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THIOSTEROIDS—XXIX[1]

STEROIDAL TRANSANNULAR 2α,5α-EPISULPHIDES PART 3. SYNTHESES OF A-NOR-3-THIA- AND A-NOR-3-OXA-STEROIDS

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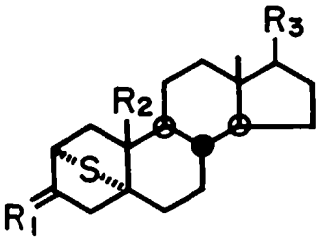
Abstract—The reaction of 3-hydroxy-2α,5α-oxides and -2α,5α-sulphides with lead tetra-acetate in boiling cyclohexane leading to 2-acetoxy-5β-formylmethyl-A-nor-3-oxa- and -3-thia-steroids, respectively, is reported. In contrast to the complicated results obtained with the oxa-steroid, the thia-steroid upon pyrolysis gives the 1-ene derivative. The corresponding 19-nor derivative on photolysis gives the A-nor-3-thia-estra-1,5(10)-diene, which is also obtained by photolysis of 3-oxo-19-nor-5α-androstane-2α,5-sulphide. Similarly, irradiation of 3-oxo-19-nor-5α-androstan-2α,5-oxide gives the A-furano-steroid.

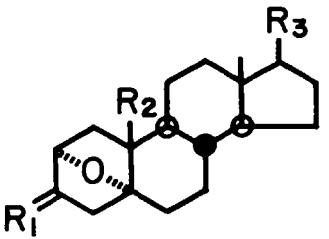
NUMEROUS modifications of steroidal functional groups and of the steroid nucleus itself have been reported in the search for compounds with unique biological activities, and of these a few A-ring heteroaromatic steroids are known.[2] In the preceding papers we synthesized a number of transannular 2α,5α-sulphides (**1**)[1,3] and -oxides, (**2**),[4] comprising heteroatom bridged bicyclo[2.2.1]heptane systems. We now describe the syntheses of A-nor-3-thia- and A-nor-3-oxa-steroids such as **3** and **4**, by converting the 5-membered heterocyclic moiety of **1** and **2**.

The reaction of alcohols with lead tetra-acetate is known to result in oxidation to ketones, ether-formation, or fragmentation reactions, depending upon the nature of the substrate alcohols and the reaction conditions employed.[5] In a nonpolar medium, the homolytic cleavage of the Pb—O bond of the initially formed alkoxy lead triacetate gives rise to the alkoxy radical. The radical, in turn, undergoes either hydrogen-abstraction from a suitably orientated C_δ—H bond less than 2·5 Å distant, resulting in the formation of the 5-membered cyclic ether, or fragmentation with fission of the C_α—C_β bond leading to a ketone (or an aldehyde) and an alkyl radical on the β-carbon. Where the alkyl radical is stabilized by an adjacent atom or group and C_α—C_β bond cleavage gives rise to a relief of ring strain in the substrate as a result of the ring-opening, fragmentation takes place as the main course of the reaction. Since sulphur and oxygen atoms are known to stabilize an adjacent radical by electron sharing conjugation and electron transfer,[6] respectively, alcohols (**1a**, **1b**, **1d**, **2a** and **2b**) are expected to be favourable substrates for the fragmentation reaction.

As a preliminary experiment, we investigated the fragmentation reaction of 7-hetero bicyclo[2.2.1]heptane system to give the substituted 5-membered heterocycles, starting with 3-hydroxycholestane derivatives. Treatment of 3β-hydroxy-5α-cholestan-2α,5-oxide (**2a**) with lead tetra-acetate in boiling cyclohexane afforded two crystalline products, **5a** and **5b**, in 62·5 and 12·1% yield, respectively. Their IR spectra showed absorption bands characteristic of an acetoxyl and an aldehyde group,

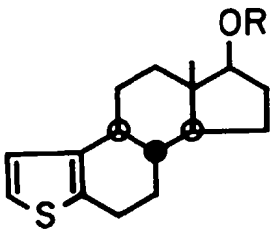


1

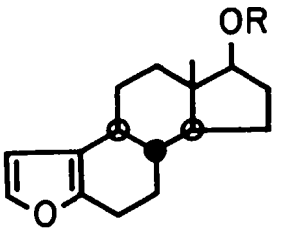


2

	a	b	c	d	e	f
R_1 :	β-OH	α-OH	O	β-OH	O	O
R_2 :	Me	Me	Me	H	H	H
R_3 :	C_8H_{17}	C_8H_{17}	C_8H_{17}	OBz	OBz	OAc



