Heptafluoro-*p*-tolyl as a Protecting Group in a Synthesis of 3-Hydroxy-17a-aza-17a-homopregn-5-en-20-one. A Potential Inhibitor of Androgen Biosynthesis

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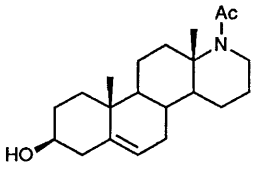
A synthesis of 3-hydroxy-17a-aza-17a-homopregn-5-en-20-one **1** using perfluorotolyl as protecting group for the hydroxy function is described. The phase-transfer-catalysed reaction of octafluorotoluene with dehydroepiandrosterone gave the perfluorotolyl ether **3**. Beckmann rearrangement of its (*E*)-oxime **4** gave the lactam **6**. This reacted with methyl trifluoromethanesulphonate to give the lactam methyl ether which was reduced by sodium borohydride to the protected 17-aza-17a-homosteroid amine **8**. Acetylation followed by cleavage of the perfluorotolyl group using sodium methoxide in dimethylformamide gave **1** in 15% overall yield.

We first reported[1,2] on the potential of heptafluoro-*p*-tolyl as a protecting group for alcoholic and phenolic functions using naturally occurring steroids as model compounds. It was subsequently used in novel syntheses of the important non-steroidal anticancer drug tamoxifen[3,4] and various analogues.[5-9] Derivatization was conveniently carried out by reaction with octafluorotoluene under conditions of phase transfer catalysis and the protecting group was removed with sodium methoxide in dimethylformamide. In an extension of this work, we discovered that, using caesium fluoride in dimethylformamide, certain keto functions could additionally be derivatized as perfluorotolyl enol ethers,[10] which could be cleaved, typically, by mineral acid. This type of reaction was applied in a convenient synthesis[10] of deuterium labelled testosterone, useful in the quantitative analysis of this steroid in human body fluids.[11] In its synthetic applications, perfluorotolyl has proved a versatile protecting group with a wide compatibility with other reagents, notwithstanding the seemingly rather harsh conditions (treatment with sodium methoxide in dimethylformamide) required for its removal. Ease of crystallization and a tendency to enhance the separability of isomers are other advantageous features. Despite its potential, illustrated in our studies, the perfluorotolyl group has received scant attention in the synthetic strategies of other research groups[4] and it is clear that further examples of its successful use, in particular of its compatibility with other synthetic procedures, are needed.



