The synthesis of antioxidants showing selective affinity for low density lipoproteins

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The syntheses of some novel indolinosteroids, indolinodecalins and spiro tetrahydroquinolinopiperidines are described. These compounds act as chain-breaking antioxidants and in some cases show very selective binding to LDL particles in human plasma. Aspects of the stereoselectivity in the Fischer indolisation of three common steroidal ketones and the reduction of the resultant indoles to indolines are considered.

Atherosclerosis is the principal cause of death in the UK and in many other developed countries.[1] A natural control agent is considered to be α-tocopherol **1**,[2] a major form of vitamin E, which acts as a chain-breaking antioxidant by inhibiting the oxidation of low density lipoproteins (LDL) in plasma and the subsequent release of foam cells. The latter cells may accumulate in the intima of an artery and eventually lead to an obstruction in the form of a fibrous plaque, to which blood platelets may adhere.[3]

Mimics of α-tocopherol are currently of interest since they may act to supplement and improve the natural protective regime against attack by radical species such as superoxide.[4,5] Typically such mimics should contain a 'polar head' capable of forming stable radical cations at an ionisation potential of *ca.* 0.45–0.65 V (*vs.* SCE) and we have already described a number of indoline derivatives, such as the tetrahydroindenoindole **2**,[6] in which the indoline unit relates to the phenolic unit of α-tocopherol. These are excellent antioxidants, which undergo one-electron oxidation to afford stable radical cations.

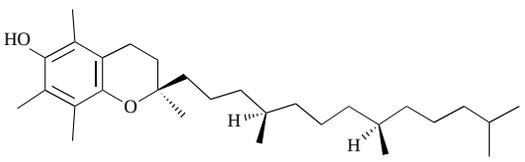
α-Tocopherol embodies a lipophilic alkyl side chain, that serves to bind it to lipoproteins. Thus, it is important that a mimic should contain a similar unit and that the compound should exhibit strong, selective binding to LDL, rather than to high density lipoproteins (HDL) for optimum protection against pathogenic radicals.[3] It may well be that the oxidation of LDL particles triggers the release of lipotriglycerides and the growth of foam cells. Certainly, oxidised LDL is more readily taken up by macrophages than normal LDL and foam cells contain high levels of oxidised LDL. Until now, most of the indoline derivatives we have described as antioxidants fail to show the desired selective binding to LDL, and for optimum therapeutic effect must be modified. The lipophilic nature of steroids is very well established and it was of interest to us to synthesize a series of indolines fused to commonly available steroidal units in an attempt to remedy this problem.

As an initial experiment we treated 5α-cholestanone **3** with 4-isopropylphenylhydrazine hydrochloride and subjected the corresponding hydrazone **4** to Fischer indolisation in glacial acetic acid using 4-sulfosalicylic acid. This gave a single indole **5** in 62% yield. None of the alternative isomer **6** was isolated, or detected. The ^{1}H NMR spectrum of the indole shows the methylene protons at C-6 to resonate at 2.37 (dd, *J* 16, 11 Hz) and 2.54 (dd, *J* 16, 5 Hz) ppm, whereas the methylene protons at C-12, resonate as doublets (*J* 15 Hz) at 2.28 and 2.76 ppm. This result is in accord with early work,[7] where it was shown that the stereochemistry at C-5 (conventional steroid numbering) in the cholestanone determines the regioselectivity of Fischer indolisation. Thus, the direction of ring closure then parallels the way in which enolisation occurs: in the case of 5α-cholestanone this involves C-2, whereas for 5β-cholestanones C-4 is utilised.[8]

Reduction of this product with sodium cyanoborohydride in glacial acetic acid gave the indoline **7** in 70% yield and the same compound was formed, now in 48% yield, when the reducing agent was triethylsilane in trifluoroacetic acid. In our experience tetrahydrocarbazoles normally react completely in 2–3 h with this last reagent to afford hexahydrocarbazoles,[6] but for **5**, complete reduction required a reaction time of 6 days. This was our first indication of the significant steric demands of the reagent. In the reactions protonation to give an iminium derivative is a prerequisite to reduction. Preferential attack on the β-face of the indolosteroid **5** causes the bond to the benzenoid unit in the iminium salt **8** to occupy the equatorial site and allows the A ring of the steroid moiety to assume a pseudo-chair conformation. Attack of the hydride reagent then occurs at the β-face to afford **7** (a *trans*-fused indolosteroid is less likely on steric grounds[9]).

Next *O*-methylestrone **9** and 4-isopropylphenylhydrazine were heated together in ethanol solution to give the corresponding hydrazone **10**. Reaction of this with sulfosalicylic acid and glacial acetic acid afforded the indole **11**, together with some *O*-methylestrone resulting from degradation of the hydrazone. Reduction with triethylsilane and trifluoroacetic acid gave only the *anti*-indoline **12** (relating to the *anti*-disposition of the C-14a methyl group and the indoline ring), whereas with sodium cyanoborohydride in acetic acid both *anti*- and *syn*-stereoisomerides **12** and **13** were formed in almost equal amounts. This result may again reflect the relative sizes of the attacking hydride reagents. The stereochemistry of the *anti*-isomer **12** was established by a single-crystal X-ray analysis (Fig. 1). In the ^{1}H NMR spectrum the protons on the junction of the two five-membered rings resonate at δ 4.00 and 4.43 ppm and are spin-spin related with a coupling constant *J* 6.5 Hz. In the *syn*-isomer **13** the chemical shifts are δ 4.10 and 4.35 ppm and *J* 9.0 Hz. The *tert*-butyl analogue **15** was similarly obtained from the corresponding indole **14** and reduction with triethylsilane.

3α-Hydroxy-5-androster-17-one **16** was converted into its 4-*tert*-butylphenylhydrazone **17** and the latter subjected to a Fischer indolisation without isolation by treatment with glacial acetic acid. This gave the indole **18**, together with the indolenine **19** and the corresponding *O*-acetyl derivatives **20** and **21** (the ratio of acetylated to non-acetylated products was 1:3). The formation of the acetylated indole **20** was unexpected, as was the presence of the indolenines **19** and **21**. Thus, indolenines were not observed as products from the indolisations of *O*-methylestrone, and it is difficult to rationalise why the non-aromatic products should form on the basis of a change from a benzene to a cyclohexane unit as the ring A ring of the polycyclic starting material. An attempt to convert the entire indolisation product to the *O*-acetylated indole and indolenine by



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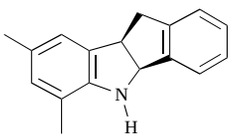

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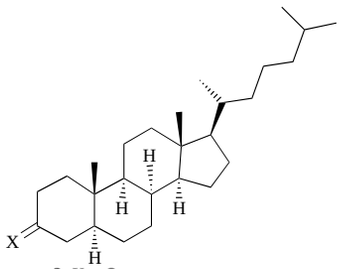
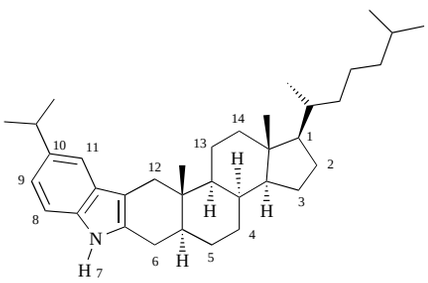


