Synthesis of Samanine

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The salamander alkaloid samanine (3-aza-A-homo-5β-androstan-16β-ol) has been synthesized in 10 steps from testosterone acetate in 17% overall yield, the transposition of the oxygen functionality from C-17 to C-16 being achieved by an elimination–hydroboration–oxidation sequence, and the A-ring expansion and insertion of nitrogen *via* a Schmidt reaction.

Samanine, 3-aza-A-homo-5β-androstan-16β-ol, **1**, is a minor component of the mixture of steroidal alkaloids obtained from the European Fire-salamander, *Salamandra maculosa*.[1] We were interested in examining the pharmacology of samanine and, as it is not readily obtained in bulk from natural sources, we decided to synthesize it from a commercially available, cheap, nitrogen-free steroid.

Although its structure is relatively simple, as compared with many of the other *Salamandra* bases, only three syntheses of samanine have been reported. Habermehl and Haaf[2] carried out a Beckmann rearrangement of the *E*/*Z* mixture of oximes prepared from the 16-*O*-acetate of 16β-hydroxy-5β-androstan-3-one **2**, separated the 16-*O*-acetates of the 3- and 4-aza-lactam **3** and **4**, respectively and reduced the former to samanine **1**. Oka and Hara[3] used a similar approach, but refined it by first separating the *E*- and *Z*-oximes of compound **2**, and showing that the former could be isomerised to the latter, which after Beckmann rearrangement gave lactam **3**, whence samanine **1** was prepared as before.

A third, formal, synthesis was reported by Rao and Weiler[4] who utilized a 2,3-seco-5β-steroid as the precursor for the 3-aza-A-homo-5β-ring system of a samanine analogue.

The Oka–Hara route to samanine appeared to us to be the most readily suited to the preparation of samanine but suffered in its original form in a rather lengthy transformation of *epi*-androsterone **5** into compound **2**. We therefore considered alternatives for its improvement.

The cheapest suitable starting materials appeared to be androst-5-ene or pregn-5-en-20-one derivatives. Shaw[5] had examined the transformation of pregn-16-en-20-ones into androstan-16-ones *via* their conversion into 17(20)-en-16-ones followed by Michael addition of water and a retro-aldol cleavage of the side-chain. However, the overall yields in this process were rather low, so we decided to concentrate upon the transformation of a 17-oxygenated androst-5-ene into the desired 16β-hydroxy system of compound **2**.

This choice then required the transposition of either a carbonyl or hydroxy function from C-17 to C-16. Numerous methods have been described for 1,2-carbonyl transpositions[6a] but after surveying them we decided to attempt first a 1,2-hydroxy transposition on a derivative of testosterone **6**, this currently being the cheapest of the readily available androstene derivatives.

Our idea was that after an elimination of the 17β-ol to produce an androst-16-ene it might be possible to achieve a regio- and stereo-selective hydration of the olefin to give the 16β-ol system. For this latter step we planned to use a sterically bulky borane, with the expectation that it would add from the α-face, with the borane remote from the quaternary system at C-13. Some precedents for the required regioselectivity existed in the observations of Calinaud *et al.*[7] who found that hydroboration of the 16-enes **7** and **8** with 9-borabicyclo-[3.3.1]nonane (**9-BBN**), followed by oxidation, gave the 16α- and 16β-hydroxy derivatives **9** and **10**, respectively.

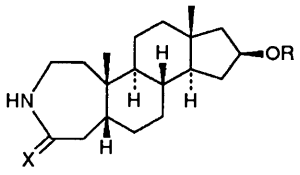
Before embarking upon this D-ring modification, we first set up the 5β-androstane system required in samanine **1**, by hydrogenation of testosterone acetate **11** in pyridine over palladium black, as described by Nishimura *et al.*[8] This resulted in the formation of compound **12** with great stereoselection and in high yield (97%).

Ester pyrolysis is a well established procedure for the preparation of alkenes. However, the conditions established for the thermolytic *syn*-elimination of acetic acid from the acetates of testosterone and hydrotestosterone are drastic (*ca.* 540 °C) and the yields of 16-alkenes not high.[9] Although the pyrolysis of steroidal 17-*O*-carbonate esters was found to give very much better yields of the 16-enes[9] the pyrolysis conditions were still severe (430 °C) and inconvenient for normal laboratory practice, and we therefore decided to explore the more readily thermolysed thionocarbonate esters.

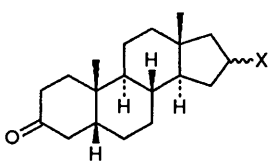
Guided by claims made for the pyrolysis of phenyl thionocarbonyl esters[10] we first examined the preparation and behaviour of the 4-chlorophenyl thionocarbonate **13**. Transesterification of compound **12** with methanolic sodium hydroxide readily gave hydroxy ketone **14**, but we found that the reaction of this alcohol with *O*-(4-chlorophenyl) chloro-(thioformate), according to the procedure of Gerlach and Müller,[10] gave a mixture containing considerable amounts of bis-(4-chlorophenyl) thionocarbonate **15** and also that chromatography was required for the removal of this by-product from the desired product **13**. Although pyrolysis of the latter afforded the desired 16-ene, albeit contaminated with impurities, the overall yield from the acetate **12** was unsatisfactory (*ca.* 38%).

We next examined the use of a thiocarbonylimidazolide derivative. Barton *et al.*[11] have established good procedures for the preparation of these compounds and we expected that they would undergo ready thermolysis. With the thought that it would be best to have the 3-keto group protected during the subsequent hydroboration reaction, we first converted keto ester **12** into the ethylene acetal **16**, deacetylated this to give the alcohol **17**, and then converted that into imidazolide **18** with thiocarbonyldiimidazole.[11] However, here too a rather tedious chromatographic purification was required to obtain compound **18**; and although the yield was reasonable (78% from **17**) and thermolysis of compound **18** at 200 °C gave an excellent yield of the desired alkene **19** (so far as we are aware the first use of a thiocarbonylimidazolide for such a purpose) we decided to examine the time-honoured Chugaev reaction before committing ourselves to this procedure.

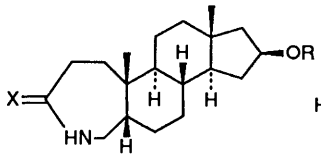
The xanthate **20** was readily produced from the alcohol **17** by sequential treatment with methyllithium, carbon disulphide and methyl iodide, and upon pyrolysis of the xanthate at 200 °C the 16-ene **19** was formed in 79% overall yield from acetate **16**. This therefore became our preferred route to that olefin.



