl)-2,5-difluoro-3-oxolen, both *ca.* 90 % of the appropriate product mixture. Fluorination pathways postulated earlier predicted these results, and are discussed further.

INTRODUCTION

Several previous papers[2,4] dealing with fluorinations by high valency transition metal fluorides (HVMF) have discussed possible pathways followed by the oxygen- and sulphur-containing heterocycles tetrahydrothiophen, tetrahydrofuran, dioxan, dithian and oxathian. The products from these saturated structures are best explained in terms of an elimination/addition (E/A) process, postulated to occur α to the hetero-atom (see Figure 1, which depicts the general case of a 5- or 6-membered ring). This process deals with molecules different in type from the aromatic carbocycles for which an addition/elimination pathway was previously invoked[3]. However, the subsequent stages of the newer (E/A) pathway may well be analogous to some of those in the earlier one. Two recent papers postulate that the saturated compounds tetrahydrofuran[2b] and tetrahydrothiophen[4] are oxidised to the corresponding aromatics over the relatively mild reagent[5] potassium

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* For Part VIII, see ref. 1.

tetrafluorocobaltate(III) ($KCoF_4$). Such an aromatisation reaction has been observed in the carbocyclic field, where passage of cyclohexane over cerium tetrafluoride at 350° yielded[6] a small amount of benzene (benzene itself is scarcely fluorinated at this temperature). Further, it has long been known[7] that fluorinations of benzene and cyclohexane over cobalt trifluoride give virtually indistinguishable product mixtures, suggesting aromatisation during the fluorination of the latter.

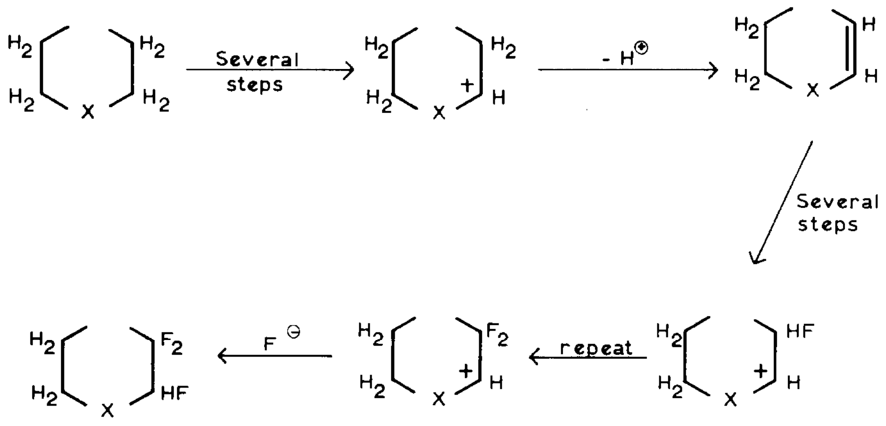


Fig. 1. The elimination/addition (E/A) process.

The E/A process has been invoked [2a,2b] for fluorinations of saturated heterocyclic compounds with both cobalt trifluoride and $KCoF_4$, but aromatic products are not particularly favoured with cobalt trifluoride, despite the E/A process providing a good explanation for aromatisation: presumably cobalt trifluoride fluorinates the intermediates in these aromatisation processes faster than they collapse to aromatics.

To assess further the importance of these postulated oxidation stages we have fluorinated 2-methyltetrahydrofuran (*A*) and 2,5-dimethyltetrahydrofuran (*B*) over $KCoF_4$, since this offered a test of the generality of the pathways.

In both cases we expected aromatisation to occur, followed by some form of 2,5-addition of fluorine to the ring (*cf.* tetrahydrofuran[2b] and tetrahydrothiophen[4]). Also, difluoromethyl groups should predominate as side chains since, in the postulated E/A process, hydrogen is removed as H^+ (presumably by F^-). Although the reactions involved are very different, it is known[8] that hydrogen in $-CF_2H$ groupings is difficult to remove with bases (Andreades[8a] quotes a difference of 10 pK_a units between a $-CF_2H$ and a $-CFH-$ compound).

