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# AXIAL AND EQUATORIAL THIOLS—III

## 17α AND 17β-MERCAPTO DERIVATIVES OF ANDROSTANE AND ANDROSTAN-3β-OL

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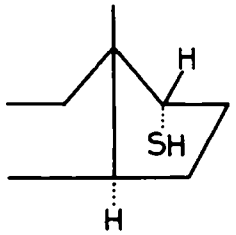
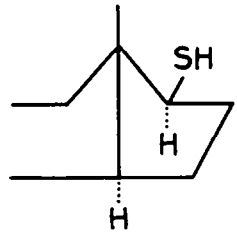
**Abstract**—17α and 17β-mercaptoandrostanes and androstan-3β-ols have been prepared as examples of axial and equatorial thiol epimers in *trans*-fused 5-membered fixed ring systems. The conformation of the epimers has been established by PMR measurements.

EARLIER papers[1 2] in this series were concerned with epimeric 3-mercapto derivatives of androstane, cholestane and pregnane. In these epimers the 3-thiol group is attached to 6-membered fused chair rings. We now describe the preparation and orientation of epimeric 17-thiols (I and II) derived from androstane and androstan-3β-ol, in which the 17-thiol group is linked respectively α-(pseudo) axial and β-(pseudo) equatorial to the 5-membered *trans*-fused D ring of the steroid nucleus.

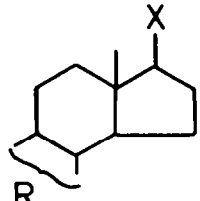



I

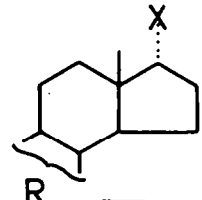



II

17α-thiols were prepared from the corresponding β-hydroxy compounds by conversion to the *p*-toluenesulphonates, followed by treatment with potassium thiolbenzoate to yield the thiobenzoyl derivatives, and alkaline hydrolysis to the thiols. In the 5α-androstane series 17β-hydroxy-5α-androstane (III R = $C_9H_{16}$, X = OH)



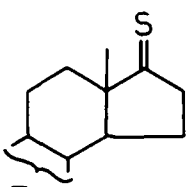

III



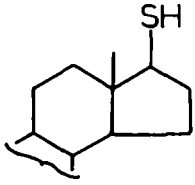

IV

was converted into 5α-androstan-17α-thiol (IV R = $C_9H_{16}$, X = SH). By similar reaction sequences 17β-hydroxy-5α-androstan-3-one (III R = $C_9H_{14}O$, X = OH) afforded the 17α-mercapto derivative (IV R = $C_9H_{14}O$, X = SH), from which

3β-hydroxy-5α-androstan-17α-thiol was prepared by reduction with lithium tritertiary butoxy aluminium hydride. This material was also synthesized by a similar reaction sequence: 3β-acetoxy-17β-hydroxy-5α-androstane (III R = $C_{11}H_{18}O_2$, X = OH) afforded the 17α-mercapto derivative (IV R = $C_9H_{16}O$, X = SH) by alkaline hydrolysis of the 3β-acetoxy 5α-androstan-17α-thiolbenzoate.




V




VI

17β-mercapto derivatives were prepared by reduction of the 17,17-bisbenzylthio derivative[3,4] using sodium in liquid ammonia followed by reduction of the resulting thione by lithium tritertiary butoxy aluminium hydride. In the 5α-androstane series the 17,17-bisbenzylthio derivative afforded the thione (V R = $C_9H_{16}$) which was converted to the thiol (VI R = $C_9H_{16}$); 3β-hydroxy-5α-androstan-17β-thiol (VI R = $C_9H_{16}O$) was prepared similarly.

*Assignment of configuration.* The stereochemical configuration of the epimeric thiols was assigned using PMR[1,2 (cf., 5-7)]. In the 5α-androstane series 5α-androstan-17α-thiol showed a triplet centred at 6·92 τ indicating that the 17-proton is (pseudo) equatorial and therefore the thiol group (pseudo) axial. Conversely the 5α-androstan-17β-thiol showed a triplet centred at 7·44 τ which by similar reasoning indicates that the thiol group is (pseudo) equatorial. In the 3β-hydroxy-5α-androstane series the 17α and 17β-mercapto derivatives showed triplets centred at 6·88 τ and 7·40 τ, respectively, consistent with the stereochemical assignments.

We were unable to distinguish between the epimers on the basis of their IR C–S stretching frequencies.

