Synthesis of 2′,2′-Difluoro-6,7-dihydro-16-methylenecyclopropa[6,7]progesterone Analogues

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17α-Acetoxy-2′,2′,6β-trifluoro-6β,7β-dihydro-16-methylenecyclopropa[6,7]progesterone (9) and its Δ^1-analogue (10) have been synthesised by a ten-step reaction sequence from 3-hydroxy-16-methylpregna-5,16-dien-20-one (1).

VARIOUS recent studies have been devoted to the synthesis of new pregnanes containing a 16-methylene group.[1-5] High progestational activity is associated with this type of structure.[6] The synthesis of the 16-methylenecyclopropa[6,7]progesterones (9) and (10) was undertaken since these molecules present several

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[4] (*a*) T. L. Popper, F. E. Carlon, E. L. Shapiro, and R. Neri, *J. Medicin. Chem.*, 1971, **14**, 33; (*b*) T. L. Popper, H. P. Faro, F. E. Carlon, and H. L. Herzog, *ibid.*, 1972, **15**, 555.
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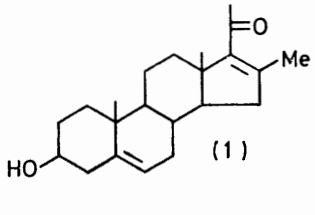
favourable structural features for potential progestational activity.[7] The 16-methylpregnadiene (1) [8] was chosen



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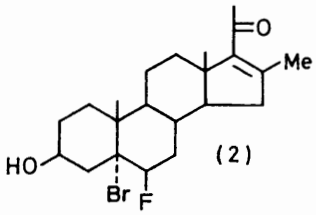

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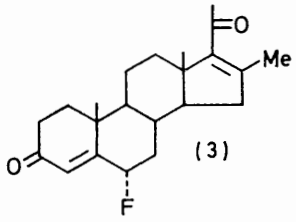

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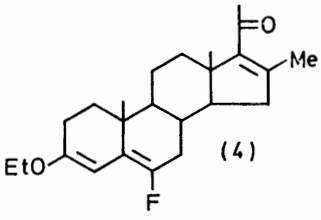

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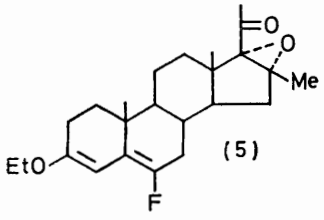

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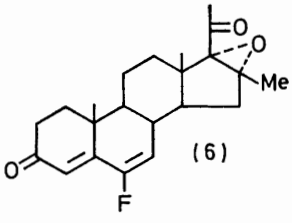

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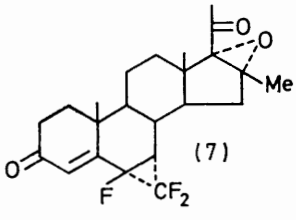

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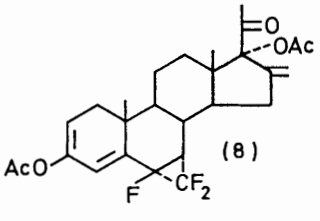

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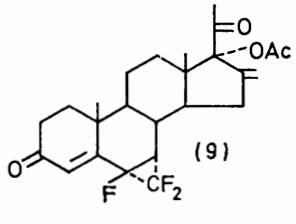

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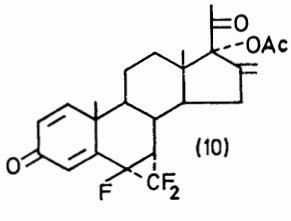

(10)

as starting material since it is readily available and already contains a C_1 substituent at C-16.

Treatment of compound (1) with *N*-bromoacetamide and hydrogen fluoride in the presence of tetrahydrofuran [9] resulted in selective addition of Br–F to the 5,6-double bond, thus affording the pregn-16-ene derivative (2) in high yield. Jones oxidation [10] of the 3-hydroxy-group, followed by brief treatment with acid, inducing both the expulsion of bromide ion and the inversion of the configuration of the fluorine substituent at C-6, provided the bis-enone (3), with strong u.v. absorption at 240 nm.

