Steroids and Steroidases. XIV.[1] Studies on the Reactions of 2-Lithio-1,3-dithianes with Steroids Possessing Spiroepoxide Functions at C-3[2]

J. Bryan Jones and Roger Grayshan
Department of Chemistry, University of Toronto, Toronto 181, Ontario

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The scope of the reactions of lithio-dithianes with spiro-epoxides for various stereospecific functionalizations of alicyclic systems has been illustrated by their application to spiro-3α- and -3β-oxiranes of the 5α-cholestane and 5α-androstane series.

La portée des réactions entre les lithio-dithianes et les époxydes spiranniques pour fonctionnaliser de façon stéréospécifique les systèmes cycliques a été illustrée par des applications sur les oxirannes-3α et 3β spiranniques dans les séries 5α-cholestane et 5α-androstane.

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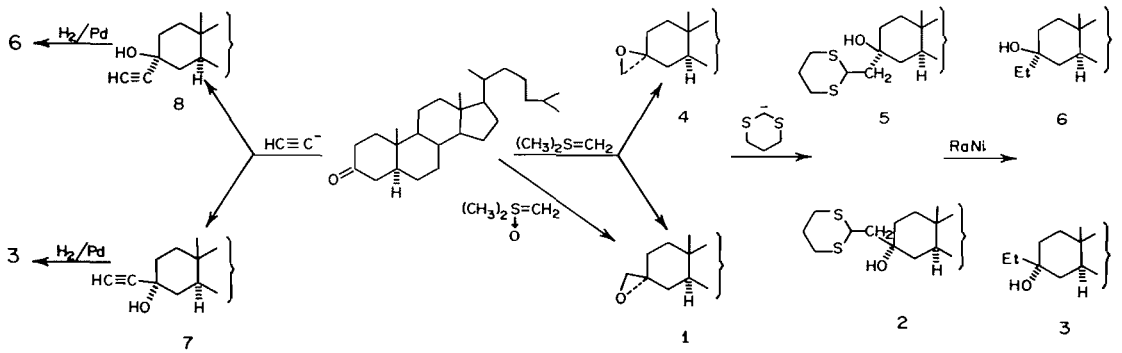
The reactions of a 2-lithio-1,3-dithiane anion with appropriate 1,2 epoxides have been demonstrated to provide a versatile, convenient, and flexible method for the stereospecific introduction of substituents into the steroid nucleus (1*a*, *c*). The facility with which such reactions occurred encouraged us to explore the scope of lithio-dithiane-epoxide reactions further and the investigations have now been successfully extended to spiro-epoxides.

The ease with which spiro-epoxides would undergo reaction with dithiane anions, and establishment of the stereochemical integrity of the reactions, were evaluated on the readily available spiro-3α- and -3β-oxiranyl-5α-cholestanes **1** and **4**. The synthetic sequences followed are outlined in Scheme 1.

Treatment of 5α-cholestan-3-one with dimethylsulfonium methylide according to the literature procedure (2) gave a 95% yield of a mixture of **1** and **5** in the ratio 3:2. Although pure samples of **1** and **5** had not been obtained by this method in the previous work (2), it was found that separation of the two epimers could be effected by careful preparative layer chromatography (p.l.c.). The supply of the 3α-oxide **1** was augmented by its preparation in 80% yield from the 5α-cholestan-3-one-dimethylsulfoxonium methylide reaction (2) and in view of the more ready availability of the latter oxide, the initial experiments were carried out on the sequence of reactions involving compounds **1**–**4**.

When the 3α-epoxide **1** was kept with 2-lithio-1,3-dithiane in tetrahydrofuran at 0° for 2 days, the spiro-epoxide ring opened smoothly to give



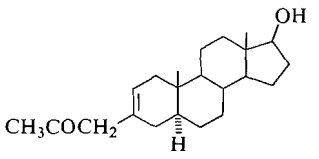
SCHEME 1

[1]For part XIII see ref. 1*a*.
[2]A communication on some of this work has been published (1*b*).

the hydroxydithianyl compound **2** in 85% yield. Although from the mode of formation of **2**, little doubt existed with regard to the stereochemistry at C-3, Raney nickel desulfurization of **2** to the hydroxyethyl derivative **3** (92% yield) was carried out in order to provide a convenient reference compound for which unambiguous assignment of the C-3 geometry could be made. That the C-3 configuration of **3** was as designated was confirmed by its preparation by catalytic hydrogenation of 3β-ethynyl-3α-hydroxy-5α-cholestane (**7**), the stereochemistry of which had been established previously (3).[3]

The corresponding reactions in the 3β-epoxide series proceeded with equal facility and treatment of **4** with 2-lithio-1,3-dithiane as described above yielded **5** in 86% yield. The C-3 configuration of the latter compound was again confirmed by its desulfurization (in 88% yield) to the corresponding hydroxyethyl derivative **6** which was shown to be identical with an authentic sample of 3α-ethyl-3β-hydroxy-5α-cholestane prepared by catalytic hydrogenation of the ethynyl compound **8** of known geometry (3).

