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# STUDIES ON CONFORMATION AND REACTIVITY—I

## THE POLYPHOSPHORIC ACID-CATALYZED RING OPENING OF 4,5-EPOXY-3-OXO STEROIDS—THE SYNTHESIS OF 4-ETHYLTHIOCHOLEST-4-EN-3-ONE AND ITS ANALOGS[1]

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**Abstract**—The efficient catalytic action of polyphosphoric acid, when used in the presence of suitable nucleophiles, of both normal and abnormal ring opening of 4$\beta$,5-epoxy-5$\beta$-cholestan-3-one (I) is reported. In acetic acid, I affords 2$\alpha$-acetoxycholest-4-en-3-one (XIIa; abnormal product) whilst, in marked contrast, ethanethiol reacts with I in dioxane affording 4-ethylthiocholest-4-en-3-one (XV; normal product) and a further product, 3,4-bis-(ethylthio)cholesta-3,5-diene (XVI). Ethanedithiol and $\beta$-mercaptoethanol react with I, as expected, affording cholesta-3,5-dieno[3,4-b]dithiane (XVII) and its oxathiane derivative (XIX) respectively. The nature of the reactions is briefly discussed and presence of some unique conjugation in the —S—$C_3$=$C_4$—S— and —O—$C_3$=$C_4$—S— systems in the dithiane (XVII) and oxathiane (XIX) is suggested on the basis of their UV absorption data.

## INTRODUCTION

A NUMBER of studies[4] on the ring opening or rearrangement of steroidal $\alpha$-epoxy-ketones (mainly of 4,5-epoxy-3-oxo and 16,17-epoxy-20-oxo steroids) have been reported in connection with the general objective of synthesizing modified steroid hormones. As the reaction, no doubt, still represents a promising approach to the synthesis of steroids with potential biological activities other than those of the natural hormones, a series of investigations have been undertaken with this aim in mind. The present paper deals with the efficient catalytic action of polyphosphoric acid[5] (PPA) in both normal and abnormal ring opening[6] of 4$\beta$,5-epoxy-5$\beta$-cholestan-3-one (I)[7] in the presence of suitable nucleophilic reagents, and also the convenient synthesis of the 4-alkylthio-4-en-3-oxo system[8] and its analogs in the steroid nucleus.

[1] Presented in part at the meeting of the Hokuriku-Branch of the Pharmaceutical Society of Japan, Kanazawa, 29th September (1963) and published in part, as a communication, in *Chem. and Pharm. Bull., Tokyo* **12**, 383 (1964).

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[4] For instance, see Refs cited in C. Djerassi, (Ed.) *Steroid Reactions* (Edited by C. Djerassi) p. 618. Holden-Day, San Francisco (1963).

[5] R. C. Gilmore, Jr. and W. J. Horton, *J. Amer. Chem. Soc.* **73**, 1411 (1951).

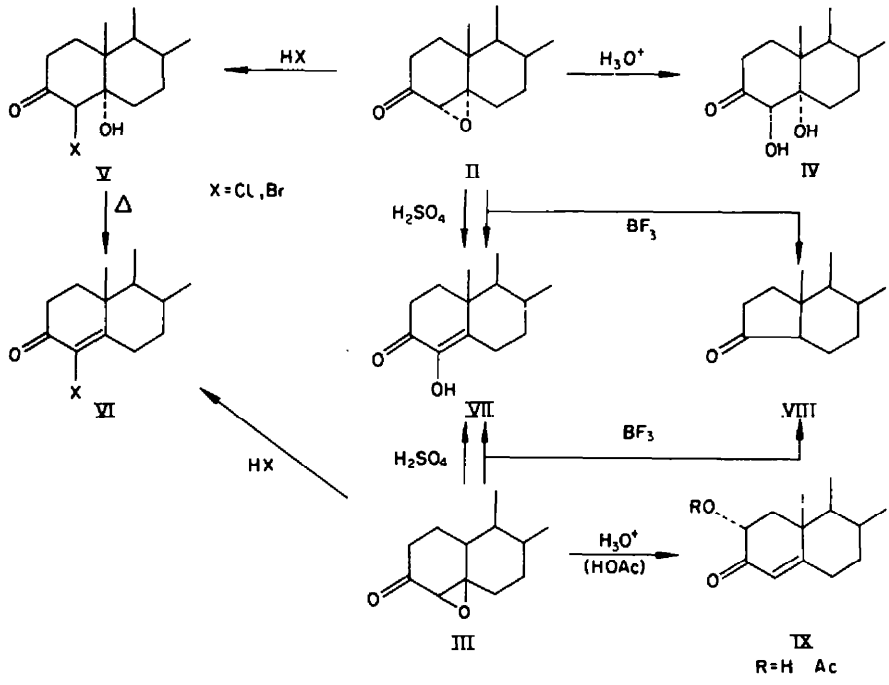
[6] Definition of the terms 'normal' and 'abnormal' in the present paper regarding the ring opening of 4,5-epoxides refers to the type of products formed; the normal ring opening is an opening (probably diaxial) which leads to the C-4 substituted compounds (normal products of epoxide fission[9]), and an abnormal opening accompanied by a rearrangement which finally affords the C-2 substituted compounds (abnormal products).

[7] P. A. Plattner, H. Heusser and A. B. Kulkarni, *Helv. Chim. Acta* **31**, 1822 (1948).

[8] After the present study had been completed, a paper (J. M. Krämer, K. Brüchner, K. Irmscher and Karl-Heinz Bork, *Chem. Ber.* **96**, 2803 (1963)) came to our hands, in which the synthesis of some 4-thiosubstituted testosterones by the base-catalyzed ring opening of 17$\beta$-hydroxy-4,5-epoxyandrostan-3-one was described.

