Formation of Ketones from Steroidal Thioacetals: Some Sulphur-containing Steroids [1]

By **P. Rodney Heaton, John M. Midgley, and W. Basil Whalley,*** The School of Pharmacy, The University, London WC1N 1AX

A selection of steroidal thioacetals has been oxidised to the disulphinyl derivatives which are readily decomposed by alkali with the regeneration of the parent ketones.

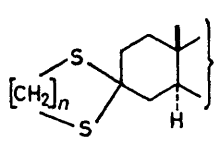
The condensation of propane-1,3-dithiol with 2α-bromo-3-oxosteroids furnishes the corresponding 2,3-dihydrodithiins.

Structures have been assigned to the condensation products of ethane-1,2-dithiol and a steroidal 4,6-diene-3-one and 1,4,6-trien-3-one.

An improved synthesis of *SS*-trimethylene 1,3-bis(toluene-*p*-thiosulphonate) is reported.

THE potential of thioacetals as acid-stable protecting groups for ketones is severely restricted by the difficulty of regenerating the carbonyl group. Daum and Clarke,[2] for example, decomposed the disulphone, from the 3,3-ethylenethioacetal of cholestan-3-one to the parent ketone under relatively rigorous conditions (boiling alcoholic sodium methoxide followed by the introduction of gaseous oxygen). In our hands, the treatment of thioacetals of steroids with, *e.g.* mercuric chloride–cadmium carbonate [3] to regenerate the ketone was uniformly unsatisfactory. In the course of other investigations concerning the mass spectrometry of sulphur-containing steroids (*cf.* ref. 4) and n.m.r. studies on the sulphonyl and sulphinyl residues (*cf.* ref. 5) we have discovered a simple method, potentially of general applicability, which uses the disulphinyl derivatives of steroidal ethylene and/or trimethylene thioacetals for the regeneration of ketones from the thio-derivatives.

The thioacetal type (1) is oxidised [6] with 1-chlorobenzotriazole, or with *m*-chloroperoxybenzoic acid, to the disulphinyl derivative, type (2), which is readily converted into the ketone, usually in yields exceeding 50%, by sodium hydroxide or sodium methoxide in alcoholic solution. Alternatively, the disulphinyl derivative need not be isolated, but may be decomposed directly by the addition of bases to the reaction mixture. This



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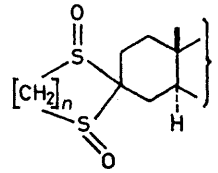

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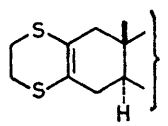

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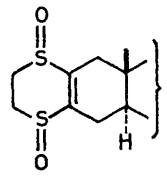

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technique operates equally well with steroidal 4-en-3-ones.

The acid-catalysed condensation of α-bromo-ketones with ethane-1,2-dithiol gives 5,6-dihydro-1,4-dithiins; [7] extension of this process to 2α-bromo-3-oxo-steroids gave

[1] Preliminary communication; P. R. Heaton, J. M. Midgley, and W. B. Whalley, *Chem. Comm.*, 1971, 750.

[2] S. J. Daum and R. L. Clarke, *Tetrahedron Letters*, 1967, 165.

[3] J. A. Marshall and H. Roebke, *J. Org. Chem.*, 1969, **34**, 4188; J. English and P. H. Grisewold, *J. Amer. Chem. Soc.*, 1945, **67**, 2039.

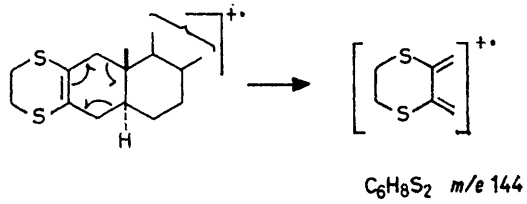
[4] J. M. Midgley, B. J. Millard, W. B. Whalley, and (in part) C. J. Smith, *J. Chem. Soc.* (*C*), 1971, 19.

[5] J. W. ApSimon, P. V. Demarco, D. W. Mathieson, W. G. Craig, A. Karim, L. Saunders, and W. B. Whalley, *Tetrahedron*, 1970, **26**, 119.

[6] W. D. Kingsbury and C. R. Johnson, *Chem. Comm.*, 1969, 365.