3



4

	a	b	c
R :	Bz	H	Ac

CHART 1

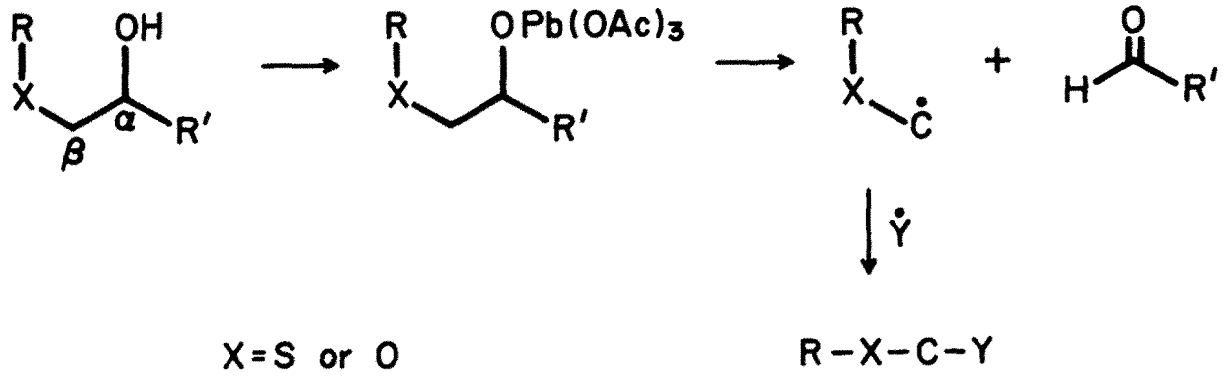


CHART 2

suggesting that fragmentation had taken place. In the NMR spectrum of the major product (**5a**), the C_4-protons* and the C_3-aldehyde proton, as well as the C_1-protons and the C_2-proton were observed as two sets of ABX patterns in accord with the structure, 2β-acetoxy-5-formylmethyl-A-nor-3-oxa-5β-cholestane (**5a**), considered to be a fragmentation product formed by C_2—C_3 bond fission. From the spectral data, **5a** and **5b** were thought to be epimeric at C_2 and the configuration of the 2β-acetoxyl in **5a** was deduced from the following evidence. Treatment of **5a** with phenyltrimethylammonium tribromide in tetrahydrofuran furnished a bicyclo-acetal *cis* bromohydrin (**6**) in 48·5% yield, supporting the *cis*-relationship between the acetoxyl and the formylmethyl groups in **5a**. In the NMR spectrum of **6**, the proton on the carbon bearing the OH group and the OH hydrogen resonated at 5·05 and 6·45 τ†, respectively, as an AB pattern, presumably caused by hydrogen-bonding of the hydroxyl to the bridged oxygen, and the proton on the bromine-bearing carbon at 5·76 τ as a doublet (*J* 2·5 Hz). While the bromohydrin (**6**) on reduction with Zn in acetic acid–ether afforded an enol–acetal (**7**) ($\nu_{C=C-O}$ 1630, 1145 cm^{-1}) in 42% yield, it did not give a corresponding epoxide on treatment with potassium hydroxide in iso-propanol and this suggests that **6** is a *cis*-bromohydrin, consistent with the NMR data mentioned above. Oxidation of **6** with chromic anhydride-pyridine complex furnished an acetal-α-bromolactone (**8**) ($\nu_{C=O}$ 1757 cm^{-1}) in 78% yield, which in turn was transformed to an acetal-lactone (**9**) ($\nu_{C=O}$ 1745 cm^{-1}) by reduction with Zn in acetic acid–ether in 69·5% yield. The acetal–lactone (**9**) was also obtained in 20% yield on heating the fragmentation product (**5a**) in collidine at 160° in an attempt to prepare 5-formylmethyl-A-nor-3-oxa-5β-cholest-1-ene (**10a**). The NMR spectrum of **9** reveals an AB quartet at 7·57 and 7·27 τ due to the protons adjacent to the carbonyl group.

These arguments led us to establish the structure and the stereochemistry of **5a** and, therefore, the configuration of the acetoxyl group in **5b** should be α-oriented. The compound (**5b**), however, was too unstable to investigate its properties further. Attempts to prepare **10a** by elimination of acetic acid from **5** were unsuccessful. Plausible mechanisms for the formation of the acetal-bromohydrin **6** and the acetal-lactone **9**, are depicted below.

Reaction of 3β-hydroxy-5α-cholestane-2α,5-sulphide (**1a**) with lead tetra-acetate afforded crystalline **11a** and a mixture of **11b** and **12** as an oil. The IR spectra of both the crystalline and the oily products exhibited absorption bands characteristic of aldehyde and acetate groups. The structure, 2β-acetoxy-5-formylmethyl-A-nor-3-thia-5β-cholestane, for **11a** was deduced from the similarity of the NMR spectrum to that of the oxa analogue (**5a**) and its mobility on TLC. The structures of the oily substances were elucidated as follows. Heating the oil in xylene at 150° gave two oily products, **13a** and **14**, in a ratio of 10 to 13, which were separated by preparative TLC. The former (**13a**) was also obtained in high yield on heating the fragmentation product **11a** in the same way. In the NMR spectrum of **13a**, the olefinic protons resonated as an AB quartet at 4·42 and 3·98 τ (*J* 6·5 Hz),‡ and the C_4-protons and the C_3-aldehyde proton as an ABX pattern analogous to that of **11a**. The NMR spectrum of

* Numbering of the carbon for NMR was based on that of the original skeleton.

