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Preparation of 2,2-Difluoro- and 2,2,4α-Trifluoro-steroids by the Reaction of Enamines with Perchloryl Fluoride

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The reaction of fluorinated steroidal enamines with perchloryl fluoride furnished 2,2-difluoro- and 2,2,4α-trifluorinated steroids. Changes in infrared absorption frequency due to the introduction of fluorine are discussed.

Keywords——fluorination of enamines; 2,2-difluoro-steroids; 2,2,4α-trifluoro-steroids; perchloryl fluoride; IR-carbonyl shift; molecular rotation

Reaction of steroidal enamines with perchloryl fluoride provides a convenient method for the introduction of a fluorine substituent adjacent or vinylogous to the carbonyl group.[2–5)] When fluorinated steroids which are capable of forming enamines are further treated with perchloryl fluoride, polyfluorinated steroids were obtained. Changes in infrared carbonyl absorption frequency as well as in molecular rotation values due to the introduction of one, two, or three fluorine atoms are significant as shown in Table I. Introduction of one fluorine atom results in a 26—30 cm^{-1} shift of carbonyl absorption to higher frequency relative to those of the nonfluorinated parent compounds. Further shifts of 17—21 cm^{-1} were

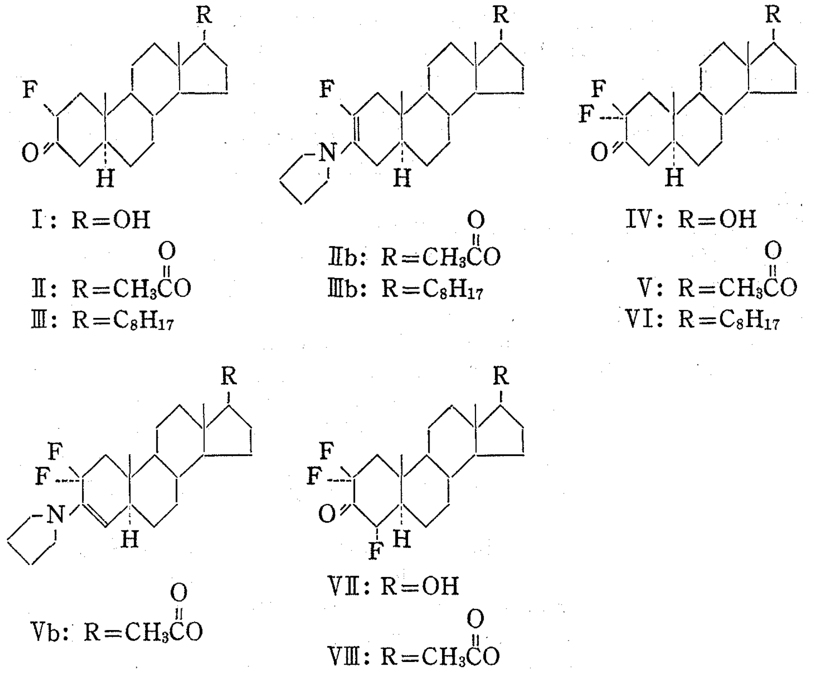

Chart 1

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[1] Location: *Chicago, Illinois 60637, U.S.A.*; *a*) Present address: *Pfizer Medical Research Laboratories, Groton, Connecticut 06340.*

[2] S. Nakanishi, K. Morita, and E.V. Jensen, *J. Am. Chem. Soc.*, **81**, 5259 (1959).

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observed by introduction of a second or a third fluorine atom such as between monofluorinated and difluorinated or difluorinated and trifluorinated steroids as listed in Table I. It was also noted that polyfluorinated steroids have tendencies to form hydrates, presumably by hydrogen bonding.

Experimental[6]

17β-Acetoxy-2-fluoro-5α-androst-2-ene-3-one 3-(N-Pyrrolidyl)enamine (IIb)——In an Erlenmeyer flask, 17β-acetoxy-2α-fluoro-5-androstan-3-one (II),[2] 2.7 g, was dissolved in 30 ml of methanol containing 3 drops of pyrrolidine and the solution was brought to boil, then 5 ml of pyrrolidine was added and the resulting mixture was boiled for 3 minutes and the formed crystalline enamine was precipitated out, filtered and washed with methanol and dried overnight *in vacuo* to give enamine IIb 2.56 g (83%), mp 171—173°. *Anal.* Calcd. for $C_{25}H_{38}FNO_2$: C, 74.40; H, 9.49; F, 4.71; N, 3.47. Found: C, 74.54; H, 9.29; F, 4.76; N, 3.61.