3 X = O

4 X = NNHC$_6$H$_4$Pr^i-4



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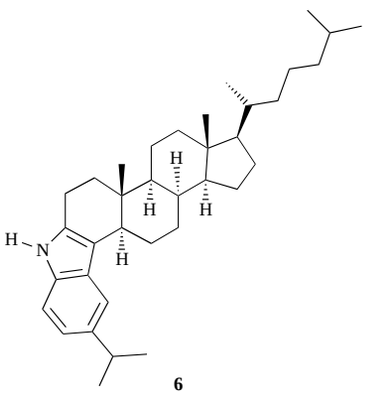

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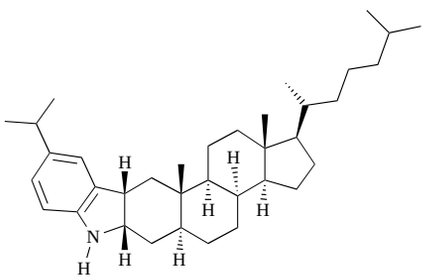

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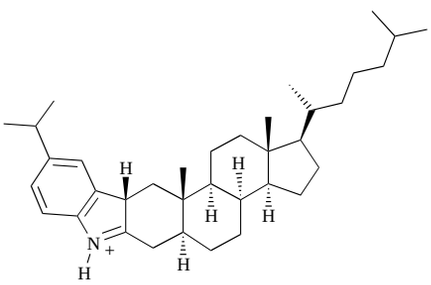


8

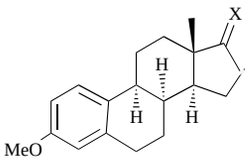
reaction with acetic anhydride and pyridine was unsuccessful and additional compounds were formed. As a result, the acetylated and non-acetylated products were separated and the mixed indole **18** and indolenine **20** were reduced with sodium borohydride in acetic acid. This led to another mixture, from which both the *syn*- and *anti*-indolines **22** and **24** were obtained. However, reduction of the mixed acetylated analogues **19** and **21** with triethylsilane gave only the *anti*-indoline **24**. The stereochemistries of the *syn*- and *anti*-compounds follow from an analysis of the NMR spectra of the estrone products. For example, the spectrum of the hydrochloride of the *anti*-indoline **23** exhibits signals for the indoline bridging protons at δ 3.96 and 4.36 ppm (J 7.0 Hz), whereas the *syn*-indoline **22** exhibits the corresponding signals at *ca*. δ 3.9 and at 4.13 ppm (J 9.5 Hz).

In our work we sought to better the selectivity exhibited by probucol **25**, a drug introduced by Marion Merell Dow as a LDL-cholesterol lowering agent, which also acts as an antioxidant and is carried within lipoprotein particles. Indeed when administered to human plasma, 45% of this compound becomes bound to LDL and 15% to very low density lipoprotein (VLDL);[10] the residual 40% is assumed to be retained by other lipids, including HDL and proteins. Binding to HDL is, therefore, wasteful and potentially undesirable since HDL is considered to be responsible for the transport of cholesterol to the liver, where it is degraded. Interference with this process would not be beneficial.[3]

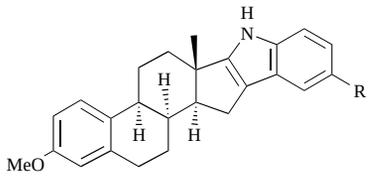
Although in some cases the selectivity for LDL *vs.* VLDL is higher than for probucol, none of our steroidal indolines are retained as well. Thus, the *O*-methylestrone derivative **12** shows a 6:1 preference for LDL over VLDL, but the incorporation is lower than for probucol and only 30% is located in LDL and 5% in VLDL. In the case of the analogue **15**, where a *tert*-butyl group replaces the isopropyl substituent, 20% is bound to LDL and none is associated with VLDL. In contrast the cholesterone derivative **7** is less readily bound to LDL (25%) than to VLDL (35%).[10]

The problem of low incorporation was solved, however, by the synthesis of the indolenines **26** (R = Pr^i and R = Bu^t),[10] which react with many different alkyllithiums, thereby affording indolines of varying lipophilicity. The best compounds we have obtained in this series are the 6-(*N*,*N*-dibenzylamino)hexyl derivative **27** (R = Pr^i) and the ethers **28** (R = Bu^t) and **29** (R = Bu^t), where alkyl chains extend from the carbon α to the indoline nitrogen atom. These compounds show better selectivities and percentage binding values than probucol. For example, the first compound has a very high LDL value of 75%, while 10% is retained in VLDL. For the ethers **28** (R = Bu^t) and **29** (R = Bu^t) the values are 60 and 10% and 55 and 15%, respectively. The stereochemistry of the phenylated indoline **30** (R = Pr^i) was confirmed by a single crystal X-ray determination[11] and we assume that the same topology applies to all four compounds in this series.

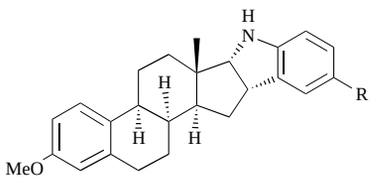
The above compounds were formed as racemates and, in order to avoid the problem of resolution prior to biological evaluation, we have synthesized the piperidinotetrahydroquinolines **33** (R = Me, and MeO), as the parents of another series of chain-breaking antioxidants of variable lipophilicity. The parent compounds were synthesized by reactions of the corresponding imines **31** (R = Me, and MeO) with 2-methylprop-2-enyllithium and cyclization of the resultant amines **32** (R = Me, and MeO) by treatment with concentrated sulfuric acid. In both cases the *N*-butoxycarbonyl group of the starting amines was cleaved during the reaction with sulfuric acid and, in the case of **33** (R = OMe) this product was accompanied by the *O*-demethyl derivative **33** (R = OH). Various mono *N*-alkyl derivatives, such as the representative compounds **34** and **35**, have been made by either, direct alkylation,



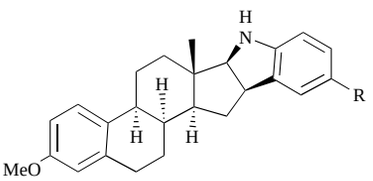
9 X = O
10 X = $NNHC_6H_4Pr^i$-4



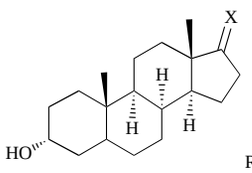
11 R = Pr^i
14 R = Bu^t



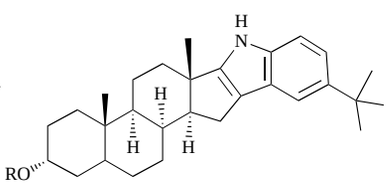
12 R = Pr^i
15 R = Bu^t



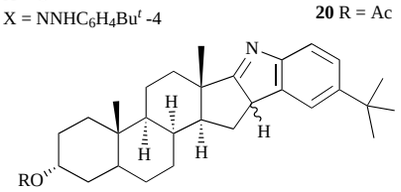
13 R = Pr^i



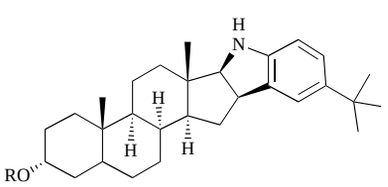
16 X = O
17 X = $NNHC_6H_4Bu^t$ -4



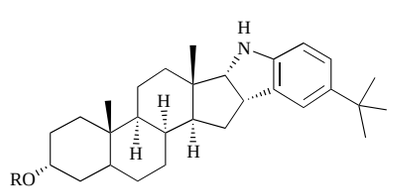
18 R = H
20 R = Ac



19 R = H
21 R = Ac

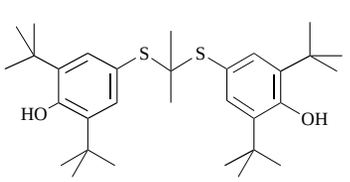


22 R = H



23 R = H
24 R = Ac

or by reductive alkylation of the amines **33**. Both the indolines, *e.g.* **27** (R = Pr^i), and the *N*-alkylspiropiperidinoquinolines, *e.g.* **34** and **35**, form stable radical cations with redox couples at *ca.* +0.6 V *vs.* SCE during cyclic voltammetry. However, the spiro compounds are less effective binders to lipoproteins and typically only 25% of the compound is bound to LDL and 10% to VLDL. As a result we are pursuing our studies in this area with the indolines, despite the requirement for resolution. The results of this biochemical evaluation will appear in due course.