## EXPERIMENTAL

The PMR spectra were determined on 5% solns in $CDCl_3$ using a Varian A60 spectrometer operating at 60 mc. The signals are referred to in the τ scale ($Me_4Si$ = 10·00 τ) with TMS as an internal reference. M.ps were determined with a Kofler hot stage.

17β-*Tosyloxy*-5α-*androstane.* This was prepared from 17β-hydroxy-5α-androstane (766 mg) by the previously described tosylation procedure.[1] Crystallization from EtOH yielded glistening plates (830 mg) m.p. 136°. (Found: C, 72·51; H, 9·06. Calc. for $C_{26}H_{38}O_3S$: C, 72·51; H, 8·91%.)

5α-*Androstan*-17α-*thiolbenzoate.* This was prepared by heating 17β-tosyloxy-5α-androstane (740 mg) and potassium thiolbenzoate (740 mg) together in dimethylformamide (15·0 ml) at 150–160° for 4 hr in a current of dry, oxygen free, $N_2$. The soln was cooled, poured on ice, the solid which separated was crystallized from EtOH as pale yellow plates (215 mg) m.p. 123°. (Found: C, 78·53; H, 9·05; S, 7·89. $C_{26}H_{36}OS$ requires: C, 78·71; H, 9·17; S, 8·08%.)

5α-*Androstan*-17α-*thiol.* 5α-androstan-17α-thiolbenzoate (113 mg) in 70% alcoholic KOH (1N; 20·0 ml) was refluxed for 3 hr. The soln was poured on ice and glacial AcOH (5·0 ml), the solid which separated was crystallized from EtOAc as plates (70 mg) m.p. 108–109°. (Found: C, 77·41; H, 10·62; S, 10·87. $C_{19}H_{32}S$ requires: C, 77·99; H, 11·05; S, 10·95%.)

17β-*Tosyloxy*-5α-*androstan*-3-*one.* This was prepared from 17β-hydroxy 5α-androstan-3-one (3·0 g) by the previously described tosylation procedure[1] giving 17β-tosyloxy-5α-androstan-3-one (4·5 g) m.p. 178–180°. (Found: C, 70·29; H, 8·17. Calc. for $C_{26}H_{36}O_4S$: C, 70·23; H, 8·18%.)

5α-*Androstan-3-one-17α-thiolbenzoate.* This was prepared similarly to 5α-androstan-17α-thiolbenzoate: 17β-tosyloxy-5α-androstan-3-one (5·0 g) yielded 5α-androstan-3-one-17α-thiolbenzoate (1·1 g) m.p. 144°, from EtOH. (Found: C, 76·28; H, 8·53; S, 7·63. $C_{26}H_{34}O_2S$ requires: C, 76·05; H, 8·36; S, 7·81%.)

5α-*Androstan-3-one-17α-thiol.* This was prepared by alkaline hydrolysis of 5α-androstan-3-one-17α-thiolbenzoate (1·1 g) which gave 5α-androstan-3-one-17α-thiol (504 mg) m.p. 148–150°, from EtOH. (Found: C, 73·89; H, 9·80; S, 10·72. $C_{19}H_{30}OS$ requires: C, 74·42; H, 9·88; S, 10·46%.)

3β-*Hydroxy-5α-androstan-17α-thiol.* 5α-androstan-3-one-17α-thiol (189 mg) in dry THF (5·0 ml) was added to a soln of lithium triteriary butoxy aluminium hydride (1·5 g) in THF at 0°. The combined solns were set aside for ½ hr at 0° and then at 20° for 1½ hr. The soln was then poured on ice and 5N HCl (10·0 ml). The solid which separated was collected and when crystallized from EtOH formed fine needles (118 mg) m.p. 167–169°. The thiol was also prepared by the alkaline hydrolysis of 3β-acetoxy-5α-androstan-17α-thiolbenzoate (500 mg) which gave 3β-hydroxy-5α-androstan-17α-thiol (276 mg) m.p. 169°. (Found: C, 73·76; H, 10·23; S, 10·24. $C_{19}H_{32}OS$ requires: C, 73·90; H, 10·47; S, 10·39%.)

3β-*Acetoxy-5α-androstan-17β-p-toluenesulphonate.* 3β-acetoxy-5α-androstan-17β-ol (1·5 g) was tosylated by the previously described procedure.[1] Crystallization from acetone gave glistening plates (0·76 g) m.p. 166–168°. (Found: C, 68·79; H, 8·12. $C_{28}H_{40}O_5S$ requires: C, 68·82; H, 8·27%.)