*PPA-catalyzed abnormal ring opening of* I*—introduction of hydroxyl function at* C-2

It has been reported[9–16] that the acid-catalyzed ring opening of 4α,5-epoxy-5α- and 4β,5-epoxy-5β-3-oxo steroids, II and III respectively, usually leads to products of normal epoxide fission or of rearrangement as shown below.




However, it has also been noted[9,17,18] that 4β,5-epoxides (III), on treatment with sulphuric acid in aqueous acetone or on refluxing in acetic acid with or without sodium acetate, afford 2-hydroxy-4-en-3-oxo analogs, the abnormal product of epoxide fission. Our stereochemical interest in this abnormality observed only in the 4β,5-series led us to examine firstly the ring opening in the 5β-cholestane series in detail.

The epoxide (I) was prepared from cholest-4-en-3-one (X)[19] by the method of Plattner *et al.*[7] and the β-configuration at C-5 of the compound was confirmed by optical rotatory dispersion analysis.[20]

[9] B. Camerino, B. Pattelli and A. Vercellone, *J. Amer. Chem. Soc.* **78**, 3540 (1956).
[10] D. J. Collins, *J. Chem. Soc.* 3919 (1959).
[11] Farmaceutici Italia Soc. Anon., *Brit. Pat.* 864,608 and 864,610 (1957).
[12] R. H. Bible, Jr., C. Placek and R. D. Muir, *J. Org. Chem.* **22**, 607 (1957).
[13] Syntex S. A., *Brit. Pat.* 855,800 and 855,802 (1957).
[14] O. Mancera and H. J. Ringold, *Canad. J. Chem.* **37**, 1785 (1959).
[15] H. J. Ringold, E. Batres, O. Mancera and G. Rosenkranz, *J. Org. Chem.* **21**, 1432 (1956).
[16] J. I. Shaw and R. Stevenson, *J. Chem. Soc.* 3549 (1955).
[17] P. L. Julian, V. Georgian and H. C. Printy, *U.S. Pat.* 2,910, 487 (1959).
[18] A. Kowitz, *Brit. Pat.* 839,376 (1960).
[19] J. F. Eastham and R. Teranishi, *Organic Synthesis* **35**, 39 (1955).
[20] M. Legrand, R. Viennet and J. Caumartin, *C.R. Acad. Sci., Paris* **253**, 2378 (1961).

When I was treated with sulphuric acid in aqueous acetone or dioxane, 2α-hydroxycholest-4-en-3-one (XI),[21] m.p. 145–147°, was obtained as the only crystalline and only isolable product (abnormal) in 50·8% yield; this result being consistent with results[9,18] in other steroid series. Treatment of XI with acetic anhydride–pyridine or *p*-toluenesulphonyl chloride–pyridine afforded 2α-acetoxy- or *2α-p-toluenesulphonyloxycholest-4-en-3-one*, (XIIa or XIIb), respectively. The acetate (XIIa), which was in turn hydrolyzed to the original alcohol (XI) with sodium bicarbonate in aqueous methanol, was proved to be identical with an authentic sample of the acetate derived from X with lead tetraacetate.[22,23]

The alcohol (XI) was also formed when I was treated with a catalytical amount of concentrated sulphuric acid in dioxane, however, the thin-layer chromatogram of the crude product showed, in addition to the spot of XI itself, five closely spaced spots.

The sulphuric acid-catalyzed ring opening of I in acetic acid was next examined with the aim of introducing an acetoxyl group at C-2. The product was carefully chromatographed on silica gel and alumina, and in agreement with previous findings,[9] 4-hydroxycholest-4-en-3-one (XIII) was the major product (17%), accompanied by, however, the 2α-acetate (XIIa) in a small yield (4·5%).

In searching for a more selective catalyst for the introduction of an acetoxyl group at C-2, anhydrous aluminium chloride, a Lewis acid, was then used. The reaction mixture was eventually heated on the steam bath and 4-chlorocholest-4-en-3-one (XIV)[16] was found to be the sole and normal product in 29% yield.

Attention was then directed to the use of PPA. The epoxide (I) was dissolved in a mixture of PPA and acetic acid, and the reaction was followed spectroscopically (absorption at 243 mμ) and by thin-layer chromatography. It was complete in 96 hr. Usual work up of the reaction mixture followed by chromatography on alumina or silica gel afforded the 2α-acetate (XIIa) as the sole crystalline product in 45% yield. No other product could be isolated.

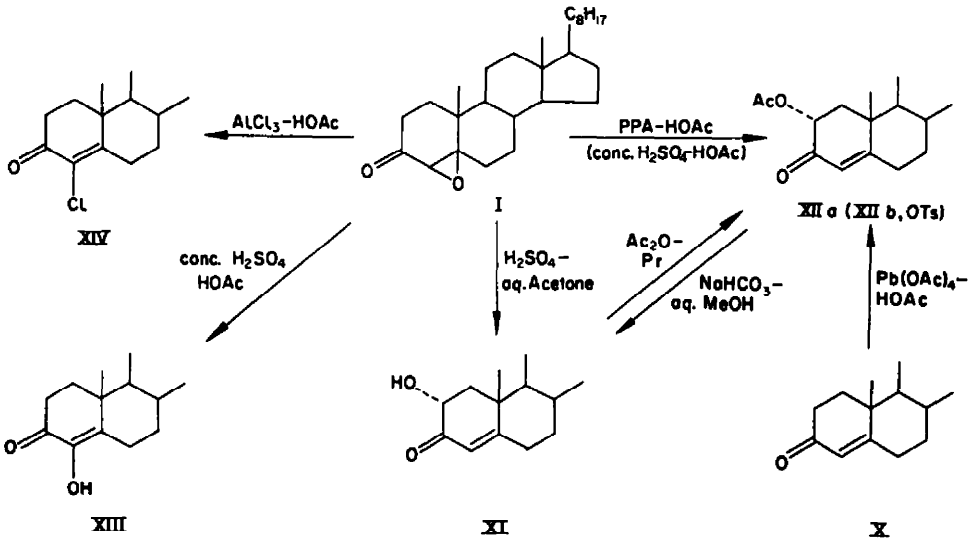
### PPA-*catalyzed normal ring opening of* I—*introduction of a thio-function at* C-4