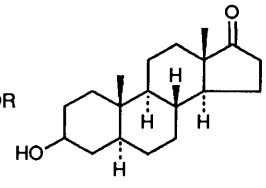
1 X = H_2, R = H
3 X = O, R = H
23 X = O, R = Bz



2 X = β-OH
21 X = α-OH
22 X = β-BzO



4 R = H, X = O
24 R = Bz, X = O
25 R = H, X = H_2



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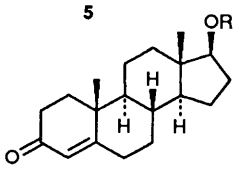
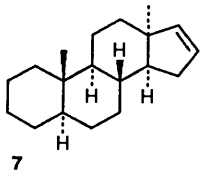


6 R = H
11 R = Ac



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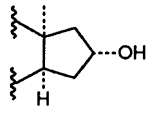

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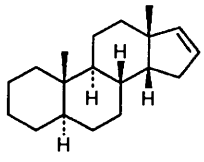

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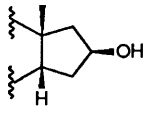

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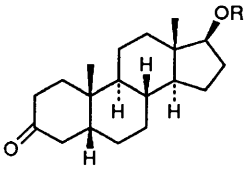
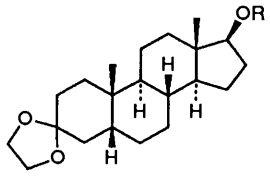
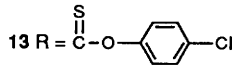


12 R = Ac

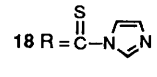


16 R = Ac
17 R = H



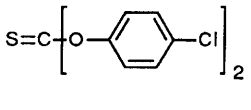
13 R = C(=S)–O–C$_6$H$_4$–Cl

14 R = H



18 R = C(=S)–N(C=CN=C)

20 R = CSMe (=S)



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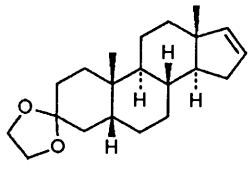

19

Hydroboration of alkene **19** with 9-BBN followed by oxidative work-up gave a mixture shown by GLC to consist of *cis*-cyclooctane-1,5-diol, starting material **19** and one other compound. Flash chromatographic fractionation of this mixture resulted in the isolation of the last compound, whose properties were in accord with its formulation as an ethylene acetal of a hydroxy-5β-androstan-3-one. That this was the expected 16α-hydroxy compound **21** was first inferred from a comparison of the ^{13}C-resonances attributed to C-13–17 of our product with those for the same D-ring carbons in other 16- and 17-hydroxylated androstanes.[12] This identification of compound **21** was then clinched by a sequence of reactions, involving its deacetalisation, inversion of the alcohol *via* a Mitsunobu reaction with acetic acid, and subsequent saponification. This gave material with properties as recorded for 16β-hydroxy-5β-androstan-3-one **2**.

Better yields of the 16β-ester were obtained when the Mitsunobu reaction was carried out using benzoic acid: this afforded the benzoate **22** in 87% yield (41% from testosterone acetate).

At this point a formal synthesis of samanine had been achieved, since both Habermehl and Haaf, and Oka and Hara, had converted the alcohol **2** or its 16-*O*-acetate derivative into that alkaloid. However, in completing the preparation of samanine we decided to explore a variation on the procedures used by these previous workers. By using the Schmidt reaction we were able to generate a mixture of the lactams **23** and **24** from benzoate **22** without the need to prepare the intermediate oximes and although this approach imposed a severe constraint of the conversion of testosterone acetate **11** into samanine, a matter to which we will return, it suited our needs: for we also needed to obtain compound **25** in order to compare its pharmacological properties with those of samanine **1**. Guided by the results obtained in a study of the model 17β-hydroxy-5β-androstan-3-one, in which the separation of the lactam mixture proved to be more difficult than that of the corresponding amines, we decided to reduce the mixed lactams (**23** and **24**) and then to separate samanine **1** from its 4-aza isomer **25**.

Numerous methods have been described for the reduction of lactams to azacycloalkanes, although in many cases the yields reported have been only moderate.[6b] Encouraged by reports which indicated that borane–dimethyl sulphide was the reagent of choice over complex hydrides in the reduction of amides to amines[6b] we first applied this procedure to the mixed lactams (**23** and **24**). However, in our hands the yield of mixed amines (**1** and **25**) obtained by this method was rather low (49%). We therefore returned to the use of lithium aluminium hydride, as described by Habermehl and Haaf,[2] with a modified work-up procedure.[13] This gave a good conversion (95%) of the mixed lactams into the corresponding amines (**1** and **25**). Separation of these proved to be more difficult than those of model amines, but was achieved by preparative TLC (PLC). This finally afforded samanine **1**, and its isomer **25**, with physical properties (m.p., MS, ^{1}H NMR) in excellent accord with those reported by Habermehl and Haaf,[2] and we extended their characterisation by ^{13}C NMR spectroscopy.

Even in its present unoptimised form our 10-step preparation of samanine in 17% from testosterone acetate compares favourably with the previous syntheses. The most obvious improvement would be to combine the first part of our synthesis, leading to 16β-hydroxy-5β-androstan-3-one **2**, with the latter part of Oka and Hara's, in which the oximes of that ketone were carried through to the alkaloid. This should provide a very practical route to samanine.

Experimental

M.p.s were determined on a Leitz hot stage and are uncorrected. A Nicolet DX system FT-IR spectrometer was used for the determination of IR spectra. All samples were prepared in KBr. The ^{1}H NMR and ^{13}C NMR spectra were determined with a Bruker AC-200 or an AM-400 spectrometer. All samples were dissolved and referenced by using deuteriochloroform (δ_C 77.0),

containing *ca.* 0.2% chloroform (δ_H 7.27), or deuteriobenzene (δ_C 128.0), containing *ca.* 0.2% benzene (δ_H 7.16). The chemical shifts of the other ^{1}H NMR and ^{13}C NMR signals are reported in ppm from these internal references, with the *J*-values in Hz. The numbers of H-atoms attached to carbon were determined using the Bruker Instrument Co. DEPT micro programs. In addition both COSY and XH-CORR micro-programs were employed in some structural assignments. Only significant, characteristic ^{1}H-resonances are reported. Low-resolution EIMS were routinely obtained on a V.G. 7070F spectrometer by Mrs. Qiao Wu, and the high-resolution EIMS were obtained on a Kratos MS80RFA GC/MS by Ms. Dorothy Fox, both of the Department of Chemistry Instrument Facility. Both instruments were operated at 70 eV. All samples were introduced using a direct insertion probe. The reported figures given in parentheses after the mass indicate the percent relative intensity of the base peak. A value of 10% was arbitrarily chosen as a cut-off, but we have also reported significant high-mass fragment ions, in addition to the molecular ion, when their abundance was lower than 10%. All GC retention times were recorded on a Hewlett-Packard 5890 Gas Chromatograph. The GC conditions were: initial oven temperature 200 °C; FID detector 250 °C; initial oven time 1 min; rate 10 °C min^{-1}; final oven temperature 250 °C; helium carrier gas flow rate 25 cm^3 min^{-1}; hydrogen flow 35 cm^3 min^{-1}; air flow 500 cm^3 min^{-1}; chart speed 5 cm min^{-1}; and a Megabore DB5 column (30 m × 0.53 mm i.d., film thickness 1.5 μm). The adsorbent used was silica gel 60 (E. Merck, 230–400 mesh). All columns were dry packed as recommended by Still *et al.*[14] The columns were eluted under positive air pressure. The solvent flow rate was 2 cm^3 min^{-1}. Column loading was based on ΔR_f and column diameter.[14] Silica gel 60 (E. Merck, F_{254}) plates (0.25 mm thick) 2.5 × 7.5 cm were used for analytical TLC, and molybdic acid was used to visualise the compounds on the developed plates. Solvent compositions are as stated in proportions by volume.

The molybdic acid spray reagent was prepared by dissolving ammonium molybdate (20 g) in a solution of sulphuric acid (25 cm^3) in water (400 cm^3). Plates sprayed with this reagent were briefly heated with a Heatgun®. The components appeared as dark blue spots on a white background. Elemental analyses for C, H and N were performed on a Perkin-Elmer CHN elemental analyser 240B by Ms. Dorothy Fox.