[7] H. Rubinstein and M. Wuerthele, *J. Org. Chem.*, 1969, **34**, 2762.

derivatives of type (3) which readily furnished the corresponding disulphinyl and disulphonyl derivatives. In accord with their structure the derivatives (3) gave intense ions in the mass spectrum at *m/e* 144, corresponding to the fragment $C_6H_8S_2$, derived from the retro-Diels–Alder fragmentation of ring A as in Scheme 1. It is noteworthy that the disulphinyl derivatives (4) are stable to alkali. All attempts to reduce the 2,3-double bond in (3) were unsuccessful; the action of calcium–liquid ammonia (*cf.* ref. 8) caused carbon–sulphur

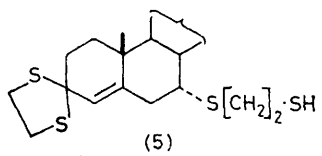


SCHEME 1

bond fission and, in the case of the derivative from cholestanone, for example, furnished cholestane, in high yield.

Whilst the boron trifluoride-catalysed condensation of propane-1,3-dithiol and ethane-1,2-dithiol with steroidal 4-en-3-ones proceeds normally the extension of this reaction to steroidal 4,6-dien- and 1,4,6-trien-3-ones produced more complex products.

Thus, 17β-acetoxyandrost-4,6-dien-3-one and ethane-1,2-dithiol furnished a compound, $C_{25}H_{38}O_2S_4$ (*m/e* 498), to which we assigned structure (5). This conclusion is



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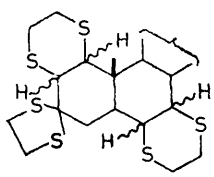

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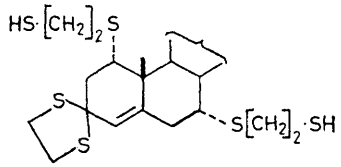


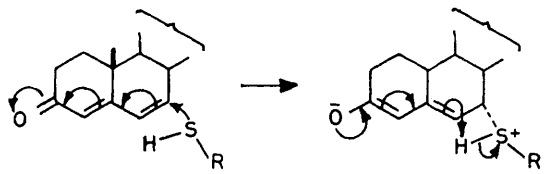
(7)

based, *inter alia*, on (*a*) the analytical and mass spectral characteristics, (*b*) absorptions at 1 725 ($OCOCH_3$) and 2 520 cm^{-1} (SH) in the i.r. spectrum, (*c*) a signal at τ 5.55 (s, *H*) assigned to the C-4 proton, and (*d*) perhaps most conclusive, the conversion of (5) into 17β-acetoxyandrost-4-ene on reduction with Raney nickel.

The mechanism for the introduction of the C-7 substituent present in (5) would seem to be as in Scheme 2, followed by normal thioacetalisation at C-3; this mechanism locates the side-chains at C-7, probably with the α-stereochemistry.

The product from ethane-1,2-dithiol and 17β-acetoxyandrost-1,4,6-trien-3-one was more complex and is provisionally assigned the constitution (6). Elemental analysis indicated a molecular formula, $C_{27}H_{38}O_2S_6$. The i.r. spectrum has absorption at 1 730 cm^{-1} (acetate); the mass spectrum was uninformative and no molecular ion was observed; the n.m.r. spectrum exhibited a singlet at τ 5.46 assigned to the C-4 proton. A formula of type (7), by analogy with (5) does not appear tenable; there are no thiol absorption bands in either the i.r. or n.m.r. spectrum: structure (6) in similar to those of several steroidal derivatives obtained by Fieser *et al.*[9]

During the course of this work an improved synthesis of *SS*-trimethylene 1,3-bis(toluene-*p*-thiosulphonate),



SCHEME 2

from propane-1,3-dithiol and toluene-*p*-sulphonyl chloride was devised.

EXPERIMENTAL

3,3-Trimethylenedithio- and 3,3-Ethylenedithio-steroids and Derivatives.—(a) *From cholestanone.* The following is illustrative of the general methods. A solution of cholestan-3-one (1 g) and propane-1,3-dithiol (1 g) in acetic acid (1.3 ml) at 60 °C was treated with boron trifluoride–diethyl ether (1.7 ml). The product separated as the mixture cooled; crystallisation from methanol–chloroform gave *3,3-trimethylene-1,3-dithiocholestane* (1.1 g) as prisms, m.p. 140 °C; $[\alpha]_D^{25}$ +30° (Found: C, 75.7; H, 10.5%; M^+, 476. $C_{30}H_{52}S_2$ requires C, 75.6; H, 10.9%; *M*, 476).