The catalytic action of PPA for the introduction of an oxy-function at C-2 suggested that analogously a thio-function may be introduced into the steroid nucleus. Thus the reaction of I with ethanathiol in PPA–dioxane was followed by thin-layer chromatography; it was complete in a shorter time than in acetic acid. Chromatography of the crystalline product on silica gel afforded 4-*ethylthiocholest*-4-*en*-3-*one* (XV), the normal product of epoxide fission, and a further product, 3,4-*bis*(*ethylthio*)*cholesta*-3,5-*diene* (XVI), in 71% and 7·5% respectively. The elemental analyses of these new thiosteroids were in agreement with the expected molecular formulae, $C_{29}H_{48}OS$ and $C_{31}H_{52}S_2$ respectively. The spectroscopic evidence for the structure of XV is as follows: the UV absorption spectrum exhibits $\lambda_{max}$ 248 (ε 12800) and 316 mμ (ε 2000), and the IR spectrum $\nu_{max}$ 1668 (s) and 1554 (m) $cm^{-1}$, which support the 4-alkylthiosubstituted 4-en-3-oxo system.[8] The NMR spectrum does not show any peak in the olefinic

[21] D. E. A. Rivett and E. S. Wallis (*J. Org. Chem.* **15**, 35 (1950)) reported the m.p. of '6α-hydroxycholest-4-en-3-one' obtained by an alkaline hydrolysis of '6α-acetoxycholest-4-en-3-one'—the structure was later identified as 2α-acetoxycholest-4-en-3-one[22]-, as 116–118°.

[22] L. F. Fieser and M. A. Romero, *J. Amer. Chem. Soc.* **75**, 4716 (1953).

[23] F. Sondheimer, S. Kaufmann, J. Romo, H. Martinez and G. Rosenkranz, *J. Amer. Chem. Soc.* **75**, 4712 (1953).




proton region, but does show a multiplet above $\tau$7·13 which can be assigned to the —S—$CH_2$-group.[24] The positive sign of the specific rotation, $[\alpha]_D^{16}$ +131°, corresponds well to other examples of the 4-substituted 4-en-3-oxo steroids.

The spectroscopic evidence for the structure of XVI is as follows: the UV spectrum exhibits $\lambda_{max}$ 292 m$\mu$ ($\varepsilon$ 14800) and the IR spectrum without any strong carbonyl band but $\nu_{max}$ 1552 (m) $cm^{-1}$, which corresponds not to the 3,3-bis(ethylthio)-4-en system but to the 3,4-bis(ethylthio)substituted 3,5-diene system.[25] The NMR spectrum does show a peak at $\tau$3·73 which can be attributed to the C-6 vinylic hydrogen,[26] and a multiplet above $\tau$7·14 to the —S—$CH_2$— group. The negative sign of the specific rotation, $[\alpha]_D^{10}$ −186°, also corresponds to the 3,4-dithiosubstituted 3,5-diene system.[25]

Chemical evidence was obtained in further confirmation of the structures of these thiosteroids. Firstly, XV afforded X on treatment with deactivated Raney nickel in acetone. Secondly, further treatment of XV with ethanethiol in PPA–dioxane resulted in the formation of XVI in a good yield. And, thirdly, XVI was in turn hydrolyzed to XV by treatment with hydrochloric acid in chloroform.

It now appeared reasonable that ethanedithiol might react first with one end at C-4, in an analogous manner to the formation of XV, followed by a spontaneous intramolecular cyclization at C-3, to form a heterocycle, dithiane. This was indeed the case and cholesta-3,5-dieno[3,4-b]dithiane (XVII)[25] was obtained in over 40% yield; no thioketalization was observed. The elemental analysis together with other physical properties were in agreement with the literature. Further confirmation of the 3,5-diene structure in the compound was supported by the fact that the diene (XVII) was recovered unchanged after treatment with hydrogen chloride–chloroform,[27] and

[24] L. M. Jackman, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry* p. 60. Pergamon Press, London (1959).

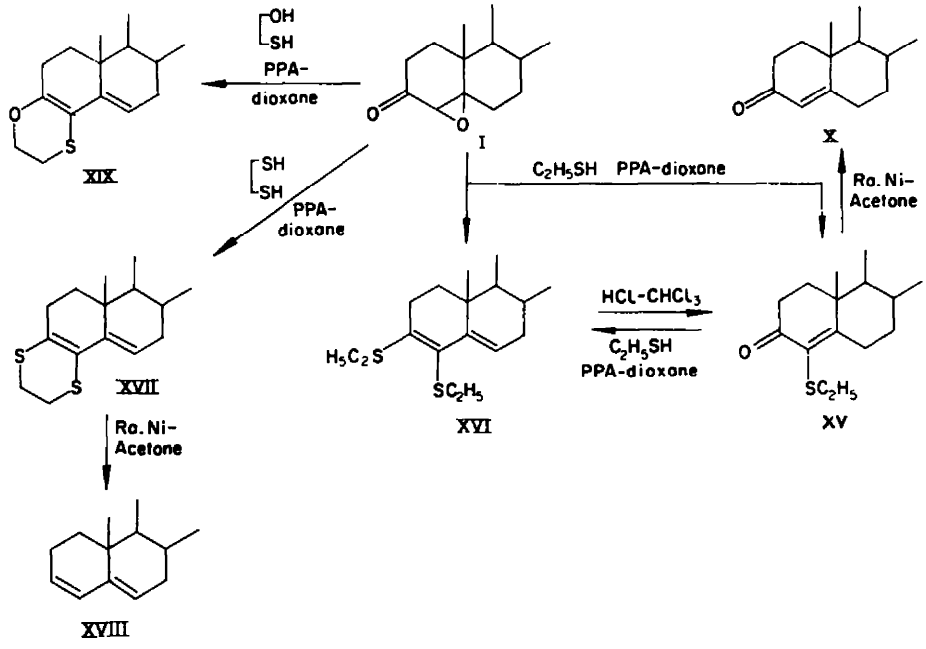
[25] L. F. Fieser, C. Yuan and T. Goto, *J. Amer. Chem. Soc.* **82**, 1996 (1961).

