970. *Steroids. Part XIV.* Some 3β-Fluoro-steroids.*

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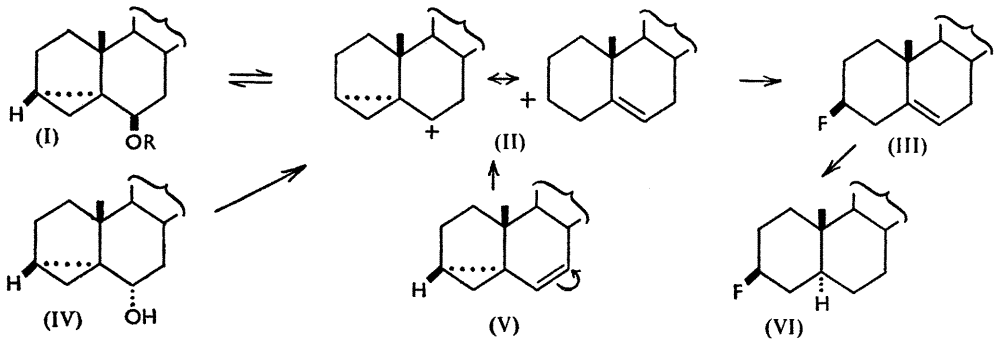
3 : 5-*cyclo*Stan-6-ols are rearranged by hydrofluoric acid in benzene to the appropriate 3β-fluoro-steroids.

It was found by Heilbron, Beynon, and Spring [1] and by Wallis and Ford [2] that 3 : 5-*cyclo*cholestan-6β-ol, its methyl ether, and its acetate (I; R = H, Me, or Ac), on treatment with hydrogen chloride, bromide, or iodide in acetic acid at 20° readily afford the mesomeric cation (II) [3-6] which, under these conditions, by thermodynamic control of the equilibria,[6]

* Part XIII, *J.*, 1957, 3107.

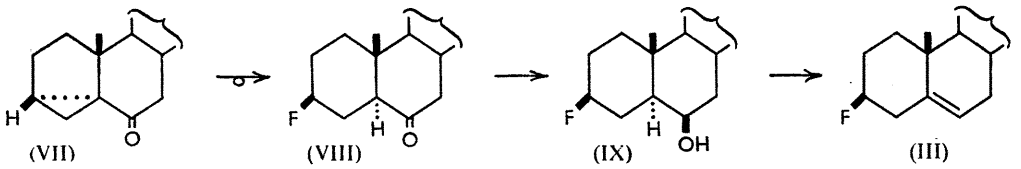
[1] Heilbron, Beynon, and Spring, *J.*, 1936, 907; 1937, 1459.
[2] Wallis and Ford, *J. Amer. Chem. Soc.*, 1937, **59**, 1415.
[3] Dodson and Riegel, *J. Org. Chem.*, 1948, **13**, 424.
[4] Winstein and Adams, *J. Amer. Chem. Soc.*, 1948, **70**, 838; Winstein and Schlesinger, *ibid.*, p. 3528; Winstein and Kosower, *ibid.*, 1956, **78**, 4347.
[5] Wagner and Wallis, *ibid.*, 1950, **72** 1047; Wagner, Wolff, and Wallis, *J. Org. Chem.*, 1952, **17**, 529; Wolff and Wallis, *ibid.*, p. 1361.
[6] Shoppee and Summers, *J.*, 1952, 3361; Shoppee and Williams, *J.*, 1956, 2488.

gives the appropriate cholesteryl halide (as III) in high yield. Similarly, 3 : 5-*cyclo*-cholestan-6α-ol [5, 6] (IV) and 3 : 5-*cyclo*cholest-6-ene [7] (V) with hydrogen chloride, bromide, or iodide in acetic acid at 20° furnish the cholesteryl halides in good yield. Some seven



years ago we applied these methods to the preparation of cholesteryl fluoride (III), and we now record this and two other examples.

