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CIS-ADDITION OF FLUORINE TO A STEROID OLEFIN.

A NEW ROUTE TO 6α-FLUORO-Δ^4-3-KETONES[1]

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It has recently been demonstrated that introduction of a 6α-fluoro substituent[2-12] to a series of steroid hormones

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[2] A.Bowers and H.J.Ringold, Tetrahedron 3, 14 (1958).

[3] A.Bowers and H.J.Ringold, J.Amer.Chem.Soc. 80, 4423 (1958).

[4] J.A.Hogg, G.B.Spero, J.L.Thompson, B.J.Magerlein, W.P.Schneider, D.H.Peterson, O.D.Sebek, H.C.Murray, J.C.Babcock, R.L.Pederson and J.A.Campbell, Chemistry and Industry 1002 (1958).

[5] J.S.Mills, A.Bowers, C.Casas Campillo, C.Djerassi and H.J.Ringold, J.Amer.Chem.Soc. 81, 1264 (1959).

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[7] A.Bowers, L.C.Ibáñez and H.J.Ringold, Tetrahedron 7, 138 (1959).

[8] A.Bowers, E.Denot, M.B.Sánchez and H.J.Ringold, ibid. 7, 153 (1959).

[9] J.A.Edwards, H.J.Ringold and C.Djerassi, J.Amer.Chem.Soc. 81, 3156 (1959).

[10] W.P.Schneider, F.H.Lincoln, G.B.Spero, H.C.Murray and J.L.Thompson, ibid. 81, 3167 (1959).

[11] S.Karaday and M.Sletzinger, Chemistry and Industry 1159 (1959).

favorably influenced biological activity. Previous approaches to these compounds had proceeded *via* (a) fission of a 5α-6α-epoxide with boron trifluoride etherate[2,3,5-9,11-13] or anhydrous hydrogen fluoride,[4,10] (b) *trans* addition of Br F to a Δ^5-3β-alcohol[14] or (c) perchloryl fluoride treatment of the derived enol ether[15] or enol acetate[16] of a Δ^4-3-ketone. All of these approaches afforded 6α-fluoro-Δ^4-3-ketones, primarily *via* their 6β-fluoro epimers. This communication describes the direct introduction of a 6α-fluoro substituent *via* the *cis* addition of fluorine to a Δ^5-3β-alcohol using an "*in situ*" preparation of lead tetrafluoride[17] as the fluorinating agent.

Δ^5-Pregnene-3β-ol-20-one acetate (I) (0.035 M) in dry methylene dichloride (200 cc.) was added to a stirred mixture of lead tetraacetate (0.07 M), anhydrous hydrogen fluoride (1.0 M) and methylene dichloride (50 cc.) at -75°. After 15 mins. at -75° the reaction mixture was neutralised with ice cold sodium carbonate solution. Chromatography of the product

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[12] A.Bowers, L.C.Ibáñez and H.J.Ringold, *J.Amer.Chem. Soc.* **81**, 5991 (1959).

[13] H.B.Henbest and T.I.Wrigley, *J.Chem.Soc.* 4765 (1957).

[14] A.Bowers, *J.Amer.Chem.Soc.* **81**, 4107 (1959).

[15] S.Nakanishi, K.Morita and E.V.Jensen, *ibid.* **81**, 5259 (1959).

[16] B.M.Bloom, V.V.Bogert and R.Pinson,Jr., *Chemistry and Industry* 1317 (1959).

[17] O.Dimroth and W.Bockemüller, *Ber.* **64**, 516 (1931).

afforded 5α,6α-difluoropregnane-3β-ol-20-one acetate (II), m.p. 178-180°, $[\alpha]_D$ +100°.[18] Alkaline hydrolysis of II gave the corresponding 3β-alcohol (III) m.p. 221-223°, $[\alpha]_D$ +88°. Alternately, III was obtained by the direct treatment of pregnenolone with lead tetrafluoride. Oxidation of III with 8N-chromic acid[19] afforded 5α,6α-difluoropregnane-3,20-dione (IV) m.p. 224-226°, $[\alpha]_D$ +78°. Treatment of this fluoroketone with sodium acetate in methanol led smoothly to 6α-fluoroprogesterone (V), identical in every respect with an authentic sample.[2] Since 6β-fluoro-Δ^4-3-ketones are known to be stable to the conditions of this elimination reaction[14] it followed that the C-6 fluorine atom in IV and hence in II had the α-configuration. From both mechanistic and conformational considerations it followed that the C-5 fluorine atom also had the α-configuration.[20]

Molecular rotation data are in accord with the 5α,6α-stereochemistry of the difluoride, $[M]_D$ (compound II - pregnenolone) = +233.[21]

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[18] All rotations were carried out in chloroform and all new compounds analysed satisfactorily for C,H and F.

[19] K.Bowden, I.M.Heilbron, E.R.H.Jones and B.C.L.Weedon, J.Chem.Soc. 39 (1946).

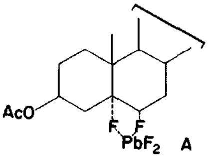
[20] For a detailed discussion of the course of halogen addition to a Δ^5-double bond cf. A.Bowers, E.Denot and R.Becerra, J.Amer.Chem.Soc. in press.

[21] cf. $[M]_D$ (5α,6α-dichlorocholestane-3β-ol - cholesterol) = +160, and $[M]_D$ (5β,6α-dibromocholestane-3β-ol - cholesterol) = +413. D.H.R.Barton and E.Miller, J.Amer.Chem.Soc. 72, 370 and 1066 (1950).

[22] cf.ref. 21 where the stability of 5α,6β-trans dichlorides towards base treatment is discussed.

Further evidence for the cis orientation of the fluorine atoms follows from the instability of II towards alkali. Treatment of II under reflux for 1 hour with 1% methanolic potassium hydroxide solution afforded an amorphous mixture which no longer contained fluorine. A trans-difluoro compound would not be expected to lose fluorine as readily.[22]

This appears to be the first demonstration of cis addition of fluorine to an olefin[23] and presumably it proceeds via a transition state such as A.



A

Although I was stable to anhydrous hydrogen fluoride at low temperature it was observed that in the presence of a proton acceptor such as tetrahydrofuran addition of HF to the double bond took place and afforded 5α-fluoropregnane-3β-ol-20-acetate (VI)[24] m.p. 194-196°, $[\alpha]_D$ +86°. The corresponding 3β-alcohol (VII) had m.p. 188-189°, $[\alpha]_D$ +109° and upon oxidation afforded 5α-fluoropregnane-3,20-one (VIII) m.p. 204-205°, $[\alpha]_D$ +100°. Sodium acetate in methanol treatment of VIII smoothly afforded progesterone.

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[23] The original work of Dimroth and Bockemüller with PbF_4 and 1:1-diphenylethylene was later shown to involve molecular rearrangements, cf. J.Bornstein and M.Borden, Chemistry and Industry 441 (1958).

[24] The configuration assigned to the fluorine atom was made by analogy with the known course of addition of hydrogen chloride to a Δ^5-steroid; cf. L.F.Fieser and M.Fieser Steroids. Reinhold Publishing Corp., New York, 1959, p. 33.