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DESULPHURIZATION OF THE THIOKETAL OF TESTOSTERONE ACETATE WITH DEACTIVATED RANEY NICKEL

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Abstract—Desulphurization of the thioketal of testosterone acetate **2**, with deactivated Raney Ni leads to the following olefins: 5β-ene **5**, 4-ene **6**, 5α-2-ene **7**, 3,5-ene **3**, and the two dimeric trienes **4**.

The formation of all these products may be rationalized by postulating the intermediacy of the allylic radical I. The deactivated Raney Ni may donate H atoms to this radical or to products subsequently formed. It may also abstract hydrogens at the allylic positions. It was found that deactivated Raney Ni converts cyclohexene to benzene.

IN CONNECTION with other work, we were interested in preparing 17β-acetoxy-androsta-2,4-diene (**1**). One of the methods leading to this compound mentioned in the literature is desulphurization of the thioketal of testosterone acetate (**2**) with deactivated Raney Ni.[1]

When **2** was treated under the described conditions,[1] (heated with deactivated Raney Ni in acetone), part of the product obtained was only very slightly soluble in most organic solvents. This material showed three high intensity absorption peaks in the UV spectrum: at λ_{max}^{EtOH} 290, 297 and 307 mμ (E_1^1 0·38, 0·44 and 0·34). On the other hand the soluble part of the reaction products had absorption maxima at 225, 236 and 247 mμ (E_1^1 0·1, 1·12 and 0·09) and only low intensity absorption peaks at higher wave lengths [at λ_{max}^{EtOH} 290, 300 and 312 mμ (E_1^1 0·013, 0·014 and 0·011)].

It became apparent that the absorption maxima at the lower wavelengths may belong to the 3,5-diene **3**. However, it seemed that the higher wavelengths absorptions are not due to the presence of the isomeric 2,4-diene **1**, which absorbs at λ_{max} 267, and 275 mμ.[1,2] The latter diene is soluble in organic solvents, and thus most of it should be present in the soluble fraction.

The mass spectrum of the insoluble materials showed peaks of highest mass numbers at *m/e* 626, 628, 630 and 632, indicating a mixture of dimeric compounds. Fractional recrystallization from ether led to two unsaturated compounds, melting at > 360° and at 297–300°. The higher melting compound which was also most insoluble showed in the mass spectrum a single molecular ion peak at *m/e* 628, the addition peaks previously observed disappeared. The NMR spectrum of this compound showed in C_6D_6 four singlets at 0·83, 1·07, 1·81 ppm (3 protons each), and at 6·58 ppm (1 proton). In the UV spectrum the three absorption peaks appeared at λ_{max}^{EtOH} 284, 295 and 307·5 mμ (ε 40,000, 50,000 and 36,000 Fig. 1). The other compound had similar mass and NMR spectra but the signal associated with its single proton appeared at higher field, at 6·41 ppm. In the UV it also showed a three peak absorption pattern which was

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shifted bathochromically by ca. 4–5 mμ (λ_{max}^{EtOH} 280, 299 and 312 mμ) and was of more diffuse shape (Fig. 1).