[26] P. Bladon and T. Sleigh, *Proc. Chem. Soc.* 183 (1962).

[27] Steroidal 2,4-dienes are known to isomerize to 3,5-diene systems under such acidic conditions: P. N. Rao and H. R. Gollberg, *Tetrahedron* **18**, 1251 (1962).

that desulphurization of XVII with deactivated Raney nickel in acetone afforded cholesta-3,5-diene (XVIII).[28]

That the PPA-catalyzed reaction selectively introduced the mercapto group at position 4 was further proved by the reaction of $\beta$-mercaptoethanol with I. The ring opening proceeded smoothly affording cholesta-3,5-dieno[3,4-b]oxathiane (XIX)[25] in 78% yield. The elemental analysis together with other physical properties corresponded to the literature.




The reaction took a different course when thioacetic acid was used as nucleophile. When I was treated with PPA–thioacetic acid, and the product subjected to repeated chromatography on alumina and silica gel, the diosphenol (XIII) was obtained as the sole crystalline product in 19% yield.

### *Consideration of the nature of the* PPA-*catalyzed ring opening of* 4,5-*epoxy*-3-*oxo steroids*

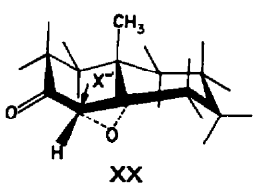
Ring opening of such asymmetrical $\alpha,\beta$-epoxy ketones as 4,5-epoxy-3-oxo steroids may occur mainly in two ways, i.e. by $S_N2$ mechanism with rupture of the $\alpha$-oxide bond, and by $S_N1$ with rupture of the $\beta$-oxide bond. This generalization appears to be valid for results of the ring openings of both the $\alpha$-(XX)[29] and $\beta$-epoxides (XXI)[29,30] referred to in the present paper. An exception would be, however, the abnormal ring opening observed in the $\beta$-series (I and III) with dilute sulphuric acid or with acetate anion as nucleophile under PPA catalysis. One would not be justified to give any

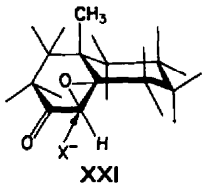
[28] H. E. Stavely and W. Bergmann, *J. Org. Chem.* **1**, 575 (1936).

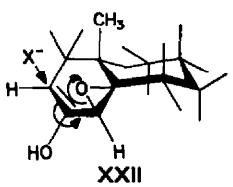
[29] In the preferred conformations of epoxides, the A-ring would be in a half-chair conformation.

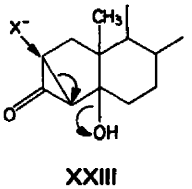
[30] Ring opening of the 4$\beta$,5-epoxide by $S_N2$ at C-4, which was actually the case, appears to be non-diaxial; yet it might be sterically preferred to the diaxial opening at C-5.

conclusive explanation of mechanisms involved in the abnormal opening on the basis of informations referred to in the paper. However, one could suggest as a possible mechanism that the opening might proceed via the enol (XXII) as intermediate; access of water or acetate anion to the sterically less hindered C-2 than C-4 would then follow. The fact that with alkyl mercaptans under PPA catalysis the opening by $S_N2$ did occur, might be, at least in part, due to the greater nucleophilicity of mercapto anions compared with acetate anion.[31] It is at present believed that the possibility of the cyclopropanone (XXIII) as intermediate does not warrant serious consideration.[32]


XX


XXI


XXII

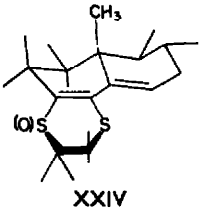

XXIII

In addition, it might be mentioned that the observed efficient catalytic action of PPA with suitable nucleophiles for the ring opening without inducing any substantial ketalization of carbonyl group present elsewhere in the compound, would be of interest both from the mechanistic and synthetic standpoints of view.

### UV *absorption spectra of cholesta*-3,5-*dieno*[3,4-*b*]*dithiane* (XVII) *and -oxathiane* (XIX)

As has been mentioned, the UV spectra of XVII and XIX exhibit two strong bands at 240 and 292 m$\mu$, and at 223 and 270 m$\mu$ respectively. The origin of the second bands at 292 m$\mu$ for XVII and at 270 m$\mu$ for XIX, has been indicated to be the 3,4-dithio- and 4-thio-substituted 3,5-diene chromophores respectively.[25] The absorption band at 292 m$\mu$ of the 3,4-bis(ethylthio)-3,5-diene (XVI) undoubtedly has a similar origin.