The above results confirmed our expectations with regard to the facility of spiro-epoxide-dithiane reactions and their potential for stereospecific exocyclic functionalization of the steroid nucleus. Although all of our studies in this area had up to this time involved conversion of the dithianyl substituents into alkyl groups, several other types of transformations of these versatile intermediates have been well documented (5). Accordingly, attention was turned towards the application of the spiro-epoxide reactions for the introduction of functional groups other than alkyl. The compounds considered first were the βγ- and αβ-unsaturated ketoandrostanes **9** and **10** which were of interest to us as a potential substrate and inhibitor respectively of the Δ^5-3-ketoisomerase of *P. testosteroni*. Furthermore, it was desired to evaluate the biological activities of androstanes possessing C-3 functions of the 2′-oxopropyl type. The reactions carried out are outlined in Scheme 2. A mixture of spiro-3α-(**11**) and spiro-3β-oxiranyl-5α-androstan-17β-ol (**12**) in the proportions of 1:2 was obtained in 90% yield by reaction of 17β-hydroxy-5α-



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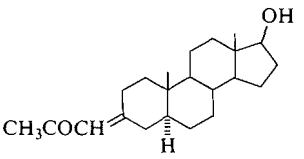

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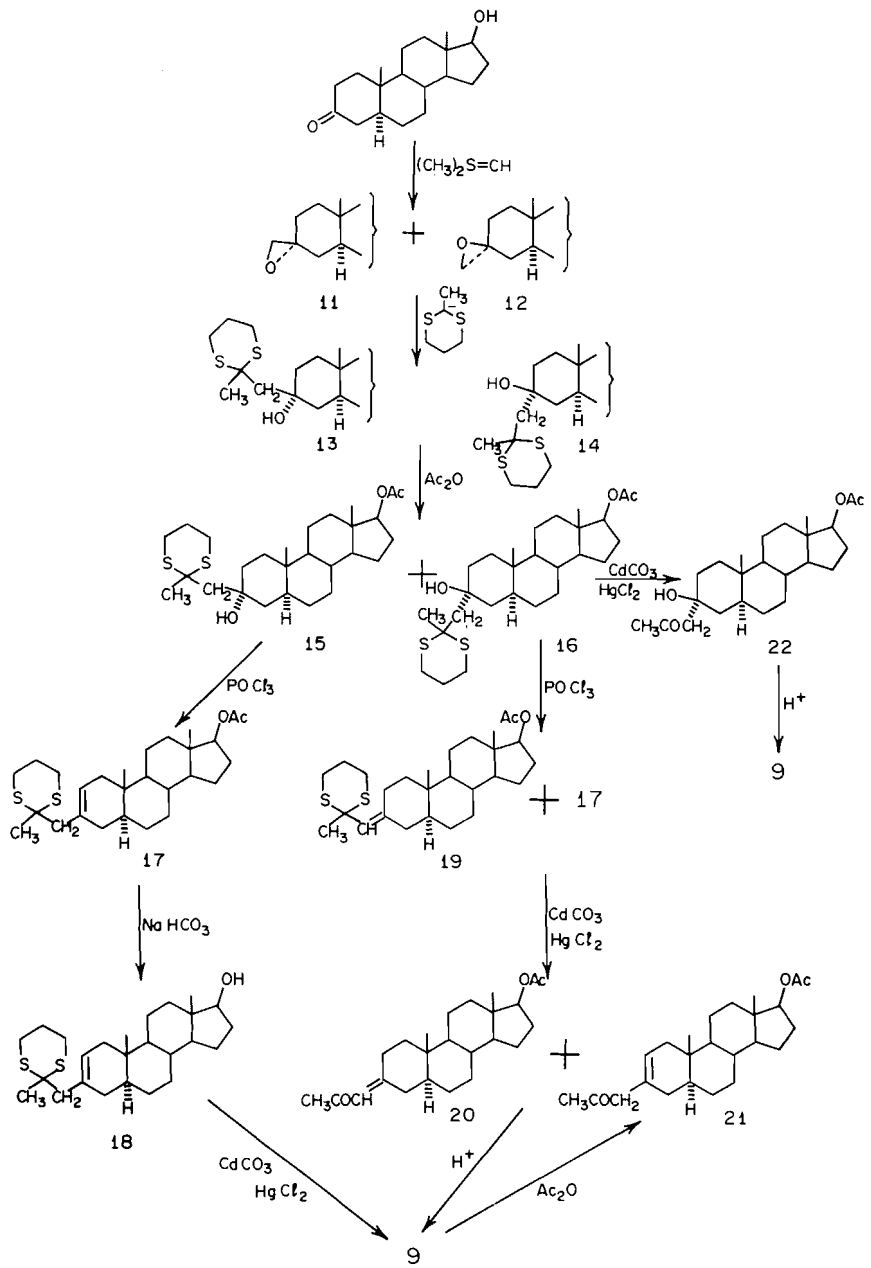
androstan-3-one with dimethylsulfonium methylide. The stereochemistry and spectral characteristics of **11** and **12** had been established previously (2) and corroboration of the assigned C-3 geometries was provided by a comparison of the spectral data of **11** and **12** with those determined for the analogous oxiranes of the cholestane series **1** and **4**. The proportions of each of **11** and **12** present were estimated from the areas of the characteristic epoxide CH_2 n.m.r. peaks at δ 2.61 and 2.57 p.p.m. respectively. The individual oxiranes could not be purified by any of the usual chromatographic methods and the subsequent dithiane reactions were therefore carried out on the mixture of the two epoxides.[4] Treatment of the epoxide mixture with 2-lithio-2-methyl-1,3-dithiane in tetrahydrofuran at 0° for 2 days yielded 68% of the corresponding dithianyl addition products **13** and **14**. The n.m.r. spectra of each isomer were quite distinctive, with the main differences being reflected in the positions of the C-19 methyl and dithianyl methyl peaks. For the 3α-hydroxy derivative **13**, these protons resonated at δ 0.75 and 1.77 p.p.m. respectively, while for the 3β-epimer **14**, they appeared at δ 0.85 and 1.80 p.p.m. Correlation of the n.m.r. spectra of **13** and **14** with the correct C-3 configuration was made using the C-19 methyl resonance of the corresponding cholestane analogues **2** and **5**, which occur at δ 0.74 and 0.83 p.p.m. respec-