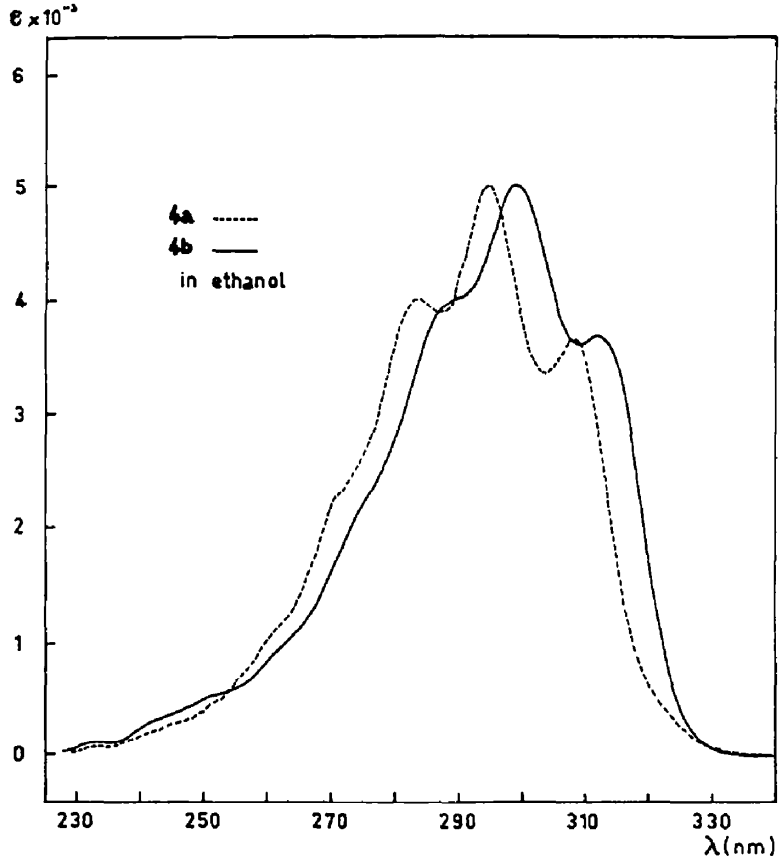


FIG. 1 UV spectra of the dimeric trienes **4a** and **4b**

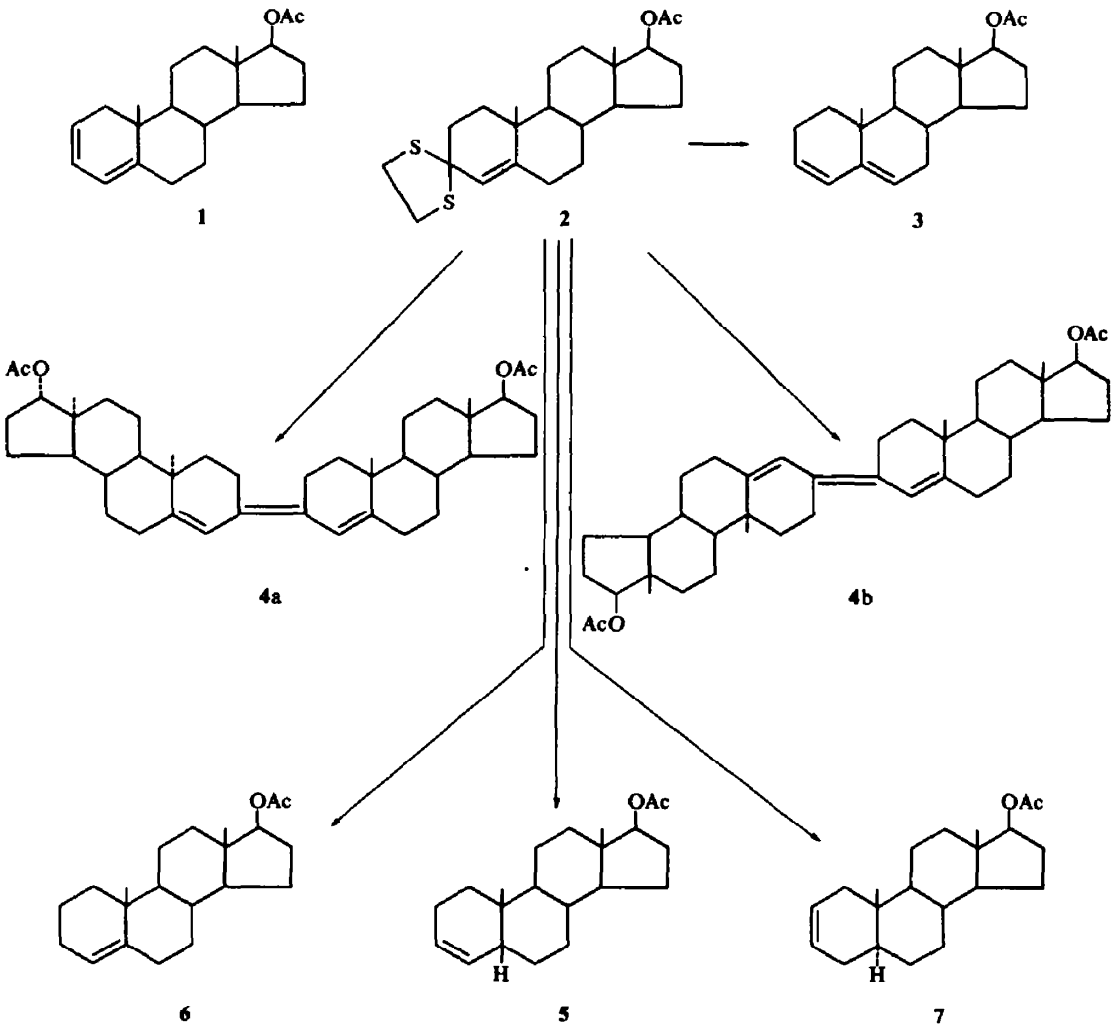
These data indicate that these two compounds are the two geometrical isomers of the dimeric triene **4**.*

