Synthesis of New Thio Corticosteroids including 1α,9α-Epidithio-11β,17α,21-trihydroxy-16β-methylpregn-4-ene-3,20-dione[1]

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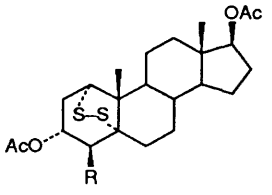
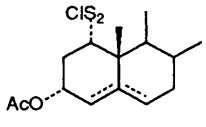
Reaction of 3-keto 1α,5α-epidithio steroids with sulphuryl dichloride cleaves the tertiary carbon–sulphur bond to afford a Δ^4-3-keto 1α-thiosulphenyl chloride which may be captured by various nucleophiles, *in situ*, to afford a number of novel 1α-substituted corticosteroid analogues. Intramolecular capture by a $\Delta^{9(11)}$-double bond leads to a synthesis of the title compound.

Corticosteroids possessing an oxygen functionality at C-11 are important adrenal hormones. As a consequence of this physiological importance we have long been interested in the development of novel corticosteroidal types.[2] Reported herein is a continuation of these studies in which we have synthesized a variety of new 1α-thio corticosteroids from 1α,5α-epidithio steroidal precursors.

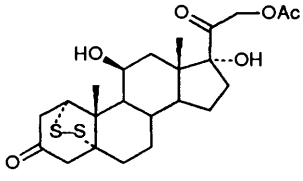
We have previously shown that treatment of the 1α,5α-epidithio steroid **1** with one molecular equivalent of sulphuryl dichloride yields the 4β-chloro-1α,5α-disulphide **2** and the Δ^5-1α-thiosulphenyl chloride **3** in approximately equimolar amounts.[3] The disulphide **2** is thought to arise *via* an intramolecular, *trans*, antiMarkovnikov addition of the intermediate Δ^4-1α-thiosulphenyl chloride **4**. We now report extension of the chemistry developed from this model system to the synthesis of novel thio corticosteroids.



1 R = H
2 R = Cl



3 Δ^5
4 Δ^4



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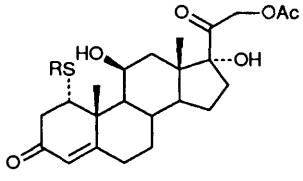


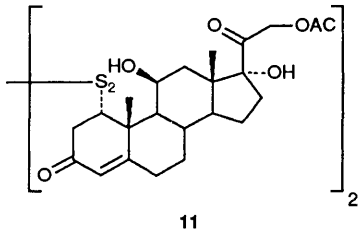
6 R = SCl
7 R = $SSCMe_3$
8 R = SSPh
9 R = SPh
10 R = H

Whereas electrophilic ring-opening of the 3α-acetate **1** gave a mixture of the Δ^5- and Δ^4-thiosulphenyl chlorides **3** and **4**, we reasoned that the presence of a 3-keto group (as in compound **5**[4]) should direct elimination exclusively toward the Δ^4-compound **6** and that the electron-deficient nature of the Δ^4-alkene in compound **6** would retard intramolecular addition of the sulphenyl halide to that moiety. Thiosulphenyl halide intermediates of type **6** were considered to offer considerable synthetic potential, particularly for functionalization of a steroidal $\Delta^{9(11)}$-double bond.

Results and Discussion

The 1α,5α-disulphide **5** was prepared in 62% yield from prednisolone 21-acetate as described by Tweit and Dodson.[4] Treatment of a solution of compound **5** with one molecular equivalent of sulphuryl dichloride, followed by addition of one molecular equivalent of 2-methylpropane-2-thiol, yielded the trisulphide **7** in 81% yield, a result consistent with and supporting the intermediacy of the expected thiosulphenyl chloride **6**. When the intermediate thiosulphenyl chloride **6** was quenched with the more nucleophilic and less hindered benzenethiol to give compound **8**, then only 0.75 molecular equivalents of thiol was added in order to avoid contamination by the disulphide **9**. This convenient reaction of the trisulphide **8** with benzenethiol was used to advantage in that treatment of compound **8** with a large excess of thiol yielded the 1α-thiol **10** (ν_{SH}) 2600 cm^{-1} in 43% yield, along with the phenyl disulphide **9** in 19–25% yield. Finally, the dimeric tetrasulphide **11** (λ_{max} 300 nm, ε 3080; tetrasulphide n ⟶ 3p-π*) was prepared in 61% yield by quenching of a solution of epidisulphide **5** and sulphuryl dichloride with potassium iodide.[5]