[3]A 3-ethyl-3-hydroxy-5α-cholestane has been reported previously (4). A comparison of the physical data for this compound with those of the current work shows that this material has the same C-3 configuration as **3**.

[4]Repeated fractional recrystallization of the epoxide mixture has been reported (2) to give low yields of each of the pure epimers. However, in view of the quantities of material required to complete the proposed synthetic schemes, and the ease with which the subsequently obtained dithianyl acetates **15** and **16** could be separated, it was decided to bypass the epoxide separation procedure.



SCHEME 2

tively, for reference. The C-19 chemical shift differences for both pairs of epimers, **2** and **5**, and **13** and **14**, reflect C-19 deshielding by the C-3β hydroxyl groups which does not occur in the 3α-hydroxy compounds.

Since no further experiments could reasonably be carried out unless pure C-3 hydroxydithiane compounds could be obtained, the mixture of **13** and **14** was converted into the corresponding 17β-acetates **15** and **16** with acetic anhydride. Fortunately, the two acetates exhibited small differences in their chromatographic behavior

and following several fractional p.l.c. separations pure samples of each epimer were obtained.[5] The C-3 configurations of the hydroxydithianyl 17β-acetates were again assigned using the chemical shifts of the C-19 n.m.r. peaks as a basis for the correlation. For the 3α-hydroxyacetate **15**, the C-19 proton resonance occurred at δ 0.76 and for the 3β-hydroxy analogue **16** at δ 0.85 p.p.m.

It was anticipated that of the two desired en-ones **9** and **10**, the non-conjugated $\beta\gamma$-unsaturated isomer **9** would be thermodynamically the less stable,[6] and consequently it was decided to attempt its preparation first by introduction of the Δ^2-double bond prior to ketonization of the dithianyl function. Accordingly, elimination of the axial 3α-hydroxyl groups of **15** was effected with phosphoryl chloride in pyridine to give the Δ^2-compound **17** in 83% yield. The predominant formation of the Δ^2-isomer **17** (C-2 H at δ 5.45 p.p.m.) was expected on thermodynamic grounds. However, some of the less stable Δ^3-isomer was formed as evidenced by the C-4 olefin resonance at 0.28 p.p.m. higher field (6) than that of the C-2 vinyl peak of **17**. No still higher field n.m.r. peak ascribable to an exocyclic olefinic proton was observed. The small amounts of the Δ^3-compound formed during the preparation of **17** did not pose any separation problem since they were readily isomerized to the desired Δ^2-isomer by a trace of acid. Hydrolysis of the 17β-acetate of **17** under conditions which did not affect the dithianyl group was accomplished with sodium bicarbonate in methanol and the 17β-hydroxy product **18** was obtained in quantitative yield. Subsequent ketonization of the dithianyl function with the aqueous cadmium carbonate/mercuric chloride reagent (5) proceeded smoothly to give 49% of 3-(2′-ketopropyl)-5α-androst-2-en-17β-ol (**9**). That the product was the desired $\beta\gamma$-nonconjugated isomer was confirmed by the spectral data.