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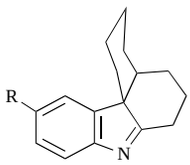
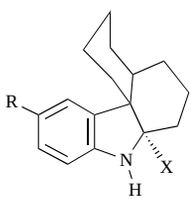
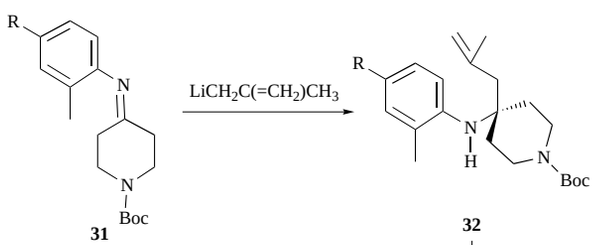


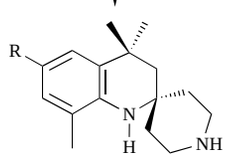
26



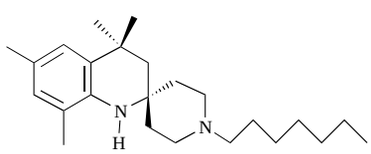
27 X = $(CH_2)_6NBn_2$
28 X = $(CH_2)_4O(CH_2)_6OPh$
29 X = $(CH_2)_6OPh$
30 X = Ph



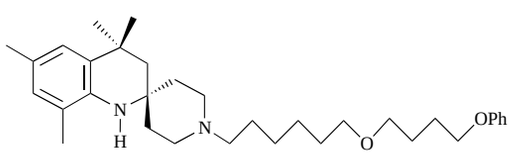
31 **32**



33



34



35

X-ray crystal structure determination of 12

A crystal of approximate dimensions 0.6 × 0.5 × 0.4 mm was used for data collection. Crystal data: $C_{28}H_{35}NO$, M = 401.57, Monoclinic, $a = 9.415(3)$, $b = 8.296(2)$, $c = 14.458(6)$ Å, $\beta = 97.90(3)°$, $U = 1118.6(6)$ Å^3, space group $P2_1$, $Z = 2$, $D_c = 1.192$ g cm^{-3}, μ(Mo-K$_\alpha$) = 0.071 mm^{-1}, $F(000) = 436$. A total of 1791 diffraction data were collected at 293(2) K on a CAD4 four-circle diffractometer in the range $2.18 < \theta < 22.97°$: these were corrected for Lorentz and polarization but not for absorption. The structure was solved by direct methods (SHELXS-86[12]). In the final least squares cycles all atoms (other than hydrogen) were allowed to vibrate anisotropically. Hydrogen atoms were included at calculated positions and an extinction correction was applied.

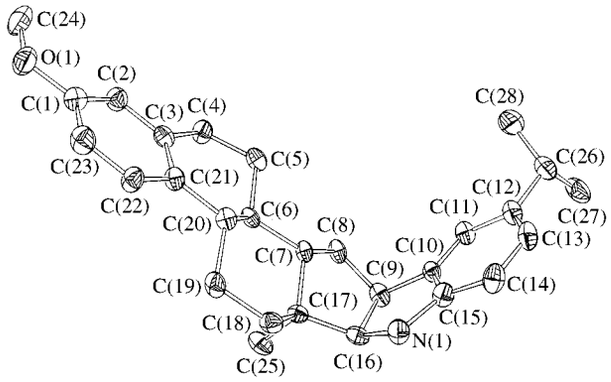


Fig. 1 Molecular plot of **12** showing the labelling scheme used. Ellipsoids are represented at the 30% probability level.

At final convergence, $R_1[1192\ F_o \geqslant 4\sigma(F_o)] = 0.0687$, wR_2 (all data) = 0.1786, $S = 1.29$ (SHELXL-93[13]). The max. and min. residual densities were 0.287 and −0.377 e Å^{-3}, respectively. The asymmetric unit (shown in Fig. 1), along with the labelling scheme used was produced using ORTEX.[14] Final fractional atomic co-ordinates and isotropic thermal parameters, bond distances and angles and anisotropic temperature factors are available as supplementary data from the Cambridge Crystallographic Data Centre.† Requests for such results should be accompanied by a full bibliographic reference for this work together with the reference number 207/123.

Experimental

Chemical synthesis

Unless stated otherwise, all solvents used were distilled and dried prior to use. Where necessary glass apparatus was dried in an oven and cooled under nitrogen. Most reactions were monitored by TLC on Whatman aluminium-backed UV_{254} silica gel plates and visualized under UV light, or developed with iodine, or a PMA dip. Flash column chromatography was carried out under medium pressure on Amicon 60 Å silica gel. Solvents were removed by rotary evaporation at, or below 45 °C. LP refers to light petroleum, bp 60–80 °C. ^{1}H NMR spectra, run in $CDCl_3$ using tetramethylsilane as an internal standard, were recorded at 270 MHz on a JEOL JNM GX FT 270 spectrometer. *J* Values are given in Hz. Mass spectra were recorded on a Fisons, VG Autospec instrument and unlss stated otherwise were obtained by the method of electron impact at 70 eV.

Lipoprotein binding assays

A 2.4 mM solution of the compound in 99.5% ethanol (10 μl) was added to human plasma (2.39 cm^3). After mixing and storage for 30 min, the reaction mixtures were centrifuged to isolate the plasma proteins (VLDL, and LDL-fractions). The levels of compounds were then determined using HPLC analysis with an electrochemical detector. The results were expressed as % of the total amount added to the plasma. So, for a 50% LDL binder 50% of the total amount of added compound was found in the LDL fraction.

10-Isopropyl-7*H*-5α-cholestano[3,2-*b*]indole 5

5α-Cholestan-3-one (750 mg) and 4-isopropylphenylhydrazine (300 mg) were treated with ethanol (20 cm^3) whereupon the hydrazone **4** began to separate as a colourless crystalline solid. The reaction mixture was left for 4 h, after which time the hydrazone (850 mg), mp 111–114 °C, was collected. A solution of this compound (420 mg) in glacial acetic acid (15 cm^3) containing 4-sulfosalicylic acid (450 mg) was heated at reflux for 1.5 h after which the mixture was concentrated by removal of solvent. The residue was stirred with water for 1 h and then filtered off and recrystallized from ethanol (5 cm^3) to afford colourless prisms (250 mg, 62%, based on the hydrazone), mp 194 °C; *m/z* (%) 501 (100, M) and 185 (75); ν_{max}/cm^{-1} 3400; δ_H 0.70 (3H, s), 0.80 (3H, s), 0.83–1.78 (23H, m), 0.85 (3H, d, *J* 6.5), 0.86 (3H, d, *J* 6.5), 0.94 (3H, d, *J* 6.5), 1.30 (6H, d, *J* 7), 1.78–1.92 (1H, m), 2.06 (1H, ddd, *J* 12.5, 2.5, 2.5), 2.28 (1H, d, *J* 15), 2.37 (1H, dd, *J* 16, 11.5), 2.54 (1H, dd, *J* 16, 5), 2.76 (1H, d, *J* 15), 2.99 (1H, sept, *J* 7), 6.99 (1H, dd, *J* 8, 1.5), 7.19 (1H, d, *J* 8), 7.28 (1H, d, *J* 1.5) and 7.55 (1H, br s) (Found: C, 86.4; H, 11.4; N, 2.8. $C_{36}H_{55}N$ requires C, 86.2; H, 10.9; N, 2.8%).