† The signal at 5·05 τ further splits with the spacing of 2·5 Hz ($J_{CHOH \cdot CHBr}$). On addition of D_2O, the signal at 6·45 τ disappeared and the signal at 5·05 τ changed to a doublet (*J* 2·5 Hz).

‡ These data were in full agreement with those for dihydrothiophene reported by Cox and Owen, ref. 7.

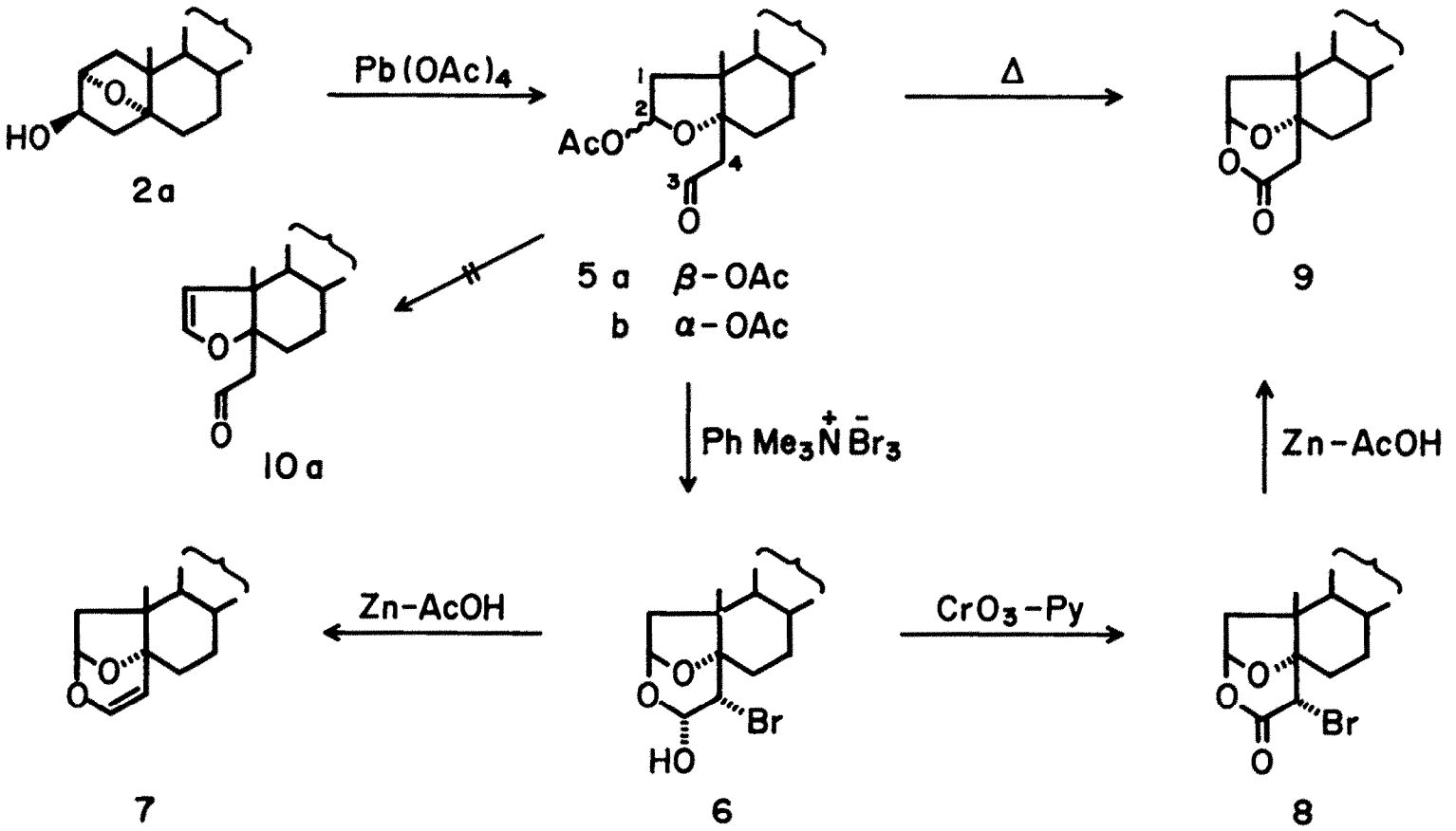

HO
2a
Pb(OAc)4
AcO
1
2
3
4
O
5 a β-OAc
b α-OAc
Δ
9
10a
Ph Me3N Br3
Zn-AcOH
Zn-AcOH
CrO3-Py
Br
HO
7
6
8