Having shown the intermediacy of a thiosulphenyl chloride and its utility for the synthesis of novel 1α-thiocorticoids, we sought to utilize that reactive intermediate in an intramolecular functionalization of the steroidal $\Delta^{9(11)}$-double bond. It was reasoned that treatment of a $\Delta^{9(11)}$-disulphide such as compound **12** with sulphuryl dichloride would first yield the thiosulphenyl chloride **13**. This was then expected readily to undergo a *trans*, antiMarkovnikov, intramolecular addition of S–Cl to the $\Delta^{9(11)}$-double bond to give the 1α,9α-disulphide **17**.[3] The 11β-chloro compound **17** has a diaxial arrangement of sulphur and chlorine similar to that found in the 4β-chloro compound **2**. As such, the two compounds ought to exhibit similar reactivity, and compound **17** might therefore be expected to



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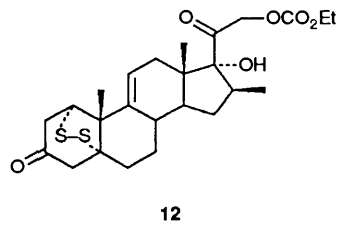

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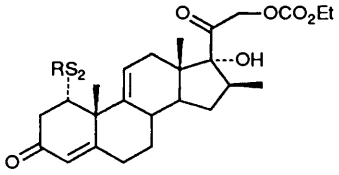
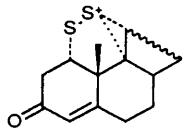
react with nucleophiles *via* a thiiranium ion intermediate **15**.[3] However, species **15** differs significantly from the thiiranium ion **16** derived from the substrate **2**, in that a nucleophile such as benzenethiol, which was found to attack ion **16** at the more substituted carbon, is prevented from reacting similarly with ion **15** (attack at C-9) by conformational factors. Therefore, attack upon the species **15** by added nucleophiles is restricted to the less substituted carbon (C-11) or to sulphur.



13 R = Cl
14 R = SPh



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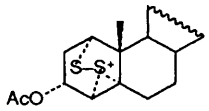

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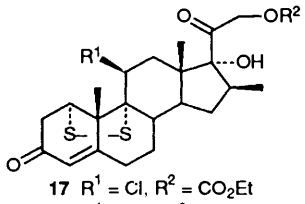
The 1α,5α-disulphide **12** was prepared in 70% yield from the corresponding dienone by using established methodology.[4] As predicted, addition of one molecular equivalent of sulphuryl dichloride resulted in rapid formation of the 11β-chloro-1α,9α-disulphide **17**. In support of the proposed structure, the fairly broad C-11 olefinic ^{1}H NMR resonance (δ 5.77) was replaced by a narrow singlet (δ 5.67) attributable to the C-4 olefinic hydrogen. The position of the 1α-hydrogen (δ 4.00) and C-21 methylene hydrogens (δ 4.90) were unchanged, but the latter now integrated for three hydrogens, consistent with the presence of a new signal attributable to the equatorial 11α-hydrogen in **17**.

No attempt was made to isolate the 11β-chloride **17**. It was, instead, treated with one molecular equivalent of benzenethiol. This reaction took over 1 h at ambient temperature, as compared with the essentially instantaneous reaction between compound **2** and benzenethiol.[3] Interestingly, the product obtained from the reaction of compound **17** was the phenyl trisulphide **14** (74% yield), indicating that benzenethiol had attacked the intermediate **15** at sulphur, rather than at the C-11 carbon.