We have been interested in the origin of the first absorption bands, at 240 m$\mu$ for XVII and at 223 m$\mu$ for XIX. Since XVI, in which the alkylthio groups at C-3 and C-4 can rotate and are not fixed in a ring as are in XVII and XIX, lacks the first band around 240 m$\mu$ (but shows end absorption at 210 m$\mu$), it is suggested that the absorption in question might be due to some unique conjugation present in the —S—$C_3$=$C_4$—S— or —O—$C_3$=$C_4$—S— systems in the conformationally rather fixed dithiane or oxathiane rings (XXIV) in a half-chair conformation. Attempt at confirmation of the suggestion on the character of the absorption is at present in progress.


XXIV

[31] E. S. Gould, *Mechanism and Structure in Organic Chemistry* p. 259. H. Holt, New York (1960).

[32] We have observed that no acidic product was obtained in the abnormal ring opening of I to XI or XIIa.

## EXPERIMENTAL[23]

*4β,5-Epoxy-5β-cholestan-3-one* (I)

Prepared according to the literature,[7] m.p. 119–121°, $[\alpha]_D^{28}$ +116° (*c* 1·70); RD in dioxane (*c* 0·235), $[\alpha]_{700}$ +85°, $[\alpha]_{333}$ ÷2151°, $[\alpha]_{333}$ +1993°, $[\alpha]_{328}$ +2108°, $[\alpha]_{287}$ −2236°, $[\alpha]_{250}$ −1244°; $\nu_{max}$ 1713 (s) $cm^{-1}$.

*Sulphuric acid-catalyzed ring opening of 4β,5-epoxy-5β-cholestan-3-one* (I)*—formation of 2α-hydroxycholest-4-en-3-one* (XI)

(1) In aqueous acetone I (24 g) was subjected to the ring opening in 6 batches as follows: compound I (4 g) was dissolved in a mixture of 2·0 ml conc. $H_2SO_4$, 6·0 ml water and 160·0 ml acetone and the reaction mixture kept at room temp for 63 hr. The mixture was poured into ice–water, and the deposited solid filtered off, washed with sat. $NaHCO_3$ aq and water, and dried *in vacuo*. The solid, m.p. 112–136° weighed 3·70 g. The total amount of the solid including that from other 5 batches was 22·80 g.

The solid (7·40 g) was chromatographed on 240 g alumina (Woelm, neutral, grade III) and elution with 2:1 pet. ether–benzene (350 ml) afforded 460 mg of an unidentified oil. Further elution with 2:1 pet. ether–benzene (300 ml) and with 1:1 pet. ether–benzene (3·5 l) afforded crude 2α-hydroxycholest-4-en-3-one (XI) as colourless crystals, m.p. 132–144°, wt. 6·98 g. The remaining solid product (15·4 g) of the ring opening was chromatographed as described above and the total amount of crude XI thus obtained was 17·56 g. Recrystallization from MeOH gave colourless needles, m.p. 143–146°, wt. 12·20 g (50·8% yield). Further recrystallization from the same solvent gave material, m.p. 145–147°. (Found: C, 81·21; H, 10·88. $C_{27}H_{44}O_2$ requires: C, 80·94; H, 11·07%.) $[\alpha]_D^{14}$ +82° (*c* 0·98); $\lambda_{max}$ 243 mμ (ε 11900); $\nu_{max}$ 3346 (m), 1675 (s), 1612 (m) $cm^{-1}$.

*The acetate*. The alcohol (XI; 200 mg) was dissolved in a mixture of 2·0 ml acetic anhydride and 2·0 ml pyridine, and the reaction mixture kept at room temp for 24 hr, and poured into ice–water. The deposited crystals were filtered off, washed with water, and dried, m.p. 125–129°, wt. 175 mg. The crystals were chromatographed on alumina (Wako Co., grade III) and elution with 19:1 benzene–ether (60 ml) afforded XIIa as colourless needles, wt. 170 mg (72%). Recrystallization from MeOH gave m.p. 139–141°, alone and on admixture with an authentic sample (m.p. 137–139·5°, $[\alpha]_D^{30}$ ÷69° (*c* 0·92), $\lambda_{max}$ 242 mμ (ε 14500)) of the acetate obtained from X with lead tetraacetate following the procedure of Seebeck and Reichstein.[24]. (Found: C, 78·87; H, 10·30. Calc. for $C_{29}H_{46}O_3$: C, 78·68; H, 10·47%.) $[\alpha]_D^{23}$ ÷67° (*c* 1·04); $\lambda_{max}$ 243 mμ (ε 14600); $\nu_{max}$ 1740 (s), 1680 (s), 1612 (m) $cm^{-1}$.

The acetate (XIIa) was in turn hydrolyzed to the original alcohol (XI) as follows: XIIa (100 mg) was added to a mixture of 100 mg $NaHCO_3$, 1·0 ml water and 4·0 ml MeOH and the mixture refluxed for 30 min. The deposited colourless needles were filtered off, washed with MeOH aq and dried, m.p. 145–146°, alone and on admixture with a sample of XI, wt. 77 mg (85%).

*The p-toluenesulphonate* (XIIb). A mixture of 380 mg XI and 1140 mg *p*-toluenesulphonyl chloride in 5·0 ml pyridine was kept at room temp for 48 hr, and poured into ice–water. The deposited oil was extracted into ether. The ethereal layer gave a solid, wt. 415 mg. Recrystallization from MeOH gave XIIb as colourless needles, m.p. 135–135·5°, (232 mg; 45%). (Found: C, 73·78; H, 9·08. $C_{34}H_{50}O_4S$ requires: C, 73·61; H, 9·09%.) $[\alpha]_D^{18}$ +29° (*c* 0·95).