Thus, the compounds predicted as major products from the fluorinations with $KCoF_4$ at moderate (<300°) temperatures were as indicated in Figure 2. *A* 1 should be a major and *A* 2 a minor product, since the E/A process demands repeated generation of a carbonium ion at C_1 (see Figure 4).

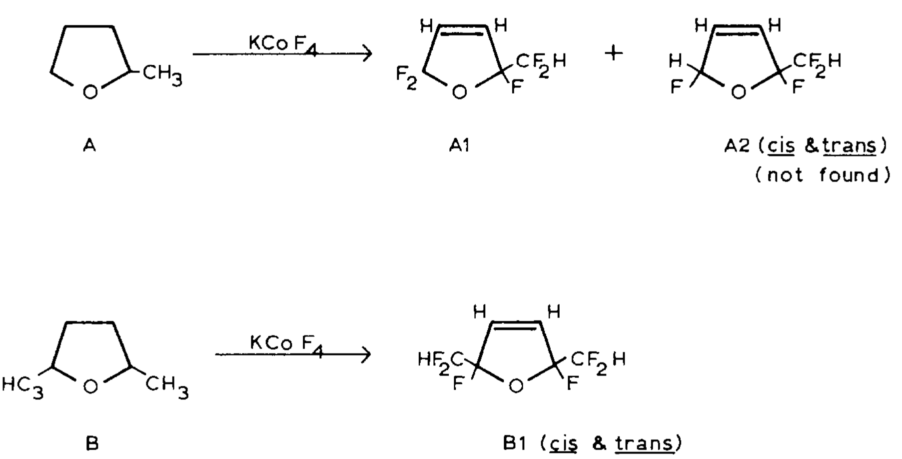


Fig. 2. Predicted major products from fluorinations of *A* and *B*.

RESULTS

The actual result from 2-methyltetrahydrofuran (*A*) was that 2-difluoromethyl-3-oxolen (*A* 1) was formed in yields of *ca.* 85 %, with only minor percentages of other products. 2,5-Dimethyltetrahydrofuran (*B*) gave a mixture (45:55 by ^{19}F NMR spectroscopy) of the two isomeric 2,5-bis-(difluoromethyl)-2,5-difluoro-3-oxolens (*B* 1), in about 75 % yield, with again only minor amounts of other products.

The high yields and percentages in the crude fluorination products of these compounds are very unusual: it has previously been our experience that the fluorination of hydrocarbon-type compounds gives large numbers of products in comparable amounts[3], and although some other fluorinations of heterocycles have given fairly simple mixtures[2b,4], the yields have not been as high as the present ones.

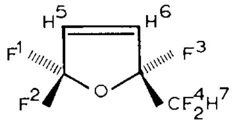
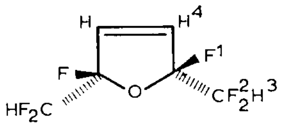
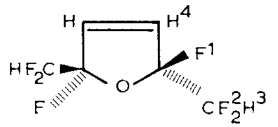
The structures of these major compounds follow quite straightforwardly from the spectral data (Table 1) and elemental analyses. The precise stereochemistries of the isomers of *B* 1 have been tentatively assigned on the assumption that the $-CF_2H$ group, which is a prochiral centre and α to a chiral centre, will show greater chemical shift difference (AB character) between the ^{19}F nuclei in the *cis* isomer: only one of the two CF_2H doublets shows further substantial splitting; neither the ^{1}H spectrum nor the tertiary fluorine signal for this isomer show any sign of such a large splitting, and this compound has therefore been assigned the *cis* configuration.

The olefins have been further characterised by reaction with permanganate to yield the corresponding dicarboxylic acids; these were isolated in one case as the dianilinium salt, and in the other case (since the dianilinium salt proved difficult to crystallise), as the bis-s-benzylisothiuronium salt.