6a,11b-Dihydro-10-isopropyl-7*H*-5α-cholestano[3,2-*b*]indole 7

Sodium cyanoborohydride (850 mg) was added in portions over a period of 45 min to a stirred suspension of the indole **5** (440 mg) in glacial acetic acid (5 cm^3) under a nitrogen atmosphere. After storage of the mixture overnight, it was concentrated by removal of solvent and the residue was partitioned between ethyl acetate (15 cm^3) and water (15 cm^3). The organic phase was collected and the aqueous layer was extracted with ethyl acetate (3 × 10 cm^3). The combined extracts and the organic phase were washed with saturated aqueous sodium hydrogen carbonate, dried and evaporated to afford the title compound as an oil. This was redissolved in LP and treated with diethyl ether, previously saturated with hydrogen chloride to give the hydrochloride salt of **7** as a colourless solid which crystallized from methanol (310 mg, 70%), mp 220–221 °C; *m/z* (CI) (%) 505 (20), 504 (70), 503 (100); $\delta_H(CD_3OD)$ 0.70–0.86 (1H, m), 0.77 (3H, s), 0.93 (6H, dd, *J* 6.5, 0.5), 0.97 (3H, d, *J* 6.5), 1.01 (3H, s), 1.04–1.07 (23H, m), 1.31 (6H, d, *J* 7), 1.77–2.13 (4H, m), 2.23 (1H, dd, *J* 13.5, 6), 3.03 (1H, sept, *J* 7), 3.51 (1H, ddd, *J* 12, 6, 6), 4.93 (1H, dd, *J* 6, 5), 7.35 (1H, dd, *J* 8.5, 1), 7.42 (1H, d, *J* 8.5), 7.42 (1H, d, *J* 1) (Found: C, 80.1; H, 11.1; N, 2.7. $C_{36}H_{57}N\cdot HCl$ requires C, 80.1; H, 10.75; N, 2.6%).

Reduction of the indole (350 mg) at room temperature using triethylsilane in trifluoroacetic acid (15 cm^3) as the reducing agent, needed 6 days to complete the reaction. Simpler tetrahydrocarbazoles are normally reduced in 2 h.[6] In addition, it was necessary to add triethylsilane (1 cm^3; 7.5 cm^3 total) at regular intervals over the 6-day period in order to maintain the reaction. On work-up the same stereoisomer as above was isolated (as its hydrochloride salt) (180 mg, 48%), mp and mixed mp 222–224 °C.

6b,11b-Dihydro-10-isopropyl-2-methoxy-7*H*-estra-1,3,4a(14a)-trieno[17,16-*b*]indole 12

(i) 3-*O*-Methylestrone **9** (4.3 g) and 4-isopropylphenylhydrazine (2.7 g) in ethanol (230 cm^3) were heated at reflux for 2.5 h, after which the reaction mixture was cooled to room temperature overnight to give pale cream needles of the hydrazone **10**. The product was collected (2.75 g), mp 112–116 °C, and the mother liquor reduced in volume to give a further hydrazone (2.5 g); δ_H 0.92 (3H, s), 1.21 (6H, d, *J* 7.0), 1.30–1.70 (6H, m), 1.67–1.70 (2H, m), 2.15–2.30 (5H, m), 2.88 (1H, sept, *J* 7.0), 2.82–2.94 (2H, m), 3.78 (3H, s), 6.64 (1H, d, *J* 2.5), 6.65 (1H, br s), 6.73 (1H, dd, *J* 8.5, 2.5), 6.98 (2H, d, *J* 8.5), 7.10 (2H, d, *J* 8.5) and 7.24 (1H, d, *J* 8.5). This compound was used directly.

(ii) A solution of the hydrazone (970 mg) and 4-sulfosalicyclic acid (1 g) in glacial acetic acid (40 cm^3) was heated at reflux for 1 h after which the solvent was removed and the residue was partitioned between ethyl acetate (50 cm^3) and water (25 cm^3). The organic phase was collected, washed with 2 M aqueous sodium hydrogen carbonate and evaporated to afford a yellow oil (1.05 g). This material, a mixture of 2-*O*-methylestrone and the indole **11** [δ_H 1.00 (3H, s), 1.30 (6H, d, *J* 7), 1.40–1.95 (6H, m), 2.02–2.12 (1H, m), 2.15–2.50 (4H, m), 2.83 (1H, dd, *J* 6, 13.0), 2.94 (1H, br d, *J* 5), 2.99 (1H, sept, *J* 7), 3.79 (3H, s), 6.66 (1H, d, *J* 2), 6.73 (1H, dd, *J* 7.5, 2.0), 6.99 (1H, dd, *J* 7.5, 1.5), 7.22 (1H, d, *J* 7.5), 7.26 (1H, d, *J* 7.5), 7.35 (1H,

† For details of the scheme, see Instructions for Authors (1997), *J. Chem. Soc., Perkin Trans 1*, 1997, Issue 1.

d, *J* 1.5) and 7.82 (1H, br s)] in approximately equal amounts, was redissolved in trifluoroacetic acid (20 cm^3) and treated with triethylsilane (2 cm^3). After 2 h, further triethylsilane (1 cm^3) was added to the mixture. Solvent and excess of reagent were then removed from the mixture to give an oil which was partitioned between ethyl acetate and water. The organic phase was collected and evaporated and the residue chromatographed on silica (20 g) eluting with 4% ethyl acetate in LP. The early fractions yielded a colourless solid (150 mg) which was a mixture of α- and β-3-(*O*-methyl)-17-trifluoroacetylestradiols, while later fractions gave the indoline **12** as a colourless solid (280 mg, 31% yield, based upon the hydrazone), mp 158–160 °C (Found: C, 83.4; H, 8.8; N, 3.4. $C_{28}H_{35}NO$ requires C, 83.8; H, 8.7; N, 3.5%). Treatment of this compound with diethyl ether saturated with hydrogen chloride gave the hydrochloride salt as a colourless microcrystalline solid (307 mg), mp 196–198 °C (Et_2O); δ_H 1.08 (3H, s), 1.27 (6H, d, *J* 7.0), 1.53–2.00 (7H, m), 2.06 (1H, br d, *J* 13.5), 2.50 (2H, br t, *J* 9), 2.80 (3H, m), 2.96 (1H, sept, *J* 7), 3.76 (3H, s), 4.00 (1H, dd, *J* 6.5, 6.5), 4.43 (1H, d, *J* 6.5), 6.59 (1H, d, *J* 2.5), 6.70 (1H, dd, *J* 7, 2.5), 7.10 (1H, br s), 7.17 (1H, d, *J* 7), 7.20 (1H, br d, *J* 8), 7.66 (1H, d, *J* 8), 10.70 (1H, br s) and 12.27 (1H, br s).