We assigned to the hgiher melting compound the "cisoid" configuration **4a**, and to the lower melting material the "transoid" configuration **4b**. This assignment follows from the lower field shift of the vinylic proton,† and the shorter wavelength absorption maxima in the former compound.‡

* Similarly substituted trienes show in the UV spectrum 3 absorption maxima at comparative wavelengths. cf. UV spectrum of isotachysterol, λ_{max} at 280, 290 and 302 mμ.[3]

† In the "cisoid" configuration the vinylic protons seem to be more deshielded by the double bonds than in the "transoid" configuration.[4]

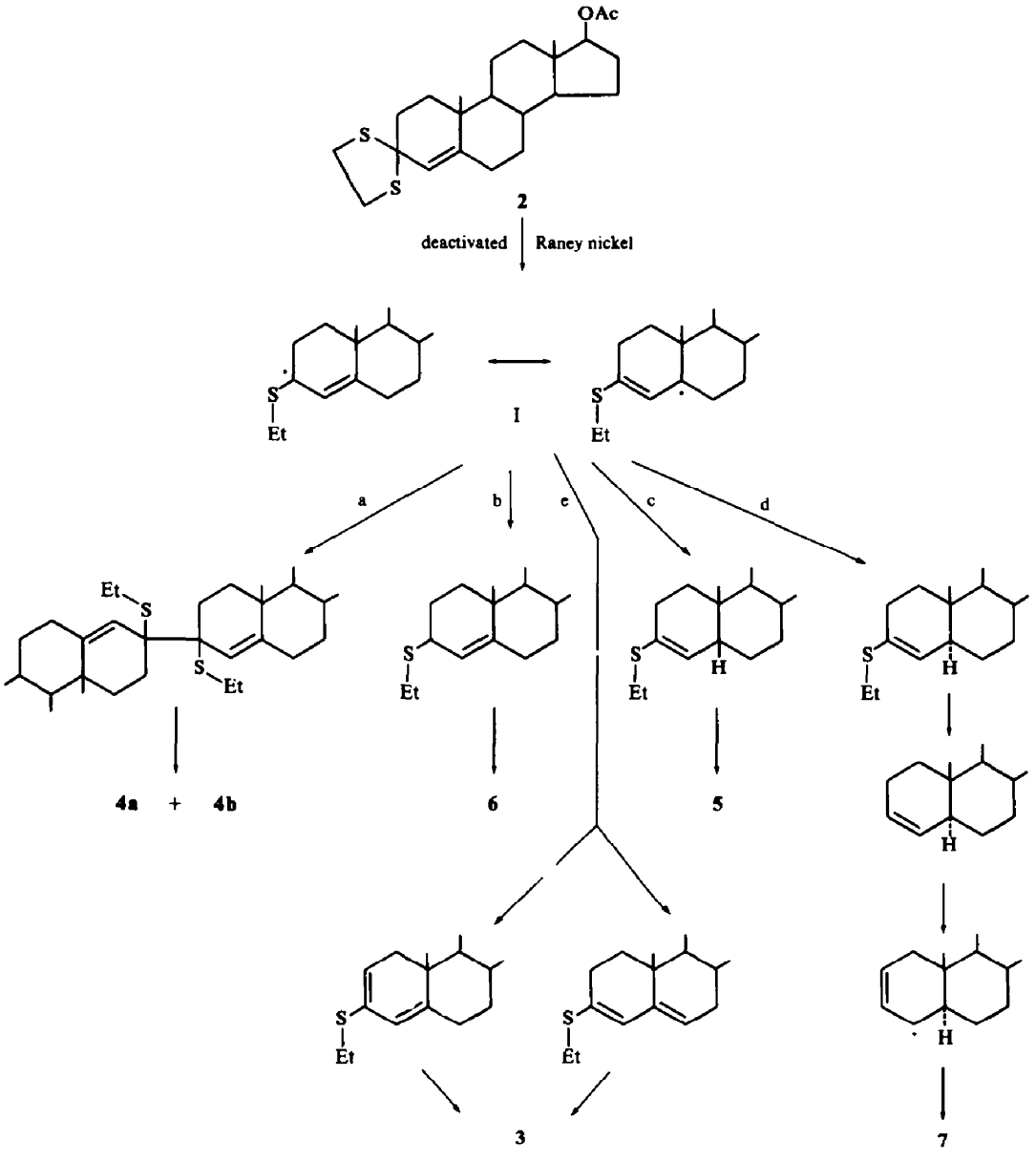
‡ In the "cisoid" configuration of one of the double bonds, the maxima in the UV spectrum are shifted to the lower wavelength when compared with "transoid" configuration, cf. UV spectrum of isotachysterol, tachysterol and precalciferol.[5]



The two dimeric trienes **4** are accompanied by other dimers with lower and higher degree of unsaturation, as indicated by the mass spectrum of the total "insoluble" fraction.

The soluble material from the desulphurization reaction was separated by chromatography. The following compounds were isolated: the 5β-3-ene, **5**, 4-ene **6**, 5α-2-ene **7**, the 3,5-diene **3**, and also the two trienes **4a** and **4b** in very small amounts. No evidence was found for the presence of the 2,4-diene **1**.

The formation of all these products may be rationalized by postulating formation of a comparatively stable allylic radical I.[6,7] This radical may dimerize by radical coupling at C-3, resulting in a di-thioether, the precursor of the two trienes **4a** and **4b** (*step* a). Direct recombination with hydrogen radical will transform the allylic radical I to an unsaturated thioether which then desulphurizes to the 4-ene **6** (*step* b).