TABLE 1

NMR PARAMETERS

^{19}F shifts in φ; ^{1}H shifts in τ

Molecule	Signals			
	relative intensity	shift	Couplings (Hz)	Assignment
	1	73.8	$J(1,2) = 158$	1
			$J(1,3) = 12$	
	1	65.6[a]	$J(2,3) = 12$	2
	1	119.0	complex multiplet	3
	2	134.0	$J(4,7) = 54$	4
			$J(D(app)) = 4.2$	
	2	3.50	singlet	5 and 6
	1	4.27	$J(4,7) = 54$ (no others apparent)	7
	[c] 1	111.9	singlet	1
	2	133.6 133.8[b]	outliers not visible; $J(HF) = 54$	2
	1	4.17	$J(2,3) = 54$	3
	1	3.52	singlet	4
	[c] 1	119.0		1
	2	133.9	$J(HF) = 54$ (many minor couplings)	2
	1	4.17	$J(2,3) = 54$	3
	1	3.52	singlet	4

[a] AB type spectrum; the assignment of nuclei to stereochemical positions is arbitrary.

[b] Believed to be centre lines of AB spectrum (see text).

[c] See text for justification of this stereochemistry.

Because we are here concerned only with the major fluorination pathways the mechanistic implications of this work are discussed below as though *A* 1 and *B* 1 were the sole products: this is justified because they predominate to a far greater degree than is usual for reactions of this type. No effort was made to isolate the minor products of the fluorinations.

DISCUSSION

The first point to be made is that aromatisation has clearly occurred in both cases: this is in line with our previous experience[2b, 4], and is probably most convincingly explained by a carbonium ion process closely allied to the E/A process (Figure 3).

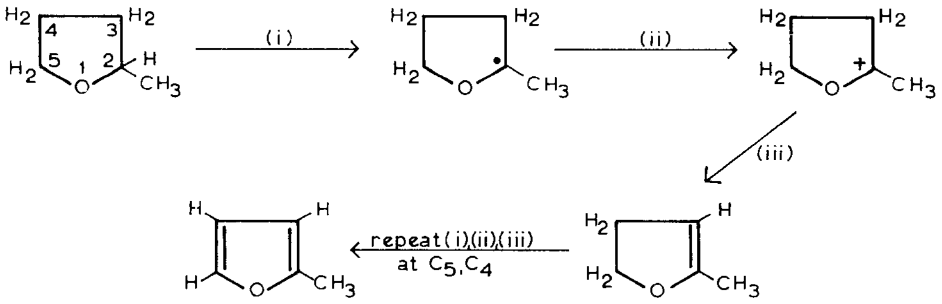
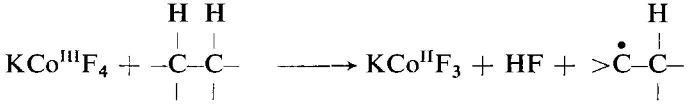


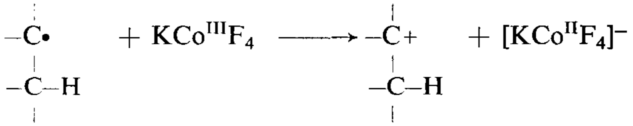
Fig. 3. A possible aromatization sequence.
(A similar process may be envisaged for the 2,5-dimethyl compound.)

