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STEROIDS CCXCIII.(1)

THE METHYLENATION OF UNSATURATED KETONES.

PART I. ADDITION OF DIFLUOROMETHYLENE TO ENONES.

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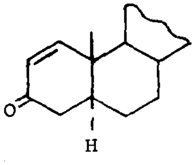
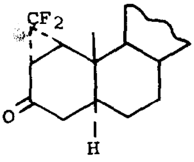
We would like to report the first examples of the addition of difluoromethylene to the conjugated double bond of an enone system to yield gem-difluorocyclopropyl ketones. The reaction is conveniently carried out by dropwise addition of a saturated diglyme or triglyme solution of sodium chlorodifluoroacetate(3) (20-50 equivalents) to a 10% solution of the enone in the same solvent at a temperature of 165-225° during 1/2 to 1 hour. Addition does not occur below 150°(4) even though decomposition of the salt is observed at 125°.(6)


I



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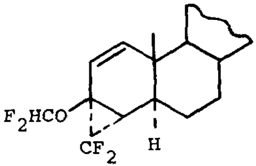
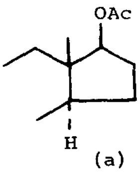
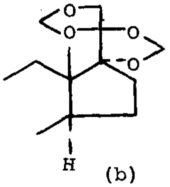


III



(a)


(b)

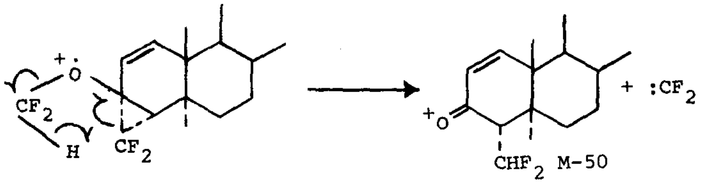
Reaction of 17β-hydroxy-5α-androst-1-en-3-one acetate (Ia) with sodium chlorodifluoroacetate (20 equivalents) in refluxing diglyme affords 1α,2α-difluoromethylene-17β-hydroxy-5α-androstan-3-one(7) (IIa) [m.p. 148-150°; $[\alpha]_D$ +67°; n.m.r. 49.5 (18-H), 64.5 (19-H), 122.5 (acetate), ca. 275 c.p.s. (m., 17α-H). Anal. Calcd. for $C_{22}H_{30}O_3F_2$: C, 69.45; H, 7.95; F, 9.99. Found: C, 69.09; H, 7.91; F, 10.04].(8)

Similarly, reaction of 17α,20:20,21-bismethylenedioxy-5α-pregn-1-en-3-one (Ib) with sodium chlorodifluoroacetate (40-50 equivalents) in refluxing diglyme yields 17α,20:20,21-bismethylenedioxy-1α,2α-difluoromethylene-5α-pregnan-3-one (IIb) [m.p. 159-160°; $[\alpha]_D$ -21°; n.m.r. 50.5 (18-H), 64 (19-H). Anal. Calcd. for $C_{24}H_{32}O_5F_2$: C, 65.73; H, 7.36; F, 8.67. Found: C, 65.86; H, 7.64; F, 8.40].

The assigned α-orientation of the difluoromethylene adducts is supported by the absence of long-range J_{HF} coupling expected for the angular methyl C-19 protons and fluorine on a β-oriented CF_2 group(9); comparison of the change in molecular rotation from Ia to IIa (ΔM_D +99°) and from Ib to IIb (ΔM_D +94°) with Ia to the corresponding 1α,2α-epoxide(10) (ΔM_D +160°) and 1β,2β-epoxide(11) (ΔM_D -22°); and the relatively unhindered approach from the rear(12) by the reacting species.

