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AXIAL AND EQUATORIAL THIOLS

3α- AND 3β-THIOL DERIVATIVES OF CHOLESTANE AND ANDROSTANONE

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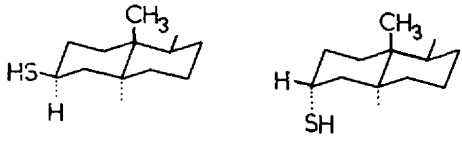
Abstract—3α- and 3β-thiol cholestanes and androstanones have been prepared as examples of axial and equatorial thiol epimers in fixed ring systems. The conformation of the epimers has been established by IR and NMR measurements.

EPIMERIC thiols derived from alicyclic systems of preferred configuration have not received much attention despite their considerable stereochemical interest. Earlier work on steroid thiols has been concerned with the problem of distinguishing between axial and equatorial thiol substituents.[1–4]

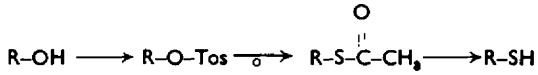
The present paper, which describes further work on this problem, deals in particular with the preparation and orientation of epimeric 3-thiols in the cholestane and androstanone series. These epimers are represented by structures I and II, in which the 3-thiol group is linked respectively β-(equatorial) and α-(axial) to *trans*-fused chair rings. Thiol pairs of this type are found to resemble one another closely in chemical and physical properties, but significant differences are found in their IR spectra in the C—S stretching frequency region.[5–7] This has enabled us to



I II

distinguish between axial and equatorial thiol groups, and to assign configurations to each epimer. These assignments have been confirmed by NMR spectroscopy.

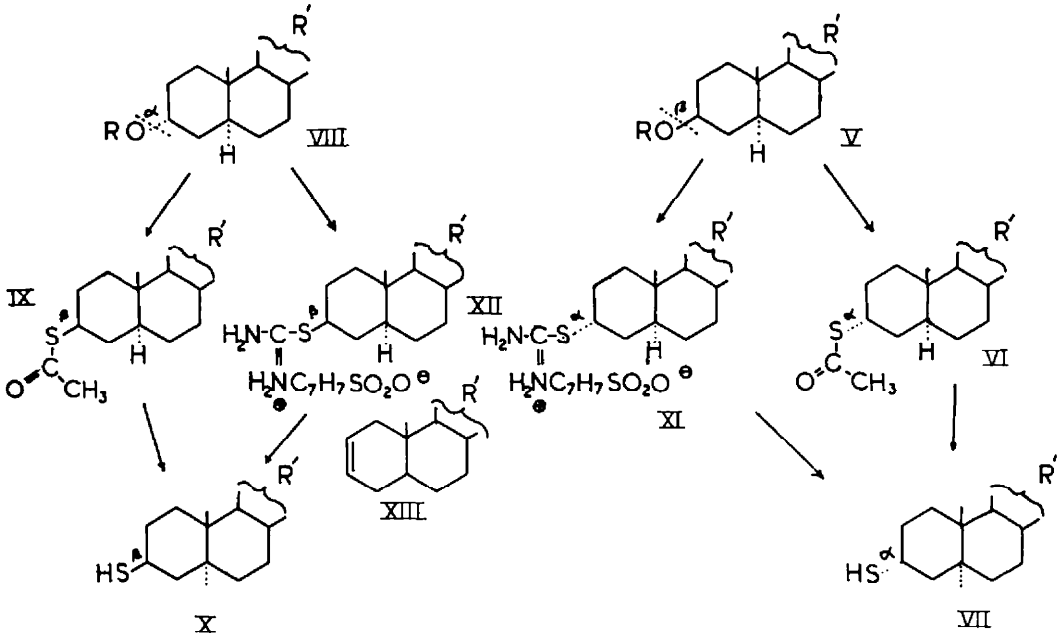
Thiols were prepared from the corresponding alcohols (III) by conversion to the *p*-toluenesulphonates, treatment with potassium thiolacetate to yield the thioacetyl derivatives, followed by alkaline hydrolysis to the thiols (IV).