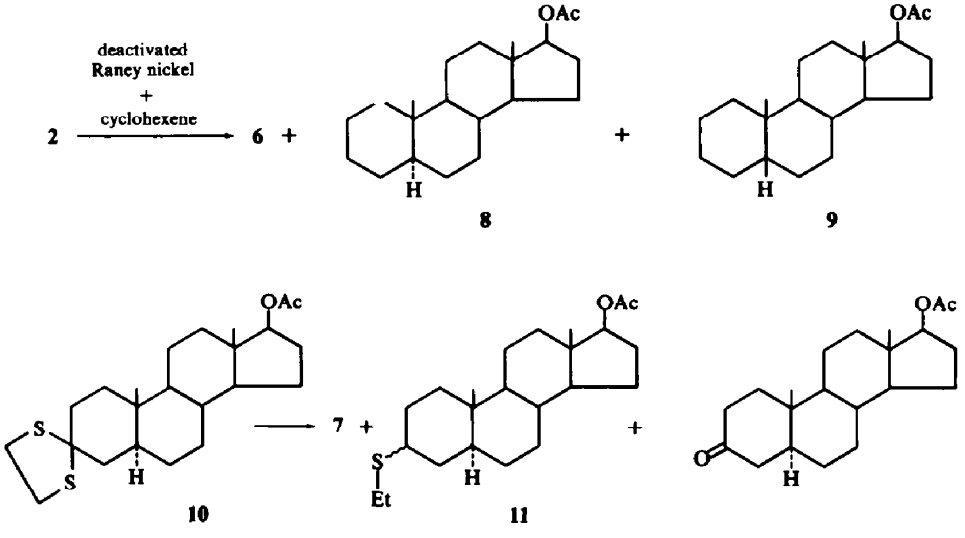
The formation of the olefin **5** may occur by a β-side attack of the hydrogen radical at C-5, and subsequent desulphurization of the corresponding enol-thioether (*step* c). The α-side attack at the C-5 position will result in the thermodynamically unstable 3-thioether. This compound, or the corresponding 5α-3-ene may isomerize to the more stable 5α-2-ene **7** by allylic hydrogen abstraction at C-2, and subsequent hydrogen addition at C-4 (*step* d). The 3,4-diene **3** is formed by a hydro-

gen abstraction at C-2 or C-6 (*step* e).* The low concentration of H atoms on the deactivated catalyst seems to be essential for the formation of all olefins but for the 4-ene **6**. The latter is the only olefinic product obtained on the desulphurization with active Raney Ni,[8] containing a high percentage of absorbed H atoms.

Desulphurization of **1** with deactivated catalyst in the presence of cyclohexene resulted in a different reaction: only one olefin was isolated, the 4-ene **6**, which was accompanied by the two saturated derivatives: 17β-acetoxy-5α-androstane (**8**) and 17β-acetoxy-5β-androstane (**9**). In addition, some of the cyclohexene was converted to benzene. It thus appeared that the hydrogen radicals abstracted from cyclohexene in turn activated the catalyst, precluding the formation of other unsaturated products.

The conversion of cyclohexene to benzene was also observed when the non-active catalyst only was heated in cyclohexene solution, indicating clearly that it is capable of abstraction of allylic H atoms.

The intermediacy of the allylic radicals seems to be essential for the formation of the dimers **4**: the thioketal of the saturated ketone, the 17β-acetoxy-androstan-3-one (**10**) does not lead to any dimeric products on desulphurization. The products obtained from this reaction were analogous to those described previously in the cholestane series[7]: the olefin 5α-2-ene (**7**), 17β-acetoxy-3-ethylthiolandrostane (**11**) in addition to the starting material and the parent ketone.



EXPERIMENTAL

All m.ps were taken in capillaries and were uncorrected, the IR spectra were determined on a Perkin–Elmer Infracord. UV absorption spectra were measured on a Cary 14 spectrophotometer. The NMR spectra were determined on a Varian A-60 spectrometer. Peak positions are indicated in ppm down-field from TMS serving as internal reference. Mass spectra were measured with an Atlas CH-4 instrument, samples being introduced directly into the ion source.

* The formation of 3 from 1 may be facilitated by a cyclic mechanism (Ref. 7), although a hydrogen abstraction at C-6 may also be postulated.

Desulphurization of the thioketal of testosterone acetate **2**

A soln of 4·0 g of **2** in 100 cc acetone was added to a slurry of deactivated Raney Ni. After boiling under reflux for 15 hr the catalyst was filtered off, and the filtrate was concentrated *in vacuo* to dryness. The residue was triturated with 250 cc ether, heated under reflux for a few min, and the insoluble material, 225 mg, was filtered off. This material melted between 200 and 310°. The mass spectrum showed molecular ion peaks at 626, 628, 630 and 632 *m/e* and other peaks at *m/e* 314, 315, 316, 508 and 567.