Catalytic Hydrogenation of Testosterone Acetate **11**; *Preparation of Compound* **12**.—Catalytic hydrogenation of testosterone acetate **11** (1.03 g, 3.03 mmol) in pyridine (100 cm^3) was carried out according to Nishimura's procedure.[8,15] The catalyst palladium black was pre-reduced prior to the reduction of the substrate. The uptake of hydrogen was measured at a rate of 0.8–1 cm^3 min^{-1}, and the hydrogenation time was 16 h. The desired 3-oxo-5β-androstan-17β-yl acetate **12** was isolated in 97% yield. This procedure was repeated numerous times with reproducible results. The product was obtained as plates, m.p. 142–145 °C (lit.,[16] 140–142 °C); ν_{max}(KBr)/cm^{-1} 2938, 1736, 1716 and 1251; δ_H($CDCl_3$) 0.84 (3 H, s), 1.20 (3 H, s), 2.05 (3 H, s), 2.69 (1 H, br t, *J* 13.5) and 4.62 (1 H, dd, *J* 7.5 and 7.6); δ_C($CDCl_3$) 37.2 (C-1), 37.1 (C-2), 212.8 (C-3), 42.3 (C-4), 44.3 (C-5), 25.4 (C-6), 26.5 (C-7), 35.4 (C-8), 40.9 (C-9), 35.0 (C-10), 20.7 (C-11), 37.1 (C-12), 42.8 (C-13), 50.8 (C-14), 23.5 (C-15), 27.6 (C-16), 82.7 (C-17), 12.1 (C-18), 22.6 (C-19), 21.1 (OCO*Me*) and 171.1 (*O*COMe) (^{13}C NMR values are within δ ±0.2 as compared with those listed for 3-oxo-5β-androstan-17β-yl acetate **12** by Blunt and Strothers);[12] *m/z* 332 (M$^+$, 6), 272 (32) and 43 (100) (Found: C, 76.1; H, 9.7%; M$^+$, 332.2353. Calc. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70%; M, 332.2333).

Preparation of 3,3-*Ethylenedioxy*-5β-*androstan*-17β-*yl Acetate* **16**.—3-Oxo-5β-androstan-17β-yl acetate **12** (6.07 g, 18.24 mmol) was dissolved in benzene (75 cm^3). To this were added toluene-*p*-sulphonic acid (12 mg) and ethylene glycol (10.2 cm^3, 183 mmol) and the mixture was then refluxed for 56 h with a Dean–Stark trap to remove water. After the reaction mixture had cooled, crushed anhydrous K_2CO_3 (0.50 g, 0.36 mmol) was added and the suspension was stirred for 10 min. Distilled water (50 cm^3) was then added to the reaction flask. The pH of the aq. solution was basic (pH 11). The benzene layer was separated from the aq. phase and the aq. layer was then extracted with chloroform (3 × 25 cm^3). The combined organic extracts were washed with brine (50 cm^3), dried over anhydrous K_2CO_3, then filtered, and the solvents were removed under reduced pressure to give a foamy residue of *compound* **16** (6.83 g, 99%), m.p. 97–99 °C; R_f 0.49 (hexanes–ethyl acetate, 4:1); ν_{max}(KBr)/cm^{-1} 2944, 1728, 1256, 1216 and 1097; δ_H($CDCl_3$) 0.77 (3 H, s), 0.96 (3 H, s), 2.03 (3 H, s), 2.20 (1 H, m), 3.94 (4 H, s, ethylenedioxy) and 4.58 (1 H, dd, *J* 7.4 and 7.5); δ_C($CDCl_3$) 37.2 (C-1), 109.9 (C-3), 39.9 (C-5), 25.8 (C-6), 27.6 (C-7), 35.5 (C-8), 40.9 (C-9), 34.7 (C-10), 20.6 (C-11), 42.8 (C-13), 50.9 (C-14), 23.5 (C-15), 27.6 (C-16), 82.9 (C-17), 12.1 (C-18), 23.1 (C-19), 64.2 and 64.1 (CH_2, ethylenedioxy resonances), 171.1 (*O*COMe) and 21.1 (OCO*Me*), [30.1, 34.3, 35.7 (unassigned CH_2 resonances for C-2, C-4, C-12)]; *m/z* 376 (M$^+$, 40), 333 (5), 316 (25), 125 (90), 99 (100), 55 (95) and 43 (92) (Found: C, 73.0; H, 9.8. $C_{23}H_{36}O_4$ requires C, 73.36; H, 9.64).

Transesterification Reaction on 3,3-*Ethylenedioxy*-5β-*androstan*-17β-*yl Acetate* **16**; *Preparation of the Alcohol* **17**.—Compound **16** (6.83 g, 18.14 mmol) was dissolved in methanol (200 cm^3). To this solution were added sodium metal spheres (0.87 g, washed with pentane, then dried and cut into small pieces). The solution which resulted was stirred for 12 h at room temperature. The reaction mixture was worked up by the addition of small lumps of solid CO_2 (*ca.* 0.50 g) and, when they had evaporated, this was followed by the addition of K_2CO_3 (0.50 g, 3.6 mmol). The resultant mixture was stirred for 10 min at room temperature. The methanol was then removed under reduced pressure. The residue was then shaken successively with water (50 cm^3) and chloroform (4 × 50 cm^3). The combined chloroform extracts were washed with brine (100 cm^3), dried over anhydrous K_2CO_3, filtered, and evaporated to dryness under reduced pressure. An amorphous material, the *alcohol* **17**, was obtained (5.70 g, 94%), m.p. 158–159 °C; R_f 0.12 (hexanes–ethyl acetate, 4:1); ν_{max}(KBr)/cm^{-1} 3487, 2924, 1447, 1369, 1260, 1108 and 1091; δ_H($CDCl_3$) 0.74 (3 H, s), 0.97 (3 H, s), 3.66 (1 H, ddd, *J* 7.5, 8.0 and 10.6) and 3.95 (4 H, s, ethylenedioxy); δ_C($CDCl_3$) 36.9 (C-1), 110.0 (C-3), 40.1 (C-5), 25.9 (C-6), 26.6 (C-7), 35.8 (C-8), 40.9 (C-9), 35.7 (C-10), 20.7 (C-11), 43.1 (C-13), 51.2 (C-14), 23.4 (C-15), 30.6 (C-16), 81.9 (C-17), 11.1 (C-18), 23.1 (C-19) and 64.2 and 64.1 (CH_2, ethylenedioxy resonances) [30.1, 34.3, 36.9 (unassigned CH_2 resonances for C-2, C-4, C-12)]; *m/z* 334 (M$^+$, 20), 125 (88), 99 (100), 55 (40), 41 (30) and 32 (37) (Found: C, 75.3; H, 10.4%; M$^+$, 334.2501. $C_{21}H_{34}O_3$ requires C, 75.41; H, 10.25%; M, 334.2509).