3 : 5-*cyclo*-5α-Cholestan-6β-ol (I; R = H) with 40% hydrofluoric acid in benzene gives cholesterol (22%) and cholesteryl fluoride (III) (76%), hydrogenated with platinum in ethyl acetate containing a trace of perchloric acid to cholestanyl fluoride (VI). Use of hydrofluoric acid in acetic acid gave only cholesteryl acetate. Cholesteryl fluoride was also obtained from 6β-methoxy-3 : 5-*cyclo*cholestane (I; R = Me) and from 3 : 5-*cyclo*cholestan-6α-ol (IV) by treatment with hydrofluoric acid in ether–acetic acid. 6β-Methoxy-3 : 5-*cyclo*cholestane (I; R = Me) has recently been converted by treatment with anhydrous hydrogen fluoride in acetic acid into cholesteryl fluoride (III), accompanied by cholesteryl acetate, by Jacobsen and Jensen [8] who, using silver fluoride in xylene–methyl cyanide, also obtained cholesteryl fluoride from cholesteryl iodide by substitution (S_N1) with retention of configuration, as the result of participation by the π-electrons of the double bond.

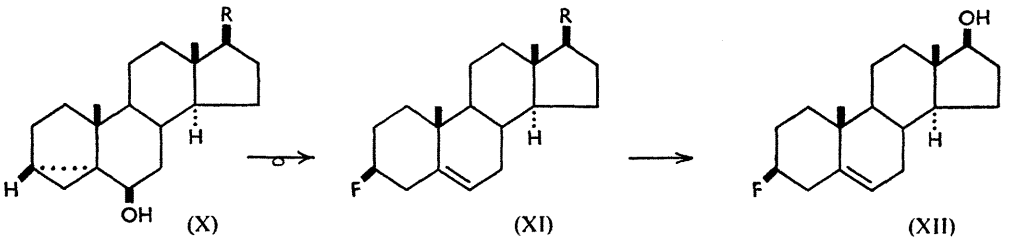


Cholesteryl fluoride was obtained on a single occasion from 3 : 5-*cyclo*cholestan-6-one (VII) by treatment with hydrofluoric acid in ether–acetic acid, reduction of the resulting product (VIII?) with lithium aluminum hydride in ether, and dehydration of the material so produced (IX?) with phosphorus oxychloride–pyridine.[9, 10] Satisfactory analyses of the intermediates could not be obtained, and several attempts to repeat the procedure were unsuccessful; the 3 : 5-*cyclo*-ketone (VII) is unchanged by hydrofluoric acid in benzene, and with hydrofluoric acid in acetic acid appears to yield only 3β-acetoxycholestan-6-one.

Solvolysis of 3β-toluene-*p*-sulphonyloxypregn-5-en-20-one [11] with aqueous acetone in presence of potassium acetate yields 6β-hydroxy-3 : 5-*cyclo*pregnan-20-one [11] (X; R = Ac). Treatment of this and of 6β-hydroxy-3 : 5-*cyclo*androstan-17-one (X; R = O) [12]

[7] Riegel, Hager, and Zenitz, *J. Amer. Chem. Soc.*, 1946, **68**, 2562.
[8] Jacobsen and Jensen, *Chem. and Ind.*, 1957, 172.
[9] Shoppee, Reilly Lectures, Univ. of Notre Dame, 1951.
[10] Shoppee and Summers, *J.*, 1952, 1786.
[11] Butenandt and Grosse, *Ber.*, 1937, **70**, 1446; Karrer, Asmis, Sareen, and Schwyzer, *Helv. Chim. Acta*, 1951, **34**, 1022; Patel, Petrow, and Stuart-Webb, *J.*, 1957, 665.
[12] Butenandt and Suranyi, *Ber.*, 1942, **75**, 591; Dingemanse, Huis in't Veld, and Hartogh-Katz, *Nature*, 1948, **162**, 492; Barton and Klyne, *ibid.*, p. 493.

with hydrofluoric acid in benzene gives 3β-fluoropregn-5-en-20-one (XI; R = Ac), accompanied by pregnenolone, and 3β-fluoroandrost-5-en-17-one (XI; R = O) respectively. These compounds have also been prepared by Jacobsen and Jensen [8] from 3β-iodopregn-5-en-20-one and 3β-iodoandrost-5-en-17-one by reaction with silver fluoride.