Oxidation of a solution of this thioacetal (1 g) in chloroform (60 ml) with *m*-chloroperoxybenzoic acid (1.8 g) added in portions at room temperature, gave *3,3-trimethylenedisulphonylcholestane* (1.1 g) which formed prisms, m.p. 307 °C (decomp.), from methanol–chloroform; $[\alpha]_D^{25}$ +44°; $\nu_{max.}$ 1 130 and 1 125 cm^{-1} (SO_2) (Found: C, 66.7; H, 9.6%; M^+, 540. $C_{30}H_{52}O_4S_2$ requires C, 66.7; H, 9.6%; *M*, 540).

Oxidation of the thioacetal (0.5 g) with *m*-chloroperoxybenzoic acid (0.4 g) in chloroform at 0 °C or with an excess of 1-chlorobenzotriazole in methanol or methylene chloride at −80 °C gave *3,3-trimethylenedisulphinylcholestane* (0.3 g) as prisms, m.p. 210—212 °C, from methanol; $\nu_{max.}$ 1 053 cm^{-1} (SO) (Found: C, 70.2; H, 10.4%; M^+, 508. $C_{30}H_{52}O_2S_2$ requires C, 70.8; H, 10.2%; *M*, 508). Treatment of a solution of this disulphoxide in methanol with 5% potassium hydroxide in methanol at room temperature during 1 h, gave a 75% recovery of cholestan-3-one (m.p. and mixed m.p.).

3,3-Ethylenedisulphinylcholestane formed plates, m.p.

[8] E. L. Eliel and T. W. Doyle, *J. Org. Chem.*, 1970, **35**, 2716.

[9] L. F. Fieser, C. Yuan, and T. Goto, *J. Amer. Chem. Soc.*, 1960, **82**, 1996.

195 °C, from methanol (Found: C, 71.0; H, 10.2%; M^+, 494. $C_{29}H_{50}O_2S_2$ requires C, 70.4; H, 10.1%; *M*, 494), and similarly formed cholestan-3-one with alkali.

(b) *From* 17β-*acetoxyandrostan*-3-*one*. 17β-*Acetoxy*-3,3-*trimethylenedithio*-5α-*androstane* formed slender needles, m.p. 219—220 °C, from methanol–chloroform: $\nu_{max.}$ 1 730 cm^{-1} (acetate) (Found: C, 68.1; H, 9.0%; M^+, 422. $C_{24}H_{38}O_2S_2$ requires C, 68.3; H, 9.0%; *M*, 422). 17β-*Acetoxy*-3,3-*trimethylenedisulphonyl*-5α-*androstane* formed needles, m.p. 288—290 °C (decomp.), from methanol–chloroform; $[\alpha]_D^{25}$ +25.6° (*c*, 0.5); $\nu_{max.}$ 1 730 (acetate), 1 130 and 1 125 cm^{-1} (SO_2) (Found: C, 59.4; H, 7.9%; M^+, 486. $C_{24}H_{38}O_6S_2$ requires C, 59.3; H, 7.8%; *M*, 486).

Hydrolysis of this acetate (0.5 g) with warm 4% ethanolic potassium hydroxide solution gave 3,3-*trimethylenedisulphonyl*-5α-*androstan*-17β-*ol* (0.4 g) as needles, m.p. 298 °C (decomp.), from methanol; $\nu_{max.}$ 1 330 and 1 125 cm^{-1} (SO_2) (Found: C, 59.4; H, 8.1%; M^+, 444. $C_{22}H_{36}O_5S_2$ requires C, 59.5; H, 8.1%; *M*, 444).

The corresponding disulphinyl derivative was decomposed *in situ* to regenerate 17β-hydroxy-5α-androstan-3-one in 60% yield.

(c) *From* 17β-*acetoxy*-19-*nor*-5α-*androstan*-3-*one*. 17β-*Acetoxy*-3,3-*ethylenedithio*-19-*nor*-5α-*androstane* formed plates, m.p. 190—191 °C, from methanol (Found: C, 66.4; H, 8.8%; M^+, 394. $C_{22}H_{34}O_2S_2$ requires C, 67.0; H, 8.7%; *M*, 394).

17β-*Acetoxy*-3,3-*ethylenedisulphonyl*-19-*nor*-5α-*androstane* separated from methanol–chloroform as long needles, m.p. 295 °C; $\nu_{max.}$ 1 320 and 1 120 cm^{-1} (SO) (Found: C, 57.8; H, 7.5%; M^+, 458. $C_{22}H_{34}O_6S_2$ requires C, 57.6; H, 7.4%; *M*, 458).