To our surprise, treatment of **9** with acid or base under a variety of conditions did not effect the expected isomerization to the conjugated isomer **10**. This was the first indication that for **9** and **10** the normal order of the thermodynamic stability of $\beta\gamma$- and $\alpha\beta$-unsaturated ketones was reversed. In order to obtain the desired compounds possessing an exocyclic C-3 double bond, phosphoryl chloride mediated dehydration of the 3β-hydroxydithiane **16** was carried out and the mixture of exocyclic olefinic **19** and Δ^2-dithianyl **17** products expected (7) was formed in 79% yield. However, the desired isomer **19** (identified by the C-19 methyl n.m.r. peak at δ 0.78) was the minor component. Disappointingly, separation of **17** and **19** could not be achieved even by repeated fractional p.l.c. and the mixture was therefore converted directly into the corresponding ketones **21** and **20** by hydrolysis under neutral conditions with aqueous cadmium carbonate/mercuric chloride. The $\beta\gamma$-unsaturated ketoacetate **21** was readily separated by p.l.c. and showed characteristic n.m.r. peaks at δ 0.80 (C-19 CH_3), 5.48 (C-2 H), and 2.99 p.p.m. (C-3 CH_2). This compound was also obtained in 89% yield by acetylation of **9** with acetic anhydride.

The presence in the mixture of the conjugated ketone **20** was established by the positions of the n.m.r. resonances of the C-19 methyl (δ 0.92) and COCH= (δ 5.99 p.p.m.) protons. Unfortunately, a pure sample of the conjugated ketone **20** could not be obtained owing to the facility with which it isomerized to **21** even under the mildest p.l.c. conditions. The attempts to prepare the $\alpha\beta$-unsaturated ketones **20** and **10** were therefore discontinued and the remaining mixture of **20** and **21** was converted directly to the $\beta\gamma$-unsaturated ketone **9** with aqueous methanolic hydrochloric acid.

The ketone **9** was also obtained smoothly *via* treatment of the dithianylacetate **16** with cadmium carbonate/mercuric chloride to give the hydroxy ketone **22** (62%). The subsequent acid-catalyzed hydrolysis and concomitant dehydration of **22** proceeded in 93% yield. Following the delineation of the reactions outlined in Scheme 2, it was found that quantities of **9** could be conveniently accumulated by direct ketonization of the mixture of the 17β-alcohols **11** and **12** (or their 17β-acetates **13** and **14**) obtained from the initial dithian-epoxide reaction.

With the ketone **9** being thermodynamically more preferred than its conjugated isomer **10**, our initial aim of studying its enzymic isomerization could obviously not be realized. It is unusual

[5]Small amounts of the two 3,17-diacetates were also present in the acetylated mixture. However, these were easily separated from the desired 17β-monoacetates **15** and **16** during the p.l.c. purification procedure.

[6]As discussed later, the converse was found to be true.

for a non-conjugated ketone to be the more stable and it is therefore of interest to consider some of the factors which would affect the relative stabilities of **9** and **10**. Spectral analyses of acid- or base-equilibrated mixtures of **9** and **10** indicated that the conjugated isomer is present to the extent of 1–2%. Thus the $\beta\gamma$-unsaturated compound **9** is favored by at least 2–3 kcal/mol (8). The marked propensity in 5α-steroids for a double bond to occupy the Δ^2-position in preference to C-3-exocyclic (9) would be a major component in the overall free energy balance favoring **9**. However, that this factor is not of overriding importance is demonstrated by the fact that for steroids analogous to **9** and **10**, but with $\alpha\beta$-unsaturated aldehyde (4, 10, 11), acid (4, 10), ester, and nitrile (12, 13) functions at C-3, the conjugated isomers are favored in each case. Such apparent contradictions are not restricted to the steroids. For example, similar reversals of isomer stabilities are observed with unsaturated keto- and carboxy-derivatives of cyclohexane (14, 15) and in view of the conflicting data currently available it is evident that a satisfactory rationalization for the relative stability of $\beta\gamma$-unsaturated ketones such as **9** must await further studies.

Experimental

Details of analytical methods, instrumentation, criteria of purity etc. used were as described previously (1). All p.l.c. separations were effected on silica gel G. Final drying of tetrahydrofuran was accomplished by distillation from lithium aluminum hydride. The i.r. and n.m.r. spectra were recorded on CCl_4 and $CDCl_3$ solutions respectively.

*Spiro-3α-oxiranyl-5α-cholestane (**1**) and Spiro-3β-oxiranyl-5α-cholestane (**4**)*

A 95% yield of a mixture of the spiro-oxiranylcholestanes **1** and **4** in the ratio 3:2 (by n.m.r.) was obtained by reaction of 5α-cholestan-3-one with dimethylsulfonium methylide in tetrahydrofuran according to the procedure of Cook *et al.* (2). The epoxides were separated by p.l.c. using benzene–hexane (1:1) as developing solvent. Final recrystallizations from methanol yielded the 3α-epoxide **1**, m.p. 127–128° (lit. (16) m.p. 129–130°) and the 3β-epoxide **4**, m.p. 172–173° (lit. (16) m.p. 175–176°).

