Organic Reactions of Fluoroxy-compounds: Addition Reactions of Unactivated and Deactivated Unsaturated Linkages of Steroids

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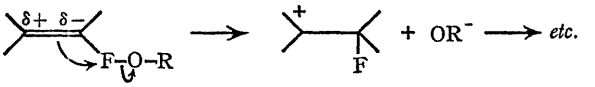
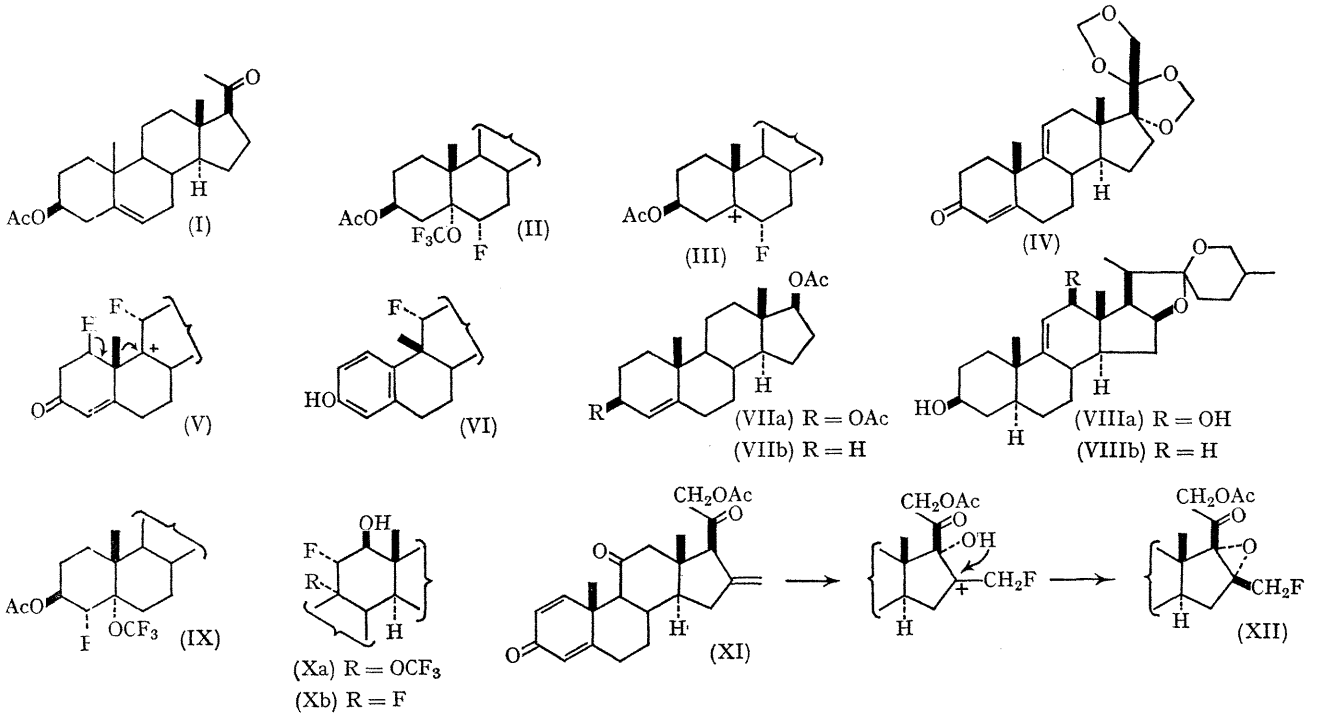
THERE are few known examples of selective addition of "electrophilic" fluorine to unactivated or deactivated unsaturated linkages.[1] Reagents so far discovered include "lead tetrafluoride", $FClO_3$ (for certain highly nucleophilic olefins[2]), the xenon fluorides,[3] and fluorine itself.[4,5] Fluoroxy-compounds[6] [and fluoroxy trifluoromethane (CF_3OF) in particular] combine the tractability and selectivity of the milder fluorinating agents with a much greater reactivity toward unsaturated linkages. We now present evidence concerning the use of CF_3OF in the electrophilic fluorination of unactivated and deactivated compounds.

Diphenylacetylene consumed† 2 mol. of CF_3OF to afford,



as major product, 1,2,2-trifluoro-2-trifluoro-methoxy-1,2-diphenylethane (m.p. 52—54°). This must have arisen from the addition of the elements of CF_3OF and F_2[6] (although not necessarily in that order) to the acetylenic link. As no intermediates were evident when the reaction mixture was investigated before the reaction had gone to completion, we conclude that the fluorinated diphenylethylene, expected as an intermediate, consumed CF_3OF at a greater rate than did the parent acetylene. A deactivated olefin, testosterone acetate, also consumed CF_3OF slowly to afford, after an alkaline work-up, 4-fluorotestosterone. These fluorinations of deactivated unsaturated linkages demonstrate the reactivity of CF_3OF. Investigation of the fluorination of non-deactivated olefins with CF_3OF revealed useful preparative reactions and was instructive regarding the mechanism of attack of CF_3OF.