III IV

[1] J. H. Turnbull, *Chem. & Ind.* 515 (1959).
[2] cf. R. Bourdon, *Bull. Soc. Chim.* 844 (1962).
[3] P. A. and F. O. Bobbio, *Chem. Ber.* **95**, 2747 (1962).
[4] H. Hauptmann and P. A. Bobbio, *Rev. Soc. Quim. Mexico* **4**, 25 (1960).
[5] N. Sheppard, *Trans. Faraday Soc.* **46**, 429 (1950).
[6] cf. G. Chiurdoglu, J. Reisse and M. Vander Stichelen Rogier, *Chem. & Ind.* 1874 (1961).
[7] cf. E. L. Eliel and B. P. Thill, *Chem. & Ind.* 88 (1963).

In the cholestane series, 3β-hydroxycholestane (V, R = H, R′ = $C_{16}H_{30}$) was converted to the tosyl derivative (V, R = $C_7H_7SO_2$-, R′ = $C_{16}H_{30}$) from which the 3α-thioacetylcholestane (VI, R′ = $C_{16}H_{30}$) was obtained by treatment with potassium thiolacetate in dimethyl formamide. Alkaline hydrolysis of the thioacetyl derivative (VI) afforded 3α-thiolcholestane (VII, R′ = $C_{16}H_{30}$). By a similar reaction sequence 3α-hydroxycholestane (VIII, R = H; R′ = $C_{16}H_{30}$) yielded successively the 3-α-tosyl derivative (VIII, R = $C_7H_7SO_2$-; R′ = $C_{16}H_{30}$), 3β-thioacetylcholestane (IX, R′ = $C_{16}H_{30}$) and 3β-thiolcholestane (X, R′ = $C_{16}H_{30}$).



In the androstane series 3β-hydroxyandrostan-17-one (V, R = H, R′ = $C_8H_{12}O$) afforded successively 3α-thioacetylandrostan-17-one (VI, R′ = $C_8H_{12}O$) and the 3α-thiol derivative (VII, R′ = $C_8H_{12}O$). The epimeric 3α-hydroxyandrostan-17-one (VIII, R = H, R′ = $C_8H_{12}O$) similarly yielded the 3β-thioacetyl (IX) and 3β-thiolandrostan-17-one (X, R′ = $C_8H_{12}O$).

The foregoing thiols were also prepared by the thiouronium method.[8] Treatment of 3β-tosyloxycholestane (V, R = $C_7H_7SO_2$-; R′ = $C_{16}H_{30}$) with ethanolic thiourea gave the 3α-thiouronium tosylate (XI, R′ = $C_{16}H_{30}$), which afforded the 3α-thiolcholestane (VII, R′ = $C_{16}H_{30}$) on alkaline hydrolysis. The epimeric 3α-tosyloxycholestane (VIII, R′ = $C_7H_7SO_2$-; R′ = $C_{16}H_{30}$) yielded the 3β-thiouronium salt (XII, R′ = $C_{16}H_{30}$), with a considerable amount of the cholestene (XIII, R′ = $C_{16}H_{30}$ formed by elimination. Hydrolysis of the thiouronium salt (XII) gave 3β-thiolcholestane (X, R′ = $C_{16}H_{30}$). Similar reaction sequences in the androstan-17-one series yielded respectively 3α-thiolandrostan-17-one (VII, R′ = $C_8H_{12}O$) and 3β-thiolandrostan-17-one (X, R′ = $C_8H_{12}O$).

[8] C. L. King, R. M. Dodson and L. A. Subluskey, *J. Amer. Chem. Soc.*, **70**, 1176 (1948).

Assignment of configuration

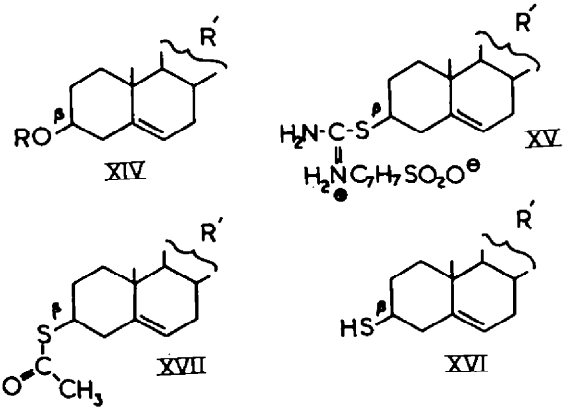
The stereochemical configuration of the epimeric thiols and their S-acetyl derivatives was determined relative to 3β-thiolcholest-5-ene (thiocholesterol, XVI, R′ = $C_{16}H_{30}$).