Reaction of compound (3) with ethyl orthoformate in the presence of a trace of acid afforded exclusively the enol ether of the ring A enone (4). With the Δ^4-3-ketone system protected as an enol system it was now possible to prepare selectively the 16,17-epoxide (5), by treatment of compound (4) with alkaline hydrogen peroxide. Bromination of the epoxide (5) with *N*-bromosuccinimide, followed by dehydrobromination with dimethylacetamide in the presence of sodium bromide, gave the dienone (6).

Difluorocarbene, generated by pyrolysis of sodium chlorodifluoroacetate,[7,11] was added to the 6,7-double bond of compound (6), to provide the adduct (7). The α-configuration of the difluorocyclopropane ring is established by the absence of long-range coupling between the CF_2 fluorine atoms and the 19-protons.[7,12]

Epoxide opening at C-16 was performed by treatment [13] of compound (7) with 5-sulphosalicylic acid in acetic anhydride, which caused simultaneous acetylation at C-17, generation of the exocyclic methylene grouping at C-16, and enol acetylation of the 3-keto-group, thus affording the 2,4-diene (8), $\lambda_{max.}$ 274 nm.

Mild alkaline hydrolysis of compound (8) with calcium carbonate provided the 17α-acetoxy-progesterone analogue (9). The introduction of the 1,2-double bond to give the 1,4-diene (10) was performed by treatment of compound (9) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

In multi-dose assays [14] it was found that the progestational activity of these new progesterone analogues was increased by 2,3- or 1,2-double bond introduction; the latter modification induced the more pronounced effect. The oral progestational activity of compound (10) was 150 times that of norethindrone and the former thus appears to be one of the most potent progestational agents yet described. Compounds (8) and (9) were respectively 60 and 30 times as active as norethindrone.

EXPERIMENTAL

Microanalyses were performed by Dr. A. Bernhardt, Mühlheim, Germany. M.p.s were determined with a Mel-temp apparatus; they are corrected. Rotations were

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taken between 16 and 22° for solutions in chloroform. I.r. spectra were taken with a Perkin-Elmer model 21 instrument (NaCl prism) and u.v. spectra with a Beckman DU spectrophotometer. Unless otherwise stated, n.m.r. spectra were recorded at 60 MHz for 5—8% w/v solutions in deuteriochloroform containing tetramethylsilane as internal reference. Coupling constants (J/Hz) are accurate to ±1 Hz.

5α-*Bromo*-6β-*fluoro*-3β-*hydroxy*-16-*methylpregn*-16-*en*-20-*one* (2).—To anhydrous tetrahydrofuran (113 ml) cooled to −70° for 4 h, then poured into aqueous potassium carbonat stirring while the temperature was maintained below −20°. The mixture was cooled to −70°, and *N*-bromoacetamide (10·65 g) was added, followed dropwise by a solution of 3-hydroxy-16-methylpregna-5,16-dien-20-one (1) (21 g) [8] in methylene chloride (157 ml), with the temperature kept below −60°. The mixture was stored at −70° for 4 h, then poured into aqueous potassium carbonate (1 kg in 3 l). The product was extracted with methylene chloride (4 × 500 ml); the extract was washed with water, dried (Na_2SO_4), and evaporated to dryness. The residue crystallised from methylene chloride–methanol to afford the *pregn*-16-*en*-20-*one* (2) (22 g, 81%), m.p. 190—191°. Recrystallisation from methylene chloride–ethyl acetate gave material of m.p. 193—194° (decomp.), $[\alpha]_D$ −92°, $\nu_{max.}$ 3400, 1650, and 1615 cm^{-1}, δ 0·98 (18-H), 1·28 (d, J 4 Hz, 19-H), 2·03 (21-H), 2·17 (16-Me), 4·42 (3α-H), and 4·40 and 5·30 p.p.m. (6β-H) (Found: C, 61·8; H, 7·6; F, 4·35. $C_{22}H_{32}BrFO_2$ requires C, 61·8; H, 7·55; F, 4·45%).