17 R^1 = Cl, R^2 = CO_2Et
18 R^1 = OH, R^2 = CO_2Et
19 R^1 = OH, R^2 = H

By analogy with the 4β-chloride **2**, we predicted that substitution at C-11 of species **15** would be accomplished by treatment of the 11β-chloride **17** with aq. silver perchlorate, leading to the 11β-hydroxy 1α,9α-disulphide **18**. Indeed the predicted 1α,9α-disulphide **18** was isosolated in a gratifying 91% yield following treatment of compound **17** with aq. silver perchlorate, thus providing an entry into a new corticosteroid series. The analytical and spectral properties of compound **18** were entirely consistent with the proposed structure. In particular the ^{1}H NMR spectrum of compound **18** exhibited three single-hydrogen signals at δ 4.05, 4.69 and 5.72 attributable to the 1β-, 11α- and 4-hydrogen, respectively. Hydrolytic removal of the ethoxycarbonyl protecting group yielded a sample of the triol **19** in 65% yield.

Experimental

General experimental methods and instrumentation details are as previously reported.[3]

1α-tert-*Butyltrithio*-3,20-*dioxo-pregn*-4-*ene*-11β,17α,21-*triol* 21-*Acetate* **7**.—SO_2Cl_2 (47 mm^3, 0.58 mmol) was added to a solution of the disulphide **5**[4] (300 mg, 0.57 mmol, acetone solvate) in dry CH_2Cl_2 (100 cm^3). The reaction mixture was stirred for 10 min at room temperature and Bu^{t}SH (62 mm^3, 0.55 mmol) was added. After being stirred for a further 10 min the mixture was given an aq. work-up. Preparative TLC (PLC) [MeOH–CH_2Cl_2 (5:95)] yielded the tert-*butyl trisulphide* **7** (256 mg, 81%) as a foam, which was precipitated as a powder (223 mg, 70%) from diethyl ether–hexane, m.p. 123–127 °C, viscous melt; $[\alpha]_D^{25}$ +411° (*c* 0.9, $CHCl_3$); λ_{max}(MeOH)/nm 232.5 (ε 13 160); ν_{max}(KBr)/cm^{-1} 3600, 2990, 1750sh (21-OAc) 1725 (C-20 C=O), 1665 (C-3 C=O), 1620 (Δ^4) and 1235; δ_H($CDCl_3$) 0.93 (3 H, s, 18-H_3), 1.40 (9 H, s, CMe_3), 1.62 (3 H, s, 19-H_3), 2.18 (3 H, s, 21-OAc), 3.69 (1 H, br s, $w_{\frac{1}{2}}$ 8, 1β-H), 4.72 (1 H, br s, $w_{\frac{1}{2}}$ 9, 11α-H), 4.97 (2 H, s, $w_{\frac{1}{2}}$ 6, 21-H_2 AB system) and 5.67 (1 H, s, $w_{\frac{1}{2}}$ 3, 4-H); *m*/*z* 122, 121, 500 (M − C_4H_8) 435 and 556 (M$^+$) (Found: C, 58.2; H, 7.35; S, 17.5. $C_{27}H_{40}O_6S_3$ requires C, 58.25; H, 7.25; S, 17.3%).