TABLE 1

C—S stretching frequencies of thiol epimers

	ν cm⁻¹			
	3β-SH	3β-SAc	3α-SH	3α-SAc
Cholestane series	758	765	730	735
Androstanone series	760	763	735	741
Cholesteryl series	761	765	—	—

Thiocholesterol (XVI, R′ = $C_{16}H_{30}$) was prepared from 3β-tosyloxycholest-5-ene (XIV, R = $C_7H_7SO_2$; R′ = $C_{16}H_{30}$) by conversion to the thiouronium salt (XV, R′ = $C_{16}H_{30}$) followed by hydrolysis.[8] The accepted structure for thiocholesterol is that of the normal cholesteryl derivative in which the β-(equatorial) configuration at C_3 is retained. The IR spectra of the thiol and its S-acetyl derivative (XVII, R′ = $C_{16}H_{30}$) show characteristic absorption bands at 761–765 cm⁻¹ in the C—S stretching region (Table 1). Assigning this absorption frequency to an equatorial S-substituent, the configuration of the β-thiols in the cholestane and androstane series follows by comparison (Table 1). Thus 3β-thiol cholestane and androstanone and their S-acetyl derivatives show the characteristic equatorial C—S absorption in the same region (758–765 cm⁻¹). In the epimeric 3α-thiols, on the other hand, the C—S absorption bands appear in each case at a lower frequency (730–741 cm⁻¹). This is typical of axial substituents in general, which show absorption bands at lower stretching frequencies than their equatorial epimers.[9] 3α-Thiol cholestane and androstanone and their S-acetyl derivatives therefore have the α-(axial) configuration. The foregoing results show that normal inversion occurs during the thioacetolysis and thiouronium replacement reactions at C_3 in A B *trans*-fused saturated ring systems.[1,2]



[9] D. H. R. Barton and R. C. Cookson, *Quart. Revs.* **10**, 64 (1956).

These assignments are confirmed by NMR data on the epimeric thiolacetates in the cholestane series. The 3β-thiolacetate (IX, R′ = $C_{16}H_{30}$) shows a broad single proton peak centered at 6·59τ indicating that the 3-proton is axial, and therefore the S-acetyl group is β-(equatorial). The 3α-thiolacetate (VI, R′ = $C_{16}H_{30}$) conversely, shows a sharper single proton peak at 5·99τ confirming that the 3-proton is equatorial, and the S-acetyl group α-(axial). Additional support is found by the slight shift observed in the peaks for the methyl protons of the S-acetyl groups.

Further studies will be concerned with the configuration of thiol epimers derived from *cis*-fused ring systems.

EXPERIMENTAL

IR spectra in the 10–23 μ region were measured in CS_2 solution on a Grubb-Parsons Double Beam Grating Spectrometer. 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 = 10·00τ) with tetramethylsilane as an internal reference.

3β-*Tosyloxy*-5α-*androstan*-17-*one*. 3β-Hydroxy-5α-androstan-17-one (290 mg) and *p*-toluene sulphonyl chloride (200 mg) were allowed to stand for 12 hr in anhydrous pyridine. The solution was poured on ice, and the solid recrystallized from benzene–cyclohexane, m.p. 164–165. (Found: C, 70·1; H, 8·4. Calc. for $C_{26}H_{36}O_4S$: C, 70·3; H, 8·17%).