Pregnenolone acetate (I) reacted with CF_3OF to afford in modest yield an adduct (II) (m.p. 178—182°) (characterized by conversion into 6α-fluoroprogesterone[7]). The stereochemistry of (II) follows from n.m.r. measurements (the 19-CH_3 resonance occurred as a singlet indicative of a 6α-fluorine and the C-3 proton resonance exhibited the large splittings expected for an axial proton and thus A,B-*trans* ring-fusion). The remainder (and major portion) of the substrate (I) was converted into a virtually inseparable mixture of fluorinated by-products. We consider that this mixture results from a nonspecific partitioning of the intermediate cation (III) formed by *specific attack* of CF_3OF at the ethylenic link of (I). The rearrangement of such a cation to give a variety of products which would themselves be susceptible to further attack by CF_3OF has precedent.[8] That cationic intermediates (and attendant rearrangements) result from the attack of CF_3OF on an ethylenic link was supported by our observation that a major product of the



† Unless otherwise stated all reactions were carried out as reported earlier (ref. 6).

reaction of the 9(11)-olefin (IV) with CF_3OF was the phenol (VI) (m.p. 109—112°, $[\alpha]_D$ −39·8°) which must have resulted from rearrangement of the cation (V), a reaction which also has precedent.[9]

Since the first step in the attack of CF_3OF on an unsaturated link must result in formation of an α-fluoro-cation, we investigated the incorporation of appropriate structural features which might direct the fate of such a cation in a predictable fashion. It appeared that the allylic acetate (VIIa) and the allylic alcohol (VIIIa) would be particularly instructive in this respect, as nucleophilic participation, if it were to occur, would lead to anti-Markovnikoff addition. This would be relevant to the question of "bridging" or equilibration of α-fluoro-cations.[10] In the event, both substrates reacted cleanly with CF_3OF to afford in each case a major and a minor product. The major products [(IX) m.p. 206—207°, $[\alpha]_D$ + 26·2°; (Xa) m.p. 129—133°, $[\alpha]_D$ −51·8°] each had the composition of adducts of CF_3OF with the appropriate substrate. Each was converted into an α-fluoro-αβ-unsaturated ketone (m.p. 184—185° and m.p. 256—257, $[\alpha]_D$ −12°, respectively), by hydrolysis (where appropriate), chromic acid oxidation, and base-induced elimination of OCF_3^-. It was evident from the n.m.r. spectra of these adducts (and derivatives) that in each case the fluorine was *trans*-diequatorially oriented with respect to the hydroxy- (or acetoxy-) group; the stereochemistry assigned is thus established. The minor product from (VIIIa) is the "fluorine" adduct (Xb) (m.p. 232—235°, $[\alpha]_D$ −59°). While the minor product from (VIIa) has not been characterized, it must be analogous to (Xb). This observation of simple Markovnikoff, but *cis*, addition with a complete absence of internal nucleophilic participation excludes the involvement of a bridged cation in these reactions.[10] As α-fluoro-carbonium ions are known to equilibrate *via* fluorine migration,[10] our observations establish that the α-fluoro-cations formed from (VIIa) and (VIIIa) must very rapidly combine with a counter ion (F^- or OCF_3^-). Also, the products of these and related fluorinations are unchanged in nucleophilic media ($CF_3{\cdot}CO_2H$–tetrahydrofuran or MeOH). The intermediate α-fluoro-cation is thus not easily captured by external anions. Although internal nucleophilic participation did not occur in the reaction of (VIIa) and (VIIIa), the allylic oxygen present in these substrates did have a beneficial effect since the corresponding hydrocarbons (VIIb) and (VIIIb) gave complex mixtures of products on reaction with CF_3OF.

An example of internal capture of the postulated α-fluoro-carbonium ion was the reaction of the 16-methylene-steroid (XI) with CF_3OF to afford the 16-fluoromethyl-16,17-epoxy-derivative (XII) (m.p. 176—177°; $[\alpha]_D$ +187°). This product must have arisen from an initial fluorination followed by internal collapse, as shown. Conventional electrophilic reagents accomplish an analogous transformation.[11]

The results we present offer further support for our contention[6] that the reactions of fluoroxy-compounds with unsaturated links proceed *via* attack of the more nucleophilic terminus of the unsaturated link upon fluorine to afford an intimate ion pair, as below. The subsequent fate of the ion pair appears to be that expected for a relatively unstabilized carbonium ion. The exclusive *cis*-addition of the reagent is noteworthy.

Fluoroxy-compounds are valuable electrophilic fluorinating agents and reaction with an unsaturated link is predictable to the extent that one can foresee the fate of a rather reactive carbonium ion. All new compounds had the correct composition as evidenced by microanalyses or high-resolution mass spectra. All spectral data (acknowledgements as before[6]) supported the structures assigned.

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