*3β-(2′-(1,3-Dithianyl))methyl-5α-cholestan-3α-ol (**2**)*

To a solution of 2-lithio-1,3-dithiane (1 g, 8.1 mmol) prepared by the slow addition of *n*-butyl lithium (4.7 ml of a 1.6 *M* hexane solution, 8.1 mmol) to 1,3-dithiane (0.9 g, 8.1 mmol) in freshly dried tetrahydrofuran (21 ml) at −20° under dry nitrogen (5) was added spiro-3α-oxiranyl-5α-cholestane (**1**, 1.08 g, 2.7 mmol) in dry tetrahydrofuran (7 ml), also at −20°. After keeping for 2 days at 0° the mixture was poured into water (500 ml) and extracted with ether (4 × 50 ml). The combined ether extracts were washed with water (2 × 25 ml) and then dried ($MgSO_4$) and evaporated. The residual gum was purified by p.l.c. using ether–benzene (1:50) as developing solvent followed by recrystallization from ether–methanol to give the 3β-dithianyl-methyl-5α-cholestan-3α-ol **2** (1.2 g) m.p. 190°; i.r. 1278 and 914 cm^{-1} (dithianyl); n.m.r. δ 0.64 (C-18 CH_3), 0.74 (C-19 CH_3), 1.90 (2H, d, J = 7 Hz, C-3 CH_2), and 4.29 p.p.m. (1 H, t, J = 7 Hz, HCS_2).

Anal. Calcd. for $C_{32}H_{56}OS_2$: C, 73.8; H, 10.8; S, 12.3. Found: C, 73.9; H, 10.8; S, 12.3.

*3β-Ethyl-5α-cholestan-3α-ol (**3**)*

The above 3β-dithianyl-3α-ol **2** (0.15 g, 0.29 mmol) in ethanol (30 ml) was refluxed with freshly prepared Raney nickel (1.5 g) for 4 h. The filtered ethanolic solution was then evaporated to give 3β-ethyl-5α-cholestan-3α-ol (**3**, 0.11 g) which after recrystallization from ether–methanol was identical with an authentic sample, m.p. and mixed m.p. 109–110°.

The authentic sample was prepared in quantitative yield from 3β-ethynyl-5α-cholestan-3α-ol (**7**) m.p. 104–105° (obtained according to the procedure of Giraud *et al.* (3)) by hydrogenation in ethanol over 10% Pd–C; n.m.r. δ 0.66 (C-18 CH_3) and 0.74 p.p.m. (C-19 CH_3).

Anal. Calcd. for $C_{29}H_{52}O$: C, 83.4; H, 12.6. Found: C, 83.5; H, 12.7.

*3α-(2′-(1,3-Dithianyl))methyl-5α-cholestan-3β-ol (**5**)*

2-Lithio-1,3-dithiane (0.9 g, 7.1 mmol) in freshly dried tetrahydrofuran (18 ml) at −20° was reacted with spiro-3β-oxiranyl-5α-cholestane (**4**, 0.99 g, 2.5 mmol) in dry tetrahydrofuran (7 ml) as described above for the 3α-hydroxy isomer **2**. The p.l.c. purification with ether–benzene (1:20) as developing solvent gave the 3α-dithianylmethyl-5α-cholestan-3β-ol **5** (1.09 g), m.p. 132°, after recrystallization from ether–methanol; i.r. 1278 and 914 cm^{-1} (dithianyl); n.m.r. δ 0.64 (C-18 CH_3), 0.83 (C-19 CH_3), 2.14 (2H, d, J = 6.5 Hz, C-3 CH_2), and 4.19 p.p.m. (1H, t, J = 6.5 Hz, HCS_2).

Anal. Calcd. for $C_{32}H_{56}OS_2$: C, 73.8; H, 10.8; S, 12.3. Found: C, 73.9; H, 11.1; S, 12.1.

*3α-Ethyl-5α-cholestan-3β-ol (**6**)*

The 3α-dithianyl-3β-hydroxycholestane **5** described above (0.21 g, 0.4 mmol) in ethanol (40 ml) was heated under reflux for 4 h with freshly prepared Raney nickel (2 g). Filtration of the mixture followed by evaporation yielded 3α-ethyl-5α-cholestan-3β-ol (**6**, 0.51 g). The material obtained was identical, m.p. and mixed m.p. 138–138.5°, n.m.r. δ 0.66 (C-18 CH_3) and 0.83 p.p.m. (C-19 CH_3), with a sample prepared (quantitative yield) by hydrogenation in ethanol over 10% Pd–C of 3α-ethynyl-5α-cholestan-3β-ol (**8**) m.p. 165–167° (3).

