Stereoselectivity in the Addition of Chlorofluorocarbene to 10-Methyl-Δ^8-2-octalone 2-Ethylene Acetal

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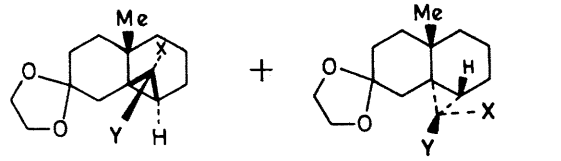
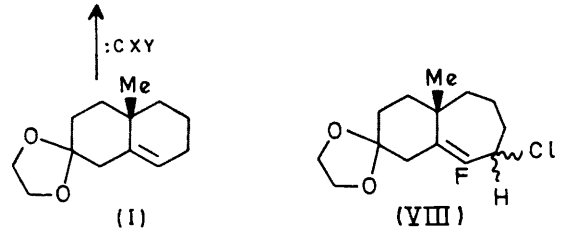
Summary Chlorofluorocarbene adds to the title olefin (I) with very marked β-*endo*-F stereoselectivity to give a mixture of the cyclopropane (II) (80—90%) and an unidentified product (10—20%).

THOUGH difluorocarbene (CF_2) adds to $\Delta^{5(6)}$-steroid olefins with formation of 5β,6β-difluorocyclopropanes, dichlorocarbene (CCl_2) is reported not to add at all,[1] even under forcing conditions.[2] Rationalizations have cited two factors. *Required axial attack* of the electrophilic CX_2 occurs through a partially charge-separated transition state, in which β-attack, biased toward C-6 (partial positive charge at tertiary C-5), is energetically preferred to α-attack, biased toward C-5 (partial positive charge at secondary C-6).[1,2a,3] Granted the necessity for β-attack, it is argued that only the smaller CF_2 can add; CCl_2 encounters severe steric hindrance originating at the 10β-methyl group.[1] If these arguments are correct, then addition of chlorofluorocarbene (ClCF) to $\Delta^{5(6)}$-steroid olefins should lead predominantly or exclusively to only *one* of the four possible product cyclopropanes. We have tested this conclusion by adding ClCF to the model compound, 10-methyl-Δ^8-2-octalone 2-ethylene acetal (I).



(II) X = F, Y = Cl (IV) X = F, Y = Cl
(III) X = Cl, Y = F (V) X = Cl, Y = F
(VI) X = Y = H (VII) X = Y = H



(I) (VIII)

10-Methyl-$\Delta^{1(9)}$-2-octalone[4] was converted into the ethylene acetal (I) (1 vinyl proton, broad multiplet at δ 5·17), by treatment with refluxing 2-ethyl-2-methyl-1,3-dioxolan containing a catalytic amount of toluene-*p*-sulphonic acid.† Slow addition of solid sodium methoxide to a stirred solution of (I) and ethyl dichlorofluoroacetate (3 hr., 0—25°, reagent ratio 2·2 : 1 : 2) gave, after aqueous work-up, a binary product mixture [16% conversion based on (I)] which could be fractionated by g.l.c. on a SE-30 column. The major product (80—90%) of the mixture was shown to be the 5β,6β-*endo*-fluorocyclopropane (II).

The ^{1}H n.m.r. spectrum of (II)† revealed a high-field multiplet, centred at δ 0·97, attributable to a cyclopropyl proton. Vinyl proton absorption was absent. Compound (II) was stable to pyridinium hydrobromide perbromide under conditions which destroyed compound (I). Compound (II) exhibited ^{35}Cl and ^{37}Cl parent ions in its mass spectrum at *m/e* 274 and 276 (ratio 3 : 1). These data led to its formulation as one of the four cyclopropanes, (II—V). ^{19}F n.m.r. revealed a single signal (envelope) at 149·2ϕ*, width at half-height, 8 Hz. This signal is consistent with the weak *trans-vic*-H–F coupling expected of *endo*-F adducts (II) or (IV), but clearly excludes *exo*-F adducts (III) or (V), in which strong (18—20 Hz) coupling would exist.[5] Under high resolution, the 100 MHz n.m.r. spectrum of (II) showed the angular methyl group (δ 1·12) to be a *doublet*, J 0·6 Hz. That this splitting involves the fluorine atom, and does not originate elsewhere in the molecule, is made likely by the lack of splitting, under identical n.m.r. conditions, of the angular methyl groups of (I) and cyclopropanes (VI) and (VII). The latter were prepared by a modified[6] Simmons–Smith reaction on (I).‡§ The existence of the long-range coupling between F and β-CH_3 differentiates between (II) and (IV), in favour of (II). Molecular models indicate that such coupling should be permitted in (II), but not in (IV).[1,8] The long-range splitting is, however, smaller than that usually observed in 5β,6β-difluorocyclopropyl-steroids (1—3 Hz).[1] This is probably due to the greater conformational mobility of (II) as compared with steroid analogues, and attendant averaging over conformations not suited to the long-range coupling. Finally, deshielding of the angular methyl group in (II), relative to (I) (3·6 Hz) is very similar to analogous effects observed with $\Delta^{5(6)}$-steroid olefins upon introduction of the 5β,6β-difluoromethylene group (2—5 Hz).[1]

The minor product isolated from the reaction of (I) and ClCF was isomeric with (II) (mass spectrum), appeared to show neither vinyl proton (n.m.r.) nor C=C (i.r.) but was

† All new compounds gave satisfactory elemental analyses for C, H, and (where required) Cl.
‡ Other ^{1}H n.m.r. signals of (II) included a "singlet" at δ 3·83 (acetyl) and a multiplet, δ 2·45—0·82 on which the CH_3 signal (δ 1·12) was superimposed. The integral ratio of acetal to other protons was 1 : 4.
§ (VI) and (VII) formed in the ratio 45 : 55 and were purified by g.l.c. Proper mass spectral parent ions were obtained.† N.m.r. angular methyl signals appeared at δ 1·00 and 1·11, respectively. The indicated stereochemistry is *tentatively* assigned on the basis of: (a) similarity of ring proton resonances of (VI) and (II); (b) analogy to $\Delta^{5(6)}$ steroid olefin CH_2 adducts in which the β-adduct has the higher 19-H_3 signal;[2b] (c) calculated values for the angular methyl signals of (VI) (δ 1·04) and (VII) (δ 1·10), based upon steroid-like chemical shift behaviour of a decalin angular methyl substituent,[7] and employing deshielding contributions of 3 and 17 Hz, respectively, for the β- and α-methylene groups.[2b]

readily destroyed by pyridinium hydrobromide perbromide under conditions where (II) was stable. The angular methyl group appeared at δ 1·20. ^{19}F n.m.r. showed a "doublet of doublets" at 129·8ϕ*, J 20·3, 5·2 Hz. The compound did not arise from (II) under various experimental conditions. No structure can be assigned at present, but possibilities include the cyclopropanes (III) and (V) and (less likely) the rearranged olefin (VIII).

We conclude that addition of ClCF to (I) proceeds with marked β-*endo*-F stereoselectivity, in accord with and supportive of extrapolations based on related steroid chemistry. We note that the results are a *reversal* of the usual *syn*-Cl, *anti*-F stereoselectivity manifested by ClCF in additions to acyclic[5] and simple cyclic olefins (*e.g.*, cyclohexene[9]), which may be attributed to the strong steric control exerted by the β-angular methyl group on β-carbene addition.¶

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¶ A similar though less pronounced, reversal is observed in *exo*-addition of ClCF to norbornene, steric demand being associated with the *syn*-7-proton.[10]

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