3,20-*Dioxo*-1α-*Phenyltrithiopregn*-4-*ene*-11β,17α,21-*triol* 21-*Acetate* **8**.—SO_2Cl_2 (47 mm^3, 0.58 mmol) was added to a solution of the disulphide **5** (300 mg, 0.57 mmol, acetone solvate) in dry CH_2Cl_2 (100 cm^3). The reaction mixture was stirred at room temperature for 10 min, PhSH (44 mm^3, 0.43 mmol) was added, and the mixture was stirred for a further 10 min. Aq. work-up and PLC [MeOH–CH_2Cl_2 (5:95)] yielded the desired *phenyl trisulphide* **8** (193 mg, 59%), which was obtained as an amorphous powder from diethyl ether–hexane (117 mg), m.p. 114–117 °C, viscous melt; $[\alpha]_D^{25}$ +388° (*c* 0.7, $CHCl_3$); λ_{max}(MeOH) 295sh (ε 3270) and 230 (22 770); ν_{max}(KBr)/cm^{-1} 3550, 2980, 1750sh (21-OAc), 1735 (C-20 C=O), 1655 (C-3 C=O), 1620 (Δ^4), 1570, 1235 and 745; δ_H($CDCl_3$) 0.92 (3 H, s, 18-H_3), 1.54 (3 H, s, 19-H_3), 2.18 (3 H, s, 21-OAc), 3.68 (1 H, br s, $w_{\frac{1}{2}}$ 8, 1β-H), 4.68 (1 H, br s, $w_{\frac{1}{2}}$ 8, 11α-H), 5.00 (2 H, s, $w_{\frac{1}{2}}$ 5, 21-H_2 AB system), 5.72 (1 H, s, $w_{\frac{1}{2}}$ 3, 4-H), 7.39 (3 H, m, $w_{\frac{1}{2}}$ 11, ArH) and 7.65 (2 H, m, $w_{\frac{1}{2}}$ 9, ArH); *m*/*z* 122, 121 and 402 (M − PhS_3H) (Found: C, 60.4; H, 6.35; S, 16.5. $C_{29}H_{36}O_6S_3$ requires C, 60.4; H, 6.3; S, 16.7%).

1α-*Mercapto*-3,20-*dioxopregn*-4-*ene*-11β,17α,21-*triol* 21-*Acetate* **10**.—A solution of the disulphide **5** (300 mg, 0.57 mmol, acetone solvate) and SO_2Cl_2 (47 mm^8, 0.58 mmol) in dry CH_2Cl_2 (60 cm^3) was stirred at room temperature for 10 min, and then PhSH (60 mm^3, 0.58 mmol) was added. Following aq. work-up, the crude trisulphide **8** was redissolved in dry diethyl ether (5 cm^3) and PhSH (1.0 cm^3, 9.7 mmol) was added. The reaction mixture was stored overnight at −20 °C, after which it was reduced to ~2–3 cm^3 and the mixture was applied directly to two preparative plates. Development with MeOH–CH_2Cl_2 (5:95) afforded to bands. (i) 3,20-*Dioxo*-1α-*phenyldithiopregn*-4-*ene*-11β,17α,21-*triol* 21-*acetate* **9** (59 mg, 19%) which was further purified by dissolution in hot ethanol and addition of hexane until the solution became cloudy. A yellow oil settled out overnight, and the mother liquors were decanted off. Addition of more hexane to the mother liquors yielded pure compound **9** as an amorphous solid, m.p. 118–120 °C, viscous melt; $[\alpha]_D^{23}$ +166° (*c* 0.5, $CHCl_3$); λ_{max}(MeOH)/nm 236 (ε 18 340); ν_{max}(KBr)/cm^{-1} 3550, 2980, 1750 (21-OAc), 1725 (C-20 C=O), 1665 (C-3 C=O), 1620 (Δ^4), 1570, 1235 and 745; δ_H($CDCl_3$) 0.92 (3 H, s, 18-H_3), 1.55 (3, s, 19-H_3), 2.20 (3 H, s, 21-OAc), 3.48 (1 H, br s,

$w_{\frac{1}{2}}$ 8, 1β-H), 4.28 (1 H, br s, $w_{\frac{1}{2}}$ 7, 11α-H), 5.00 (2 H, s, $w_{\frac{1}{2}}$ 5, 21-H_2 AB system), 5.70 (1 H, s, $w_{\frac{1}{2}}$ 4, 4-H), 7.38 (3 H, m, $w_{\frac{1}{2}}$ 12, ArH) and 7.56 (2 H, m, $w_{\frac{1}{2}}$ 9, ArH); *m/z* 122, 121 and 402 (M − PhS_2H) (Found: C, 63.0; H, 6.65; S, 11.7. $C_{29}H_{36}O_6S_2$·0.5H_2O requires C, 62.9; H, 6.75; S, 11.6%).

