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STEROIDS CCC.(1)

PHOTOCHEMICAL CYCLOADDUCTS.

PART I. ADDITION TO 16-DEHYDRO-20-KETO STEROIDS.

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The intermolecular photochemical cycloaddition of ethylenes to conjugated systems has recently attracted considerable attention.(4) We now wish to report the preparation of the hitherto inaccessible steroid cyclobutanes, with examples in the progestational and corticoid series, by photochemical addition of ethylene and tetrafluoroethylene to 16-dehydro-20-keto steroids.

Irradiation(5) of 3β-acetoxypregna-5,16-dien-20-one (I) in a benzene solution saturated with ethylene (maintained by bubbling the gas through the solution) afforded 3β-acetoxy-16α,17α-ethylenepregn-5-en-20-one [IIa (52%); m.p. 186-187°; $[\alpha]_D$ +19°; ν_{max} 1695, 1730 cm^{-1}; n.m.r. 35 (18-H), 62 (19-H) c.p.s. Anal. Calcd. for $C_{25}H_{36}O_3$: C, 78.08; H, 9.44; O, 12.48. Found: C, 78.01; H, 9.12; O, 12.94](6) and the epimeric 3β-acetoxy-16β,17β-ethylenepregn-5-en-20-one [IIb (7%); m.p. 195-196°; $[\alpha]_D$ -84°; ν_{max} 1695, 1730 cm^{-1}; n.m.r. 62 (19-H), 69.5 (18-H) c.p.s. Anal. Found: C, 78.16; H, 9.43; O, 12.56].(7)

The stereochemistry of addition follows from the n.m.r. frequency of the 18-protons which correlate well with the observed frequencies for the unsubstituted 17α- and 17β-pregnanes.(8) The addition is considered to be cis in view of Eaton's(9) results for the dimerization of cyclopentenone and the addition of cyclopentene to cyclopentenone. In the present instance, trans addition would be even less likely due to the rigidity of the C/D trans fused tetracyclic system.

Hydrolysis of IIa with potassium carbonate in aqueous methanol afforded the corresponding 3-carbinol [III, m.p. 217-219°; $[\alpha]_D$ +24°; ν_{max} 1680, 3480 cm^{-1}; n.m.r. 35.5 (18-H), 61.5 (19-H) c.p.s. Anal. Calcd. for $C_{23}H_{34}O_2$: C, 80.65; H, 10.01; O, 9.34. Found: C, 81.05; H, 10.09; O, 9.11] which on Oppenauer oxidation yielded 16α,17α-ethyleneprogesterone [IV, m.p. 196-197°; $[\alpha]_D$ +162°; λ_{max} 241 mμ (ε 16,860); ν_{max} 1695, 1675, 1620 cm^{-1}; n.m.r. 37.5 (18-H), 73 (19-H) c.p.s. Anal. Calcd. for $C_{23}H_{32}O_2$: C, 81.13; H, 9.47; O, 9.40. Found: C, 81.28; H, 9.56; O, 9.50].

Similarly, photochemical cycloaddition of tetrafluoroethylene to I yielded 3β-acetoxy-16α,17α-tetrafluoroethylenepregn-5-en-20-one [Va (24%); m.p. 172 - 173°; $[\alpha]_D$ -109°; ν_{max} 1730, 1720 cm^{-1}; n.m.r. 39.5 (18-H), 60.5 (19-H), 136 (J_{HF} 2.3 c.p.s., 21-H) c.p.s. Anal. Calcd. for $C_{25}H_{32}O_3F_4$ (MW 456.5): C, 65.77; H, 7.07. Found: C, 66.07; H, 7.07. Mass spectrum: 456 (M+), 396, 381] and 16β, 17β-tetrafluoroethylenepregn-5-en-20-one [Vb (11%); m.p. 147-148°; $[\alpha]_D$ -76°; ν_{max} 1740, 1715 cm^{-1}; n.m.r. 61.5 (19-H), 69 (J_{HF} 3.7 c.p.s., 18-H), 136.5 (J_{HF} 2.6 c.p.s., 21-H) c.p.s. Anal. Found: C, 65.92; H, 6.62. Mass spectrum: 456 (M+), 396, 381]. The assignment of stereochemistry is supported by the position of the 19-proton frequencies found with Va and Vb and the observation with Vb of long range coupling(10) of the 18-protons with fluorine on the β oriented tetrafluoroethylene bridge.