3α-*Thioacetyl*-5α-*androstan*-17-*one*. 3β-Tosyloxy-5α-androstan-17-one (950 mg), potassium thiol acetate (950 mg) and dimethyl formamide (20 ml) were heated at 100° for 4 hr. The solution was poured on to ice and the solid recrystallized from 1:1 acetic acid and water, m.p. 144°. (Found: C, 72·3; H, 9·4; S, 9·3. $C_{21}H_{32}O_2S$ requires: C, 72·4; H, 9·3; S, 9·2%).

3α-*Thiol*-5α-*androstan*-17-*one*. 3α-Thioacetyl-5α-androstan-17-one (80 mg), ethanol (3·0 ml) and alcoholic KOH (0·5 N; 3·0 ml) was refluxed 3 hr. The solution was poured on ice and the solid recrystallized from ethanol, m.p. 135 136°. (Found: S, 10·3. $C_{19}H_{30}OS$ requires: S, 10·45%). The compound was identical (mixed m.p.) with the 3α-thiol prepared by the thiouronium method.

3α-*Tosyloxy*-5α-*androstan*-17-*one*. This was prepared from 3α-hydroxy-5α-androstan-17-one in a similar manner to the 3β-compound, m.p. 149–150°. (Found: C, 70·2; H, 8·6. Calc. for $C_{26}H_{36}O_4S$: C, 70·3; H, 8·2%).

3β-*Thioacetyl*-5α-*androstan*-17-*one*. This was prepared by acetolysis in a manner similar to the 3α-compound and recrystallized from aqueous acetic acid, m.p. 135°. (Found: C, 72·7; H, 9·5; S, 9·5. $C_{21}H_{32}O_2S$ requires: C, 72·4; H, 9·3; S, 9·2%).

3α-*Isothiouronium*-5α-*androstan*-17-*one tosylate*. 3β-Tosyloxy-5α-androstan-17-one (550 mg), thiourea (1 g) and ethanol (20 ml) were refluxed for 2 hr. The solid obtained after pouring on to ice was triturated with acetone and dried, m.p. 286° dec. (Found: N, 5·2. $C_{27}H_{40}O_4S_2N_2$ requires: N, 5·38%).

3α-*Thiol*-5α-*androstan*-17-*one*. 3α-Isothiouronium-5α-androstan-17-one tosylate (310 mg), NaOH (72 mg), ethanol (10·0 ml) and water (1·0 ml) were refluxed 2 hr. The solid obtained on acidification and cooling was recrystallized from ethanol, m.p. 138–139°. (Found: C, 74·7; H, 9·85; S, 10·15. $C_{19}H_{30}OS$ requires: C, 74·6; H, 9·9; S, 10·45%).

3α-*Thioacetyl*-5α-*androstan*-17-*one*. 3α-Thiol-5α-androstan-17-one (100 mg) was refluxed with acetic anhydride (2·0 ml) for 2 hr. The solid obtained on cooling was recrystallized from 1:1 acetic acid and water, m.p. 145°. (Found: C, 72·3; H, 9·3; S, 9·4. $C_{21}H_{32}O_2S$ requires: C, 72·4; H, 9·3; S, 9·2%). The compound did not depress the m.p. of the 3α-thioacetyl derivative prepared by the thioacetolysis method.

3β-*Isothiouronium*-5α-*androstan*-17-*one tosylate*. This was prepared from 3α-tosyloxy-5α-androstan-17-one in a similar manner to the 3α-compound, m.p. 258–260. (Found: N, 5·72. $C_{27}H_{40}O_4S_2N_2$ requires: N, 5·38%).

3β-*Thiol*-5α-*androstan-one*. This was prepared (by hydrolysis of the 3β-isothiouronium-5α-androstan-17-one tosylate) in a similar manner to the 3α-compound and recrystallized from ethanol, m.p. 134–136°. (Found: C, 74·3; H, 10·2; S, 10·4. $C_{19}H_{30}OS$ requires: C, 74·6; H, 9·9; S, 10·45%).

3β-*Thioacetyl*-5-α-*androstan*-17-*one*. This was prepared by acetylation of the foregoing thiol and recrystallized from aqueous acetic acid, m.p. 136–136·5°. (Found: C, 72·8; H, 9·3; S, 9·3. $C_{21}H_{32}O_2S$

requires: C, 72·4; H, 9·3; S, 9·2%). The compound did not depress the m.p. of the 3β-thioacetyl derivative prepared by the thioacetolysis reaction.