17β-Acetoxy-2,2-difluoro-5α-androstan-3-one (V)——A solution of IIb (2.5 g) in 500 ml of anhydrous ether and 25 ml of pyridine was cooled to 0°, then perchloryl fluoride was bubbled for 5 minutes. After removing excess perchloryl fluoride by water pump for 10 min, it was diluted with water, acidified with concentrated HCl and extracted with ether. The ethereal solution was washed with water, sodium bicarbonate solution and saturated sodium chloride solution and dried over magnesium sulfate. Evaporation of ether gave 2.22 g (97%) of crude V, mp 115—121°, which was further purified using 150 g of Florisil column prepared in *n*-pentane. Elutions with methylene dichloride and ether (9: 1) gave purified V, mp 140—141°, $[\alpha]_D^{25}$ +25° (c=1, chloroform), ν_{max}^{KBr} cm^{-1}: 1745 (C=O). *Anal.* Calcd. for $C_{21}H_{30}F_2O_3$: C, 68.45; H, 8.21; F, 10.31. Found: C, 68.69; H, 8.19; F, 10.21.

17β-Hydroxy-2,2-difluoro-5α-androstan-3-one (IV)——To a solution of V (700 mg) in 100 ml of methanol and 1 ml of concentrated hydrochloric acid was added and the solution was kept overnight (18 hours) at room temperature. Evaporation of methanol gave the residue of 620 mg, mp 112—124°, which was purified using 20 g of Florisil column prepared in *n*-pentane. Elutions with methylene dichloride gave crude product of 593 mg (95%), mp 101—109°. Upon repeated recrystallizations from *n*-hexane and methylene dichloride gave 354 mg (57%) of IV, mp 114—115°. ν_{max}^{KBr} cm^{-1}: 1744 (C=O), $[\alpha]_D^{25}$ +37° (c=1, chloroform). *Anal.* Calcd. for $C_{19}H_{28}F_2O_2$: C, 69.91; H, 8.65; F, 11.64. Found: C, 69.74; H, 8.68; F, 11.58.

17β-Acetoxy-2,2-difluoro-5α-androst-3-ene-3-one 3-(N-Pyrrolidyl)enamine (Vb)——A solution of V (737 mg) in 20 ml of absolute methanol containing 2 drops of pyrrolidine was warmed to boil and 3 ml of pyrrolidine was added and the mixture was boiled for 5 min. Upon cooling crystalline was formed which was filtered and washed with methanol and was dried *in vacuo* overnight to give enamine Vb 837 mg (99%), mp 214—215°. *Anal.* Calcd. for $C_{25}H_{37}F_2NO_2$: C, 71.23; H, 8.85; F, 9.01; N, 3.32. Found: C, 72.88; H, 8.86; F, 8.85; N, 3.27.

17β-Acetoxy-2,2,4α-trifluoro-5α-androstan-3-one (VIII)——Experiment 1: A mixture of 3-(N-pyrrolidyl)enamine Vb (600 mg) in 100 ml of anhydrous ether and 5 ml of dry puridine was cooled to 0°, then perchloryl fluoride was bubbled for 5 min. After taking off excess perchloryl fluoride by water pump for 10 min, the reaction mixture was diluted with water, acidified with 6 ml of concentrated HCl, extracted with ether, washed with water, sodium bicarbonate solution and salt water, and was dried over magnesium sulfate, filtered and evaporated to give crude product #A 501 mg (91%), mp 158—166°. *Anal.* Calcd.: F, 14.75. Found: F, 13.33. #A (490 mg) was purified using 20 g of Florisil column prepared in *n*-pentane. Elutions with methylene dichloride gave 298 mg, mp 174—185°, which was recrystallized from methylene dichloride–*n*-hexane to give 52 mg of 3-hydrate of VIII, mp 201—202°, which infrared spectrum (IR) showed hydroxyl group and diminishing 3-CO. *Anal.* Calcd. for $C_{21}H_{29}F_3O_3 \cdot H_2O$: C, 62.36; H, 7.73; F, 14.09. Found: C, 62.86; H, 8.01; F, 13.62.

Experiment 2: A solution of 3-(N-pyrrolidyl)enamine Vb (230 mg) in 60 ml of anhydrous ether and 3 ml of dry pyridine was treated with perchloryl fluoride for 5 min at 0°. After removing excess perchloryl fluoride by water pump for 5 min, the reaction mixture was diluted with about 200 ml of water, acidified with 5 ml of concentrated HCl, extracted with ether, washed with water, sodium bicarbonate and salt water, and dried over magnesium sulfate, filtered and evaporated to give 213 mg, mp 156—164°, which was purified using 8 g of Florisil column prepared in *n*-pentane. Elutions with methylene dichloride gave 94 mg of crude compound of VIII, mp 180—184°. After repeated recrystallizations from methylene dichloride and *n*-heptane gave an analytical sample of 17β-acetoxy-2,2,4α-trifluoro-5α-androstan-3-one VIII, mp 184—185°.

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[6] Comparative nuclear magnetic resonance (NMR) studies on the compound (IIb), (IV), (IVb), (V), (VI), and (VIII) against the enamines of 3-keto-5α-steroids,[4] and 4-mono- and 4,4-difluorinated steroids[4] as well as 2α-fluoro-steroids[2] have kindly been carried out by Dr. George Slomp of Upjohn Co., which are in agreement with the structures assigned. The details of the NMR spectroscopic studies will be published elsewhere.

