Fluorinated Sterols. Part I. 26,26,26,27,27,27-Hexafluorodesmosterol

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The synthesis of hexafluorodesmosterol (VIII) by a Wittig condensation between a steroidal triphenylphosphonium ylide and hexafluoroacetone is described. The 24,25-double bond in structure (VIII) is resistant to hydrogenation over palladium and to hydroboration.

It is not established at what point the 24,25-double bond of lanosterol is saturated in the overall process of conversion into cholesterol. Desmosterol (cholesta-5,24-dien-3β-ol), isolated from chick embryo, has been shown to be converted into cholesterol,[1] and may be an intermediate in its biosynthesis. It is therefore of interest to synthesise sterols in which the reactivity of the 24,25-double bond has been altered and to observe whether these compounds interfere with the biosynthesis of cholesterol.

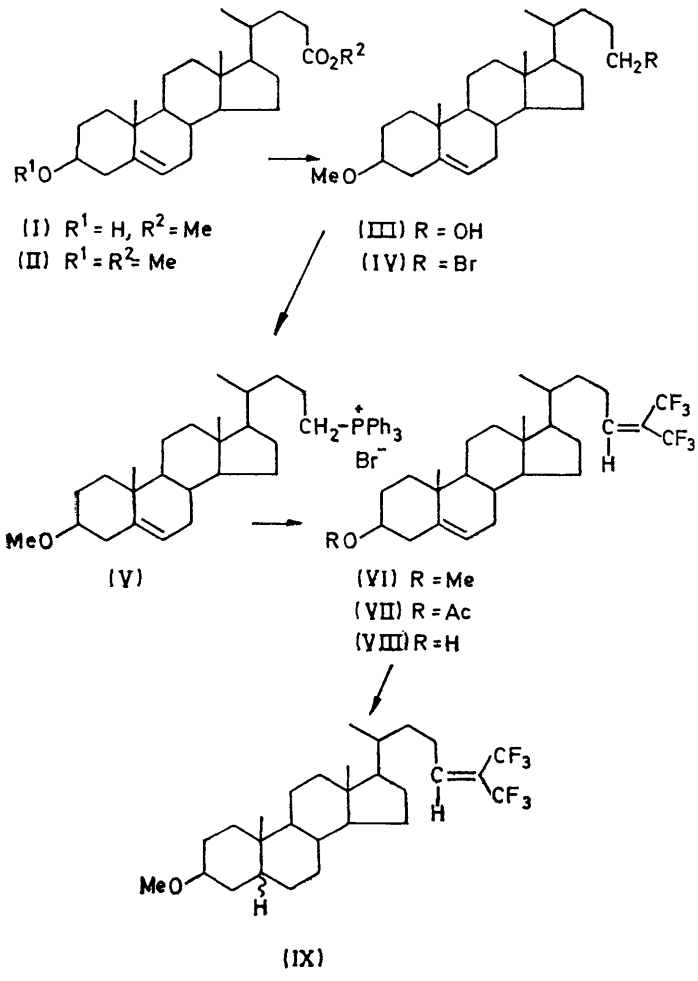
Although fluorine has been introduced into several positions in corticoids and progesterones, resulting in important enhancements and changes in biological activities,[2] no fluorine-containing sterols have so far been synthesised. We decided to utilise the steroidal triphenylphosphonium salts[3] as intermediates in a Wittig condensation with fluorinated acetone, to synthesise the title compound.

The availability of an efficient method for the cleavage of methyl ethers in the homoallylic 5-en-3β-ol system[4] induced us to prefer this stable group for protecting the 3β-OH to the tetrahydropyranyl ether; the *O*-tetrahydropyranyl compound could only be obtained in poor yield. The alcohol (III), obtained by hydride reduction of the ester (II) was converted into the bromide (IV) with triphenylphosphine and tetrabromomethane in dry ether.[5] The bromide (IV) gave the triphenylphosphonium bromide (V) on refluxing with triphenyl phosphine in dimethylformamide. The ylide obtained from the phosphonium salt with phenyl-lithium condensed with hexafluoroacetone to yield hexafluorodesmosterol methyl ether (VI), which on treatment with boron trifluoride–ether and acetic anhydride[4] gave the acetate (VII). Transesterification of (VII) in methanol in the presence of toluene-*p*-sulphonic acid finally yielded the free 26,26,26,27,27,27-hexafluorodesmosterol