(ii) 1α-*Mercapto*-3,20-*dioxopregn*-4-*ene*-11β,17α,21-*triol* 21-*acetate* **10** (107 mg, 43%) as a crystalline solid, m.p. 231–238 °C (decomp.). Recrystallization from $CHCl_3$–ethanol (trace)–diethyl ether yielded prisms (56 mg), m.p. 218–225 °C (decomp.) with evolution of gas; after recrystallization, final m.p. 235–238 °C; $[\alpha]_D^{23}$ +196° (*c* 0.4, $CHCl_3$); λ_{max}(MeOH)/nm 240 (ε 13 380); ν_{max}(KBr)/cm^{-1} 3550, 2990, 2600 (SH), 1740 (C-20 C=O and 21-OAc), 1665 (C-3 C=O), 1620 (Δ[4]), 1425, 1380 and 1250; δ_H[$CDCl_3$–$(CD_3)_2SO$–D_2O (3:1:1)] 0.88 (3 H, s, 18-H_3), 1.58 (3 H, s, 19-H_3), 2.13 (3 H, s, 21-OAc), 3.70 (1 H, br s, $w_{\frac{1}{2}}$ 9, 1β-H), 4.43 (1 H, br s, $w_{\frac{1}{2}}$ 8, 11α-H), 4.95 (2 H, d, *J* 4.5, 21-H_2 AB system) and 5.80 (1 H, s, $w_{\frac{1}{2}}$ 4, 4-H); *m/z* 122, 121, 402 (M − H_2S) and 436 (M^+) (Found: C, 63.0; H, 7.5; S, 7.55. $C_{23}H_{32}O_6S$ requires C, 63.3; H, 7.4; S, 7.35%).

Bis-(21-*Acetoxy*-11β,17α-*dihydroxy*-3,20-*Dioxopregn*-4-*en*-1α-*yl*) *Tetrasulphide* **11**.—A solution of the disulphide **5** (300 mg, 0.57 mmol) was treated with SO_2Cl_2 (47 mm^3, 0.58 mmol) and stirred for 10 min, then treated with a solution of potassium iodide (100 mg, 0.60 mmol) in 98:2 acetone–water (10 cm^3). The mixture was stirred for a further 5 min, and then given a thiosulphate work-up. Evaporation and PLC [MeOH–CH_2Cl_2 (5:95)] yielded the dimeric *tetrasulphide* **11** (162 mg, 61%), which was further purified by HPLC [MeOH–$CHCl_3$ (2:98) ($CHCl_3$ contains 0.75% ethanol as a stabilizer)] to yield an amorphous solid (107 mg, 40%), m.p. 165–167 °C (decomp.) with evolution of gas. This material underwent slow decomposition during crystallization/precipitation attempts, and invariably came out of solution as a gel. Repurification by PLC, using purified solvents to elute the compound from the plate, yielded compound **11** as a solid, m.p. 175–177 °C (decomp.) with evolution of gas; $[\alpha]_D^{15}$ +872° (*c* 0.4, $CHCl_3$); λ_{max}(MeOH)/nm 300sh (ε 3080) and 238 (26 800); ν_{max}(KBr)/cm^{-1} 3600, 2990, 1750 (21-OAc), 1730 (C-20 C=O), 1665 (C-3 C=O) and 1235; δ_H[$CDCl_3$–$(CD_3)_2SO$–D_2O (3:1:1)] 0.90 (3 H, s, 18-H_3), 1.67 (3 H, s, 19-H_3), 2.15 (3 H, s, 21-OAc), 3.78 (1 H, br s, $w_{\frac{1}{2}}$ 8, 1β-H), 4.63 (1 H, br s, $w_{\frac{1}{2}}$ 7, 11α-H), 4.96 (2 H, d, *J* 2.5, 21-H_2 AB system) and 5.68 (1 H, s, $w_{\frac{1}{2}}$ 3.5, 4-H); *m/z* 121, 122, 402 and 468 [Found: C, 56.5; H, 6.5; S, 12.65. $(C_{23}H_{31}O_6S_2$·$H_2O)_2$ requires C, 56.9; H, 6.85; S, 13.2%].