Anal. Calcd. for $C_{21}H_{29}F_3O_3$: C, 65.26; H, 7.56; F, 14.75. Found: C, 65.55; H, 7.89; F, 14.69. $[\alpha]_D^{25}$ +15° (c=1, chloroform), ν_{max}^{KBr} cm^{-1}: 1765 (C=O).

17β-Hydroxy-2,2,4α-trifluoro-5α-androstan-3-one (VII)——Hydrolysis of VIII (1.11 g) in 200 ml of absolute methanol and 2 ml of conc. HCl at room temperature for 17 hr gave 985 mg of crude VII, mp 120—136°, which was purified using 30 g of Florisil column. Elutions with methylene dichloride–ether (8:2) gave 764 mg of crude hydrate-VII. Repeated recrystallization from benzene and n-heptane containing a trace of conc. HCl gave 413 mg (42%) of the pure 17β-hydroxy-2,2,4α-trifluoro-5α-androstan-3-one VII, mp 111—112°. *Anal.* Calcd. for $C_{19}H_{27}F_3O_2$: C, 66.26; H, 7.90; F, 16.55. Found: C, 66.02; H, 8.03; F, 16.61. $[\alpha]_D^{25}$ +22° (c=1, chloroform) ν_{max}^{KBr} cm^{-1}: 1765 (C=O).

Preparation of 3-(N-Pyrrolidyl)enamine (IIIb)——2α-Fluoro-5α-cholestan-3-one,[2] 410 mg, was dissolved in 30 ml of methanol containing a small drop of pyrrolidine and the solution was brought to boil, then 0.8 ml of pyrrolidine was added and boiled for 3 min. The formed crystalline enamine was filtered, washed with cold methanol, dried overnight *in vacuo* to give 392 mg (85%) of 2α-fluoro-5α-cholestan-3-one 3-(N-pyrrolidyl)enamine IIIb, mp 111—112°, $[\alpha]_D^{25}$ +41° (c=1, chloroform). *Anal.* Calcd. for $C_{31}H_{52}FN$: C, 81.34; H, 11.45; F, 4.15. Found: C, 80.87; H, 11.55; F, 4.18; N, 3.09.

TABLE I. Changes of Carbonyl Absorption Frequency in Infrared Absorption Spectroscopy and Molecular Rotation Values[f] Resulted from Introduction of Fluorine

Compounds	$\nu_{3C=O}^{KBr}$ (cm^{-1})[a]	$[M]_D$[a]	$\nu_{3C=O}^{KBr}$[b]	$[M]_D$[b]	$\Delta\nu$ 3C=O[c]	$\Delta[M]_D$[c]	$\Delta\nu$ 3C=O[d]	$\Delta[M]_D$[d]	$\Delta\nu$ 3C=O[e]	$\Delta[M]_D$[e]
17β-Hydroxy-2α-fluoro-5α-androstan-3-one (I)	1727	+191°	1697	+93°	+28	+98°	+17	−30°	+21	−45°
17β-Acetoxy-2α-fluoro-5α-androstan-3-one (II)	1725	+207	1695	+86	+27	+121	+20	−115	+20	−34
2α-Fluoro-5α-cholestan-3-one (III)	1727	+243	1701	+158	+26	+85	+19	−181	—	—
17β-Hydroxy-2,2-difluoro-5α-androstan-3-one (IV)	1744	+121	—	+93	+45	+28				
17β-Acetoxy-2,2-difluoro-5α-androstan-3-one (V)	1745	+92	—	+86	+47	−6				
2,2-Difluoro-5α-cholestan-3-one (VI)	1746	+72	—	+158	+45	−86				
17β-Hydroxy-2,2,4α-trifluoro-5α-androstan-3-one (VII)	1765	+76	—	+93	+66	−17				
17β-Acetoxy-2,2,4α-trifluoro-5α-androstan-3-one (VIII)	1765	+58	—	+86	+67	−27				

a) Fluorinated compounds. b) Non-fluorinated parent compounds. c) Differences.
d) Differences between mono-fluorinated and difluorinated compounds.
e) Differences between difluorinated and trifluorinated compounds.
f) $[M]_D$=Molecular Rotation; C. Djerassi, *J. Org. Chem.*, 12, 823 (1947).

2,2-Difluoro-5α-cholestan-3-one (VI)——Treatment of IIIb (330 mg) in 100 ml ot anhydrous ether and 5 ml of dry pyridine at 0° with perchloryl fluoride and working up in the same manner, there was obtained 304 mg of crude VI, mp 140—152°. Florisil chromatography of 280 mg gave a fraction eluted with n-pentane and methylene dichloride (7:3), which was recrystallized from n-hexane to give 128 mg (42%) of 2,2-difluoro-5α-cholestan-3-one VI, mp 106—107°, $[\alpha]_D^{25}$ +17° (c=1, chloroform), ν_{max}^{KBr} cm^{-1}: 1746 (C=O). *Anal.* Calcd. for $C_{27}H_{44}F_2O$: C, 76.73; H, 10.49; F, 8.99. Found: C, 76.29; H, 10.49; F, 8.74.