(2) In dioxane-I (500 mg) was treated with a mixture of 0·2 ml conc. $H_2SO_4$ and 20·0 ml dioxane and the reaction mixture was kept at room temp for 15 days. Work-up of the mixture followed by chromatography on silica gel (Davison Co.) as in (1) afforded XI as colourless needles, m.p. 143·5–146°, wt. 50 mg (10%); $\lambda_{max}$ 243 mμ (ε 13800); $\nu_{max}$ 3346 (m), 1682 (s), 1613 (m) $cm^{-1}$; this was the only isolable product. Another crop of XI, m.p. 141–142°, wt. 19 mg (4%), was obtained from the recrystallization mother liquor.

[23] M.ps were taken on the Kofler block, and are uncorrected. $[\alpha]_D$ Refers to $CHCl_3$, UV absorption spectra to 95% EtOH, and IR spectra to nujol unless otherwise stated. PMR spectra were run on a Varian Associates A-60 high resolution spectrometer, and the intensities or peak areas were measured by the integrator.

[24] E. Seebeck and T. Reichstein, *Helv. Chim. Acta* **27**, 948 (1944).

*Sulphuric acid-catalyzed ring opening of* I *in glacial acetic acid—formation of 4-hydroxycholest-4-en-3-one* (XIII) *and* XIIa

A mixture of 3·0 g I and 0·6 ml conc. $H_2SO_4$ in 120 ml glacial acetic acid was kept at room temp for 24 hr, and poured into ice–water. The deposited oil was extracted into ether and the ethereal solution washed with water, sat. $NaHCO_3$ aq and water, and dried ($Na_2SO_4$). Concentration of the filtrate *in vacuo* gave an oil, (2·69 g). This was chromatographed on silica gel (135 g) (Davison Co.). Elution with benzene (2400 ml) afforded XIII as a solid which was recrystallized from pet. ether to give colourless needles, m.p. 143–145·5°, (274 mg; 17%). Further recrystallization from the same solvent gave m.p. 146–147°. (Found: C, 81·42; H, 10·80; Calc. for $C_{27}H_{44}O_2$: C, 80·94; H, 11·07%.) $[\alpha]_D^{13.5}$ +88° (*c* 0·78); $\lambda_{max}$ 278 m$\mu$ ($\varepsilon$ 13300); $\nu_{max}$ 3364 (s), 1662 (s), 1629 (m) cm$^{-1}$. The physical properties are in agreement with those recorded in the literature.[10]

Further elution with 19:1 benzene–ether afforded a solid which was rechromatographed on alumina (Woelm, neutral, grade III). Elution of the first chromatogram with 19:1 benzene–ether (90 ml) gave the 2$\alpha$-acetate (XIIa). Recrystallization from MeOH gave colourless needles, m.p. 139°, alone and on admixture with an authentic sample of the acetate,[34] wt. 67 mg (4·7%). $[\alpha]_D^{13.5}$ +74° (*c* 1·06); $\lambda_{max}$ 243 m$\mu$ ($\varepsilon$ 15000); $\nu_{max}$ 1737 (s), 1680 (s), 1610 (m) cm$^{-1}$.

Elution of the second chromatogram with 19:1 benzene–ether (270 ml) gave a solid which was recrystallized from MeOH to give colourless needles, m.p. 153–154°, (73 mg). Further recrystallization from the same solvent gave material, m.p. 154–155·5°. (Found: C, 74·17; H, 10·23%.) $[\alpha]_D^{13.5}$ +79° (*c* 1·04); $\lambda_{max}$ 243 m$\mu$ (E, 1%, 1 cm, 342); $\nu_{max}$ 3570 (w), 3380 (m), 1730 (m), 1690 (s), 1621 (w), 1600 (w) cm$^{-1}$. The compound was not further investigated.

*Aluminium chloride-catalyzed ring opening of* I *in glacial acetic acid—formation of 4-chlorocholest-4-en-3-one* (XIV)

Anhydrous $AlCl_3$ (100 mg) was added to a solution of 500 mg I in 20·0 ml glacial acetic acid and the mixture heated on the steam bath for 5 hr, cooled and poured into ice–water. The deposited brown oil was extracted into ether and the ethereal layer washed with water, sat. $NaHCO_3$ aq and water, and dried ($Na_2SO_4$). Concentration of the filtrate gave a reddish brown oil, (438 mg); the UV absorption spectrum showed a single band at 257 m$\mu$. The oil was chromatographed on alumina (13 g) (Woelm, neutral, grade III), and elution with 19:1 benzene–ether gave an oil which crystallized on addition of pet. ether. Recrystallization from MeOH gave XIV as colourless needles, m.p. 121–123·5°, (150 mg; 29%). Further recrystallization from the same solvent gave material of m.p. 124–125°, alone and on admixture with an authentic sample of XIV derived from I with conc. HCl.[16] (Found: C, 77·11; H, 10·12. Calc. for $C_{27}H_{45}OCl$: C, 77·37; H, 10·26%.) $[\alpha]_D^{24}$ +104° (*c* 0·99); $\lambda_{max}$ 258 m$\mu$ ($\varepsilon$ 14900); $\nu_{max}$ 1680 (s), 1580 (m) cm$^{-1}$.

