Organic Reactions of Fluoroxy-compounds: Electrophilic Fluorination of Aromatic Rings

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OUR recent discovery[1] that fluoroxy-compounds, particularly fluoroxytrifluoromethane (CF_3OF), could selectively and rapidly effect the electrophilic fluorination of activated olefins suggested that these reagents might constitute sources of "electrophilic fluorine" sufficiently reactive to fluorinate directly (suitably activated) aromatic rings. We now report evidence in support of this contention.

Oestrone methyl ether (Ia) on treatment† with a slight excess of CF_3OF was smoothly converted into 10β-fluoro-19-norandrosta-1,4-dien-3,17-dione[2] (II). This same product resulted from the

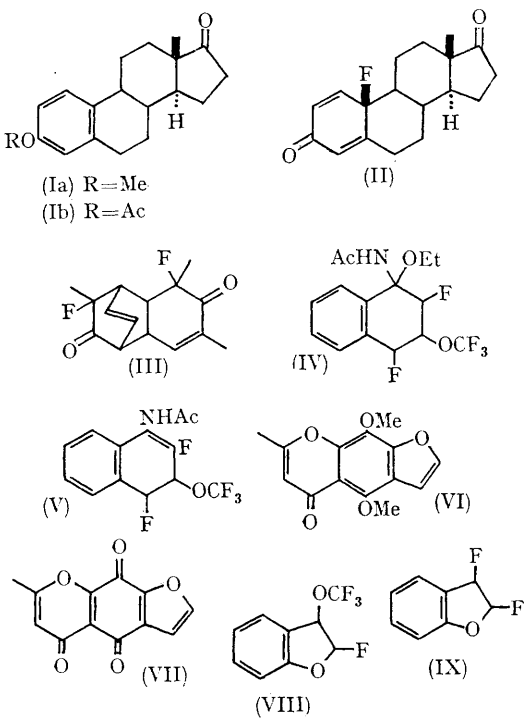
† Unless otherwise stated all reactions were carried out as described in previous Communication.

treatment of oestrone acetate (Ib) with CF_3OF. A less elaborate substrate, 2,6-dimethylphenol reacted with CF_3OF to afford as a major product the dimer of 6-fluoro-2,6-dimethylcyclohexa-2,4-dienone[3] (III). A more typical aromatic substitution was to allow salicylic acid to react in $CHCl_3$ at 0° with CF_3OF. The major product obtained was the monofluorinated derivative, 5-fluorosalicyclic acid[4] [^{19}F n.m.r. analysis of the crude monofluorinated product (*ca.* 70% yield) showed it to be a 4 : 1 mixture of 5- and 3-fluorosalicylic acid].

Treatment of *N*-acetyl-β-naphthylamine (in $CHCl_3/CFCl_3$) with CF_3OF formed in good yield (>50%) a single monofluorinated product, m.p. 120—121°. Spectral analysis confirmed that this product was the result of the replacement of an aromatic hydrogen with a fluorine. ^{19}F n.m.r. (94 Mc./sec.) revealed the fluorine atom as a broad singlet at 1962 c./sec. downfield from C_6F_6. This, taken with the well known tendency of β-activated naphthalenes to react at the α-position,[5] leads to the characterization of this product as *N*-acetyl-α-fluoro-β-naphthylamine.

The reaction of *N*-acetyl-α-naphthylamine with CF_3OF in $CFCl_3$ (containing traces of ethanol) followed a somewhat different course. A major component (m.p. 159–162°) of the mixture (the remainder comprised an unresolvable mixture of monofluorinated derivatives with starting material) had the composition $C_{15}H_{16}F_5NO_3$. The ultraviolet absorption spectrum of this constituent revealed the presence of a benzenoid chromophore [λ_{max}^{EtOH} 273 (log ε 2·43), 266 (2·55), 262 mμ (2·53)]. The proton magnetic resonance spectrum (100 Mc./sec.) of this tetrahydronaphthalene derivative consisted of signals at: δ 1·1 (3 protons, t, *J* 7·5 c./sec.; CH_3–CH_2–O); δ 1·85 (3 protons, s; CH_3–CON–); δ 3·17 [2 protons, m, $CH_2(CH_3)O$–R]; δ 6·17 (1 proton, br s, N*H*–$COCH_3$); δ 7·2—7·7 (4 protons, virtually a doublet, aryl C–*H*) and a complex multiplet from δ 4·8—6·1 (4 protons X–C–*H*). These data fit in with formula (IV) for this product. The mass spectrum of (IV), which showed major peaks at *m/e* 307 [(IV) — EtOH]; 221 [(IV) — EtOH–CF_3OH] and the further fragmentations to be expected of a substituted *N*-acetylnaphthylamine, supported this assignment. Alkaline hydrolysis of (IV) gave *N*-acetyl-2,4-difluoro-1-naphthylamine, m.p. 180—182°. The tetrahydronaphthalene derivative (IV) undoubtedly arises by addition of ethanol (from the reaction medium) to the fluorinated adduct (V) which must in turn result from fluorination of the substrate and addition of CF_3OF (not necessarily in that order). Electrophilic addition (rather than substitution) at an aromatic double bond, while uncommon, is not without precedent.[6] Elemental fluorine, in fact, reacts in this fashion.[7]

The heterocyclic natural product khellin (VI) reacts cleanly with CF_3OF to afford the quinone (VII). This oxidation must result from electrophilic addition followed by elimination and finds precedent in the reaction of khellin with conventional electrophiles (*e.g.* HNO_3).[8]



A simpler heterocyclic substrate, 2,3-benzofuran, reacted cleanly with CF_3OF to afford a major and minor product. While wholly satisfactory microanalytical values are not available for these compounds (the difficulty of obtaining accurate microanalytical values for highly fluorinated, volatile compounds is well known[9]), spectral analysis including mass spectra, establishes the products as adducts of the substrate with the reagent [to give (VIII)] and F_2 [to give (IX)], respectively. The location of the fluorine and trifluoromethoxyl groups in adduct (VIII) is suggested by the n.m.r. spectrum [δ 5·5, br s, *w*/2 4 c./sec., (1 proton) Ph–C*H*–OCF_3; and δ 6·2, qt, *J* 48·5, 4 c./sec. (1 proton) –O–C*H*–F] and the hydrolysis of (VIII) with alkali to give a trifluoromethoxylated 2,3-benzofuran; such is expected

on the basis of theoretical considerations[10] and is in keeping with the reactions of 2,3-benzofuran with conventional electrophiles.[11]

The foregoing examples strengthen our contention[1] that CF_3OF is a versatile electrophilic fluorinating agent, potentially of considerable utility in organic synthesis. The great reactivity of this reagent allows transformations difficult or impossible with $FClO_3$ (see references 2 and 3), while its selectivity makes possible controlled substitution (compare with F_2 ref. 7). Of particular significance is our realization of direct aromatic substitution by "electrophilic" fluorine. We are currently exploring the scope of this reaction and attempting to establish the factors which favour substitution over addition. All new compounds, unless otherwise indicated, had the correct analytical values. All spectral data (acknowledgements as in ref. 1) supported the assigned structures.

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