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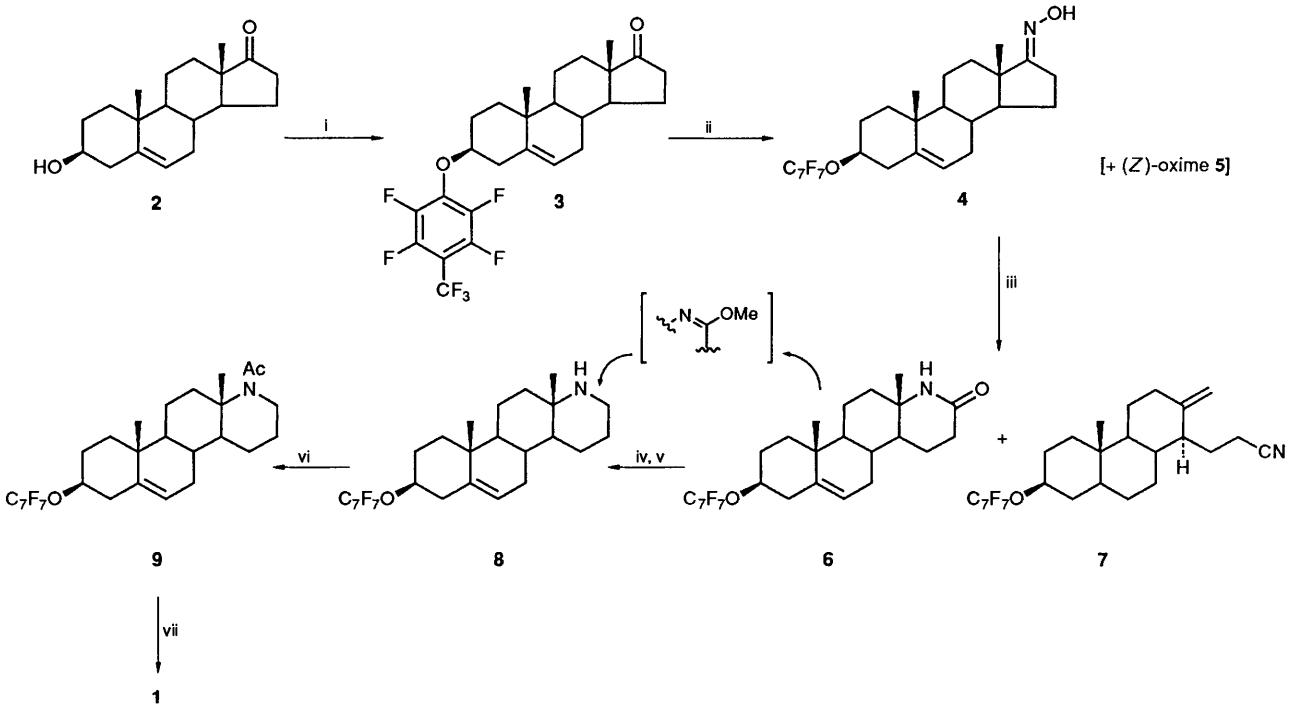
The target compound 3-hydroxy-17a-aza-17a-homopregn-5-en-20-one **1** was of interest to us as an analogue of pregnenolone, a natural substrate for the enzyme 17α-hydroxylase/C_{17-20}lyase which catalyses[12] its conversion, *via* 17α-hydroxypregnenolone into dehydroepiandrosterone (3β-hydroxyandrost-5-en-17-one, **2**), a precursor for the production of androgens. Inhibitors of this pathway have potential for the treatment of prostatic cancer,[13] and it was hoped that **1**, as a substrate analogue which cannot be hydroxylated at the 17-position, might prove inhibitory to the target enzyme. This paper describes a route to **1** which makes use of the perfluorotolyl protecting group.

Results and Discussion

As in the published synthesis[14,15] of **1**, the starting material used here (see Scheme 1) was **2** and the aza substituent was introduced *via* a Beckmann rearrangement of a 17-oxime following protection of the 3-hydroxy function. In the literature route the use of acetyl as protecting group was generally satisfactory, though it proved labile to the basic conditions used in one of the steps. However, in our hands[16] two other steps, the formation of an oxime from 3-acetoxyandrost-5-en-17-one and the subsequent Beckmann rearrangement were accompanied by some loss of the protecting group, prompting us to seek an alternative. It appeared to us that perfluorotolyl might prove suitable. The reaction between **2** and octafluorotoluene under phase transfer catalysis using tetrabutylammonium hydrogen sulphate in a two phase system of dichloromethane and aqueous sodium hydroxide during 6 days afforded the 3-*O*-perfluorotolyl ether **3** in 79% yield. This relatively slow reaction of the 3-hydroxy function in steroids having the 5-en-3-ol function has been noted in the previously reported[1,2] reaction of cholesterol with octafluorotoluene.