17β-*Acetoxy*-3,3-*ethylenedisulphonyl*-19-*nor*-5α-*androstane* separated from aqueous methanol as needles, m.p. 199 °C; $\nu_{max.}$ 1 035 cm^{-1} (SO_2) (Found: C, 62.0; H, 8.1%; M^+, 426. $C_{22}H_{34}O_4S_2$ requires C, 61.9; H, 8.0%; *M*, 426). 17β-Hydroxy-19-norandrostan-3-one was regenerated (70%) during 12 h, by the action of 5% methanolic potassium hydroxide solution.

Prepared as previously 17β-*acetoxy*-3,3-*trimethylenedithio*-19-*nor*-5α-*androstane* formed needles, m.p. 214 °C, from methanol–chloroform (Found: C, 67.0; H, 8.4%; M^+, 408. $C_{23}H_{36}O_2S_2$ requires C, 67.6; H, 8.8%; *M*, 408).

The corresponding disulphinyl derivative was decomposed *in situ* to regenerate 17β-acetoxy-19-nor-5α-androstan-3-one (70%).

(d) *From* 17β-*hydroxyandrost*-4-*en*-3-*one*. Similarly 17β-*acetoxy*-3,3-*trimethylenedisulphonylandrost*-4-*ene* formed stout prisms, m.p. 290 °C (decomp.), from aqueous methanol; $\nu_{max.}$ 1 724 (acetate), 1 330, and 1 130 cm^{-1} (SO_2) (Found: C, 59.2; H, 7.3%; M^+, 484. $C_{24}H_{36}O_6S_2$ requires C, 59.5; H, 7.4%; *M*, 484): 17β-*hydroxy*-3,3-*trimethylenedisulphonyl*-*androst*-4-*ene* formed stout prisms, m.p. 285 °C, from methanol (Found: C, 59.9; H, 7.7. $C_{22}H_{34}O_5S_2$ requires C, 59.7; H, 7.7%).

17β-*Acetoxy*-3,3-*trimethylenedisulphinylandrost*-4-*ene* separated from methanol as needles, m.p. 183—185 °C; $\nu_{max.}$ 1 725 (acetate) and 1 035 cm^{-1} (SO) (Found: C, 64.0; H, 8.1%; M^+, 452. $C_{24}H_{36}O_4S_2$ requires C, 63.7; H, 8.0%; *M*, 452). Treatment of this sulphoxide with warm (60 °C) 5% methanolic potassium hydroxide during ½ h, gave testosterone (75%).

(e) *From* 17β-*acetoxy*-19-*norandrost*-4-*en*-3-*one*. Crystallised from methanol–chloroform 17β-*acetoxy*-3,3-*trimethylenedithio*-19-*norandrost*-4-*ene* formed needles, m.p. 221 °C (Found: C, 67.5; H, 8.6%; M^+, 406. $C_{23}H_{34}O_2S_2$ requires C, 67.9; H, 8.4%; *M*, 406): τ 5.50 (s, C-4*H*, H).

The *disulphonyl-derivative* formed needles, m.p. 268 °C (decomp.), from methanol; $\nu_{max.}$ 1 335 and 1 150 cm^{-1} (SO_2) (Found: C, 58.7; H, 7.2. $C_{23}H_{34}O_6S_2$ requires C, 58.7; H, 7.2%).

2,3-*Ethylenedithiocholest*-2-*ene*.—Prepared from 2α-bromocholestan-3-one (2.75 g), ethanedithiol (0.6 ml), and toluene-*p*-sulphonic acid (0.02 g) in refluxing benzene (60 ml), with continuous removal of water during 4 h 2,3-*ethylenedithiocholest*-2-*ene* (2.2 g) formed needles, m.p. 173 °C, from methanol–chloroform (Found: C, 75.5; H, 10.4%; M^+, 460. $C_{29}H_{48}S_2$ requires C, 75.7; H, 10.4%; *M*, 460).

2,3-*Ethylenedisulphonylcholest*-2-*ene* formed needles, m.p. 273 °C, from methanol–chloroform (Found: C, 66.2; H, 9.2%; M^+, 524. $C_{29}H_{48}O_4S_2$ requires C, 66.4; H, 9.2%; *M*, 524).