1α,5α-*Epidithio*-16β-*methyl*-3,20-*dioxopregn*-9(11)-*ene*-17α,21-*diol* 21-(*Ethyl carbonate*) **12**.—Dry ($CaSO_4$) H_2S was bubbled for 30 min through a solution of 16β-methyl-3,20-dioxopregna-1,4,9-11)-triene-17α,21-diol 21-(ethylcarbonate) (2.00 g, 4.7 mmol) and sulphur (150 mg, 1 mol equiv.) in dry pyridine (30 cm^3). After storage at room temperature for 2 days the solution was purged with argon and evaporated to dryness. Toluene (20 cm^3) was added, and the solution was re-evaporated to give a yellow foam. Flash chromatography [25 g, Merck silica gel 60 H; product eluted with EtOAc–benzene (7:93)] yielded 1α,5α-*epidithio*-16β-*methyl*-3,20-*dioxopregn*-9(11)-*ene*-17α,21-*diol* 21-(*ethyl carbonate*) **12** (1.62 g, 70%) as a yellow, crystalline solid, m.p. 198–202 °C, which was recrystallized from diethyl ether as yellow needles (1.30 g, 56%), m.p. 207–210 °C; $[\alpha]_D^{22}$ +17° (*c* 1.0, $CHCl_3$); λ_{max}(MeOH)/nm 372 (ε 60) and 255 (infl.) (420); ν_{max}(KBr)/cm^{-1} 3600, 2980, 1760, (C-21 OC=O), 1725 (C-3 and C-20 C=O) and 1260; δ_H($CDCl_3$) 0.79 (3 H, s, 18-H_3), 1.17 (3 H, d, *J* 7, 16β-Me), 1.33 (3 H, t, *J* 6.5, 21-OCO_2CH_2*Me*), 1.48 (3 H, s, 19-H_3), 4.06 (1 H, br s, $w_{\frac{1}{2}}$ 8, 1β-H), 4.23 (2 H, q, *J* 6.5, 21-OCH_2Me), 4.97 (2 H, s, $w_{\frac{1}{2}}$, 3.5, 21-H_2 AB system) and 5.77 (1 H, br s, $w_{\frac{1}{2}}$ 10, 11-H); *m/z* 494 (M^+), 281, 279, 297 and 429 (M − S_2H) (Found: C, 60.55; H, 6.95; S. 12.9. $C_{25}H_{34}O_6S_2$ requires C, 60.7; H, 6.95; S, 12.95%).

Treatment of 1α,5α-*Epidithio*-16β-*methyl*-3,20-*dioxopregn*-9(11)-*ene*-17α,21-*diol* 21-(*Ethyl carbonate*) **12** *with Sulphuryl Dichloride*.—SO_2Cl_2 (8 mm^3, 0.10 mmol) was added to a solution of the disulphide **12** (50 mg, 0.10 mmol) in $CDCl_3$ (1 cm^3) in a ^1H NMR tube. The ^1H NMR spectrum, recorded after 1 min, indicated clean conversion into 11β-chloro-1α,9α-epidithio-16β-methyl-3,20-dioxopregn-4-ene-17α,21-diol 21-(ethyl carbonate) **17**: δ 1.20 (6 H, s, $w_{\frac{1}{2}}$ 10, 18-H_3 and 16β-Me), 1.32 (3 H, t, *J* 7, 21-OCO_2CH_2*Me*), 1.74 (3 H, s, 19-H_3), 4.00 (1 H, br s, $w_{\frac{1}{2}}$ 8, 1β-H), 4.18 (2 H, q, *J* 7, 21-OCO_2CH_2Me), 4.90 (3 H, s, $w_{\frac{1}{2}}$ 7, 11α-H and 21-H_2 AB system) and 5.67 (1 H, s, $w_{\frac{1}{2}}$ 4, 4-H).