[1] W. M. Stocker, W. A. Fish, and F. C. Hickey, *J. Biol. Chem.*, 1956, **220**, 415.
[2] L. F. Fieser and M. Fieser, ' Steroids,' Reinhold, New York, 1959, p. 682.
[3] J. E. Herz and S. Cruz Montalvo, *Steroids*, 1971, **17**, 649.
[4] C. R. Narayanan and K. N. Iyer, *J. Org. Chem.*, 1965, **30**, 1734.
[5] I. M. Downie, J. B. Holmes, and J. B. Lee, *Chem. and Ind.*, 1966, 900; J. Hooz and S. S. H. Gilani, *Canad. J. Chem.*, 1968, **46**, 86.

(VIII), δ 6·75 (t, olefinic C-24 proton) and 5·4 (broad, olefinic C-5 proton).

Attempted selective hydrogenation of the 24,25-double bond of (VI) over palladium–carbon showed this double bond to be much less reactive than the 22,23-double bond in stigmasterol. When the ether (VI) was



treated with diborane and the resulting organoborane was refluxed with propionic acid,[6] the 5,6-double bond was saturated preferentially, the product showing no n.m.r. peak at δ 5·4 but an unchanged triplet at δ 6·7.

EXPERIMENTAL

M.p.s were taken with a Kofler hot-stage apparatus and are corrected. Optical rotations were determined for solutions in chloroform with a Perkin-Elmer 141 Polarimeter. N.m.r. spectra were determined for solutions in deuteriochloroform with a Varian A60 spectrophotometer.

Methyl 3β-Methoxychol-5-en-24-oate (II).—Methyl 3β-hydroxychol-5-en-24-oate (I) (500 mg) was dissolved in trimethyl orthoformate (5 ml) and 70% perchloric acid (0·3 ml). After 2 h stirring at room temperature a solution of sodium hydrogen carbonate was added dropwise (to pH 7·0), ether was added, and the ethereal solution was washed with water and evaporated. The residue crystallised from methanol to give the methyl ether (II), m.p. 107—109 °C, $[\alpha]_D$ −46·1° (lit.,[7] m.p. 109 °C, $[\alpha]_D$ −49·6°).

3β-Methoxychol-5-en-24-ol (III).—To a solution of the ester (II) (3 g) in dry tetrahydrofuran (24 ml) was added slowly and with stirring a solution (70%; 1 ml, 0·5 equiv.) of sodium hydridobis-(2-methoxyethoxy)aluminate in benzene. After refluxing for 1 h, the excess of reagent was destroyed and the *product* (84%) was precipitated in ice–water; m.p. 149—150 °C (from acetone), $[\alpha]_D$ −45·3° (Found: C, 80·15; H, 11·25. $C_{25}H_{42}O_2$ requires C, 80·15; H, 11·3%).

24-Bromo-3β-methoxychol-5-ene (IV).—To a solution of the alcohol (III) (1·8 g) and carbon tetrabromide (2·7 g) in dry diethyl ether (100 ml) was added, with stirring at room temperature, a solution of triphenylphosphine (2·15 g) in dry ether (20 ml). The mixture was stirred overnight with exclusion of moisture. The precipitate was filtered off and the filtrate evaporated to dryness. The residue was partitioned between 90% aqueous methanol and light petroleum. The petroleum layer was evaporated and the residue crystallised from acetone to give the *bromide* (69%), m.p. 117—118 °C, $[\alpha]_D$ −46·9° (Found: C, 68·9; H, 9·25; Br, 18·55. $C_{25}H_{41}BrO$ requires C, 68·65; H, 9·45; Br, 18·25%).