(i) Abstraction of H• as HF, *e.g.*



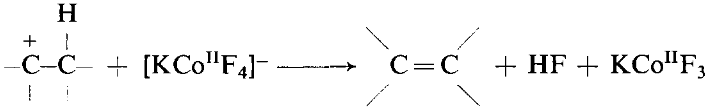
$$\mathrm{KCo^{III}F_4} + -\overset{\mathrm{H}}{\underset{|}{\overset{|}{\mathrm{C}}}}-\overset{\mathrm{H}}{\underset{|}{\overset{|}{\mathrm{C}}}}- \longrightarrow \mathrm{KCo^{II}F_3} + \mathrm{HF} + {>}\overset{\bullet}{\mathrm{C}}-\overset{\mathrm{H}}{\underset{|}{\overset{|}{\mathrm{C}}}}-$$

(ii) Oxidation of a radical to a carbonium ion, *e.g.*



$$\begin{array}{c}|\\-\mathrm{C}\bullet\\|\\-\mathrm{C}-\mathrm{H}\\|\end{array} + \mathrm{KCo^{III}F_4} \longrightarrow \begin{array}{c}|\\-\mathrm{C}+\\|\\-\mathrm{C}-\mathrm{H}\\|\end{array} + [\mathrm{KCo^{II}F_4}]^-$$

(iii) Abstraction of H^+ as HF, *e.g.*



$$-\overset{+}{\underset{|}{\mathrm{C}}}-\overset{\mathrm{H}}{\underset{|}{\overset{|}{\mathrm{C}}}}- + [\mathrm{KCo^{II}F_4}]^- \longrightarrow {>}\mathrm{C}{=}\mathrm{C}{<} + \mathrm{HF} + \mathrm{KCo^{II}F_3}$$

Direct 2,5-addition of two fluorine atoms to the aromatic heterocycle (analogous to the early postulates for carbocyclic aromatics), or a cation–radical[9] style attack can now lead eventually to the observed products. The cation–radical process[9] is increasingly the one we favour, and can in fact provide a mechanistically plausible pathway for the experimentally[2b, 3, 4, 5] well-established 2,5- (and 1,4-) addition processes. We have set out the cation–radical pathway for *A* in Figure 4, analogous processes accounting for the formation of B 1. Although we have included a Lewis acid abstraction of fluoride ion in the scheme (step (vii)), it is not clear whether or not $KCoF_4$ is a powerful enough Lewis acid to make this a dominant reaction; the point cannot, however, be settled at present.

In the equations following Figs. 3 and 4 strict stoichiometry has been preserved overall: this may not be so, however, since the surfaces of the $KCoF_4$ crystals will probably contain many different types of defect, both positively and negatively charged, and with either excess fluoride or excess cobalt and potassium nearby. These may be important in the various reactions shown functioning, for example, as active sites. Indeed, since the structures of most common fluorinating agents

