

STERIODS CCCII⁽¹⁾. THE METHYLENATION OF UNSATURATED KETONES
PART IV⁽²⁾. THE 1:4-ADDITION OF DIFLUOROMETHYLENE TO AN ENONE

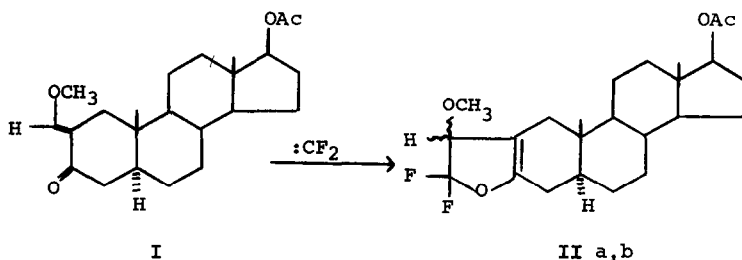
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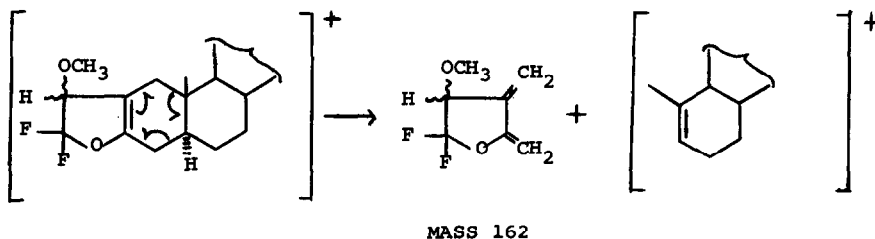
The reactions of carbenes with conjugated dienes usually proceed by 1,2-addition to give cyclopropane derivatives⁽⁴⁾. The only well-authenticated example of a 1,4-addition is the reaction between buta-1,3-diene and photochemically produced methylene to afford cyclopentene in 6-10% yield^(5,6). 1,2-Addition and methylene insertion products were also obtained.

Previous reports from this laboratory have described the reactions between "difluoromethylene" and conjugated dienones to afford cyclopropyl ketones⁽⁷⁾. We now wish to report a novel reaction in which "difluoromethylene" adds to a cisoid enone to give 1,4-adducts in high yield.

Treatment of 17 β -acetoxy-2-methoxymethylene-5 α -androstane-3-one (I) in refluxing diglyme (163°)⁽⁹⁾ with twelve equivalents of "difluoromethylene" generated by thermal decomposition of sodium chlorodifluoroacetate⁽¹⁰⁾, afforded, after column chromatography, two mono-adducts, one with m.p. 120.5-121.5°; $[\alpha]_D^{CHCl_3} +38^\circ$ (Found: C, 68.11; H, 7.81; F, 8.85) and the other with m.p. 166.5-168°; $[\alpha]_D^{CHCl_3} +31^\circ$ (Found: C, 67.87; H, 8.07; F, 8.79) in 42 and 28% yields respectively. These have been identified as the 3' epimers of 17 β -acetoxy-5 α -androstane-[2,3-d]-2',2'-difluoro-3'-methoxy-2',3'-dihydrofuran (IIa,b) from the following spectral data.



Neither isomer showed significant ultraviolet absorption above 220 m μ and infrared and optical rotatory dispersion measurements excluded the presence of carbonyl groups other than that of the 17 β -acetate. The proton magnetic resonance spectra⁽¹¹⁾ showed a 3-H singlet at 207 c.p.s. due to a methoxyl group, and a 1-H multiplet at ca. 255 c.p.s. due to the proton on the furan ring. This proton was coupled to both of the fluorine nuclei. The mass spectra of both isomers were very similar and had a prominent peak at $m/e = M^+ - 162$ which is attributed to the occurrence of a retro-Diels-Alder cleavage as shown⁽¹²⁾.



The ¹⁹F nuclear magnetic resonance spectrum⁽¹³⁾ of the higher melting isomer showed two quartets centered at +90 δ (J_{FF} 155 c.p.s., J_{FH} 4 c.p.s.) and +71 δ (J_{FF} 155 c.p.s., J_{FH} 12 c.p.s.), and that of the

lower melting isomer showed quartets centered at $+90\delta$ (J_{FF} 150 c.p.s., J_{FH} 5 c.p.s.) and $+71\delta$ (J_{FF} 150 c.p.s., J_{FH} 12 c.p.s.). These δ - values are in good agreement with those quoted for fluorine nuclei in the environment $-OCF_2-C$ ($\delta+70$ to $+90$ p.p.m.)⁽¹⁴⁾, but quite different from those for fluorine nuclei in 1:1-difluorocyclopropanes ($\delta+120$ to $+155$ p.p.m.)⁽¹⁵⁾.