The reaction of **3** with hydroxylamine gave as expected[17] preponderantly the (*E*)-oxime **4** (80% yield) which was readily separated from the (*Z*)-oxime **5** (3% yield) by column chromatography and was used for the next step, the Beckmann rearrangement. The compatibility of the perfluorotolyl group with oxime formation is noteworthy since hydroxylamine can react with perfluoroarenes.[18] Also the easy chromatographic separation of **4** and **5** was in apparent contrast with corresponding 3-*O*-acetyl derivatives for which isolation of the (*Z*)-isomer required repeated chromatography.[17] This tendency for perfluorotolyl to enhance the chromatographic separability of geometrical isomers has been noted previously.[3,7,8] Cleavage of the C(13)–C(17) bond resulting in an 'abnormal' Beckmann rearrangement product accompanies formation of the normal product in the rearrangement of 3-acetoxyandrost-5-en-17-one oxime.[19] We used thionyl chloride, reported[17] to give 61% yield of the lactam for this oxime, in the Beckmann rearrangement of **4** and obtained the normal product **6** (59% yield) and the nitrile **7** (25%). We also investigated the use of the reagent combination dipyridyl disulphide with tributylphosphine, reported[20] to give, in a small (100 mg) scale reaction, an 89% yield of lactam from 3-acetoxyandrost-5-en-17-one oxime, but in our hands this reaction gave only a 34% yield of **6** accompanied by a 15% yield of the nitrile **7** and 50% of unchanged **4**.

The next step, reduction of the lactam **6**, required a different strategy from that used to reduce the corresponding 3-*O*-acetyl derivative, for which lithium aluminium hydride was the



Scheme 1 *Reagents:* i, C_7F_8, $(C_4H_9)_4N^+HSO_4^-$, CH_2Cl_2, NaOH (aq.); ii, NH_2OH·HCl, EtOH; iii, $SOCl_2$, dioxane; iv, CF_3SO_3Me, CH_2Cl_2; v, Me_2NCHO, $NaBH_4$, EtOH; vi, Ac_2O, C_5H_5N; vii, NaOMe, Me_2NCHO

reducing agent.[14,15] Parenthetically, it may be noted that the acetyl group was cleaved under the nucleophilic conditions of this reduction. Exploratory studies on the reduction of **6** by lithium aluminium hydride revealed that the reagent in part reduced the perfluorotolyl function, as evidenced by changes in the ^{19}F NMR spectrum, and the appearance of aromatic proton signals in the ^1H NMR spectrum, and that the products could only be partly cleaved by sodium methoxide in dimethylformamide to liberate the 3-hydroxy function, prompting a different approach to **8**. Borch[21] has described a procedure for reducing secondary and tertiary amides using triethyloxonium tetrafluoroborate to form the iminoether tetrafluoroborate followed by reduction with sodium borohydride, with which the perfluorotolyl group is known to be compatible.[2,10] Triethyloxonium fluoroborate proved insufficiently reactive to form the imino ether from **6**, but the conversion was achieved with methyl trifluoromethanesulphonate. Thus in a small scale reaction of **6** with methyl triflate (10 equiv.) monitored by ^1H NMR spectroscopy, after 5 h the original signal for 18-H at δ 1.19 was replaced by one at δ 1.39. However, when an ethanolic solution of this intermediate reacted with sodium borohydride, the products included some 30% of an *N*-methylated component as evidenced by the integration of a singlet at δ 2.6 (ascribed to N–CH_3) and by mass spectrometry (molecular ion at *m/z* 519) of a sample isolated by chromatography. To avoid this side-reaction, attributable to excess of methyl trifluoromethanesulphonate reacting with the reduction product **8**, the preparative procedure included addition of dimethylformamide at the intermediate stage to destroy this excess. The resulting product **8**, an oil, was converted into the crystalline *N*-acetyl derivative **9**, each step (**6**→**8**, **8**→**9**) giving a 71% yield. The resistance of the perfluorotolyl function to refluxing pyridine during the acetylation step is noteworthy. Finally, the perfluorotolyl group was removed using sodium methoxide in dimethylformamide to give the desired product **1**. The yield in this final step (82%) was noticeably better than the 64% obtained for the regeneration of cholesterol from its perfluorotolyl ether and allays our concern that elimination of heptafluoro-*p*-cresol to generate a diene might be an important general side-reaction in the regeneration of steroids having the 5-en-3-ol structure. Such a side-reaction would have had a precedent in the preponderant formation of styrene during attempted regeneration of 2-phenylethanol from its perfluorotolyl ether, which likewise has an activated proton β to the perfluorotolyl group.[2]

In summary we have described a synthesis of 3-hydroxy-17a-aza-17a-homopregn-5-en-20-one **1** in 6 stages, from 3-hydroxyandrost-5-en-17-one **2** in 15% overall yield, using perfluorotolyl as a protecting group for the hydroxy function, which compares favourably with the published route[15] using acetyl as protecting group. This study provides further evidence for the versatility of perfluorotolyl as a protecting group in organic synthesis.