6α-*Fluoro*-16-*methylpregna*-4,16-*diene*-3,20-*dione* (3).—Compound (2) (10 g) was dissolved in dimethylformamide (200 ml) by heating. The solution was cooled to 20° and treated dropwise (20 min) with Jones reagent (25 ml).[10] After a further 20 min the mixture was poured into iced water (1 l). The crystals were filtered off, washed successively with water, sodium hydrogen carbonate solution, and water, and dissolved in methylene chloride. The solution was dried (Na_2SO_4) and evaporated; the residue was dissolved in a saturated solution of hydrogen chloride in ethyl acetate (100 ml), kept at 5° for 2 h, diluted with ethyl acetate, and poured into water (150 ml). The organic phase was separated, washed with water, 5% aqueous sodium hydrogen carbonate, and water, dried (Na_2SO_4), and evaporated. The residue crystallised from ethyl acetate–ether to give material (5 g, 62%) which was recrystallised from methylene chloride to afford the *bis-enone* (3), m.p. 200—201° (decomp.), $[\alpha]_D$ +92°, $\lambda_{max.}$ 240 nm (ε 23,700), $\nu_{max.}$ 1670, 1655, 1630, and 1610 cm^{-1}, δ 1·00 (18-H), 1·22 (19-H), 2·05 (21-H), 2·28 (16-Me), 4·75 and 5·50 (6β-H), and 6·10 p.p.m. (4-H) (Found: C, 76·85; H, 8·5; F, 5·45. $C_{22}H_{29}FO_2$ requires C, 76·7; H, 8·5; F, 5·5%).

3-*Ethoxy*-6-*fluoro*-16-*methylpregna*-3,5,16-*trien*-20-*one* (4).—From a solution of compound (3) (10 g) in methylene chloride (500 ml), *ca.* 50 ml of solvent were removed and the mixture was cooled to room temperature. Ethyl orthoformate (10 ml) and toluene-*p*-sulphonic acid (160 mg) were added. The mixture was stirred at room temperature for 1·15 h. Pyridine (1 ml) was then added and the solvent was removed. The residue was dissolved in methylene chloride and the solution was passed through a column of Florisil (*ca.* 50 g). The product crystallised from methanol affording material (8·3 g, 77%) of m.p. 144—147°. Recrystallisation from methylene chloride–methanol gave the *trienone* (4), m.p. 145—146°, $[\alpha]_D$ −154°, $\lambda_{max.}$ 242 nm (ε 28,200), $\nu_{max.}$ 1695, 1660, 1635, and 1610 cm^{-1}, δ 1·00 (18-H and 19-H), 1·30 (t, J 7 Hz, O·CH$_2$·CH_3), 2·03 (21-H), 2·27 (16-Me), 3·63, 3·76, 3·87, and 4·00 (2 d, J 7 Hz, O·CH_2·CH$_3$), and 5·27 p.p.m. (4-H) (Found: C, 76·75; H, 9·05; F, 5·35. $C_{24}H_{33}FO_2$,0·25MeOH requires C, 76·6; H, 9·0; F, 5·0%).

3-*Ethoxy*-16α,17α-*epoxy*-6-*fluoro*-16β-*methylpregna*-3,5-*dien*-20-*one* (5).—Chloroform–methanol (1 : 1; 216 ml) containing compound (4) (8·3 g) was cooled to 0° and treated, with stirring, with sodium hydroxide (5 g) in water (16·6 ml). Hydrogen peroxide (30%; 28·8 ml) was added, and the mixture was stirred for 66 h, then poured into water. The organic phase was separated and the aqueous layer was extracted with methylene chloride. The combined extracts were washed with water, dried (Na_2SO_4), and evaporated to dryness in the presence of a few drops of pyridine. The residue was dissolved in methylene chloride–hexane and passed through a column of Florisil (*ca.* 80 g) (eluant methylene chloride) to give material which was crystallised from hexane (yield 6 g, 69%), m.p. 118—122°. Recrystallisation from methylene chloride–hexane gave the *epoxide* (5), m.p. 120—121°, $[\alpha]_D$ −67°, $\lambda_{max.}$ 240 nm (ε 20,000), $\nu_{max.}$ 1710 and 1635 cm^{-1}, δ 1·00 (18-H), 1·05 (19-H), 1·30 (t, J 7 Hz, O·CH$_2$·CH_3), 1·45 (21-H), 2·20 (16-Me), 3·63, 3·74, 3·87 and 3·98 (2 d, J 7 Hz, O·CH_2·CH$_3$), and 5·43 p.p.m. (4-H) (Found: C, 74·6; H, 8·4; F, 5·3. $C_{24}H_{33}FO_3$ requires C, 74·2; H, 8·55; F, 4·9%).