Preparation of 17β-*Hydroxy*-5β-*androstan*-3-*one* **14**.—The ester **12** (2.72 g, 8.2 mmol) was dissolved in tetrahydrofuran (THF) (75 cm^3) containing aq. HCl (6 mol dm^{-3}; 10 cm^3) and the solution was stirred overnight (12 h) at room temperature. The solvent was removed under reduced pressure and the solid which remained was then dissolved in distilled water (25 cm^3) and extracted with diethyl ether (4 × 25 cm^3). The extracts were combined, dried ($MgSO_4$), filtered and evaporated to dryness under reduced pressure. Recrystallisation from acetone–hexanes gave the title ketone **14** as flakes (2.20 g, 92%), m.p. 139.5–141 °C (lit.,[16] 142–142.5 °C from aq. acetone); R_f 0.39 (hexanes–ethyl acetate, 3:2); ν_{max}(KBr)/cm^{-1} 3467, 2951, 1701 and 1052; δ_H($CDCl_3$) 0.76 (3 H, s), 1.03 (3 H, s), 2.67 (1 H, br t,

J 13.4) and 3.66 (1 H, br t, *J* 8.3); $\delta_C(CDCl_3)$ 31.1 (C-1), 36.8 (C-2), 212.9 (C-3), 42.2 (C-4), 44.2 (C-5), 25.3 (C-6), 26.4 (C-7), 35.6 (C-8), 40.9 (C-9), 34.9 (C-10), 20.7 (C-11), 36.9 (C-12), 43.1 (C-13), 50.9 (C-14), 23.3 (C-15), 30.5 (C-16), 81.7 (C-17), 11.1 (C-18), 22.6 (C-19) (as lit.,[14] for 17β-hydroxy-5β-androstan-3-one **14**); *m/z* 290 (M^+, 45), 272 (19), 257 (19), 247 (30), 220 (36), 161 (30), 121 (37), 107 (52), 95 (55), 81 (72), 67 (71), 55 (100) and 41 (95) (Found: M^+, 290.2234. Calc. for $C_{19}H_{30}O_2$: M, 290.2247).

Formation of O-(4-*Chlorophenyl*) O-(3-*Oxo*-5β-*androstan*-17β-*yl*) *Thiocarbonate* **13**.—Following the procedure described by Gerlach and Müller,[10] 17β-hydroxy-5β-androstan-3-one **14** (0.50 g, 1.70 mmol) was dissolved in dry pyridine (10 cm^3) under N_2. To this was added dropwise a solution of *O*-(4-chlorophenyl) chloro(thioformate) (0.39 g, 0.19 mmol) in 1,4-dioxane (1 cm^3). After the addition of the reagent, the solution turned amber yellow in colour. The reaction was stirred at room temperature for 36 h. The solvent pyridine was then evaporated off under reduced pressure and the residue was redissolved in chloroform (15 cm^3). The chloroform solution was washed with aq. HCl (0.5 mol dm^{-3}; 2 × 20 cm^3), dried over anhydrous $MgSO_4$, filtered and evaporated to dryness under reduced pressure. The brown coloured residue (0.60 g) was flash chromatographed on silica gel (hexanes–ethyl acetate, 8:1) to yield two components, with R_f 0.36 and 0.24. The major product was the bis-(4-chlorophenyl) thionocarbonate **15** a solid (0.204 g), m.p. 150–154 °C; R_f 0.73 (hexanes–ethyl acetate, 8:1); ν_{max}(KBr)/cm^{-1} 3100, 2924, 1778, 1483, 1262, 1209, 1082, 1012 and 829; $\delta_H(CDCl_3)$ 7.17 (2 H, m) and 7.43 (2 H, m); $\delta_C(CDCl_3)$ 194.1 (C=S) (151.9, 129.8, 123.2, 122.2 aromatic-ring resonances); *m/z* 298 (M^+, 2), 270 (60), 171 (75), 143 (92), 111 (100), 99 (58), 75 (94) and 40 (82) (Found: M^+, 297.9662. Calc. for $C_{13}H_8Cl_2O_2S$: M, 297.9623).

The second component, the carbonate **13**, was a fluffy solid consisting of fine needles (0.20 g, 25%), m.p. 196.5–197 °C; ν_{max}(KBr)/cm^{-1} 2982, 2931, 2854, 1715, 1490, 1305, 1209, 1186 and 833; $\delta_H(CDCl_3)$ 0.91 (3 H, s), 1.05 (3 H, s), 2.68 (1 H, br t, *J* 14.2), 5.12 (1 H, dd, *J* 7.3 and 7.3), 7.07 (2 H, m, ArH) and 7.73 (2 H, m, ArH); $\delta_C(CDCl_3)$ 37.1 (C-1), 36.9 (C-2), 212.6 (C-3), 42.3 (C-4), 44.2 (C-5), 23.3 (C-6), 26.4 (C-7), 35.3 (C-8), 40.9 (C-9), 35.0 (C-10), 20.6 (C-11), 37.0 (C-12), 43.4 (C-13), 50.4 (C-14), 23.5 (C-15), 26.8 (C-16), 95.6 (C-17), 12.5 (C-18), 22.6 (C-19) and 194.6 (C=S) [151.8, 131.9, 129.5, 123.4 (aromatic-ring resonances)].

Some remaining starting material **14** (0.30 g) was retained on the column during the chromatographic process.

Pyrolysis of O-(4-*Chlorophenyl*) O-(3-*Oxo*-5β-*androstan*-17β-*yl*) *Thiocarbonate* **13**.—The pyrolysis of compound **13** (0.11 g, 0.23 mmol) was performed in a Kugelrohr apparatus. The pyrolysis oven-temperature was held at 200 °C for 0.5 h, while the contents of the flask were kept under a vacuum of 15 mmHg provided by a water aspirator. The volatiles were collected using a solid CO_2–acetone cooling bath. The collected material was dissolved in chloroform (10 cm^3) and washed twice with aq. NaOH (0.2 mol dm^{-3}; 10 cm^3). The chloroform layer was then dried over anhydrous $MgSO_4$, filtered and evaporated to dryness under reduced pressure to yield crude 5β-androst-16-en-3-one (0.04 g); $\delta_H(CDCl_3)$ 0.79 (3 H, s), 1.07 (3 H, s), 2.73 (1 H, br t, *J* 15.8), 5.72 (1 H, m, vinylic proton) and 5.86 (1 H, m, vinylic proton); *cf.* the data for the pure acetal **19** (see below).

Despite repeated washing of this product with aq. NaOH, and column chromatography, we were unable to completely purify the 16-olefin. TLC (hexanes–ethyl acetate, 6:1) after column chromatography revealed three components: one major, R_f 0.46 (16-ene), and two minor components, R_f 0.28 (starting material **14**) and 0.16 (not identified).

Preparation of O-(3,3-*Ethylenedioxy*-5β-*androstan*-17β-*yl*) O-(*Imidazol*-1-*yl*) *Thiocarbonate* **18**.—The esterification of 3,3-ethylenedioxy-5β-androstan-17β-ol **17** (1.04 g, 3.1 mmol) with *N,N'*-thiocarbonyldiimidazole (3.32 g, 18.9 mmol) in dry THF (60 cm^3) was carried out as described by Barton *et al.*[11] The solution was boiled under reflux for 16 h. The work-up involved pouring the yellow coloured reaction mixture into distilled water (100 cm^3) and evaporation of the resultant mixture to half-volume under reduced pressure, and then extraction of the aq. suspension with diethyl ether (4 × 50 cm^3). The combined extracts were washed with brine (100 cm^3), dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product (2.01 g) was purified by flash column chromatography on silica gel with an isocratic solvent system (hexanes–ethyl acetate, 3:2). This gave the desired *product* **18** (1.07 g, 78%), m.p. 216–218 °C; R_f 0.48 (hexanes–ethyl acetate, 3:2); ν_{max}(KBr)/cm^{-1} 3135, 3114, 2931, 1475, 1330, 1282, 1230, 1101 and 1001; $\delta_H(CDCl_3)$ 0.95 (3 H, s), 0.98 (3 H, s), 3.95 (4 H, s, ethylenedioxy), 5.29 (1 H, dd, *J* 7.2, 7.2), 7.04 (1 H, t, *J* 1.6), 7.62 (1 H, t, *J* 1.5) and 8.33 (1 H, t, *J* 1.0); $\delta_C(CDCl_3)$ 109.8 (C-3), 39.8 (C-5), 35.4 (C-8), 40.8 (C-9), 34.6 (C-10), 20.5 (C-11), 43.7 (C-13), 50.4 (C-14), 23.6 (C-15), 91.9 (C-17), 13.0 (C-18), 23.0, (C-19), 64.2 and 64.0 ($(CH_2$, ethylenedioxy resonances), 184.1 (C=S) (136.6, 130.7 and 117.8 imidazolide ring resonances) (additional unassigned CH_2 resonances for C-1, C-2, C-4, C-6, C-7, C-12, C-16 are at δ_C 37.2, 35.6, 34.2, 30.1, 27.0, 26.5 (and 25.7); *m/z* 444 (M^+, 20), 316 (15), 125 (35), 99 (100), 81 (23), 69 (35), 55 (46) and 41 (53) (Found: C, 67.7; H, 8.1; N, 6.4%; M^+, 444.2456. $C_{25}H_{36}N_2O_3S$ requires C, 67.53; H, 8.16; N, 6.30%; M, 444.2449).