(X) (XI) (XII)

By reduction with lithium aluminium hydride or sodium borohydride, 3β-fluoroandrost-5-en-17-one affords 3β-fluoroandrost-5-en-17β-ol (XII).

Experimental

For general directions see *J.*, 1957, 3107. $[\alpha]_D$ are in $CHCl_3$.

3β-*Fluorocholest-5-ene.*—(*a*) 3 : 5-*cyclo*Cholestan-6β-ol (m. p. 74°; 1 g.) in benzene (30 c.c) was treated with 40% hydrofluoric acid (20 c.c.) in a Polythene flask at 20° for 4 hr. The mixture was poured into 4N-sodium hydroxide, and the product extracted with ether and worked up in the usual way to give an oil, which was chromatographed on aluminium oxide (Spence type H, activity ~II; 30 g.). Elution with pentane gave 3β-fluorocholest-5-ene (760 mg.), m. p. 94—96°, $[\alpha]_D$ −45·5° (*c* 1·4), after recrystallisation from acetone (cf. ref. 8) (Found: C, 83·4; H, 11·4. Calc. for $C_{25}H_{45}F$: C, 83·45; H, 11·65%), giving a yellow colour with tetranitromethane and a negative Beilstein test; elution with ether gave cholesterol (224 mg.), m. p. and mixed m. p. 148° after recrystallisation from ethyl acetate. When 3 : 5-*cyclo*cholestan-6β-ol (835 mg.) was treated similarly in "AnalaR" acetic acid (30 c.c.), the sole product appeared to be cholesteryl acetate; it was hydrolysed with hot 5N-methanolic potassium hydroxide for 0·5 hr. and the resulting solid chromatographed on aluminium oxide (25 g.); elution with pentane gave a trace of oil (8 mg.), and elution with chloroform gave cholesterol (823 mg.), m. p. and mixed m. p. 146—148°.

(*b*) 6β-Methoxy-3 : 5-*cyclo*cholestane (m. p. 79°) in ether was treated with 40% hydrofluoric acid and a little acetic acid added to give a homogeneous solution. The usual working up gave 3β-fluorocholest-5-ene, m. p. 94° after crystallisation from ethanol.

(*c*) 3 : 5-*cyclo*Cholestan-6α-ol (m. p. 79—80°) by similar treatment with 40% hydrofluoric acid in ether containing acetic acid gave 3β-fluorocholest-5-ene, m. p. 91—94°, and cholesteryl acetate; the latter was separated by hydrolysis to cholesterol followed by chromatography on aluminium oxide.

(*d*) 3 : 5-*cyclo*Cholestan-6-one (m. p. 96°; 450 mg.) in ether containing acetic acid with 40% hydrofluoric acid gave, on a single occasion by the usual working up, a substance, m. p. 136° after crystallisation from acetone (Found: C, 62·5; H, 8·4%), converted by treatment with lithium aluminium hydride in ether at 36° into a substance, m. p. 110° after crystallisation from methanol–ethyl acetate (Found: C, 63·5; H, 8·9%), which was dehydrated by phosphorus oxychloride in pyridine at 20° to 3β-fluorocholest-5-ene, m. p. and mixed m. p. 90—94°. Attempts to repeat this preparation of the substance, m. p. 136°, with new specimens of hydrofluoric acid in acetic acid invariably gave 3β-acetoxycholestan-6-one, m. p. 129—130°. When 3 : 5-*cyclo*cholestan-6-one (1·7 g.) was treated with 40% hydrofluoric acid (20 c.c.) in benzene (20 c.c.) for 24 hr. and the product chromatographed on aluminium oxide (60 g.) to give seven fractions by elution with pentane, benzene–pentane (1 : 9), and benzene, all fractions had m. p. 94—96°, with $[\alpha]_D$ +41° (*c* 1·8), +39° (*c* 1·2), and +40° (*c* 1·4) for fractions 1, 4, and 7 respectively, and consisted of unchanged 3 : 5-*cyclo*cholestan-6-one.