Anal. Calcd. for $C_{29}H_{52}O$: C, 83.4; H, 12.6. Found: C, 83.3; H, 12.6.

*The Reactions of 2-Lithio-2-methyl-1,3-dithiane with Spiro-3α-oxiranyl-5α-androstan-17β-ol (**11**) and Spiro-3β-oxiranyl-5α-androstan-17β-ol (**12**)*

5α-Androstan-17β-ol-3-one and dimethylsulfonium methylide were reacted as described by Cook *et al.* (2) to give, after p.l.c. purification, a 90% yield of a mixture of the spiro-epoxides **11**, n.m.r. δ 0.75 (C-18 CH_3), 0.87 (C-19 CH_3), and 2.62 p.p.m. (2H, broad s, C-3 CH_2), and **12**, n.m.r.

δ 0.75 (C-18 CH_3), 0.88 (C-19 CH_3), and 2.57 p.p.m. (2H, broad s, C-3 CH_2) in the ratio 1:2.

To a solution of 2-lithio-2-methyl-1,3-dithiane (8.25 g, 60 mmol), prepared by the slow addition of *n*-butyl lithium (3.78 g, 60 mmol, 36.75 ml of a 1.6 *M* in hexane solution) to 2-methyl-1,3-dithiane (7.95 g, 60 mmol) in freshly dried tetrahydrofuran (150 ml) at $-20°$ under nitrogen (5), was added the above mixture of spiro-epoxides **11** and **12** (4.3 g, 14 mmol) dissolved in dry tetrahydrofuran (37 ml) at $-20°$. The mixture was kept for 2 days at 0° and was then worked-up as described previously for the analogous cholestane compounds **2** and **5**. The p.l.c. purification of the gum obtained yielded 4.2 g of an inseparable mixture of the 3α-hydroxydithiane **13**, n.m.r. δ 0.73 (C-18 CH_3), 0.75 (C-19 CH_3), and 1.77 p.p.m. (CH_3CS_2), and the 3β-hydroxy-dithiane **14**, n.m.r. δ 0.73 (C-18 CH_3), 0.85 (C-19 CH_3), and 1.80 p.p.m. (CH_3CS_2).

The above mixture of **13** and **14** (4.2 g) was refluxed with acetic anhydride (20 ml) for 20 min and the cooled reaction mixture was then evaporated. Fractional p.l.c. of the residue (4.8 g) using ethylacetate–hexane (1:4) developments yielded samples of the two 17β-acetates. The 17β-acetoxy-3β-(2′-oxopropyl)-5α-androstan-3α-ol 1,3-propylenethioketal (**15**) was recrystallized from methanol to give 0.46 g of material m.p. 184°; i.r. 908 cm^{-1} (dithianyl); n.m.r. δ 0.76 (C-18 CH_3), 0.78 (C-19 CH_3), 1.78 (3 H, s, CH_3CS_2), 2.03 (3 H, s, 17β-OAc), 2.18 (2 H, s, C-3 CH_2), and 4.59 p.p.m. (1 H, t, $J = 7.5$ Hz, C-17α H).

Anal. Calcd. for $C_{27}H_{44}O_3S_2$: C, 67.5; H, 9.2; S, 13.4. Found: C, 67.5; H, 9.4; S, 13.4.

The 17β-acetoxy-3α-(2′-oxopropyl)-5α-androstan-3β-ol 1,3-propylenethioketal (**16**) fraction was recrystallized from methanol to give 0.8 g of pure material, m.p. 136–137°, i.r. 906 cm^{-1} (dithianyl); n.m.r. δ 0.79 (C-18 CH_3), 0.85 (C-19 CH_3), 1.81 (3H, s, CH_3CS_2), 2.04 (3H, s, 17β-OAc), 2.30 (2H, s, C-3 CH_2), and 4.59 p.p.m. (1H, t, $J = 7.5$ Hz, C-17α H).

Anal. Calcd. for $C_{27}H_{44}O_3S_2$: C, 67.5; H, 9.2; S, 13.4. Found: C, 67.8; H, 9.4; S, 13.5.