CHART 3

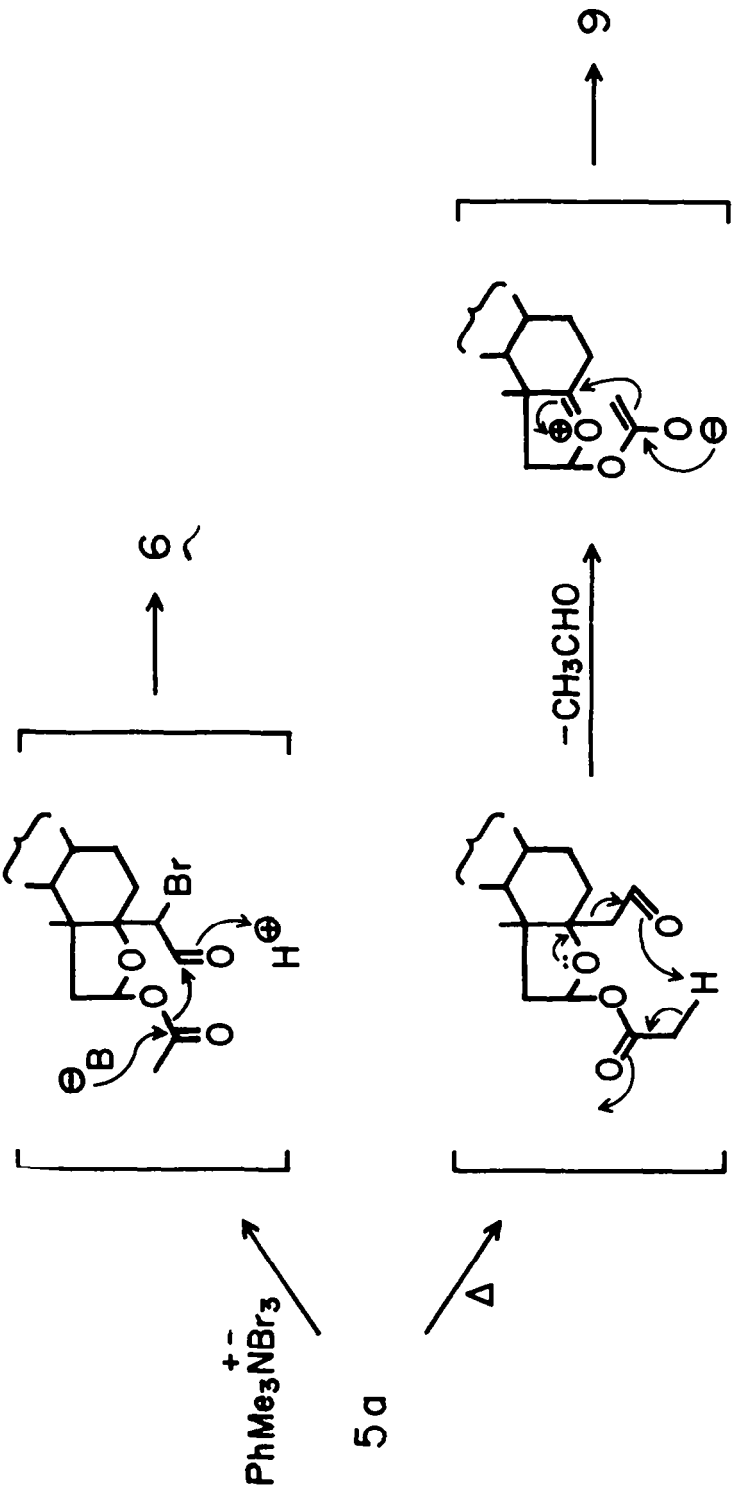


CHART 4

14 showed two sets of AB quartets due to the olefinic protons and the C_4-methylene protons. Reduction of **13a** with $NaBH_4$ in MeOH–ether at 0° furnished the corresponding alcohol **16** as a crystalline solid. Its tosylate, mesylate, bromide or chloride could not be prepared. Only the bis-sulphite **17** was isolated, in 80·4% yield, from the reaction of **16** with thionyl chloride in pyridine at 0°. Saponification of the oily **14** gave a crystalline alcohol (**15**).