Compound **1** proved an inhibitor of the 17α-hydroxylase/C_{17}–C_{20}lyase enzyme from human testis with an IC_{50} value (50% inhibition of the conversion of pregnenolone into **2**) of 4.9 μM. Detailed methodology and results for this assay, carried out by Dr. S. E. Barrie, will be reported elsewhere.

Experimental

Unless otherwise stated the following conditions apply. M.p.s are uncorrected. NMR spectra were determined using a Bruker AC250 spectrometer operating at 250 MHz (^1H spectra) or 235 MHz (^{19}F spectra), in deuteriochloroform, using tetramethylsilane and hexafluorobenzene (δ −163.0) respectively as internal standards. *J* Values are in Hz. Although ^{19}F spectra were recorded for all fluorine-containing products synthesised except compound **7** the details are reported for compound **2** only, since spectra for the other compounds were essentially identical. Electron-impact mass spectra were recorded using a VG 7070H spectrometer and VG 2235 data system with an ionizing voltage of 70 eV and ion-source temperature of 160–200 °C. IR spectra were determined with a Perkin-Elmer 1720-X spectrometer. Chromatography refers to column

chromatography on silica gel (Merck 15111). Light petroleum refers to the fraction of b.p. 60–80 °C.

3-[2,3,5,6-*Tetrafluoro*-4-(*trifluoromethyl*)*phenoxy*]*androst*-5-*en*-17-*one* **3**.—A mixture of 3β-hydroxyandrost-5-en-17-one **2** (15 g, 52 mmol), octafluorotoluene (13.52 g, 57.3 mmol), tetrabutylammonium hydrogen sulphate (2.12 g, 6.25 mmol), dichloromethane (150 ml) and aqueous sodium hydroxide (1 mol dm^{-3}; 150 ml) was stirred at room temperature for 96 h. More octafluorotoluene (5 g, 21 mmol) and tetrabutylammonium hydrogen sulphate (0.9 g, 2.7 mmol) was added and stirring continued for 48 h. The organic phase was separated and the aqueous phase was acidified with aqueous hydrochloric acid (1 mol dm^{-3}) then extracted with dichloromethane (5 × 100 ml). Chromatography and elution with toluene gave the title compound **3** (20.7 g, 79%) as crystals, m.p. 206–208 °C (from hexane) (Found: C, 62.0; H, 5.4; F, 26.15. $C_{26}H_{27}F_7O_2$ requires C, 61.90; H, 5.40; F, 26.36%); δ_H 0.89 (3 H, s, 18-H_3), 1.09 (3 H, s, 19-H_3), 4.2–4.4 (1 H, m, 3-H) and 5.43 (1 H, d, *J* 5.1, 6-H); δ_F −155.7 (2 F, m, 2-F, 6-F), −143.1 (2 F, m, 3-F, 5-F) and −57.0 (3 F, t, *J* 11, CF_3); *m*/*z* 504 (M^+; 2%) and 271 ($M^+ - OC_7F_7$, 100%).

Elution with dichloromethane–toluene gave the starting material **2** (2.1 g, 14%).

3-[2,3,5,6-*Tetrafluoro*-4-(*trifluoromethyl*)*phenoxy*]*androst*-5-*en*-17-*one* (E)-(**4**) *and* (Z)-(**5**) *Oximes*.—To a refluxing solution of the perfluorotolyl ether **3** (13 g, 26 mmol) in ethanol (850 ml) was added hydroxylamine hydrochloride (3.6 g, 52 mmol). After 16 h the solution was concentrated and a solution of the residue in dichloromethane–diethyl ether (1:1 v/v; 300 ml) was extracted successively with water (100 ml), aqueous hydrochloric acid (1 mol dm^{-3}; 50 ml) and water (2 × 100 ml). Chromatography of the concentrated organic phase and elution with light petroleum gave starting material **3** (570 mg, 4.4%) and unidentified by-products (650 mg).