Reduction of the indole **11** with sodium cyanoborohydride in acetic acid, rather than triethylsilane in trifluoroacetic acid, gives the indoline **12** accompanied by its isomer **13**. The latter can be eluted from the chromatography column with 4% ethyl acetate in LP as colourless prisms, 148–150 °C (EtOH) (Found: C, 83.6; H, 8.7; N, 3.5. $C_{28}H_{35}NO$ requires C, 83.8; H, 8.7; N, 3.5%).

Hydrochloride salt, mp 168–171 °C (Et_2O); *m/z* (CI) 402, 401 and 136; δ_H 0.79 (3H, s), 1.26 (6H, d, *J* 7), 1.40–1.65 (6H, m), 1.90–1.97 (1H, m), 2.26–2.39 (2H, m), 2.53 (1H, dd, *J* 9, 6), 2.61 (1H, d, *J* 11), 2.84–2.89 (2H, m), 2.94 (1H, sept, *J* 7), 3.78 (3H, s), 4.10 (1H, ddd, *J* 9, 9, 6), 4.35 (1H, d, *J* 9), 6.63 (1H, d, *J* 2.5), 6.73 (1H, dd, *J* 8.5, 2.5), 7.14 (1H, br s), 7.18 (1H, br d, *J* 8), 7.22 (1H, d, *J* 8.5), 7.58 (1H, d, *J* 8), 12.76 (1H, br s) and 13.6 (1H, br s).

10-*tert*-Butyl-2-methoxy-7*H*-estra-1,3,4a(14a)-trieno[17,16-*b*]-indole 14

A mixture of 3-*O*-methylestrone (0.8 g, 2.8 mmol) and 4-*tert*-butylphenylhydrazine (0.8 g, 40 mmol) was heated at 110 °C in glacial acetic acid (12 cm^3) for 3.5 h. After concentration of the solution by evaporation, the residue was partitioned between ethyl acetate and water. The organic layer was collected, washed with saturated aqueous sodium hydrogen carbonate, dried and evaporated to give a gum (1.0 g). This was chromatographed on silica (9.2 g) eluting with ethyl acetate in LP (2→3%) to give three fractions by TLC: fraction 1 contained a mobile oil (80 mg) and fraction 2 yielded the crude indole **14** (400 mg) as a clear yellow gum. Fraction 3 contained the starting ketone (250 mg).

10-*tert*-Butyl-6b,11b-dihydro-2-methoxy-7*H*-estra-1,3,4a(14a)-trieno[17,16-*b*]indole 15

To a well stirred solution of the crude indole **14** (400 mg) from the previous experiment in trifluoroacetic acid (5 cm^3) was added triethylsilane (0.2 cm^3, 150 mg) in one portion. After 2 h at room temperature, work-up gave the indole **15** (0.4 g), which was dissolved in diethyl ether (5 cm^3) and treated with a saturated solution of hydrogen chloride in diethyl ether (0.3 cm^3). Stirring of the mixture for 30 min gave a crystalline solid which was collected and washed with a few drops of diethyl ether and then with acetone; this afforded a pale pink solid (240 mg, 19% yield from *O*-methylestrone), mp 205–209 °C; δ_H 1.08 (3H, s), 1.25–2.00 (7H, m), 1.35 (9H, m), 2.06 (1H, br d, *J* 13.5), 2.50 (2H, m), 2.80 (3H, m), 3.76 (3H, s), 4.00 (1H, dd, *J* 7.5, 7.5), 4.43 (1H, d, *J* 7.5), 6.59 (1H, d, *J* 3), 6.70 (1H, dd, *J* 8.5, 3), 7.21 (1H, d, *J* 8.5), 7.31 (1H, d, *J* 2), 7.41 (1H, dd, *J* 8, 2) and 7.63 (1H, br d, *J* 8) (NH_2^+ not observed) (Found: C, 76.7; H, 8.4; N, 3.0. $C_{29}H_{37}NO{\cdot}HCl$ requires C, 77.1; H, 8.4; N, 3.1%).

2α-Acetoxy-10-*tert*-butyl-7*H*-(14α-androstano[17,16-*b*]indole) 20

3α-Hydroxy-5α-androstan-17-one **16** (1.0 g, 0.345 mmol) and 4-*tert*-butylphenylhydrazone hydrochloride (0.82 g, 0.41 mmol) were stirred together in glacial acetic acid (17 cm^3) and then heated to 110 °C when a clear solution formed. After 1.5 h, the reaction mixture was cooled and filtered to afford colourless crystals (680 mg) which were washed with a few drops of diethyl ether. The filtrate was concentrated to 8 cm^3 and stored at 0 °C overnight when more product (60 mg) was obtained (total 740 mg). This was shown to be a mixture of the indole **18** and the tautomeric indolenine **19**, together with the corresponding acetates **20** and **21**; the ratio of the non-acetylated to the acetylated products was 3:1; δ_H(partial) indole **18** 4.04 (2H), 7.13 (1H, dd, *J* 8.5, 2), 7.25 (1H, d, *J* 8.5), 7.42 (1H, br d, 2.5) and 8.83 (1H, br s, exchangeable); δ_H(partial) indolenine **19** 7.04 (1H, d, *J* 8.5), 7.49 (1H, dd, *J* 8.5, 2.5) and 7.82 (1H, br); δ_H(partial) acetoxyindole **20** 5.01 (1H, m), 7.17 (1H, dd, *J* 7.5, 1.5), 7.26 (1H, d, *J* 7.5), 7.45 (1H, d, *J* 1.5) and 7.78 (1H, br s, exchangeable); δ_H(partial) acetoxyindolenine **21** 5.01 (1H, m), 6.95 (1H, d, *J* 8.5), 7.50 (1H, dd, *J* 8.5, 2.5) and 7.87 (1H, br, *J* 2.5) [Found: (indole and indolenine) *m/z* 419.3185. $C_{29}H_{41}NO$ requires 419.3182: (acetoxyindole and indolenine) *m/z* 461.3300. $C_{31}H_{43}NO_2$ requires 461.3294].

The above mixture (680 mg) in dry pyridine (4 cm^3) was treated with acetic anhydride (6 cm^3) and heated at 100 °C for 3 h. Excess of reagents removed from the reaction mixture by evaporation and the residue was partitioned between ethyl acetate and 2 M aqueous hydrochloric acid. The organic layer was collected and washed with 2 M aqueous sodium hydrogen carbonate, dried and evaporated to give a resin (800 mg). This was subjected to column chromatography on silica (10 g) using ethyl acetate in LP, 4%→10% as the eluent to give colourless crystals (330 mg); ^1H NMR spectroscopy showed that this was a still mixture, containing the expected acetoxyindole **20** and acetoxyindolenine **21** together with other compounds. All attempts to obtain these compounds in a pure state by repeated chromatography, or by crystallization failed.