Preparation of the 17β-*Xanthate Ester* **20**.—In flame-dried glassware and under nitrogen was placed a solution of the alcohol **17** (1.02 g, 3.05 mmol in 20 cm^3 of dry THF). After the reaction flask had been cooled in an acetone–solid CO_2 bath, dry THF (20 cm^3) and a trace of 2,2'-biquinoline (*ca.* 5 mg) was added to the solution. To this solution was added methyllithium in THF (0.5 mol dm^{-3}, concentration determined by titration against diphenylacetic acid, 6 cm^3, 3.0 mmol) was added. The solution turned light lime-green in colour. This was quickly followed by the addition of carbon disulphide (0.75 cm^3, 3.36 mmol), which turned the colour of the solution to a dark maroon. The reaction mixture was stirred for 15 min, and then methyl iodide (1 cm^3, 16 mmol) was added. The mixture was stirred while it was allowed to warm to room temperature gradually during 3 h, and was then poured into a beaker containing distilled water (200 cm^3), and this mixture was then transferred into a separating funnel and extracted with diethyl ether (4 × 50 cm^3). The combined extracts were washed with brine (100 cm^3), dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The brown coloured crude product (1.45 g) was shown on TLC (hexanes–ethyl acetate, 9:1) to consist of three components, with R_f 0.66, 0.53 and 0.37, the first two of which stained weakly with I_2, the latter intensely. The entire sample was then subjected to flash column chromatography on silica gel with an isocratic solvent system (hexanes–ethyl acetate, 9:1). Combination of those fractions which were homogeneous on TLC (R_f 0.37) and evaporation under reduced pressure gave the xanthate ester *O*-(3,3-ethylenedioxy-5β-androstan-17β-yl) *S*-methyl dithiocarbonate **20** (1.17 g, 91%). This result was reproduced in subsequent experiments. A small sample of this product was recrystallised from diethyl ether–hexanes to give *compound* **20** as flat, translucent flakes, m.p. 117–117.5 °C; ν_{max}(KBr)/cm^{-1} 2917, 1448, 1230 and 1070; $\delta_H(CDCl_3)$ 0.88 (3 H, s), 0.95 (3 H, s), 2.52 (3 H, s, SMe), 3.92 (4 H, s, ethylenedioxy) and 5.33 (1 H, dd, *J* 7.2 and 7.2); $\delta_C(CDCl_3)$ 109.7 (C-3), 39.9 (C-5), 335.4 (C-8), 40.8 (C-9), 34.7 (C-10), 20.5 (C-11), 43.7 (C-13), 50.5 (C-14), 23.6

(C-15), 91.9 (C-17), 12.7 (C-18), 23.9 (C-19), 64.2 and 64.9 (CH_2, ethylenedioxy resonances), 18.7 (SMe) and 215.5 (C=S) [37.3, 35.7, 34.2, 30.1, 27.1, 26.6, 25.7 (additional unassigned CH_2 resonances for C-1, C-2, C-4, C-6, C-7, C-12, C-16)]; *m/z* 424 (M^+, 1), 317 (50), 225 (35), 203 (18), 125 (50), 99 (100) and 55 (40) (Found: C, 65.45; H, 8.4%; M^+, 424.2113. $C_{23}H_{36}O_3S_2$ requires C, 65.05; H, 8.55%; M, 424.2108).

Pyrolysis of the Thiocarbonylimidazolide **18**.—A sample of compound **18** (0.25 g) was heated at 210 °C (bath) in a Kugelrohr apparatus under water aspirator vacuum (*ca.* 15 mmHg) for 2 h. The product, which was collected in the first bulb cooled in acetone–solid CO_2, was dissolved in $CHCl_3$ (*ca.* 15 cm^3) and washed successively with 5% aq. HCl (3 × 5 cm^3), followed by brine (10 cm^3). The $CHCl_3$ solution was then dried (Na_2SO_4) and the solvent was removed under reduced pressure to yield compound **19** (0.16 g, 91%) with ^1H and ^{13}C NMR spectra identical with those of the alkene produced by pyrolysis of the xanthate **20** in the next experiment.

Pyrolysis of the 17β-*Xanthate Ester* **20**.—The pyrolysis of ester **20** (0.67 g, 1.58 mmol) was performed in a Kugelrohr apparatus. The pyrolysis-oven temperature was held at 200 °C for 4 h, while the contents of the flask were kept under a vacuum of 12 mmHg provided by a water aspirator. The volatiles were collected using a solid CO_2–acetone cooling-bath. TLC (hexanes–ethyl acetate, 12:1) of the crude product revealed one major component, R_f 0.33 (3,3-ethylenedioxy-5β-androst-16-ene **19**) and one minor component, R_f 0.24 (residual **20**). Flash column chromatography, on silica gel with the usual solvent system (hexanes–ethyl acetate, 12:1), of crude material (0.44 g) separated the 16-ene product **19** (0.33 g) from the 17β-xanthate ester **20** (0.035 g). In subsequent pyrolyses the yield of ene product **19** after chromatography was typically *ca.* 87%. 3,3-*Ethylenedioxy*-5β-*androst*-16-*ene* **19** was obtained as an amorphous, pale yellow solid, m.p. 69–70 °C; ν_{max}(KBr)/cm^{-1} 3031, 2924, 1448, 1096 and 706; δ_H($CDCl_3$) 0.76 (3 H, s), 1.0 (3 H, s), 2.04 (1 H, br t, *J* 13.5), 3.95 (4 H, s, ethylenedioxy), 5.70 (1 H, m) and 5.84 (1 H, m); δ_C($CDCl_3$) 110.0 (C-3), 40.7 (C-5), 34.3 (C-8), 40.0 (C-9), 34.9 (C-10), 20.9 (C-11), 45.7 (C-13), 56.2 (C-14), 129.3 (C-16), 143.9 (C-17), 17.0 (C-18), 23.1 (C-19), 64.2 and 64.0 (CH_2, ethylenedioxy resonances) [35.1, 35.8, 34.2, 31.9, 30.1, 26.7, 26.4 (unassigned CH_2 resonances for C-1, C-2, C-4, C-6, C-7, C-12, C-15)]; *m/z* 316 (M^+, 50), 187 (10), 125 (88), 99 (100), 79 (28), 55 (38) and 41 (33) (Found: C, 79.6; H, 10.0%; M^+, 316.2405. $C_{21}H_{32}O_2$ requires C, 79.70; H, 10.19%; M, 316.2404).

