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AXIAL AND EQUATORIAL THIOLS—II

3β- AND 3α-THIOL DERIVATIVES OF 5β-PREGNAN-20-ONE AND 5β-ANDROSTAN-17-ONE

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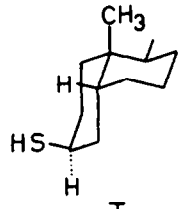
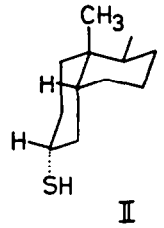
Abstract—3β- and 3α-thiol 5β-pregnan-20-ones and 5β-androstan-17-ones have been prepared as examples of axial and equatorial thiol epimers in *cis*-fused fixed ring systems. The conformation of the epimers has been established by IR and NMR measurements.

IN AN earlier paper[1] we discussed the preparation and conformation of epimeric 3-thiols in the cholestane and 5α-androstan-17-one series. In these epimers the 3-thiol group is linked to *trans*-fused chair rings. We now describe the preparation and orientation of epimeric 3-thiols in the 5β-pregnan-20-one and 5β-androstan-17-one series. These epimers are represented by structures I and II in which the 3-thiol group is now linked respectively β- (axial) and α-(equatorial) to *cis*-fused chair rings.



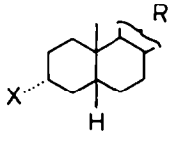
I



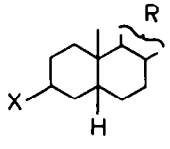
II

As in the A/B *trans*-fused series we have observed characteristic differences between the thiol epimers in their IR and NMR spectra. This has enabled us to distinguish between axial and equatorial thiol groups and to assign configurations to each epimer.

Thiols were prepared from the corresponding hydroxy compounds by conversion to the *p*-toluenesulphonates followed by the thiouronium method, as described previously.[1] In the 5β-pregnan-20-one series 3α-hydroxy-5β-pregnan-20-one (III, R = $C_{10}H_{16}O$ X = OH) was converted into 3β-thiol-5β-pregnan-20-one (IV,



III



IV

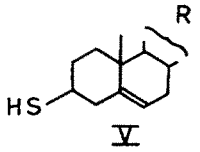
R = $C_{10}H_{16}O$ X = SH). By similar reaction sequences 3β-hydroxy-5β-pregnan-20-one (IV, R = $C_{10}H_{16}O$ X = OH) afforded 3α-thiol-5β-pregnan-20-one (III, R = $C_{10}H_{16}O$ X = SH). In the 5β-androstan-17-one series, 3α-hydroxy and 3β-hydroxy

[1] D. A. Swann and J. H. Turnbull, *Tetrahedron* **20**, 1265 (1964).

5β-androstan-17-ones (III, IV, R = $C_8H_{12}O$ X = OH) likewise afforded their respective 3β- and 3α-thiols (IV, III, R = $C_8H_{12}O$ X = SH). The thioacetolysis reaction was used as an alternative route to the thiols in the 5β-androstane series but proved unsatisfactory in the 5β-pregnane series.

Assignment of configuration

The stereochemical configuration of the epimeric thiols and their S-acetyl derivatives was assigned, as in the previous paper,[1] on the basis of their characteristic C–S stretching frequencies in the IR spectrum, and by the position of the 3-proton peak in the NMR spectrum. The 3β-(equatorial) thiols of Δ⁵-pregnen-20-one (V, R = $C_{10}H_{16}O$) and Δ⁵-androsten-17-one (V, R = $C_8H_{12}O$) were used as reference compounds.