Elution with light petroleum containing an increasing proportion of diethyl ether (up to 30% v/v) afforded the (*E*)-oxime **4** (10.53 g, 80%) as crystals, m.p. 179–180 °C (from dichloromethane–light petroleum, 1:1) (Found: C, 60.1; H, 5.55; N, 2.55. $C_{26}H_{28}F_7NO_2$ requires C, 60.14; H, 5.44; N, 2.70%); δ_H 0.94 (3 H, s, 18-H_3), 1.09 (3 H, s, 19-H_3), 4.2–4.4 (1 H, m, 3-H), 5.42 (1 H, br d, 6-H) and 6.7 (1 H, br s, N–OH); *m*/*z* 519 (M^+; 5%), 504 ($M^+ - CH_3$, 40), 502 ($M^+ - OH$, 80) and 286 ($M^+ - OC_7F_7$, 100).

Elution with diethyl ether gave the (*Z*)-oxime **5** (0.4 g, 3%); δ_H 1.03 (3 H, s, 19-H_3), 1.33 (3 H, s, 18-H_3), 4.15–4.3 (1 H, m, 3-H) and 5.42 (1 H, br d, 6-H).

Beckmann Rearrangement of the (E)-*Oxime* **4**.—Thionyl chloride (30 ml, 0.41 mol) was added dropwise over 5 min into a stirred solution of the (*E*)-oxime **4** (13 g, 0.025 mol) in dioxane (200 ml) at −15 to −5 °C. After 20 min water (200 ml) was added dropwise (care!) and the solution neutralised by addition of aqueous ammonia (100 ml); it was then diluted with water (600 ml) and extracted with dichloromethane–diethyl ether (3:7) (10 × 200 ml). The organic extracts were diluted with ethanol (100 ml) and concentrated. Chromatography of the residue and elution with dichloromethane gave 3-[2,3,5,6-*tetrafluoro*-4-(*trifluoromethyl*)*phenoxy*]-13,17-*secoandrosta*-5,13(18)-*diene*-17-*carbonitrile* **7** (3.25 g, 25%) as needles, m.p. 109–110 °C (from hexane) (Found: C, 61.0; H, 5.0; N, 2.85. $C_{26}H_{26}F_7NO$ requires C, 62.27; H, 5.23; N, 2.79%); ν_{max}/cm^{-1} 2 250 (C≡N str); δ_H 1.02 (3 H, s, 19-H_3), 4.2–4.35 (1 H, m, 3-H), 4.51 (1 H, s, 18-H), 4.84 (1 H, s, 18-H) and 5.40 (1 H, br d, 6-H).

Elution with dichloromethane containing an increasing proportion of diethyl ether (up to 20% v/v) gave starting material **4** (1.3 g, 10%).

Elution with a further increase in proportion of diethyl ether (up to 100%) followed by diethyl ether–methanol–triethylamine (90:9:1) gave 3-[2,3,5,6-*tetrafluoro*-4-(*trifluoromethyl*)-*phenoxy*]-17a-*aza*-17a-*homoandrost*-5-*en*-17-*one* **6** (7.7 g, 59%) as colourless crystals, m.p. 230–231 °C (from dichloromethane) (Found: C, 60.2; H, 5.5; N, 2.75. $C_{26}H_{28}F_7NO_2$ requires C, 60.14; H, 5.44; N, 2.70%); δ_H 1.04 (3 H, s, 19-H_3), 1.17 (3 H, s, 18-H_3), 4.2–4.35 (1 H, m, 3-H), 5.41 (1 H, br d, 6-H) and 5.86 (1 H, br s, NH).