Preparation of 3,3-*Ethylenedioxy*-5β-*androstan*-16α-*ol* **21**.—Hydroboration of the 16-ene steroid **19** (1.01 g, 3.2 mmol) with a solution of 9-BBN in THF (0.5 mol dm^{-3}; 9.4 cm^3, 4.8 mmol) was carried out as described by Brown.[17] The reaction mixture was stirred at 60 °C for 16 h under an atmosphere of N_2 before being subjected to oxidative work-up. The reaction flask was first cooled in an ice–water-bath, then aq. NaOH (3 mol dm^{-3}; 40 cm^3) was added, followed by the slow addition of H_2O_2 (30% aq.; 40 cm^3), and finally potassium carbonate (0.50 g), after which the solution was stirred vigorously for 1 h. The organic layer was then separated and the aq. layer was extracted using diethyl ether (4 × 50 cm^3). All organic layers were combined, washed with saturated aq. potassium carbonate (150 cm^3), dried over anhydrous $MgSO_4$, filtered and evaporated to dryness under reduced pressure. TLC (hexanes–ethyl acetate, 3:2) revealed 3 minor components, with R_f 0.84 (starting material), 0.55 (unidentified), 0.12 (unidentified material) and a major component, R_f 0.43 (3,3-ethylenedioxy-5β-androstan-16-α-ol **21**). Analysis by GLC revealed components with retention times of 2.24, 10.37 and 10.86 min, corresponding to cyclooctane-1,5-diol; 3,3-ethylenedioxy-5β-androst-16-ene **19**, and 3,3-ethylenedioxy-5β-androstan-16α-ol **21**, respectively. Isolation of the major component was achieved by flash column chromatography on silica gel with hexane–ethyl acetate (3:2) to give *compound* **21** (0.72 g, 68%), m.p. 165–166.5 °C; ν_{max}(KBr)/cm^{-1} 3466, 2931, 1448 and 1056; δ_H($CDCl_3$) 0.70 (3 H, s), 0.95 (3 H, s), 3.96 (4 H, s, ethylenedioxy) and 4.46 (1 H, m, *J* 6.5); δ_C($CDCl_3$) 110.1 (C-3), 40.1 (C-5), 40.9 (C-9), 34.8 (C-10), 20.7 (C-11), 38.9 (C-12), 41.9 (C-13), 52.2 (C-14), 71.9 (C-16), 52.2 (C-17), 18.7 (C-18), 23.1 (C-19), 64.2 and 64.0 (CH_2, ethylenedioxy resonances) (*cf.* lit.,[12] reference compounds 5α-androstan-16α- and 16β-ol) [37.3, 35.8, 35.6, 34.2, 30.2, 26.7, 26.6 (unassigned CH_2 resonances for C-1, C-2, C-4, C-6, C-7, C-8, C-15)]; *m/z* 334 (M^+, 18), 125 (92), 99 (100), 55 (32), 41 (27) and 32 (60) (Found: C, 76.05; H, 10.2%; M^+, 334.2506. $C_{21}H_{34}O_3$ requires C, 75.40; H, 10.25%; M, 334.2509).

Deprotection of 3,3-*Ethylenedioxy*-5β-*androstan*-16α-*ol* **21**; *Preparation of* 16α-*hydroxy*-5β-*androstan*-3-*one*.—Acetal deprotection of 3,3-ethylenedioxy-5β-androstan-16α-ol **21** was carried out by a procedure similar to that described by Grieco *et al.*[18] To a solution of the acetal (0.31 g, 0.98 mmol) in THF (20 cm^3) was added aq. HCl [5% (w/v); 25 cm^3]. The reaction mixture was stirred at room temperature for 18 h. Work-up involved the extraction of the aq. layer with diethyl ether (4 × 20 cm^3). The combined extracts were washed with brine (50 cm^3), dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The residue of 16α-hydroxy-5β-androstan-3-one was dried under high vacuum to afford the title *product* (0.25 g, 97%), m.p. 160–161 °C (from acetone–hexanes); ν_{max}(KBr)/cm^{-1} 3416, 2945, 1701 and 1047; δ_H($CDCl_3$) 0.70 (3 H, s), 1.00 (3 H, s), 2.67 (1 H, br t, *J* 14) and 4.44 (1 H, ddd, *J* 2.1, 5.0 and 7.7); δ_C($CDCl_3$) 37.1 (C-1), 36.9 (C-2), 213.2 (C-3), 42.3 (C-4), 44.2 (C-5), 25.9 (C-6), 26.5 (C-7), 33.3 (C-8), 40.9 (C-9), 34.9 (C-10), 20.8 (C-11), 37.1 (C-12), 41.8 (C-13), 52.0 (C-14), 38.8 (C-15), 7.16 (C-16), 52.0 (C-17), 18.6 (C-18), 22.6 (C-19) (reference compounds used 5α-androstan-16α-ol and 17β-hydroxy-5β-androstan-3-one;[12] *m/z* 290 (M^+, 45), 272 (80), 201 (60), 95 (48), 81 (77), 69 (90), 55 (93) and 41 (100) (Found: C, 78.5; H, 10.5%; M^+, 290.2238. $C_{19}H_{30}O_2$ requires C, 78.57; H, 10.41%; M, 290.2247).

Mitsunobu Reaction on 16α-*Hydroxy*-5β-*androstan*-3-*one*.—Following the Mitsunobu procedure[19] the 16α-hydroxy steroid **21** (0.19 g, 0.7 mmol) was dissolved in dry benzene (15 cm^3). To this solution were added triphenylphosphine (0.19 g, 0.72 mmol) and glacial acetic acid (0.041 cm^3, 0.72 mmol) and the mixture was stirred for 5 min. Lastly, diethyl azodicarboxylate (DEAD) (0.12 cm^3; 0.72 mmol) in dry benzene (5 cm^3) was added and the solution was refluxed for 36 h. After the reaction flask had cooled to room temperature, the solvent was evaporated off under reduced pressure. The residue (0.78 g) was subjected to flash chromatography on silica gel and eluted using an isocratic solvent mixture (hexanes–ethyl acetate, 3:1). The fractions were collected which corresponded to 3-*oxo*-5β-*androstan*-16β-*yl acetate* (0.10 g, 47%) [R_f 0.39 (hexane–ethyl acetate, 3:1)]. The solid crystalline material had m.p. 143.5–144 °C (from hexanes–acetone), [lit.,[2] 143 °C (from acetone)]; ν_{max}(KBr)/cm^{-1} 2931, 2861, 1724, 1709 and 1251; δ_H($CDCl_3$) 0.92 (3 H, s), 1.05 (3 H, s), 2.03 (3 H, s), 2.69 (1 H, br t, *J* 13) and 5.14 (1 H, m); δ_C($CDCl_3$) 37.1 (C-1), 36.9 (C-2), 212.9 (C-3), 42.3 (C-4), 44.2 (C-5), 26.0 (C-6), 26.5 (C-7), 35.3 (C-8), 40.8 (C-9), 35.0 (C-10), 20.8 (C-11), 34.3 (C-12), 40.1 (C-13), 53.4 (C-14), 38.8 (C-15), 74.6 (C-16), 48.0 (C-17), 18.4 (C-18), 22.6 (C-19), 170.9 (*C*OMe) and 21.3 (OCO*Me*); *m/z* 332 (M^+, 3), 272 (100), 257 (63), 231 (32), 201 (70), 107 (55), 94 (68), 81 (62), 69 (55) and 55 (84) (Found: C, 75.9; H, 9.75%; M^+, 332.2348. Calc. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70%; M, 332.2353).