16α,17β-*Epoxy*-6-*fluoro*-16β-*methylpregna*-4,6-*diene*-3,20-*dione* (6).—Compound (5) (6 g) dissolved in acetone (60 ml) containing 1% of water was cooled to −10° and treated, with stirring, with sodium acetate (3·02 g) and *N*-bromosuccinimide (3·02 g). After 15 min under the same conditions the mixture was poured into water (250 ml) and extracted with methylene chloride. The extract was washed with water, dried (Na_2SO_4), and evaporated to dryness *in vacuo*, in the presence of sodium bromide (3·30 g) and sodium hydrogen carbonate (1·65 g). To the residue was added dimethylacetamide (100 ml) and the mixture was heated at 50—60° with stirring for 1 h. It was then poured into water (500 ml). The oily precipitate was separated and dissolved in methylene chloride; the solution was dried (Na_2SO_4) and evaporated to dryness. The residue was chromatographed on Florisil (150 g) [eluants methylene chloride and methylene chloride–ether (98 : 2)]. The product crystallised from methanol–water to give material (2·8 g, 70%) of m.p. 134—137°. Two recrystallisations from methanol–water gave the *bis-enone* (6), m.p. 137—138°, $[\alpha]_D$ +38°, $\lambda_{max.}$ 282 nm (ε 23,300), $\nu_{max.}$ 1700, 1665, 1645, and 1605 cm^{-1}, δ 1·13 (18-H), 1·17 (19-H), 1·25 (21-H), 2·10 (16-Me), 5·43, 5·47, 5·68, and 5·72 (q, J 10 Hz, 7-H), and 6·06 p.p.m. (4-H) (Found: C, 73·25; H, 7·75; F, 6·15. $C_{22}H_{27}FO_3$,0·25MeOH requires C, 73·0; H, 7·7; F, 5·2%).

16α,17α-*Epoxy*-2′,2′,6β-*trifluoro*-6β,7β-*dihydro*-16β-*methylcyclopropa*[6,7]*pregn*-4-*ene*-3,20-*dione* (7).—Compound (6) (11·63 g) was dissolved in bis-(2-methoxyethyl) ether (150 ml), and 50 ml of solvent were distilled off at atmospheric pressure (fractionating column). The slow distillation was continued while a solution of sodium chlorodifluoroacetate [7,11] (39 g) in anhydrous bis-(2-methoxyethyl) ether (100 ml) was added. Distillation was continued for 15 min. The mixture was cooled and the remaining solvent was distilled off under vacuum. The residue was dissolved in ether; the solution was filtered through charcoal and evaporated to dryness. Two crystallisations of the residue from methanol–hexane–ether gave the product (3·68 g). The combined mother liquors were purified on preparative

t.l.c. (silica gel) affording a further 2·14 g (total yield 8·82 g, 43%). Recrystallisation afforded the *cyclopropapregnene* (7), m.p. 149—150°, $[\alpha]_D$ +27°, $\lambda_{max.}$ 244 nm (ε 11,500), $\nu_{max.}$ 1695 cm^{-1}, δ 1·10 (18-H), 1·22 (19-H), 1·50 (21-H), 2·20 (16-Me), and 6·30 p.p.m. (4-H) (Found: C, 67·9; H, 6·95; F, 14·5. $C_{23}H_{27}F_3O_3$ requires C, 67·65; H, 6·65; F, 13·95%).