*17β-Acetoxy-3-(2′-oxopropyl)-5α-androst-2-ene 1.3-propylenethioketal (**17**)*

Phosphoryl chloride (7 ml) was added dropwise with vigorous stirring at 0° to the dithianyl acetate **15** (0.35 g, 0.73 mmol) in dry pyridine (70 ml). The mixture was stirred overnight at 20° and was then poured into ice-water and extracted with ether (3 × 50 ml). The ether extracts were washed *rapidly* with ice-cold 0.1 *N* aqueous hydrochloric acid (50 ml) and were then dried ($MgSO_4$) and evaporated. The residual solid was purified by p.l.c. using ether–benzene (1:1) as developing solvent followed by recrystallization from ether–methanol to give the 17β-acetoxy-Δ^2-dithiane **17** (0.28 g) m.p. 164–165°; i.r. 908 cm^{-1} (dithianyl); n.m.r. δ 0.77 (C-18 CH_3), 0.79 (C-19 CH_3), 1.67 (3H, s, CH_3CS_2), 2.03 (3H, s, C-17β OAc), 2.58 (2H, s, C-3 CH_2), 4.60 (1H, t, $J = 7$ Hz, C-17α H), and 5.45 p.p.m. (1H, m, C-2 H).

Anal. Calcd. for $C_{27}H_{42}O_2S_2$: C, 70.1; H, 9.2; S, 13.9. Found: C, 70.1; H, 9.2; S, 14.0.

*17β-Hydroxy-3-(2′-oxopropyl)-5α-androst-2-ene 1.3-propylenethioketal (**18**)*

The 17β-acetate **17** (0.22 g) in methanol (40 ml) containing saturated aqueous sodium bicarbonate (2 ml) was refluxed for 12 h and then poured into water (200 ml). Extraction with chloroform (3 × 50 ml) followed by evaporation of the dried ($MgSO_4$) chloroform solution yielded the 17β-hydroxy-Δ^2-dithiane **18** (0.18 g) m.p. 158–159°, i.r. 3460, and 908 cm^{-1} (dithianyl); n.m.r. δ 0.75 (6H, s, C-18 and C-19 CH_3), 1.67 (3H, s, CH_3CS_2), 2.58 (2H, s, C-3 CH_2), 3.65 (1H, t, $J = 7$ Hz, C-17α H), and 5.45 (1H, m, C-2 H).

*Preparation and Attempted Isolation of 17β-Acetoxy-3-(2′-oxopropylidene)-5α-androstane (**20**)*

Phosphoryl chloride (25 ml) was added dropwise with vigorous stirring at 0° to the 3β-hydroxydithianyl acetate **16** (1.1 g, 2.3 mmol) in dry pyridine (250 ml). The mixture was stirred for a further 12 h at 20° and was then worked-up as described above for **17**. The product (0.84 g) was not resolvable by p.l.c. but was shown by n.m.r. analysis to be a mixture of the Δ^2-dithiane **17** isolated previously and 17β-acetoxy-3-(2′-oxopropylidene)-5α-androstane 1,3-propylidenethioketal (**19**), n.m.r. δ 0.78 (C-18 CH_3), 0.88 (C-19 CH_3), 1.83 (3H, s, CH_3CS_2), 2.03 (3H, s, C-17β OAc), and 5.33 p.p.m. (1H, s, COCH=).

The above mixture of **17** and **19** (0.8 g) in acetone–water (80 ml, 20:1) was stirred with mercuric chloride (0.8 g) and cadmium carbonate (0.8 g) at 20° for 1 day and was then filtered and evaporated (5). The residue was extracted with chloroform (100 ml) and the chloroform solution dried ($MgSO_4$) and evaporated. Fractional p.l.c. of the residue (0.56 g) with ether–benzene (1:15) as the developing solvent yielded only the Δ^2-ketone **21** (characterized as described later) in a pure form. The desired exocyclic olefin **20** present in the fractions isomerized progressively during the p.l.c. procedure and isolation of a pure sample by this approach was precluded by its instability.

*17β-Acetoxy-3α-(2′-oxopropyl)-5α-androstan-3β-ol (**22**)*

A solution of the 3β-hydroxydithianylacetate **16** (0.3 g, 0.63 mmol) in acetone–water (30 ml, 20:1) was treated with mercuric chloride (0.3 g) and cadmium carbonate (0.3 g) by the general ketonization procedure detailed in the attempted preparation of **20**. P.l.c. purification with ether–benzene (2:3) as developing solvent, followed by recrystallization from ether–methanol gave 17β-acetoxy-3α-(2′-oxopropyl)-5α-androstan-3β-ol (**22**, 0.15 g), m.p. 164–165°; i.r. 3534 and 1718 cm^{-1} (broad).

Anal. Calcd. for $C_{24}H_{38}O_4$: C, 73.8; H, 9.7. Found: C, 73.9; H, 9.8.

*17β-Hydroxy-3-(2′-oxopropyl)-5α-androst-2-ene (**9**)*

*(a) From the Pure Dithiane **18***

The dithiane **18** (0.18 g, 0.43 mmol) was dissolved in acetone–water (20 ml, 20:1) and the dithianyl function hydrolyzed in the presence of mercuric chloride (0.2 g) and cadmium carbonate (0.2 g) by the general procedure described for compound **20**. P.l.c. of the crude product with ether–benzene (1:4) as the developing solvent and recrystallization from cold ether afforded 17β-hydroxy-3-(2′-oxopropyl)-5α-androst-2-ene (**9**, 70 mg), m.p. 110–111°; i.r. 1708 cm^{-1}; n.m.r. 0.77 (6H, s, C-18 and C-19 CH_3), 2.13 (3H, s, CH_3CO), 3.01 (2H, s, C-3 CH_2), 3.64 (1H, t, $J = 8$ Hz, C-17α H), and 5.48 p.p.m. (1H, m, C-2 H).