Fractional recrystallization from ether gave two trienes **4a** and **4b**. The first triene **4a**, melted at >360°, λ_{max}^{EtOH} 284, 295 and 307·5 mμ (ε 40,000, 50,500 and 36,000); λ_{max} (in dimethyl formamide) 285, 296 and 310 mμ. Its mass spectrum showed molecular peak at 628 *m/e*; other prominent peaks appeared at *m/e* 568 (628 − 60) and *m/e* 508 (628 − 2 × 60). The peaks at *m/e* 314, 315 and 316 seen in the total insoluble fraction were missing. (Found: C, 79·81; H, 9·42. Calc. for $C_{21}H_{30}O_2$: C, 80·21; H, 9·62%).

The second compound **4b** melted at 297–300°, λ_{max}^{EtOH} 288, 299 and 312 mμ (ε 41,000, 50,000 and 38,000) λ_{max} in dimethylformamide 292, 302 and 313 mμ. (Found: C, 79·85; H, 9·75. Calc. for $C_{21}H_{30}O_2$: C, 80·21; H, 9·62%).

The filtrate, 2·73 g, was dissolved in pentane and chromatographed on 400 g acid washed alumina.

Fraction a: eluted with 4% ether in pentane gave 80 mg of **5**, m.p. 138–141°; δ^{CDCl_3} 0·79 (C-18), 0·97 (C-19), 5·28, 5·45, 5·67 and 5·84 ppm (C-3 and C-4); λ_{max}^{KBr} 14·6 μ, identical with an authentic sample (lit.[9], m.p. 144–145°; NMR spectrum[10]).

Fraction b: eluted with the same solvent gave 66 mg of a mixture of **5** and **6** (see later), in 2:1 ratio (according to its NMR spectrum).

Fraction c: eluted with the same solvent gave 710 mg of **6** (after crystallization from ether and MeOH), m.p. 109–111°; δ^{CDCl_3} 0·80 (C-18), 1·02 (C-19), 2·01 (OAc) and 5·34 (C-4) ppm; λ_{max}^{KBr} 12·16, 12·35 and 14·75 μ. (Found: C, 79·77; H, 10·25. Calc. for $C_{21}H_{32}O_2$: C, 79·70; H, 10·19%). (Lit.[11] m.p. 111–113°; NMR spectrum[10]).

Fraction d: eluted with the same solvent mixture, 190 mg, consisted according to its NMR spectrum of a 1:2 mixture of **5** and **7**.

Fraction e: eluted with the same solvent mixture gave 207 mg of **7**, m.p. 93·5–95°; δ^{CDCl_3} 0·77, 0·79 (C-18 and C-19), 2·01 (OAc) and 5·65 (C-2 and C-3) ppm; λ_{max}^{KBr} 12·84 and 14·76 μ, identical with an authentic sample (lit.[9] m.p. 94–95°, NMR spectrum).[10]

Fraction f: eluted with 10% ether in pentane gave 98 mg of **3** (after crystallization from ether MeOH) m.p. 126–127·5°, λ_{max}^{EtOH} 228, 235 and 243 mμ (ε 18,500, 20,000 and 13,000). δ^{CDCl_3} 0·83 (C-18), 0·95 (C-19), 2·01 (OAc), 5·42, 5·70, 5·88 and 6·07 (C-3, C-4 and C-6) ppm; λ_{max}^{KBr} 11·77; 11·16 and 12·41 μ, identical with an authentic sample; (lit.[8] m.p. 125·8–130·2°).

Fraction g: eluted with 40% ether in pentane gave 70 mg of material which after crystallization from ether melted at >360° and was identical with **4a**.

Fraction h: eluted with 50% ether in pentane gave 20 mg of crystals melting at 290–297° identical with **4b**.