3β-*Acetoxy-5α-androstan-17α-thiolbenzoate.* This was prepared similarly to 5α-androstan-17α-thiolbenzoate. 3β-Acetoxy-5α-androstan-17β-*p*-toluenesulphonate (2·0 g) yielded 3β-acetoxy-5α-androstan-17α-thiolbenzoate (800 mg) m.p. 127–128°, from EtOH. (Found: C, 74·48; H, 8·51; S, 7·01. $C_{28}H_{38}O_3S$ requires: C, 73·90; H, 8·66; S, 7·05%.)

17,17-*Bisbenzylthio-5α-androstane.* 5α-Androstan-17-one (5·5 mg) in glacial AcOH (10·0 ml), *p*-toluenesulphonic acid (50·0 mg) and toluene-ω-thiol (1·0 ml) were added and the soln set aside for 2 hr needle-like crystals separated (677 mg) m.p. 146°. (Found: C, 78·23; H, 8·65; S, 12·56. Calc. for $C_{33}H_{44}S_2$: C, 78·49; H, 8·80; S, 12·70%.)

5α-*Androstan-17-thione.* 17,17-Bisbenzylthio-5α-androstane (1·2 g) in dry THF (15·0 ml) and Na-dried ether (40·0 ml) was added slowly to a stirred soln of Na (1·3 g) in anhyd liq $NH_3$ (40·0 ml), the reaction was stirred for 3 hr, abs EtOH (5·0 ml) was added, followed by 95% EtOH (10·0 ml). The soln was carefully poured into water (100 ml), extracted with ether, and the aqueous layer acidified to pH 6·0. The aqueous soln was extracted with ether, the ether was dried over $CaCl_2$ and evaporated to dryness. An orange-pink solid (488 mg) was obtained which was chromatographed on a column of "Florisil". An orange solid (268 mg) m.p. 87–90° was obtained on eluting the column with pet. ether (30–40° and free from aromatic hydrocarbons). (Found: S, 11·46. Calc. for $C_{19}H_{30}S$: S, 11·03%.)

5α-*Androstan-17β-thiol.* 5α-Androstan-17-thione (610 mg) in dry THF (15·0 ml) was added slowly to lithium tritertiary butoxy aluminium hydride (2·3 g) in THF at 0°. The soln was set aside at 0° for ½ hr and then at 20° for 1½ hr; it was then poured on ice and 5N HCl (10·0 ml). The solid that separated was crystallized from EtOAc as short needles (450 mg) m.p. 116–117°. (Found: C, 77·66; H, 10·72; S, 10·73. $C_{19}H_{32}S$ requires: C, 77·99; H, 11·05; S, 10·95%.)

17,17-*Bisbenzylthio-5α-androstan-3β-ol.* *p*-Toluenesulphonic acid (600 mg) and toluene-ω-thiol (5·0 ml) was added to 3β-acetoxy-5α-androstan-17-one (5·6 g) in glacial AcOH (25·0 ml), well shaken and set aside for 2 hr. The solid (6·0 g) which separated was hydrolysed with 70% alcoholic KOH (1N; 150 ml) for 2 hr, the product was poured on ice and glacial AcOH (10·0 ml), the solid which separated (5·4 g) was collected and dried, m.p. 190–191°. (Found: C, 76·34; H, 8·34; S, 12·17. Calc. for $C_{33}H_{44}OS_2$: C, 76·09; H, 8·53; S, 12·31%.)

3β-*Hydroxy-5α-androstan-17-thione.* 17,17-Bisbenzylthio-5α-androstan-3β-ol (630 mg) in dry THF (10·0 ml) and ether (40·0 ml) was added to Na (525 mg) in anhyd liq $NH_3$ (40·0 ml). It was stirred for 3 hr, abs EtOH (5·0 ml) added, followed by 95% EtOH (5·0 ml). The reaction product was poured into water, acidified to pH 6·0 and extracted with ether. The ether extract was dried over $CaCl_2$ which on evaporation gave a salmon-pink solid (209 mg) m.p. 94–96°. (Found: S, 10·59. Calc. for $C_{19}H_{30}OS$: S, 10·45%.)

3β-*Hydroxy-5α-androstan-17β-thiol.* 3β-Hydroxy-5α-androstan-17-thione (688 mg) was reduced similarly to 5α-androstan-17-thione to give 3β-hydroxy-5α-androstan-17β-thiol (500 mg) m.p. 158–160°, from EtOH. (Found: C, 73·38; H, 10·17; S, 10·82. Calc. for $C_{19}H_{32}OS$: C, 73·90; H, 10·47; S, 10·39%.)

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