3,17α-*Diacetoxy*-2′,2′,6β-*trifluoro*-6β,7β-*dihydro*-16-*methylenecyclopropa*[6,7]*pregna*-2,4-*dien*-20-*one* (8).—From a solution of compound (7) (3 g) in toluene (85 ml) were distilled *ca.* 20 ml of solvent (fractionating column). The distillation was continued while a solution of 5-sulphosalicylic acid (50 mg) in acetic anhydride (7·5 ml) was added during a 10 min period and for a further 3 h. Pyridine (0·5 ml) was added and the mixture was evaporated to dryness. Methanol–water was added to the isolated material and the crystals were filtered off (2·02 g, 56%), m.p. 155—162°. Recrystallisation from ether–hexane gave *compound* (8), m.p. 173—175°, $[\alpha]_D$ −143°, $\lambda_{max.}$ 274 nm (ε 6500), $\nu_{max.}$ 1760, 1745, 1720, 1670, and 1215 cm^{-1}, δ 0·68 (18-H), 1·10 (19-H), 2·08 (21-H), 2·18 (3-OAc), 2·20 (17-OAc), 5·48 (16-CH_2), 5·62 (4-H), and 6·10 p.p.m. (2-H) (Found: C, 66·0; H, 6·75; F, 12·05. $C_{27}H_{31}F_3O_5$ requires C, 65·85; H, 6·35; F, 11·55%).

17α-*Acetoxy*-2′,2′,6β-*trifluoro*-6β,7β-*dihydro*-16-*methylene-cyclopropa*[6,7]*pregn*-4-*ene*-3,20-*dione* (9).—Compound (8) (1 g) was dissolved in methanol (30 ml), and calcined calcium carbonate (275 mg) in water (12 ml) was added. The mixture was stirred for 30 min at room temperature and then poured into water. The precipitate was filtered off, washed with water, and dissolved in methylene chloride. The extract was dried (Na_2SO_4) and evaporated to dryness. T.l.c. and crystallisation from ether–hexane gave *compound* (9) (700 mg, 76%), m.p. 185—186°, $[\alpha]_D$ −144°, $\lambda_{max.}$ 244 nm (ε 12,300), $\nu_{max.}$ 1745, 1715, 1685, and 1235 cm^{-1}, δ 0·73 (18-H), 1·23 (19-H), 2·70 (21-H), 2·13 (17-OAc), 4·90—6·20 (16-CH_2), and 6·30 p.p.m. (4-H) (Found: C, 67·9; H, 6·7; F, 13·3. $C_{25}H_{29}F_3O_4,0{\cdot}5C_6H_4$ requires C, 68·0; H, 7·3; F, 11·65%).

17α-*Acetoxy*-2′,2′,6β-*trifluoro*-6β,7β-*dihydro*-16-*methylene-cyclopropa*[6,7]*pregna*-1,4-*diene*-3,20-*dione* (10).—Compound (9) (1·75 g) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (1·63 g) were added to anhydrous dioxan (17 ml). The mixture was refluxed for 24 h, cooled, diluted with methylene chloride, filtered through Celite, and evaporated to dryness. The residue was purified by t.l.c. and then crystallised from methylene chloride–ether–hexane to give *compound* (10) (960 mg, 55%), m.p. 209—210°, $[\alpha]_D$ −225°, $\lambda_{max.}$ 244 nm (ε 15,900), $\nu_{max.}$ 1735, 1720, 1690, 1670, 1650, and 1240 cm^{-1}, δ 0·77 (18-H), 1·35 (19-H), 2·03 (21-H), 2·13 (17-OAc), 5·20—6·00 (16-CH_2), 6·17, 6·20, 6·35, and 6·38 (q, *J* 10 Hz, 2-H), 6·60 (4-H), and 6·93 and 7·10 p.p.m. (d, *J* 10 Hz, 1-H) (Found: C, 66·65; H, 6·15; F, 12·5. $C_{25}H_{27}F_3O_4$ requires C, 66·95; H, 6·05; F, 12·7%).

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