Saponification of 3-*Oxo*-5β-*androstan*-16β-*yl Acetate*; *Preparation of Compound* **2**.—Following the procedure of Mashimo and Sato,[20] saponification of 3-oxo-5β-androstan-16β-yl acetate (0.052 g, 0.16 mmol) with 1% NaOH–methanol (10 cm^3) was complete in 2 h at room temperature. The work-up procedure involved adjusting the pH to 5–6 by using aq. HCl (6 mol dm^{-3}). Methanol was then removed under reduced pressure, and distilled water (10 cm^3) was added. The solution was then extracted with diethyl ether (5 × 10 cm^3), and the extracts were combined and washed with brine (25 cm^3). The organic layer was then dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The product, 16β-hydroxy-5β-androstan-3-one **2** was obtained as needles (0.043 g, 95%), m.p. 128.5–129 °C (from hexanes–acetone) [lit.,[2] 128 °C (from aq. methanol)]; ν_{max}(KBr)/cm^{-1} 3501, 2924, 2834, 1708, 1447, 1342 and 1005; δ_H($CDCl_3$) 0.97 (3 H, s), 1.03 (3 H, s), 2.67 (1 H, br t, *J* 13.3) and 4.42 (1 H, m, *J* 2.1, 5.5 and 7.6); δ_C($CDCl_3$) 37.1 (C-1), 36.9 (C-2), 213.3 (C-3), 42.3 (C-4), 44.2 (C-5), 26.1 (C-6), 26.5 (C-7), 35.3 (C-8), 26.1 (C-9), 35.0 (C-10), 20.8 (C-11), 39.1 (C-12), 40.3 (C-13), 53.9 (C-14), 37.1 (C-15), 71.9 (C-16), 51.3 (C-17), 19.9 (C-18) and 22.6 (C-19) (Found: M^+, 290.2239. Calc. for $C_{19}H_{30}O_2$: M, 290.2247).

Formation of 3-*Oxo*-5β-*androstan*-16β-*yl Benzoate* **22**.—Following Mitsunobu's procedure,[19] 16α-hydroxy-5β-androstan-3-one (0.50 g, 1.70 mmol), triphenylphosphine (0.50 g, 1.90 mmol), and benzoic acid (0.24 g, 1.90 mmol) were dissolved in dry benzene (10 cm^3) and the solution was stirred for 5 min. This was followed by the addition of a solution of DEAD (0.30 cm^3, 1.90 mmol) in dry benzene (1 cm^3) and the mixture was refluxed for 24 h, then allowed to cool to room temperature and the solvent was removed under reduced pressure. The crude material (1.55 g) was flash column chromatographed on silica gel and eluted using a mixture of hexanes–ethyl acetate (3:1) to give crystalline *material* **22** (0.59 g, 87%), m.p. 167.5–168 °C (from acetone–hexanes); R_f 0.41 (hexanes–ethyl acetate, 3:1); ν_{max}(KBr)/cm^{-1} 3052, 1715, 1708, 1448, 1292 and 716; δ_H($CDCl_3$) 1.02 (3 H, s), 1.05 (3 H, s), 2.7 (1 H, br t, *J* 14), 5.42 (1 H, m), 8.04 (2 H, m) and 7.48 (3-H, m); δ_C($CDCl_3$) 37.2 (C-1), 37.0 (C-2), 212.8 (C-3), 42.3 (C-4), 44.3 (C-5), 26.0 (C-6), 25.6 (C-7), 35.5 (C-8), 41.1 (C-9), 35.1 (C-10), 20.9 (C-11), 37.0 (C-12), 40.3 (C-13), 53.7 (C-14), 38.8 (C-15), 75.2 (C-16), 48.3 (C-17), 18.5 (C-18), 22.7 (C-19), 166.3 (C=O, benzoate ester) and 132.7, 130.9, 129.5, 128.4, 128.3 and 128.3 (aromatic-ring resonances); *m/z* 394 (M^+, 9), 378 (0.3), 272 (73), 257 (60), 231 (30), 202 (50), 147 (35), 105 (100), 77 (82), 55 (60) and 41 (55) (Found: C, 79.5; H, 8.3%; M^+, 394.2513. $C_{26}H_{34}O_3$ requires C, 79.15; H, 8.69%; M, 394.2509).

Schmidt Reaction on 3-*Oxo*-5β-*androstan*-16β-*yl Benzoate* **22**.—A solution of 3-oxo-5β-androstan-16β-yl benzoate **22** (0.44 g, 1.10 mmol) in anhydrous chloroform (60 cm^3) was treated with freshly standardised HN_3 in chloroform (0.86 cm^3; 1.41 mol dm^{-3}), placed in an ice-bath (0 °C) and the mixture was stirred for 5 min. This was followed by the slow addition of conc. H_2SO_4 (0.4 cm^3) and the reaction mixture was stirred for a further 20 min at 0 °C. Ice–water (25 cm^3, ice *ca.* 5 g) was added and the mixture was stirred for 5 min.

The pH of the reaction mixture was then adjusted to 6–7 by addition of a solution of aq. 5% NaOH, and the organic layer was then separated. The aq. layer was further extracted with chloroform (7 × 30 cm^3). All the organic layers were then combined, washed with brine (100 cm^3), dried (Na_2SO_4), filtered, and evaporated to dryness under reduced pressure to yield a solid (0.53 g). Flash column chromatography on silica gel [hexanes–ethyl acetate–methanol (3:2:0.5)] of this product produced two components: a minor component, R_f 0.6 (0.012 g), and a major component, R_f 0.40 (0.44, g, 97%).

The spectroscopic properties of the minor component, which corresponds to a mixture of tetrazoles, were as follows: ν_{max}(film)/cm^{-1} 3346, 3065, 2931, 1715, 1448, 1229 and 1110; δ_H($CDCl_3$) 1.03 (3 H, s), 1.15 (3 H, d, *J* 2.3), 2.43 (1 H, m), 3.18 (1 H, m), 4.3 (1 H, m), 4.55 (1 H, m), 5.44 (1 H, m), 7.48 (3 H, m) and 8.01 (2 H, m); δ_C($CDCl_3$) 17.8, 18.4, 20.8, 21.1, 21.2, 25.3, 26.5, 27.2, 27.9, 29.2, 29.7, 34.5, 35.7, 35.8, 36.0, 37.5, 38.4, 38.7, 40.1, 40.9, 42.4, 43.1, 45.9, 46.3, 48.2, 49.5, 53.3, 75.0, 128.3, 129.4, 130.8, 132.7 and 166.3; *m/z* 434 (M^+, 1), 329 (50), 312 (75), 297 (55), 105 (100) and 77 (75) [Found: M^+, 329.2322. Calc. for $C_{19}H_{29}N_4O$: M, 329.2344; Found: (M^+ – OH), 312.2289. Calc. for $C_{19}H_{28}N_4$: *m/z* 312.2316]. The major product (the mixed lactams **23** and **24**) had the following spectroscopic properties: ν_{max}(film)/cm^{-1} 3304, 3227, 3065, 2931, 1715, 1666, 1448, 1279 and 1117; δ_H($CDCl_3$) 0.99 (3 H, s), 2.45 (2 H, m), 3.04 (1 H, m), 5.39 (1 H, m), 6.95 (1 H, br s), 7.48 (3 H, m) and 8.00 (2 H, m); δ_C($CDCl_3$) 18.3, 20.6, 20.9, 23.0, 23.4, 26.2, 27.1, 28.0, 29.6, 29.9, 33.9, 34.3, 34.4, 35.6, 36.7, 37.2, 37.4, 38.7, 39.6, 40.1, 40.3, 42.3, 43.1, 44.1, 45.4, 48.1, 48.1, 53.3, 53.4, 75.0, 128.2, 128.5, 128.9, 129.3, 130.3, 130.7, 132.6, 166.1 (C=O, benzoate ester), and 177.7 and 178.4 (C=O, lactam carbonyls).