The alpha adduct was hydrolyzed to yield VI [m.p. 176-177°; $[\alpha]_D$ -18°; ν_{max} 3530, 1720, 1700 cm^{-1}; n.m.r. 39 (18-H); 60 (19-H); 137 (J_{HF} 2.4 c.p.s., 21-H) c.p.s. Anal. Calcd. for $C_{23}H_{30}O_2F_4$: C, 66.65; H, 7.30. Found: C, 66.82; H, 7.36] and converted to 16α,17α-tetrafluoroethylenepregn-4-ene-3,20-dione [VII, m.p. 271°; $[\alpha]_D$ +91°; λ_{max} 237 mμ (ϵ 16,000); ν_{max} 1720, 1675 cm^{-1}; n.m.r. 42 (18-H), 71 (19-H), 137.1 (J 2.2 c.p.s., 21-H) c.p.s. Anal. Calcd. for $C_{23}H_{28}O_2F_4$: C, 66.97; H, 6.84; F, 18.43. Found: C, 67.05; H, 6.89; F, 18.34] by Oppenauer oxidation.(11)

Photochemical cycloaddition of ethylene to 3-ethylenedioxy-9α-fluoro-11β,21-dihydroxypregna-5,16-dien-20-one 21-acetate(12) afforded the 16α,17α-ethylene adduct [VIII (40%); m.p. 209-212°; $[\alpha]_D$ +17° (dioxane); ν_{max} 3540, 1750, 1705 cm^{-1}; n.m.r. deuterio-pyridine 51.5 (18-H), 83.5 (19-H) c.p.s. Anal. Calcd. for $C_{27}H_{37}O_6F$: C, 68.04; H, 7.83; F, 3.99. Found: C, 67.90; H, 7.87; F, 3.87] which on hydrolysis with p-toluenesulfonic acid in acetone yielded 16α,17α-ethylene-9α-fluoro-11β,21-dihydroxypregn-4-ene-3,20-dione 21-acetate [IX, m.p. 206-208°; $[\alpha]_D$ +141°; λ_{max}^{MeOH} 237 mμ (ϵ 15,800); ν_{max} 3470, 1755, 1720, 1660 cm^{-1}; n.m.r. 53 (18-H), 94 (19-H) c.p.s. Anal. Calcd. for $C_{25}H_{33}O_5F$: C, 69.42; H, 7.69; F, 4.39. Found: C, 69.65; H, 7.89; F, 4.55].

The photochemical addition of ethylene to 9α-fluoro-11β,21-dihydroxypregna-4,16-diene-3,20-dione 21-acetate allowed a qualitative comparison of the reactivity of the A ring enone system with the 16-en-20-one. Irradiation(5) for a period of 45 minutes afforded 60% of 4α,5α-ethylene-9α-fluoro-11β,21-dihydroxy-pregn-16-ene-3,20-dione 21-acetate [X, m.p. 178-180°; $[\alpha]_D$ +103°; R.D. $[\alpha]_{600}$ +106°, $[\alpha]_{350}$ +1181°, $[\alpha]_{320}$ ±0°, $[\alpha]_{280}$ -1317°, $[\alpha]_{253}$ -2030°, $[\alpha]_{233}$ ±0°, (dioxane); λ_{max} 241 mμ (ϵ 8900); ν_{max}

3495, 1755, 1695, 1685, 1585 cm^{-1}; n.m.r. 68.5 (19-H), 71 (18-H), 407 (16-H) c.p.s. Anal. Calcd. for $C_{25}H_{33}O_5F$: C, 69.42; H, 7.69; F, 4.39. Found: C, 69.61; H, 7.74; F, 4.60] in addition to small quantities of X and of a 4,5:16,17-bisethylene adduct. The 4α,5α-stereochemistry is assigned to X on the basis of the n.m.r. and O.R.D. results. The shielding of ca. 18 c.p.s. of the 19-H resonance as compared to the calculated$^{(8)}$ value of 87 c.p.s. for 9α-fluoro-11β,21-dihydroxy-5α or 5β-pregn-16-ene-3,20-dione 21-acetate suggests an A ring boat or twist boat conformation, bringing the 19-protons within the shielding cone of the 3-ketone. The O.R.D. results are consistent with the twist boat conformation but cannot be accommodated by a β-adduct. Neither of the two possible *trans* adducts is consistent with both the O.R.D. and n.m.r. data.