3β-Tosyloxy-5α-cholestane. This was prepared in a similar manner to 3β-tosyloxy-5α-androstan-17-one, m.p. 136°. (Found: C, 75·38; H, 9·8; S, 6·13. Calc. for $C_{34}H_{54}O_3S$: C, 74·91; H, 10·0; S, 5·9%).

3α-Thioacetyl-5α-cholestane. 3β-Tosyloxy-5α-cholestane (300 mg), potassium thiolacetate (300 mg) and dimethylformamide (10·0 ml) was refluxed 1 hr. On cooling, the solid that separated was recrystallized from acetic acid, m.p. 120–121°. (Found: C, 77·9; H, 11·3; S, 7·1. Calc. for $C_{29}H_{50}OS$: C, 78·0; H, 11·3; S, 7·2%).

3α-Thiol-5α-cholestane. This was prepared from the foregoing thioacetyl compound by hydrolysis as in the androstan-17-one series, and recrystallized from ethanol, m.p. 80°. (Found: S, 7·9. Calc. for $C_{27}H_{48}S$: S, 7·9%). This compound did not depress the m.p. of the 3α-thiol prepared by the thiouronium method.

3α-Tosyloxy-5α-cholestane. This was prepared according to Nace[10] and recrystallized from 40–60 pet. ether, m.p. 110°. (Found: C, 75·1; H, 10·0; S, 6·14. Calc. for $C_{34}H_{54}O_3S$: C, 74·9; H, 10·0; S, 5·9%).

3β-Thioacetyl-5α-cholestane. This was prepared from 3α-tosyloxy-5α-cholestane in a similar manner to the 3α-thioacetyl-5α-cholestane and recrystallized from acetic acid, m.p. 109°. (Found: C, 77·9; H, 11·37; S, 7·7. Calc. for $C_{29}H_{50}OS$: C, 78·0; H, 11·3; S, 7·2%).

3β-Thiol-5α-cholestane. Hydrolysis of 3β-thioacetyl-5α-cholestane, similar to 3α-compound and recrystallization from ethanol gave a compound, m.p. 103°. (Found: S, 8·2. Calc. for $C_{27}H_{48}S$: S, 7·9%). This compound did not depress the m.p. of 3β-thiol prepared by the thiouronium method.

3α-Isothiouronium-5α-cholestane tosylate. This was prepared by a similar route to that of 3α-isothiouronium-5α-androstan-17-one, m.p. 270°. (Found: N, 4·2, S, 10·1. Calc. for $C_{35}H_{58}O_3N_2S_2$: N, 4·5, S, 10·4%).

3α-Thiol-5α-cholestane. This was prepared by hydrolysis of the 3α-isothiouronium-5α-cholestane tosylate and recrystallized from ethanol, m.p. 80°; Bourdon[8] quotes 81°. (Found: S, 8·2. Calc. for $C_{27}H_{48}S$: S, 7·9%).

3α-Thioacetyl-5α-cholestane. This was prepared by acetylation of 3α-thiol-5α-cholestane with acetic anhydride, m.p. 121°. This compound did not depress the m.p. of 3α-thioacetyl prepared by the thiol acetate method.

3β-Isothiouronium-5α-cholestane tosylate. This was prepared from 3α-tosyloxy-5α-cholestane by the method used for the 3α-compound, m.p. 244–245°; Bourdon[8] quotes m.p. 249°.

3β-Thiol-5α-cholestane. This was prepared by hydrolysis of 3β-isothiouronium-5α-cholestane tosylate and recrystallized from ethanol, m.p. 105°; Bourdon quotes m.p. 98°. This compound did not depress the m.p. of 3β-thiol prepared by hydrolysis of 3β-thioacetyl-5α-cholestane.

Acknowledgements—We are most grateful to Dr. J. E. Page of Glaxo Laboratories Limited for obtaining the NMR data and for helpful discussions.

[10] H. R. Nace, *J. Amer. Chem. Soc.* **74**, 5937 (1952).