Fraction i: eluted with ether gave 80 mg of testosterone acetate m.p. 139–140°.

Desulfurization of the thioketal of testosterone acetate (**2**) *in the presence of cyclohexene*

Cyclohexene, 300 cc, was added to a slurry of deactivated Raney Ni (15 g) in acetone, and the solvent was distilled off until ca. 20 cc of solvent remained. A soln of 1·2 g of **2** in 150 cc cyclohexene and 100 cc cyclohexane was added to this slurry. It was then heated under reflux overnight, the soln decanted, and its UV spectrum determined after diluting with cyclohexane. It showed absorption maxima at 239·5, 244, 249, 255 and 261 mμ with optical densities corresponding to a ca. 8% of benzene in the original soln. Evaporation of this solution gave 1 g of a residue which was chromatographed on 100 g alumina.

Fraction a: eluted with 5% ether in pentane gave 50 g of **9** m.p. 96–98° (after recrystallization from MeOH); δ^{CDCl_3} 0·77 (C-19) and 0·92 (C-18) ppm, identical with an authentic sample.

Fraction b: eluted with the same solvent mixture gave 100 mg of **8** m.p. 76–78° (after crystallization from MeOH) δ^{CDCl_3} 0·77 ppm (C-18 and C-19), identical with an authentic sample.

Fraction c: eluted with the same solvent mixture, 60 mg, consisted of a 2:3 mixture of 17β-acetoxy-5α-androstane and **6** (according to its NMR spectrum).

Fraction d: eluted with the same solvent mixture gave 420 mg of 17β-acetoxy-androst-4-ene m.p. 107–109° (after recrystallization from ether:MeOH) identical with the sample obtained from desulphurization of **2**.

Dehydrogenation of cyclohexene with deactivated Raney Ni

Active Raney Ni 10 g was deactivated by heating under reflux for 2 hr with acetone. The acetone was decanted, 150 cc cyclohexene was added to the slurry and the heating was continued overnight. The soln was decanted and its UV spectrum measured, after diluting with cyclohexane. It showed absorption maxima at 239·5, 244, 249, 255 and 261 mμ with optical densities corresponding to 10% benzene in the original soln.

Desulfurization of thioketal of 17β-*acetoxy-5α-androstan-3-one* (**10**)

A soln of 1 g of **10** in 40 cc acetone containing 10 g deactivated Raney Ni was heated under reflux for 22 hr. Aliquots were taken out during the reaction and their NMR spectra measured. The intensity of the signal at 3·25 ppm (due to the —CH_2— protons of the thioketal group) gradually decreased, reaching after 18 hr a constant value corresponding to 70% of conversion. The solution was decanted and evaporated to dryness *in vacuo*. The residue, 0·6 g, was chromatographed over 50 g alumina.

Fraction a: eluted with 3% ether in pentane, 0·15 g, was recrystallized from ether:MeOH to give **7** m.p. 95–97° identical with sample obtained from desulphurization of **2**.

Fraction b: eluted with 4% and 5% ether in pentane, 50 mg, was recrystallized from ether:MeOH to give 25 mg of **11** m.p. 121–124°; δ^{CDCl_3} 0·77 and 0·79 (C-18 and C-19), 2·43 (—CH_2—S), 3·11 (—CH—S—) 2·01 (OAc) and 4·6 (H—C—OAc) ppm; mass spectrum molecular peak at *m/e* 378; λ_{max}^{KBr} 9·57 and 0·68 μ. (Found: C, 73·26; H, 10·23; S, 8·38. Calc. for $C_{23}H_{38}O_2S$; C, 72·98; H, 10·12; S, 8·45%).

Fraction c: eluted with 8% ether in pentane, was recrystallized from ether:MeOH to give the starting material m.p. 185–187°.

Fraction d: eluted with 30% ether in pentane, 50 mg, was recrystallized from ether:pentane to give 35 mg 17β-acetoxy-5α-androstan-3-one m.p. 157–159°.

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