10-*tert*-Butyl-6b,11b-dihydro-2α-hydroxy-7*H*-(14α-androstano-[17,16-*b*]indole) (*syn*-22 and *anti*-23 forms)

To a mixture of the crude indole **18** and indolenine **19** (420 mg) (from the Fischer indolisation, after chromatographic separation from the acetylated analogues) in glacial acetic acid (20 cm^3) at 15 °C was added sodium cyanoborohydride (80 mg) in portions over 30 min. The solvent was evaporated and the residue partitioned between dichloromethane and water. The combined organic extracts were washed with 2 M aqueous sodium hydrogen carbonate, dried and evaporated to give a gum. This was chromatographed on silica (8 g) eluting with 10→14% ethyl acetate in LP. Two main fractions were collected and evaporated to give the following. (a) The impure *anti*-isomer **23** (40 mg, *ca* 4.5% yield, based upon androsterone). This compound (40 mg) was acetylated (acetic anhydride–pyridine) and the product converted into the hydrochloride salt (15 mg), mp 213–216 °C (for further data see below); and (b) the *syn*-isomer **22** (240 mg, 27% yield, based on androstanone), colourless solid, mp 200–202 °C. Hydrochloride salt, mp 256–260 °C, *m/z* 421 (100, *M*) and 406 (50), 186 (70); δ_H($CDCl_3$–[$^2H_6$]-DMSO) 0.64 (3H, s), 0.74 (3H, s), 0.83 (1H, m), 1.10 (2H, m), 1.20–1.50 (10H, m), 1.30 (9H, s), 1.48–1.68 (5H, m), 2.24 (1H, dd, *J* 7, 1.5), 2.42 (1H, ddd, *J* 6, 6, 3.5), 3.90–4.40 (3H, m), 4.12 (1H, d, *J* 9.5), 7.24 (1H, d, *J* 1.5), 7.30 (1H, dd, *J* 7.5, 1.5), 7.39 (1H, d, *J* 7.5), 11.03 (1H, br s) and 12.11 (1H, br s) (Found: C, 75.8; H, 9.7; N, 3.0. $C_{29}H_{43}NO{\cdot}HCl$ requires C, 76.1; H, 9.6; N, 3.1%).

Anti-2α-Acetoxy-10-*tert*-butyl-6b,11b-dihydro-7*H*-(14α-androstano[17,16-*b*]indole) 24

To a well stirred solution of the crude, mixed acetoxyindole **20** and acetoxyindolenine **21** (400 mg) in TFA (6 cm^3) was added

triethylsilane (190 mg, 1.6 mmol) in one portion. After 1 h, the mixture was concentrated by solvent evaporation and the residue partitioned between diethyl ether and water. The combined extracts were dried and evaporated and the residue redissolved in diethyl ether (14 cm^3) and then treated with a saturated solution of hydrogen chloride in the same solvent (0.5 cm^3) to give a colourless powder. After this had been stirred for 1 h with diethyl ether, it was collected and washed with a few drops of the same solvent to afford the acetoxyindoline **24** (310 mg, 20% based on androstanone), mp 212–216 °C; δ_H 0.82 (3H, s), 1.00 (2H, m), 1.03 (3H, s), 1.17 (1H, m), 1.33 (9H, s), 1.37–1.95 (16H, m), 2.01 (3H, s), 2.44 (1H, br t), 3.96 (1H, dd, *J* 7, 7), 4.36 (1H, d, *J* 7), 4.98 (1H, br s), 7.28 (1H, d, *J* 1.5), 7.37 (1H, dd, *J* 8.5, 1.5), 7.60 (1H, d, *J* 8.5), 10.5 (1H, br) and 11.7 (1H, br) (Found: C, 74.5; H, 9.2; N, 2.8. $C_{31}H_{46}NO_2$·HCl requires C, 74.2; H, 9.0; N, 2.9%).

6-Phenoxyhexyl bromide

A stirred solution of sodium phenolate (10 g, 86 mmol) and 1,6-dibromohexane (21 g, 86 mmol) in 95% EtOH (200 cm^3) was heated at 85 °C for 3 h. The mixture was then concentrated by solvent evaporation and the residue partitioned betwen ethyl acetate and water. The organic phase was collected, dried and evaporated to afford a gum, which was mixed with a LP (15 cm^3) and left at 3 °C overnight. Colourless shiny plates of 1,6-diphenoxyhexane formed (3.8 g), mp 76 °C and these were collected and washed with small portions of LP. The filtrate was evaporated and the residue was chromatographed on silica (300 g). Elution with LP gave unchanged dibromide (3.0 g, 14%) whilst 1–2% ethyl acetate in LP produced the title compound (7.8 g); δ_H 1.49 (4H, quintet, *J* 3.5), 1.78 (2H, m), 1.88 (2H, m), 3.40 (2H, t, *J* 7), 3.94 (2H, t, *J* 6.5), 6.88 (2H, d, *J* 7.5), 6.92 (1H, t, *J* 7.5) and 7.27 (2H, t, *J* 7.5) (Found: *m/z* 258.0454. $C_{12}H_{17}O^{81}Br$ requires 258.0442).

11-Phenoxy-5-oxaundecyl bromide

(i) A mixture of 6-phenoxyhexyl bromide (7.7 g, 30 mmol), butane-1,4-diol (7.2 g, 800 mmol) and potassium hydroxide (4.0 g) was vigorously stirred and heated at 85 °C for 1.5 h after which it was poured into water (500 cm^3) to which ethyl acetate (250 cm^3) was then added. After continued stirring of the mixture for 15 min, the organic phase was separated, washed with water (3 × 50 cm^3), dried and evaporated to give 11-phenoxy-5-oxaundecan-1-ol as a colourless viscous liquid. This was used directly in the next step.

(ii) Phosphorus tribromide (2.5 g, 9.2 mmol) was added dropwise to well stirred 11-phenoxy-5-oxaundecan-1-ol (6.8 g, 25.6 mmol) over 15 min after which the mixture was cooled in a water-bath maintained at room temperature. After 1 h, water (250 cm^3) was added rapidly to the mixture, followed by ethyl acetate (150 cm^3); the reaction mixture was then stirred for 15 min after which the organic layer was separated and the aqueous phase extracted with ethyl acetate (50 cm^3). The combined organic layer and extracts were dried and evaporated to give the title compound as a pale-yellow, mobile oil (7.9 g), contaminated with a little 6-phenoxyhexyl bromide, formed by cleavage of one of the ether linkages. Column chromatography of this material on silica (140 g) eluting with LP→1.3% ethyl acetate in LP gave pure 11-phenoxy-5-oxaundecyl bromide (2.0 g, 29%); δ_H 1.35–1.50 (4H, m), 1.58 (2H, quintet, *J* 7.0), 1.67 (2H, quintet, *J* 7.0), 1.77 (2H, quintet, *J* 7.0), 1.91 (2H, quintet, *J* 7.0), 3.38 (2H, t, *J* 6.5), 3.39 (2H, t, *J* 6.5), 3.91 (2H, t, *J* 6.5), 4.04 (2H, t, *J* 6.5), 6.86 (2H, d, *J* 7.5), 6.90 (1H, t, *J* 7.5) and 7.24 (2H, t, *J* 7.5) (Found: *m/z* 329.1102. $C_{16}H_{25}O_2Br$ requires 329.1116).

6-(*N*,*N*-Dibenzylamino)hexyl bromide

A mixture of dibenzylamine (5.0 g, 25 mmol), 1,6-dibromohexane (9.3 g, 1.5 equiv.), anhydrous potassium carbonate (1.7 g) and ethanol (25 cm^3) were heated at reflux for 3 h after which the solids were filtered off and the filtrate evaporated to give an oil. This proved to be a mixture of the title compound and unchanged 1,6-dibromohexane. The latter compound could be removed by chromatography on silica (40 g) eluting with LP. The title compound was removed from the column by elution with 2% ethyl acetate in LP, as a colourless oil (4 g, 42.8%); δ_H 1.31 (4H, m), 1.50 (2H, quintet, *J* 7), 1.79 (2H, quintet, *J* 7), 2.40 (2H, t, *J* 7), 3.34 (2H, t, *J* 7), 3.53 (4H, s) and 7.18–7.40 (10 H, m). It was used directly in the next experiment.

