Addition of Difluorocarbene to Steroidal Unsaturated Ketones: Formation of Novel Difluoromethyl Ethers

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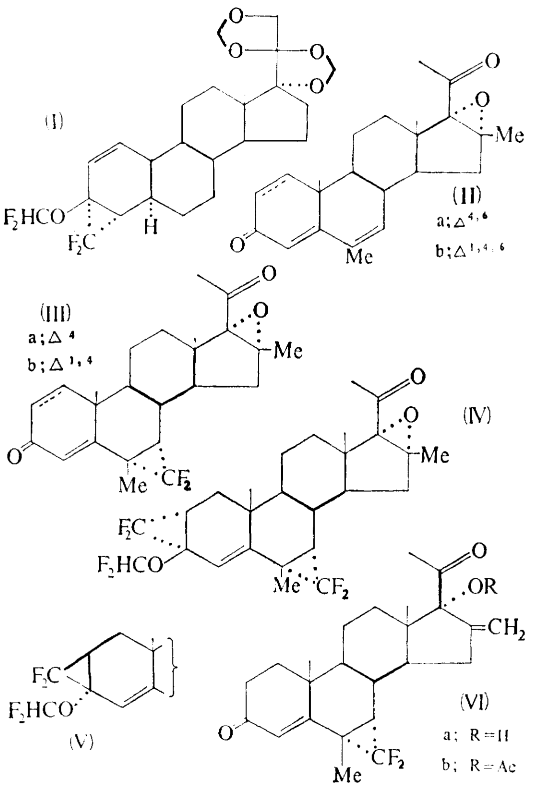
THE addition of difluoro- and dichloro-carbene to unsaturated steroids has been shown by Cross and his co-workers[1] to proceed readily. Subsequently, J. H. Fried and his colleagues[2,3] reported the formation of *gem*-difluorocyclopropanes by the addition of difluorocarbene to steroidal unsaturated ketones, and the formation of the difluoromethyl ether bis-adduct (I) from the corresponding Δ^1-3-keto-steroid.[2] We now report the isolation of two new steroidal difluoromethyl ethers formed by incorporation of three CF_2 moieties into the steroid nucleus.

On reaction of (IIa) with excess of sodium chlorodifluoroacetate in triglyme at 170°, three compounds were formed which were separated by chromatography. The expected 6α,7α-difluoromethylene adduct (IIIa)† was isolated in 33% yield: [m.p. 169—170°; $[\alpha]_D^{25}$ + 98°; λ_{max} (MeOH) 244·5 mμ (ε 15,100); n.m.r. δ 1·11 and 1·13 (C-10 and C-13 CH_3), 1·40 (C-6 CH_3, t, J_{HF} 2·4 c./sec.), 6·03 (C-4 H); M calc.: 404, found: M^+ (m/e) 404]. α-Addition of difluorocarbene to the C-6 double bond is based on the absence of fluorine C-10 methyl proton coupling expected for the β-oriented difluoromethylene ring.[4]

Two additional products, each with three equivalents of difluorocarbene, were isolated in lesser amounts: (IV), 15% [m.p. 157—161°; $[\alpha]_D^{25}$ + 58°; n.m.r. δ 1·06 (C-10 and C-13 CH_3), 1·39 (C-6 CH_3, t, J_{HF} 2·5 c./sec.), 5·81 (C-4, H, b), 6·32 (C-3, $OCHF_2$, q, J_{HF_1} 72·8, J_{HF_2} 74·0 c./sec.); M calc.: 504, found: M^+ (m/e) 504] and (V), 5% [m.p. 188—191°; $[\alpha]_D^{25}$ −20°; λ_{max} (MeOH) 217 mμ (ε 8,330); n.m.r. δ 1·03 (C-13 CH_3), 1·10 (C-10 CH_3), 1·34 (C-6 CH_3, t, J_{HF} 2·5 c./sec.), 5·80 (C-4 H, b), 6·32 (C-3 $OCHF_2$, q, J_{HF_1} = 73·5, J_{HF_2} = 74·7 c./sec.); M calc.: 504, found: M^+ (m/e) 504].