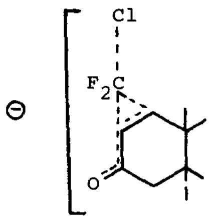
Further products isolated were starting material (Ib) and 17α,20:20,21-bismethylenedioxy-3α,4α-difluoromethylene-3β-hydroxy-5α-pregn-1-ene 3-difluoromethyl ether (IIIb) [m.p. 151-152°; $[\alpha]_D$ -78°; no selective absorption in the UV; no absorption in the region 1500-1800 cm^{-1}; n.m.r. 50.5 (18-H), 63.5 (19-H), 343 (2-H, doublet J 9 c.p.s.), 392 (1-H, doublet J 10 c.p.s.) and 381 ($-OCHF_2$, two doublets, J 74 c.p.s. and J 76 c.p.s., for coupling of a proton with nonequivalent fluorines). Anal. Calcd. for $C_{25}H_{32}O_5F_4$: C, 61.46; H, 6.60; F, 15.56. Found: C, 61.63; H, 6.84; F, 15.41. Mass spectrum: 488 (M+), 438 (M-50)].

The structure of IIIb is based on chemical, n.m.r. and mass spectral data, and can be rationalized as proceeding through the enolate. The observed J_{HF} coupling constants are consistent with results obtained by Arison, et al.,(13) with a series of difluoromethyl ethers and can be readily distinguished from the proton-fluorine couplings observed with difluoromethyl attached directly to carbon. The nonequivalence of the two fluorines suggests the existence of preferred rotamers about the carbon oxygen bond. The base peak in the mass spectrum of IIIb appears at M-50 (loss of CF_2), and probably arises by the following process:



The presence of the 1,2-double bond was confirmed by catalytic reduction of IIIb to the dihydro derivative [m.p. 183-184°; $[\alpha]_D$ -56°; n.m.r. 49.5 (18-H), 52 (19-H), 376.5 ($-OCHF_2$, J_{HF} 74 and 76 c.p.s.). Anal. Calcd. for $C_{25}H_{34}O_5F_4$: C, 61.21; H, 6.99; F, 15.49. Found: C, 61.22; H, 7.20; F, 15.01].

Among the possible mechanisms that can be conceived for the formation of difluorocyclopropyl ketones are: (1) nucleophilic addition of $^-CClF_2$ anion formed by thermal decarboxylation of sodium chlorodifluoroacetate, followed by ring closure with displacement of chloride by the enolate, (2) addition of "free" difluorocarbene,(14) or (3) concerted nucleophilic attack on carbon with cation assisted elimination of chloride.(15)



Process (1) is considered to be less attractive since the intermediate 1α-chlorodifluoromethyl adduct was not isolated.(16) From the available data it is difficult to distinguish between a "free" carbene(17) mechanism (2) or the concerted mechanism (3). However, in view of the considerable electrophilic character of "free" carbene, the latter is the more likely. This question is receiving further attention in our laboratory.

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(4) The relatively high temperature required for addition to the double bond compared to carbene formation from the salt is consistent with the considerable activation(5) energy necessary for addition of difluorocarbene to simple olefins. This energy requirement would be expected to be more pronounced in the present case.

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(7) No effort was made to optimize the yields of the difluoromethylene adducts which ranged from 33 to 42% in addition to *ca*. 25% recovered starting materials.

(8) 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.

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(14) For recent summaries of carbene chemistry see J. Hine, Divalent Carbon, Ronald Press, New York, N.Y. (1964); W. Kirmse, Carbene Chemistry, Academic Press, Inc., New York, N.Y. (1964).

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(16) D. Seyferth, J. Yick-Pui Mui, M. E. Gordon and J. M. Burlitch, J. Am. Chem. Soc., 87, 681 (1964), have

demonstrated that $CBrCl_2$ anion prepared from sodium iodide and $C_6H_5HgBrCl_2$ reacts with acrylonitrile to yield both 4-bromo-4,4-dichlorobutyronitrile and 1,1-dichloro-2-cycanocyclopropane.

(17) The addition of an α-ketocarbene to a conjugated enone bond has been described by D. Becker and H. J. E. Loewenthal, Chem. Comm., 149 (1965). It is quite probable that this reaction proceeds *via* a "free" carbene mechanism.