Anal. Calcd. for $C_{22}H_{34}O_2$ (mol. wt. 330.2559): C, 80.0; H, 10.4. Found (330.2553 (mass spectrum)): C, 80.1; H, 10.3.

(b) From Mixtures of ***13*** *and* ***14****, and* ***15*** *and* ***16***

In a typical experiment, a mixture of the 17β-acetates **15** and **16** (2 g) was dissolved in acetone–water (200 ml, 20:1) and treated with mercuric chloride (2 g) and cadmium carbonate (2 g) in the usual way. The gum (1.5 g) obtained was then refluxed for 1 day in methanol (150 ml) containing 10% aqueous hydrochloric acid (10 ml). Purification of the product as in section *a* yielded 1.4 g of **9**, m.p. 110–111°.

When the 17β-hydroxy compounds **13** and **14** were used, the final acid-catalyzed hydrolysis step was omitted.

(c) From a Mixture of ***20*** *and* ***21***

The mixture of the unsaturated ketones **20** and **21** (0.1 g) obtained from **19**, dissolved in methanol (20 ml) containing 0.1 *N* aqueous hydrochloric acid (1 ml), was heated under reflux for 12 h. The usual work-up and purification afforded **9** (80 mg), m.p. 108–110°.

(d) From ***22***

Hydrolysis of the 17β-acetate **22** (0.14 g) as described for section *c* above yielded 0.11 g of **9**, m.p. 110–111°.

Equilibration of **9** by treatment with methanolic hydrochloric acid or methanolic sodium hydroxide did not result in the formation of a detectable amount of the $\alpha\beta$-unsaturated isomer **10**.

*17β-Acetoxy-3-(2′-oxopropyl)-5α-androst-2-ene (****21****)*

The 17β-ol **9** (0.1 g) and acetic anhydride (5 ml) were refluxed for 20 min. The mixture was then evaporated and purified by p.l.c. (developing solvent ether–benzene (1:12)) followed by recrystallization from ether–methanol to give **21** (98 mg), m.p. 123–124°; i.r. 1718 cm^{-1} (broad); n.m.r. δ 0.76 (C-18 CH_3), 0.80 (C-19 CH_3), 2.03 (3H, s, C-17β-OAc), 2.13 (3H, s, CH_3CO), 2.99 (2H, s, C-3 CH_2) and 5.48 p.p.m. (C-2 H).

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1. (*a*) J. B. Jones and R. Grayshan. Can. J. Chem. **50**, 810 (1972); (*b*) Chem. Commun. 741 (1970); (*c*) Chem. Commun. 141 (1970).
2. C. E. Cook, R. C. Corley, and M. E. Wall. J. Org. Chem. **33**, 2789 (1968).
3. A. M. Giraud, A. Rassat, P. Witz, and G. Ourisson. Bull. Soc. Chim. Fr. **31**, 3240 (1964).
4. N. A. Milas and C. P. Priesing. J. Am. Chem. Soc. **80**, 2189 (1958).
5. E. J. Corey and D. Seebach. Angew. Chem. Int. Ed. **4**, 1075 (1965); D. Seebach. Synth. 17 (1969).
6. G. M. L. Cragg, C. W. Davey, D. N. Hall, G. D. Meakins, E. E. Richards, and T. L. Whateley. J. Chem. Soc. C, 1266 (1966).
7. D. N. Kirk and P. M. Shaw. J. Chem. Soc. C, 182 (1970).
8. E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison. Conformational analysis. Interscience, New York, 1965, p. 11.
9. R. C. Cookson, D. P. G. Hamon, and R. E. Parker. J. Chem. Soc. 5014 (1962).
10. N. A. Milas. U.S. Pat. 2 997 486.
11. W. Nagata and Y. Hayase. Ger. Pat. 1 911 768.
12. G. Drefahl, K. Ponsold, and H. Schick. Chem. Ber. **97**, 2011 (1966).
13. A. K. Bose and R. T. Dahill. J. Org. Chem. **30**, 505 (1965).
14. J. K. Groves and N. Jones. Tetrahedron Lett. 1161 (1970).
15. H. Gerlach. Helv. Chim. Acta, **49**, 1291 (1966).
16. B. N. Blackett, J. M. Coxon, M. P. Hartshorn, and C. N. Muir. Tetrahedron, **25**, 1479 (1969).