3-[2,3,5,6-*Tetrafluoro*-4-(*trifluoromethyl*)*phenoxy*]-17a-*aza*-17a-*homoandrost*-5-*ene* **8**.—To a stirred solution of the lactam **6** (500 mg, 0.96 mmol) in dichloromethane (15 ml) under argon was added methyl trifluoromethanesulphonate (1.09 ml, 9.63 mmol, 10 equiv.). After 5.5 h the solution was concentrated under reduced pressure (0.5 mmHg) at 20 °C and dimethylformamide (1.1 ml, 10 equiv.) was added. After 5 min, a solution of sodium borohydride (729 mg, 1.93 mmol) in ethanol (15 ml) was added dropwise under argon. The mixture was stirred for 12 h and concentrated. Chromatography (Merck 9385), eluting successively with diethyl ether–triethylamine (95:5) and diethyl ether–methanol–triethylamine (80:20:5 followed by 70:30:5) gave the title compound **8** (350 mg, 71%), as an oil; δ_H 0.85 (3 H, s, 18-H_3), 1.03 (3 H, s, 19-H_3), 4.15–4.35 (1 H, m, 3-H) and 5.41 (1 H, br d, 6-H).

3-[2,3,5,6-*Tetrafluoro*-4-(*trifluoromethyl*)*phenoxy*]-17a-*aza*-17a-*homopregn*-5-*en*-20-*one* **9**.—To a solution of the amine **8** (350 mg, 0.69 mmol) in pyridine (5 ml) was added acetic anhydride (2 ml, 0.021 mol). The solution was heated under reflux for 1 h and then diluted with water (50 ml) and extracted with diethyl ether (3 × 50 ml). Chromatography (Merck 9385) with diethyl ether–methanol (9:1) gave the title compound **9** (270 mg, 71%) as crystals, m.p. 142–144 °C (from hexane) (Found: C, 62.35; H, 6.1; N, 2.4. $C_{28}H_{32}F_7NO_2$ requires C, 61.42; H, 5.89; N, 2.56%); δ_H 1.02 (3 H, s, 19-H_3), 1.44 (3 H, s, 18-H_3), 2.05 (3 H, s, 21-H_3), 3.25–3.5 (2 H, m, 17-H), 4.15–4.35 (1 H, m, 3-H) and 5.41 (1 H, br d, 6-H).

3-*Hydroxy*-17a-*aza*-17a-*homopregn*-5-*en*-20-*one* **1**.—To a stirred solution of the acetyl derivative **9** (120 mg, 0.22 mmol) in dimethylformamide (2 ml) was added sodium methoxide (600 mg, 11.1 mmol) and the solution was heated at 60 °C for 150 min. The cooled mixture was diluted with water (50 ml) and extracted with diethyl ether (5 × 100 ml). Chromatography and elution with diethyl ether–light petroleum (8:2) gave starting material **9** (20 mg, 17%).

Elution with diethyl ether containing an increasing proportion of methanol (up to 30% v/v) gave the title compound **1** (60 mg, 82%) as a crystalline powder (acetone), m.p. 270–272 °C (lit.,[14] 271–273 °C and lit.,[15] 278–280 °C) (Found: C, 76.05; H, 10.3; N, 4.5. Calc. for $C_{21}H_{33}NO_2$: C, 76.1; H, 10.05; N, 4.25%); δ_H 0.99 (3 H, s, 19-H_3), 1.44 (3 H, s, 18-H_3), 2.04 (3 H, s, 21-H_3), 3.2–3.4 (2 H, m, 17-H), 3.4–3.6 (1 H, m, 3-H) and 5.35 (1 H, br d, 6-H); *m*/*z* 331 (M^+; 35%) and 316 ($M^+ - CH_3$, 100).

Acknowledgements

This investigation was supported by grants to the Institute of Cancer Research, Royal Cancer Hospital from the Cancer Research Campaign and the Medical Research Council. The award of a studentship by the Cancer Research Campaign (to J. J. D.) is gratefully acknowledged. We thank Mr. M. H. Baker for determining the mass spectra.

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Paper 1/01958I
Received 25*th April* 1991
Accepted 4*th June* 1991