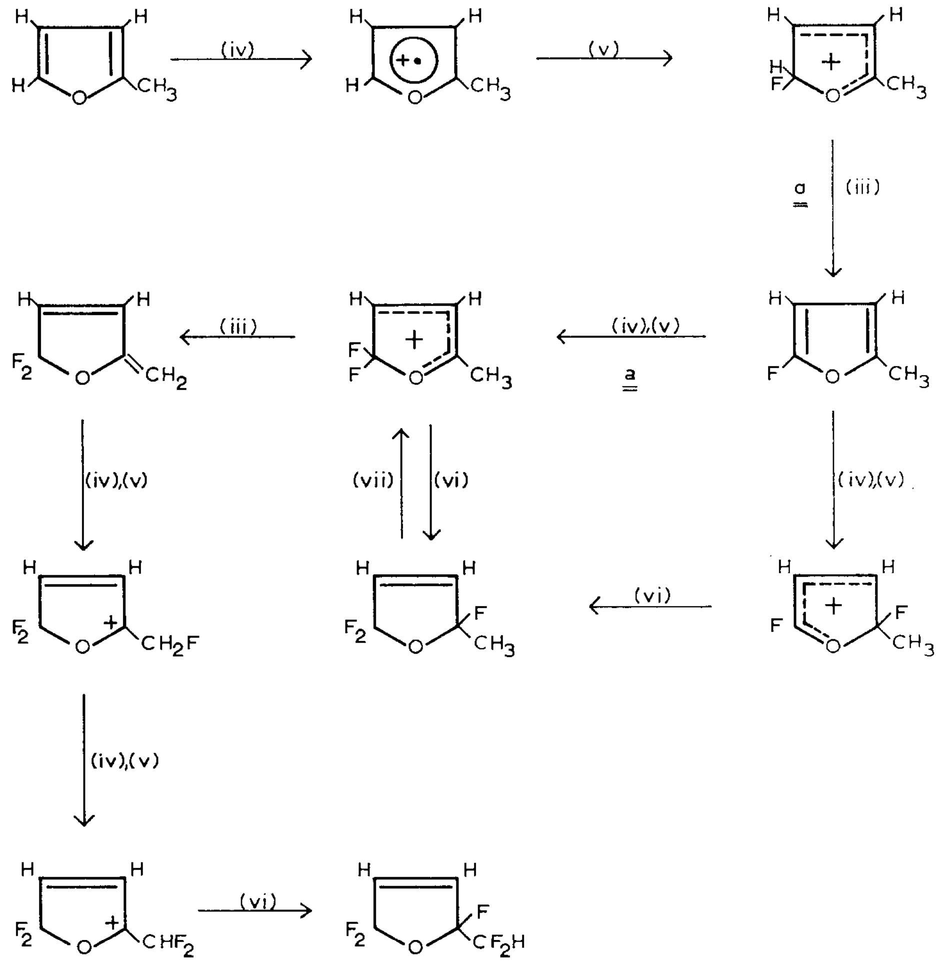


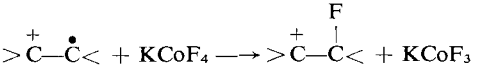
Fig. 4.

Footnotes

(iii) see Figure 3.

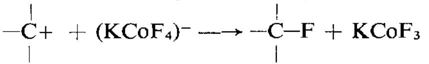
(iv) One-electron oxidation of the π system by the complex metal ion.

(v) Donation of F• from the $KCoF_4$: *e.g.*



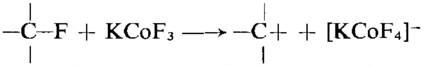
$$>\overset{+}{C}-\overset{\bullet}{C}< + KCoF_4 \longrightarrow >\overset{+}{C}-\overset{\overset{F}{|}}{C}< + KCoF_3$$

(vi) Donation of F^- by $KCoF_4$ or $(KCoF_4)^-$: *e.g.*



$$-\overset{|}{\underset{|}{C}}+ \;+\; (KCoF_4)^- \longrightarrow -\overset{|}{\underset{|}{C}}-F + KCoF_3$$

(vii) Abstraction of F^- by the metal fluoride acting as a Lewis acid:



$$-\overset{|}{\underset{|}{C}}-F + KCoF_3 \longrightarrow -\overset{|}{\underset{|}{C}}+ \;+\; [KCoF_4]^-$$

[a] It is, of course, possible that H^+ is abstracted from the methyl group at this stage, but at present this possibility cannot be dismissed or established.

are known[10] to be infinite lattices, the presence of a surface demands the existence of some form of defect there.

The present work provides very strong evidence that the elimination/addition pathway, going through an aromatic intermediate, operates in the fluorinations of these two oxygen heterocycles with the mild reagent $KCoF_4$. It is, in fact, the most unambiguous evidence so far for the utilisation of such a pathway by any HVMF.

EXPERIMENTAL

Apparatus

Gas–liquid chromatography

Three columns were used in this work, in a Pye series 104 gas chromatograph. These were: column I, silicone oil on Celite, 1:10, 9.1 m × 9.5 mm; column II, di-isodecylphthalate on Chromosorb P, 1:2, 1.5 m × 4 mm; column III, UCON oil on Chromosorb P, 1:5, 9.1 m × 9.5 mm. In each case the temperature and nitrogen pressure are given.

Infrared spectra

These were recorded on a Perkin–Elmer 257 grating spectrophotometer.