PhSH (10 mm^3, 0.10 mmol) was added 10 min after the addition of SO_2Cl_2, and the formation of the phenyl trisulphide **14** was monitored by observation of the decrease in the integral of the δ 4.90 peak, and the increase in the integral of the olefinic resonances. After 80 min the reaction was judged to be complete, and the mixture was poured into EtOAc (50 cm^3). Aq. work-up and PLC [MeOH–CH_2Cl_2 (3:97)] yielded 16β-*methyl*-3,20-*dioxo*-1α-*phenyltrithiopregna*-4,9-11)-*diene*-17α,21-*diol* 21-(*ethyl carbonate*) **14** (45 mg, 74%) as a slightly yellow glass, which was crystallized as prisms from diethyl ether–hexane, m.p. 135–138 °C (decomp.); $[\alpha]_D^{22}$ +355° (*c* 0.7, $CHCl_3$); λ_{max}(MeOH)/nm 295sh (ε 3760) and 225 (29 700); ν_{max}(KBr)/cm^{-1} 3500, 2990, 1755 (21-OC=O), 1725 (C-20 C=O), 1660 (C-3 C=O), 1615 (Δ[4]) and 1260; δ_H($CDCl_3$) 0.78 (3 H, s, 18-H_3), 1.15 (d, *J* 7, 16β-Me), 1.33 (t, *J* 7, 21-OCO_2CH_2*Me*), 1.47 (3 H, s, 19-H_3), 3.82 (1 H, br s, $w_{\frac{1}{2}}$ 9, 1β-H), 4.25 (2 H, q, *J* 7, 21-OCO_2CH_2Me), 5.00 (2 H, s, $w_{\frac{1}{2}}$ 3, 21-H_2 AB system), 5.72 (1 H, br s, $w_{\frac{1}{2}}$ 10, 11-H), 5.80 (1 H, s, $w_{\frac{1}{2}}$ 4, 4-H), 7.37 (3 H, m, $w_{\frac{1}{2}}$ 12, ArH) and 7.58 (2 H, m, $w_{\frac{1}{2}}$ 10, ArH); *m/z* 279, 297, 382, 494 (M − PhS + H), 428 (M − PhS_3H) and 462 (M − PhS_2 + H) (Found: C, 61.7; H, 6.3; S, 15.95. $C_{31}H_{38}O_6S_3$ requires C, 61.75; H, 6.35; S, 15.95%).

1α,9α-*Epidithio*-16β-*methyl*-3,20-*dioxopregn*-4-*ene*-11β,17α,21-*triol* 21-*Ethyl Carbonate*) **18**.—SO_2Cl_2 (32 mm^3, 0.40 mmol) was added to a solution of the disulphide **12** (200 mg, 0.40 mmol) in dry CH_2Cl_2 (50 cm^3). The reaction mixture was stirred at room temperature for 5 min. The solvent was then evaporated off under reduced pressure at 27 °C, and the crude 11β-chloro compound **17** was redissolved in dry benzene and the solution placed under argon. A mixture of $AgClO_4$ (200 mg, 0.96 mmol) in water (2 cm^3) and acetone (20 cm^3) was added and the reaction mixture immediately became cloudy. The mixture was then stirred at room temperature for 20 min, saturated aq. NaCl (1.0 cm^3) was added, and the mixture was stirred for a further 5 min to allow the precipitated solids to 'granulate'. Following filtration of the product, EtOAc (100 cm^3) was added and the reaction mixture was given an aq. work-up. PLC [MeOH–CH_2Cl_2 (5:95)] yielded the 11β-*hydroxy* 1α,9α-*epidisulphide* **18** (187 mg, 91%) as a yellow, crystalline solid, m.p. 201–204.5 °C. Recrystallization from acetone–hexane afforded pale yellow needles (136 mg, 66%), m.p. 218–221 °C (decomp.); $[\alpha]_D^{16}$ +144° (*c* 1.0, $CHCl_3$); λ_{max}(MeOH)/nm 355 (infl.) (ε 815), 320 (1550) and 244 (12 500); ν_{max}(KBr)/cm^{-1} 2550, 2990, 1755 (C-21 OC=O), 1735 (C-20 C=O), 1660 (C-3 C=O), 1625sh (Δ[4]) and 1260; δ_H($CDCl_3$) 1.13 (s, 18-H_3), 1.18 (d, *J* 7, 16β-Me), 1.33 (t, *J* 7, 21-OCO_2CH_2*Me*), 1.68 (3 H, s, 19-H_3), 4.05 (1 H, br s, $w_{\frac{1}{2}}$ 8, 1β-H), 4.22 (2 H, q, *J* 7, 21-OCO_2CH_2Me), 4.69 (1 H, br s, $w_{\frac{1}{2}}$ 8.5, 11α-H), 4.96 (2 H, s, $w_{\frac{1}{2}}$ 5, 21-H_2 AB system) and 5.72 (1 H, s, $w_{\frac{1}{2}}$ 5, 5-H); *m/z* 121, 510 (M^+), 279, 460 (M − S − H_2O), 297 and 427 (Found: C, 59.05; H, 6.65; S, 12.8. $C_{25}H_{34}O_7S_2$ requires C, 58.8; H, 6.7; S, 12.55%).