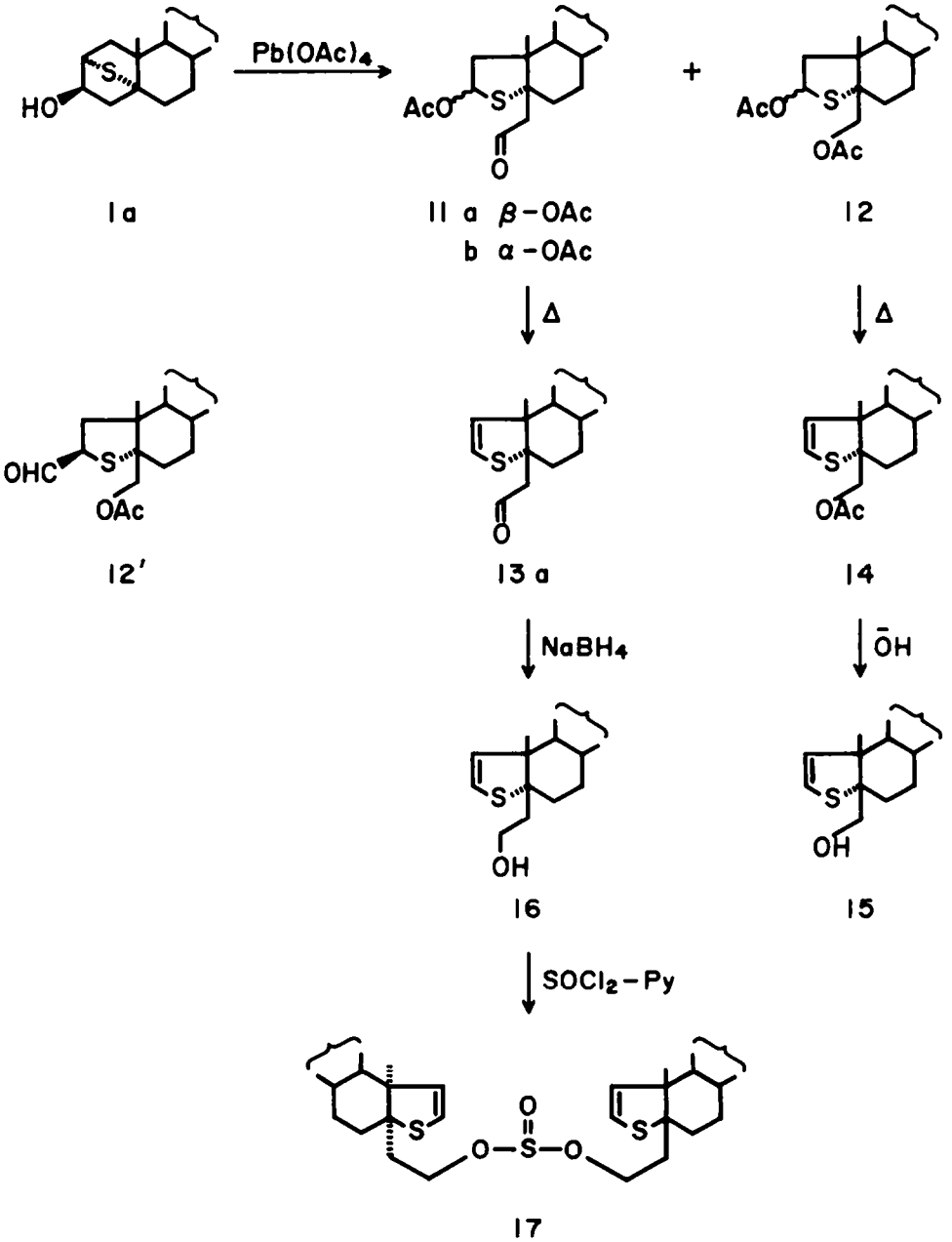


CHART 5

The mass spectral analyses of the crystalline alcohols, **15** and **16**, revealed their structural differences in that the side chain at C_5 in the former was shorter than that in the latter by one methylene. Thus, the mass spectrum of **15** exhibited a molecular ion (M^+) peak at *m/e* 404 and the highly abundant fragment ion (I) peak at *m/e* 373, corresponding to the extrusion of the hydroxymethyl radical from M^+. Cleavage across the B-ring in I afforded a methyl-thiapyrilium cation (II) at *m/e* 111 as the base peak. On the other hand, M^+ appeared at *m/e* 418 (404 + CH_2) as the base peak in the mass spectrum of **16** and the same fragmentation mode as that of **15** was observed except that the hydroxyethyl radical was extruded as depicted below.