V

The data (Table 1) are very similar to those previously obtained in the 5α-series. In each case the 3α-thiols and their S-acetyl derivatives show characteristic *equatorial*

TABLE 1

C–S Stretching frequencies of thiol epimers, ν cm^{-1}				
Series	3βSH	3βSAc	3αSH	3αSAc
5β-Pregnan-20-one	738	734	755	762
5β-Androstan-17-one	739	739	756	762
Δ⁵-Pregnen-20-one	761	768	—	—
Δ⁵-Androsten-17-one	761	768	—	—

C–S absorption bands in the region 755–762 cm^{-1}. In the 3β-thiols the *axial* C–S absorption bands appear in each case in the lower frequency range 734–739 cm^{-1}, as expected. The assignments are confirmed by the PMR spectra. The 3β-thiols (IV R = $C_8H_{12}O$, R = $C_{10}H_{16}O$ X = SH) show peaks centred at 6·41 τ and 6·42 τ respectively, indicating that the 3-protons are equatorial and therefore the 3-thiol groups are β-(axial). Conversely the epimeric thiols (III R = $C_8H_{12}O$, R = $C_{10}H_{16}O$ X = SH) both show a broad band at 7·25 τ indicating the 3-protons are axial and therefore the 3-thiol groups are α-(equatorial). It is evident that inversion occurs during the thiouronium and thioacetolysis replacement reactions at C_3 in AB *cis*-fused saturated ring systems. These systems therefore conform to the behaviour of the *trans*-fused systems described previously.

EXPERIMENTAL

IR Spectra in the 10–23 μ region were measured in CS_2 solution on a Grubb–Parsons Spectromaster. The PMR spectra were determined on 5% solutions 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 tetramethylsilane as an internal reference. M.ps were determined with a Kofler hot stage. Derivatives were prepared by the same procedures described in the previous paper, except where otherwise indicated.

3β-Tosyloxy-5β-androstan-17-one m.p. 132° (dec). (Found: C, 70·00; H, 8·13 Calc. for $C_{26}H_{36}O_4S$: C, 70·3; H, 8·17%.)

3α-Thioacetyl-5β-androstan-17-one. 3α-thiol-5β-androstan-17-one (20 mg), anhydrous pyridine

(0·5 ml), acetic anhydride (0.5 ml) were cooled to 0° and acetyl chloride (0·25 ml) added drop by drop. The solution was allowed to stand at room temp for 2 hr, poured on ice and the solid recrystallized from EtOH, m.p. 120°. This was also prepared by the reaction of potassium thiol acetate on 3β-tosyloxy-5β-androstan-17-one and recrystallized from EtOH m.p. 120°.

The m.p. was not depressed on mixing. (Found: C, 72·42; H, 8·92; S, 9·39. $C_{21}H_{32}O_2S$ requires: C, 72·35; H, 9·27; S, 9·22%.)

3α-*Isothiouronium-5β-androstan-17-one tosylate* m.p. 262°. (Found: N, 5·17. $C_{27}H_{40}O_4S_2N_2$ requires: N, 5·38%.)

3α-*Thiol-5β-androstan-17-one.* This was prepared by hydrolysis of the isothiouronium salt and the thioacetyl derivative and recrystallized from EtOH m.p. 143–144°. (Found: C, 74·5; H, 9·75; S, 10·67. $C_{19}H_{30}OS$ requires: C, 74·41 H, 9·88; S, 10·45%.)

3α-*Tosyloxy-5β-androstan-17-one* m.p. 147°. (Found: C, 70·17; H, 8·18. $C_{26}H_{36}O_4S$ requires: C, 70·23; H, 8·17%.)

3β-*Thioacetyl-5β-androstan-17-one.* This was prepared in a similar manner to the 3α-thioacetyl and recrystallized from EtOH m.p. 150°. (Found: S, 9·9 $C_{21}H_{32}O_2S$ requires: S, 9·2%.)

3β-*Isothiouronium-5β-androstan-17-one tosylate* m.p. 259°. (Found: N, 5·21 $C_{27}H_{40}O_4S_2N_2$ requires: N, 5·38%.)

3β-*Thiol-5β-androstan-17-one.* This was prepared by hydrolysis of the isothiouronium salt and the thioacetyl derivative and recrystallized from EtOH m.p. 125–126°. (Found: C, 74·62; H, 9·99; S, 10·42 $C_{19}H_{30}OS$ requires: C, 74·41; H, 9·88; S, 10·45%.)