Each isomer consumed one equivalent of bromine in carbon tetrachloride. Unlike simple enol-ethers⁽¹⁶⁾, the enol-ether grouping in the adducts IIa,b was stable to boiling 95% acetic acid during 2.5 hours. This, and the lack of enol-ether bands between 1550 and 1700 cm^{-1} in the infrared spectra, is attributed to the strong electron-attracting effect of the CF_2 group which probably reduces the interaction between the non-bonding electrons of the furan oxygen and the π -electrons of the double bond⁽¹⁷⁾

REFERENCES

1. STEROIDS CCCI, D. L. Wren, J. B. Siddall and J. A. Edwards, Steroids, submitted for publication.
2. Part III, N. H. Dyson, J. A. Edwards and J. H. Fried, Tetrahedron Letters., No.17, 1841 (1966).
3. Syntex Postdoctoral Fellow, 1965-66.
4. See, for example, W. Kirmse, in "Carbene Chemistry", Academic Press, Inc., New York, N.Y. (1964), or J. Hine in "Divalent Carbon" Ronald Press, New York, N.Y. (1964).
5. V. Franzen, Chem. Ber., 95, 571 (1962).
6. B. Grzybowska, J. H. Knox, and A. F. Trotmann-Dickenson, J. Chem. Soc., 3826 (1962).
7. a) C. Beard, N. H. Dyson and J. H. Fried; b) C. Beard, I. T. Harrison, L. Kirkham and J. H. Fried, Tetrahedron Letters, in press.
8. Prepared (84% yield) by treating 17 β -acetoxy-2-acetoxymethylene-5 α -androstan-3-one [S. H. Burstein and H. J. Ringold, J. Org. Chem., 26, 3084 (1961)] for four minutes with refluxing methanol containing a trace of *p*-toluenesulfonic acid. An analytical sample had m p. 177-181° (acetone/hexane); $[\alpha]_D^{25} +19^\circ$;

$\lambda_{\text{max}}^{\text{EtOH}}$ 275 m μ (log ϵ 4.11) (Found: C, 74.04; H, 9.15). The proton magnetic resonance spectrum indicated that this material was a mixture of isomers, ca. 80% being that shown in (I).

9. Compound (I) was recovered unchanged after a solution in diglyme had been refluxed for 2 hr.
10. Inter alia see L. H. Knox, E. Verlade, S. Berger, D. Cuadriello, P. W. Landis, and A. D. Cross, J. Amer. Chem. Soc., **85**, 1851 (1963)
11. Spectra were recorded for ca. 11% solutions in deuteriochloroform containing tetramethylsilane as an internal reference, on a Varian A-60 spectrometer. Chemical shifts are reported in cycles per second (c.p.s.) downfield from the reference.
12. Similar fragmentations occur with other Δ^2 -steroids. See, for example, H. Budzikiewicz, C. Djerassi, and D. H. Williams in "Structure Elucidation of Natural Products by Mass Spectrometry", Vol. 2, Holden-Day, Inc., San Francisco (1964), pp. 98-101.
13. The ^{19}F nuclear magnetic resonance spectra were measured on a Varian A-100 spectrometer for ca. 15% solutions in chloroform containing 2% trichlorofluoromethane as an internal reference. δ -Values measured to the high field side of the reference are positive, to the low field side negative.
14. See J. A. Pople, W. G. Schneider, and H. J. Bernstein in "High-Resolution Nuclear Magnetic Resonance", McGraw-Hill Book Co., Inc., New York, N.Y. (1959), p. 323; E. G. Brame, Anal. Chem., **34**, 591 (1962). These authors used as a reference trifluoroacetic acid, $\delta_{\text{F}} = +76.5$ p.p.m. with respect to trichlorofluoromethane.
15. Obtained from the ^{19}F spectra of a series of 6,7-difluoromethylene steroids prepared in these laboratories⁽⁷⁾. See also, W. D. Phillips, J. Chem. Phys., **25**, 949 (1956), who used as a reference 1,1,2,2-tetrafluorocyclobutane, $\delta_{\text{F}} = +114.5$ p.p.m. with respect to trichlorofluoromethane.
16. See, for example, B. J. Magerlein and J. A. Hogg, J. Amer. Chem. Soc., **80**, 2226 (1958).
17. The $-\text{CF}_2-$ group generally has a strong electron-attracting effect which can often radically alter the properties of neighboring groups. For example, the acidic character of 2,2-difluoroethanol is comparable to that of phenols. See, R. N. Haszeldine and A. G. Sharpe in "Fluorine and its Compounds", Methuen and Co. Ltd., London (1951), pp. 89 and 109.