PPA-*catalyzed ring opening of* I *in glacial acetic acid—formation of* XIIa

A mixture of 500 mg I and 500 mg PPA in 20·0 ml glacial acetic acid was kept at room temp for 96 hr. A solution of 500 mg PPA in 20·0 ml glacial acetic acid was then added and the reaction mixture kept at room temp for a further 96 hr, and poured into ice–water, depositing an oil. The oil was extracted into ether, and the ethereal layer washed with sat. $NaHCO_3$ aq and water, and dried ($Na_2SO_4$). Concentration of the filtrate gave an oil, (398 mg). This was chromatographed on 20 g of silica gel (Davison Co.) and elution with 19:1 benzene–ether (180 ml) afforded XIIa as colourless needles, m.p. 135–136·5°, (250 mg) (45%). Recrystallization from MeOH gave material, m.p. 139–141°, $\lambda_{max}$ 243 m$\mu$ ($\varepsilon$ 14600); $\nu_{max}$ 1736 (s), 1678 (s), 1610 (m) cm$^{-1}$. The sample did not depress the m.p. of an authentic sample of the 2$\alpha$-acetate.[34]

PPA-*catalyzed ring opening of* I *with ethanethiol—formation of 4-ethylthiocholest-4-en-3-one* (XV) *and 3,4-bis(ethylthio)cholesta-3,5-diene* (XVI)

Compound I (1 g) was dissolved in a mixture of 2·0 ml ethanethiol, 2·0 g PPA and 38·0 ml dioxane and the reaction mixture kept at room temp for 72 hr, after which it was poured into ice–water. The deposited solid was washed with water, sat. $NaHCO_3$ aq and then water, and dried, m.p. 121–123°, but not clearing until 172°, (1·01 g). This was chromatographed on 30 g silica gel (Davison Co.) and elution with pet. ether (50 ml) afforded XVI as pale yellow crystals, m.p. 170–173°, (90 mg; 7·5%). Recrystallization from acetone gave colourless leaflets, m.p. 175–175·5°. (Found: C, 76·12; H, 10·70; S, 13·23. $C_{31}H_{52}S_2$ requires: C, 76·16; H, 10·72; S, 13·09.) $[\alpha]_D^{10}$ −186° (*c* 1·04); $\lambda_{max}$

292 mμ (ε 14800); $\nu_{max}$ 1552 (m) cm$^{-1}$; NMR absorption in $CHCl_3$, $C_6$—H, τ3·73 (one proton, broad), —S—$CH_2$—, τ7·14–7·60 (four protons, multiplet).

Elution with 1:4 pet. ether–benzene (150 ml) afforded XV as pale yellow crystals, m.p. 126–128°, (780 mg; 71%). Recrystallization from MeOH gave colourless prisms, m.p. 129·5–130·5°. (Found: C, 78·13; H, 10·69; S, 7·38. $C_{29}H_{48}OS$ requires: C, 78·31; H, 10·87; S, 7·21%.) $[\alpha]_D^{16}$ +131° (*c* 1·02); $\lambda_{max}$ 248 (ε 12800), 316 mμ (ε 2000); $\nu_{max}$ 1668 (s), 1554 (m) cm$^{-1}$; NMR absorption in $CHCl_3$, no peak in the olefinic proton region, $C_6\alpha$—H, τ6·22 (one proton, doublet (J = 14·5 c/s)),[35] —S—$CH_2$—, τ7·13–7·61 (two proton, multiplet).

*Desulphurization of* XV *with deactivated Raney nickel—formation of cholest-4-en-3-one* (X)

A mixture of 140 mg XV and ca. 1·5 g deactivated Raney Ni[36] in 25 ml acetone was refluxed for 9 hr. A further ca. 1 g deactivated Raney Ni was added and the reaction mixture refluxed for a further 4 hr. After cooling, the filtrate was concentrated *in vacuo* to give an oil which, on addition of MeOH, crystallized, m.p. 74–77°, wt. 90 mg (69%). Recrystallization from MeOH gave material, m.p. 79–80°, alone and on admixture with an authentic sample of X,[18] $[\alpha]_D^{15}$ +88° (*c* 1·03); $\lambda_{max}$ 243 mμ (ε 17500); $\nu_{max}$ 1672 (s), 1612 (m) cm$^{-1}$.

*Treatment of* XV *with ethanethiol in* PPA*–dioxane—formation of* XVI

To a solution of 470 mg XV and 2·0 g PPA in 40·0 ml dioxane, was added 2·0 ml ethanethiol and the mixture kept at room temp for 45 hr, and then poured into ice–water. The deposited colourless solid was washed with water, sat. $NaHCO_3$ aq and then water, and dried, m.p. 162–168°, (420 mg, 81%). Recrystallization from acetone gave colourless needles, m.p. 172·5–174·5°, alone and on admixture with a sample of XVI obtained directly from I with ethanethiol, wt. 264 mg (52%), $\lambda_{max}$ 292 mμ (ε 13400); $\nu_{max}$ 1550 (m) cm$^{-1}$.

*Acid-hydrolysis of* XVI *to* XV

Gaseous HCl was passed, with cooling, into a solution of 100 mg XVI in 10·0 ml $CHCl_3$ for 3 hr, after which the solution was concentrated *in vacuo* to give a solid, m.p. 121–124°, wt. 47 mg (52%) Recrystallization from MeOH gave a substance, crystallizing in colourless prisms, m.p. 126–128°, which was shown to be XV by comparison with an authentic specimen. The mixed m.p. showed no depression, and their IR and UV spectra were superposable, $\lambda_{max}$ 248 (ε 11100), 314 mμ (ε 2000); $\nu_{max}$ 1668 (s), 1554 (m) cm$^{-1}$.