11-*tert*-Butyl-1,2,3,4,4a,5,6,7,7a,8-decahydro-7a-[6-(*N*,*N*-dibenzylamino)hexyl]benzo[*d*]carbazole 27 (R = Bu^t)

A solution of 11-*tert*-butyl-1,2,3,4,4a,5,6,7-octahydrobenzo-[*f*]carbazole **26** (R = Bu^t) (1.5 g, 5.3 mmol) and 6-(*N*,*N*-dibenzylamino)hexyl bromide (1.9 g, 1 equiv.) in dry tetrahydrofuran (50 cm^3) under a nitrogen atmosphere was maintained at 0 °C whilst a solution of 1.7 M *tert*-butyllithium in pentane (7 cm^3, 2 equiv.) was added to it over 5 min. The reaction mixture was then warmed to room temperature over 1 h and stored for a further 16 h. Saturated aqueous ammonium chloride (3 cm^3) was then added to the mixture after which solvent was removed by evaporation. The residue was partitioned between ethyl acetate and water and the combined organic extracts were dried and evaporated to give a gum. This was chromatographed on silica (20 g), eluting with 1→2% ethyl acetate in LP to afford a colourless oil (0.5 g, 17.5%) which upon treatment with diethyl ether (50 cm^3) saturated with hydrogen chloride gave the dihydrochloride salt as colourless prisms, mp 150–154 °C (decomp.); ν_{max}/cm^{-1} 2730–2550 and 1605; δ_H 1.1–2.6 (25 H, m), 1.3 (9H, s), 2.8 (1H, br m), 4.08 (2H, q, *J* 7.5), 4.50 (2H, m), 4.72 (1H, dd, *J* 14, 4.5), 7.23 (1H, d, *J* 2), 7.27 (1H, dd, *J* 8.0, 2), 7.61 (1H, d, *J* 8), 7.4–7.8 (10H, m), 11.2 (2H, br s, exchangeable) and 12.3 (1H, br s, exchangeable) (Found: C, 76.2; H, 8.7; N, 4.0. $C_{40}H_{54}N_2$·2HCl requires C, 76.0; H, 8.8; N, 4.4%).

The following compounds **27** (R = Pr^i), **28** (R = Bu^t) and **29** (R = Bu^t) were prepared similarly.

1,2,3,4,4a,5,6,7,7a,8-Decahydro-7a-[6-(*N*,*N*-dibenzylamino)-hexyl]-11-isopropylbenzo[*d*]carbazole 27 (R = Pr^i)

This compound was prepared in 35% yield from 1,2,3,4,4a,5,6,7-octahydro-11-isopropylbenzo[*f*]carbazole **26** (R = Pr^i) and 6-(*N*,*N*-dibenzylamino)hexyl bromide. It was characterized as the dihydrochloride salt, mp 180 °C; ν_{max}/cm^{-1} 3354, 2720–2600 and 1610; δ_H 1.22 (6 H, d, *J* 6.5), 1.40–1.76 (13H, m), 1.86 (2H, m), 2.05–2.60 (10H, m), 2.82 (1H, m), 2.90 (1H, sept, *J* 6.5), 3.92 (1H, m), 4.13 (1H, dd, *J* 13.5, 7.0), 4.44 (2H, m), 4.65 (1H, dd, *J* 13.5, 4.5), 7.08 (1H, d, *J* 1.5), 7.10 (1H, dd, *J* 8, 1.5), 7.39–7.52 (6H, m), 7.59 (1H, d, *J* 8), 7.66 (2H, m), 7.74 (2H, m), 11.14 (2H, br s, exchangeable) and 12.14 (1H, br s, exchangeable) (Found: C, 75.0; H, 8.8; N, 4.4. $C_{39}H_{52}N_2$·2HCl requires C, 75.4; H, 8.7; N, 4.5%).

11-*tert*-Butyl-1,2,3,4,4a,5,6,7,7a,8-decahydro-7a-(11-phenoxy-5-oxaundecyl)benzo[*d*]carbazole 28 (R = Bu^t)

This compound was prepared from 11-*tert*-butyl-1,2,3,4,4a,5,6,7-octahydrobenzo[*f*]carbazole **26** (R = Bu^t) and 11-phenoxy-5-oxaundecyl bromide in 52% yield. Its hydrochloride salt formed colourless prisms, mp 137–139 °C; ν_{max}/cm^{-1} 2730–2500 and 1605; δ_H 1.32 (9H, s), 1.34–1.72 (19H, m), 1.78 (4H, quintet, *J* 6.5), 1.90–2.15 (6H, br m), 3.36 (2H, t, *J* 7.0), 3.41 (2H, t, *J* 6.5), 3.94 (2H, t, *J* 6.5), 6.88 (2H, d, *J* 7.5), 6.92 (1H, t, *J* 7.5), 7.26 (2H, t, *J* 7.5), 7.32 (1H, dd, *J* 8.0, 1.5), 7.44 (1H, br s), 7.69 (1H, br d, *J* 8.0), 11.35 (1H, br s, exchangeable) and 11.45 (1H, br s, exchangeable) (Found: C, 75.7; H, 9.5; N, 2.5. $C_{36}H_{53}NO_2$·HCl requires C, 76.1; H, 9.5; N, 2.4%).

11-*tert*-Butyl-1,2,3,4,4a,5,6,7,7a,8-decahydro-7a-(6-phenoxyhexyl)benzo[*d*]carbazole 29 (R = Bu^t)

This compound was also formed from 11-*tert*-butyl-1,2,3,4,4a,5,6,7-octahydrobenzo[*f*]carbazole **26** (R = Bu^t) and 6-phenoxyhexyl bromide in 50% yield. Since it failed to

crystallize it was characterized as its hydrochloride salt; colourless prisms, mp 150–152 °C; ν_{max}/cm^{-1} 2730–2500 and 1615; δ_H 1.25–1.30 (2H, m), 1.32 (9H, s), 1.43–2.17 (23H, m), 3.91 (2H, t, *J* 6.5), 6.86 (2H, d, *J* 7.5), 6.91 (1H, t, *J* 7.5), 7.26 (2H, t, *J* 7.5), 7.32 (1H, dd, *J* 8.0, 1.5), 7.43 (1H, d, *J* 1.5), 7.70 (1H, d, *J* 8.0), 11.33 and 11.49 (1H, br s) [Found: C, 77.2; H, 9.4; N, 2.8. $C_{32}H_{45}NO\cdot HCl$ requires C, 77.5; H, 9.3; N, 2.8%].

1-*tert*-Butoxycarbonyl-4-(2,4-dimethylanilino)piperidine 31 (R = Me)

A mixture of 2,4-dimethylaniline (4.8 g) and *N*-*tert*-butoxycarbonyl-4-piperidone (7.4 g) in toluene (50 cm^3) was heated at reflux for 4 h under Dean–Stark conditions in the presence of a few crystals of toluene-4-sulfonic acid. The solvent was then removed from the mixture and the product used directly in the next step.