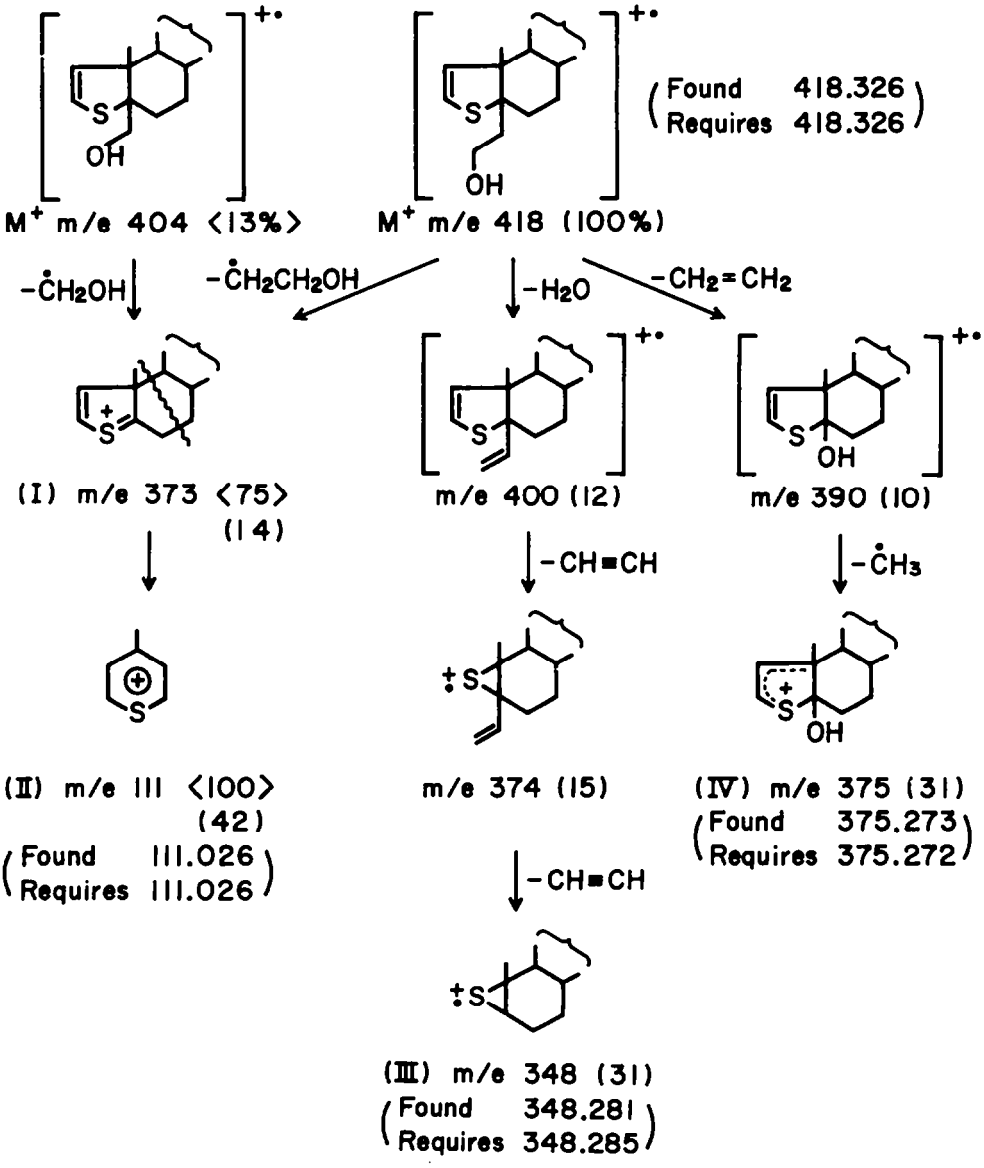


CHART 6

The fragment (III) at *m/e* 348 was thought to arise from M^+ by loss of water, followed by double eliminations of acetylene. Another prominent ion (IV) at *m/e* 375 might be formed by successive elimination of ethylene and a Me radical. The compositions of these prominent ions were determined by high resolution mass-spectroscopy.* From this data, **13a** and **14** were characterized as 5-formylmethyl-A-nor-3-thia-5β-cholest-1-ene and 5-acetoxymethyl-A-nor-3-thia-5β-cholest-1-ene, respectively, which in turn, led to the structures **11b** and **12** for 2α-acetoxy-5-formylmethyl-A-nor-3-thia-5β-cholestane, and 2-acetoxy-5-acetoxymethyl-A-nor-3-thia-5β-cholestane† respectively. The compound (**13a**) on treatment with $Pb(OAc)_4$ remained unchanged and the nor-acetate (**14**) was not detected in the reaction. The compound (**12**), therefore, was not a secondary product arising from **11**. It is interesting to note that **11** and **12** on heating easily gave the corresponding olefins, **13a** and **14**, with elimination of acetic acid, whereas **5a** was recovered unchanged.

The results of the fragmentation reaction carried out with 3α-alcohols (**1b**) and (**2b**) are shown in Table 1. It is observed that the C_2—C_3 bond cleavage is exclusive in the 2α,5α-oxide series, and predominant in the 2α,5α-sulphides reflecting the high potency of the oxygen and the sulphur atoms for stabilizing an adjacent radical. The fragmentation product (**12**) resulting from C_3—C_4 bond cleavage is peculiar to the 2α,5α-sulphide system and this is explicable in terms of stabilization of the homoallyl radical resulting from C_3—C_4 bond cleavage by sulphur participation,[8] as shown below. Whereas both 3β- and 3α-hydroxy-2α,5α-oxide gave the same products in the same ratio, the configurational change of the 3-OH group in the 2α,5α-sulphides resulted in different product distribution. Unique formation of 3-oxo-5α-cholestane-2α,5-sulphide (**1c**) may be explained as follows. In the alkoxy lead triacetate initially formed, nucleophilic attack of the lead, by sulphur owing to the proximity of these atoms, will predominate over the usual homolysis of Pb—O bond, leading to fragmentation. The resulting sulphonium salt will undergo heterolytic fission in a manner similar to that reported in the reaction of an alcohol with lead tetra-acetate in the presence of base.[5a] Lack of formation of ether-bridging between C_3 and C_{19} is predictable from the fact that the C_{19}—O distance is more than 3·3 Å in a Dreiding model.[5a]

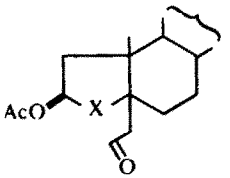
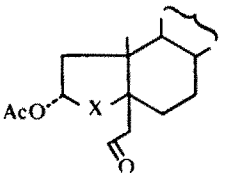
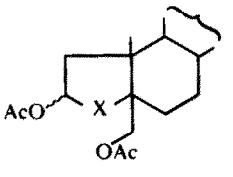
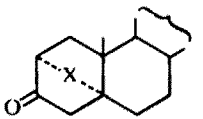
Next, our attention was directed to the 19-nor-androstane series. When 3β-hydroxy-17β-benzoyloxy-19-nor-5α-androstane-2α,5-sulphide (**1d**) was reacted with lead tetra-acetate in boiling cyclohexane-benzene containing a small amount of pyridine, two fragmentation products, 2β-acetoxy-5-formylmethyl-17β-benzoyloxy-A-nor-3-thia-5β-estrane (**11c**) and its 2α-epimer (**11d**) were formed in 37·3 and 14·4% yield, respectively. The nor-acetate of the type **12** was not isolated in the present case. Heating both **11c** and **11d** in xylene as previously described afforded identical 5-formylmethyl-17β-benzoyloxy-A-nor-3-thia-5β-estr-1-ene (**13b**).