NMR Spectra

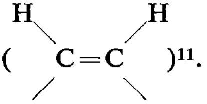
These were run, on a Perkin–Elmer R10 instrument at 60 MHz (^1H) and 56.4 MHz (^{19}F), as dilute (~10 %) solutions in CCl_4, with TMS and CCl_3F as internal standards. The results are shown in Table 1.

Preparative

Fluorination of 2-methyltetrahydrofuran (A) with $KCoF_4$

Commercial 2-methyltetrahydrofuran (141 g) — Ega Chemie, purity 99 % by GLC, used without further purification — was fluorinated at 200° over a stirred bed of $KCoF_4$ (6 kg) in the usual way; the apparatus and techniques have been described before[3a]. The products were trapped in a copper vessel at —78°, and washed with water before weighing (255 g).

Analytical GLC [column I, 60°, 10 lb/in^2; column II, 80°, 5 lb/in^2] showed a single major component (>90 %, from peak areas) and at least six minor components. The major component was purified on a 200 mm^3 scale; (column III, 130°, 20 lb/in^2) to yield 2-difluoromethyl-2,5,5-trifluoro-3-oxolen (nc) (*A* 1), b.p. 96–98° (Found: C, 34.0; H, 1.9; F, 54.9. $C_5H_3F_5O$ requires C, 34.4; H, 1.7; F, 54.5 %). IR spectroscopy showed a weak absorption at 1640 cm^{-1}


($\mathrm{HC{=}CH}$)[11].

Fluorination of 2,5-dimethyltetrahydrofuran (B) with $KCoF_4$

Commercial 2,5-dimethyltetrahydrofuran (120 g) — Ega Chemie, used without further purification — was fluorinated at 200° as before. The products were again trapped at $-78°$ and washed with water before weighing (200 g).

Analytical GLC [column I, 85°, 15 lb/in^2; column II, 105°, 5 lb/in^2; column III, 130°, 25 lb/in^2] showed a single major component (>90 %, from peak areas) together with at least twelve others. Purification of the major component (300 mm^3 samples) (column III, 110°, 20 lb/in^2) gave a mixture (55/45 by ^{19}F NMR spectroscopy) of *cis*- and *trans*-2,5-bis-(difluoromethyl)-3-oxolens (nc) (*B* 1) b.p. 130° (Found: C, 35.0; H, 2.0; F, 55.2. $C_6H_4F_6O$ requires C, 35.0; H, 1.9; F, 55.3 %). All attempts to separate these isomers failed.

Oxidation of 2-difluoromethyl-2,5,5-trifluoro-3-oxolen (A 1)

The oxolen (7.0 g) was oxidised with $KMnO_4$ (3.0 g) in 50:50 acetone/water (200 ml) in the usual way[12], and the product worked up to give the dianilinium salt. This, however, proved difficult to crystallise and was converted in the normal[12] manner to bis-s-benzylisothiuronium 2-difluoromethyl-2,4,4-trifluoro-3-oxaglutarate (nc) (6.1 g) m.p. 190–192° (from H_2O) (Found: C, 44.1; H, 4.1; F, 16.1; N, 9.8. $C_{21}H_{23}F_5N_4O_5S_2$ requires C, 44.2; H, 4.0; F, 16.6; N, 9.8 %).

Oxidation of mixed isomers of 2,5-bis-(difluoromethyl)-2,5-difluoro-3-oxolen (B 1)

The oxolens (5.1 g) were oxidised as usual[12] with $KMnO_4$ (4.0 g) in 50 % aqueous acetone (150 ml) and the product isolated as dianilinium 2,4-bis-(difluoromethyl)-2,4-difluoro-3-oxaglutarate (nc) (2.3 g) m.p. 195–196° (from CCl_3H/acetone) (Found: C, 47.2; H, 3.8; F, 24.7. $C_{18}H_{18}F_6N_2O_5$ requires C, 47.3; H, 3.9; F, 25.0 %).

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