Reduction of the Lactam Mixture **23** *and* **24** *with LAH: Preparation of Samanine* **1** *and its Isomer* **25**.—The LAH reduction of the lactam mixture (**23** and **24**) was performed following the procedure of Habermehl and Haaf.[2] The lactam mixture (0.20 g, 0.5 mmol) was dissolved in dry THF (25 cm^3), added to a flame-dried flask and kept under N_2 atmosphere. The flask was cooled in an ice–water-bath and the solution was stirred while a suspension of LAH (0.44 g, 10.2 mmol) in dry THF (20 cm^3) was added *via* a syringe. After the addition of the LAH was complete the syringe contents were rinsed into the reaction vessel with a little THF (5 cm^3). The reaction mixture was then refluxed for 20 h, cooled in an ice–water-bath, and then worked up by the method of Mićović and Mihailoviv.[13] The stirred reaction mixture was first cautiously treated, dropwise, with distilled water (0.44 cm^3) then, after the reaction had subsided, with 15% aq. NaOH (0.44 cm^3), and then finally with more distilled water (1.3 cm^3). This produced a fine granular grey precipitate which was easily filtered off on a Celite pad. The filter cake was washed with diethyl ether (3 × 15 cm^3), and the combined filtrate and washings were evaporated to dryness under reduced pressure. The filter cake was then stirred in diethyl ether overnight and the ethereal phase was evaporated to yield a little more solid. TLC (hexanes–ethyl acetate–methanol–NH_4OH, 2:3:2:0.5) of the combined residues (0.14 g) revealed two major components, with R_f 0.66 and 0.61. A portion of the crude mixture (0.08 g) was separated on silica gel PLC plates and developed twice with hexanes–ethyl acetate–methanol–NH_4OH (2:3:2:0.5). Bands corresponding to the two major products were located using iodine-impregnated silica gel sprinkled on the sides of the plate, then scraped from the plates, and the products were eluted using ethyl acetate–methanol–NH_4OH (6:2:1) (25 cm^3). The solvent was then removed under reduced pressure and the residues were redissolved in benzene (*ca.* 5 cm^3); the solutions were dried over anhydrous K_2CO_3, then filtered, and the solutes were recovered by removal of the solvent under reduced pressure. The component with R_f 0.66, *compound* **25**, was a solid (0.032 g, 40%), m.p. 166.5–168 °C (from aq. ethanol), [lit.,[2] 166–168 °C (from aq. ethanol)]; ν_{max}(KBr)/cm^{-1} 3381, 3283, 3220, 2924, 2847, 1560, 1448, 1413, 1377, 1342, 1293, 1251, 1181, 1159, 1131, 1082, 1047, 1040, 1012, 955, 927, 899, 871, 836, 815, 794, 674, 618 and 541; δ_H(C_6D_6) 0.88 (3 H, s), 1.04 (3 H, s), 2.03 (1 H, m), 2.52 (2 H, m), 2.79 (1 H, dd, *J* 8.3 and 8.3), 2.91 (1 H, m) and 4.16 (1 H, m); δ_C(C_6D_6) 41.1 (C-1), 29.4 (C-2), 50.8 (C-3), 51.9 (C-4a), 50.1 (C-5), 24.9 (C-6), 28.2 (C-7), 36.2 (C-8), 48.6 (C-9), 37.3 (C-10), 21.3 (C-11), 39.7 (C-12), 40.3 (C-13), 53.9 (C-14), 37.6 (C-15),

71.6 (C-16), 51.2 (C-17), 19.2 (C-18) and 22.6 (C-19); *m/z* 291 (M^+, 24), 289 (7), 276 (45), 274 (10), 260 (12), 217 (7), 201 (8), 124 (9), 121 (9), 110 (30), 109 (11), 107 (15), 105 (15), 97 (14), 96 (16), 95 (24), 93 (23), 91 (20), 84 (20), 83 (16), 82 (19), 81 (29), 79 (23), 77 (14), 72 (19), 71 (49), 70 (100), 69 (41), 68 (25), 67 (29), 57 (48), 56 (52), 55 (46), 53 (14), 44 (88), 43 (71), 42 (24) and 41 (59) (Found: M^+, 291.2565. Calc. for $C_{19}H_{33}NO$: M, 291.2564).

The component with R_f 0.61, samanine **1**, was obtained as translucent crystals (0.042 g, 52%), m.p. 194–195 °C (from aq. ethanol) [lit.,[2] 193–195 °C (from aq. ethanol)]; ν_{max}(KBr)/cm^{-1} 3395, 3290, 3135, 2924, 1448, 1377, 1342, 1300, 1270, 1244, 1221, 1204, 1185, 1174, 1159, 1141, 1131, 1114, 1092, 1079, 1062, 1043, 1010, 797, 958, 957, 920, 877, 836, 821, 809 and 796; $\delta_H(C_6D_6)$ 0.78 (2 H, m), 0.90 (3 H, s), 1.08 (3 H, s), 2.07 (1 H, dt, *J* 7.2 and 7.4), 2.60 (2 H, m), 2.73 (1 H, m, *J* 7.6 and 7.8), 3.06 (1 H, m) and 4.10 (1 H, m); $\delta_H(CDCl_3)$ 0.91 (1 H, m), 0.96 (6 H, s), 1.05 (2 H, m), 2.19 (1 H, m), 2.67 (2 H, m), 2.89 (1 H, dd, *J* 7.9 and 14.0), 3.12 (1 H, m) and 4.39 (1 H, m); $\delta_C(C_6D_6)$ 3.14 (C-1), 51.9 (C-2), 43.0 (C-4), 46.6 (C-4a), 49.6 (C-5), 27.6 (C-6), 30.2 (C-7), 36.4 (C-8), 45.4 (C-9), 34.6 (C-10), 21.3 (C-11), 39.8 (C-12), 37.3 (C-13), 54.0 (C-14), 37.6 (C-15), 71.7 (C-16), 51.4 (C-17), 19.2 (C-18) and 22.4 (C-19); *m/z* 291 (M^+, 44), 290 (15), 289 (24), 276 (71), 274 (24), 258 (9), 219 (10), 217 (9), 124 (17), 123 (16), 122 (59), 121 (14), 119 (12), 111 (11), 110 (27), 109 (25), 108 (18), 107 (23), 105 (20), 97 (20), 96 (62), 95 (27), 93 (33), 91 (25), 84 (16), 83 (29), 82 (46), 81 (42), 80 (12), 79 (3), 77 (17), 71 (25), 70 (58), 69 (36), 68 (18), 67 (36), 58 (54), 57 (79), 56 (91), 55 (56), 53 (16), 45 (12), 44 (100), 43 (84), 42 (32) and 41 (66) (Found: M^+, 291.2558. Calc. for $C_{19}H_{33}NO$: M, 291.2564).

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