1-*tert*-Butoxycarbonyl-4-(2,4-dimethylphenylamino)-4-(2-methylprop-2-enyl)piperidine 32 (R = Me)

Sodium-enriched lithium sand (1.12 g, 0.16 mol) was added slowly to pentane (50 cm^3) protected by an atmosphere of argon. 3-Chloro-2-methylprop-2-ene (11 g, 0.12 mol) was then added to the reaction mixture followed by the imine from the previous experiment (12 g, 0.04 mol) dissolved in THF (15 cm^3). Two drops of propan-2-ol were added to the mixture to initiate the reaction. After 30 h, saturated aqueous ammonium chloride was added to the mixture after which the organic phase was separated, washed with water (25 cm^3), dried and evaporated to give an oil. Chromatography of this eluting with 4% EtOAc–LP gave the title compound (4.8 g, 33.5%); ν_{max}/cm^{-1} 3410 and 1679; δ_H 1.5 (9H, s), 1.6 (2H, m), 1.71 (3H, s), 2.05 (2H, m), 2.12 (3H, s), 2.21 (3H, s), 2.50 (2H, s), 3.08 (2H, ddd, *J* 12, 12, 3), 3.15 (1H, br s, exchangeable), 3.78 (2H, m), 4.58 (1H, d, *J* 0.5), 4.86 (1H, d, *J* 0.5), 6.73 (1H, dd, *J* 8, 1), 6.88 (1H, d, *J* 8) and 6.89 (1H, d, *J* 1) (Found: *m/z* 358.2623. $C_{22}H_{34}N_2O_2$ requires 358.2620).

4′,4′,6′,8′-Tetramethylspiro[piperidine-4,2′-(1,2,3,4-tetrahydroquinoline)] 33 (R = Me)

Concentrated sulfuric acid (7 cm^3) was added slowly to the amine **32** (R = Me) (1.7 g) cooled in an ice-bath, after which the reaction mixture was warmed to 50–60 °C for 10 min. Ice (20 g) was added to the mixture after which it was basified with 6 M aqueous ammonium hydroxide and extracted with ethyl acetate (4 × 25 cm^3). Removal of the solvent from the combined extracts gave the title compound as an oil (1.03 g), a sample of which was purified by chromatography eluting with 40% EtOAc–LP to give a colourless gum; ν_{max}/cm^{-1} 3420 and 3350; δ_H 1.32 (6H, s), 1.64 (4H, m), 1.75 (2H, s), 2.14 (3H, s), 2.23 (3H, s), 2.40 (1H, br s, exchangeable), 2.90 (4H, m), 3.80 (1H, br s, exchangeable), 6.74 (1H, br s) and 6.90 (1H, br s) (Found: *m/z* 258.2092. $C_{17}H_{26}N_2$ requires 258.2096).

6′-Methoxy-4′,4′,8′-trimethylspiro[piperidine-4,2′-(1,2,3,4-tetrahydroquinoline] 33 (R = OMe) and 6′-hydroxy-4′,4′,8′-trimethylspiro[piperidine-4,2′-(1′,2′,3′,4′-tetrahydroquinoline)] 33 (R = OH)

The title compound was prepared from 4-methoxy-2-methylaniline and *N*-*tert*-butoxycarbonyl-4-piperidone by the same method as for **33** (R = Me). However, the crude product after the sulfuric acid treatment consisted of a mixture of the required spiro compound and its *O*-demethyl derivative **33** (R = OH) in the ratio 4:3. These two compounds were separated by chromatography; **33** (R = OMe); ν_{max}/cm^{-1} 3415 and 3300; δ_H 1.32 (6H, s), 1.57 (4H, m), 1.75 (2H, s), 2.20 (3H, s), 2.50 (1H, br s, exchangeable), 2.91 (4H, m), 3.67 (1H, br s, exchangeable), 3.75 (3H, s), 6.54 (1H, d, *J* 3) and 6.70 (1H, d, *J* 3) (Found: *m/z* 274.2046. $C_{17}H_{26}N_2O$ requires 274.2045); **33** (R = OH); ν_{max}/cm^{-1} 3470–3300; δ_H 1.29 (6H, s), 1.60 (4H, m), 1.73 (2H, s), 2.12 (3H, s), 2.50 (1H, br s, exchangeable), 2.88 (4H, m), 3.60 (1H, br s, exchangeable), 6.42 (1H, d, *J* 2.5) and 6.59 (1H, d, *J* 2.5) (Found: *m/z* 260.1870. $C_{16}H_{24}N_2O$ requires 260.1889).

1-Heptyl-4′,4′,6′,8-tetramethylspiro[piperidine-4,2′-(1,2,3,4-tetrahydroquinoline)] 34

A mixture of compound **33** (R = Me) (0.4 g, 1.6 mmol) in 1,2-dichloroethane (20 cm^3) and heptanal (0.2 g, 1 equiv.) was treated with portions of sodium triacetoxyborohydride (total 0.7 g, 2 equiv.). The reaction mixture was then stirred at room temperature for 4 h after which it was partitioned between dichloromethane (25 cm^3) and water (25 cm^3). The organic phase was collected, washed with water (10 cm^3), dried and evaporated. The residual gum was chromatographed on silica (50 g) eluting with 30% ethyl acetate in LP to give the title compound as a thick oil (0.36 g, 65.2%); ν_{max}/cm^{-1} 3399; δ_H 0.88 (3H, t, *J* 7), 1.3 (8H, m), 1.32 (6H, s), 1.50 (2H, m), 1.70 (4H, m), 1.73 (2H, s), 2.13 (3H, s), 2.22 (3H, s), 2.30 (2H, m), 2.33 (2H, t, *J* 8), 2.64 (2H, br m), 3.86 (1H, br s, exchangeable), 6.74 (1H, s) and 6.90 (1H, s); *m/z* (%) 356 (25, M^+). The dihydrochloride salt was a colourless solid, mp 201–203 °C (EtOH) was prepared by dissolving the amine in diethyl ether and adding diethyl ether saturated with hydrogen chloride; ν_{max}/cm^{-1} 3300, 2679, 2577 and 1605 (Found: C, 67.0; H, 9.9; N, 6.2. $C_{24}H_{40}N_2\cdot 2HCl$ requires C, 67.1; H, 9.8; N, 6.5%).

4′,4′,6′,8′-Tetramethyl-1-(11-phenoxy-7-oxaundecyl)spiro-[piperidine-4,2′-(1,2,3,4-tetrahydroquinoline)] 35

A mixture of compound **33** (R = Me) (0.48 g, 1.9 mmol), 11-phenoxy-7-oxaundecyl bromide‡ (0.74 g, 1.2 equiv.), potassium carbonate (0.6 g, 2 equiv.) and acetonitrile (30 cm^3) was heated under reflux for 4 h to give, after work-up and column chromatographic purification as in the case of the previous compounds, the title compound as an oil (0.49 g, 52%); ν_{max}/cm^{-1} 3410; δ_H 1.32 (6H, s), 1.4 (4H, m), 1.59 (4H, m), 1.7–1.95 (8H, m), 1.80 (2H, s), 2.14 (3H, s), 2.24 (3H, s), 2.8–3.2 (6H, m), 3.4 (1H, br s exchangeable), 3.41 (2H, t, *J* 6.5), 3.47 (2H, t, *J* 6.5), 3.99 (2H, t, *J* 6), 6.67 (1H, s), 6.88 (1H, s), 6.92 (3H, m) and 7.27 (2H, m) (Found: *m/z* 506.3884. $C_{33}H_{50}N_2O_2$ requires 506.3872).

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‡ Prepared in a similar manner to 11-phenoxy-5-oxaundecyl bromide.

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