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(2) Syntex Postdoctoral Fellow, 1964-1965.

(3) Syntex Corporation, Apartado M-10063, Mexico D.F., Mexico

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(5) Irradiation experiments were carried out with a 70 Watt Hanau Q-81 high pressure burner fitted with a pyrex filter.

(6) Except where stated otherwise, infrared spectra are for KBr disks and rotations are for chloroform solutions. Nuclear magnetic resonance spectra were recorded on a Varian A-60 spectrometer in deuteriochloroform solution. We are indebted to Dr. L. Throop and his associates for the physical properties herein reported.

(7) In addition to the primary photoadducts, several compounds derived by further photochemical transformation were isolated. The structure of these compounds is presently under active investigation.

(8) N. S. Bhacca and D. H. Williams, Applications of NMR Spectroscopy in Organic Chemistry, Holden Day, San Francisco (1964) p. 19, and unpublished results of these laboratories.

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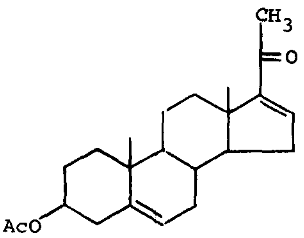
(10) A. D. Cross and P. W. Landis, J. Am. Chem. Soc., 84, 1736, 3784 (1962); ibid., 86, 4005 (1964).

(11) Experiment carried out by H. Hänni.

(12) Prepared from 9α-fluoro-11β,21-dihydroxypregna-4,16-diene-3,20-dione 21-acetate(13) and butanone dioxolane in the presence of p-toluene sulfonic acid.

(13) Merck & Co., Inc., German Patent 1,128,425, April 26, 1962.



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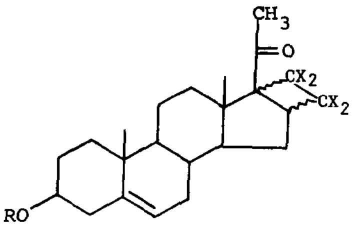
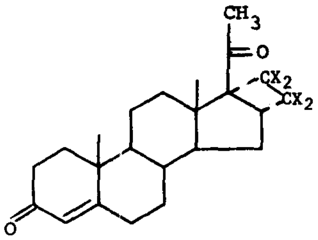
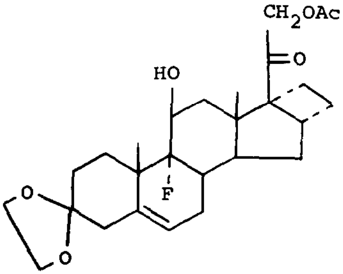


IIa R=Acetyl; 16α,17α; X=H
IIb R=Acetyl; 16β,17β; X=H
III R=H; 16α,17α; X=H
Va R=Acetyl; 16α,17α; X=F
Vb R=Acetyl; 16β,17β; X=F
VI R=H; 16α,17α; X=F



IV X=H
VII X=F



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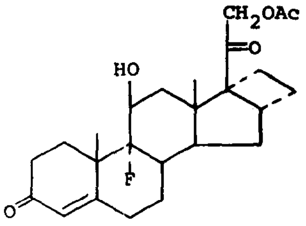

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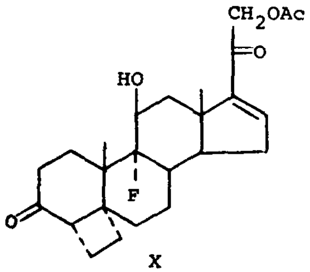

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