* The spectra were kindly measured by JEOL Co. with a JMS-01SG mass spectrometer.

† Although 2β-formyl-5-acetoxymethyl-A-nor-3-thia-5β-cholestane (**12'**) is thought to be the product initially formed by fragmentation accompanied by C_3—C_4 bond cleavage, close examination of the NMR spectrum of the oily product mixture suggests the 2-acetoxy structure (**12**) rather than the 2-formyl one (**12'**). Three distinct acetoxy groups and a single aldehyde were observed in the NMR spectrum. The compound (**12**) may be a secondary product arising from **12'**.

‡ In the absence of pyridine, the reaction was complicated by the formation of other products and the yields of **11c** and **11d** were low.

TABLE 1. THE RESULTS OF THE FRAGMENTATION REACTION WITH 3-HYDROXY-5α-CHOLESTANE-2α,5-SULPHIDES AND -OXIDES

Substrate	Configuration of OH group	X	Total yield	Product and yield (%) 			
1a	β-*endo*	S	70·4	45·3	11·3*	13·8*	0
1b	α-*exo*	S	99·5	25·9	4·9*	0·5*	68·2
2a	β-*endo*	O	74·6	62·5	12·1	0	0
2b	α-*exo*	O	77·6	63·1	14·5	0	0

* These yields were based on the pyrolysis product ratio of **11b** to that of **12**