Oxidation of the dithiocholestane (0.2 g) in dichloromethane (20 ml) at −80 °C during 45 min, with 1-chlorobenzotriazole (0.15 g) gave 2,3-*ethylenedisulphinylcholest*-2-*ene* (0.15 g) as plates, m.p. 186 °C, from light petroleum (b.p. 60—80 °C)–chloroform; $\nu_{max.}$ 1 035 cm^{-1} (SO) (Found: C, 71.1; H, 9.5. $C_{29}H_{48}O_2S_2$ requires C, 70.7; H, 9.7%).

Prepared similarly 17β-*acetoxy*-2,3-*ethylenedithioandrost*-2-*ene* formed plates, m.p. 195 °C, from methanol–chloroform (Found: C, 67.5; H, 8.1; M^+, 406. $C_{23}H_{34}O_2S_2$ requires C, 67.9; H, 8.4%; *M*, 406).

The *disulphonyl*-derivative formed needles, m.p. 304—305 °C, from methanol; $[\alpha]_D^{25}$ +56° (*c*, 0.1); $\nu_{max.}$ 1 310 and 1 130 cm^{-1} (SO_2) (Found: C, 58.6; H, 7.3%; M^+, 470. $C_{23}H_{34}O_6S_2$ requires C, 58.8; H, 7.3%; *M*, 470).

17β-*Acetoxy*-7α-(2-*mercaptoethylthio*)-3,3-*ethylendithio*-*androst*-4-*ene*.—A solution of 17β-acetoxyandrosta-4,6-dien-3-one (0.5 g) in acetic acid (10 ml) containing ethanedithiol (10 ml) was treated with boron trifluoride–diethyl ether (0.2 ml) at 60 °C. After addition of water (50 ml) and methanol (100 ml) to the cooled solution, the title *compound* separated and was crystallised from methanol–chloroform as needles, m.p. 140 °C (Found: C, 60.5; H, 7.8%; M^+, 498. $C_{25}H_{38}O_2S_4$ requires C, 60.2; H, 7.7%; *M*, 498). The n.m.r. spectrum showed signals at τ 4.45 (s, 1 H, 4-H), 5.34 (t, 1 H, 17-H), 6.67br (s, 4 H, thioacetal H), 7.37 (tt, 4 H, S–CH_2CH_2–SH), and 7.70 (s, 1 H, S*H*, replaceable by D_2O); $\nu_{max.}$ (Nujol) 2 520 (thiol) and 1 720 cm^{-1} (acetate).

Desulphurisation of this derivative (0.4 g) in boiling ethanol (25 ml) with Raney nickel (W-2) (1 g) during 6 h gave 17β-acetoxyandrost-4-ene (90%).

17β-*Acetoxy*-1,2:3,3:6,7-*tris*(*ethylenedithio*)*androst*-4-*ene*.—A solution of 17β-acetoxyandrosta-1,4,6-trien-3-one (1 g) in acetic acid (10 ml) was treated with ethanedithiol (1.2 ml) and boron trifluoride–diethyl ether (2 ml) to yield the title *compound* as prisms (1 g), m.p. 168—172 °C, from methanol (Found: C, 57.9; H, 6.9. $C_{27}H_{38}O_2S_6$ requires C, 55.3; H, 6.5%), $\nu_{max.}$ (Nujol) 1 730 (acetate) and 1 645 cm^{-1} [C(4),C(5) double bond]; τ 4.54 (s, 1 H, 4-H), 5.34 (t, 1 H, 17-H), 6.72 (t, *J* 3 Hz, 4 H, C-3–S–CH_2–CH_2–S–C-3), 6.92—7.39 (m, 12 H, 1-, 2-, 6-, 7-H), 7.97 (s, 3 H, OCOCH_3), 8.82 (s, 3 H, 19-CH_3), and 9.20 (s, 3 H, 18-CH_3).

SS-*Trimethylene* 1,3-*Bis*(*toluene*-p-*thiosulphonate*) (*with* P. J. Hylands).—Toluene-*p*-sulphonyl chloride (19 g) was added at 0 °C to a stirred solution of propane-1,3-dithiol (5 g) in pyridine (40 ml). An oily precipitate commenced to separate after 10 min; next day the mixture was added to ice, and the solid product collected and washed with

96% ethanol to yield *SS*-trimethylene 1,3-bis(toluene-*p*-thiosulphonate) (20 g), m.p. 65—70°, identical with an authentic specimen.

N.m.r. spectra were determined in deuteriochloroform at 60 MHz.

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