3β-Methoxychol-5-en-24-yl(triphenyl)phosphonium Bromide (V).—A solution of the bromide (IV) (1 g) and triphenylphosphine (0·6 g) in dry dimethylformamide (20 ml) was refluxed for 36 h under nitrogen. The *salt* (74%) was precipitated with ether, filtered off, and washed with ether; m.p. 189 °C, $[\alpha]_D$ −23·9° (Found: C, 73·55; H, 8·25; Br, 11·75; P, 4·15. $C_{43}H_{56}BrOP$ requires C, 73·8; H, 8·05; Br, 11·4; P, 4·4%).

26,26,26,27,27,27-Hexafluoro-3β-methoxycholesta-5,24-diene (VI).—To a suspension of the salt (V) (1 g) in dry ether (20 ml) was added dropwise, under nitrogen, 1M-phenyllithium in benzene–ether (3 ml), until a deep red solution of the ylide was obtained. After 1 h, hexafluoroacetone was bubbled into the solution until the latter became slightly decoloured and precipitation began. The solution was then stirred overnight; the solvent was evaporated off in a stream of dry nitrogen and replaced with dry tetrahydrofuran. The mixture was refluxed for 6 h, then evaporated, and the residue was extracted with petroleum. The extract was washed with 90% aqueous methanol, then evaporated, and the product was chromatographed on neutral alumina. The fraction containing *compound* (VI) (68%) was eluted with pentane; m.p. 70—71 °C (from acetone), $[\alpha]_D$ −26·8° (Found: C, 66·1; H, 7·95; F, 22·55. $C_{28}H_{40}F_6O$ requires C, 66·4; H, 7·95; F, 22·5%).

26,26,26,27,27,27-Hexafluorocholesta-5,24-dien-3β-yl Acetate (VII).—A solution of the hexafluoride (VI) (200 mg) in acetic anhydride (8 ml), boron trifluoride–ether (1·4 ml), and dry ether (3 ml) was left for 15 h at 0 °C. It was then added to ice–water, left for 4 h, and extracted with ether. The extract was washed, dried, and evaporated. The residue crystallised from acetone to yield the *acetate* (VII) (76%), m.p. 99 °C, $[\alpha]_D$ −35·9° (Found: C, 65·4; H, 7·75; F, 21·4. $C_{29}H_{40}F_6O_2$ requires C, 65·15; H, 7·55; F, 21·3%).

26,26,26,27,27,27-Hexafluorocholesta-5,24-dien-3β-ol (VIII).—A solution of the acetate (VII) (100 mg) and of toluene-*p*-sulphonic acid monohydrate (10 mg) in methanol (20 ml) was refluxed during 1 h under nitrogen. The

[6] H. C. Brown and K. Murray, *J. Amer. Chem. Soc.*, 1959, **81**, 4108.

[7] B. Riegel, M. F. W. Dunker, and M. J. Thomas, *J. Amer. Chem. Soc.*, 1942, **64**, 2115.

solvent was partially removed under vacuum and the solution added to ice–water. The product (83%) was extracted with ether and crystallised from acetone; m.p. 111—112 °C, $[\alpha]_D$ −20·2° (Found: C, 65·85; H, 7·85; F, 23·15%; M^+, 492·28273. $C_{27}H_{38}F_6O$ requires C, 65·85; H, 7·75; F, 23·15%; M, 492·28266), m/e 492 (M^+), 477 ($M - CH_3$), 474 ($M - H_2O$), 459 ($M - H_2O - CH_3$), and 455 ($M - H_2O - F$).

Attempted Reduction of the Ether (VI).—(*a*) To a solution of compound (VI) (200 mg) in anhydrous tetrahydrofuran (5 ml) was added, under nitrogen at 0 °C, 0·1M-diborane in tetrahydrofuran (5 ml).[6] After 4 h at 0 °C the solvent was removed and replaced with dry propionic acid (2 ml), and the mixture was refluxed for 1 h and added to ice–water. Extraction with ether gave material showing δ 6·75 (t, olefinic proton at C-24) but not the band at δ 5·4 (olefinic proton at C-5).

(*b*) A solution of compound (VI) (100 mg) in ethyl acetate (10 ml) containing 10% palladium–charcoal (100 mg) was agitated under hydrogen at room temperature. No hydrogen was absorbed and (VI) was recovered unchanged.

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