PPA*-catalyzed ring opening of* I *with ethanedithiol—formation of cholesta-3,5-dieno*[3,4-*b*]*dithiane* (XVII)

A mixture of 500 mg I, 1·0 ml ethanedithiol, 1·0 g PPA and 19·0 ml dioxane was kept at room temp for 24 hr, after which it was poured into ice–water. A pale yellow solid, m.p. 153–157°, was deposited (560 mg). This was chromatographed on 16·8 g silica gel (Davison Co.), and elution with 4:1 pet. ether–benzene (165 ml) afforded XVII[25] as a colourless solid, m.p. 155·5–159°, (300 mg; 40%). The solid was repeatedly redeposited from acetone to give material, m.p. 161–162·5°. (Found: C, 76·28; H, 10·30; S, 13·58. Calc. for $C_{29}H_{46}S_2$: C, 75·95; H, 10·11; S, 13·98%.) $[\alpha]_D^{21}$ −131° (*c* 1·02); $\lambda_{max}$ 240 (ε 11900), 292 mμ (ε 13900); $\nu_{max}$ 1575 (w) cm$^{-1}$; NMR absorption in $CCl_4$, $C_6$—H, τ4·23 (one proton, broad), —S—$CH_2CH_2$—S—, τ6·94 (four protons, singlet).

*Desulphurization of* XVII *with deactivated Raney nickel—formation of cholesta-3,5-diene* (XVIII)

A mixture of 107 mg XVII and ca. 2 g deactivated Raney Ni (prepared as mentioned above) in acetone was refluxed for 8 hr when a further ca. 2 g of deactivated Raney Ni was added and the reaction mixture, refluxed for a further 3 hr. Concentration of the filtrate gave colourless needles, m.p. 73–74°, alone and on admixture with an authentic sample of XVIII obtained from cholesterol,[25] $\lambda_{max}$ 228 (ε 16600), 236 (ε 18000), 244 mμ (ε 11600); $\nu_{max}$ 1544 (w) cm$^{-1}$. The sample depressed the m.p. of cholesta-2,4-diene.[25]

[35] For the evidence for the assignment of the signal at τ6·22, doublet, to the $C_6\alpha$—H, see M. Tomoeda, M. Inuzuka, T. Furuta and T. Takahashi, *Tetrahedron Letters* 1233 (1964).

[36] Prepared according to the procedure of R. Mozingo, *Organic Synthesis* Collective Vol. III, p. 181, and refluxed in ethyl acetate and in acetone for 15 min each before use.

*Acid-treatment of* XVII*—recovery of the starting material*

Gaseous HCl was passed for 3 hr with ice-cooling into a solution of 100 mg diene (XVII) in 10·0 ml $CHCl_3$. The solution was then concentrated *in vacuo* to give a colourless solid, m.p. 154–156°, alone and on admixture with a sample of the starting material (XVII), wt. 99 mg (99%); $\lambda_{max}$ 240 ($\varepsilon$ 10900), 294 m$\mu$ ($\varepsilon$ 11700); $\nu_{max}$ 1573 (s) cm$^{-1}$. Their IR and UV spectra were superposable.

PPA*-catalyzed ring opening of* I *with β-mercaptoethanol—formation of cholesta-*3,5*-dieno*[3,4*-b*]*oxathiane* (XIX)

A solution of 1·0 g I, 2·0 ml $\beta$-mercaptoethanol and 4·0 g PPA in 80·0 ml dioxane was kept at room temp for 23·5 hr, and then poured into ice-water. The deposited solid, m.p. 120–145°, was chromatographed on 43 g of silica gel (Davison Co.), when elution with 4:1 pet. ether–benzene (840 ml) afforded XIX[25] as colourless crystals, m.p. 152–155°, (857 mg; 78%). Recrystallization from acetone gave colourless prisms, m.p. 154–155·5°. (Found: C, 78·68; H, 10·65; S, 7·34. Calc. for $C_{29}H_{46}OS$: C, 78·68; H, 10·47; S, 7·24.) $[\alpha]_D^{30}$ −162° (*c* 0·55); $\lambda_{max}^{hexane}$ 223 ($\varepsilon$ 9300), 270 m$\mu$ ($\varepsilon$ 8800); $\nu_{max}$ 1630 (w), 1613 (m) cm$^{-1}$.

*Attempted* PPA*-catalyzed ring opening of* I *in thioacetic acid—formation of 4-hydroxycholest-*4*-en-*3*-one* (XIII)

A mixture of 2·0 g I and 2·0 g PPA in 20·0 ml freshly distilled thioacetic acid, b.p. 94–97°, was kept at room temp for 45 hr and then poured into ice-water. A reddish oil was deposited. The oil, isolated with ether in the usual way, was chromatographed on 84 g silica gel (Davison Co.). Elution with 1:4 pet. ether–benzene (1350 ml) afforded an oily residue, (600 mg). Addition of pet. ether gave a solid, m.p. 143–146°, (388 mg; 19%). Recrystallization from pet. ether gave colourless needles, m.p. 147–148·5°, alone and on admixture with a sample of XIII.[10] (Found: C, 81·01; H, 10·88. Calc. for $C_{27}H_{44}O_2$: C, 80·94; H, 11·07%.) $[\alpha]_D^{14}$ +88° (*c* 1·02); $\lambda_{max}^{hexane}$ 276 m$\mu$ ($\varepsilon$ 14500); $\nu_{max}$ 3372 (s), 1664 (s), 1630 (m) cm$^{-1}$.

Elution with 19:1 benzene–ether (690 ml) afforded an oil which was rechromatographed on alumina (Woelm, neutral, grade III) to give an oil, $\lambda_{max}$ 246 m$\mu$ (E, 1%, 1 cm, 216); $\nu_{max}$ 1757 (s), 1682 (s), 1628 (w) cm$^{-1}$. The IR and UV spectra were almost superposable with those of 4-acetoxycholest-4-en-3-one, colourless needles, m.p. 99–100°, $\lambda_{max}$ 248 m$\mu$ ($\varepsilon$ 15700); $\nu_{max}$ 1760 (s), 1685 (s), 1625 (w) cm$^{-1}$, obtained from XIII by treatment with acetic anhydride–pyridine.

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