1α,9α-*Epidithio*-11β,17α,21-*trihydroxy*-16β-*methylpregn*-4-*ene*-3,20-*dione* **19**.—A solution of the disulphide **12** (400 mg, 0.80

mmol) in dry CH_2Cl_2 (100 cm^3) was treated with SO_2Cl_2 (64 mm^3, 0.80 mmol) and then with $AgClO_4$ (400 mg, 1.93 mmol) in water (4 cm^3)–acetone (40 cm^3) as described above. The crude 11β-hydroxy 1α,9α-epidisulphide **18** was dissolved in dry, vacuum-degassed MeOH (20 cm^3), and solid $NaHCO_3$ (84 mg, 1.0 mmol) and sodium acetate (20 mg, 0.24 mmol) were added. The reaction mixture was stirred at room temperature for 24 h, then was reduced in volume to 10 cm^3 under reduced pressure at 23 °C. Water (25 cm^3) was added, and the precipitated yellow solid was filtered off, washed with water, and dried *in vacuo* (235 mg). TLC [MeOH–CH_2Cl_2 (5:95)] indicated this material to be a mixture of compounds, while the mother liquors contained pure compound **19**. The mother liquors were extracted with EtOAc (3 × 50 cm^3), and the combined extracts were washed with saturated aq. NaCl (50 cm^3), dried ($MgSO_4$), and evaporated to yield the 21-*hydroxy* 1α,9α-*epidisulphide* **19** (139 mg, 39%) as a crystalline solid, m.p. 200–206 °C (decomp.). PLC [MeOH–CH_2Cl_2 (5:95)] of the above described precipitated solid yielded a further quantity of the 21-*alcohol* **19** (90 mg, 25%).

The 21-hydroxy 1α,5α-epidisulphide **19** (total crop 229 mg, 65%) was recrystallized from acetone–hexane as pale yellow prisms (147 mg, 41%), m.p. 233–235 °C (decomp. with evolution of gas); $[\alpha]_D^{26}$ +135° (*c* 0.3 EtOH); λ_{max}(MeOH)/nm 348 (infl.) (ε 860), 318 (1590) and 244 (12 590); ν_{max}(KBr)/cm^{-1} 3550, 2990, 1720 (C-20 C=O) and 1660 (C-3 C=O); δ_H([$^2H_6$]acetone–D_2O, (4:1)] 1.11 (s, 18-H_3), 1.12 (d, *J* 6, 16β-Me), 1.73 (3 H, s, 19-H_3), 4.19 (1 H, br s, $w_{\frac{1}{2}}$ 8, 1β-H), 4.42 (2 H, d, *J* 2.5, 21-H_2 AB system), 4.63 (1 H, br s, $w_{\frac{1}{2}}$ 8, 11α-H) and 5.67 (1 H, s, $w_{\frac{1}{2}}$ 4, 4-H) (Found: C, 60.0; H, 7.05; S, 14.65. $C_{22}H_{30}O_5S_2$ requires C, 60.25; H, 6.9; S, 14.6%).

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