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STEROIDS CCXCIV.(1)

THE METHYLENATION OF UNSATURATED KETONES.

PART II. ADDITION OF DIFLUOROMETHYLENE TO DIENONES AND TRIENONES.

C. Beard, I. T. Harrison, L. Kirkham, J. H. Fried

Institute of Steroid Chemistry
Syntex Research
Palo Alto, California

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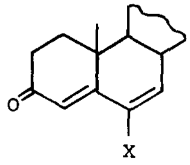
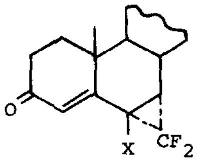
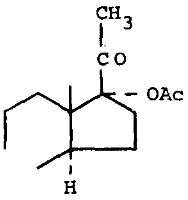
We have reported that addition of difluoromethylene to the double bond of conjugated ketones affords the corresponding difluorocyclopropyl ketones.(1) This reaction has been extended to the conjugated dienones I and II and the cross-conjugated trienone III. Addition occurs predominately at the double bond most distant from the ketone function.



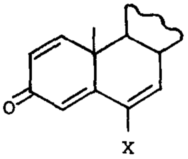
I X:H
II X:Cl



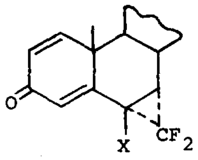
IV X:H
V X:Cl



(a)



III



VI

Addition of a saturated solution of sodium chlorodifluoroacetate (10 equivalents) in diglyme during 30-60 minutes to a solution of 17α-hydroxypregna-4,6-diene-3,20-dione acetate (Ia) in refluxing diglyme affords 6α,7α-difluoromethylene-17α-hydroxypregn-4-ene-3,20-dione acetate$^{(2)}$ (IVa) [m.p. 228-230°; $[\alpha]_D$ +61°; λ_{max}^{MeOH} 247 mμ (ε 15,200); n.m.r. 361 c.p.s. (4-H, half-band width 3 c.p.s.). Anal. Calcd. for $C_{24}H_{30}O_4F_2$: C, 68.56; H, 7.19; F, 9.05. Found: C, 68.68; H, 7.19; F, 9.00].$^{(3)}$ Similarly the 6-chloro derivative IIa affords Va [m.p. 210-211°; $[\alpha]_D$ -27°; λ_{max}^{EtOH} 247 mμ (ε 10,400); n.m.r. 43 (18-H), 76 (19-H), 149 (7-H, $J_{7,8}$ 4 c.p.s.),$^{(4)}$ 386.5 (4-H, half-band width 1.5 c.p.s Anal. Calcd. for $C_{24}H_{29}O_4ClF_2$: C, 63.36; H, 6.43; F, 8.35. Found: C, 63.45; H, 6.51; F, 8.06].

Reaction of 6-chloro-17α-hydroxypregna-1,4,6-triene-3,20-dione acetate (IIIa) and sodium chlorodifluoroacetate (20 equivalents) in refluxing diglyme affords 6β-chloro-6α,7α-difluoromethylene-17α-hydroxypregna-1,4-diene-3,20-dione acetate (VIa) [m.p. 221-223°; $[\alpha]_D$ -116°; λ_{max}^{MeOH} 245 mμ (ε 16,470); n.m.r. 377 (2-H, pair of doublets, $J_{1,2}$ 10, $J_{2,4}$ 2 c.p.s.), 396.5 (4-H, doublet $J_{2,4}$ 2 c.p.s.), 421 c.p.s. (1-H, doublet $J_{1,2}$ 10 c.p.s.). Anal. Calcd. for $C_{24}H_{27}O_4ClF_2$: C, 63.63; H, 6.01; F, 8.39. Found: C, 63.74; H, 6.02; F, 8.84]. In contrast with these examples the cross-conjugated 1,4-dienone, 17β-hydroxyandrosta-1,4-dien-3-one acetate, affords only recovered starting material in refluxing diglyme.$^{(5)}$

The stereochemistry assigned to IV, V and VI is consistent with the absence of proton-fluorine coupling expected for fluorine on a β-oriented difluoromethylene with the 19-hydrogens$^{(6)}$ and the relatively unhindered approach from the α-side of the molecule.(7) Analogy is found in the formation of the 6α,7α-oxide with peracids.(8)

References

(1) Steroids CCXCIII. Part I. C. Beard, N. H. Dyson and J. H. Fried, Tetrahedron Letters (manuscript submitted for publication).

(2) No effort was made to optimize the yields which ranged from 26 to 74%. Addition of sodium chlorodifluoroacetate (10-20 equivalents) was continued until no further change in the ultraviolet spectrum was observed.

(3) Rotations are taken in $CHCl_3$ (C 0.1). We wish to thank Dr. L. Throop and his associates for the physical constants herein reported.

(4) This coupling constant is consistent with either the α or β orientation of the difluoromethylene, c.f., N.S. Bhacca and D. H. Williams, Application of NMR Spectroscopy in Organic Chemistry, Holden-Day, Inc., San Francisco, California (1964) p. 50.

(5) A reaction leading to several rearranged adducts has been observed at 220° by Dr. N. Dyson. The structure of these compounds will be the subject of a future report.

(6) A. D. Cross and P. W. Landis, J. Am. Chem. Soc., 84, 1736, 3784 (1962); 86, 4011 (1964).

(7) c.f., L. Fieser, Experientia, 6, 312 (1950).

(8) A. L. Nussbaum, G. Brabazon, T. L. Popper and E. P. Oliveto, J. Am. Chem. Soc., 80, 2722 (1958).