3β-*Fluorocholestane.*—3β-Fluorocholest-5-ene (200 mg.), in ethyl acetate (20 c.c.) containing 4 drops of 60% perchloric acid, was hydrogenated with platinum oxide (70 mg.). Reduction was complete in 5 min. and the usual working up gave an oil which crystallised. To remove any unsaturated material the product was warmed with a 2% solution of chromium trioxide in

acetic acid (7 c.c.) at 60° for 0·5 hr.; [13] the saturated material was extracted with ether, washed with 2N-sodium carbonate and with water, and dried. The product (196 mg.), in pentane, was filtered through aluminium oxide and crystallised from acetone, to give 3β-*fluorocholestane*, m. p. 80—82°, $[\alpha]_D$ +23° (*c* 1·0) (Found: C, 82·75; H, 11·8. $C_{27}H_{47}F$ requires C, 83·0; H, 12·1%).

3β-*Fluoropregn-5-en-20-one*.—Solvolysis of 3β-toluene-*p*-sulphonyloxypregn-5-en-20-one (m. p. 141°) [11] with aqueous acetone in presence of potassium acetate furnished 6β-hydroxy-3 : 5-*cyclo*pregnan-20-one, m. p. 181—182°, $[\alpha]_D$ +124° (*c* 1·0), after crystallisation from acetone. The 3 : 5-*cyclo*-alcohol (440 mg.) in benzene (20 c.c.) with 40% hydrofluoric acid (10 c.c.) at 20° for 4 hr., after the usual isolation procedure, gave 3β-fluoropregn-5-en-20-one (295 mg.), m. p. 170—172° (lit.,[8] m. p. 164—165°), $[\alpha]_D$ +114° (*c* 1·27) after recrystallisation from acetone (Found: C, 79·1; H, 9·5. Calc. for $C_{21}H_{31}OF$: C, 79·2; H, 9·8%), and 3β-hydroxypregn-5-en-20-one, m. p. and mixed m. p. 192—194°, which were separated by chromatography on aluminium oxide and elution with benzene and chloroform, respectively.

3β-*Fluoroandrost-5-en-17-one*.—6β-Hydroxy-3 : 5-*cyclo*androstan-17-one [12] (m. p. 140°; 734 mg.) in benzene (20 c.c.) was treated with 40% hydrofluoric acid at 20° for 3 hr. The usual working up gave a solid, which was purified by chromatography on aluminium oxide (20 g.); elution with benzene gave 3β-fluoroandrost-5-en-17-one (506 mg.), m. p. 154—155°, $[\alpha]_D$ −19° (*c* 1·0), after crystallisation from ethyl acetate and recrystallisation from acetone (Found: C, 78·4; H, 9·5. Calc. for $C_{19}H_{27}OF$: C, 78·6; H, 9·3%) (cf. ref. 8). Elution with ether gave 3β-hydroxyandrost-5-en-17-one, m. p. 153° (260 mg.).

3β-*Fluoroandrost-5-en-17β-ol*.—3β-Fluoroandrost-5-en-17-one (60 mg.) was reduced with lithium aluminium hydride in ether at 36° for 15 min. The solid product, isolated in the usual manner, by recrystallisation from acetone, gave 3β-*fluoroandrost-5-en-17β-ol*, m. p. 160—162°, $[\alpha]_D$ −60° (*c* 0·8) (Found: C, 78·0; H, 9·7. Calc. for $C_{19}H_{29}OF$: C, 78·05; H, 10·0%) (cf. ref. 8).

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[13] Shoppee, *J.*, 1946, 1151.