3β-*Tosyloxy-5β-pregnan-20-one.* This was recrystallized from MeOH m.p. 133° (dec). (Found: C, 70·56; H, 8·46; $C_{28}H_{40}O_4S$ requires: C, 71·14; H, 8·55%.)

3α-*Thioacetyl-5β-pregnan-20-one.* This was prepared by acetylating the 3-thiol by the method used in the 5β-androstane series and recrystallized from EtOH m.p. 110°. (Found: S, 8·47 $C_{23}H_{36}O_2S$ requires: S, 8·52%.)

3α-*Isothiouronium-5β-pregnan-20-one tosylate* m.p. 190°. (Found: N, 5·06 $C_{29}H_{44}O_4S_2N_2$ requires: N, 5·11%.)

3α-*Thiol-5β-pregnan-20-one.* This was prepared by hydrolysis of the 3α-isothiouronium tosylate and recrystallized from EtOH m.p. 126–128°. (Found: C, 75·14; H, 9·94; S, 9·56 $C_{21}H_{34}OS$ requires: C, 75·37; H, 10·27; S, 9·58%.)

3α-*Tosyloxy-5β-pregnan-20-one.* This was recrystallized from MeOH m.p. 176°. (Found: C, 71·06; H, 8·71 $C_{28}H_{40}O_4S$ requires: C, 71·14; H, 8·55%.)

3β-*Thioacetyl-5β-pregnan-20-one.* This was prepared by acetylating the 3β-thiol by the method used in the 5β-androstane series and recrystallized from EtOH m.p. 86°. (Found: S, 8·76 $C_{23}H_{36}O_2S$ requires: S, 8·51%.)

3β-*Isothiouronium-5β-pregnan-20-one tosylate* m.p. 242–243°. (Found: N, 4·78 $C_{29}H_{44}O_4S_2N_2$ requires: N, 5·11%.)

3β-*Thiol-5β-pregnan-20-one.* This was prepared by hydrolysis of the 3β-isothiouronium tosylate and recrystallized from MeOH m.p. 106–107°. (Found: C, 75·41; H, 10·11; S, 9·17 $C_{21}H_{34}OS$ requires: C, 75·37; H, 10·27; S, 9·58%.)

3β-*Thiol-Δ⁵-pregnen-20-one.*[2] This was prepared by the thiouronium route and recrystallized from EtOH m.p. 154°. (Found: C, 75·41; H, 9·99, S, 9·49. Calc. for $C_{21}H_{32}OS$: C, 75·83; H, 9·72; S, 9·64%.)

3β-*Thioacetyl-Δ⁵-pregnen-20-one.*[2] This was prepared by acetylating the thiol using the method described in 5β-androstane series and recrystallized from EtOH, m.p. 169–170°. (Found: C, 73·40; H, 9·18; S, 8·30 Calc. for $C_{23}H_{34}O_2S$; C, 73·72; H, 9·17; S, 8·56%.)

3β-*Thiol-Δ⁵-androsten-17-one.*[2] This was prepared by the thiouronium route and recrystallized from EtOH m.p. 176°. (Found: C, 74·53, H, 9·40; S, 10·85. Calc. for $C_{19}H_{28}OS$; C, 74·93; H, 9·29; S, 10·53%.)

3β-*Thioacetyl-Δ⁵-androsten-17-one.*[2] This was prepared by acetylating the thiol using the method described in the 5β-androstane series and recrystallized from EtOH m.p. 191–192°. (Found: C, 72·32; H, 8·77; S, 9·35. Calc. for $C_{21}H_{30}O_2S$: C, 72·74; H, 8·74; S, 9·25%.)

Acknowledgments—We are very grateful to Dr. J. E. Page of Glaxo Research for furnishing the NMR data and for helpful discussions.

[2] F. A. Kincl, *Chem. Ber.* **93**, 1043 (1960).

[3] A. Segaloff and R. B. Gabbard, *Steroids* **5**, 219 (1965).