The assignments of structures (IV) and (V) to the minor products are supported by the following observations. The mass spectral data and the loss of αβ-unsaturated carbonyl absorptions in the i.r. and the u.v. spectra are consistent with the addition of three equivalents of difluorocarbene to the 3-keto-4,6-diene system. A characteristic n.m.r. signal is observed for the difluoromethyl ether proton[5] in both products. The 2α,3α,6α,7α-bis-difluoromethylene configuration is assigned to (IV) since a sharp signal is observed for the C-10 methyl proton resonance with no indication of long range fluorine coupling. However, the n.m.r. spectrum of the isomeric product (V) showed a broadened signal for the C-10 methyl protons ($W\frac{1}{2}$ = 2·5) compared to that of the C-13 methyl proton band ($W\frac{1}{2}$ = 1·0 c./sec.). This small but significant fluorine C-10 methyl proton coupling is consistent with a 2β,3β-difluoromethylene configuration. Molecular models show that introduction of the C-4 double bond should decrease the magnitude of


(I)

(II)
a; $\Delta^{4,6}$
b; $\Delta^{1,4,6}$

(III)
a; Δ^4
b; $\Delta^{1,4}$

(IV)

(V)

(VI)
a; R=H
b; R=Ac

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† Satisfactory elementary analyses have been obtained for all new compounds. Rotations were determined in dioxane. N.m.r. spectra measured on a Varian A-60-A spectrometer in $CDCl_3$ solutions using Me_4Si as internal standard. Mass spectra were determined on a CEC 21-103 spectrometer using a heated inlet system at a temperature of 200—230°. We thank Dr. T. Traubel for these measurements.

this coupling compared to the saturated ring system. Since the 6β,7β-difluoromethylene configuration shows a relatively large fluorine C-10 methyl proton coupling (J_{HF} 2—3 c./sec.),[6] (V) is favoured over the 2α,3α,6β,7β- or the 2β,3β,6β,7β-bisdifluoromethylene structures. The u.v. absorption maximum observed for (V) [λ_{max} (MeOH) 217 mμ (ϵ 8,330)] and not for (IV) further substantiates the relative stereochemical assignments of the A-ring cyclopropyl group. Kosower[7] has shown that interaction of a cyclopropyl and a carbonyl group, resulting in a bathochromic shift of the $\pi \rightarrow \pi^*$ transition, is maximal when the plane of the ring and the *p*-orbitals of the carbonyl group are parallel. Dreiding models show that the plane of the 2,3-cyclopropyl group is approximately parallel to the plane of the *p*-orbitals of the C-4 double bond for (V) and close to perpendicular for (IV). A similar u.v. maximum [λ_{max} (C_6H_{12}) 218 mμ (ϵ 9,000)] was observed for the $\alpha\beta$-unsaturated cyclopropyl chromophore in 3β-acetoxy-5α,6α-dibromomethylene-7,22-ergostadiene.[8]

Treatment of (IIb) under similar difluorocarbenylation conditions resulted in (IIIb) [m.p. 223—225·5°; λ_{max} (MeOH) 243 mμ (ϵ 14,950); n.m.r. δ 1·12 (C-13 CH_3), 1·25 (C-10 CH_3), 1·45 (C-6 CH_3, t, J_{HF} 2·4), 6·23 (C-2 H, q, $J_{H_1H_2} = 11$, $J_{H_2H_4} = 2$), 6·33 (C-4 H), 6·95 (C-1 H, d, $J_{H_1H_2} = 11$ c./sec.); M calc.: 402, found: M^+ (m/e) 402].

Reaction of (IIIa) with catalytic amounts of sulphuric acid in dioxan[9] gave (VIa), which on acetylation with acetic acid, trifluoroacetic anhydride, and toluene-*p*-sulphonic acid at room temperature[10] yielded (VIb) [m.p. 205—207°; $[\alpha]_D^{25}$ $-60°$; λ_{max} (MeOH) 244·5 mμ (ϵ 14,100); n.m.r. δ 0·74 (C-13 CH_3), 1·14 (C-10 CH_3), 1·42 (C-6 CH_3, t, $J_{HF} = 2·4$ c./sec.), 6·04 (C-4 H)]. (VIb) was also obtained when 17α-acetoxy-6-methyl-16-methylene-4,6-pregnadien-3,20-dione was treated with an excess of sodium chlorodifluoroacetate in triglyme at 200°.

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