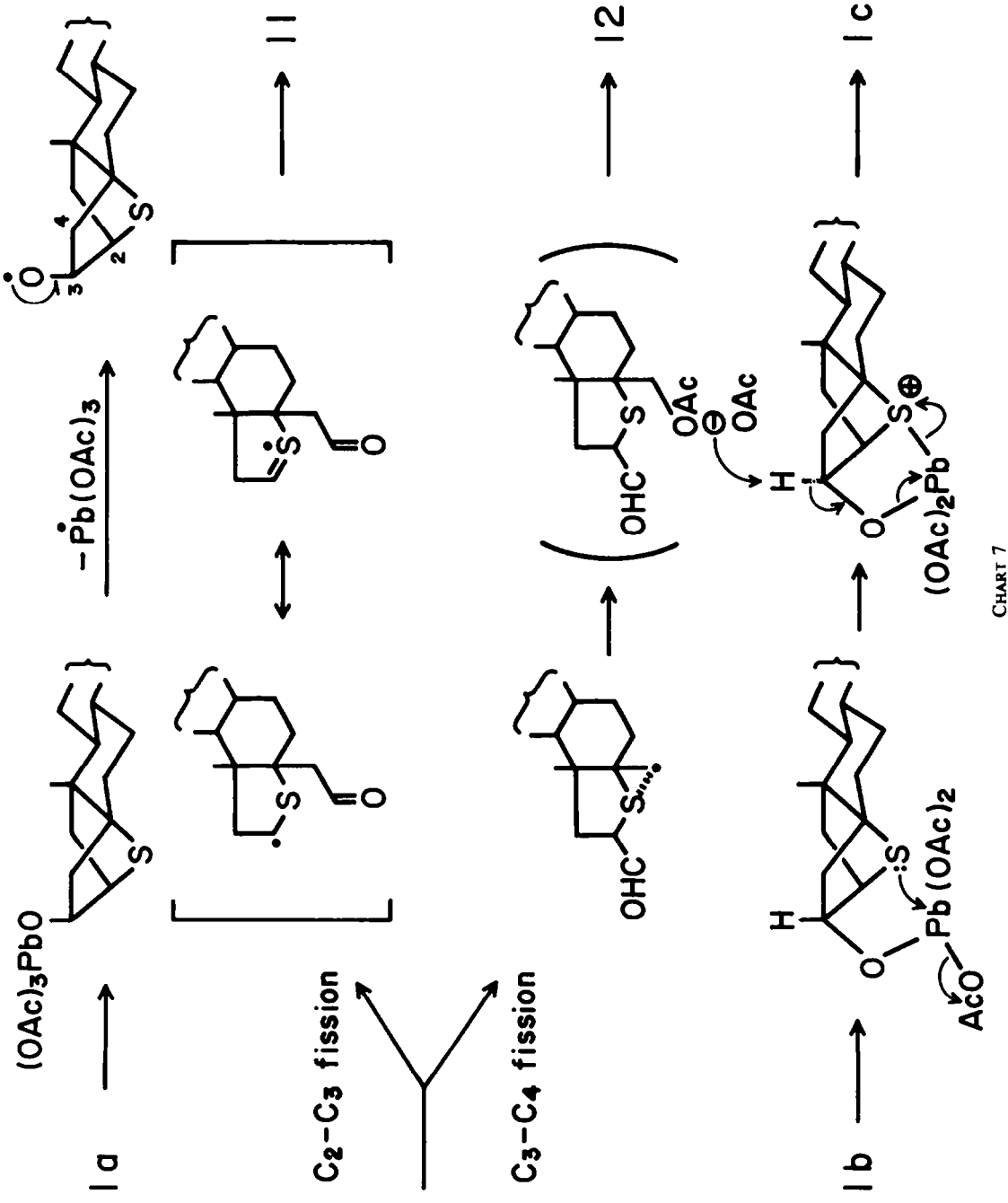

Ia
(OAc)3PbO
-Pb(OAc)3
C2-C3 fission
C3-C4 fission
11
12
Ic
Ib
OHC
OAc
OAc
(OAc)2Pb
Pb(OAc)2
AcO

CHART 7

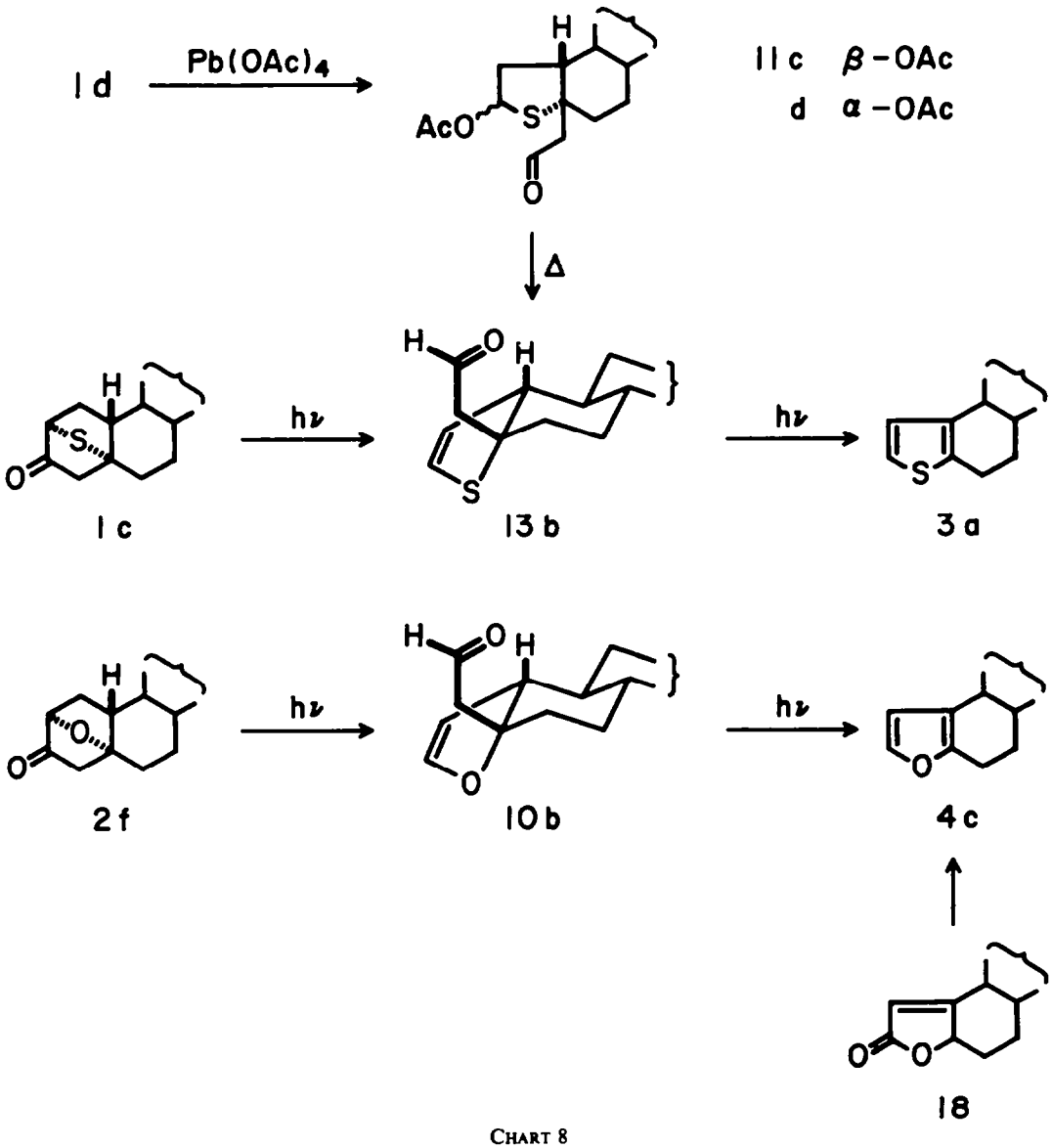


CHART 8

Preparation of an A-nor-3-thia-steroid containing thiophene as the A-ring was successfully accomplished by photolysis of **13b**. When a cyclohexane solution of **13b** under argon in a Pyrex vessel, was externally irradiated by a high pressure mercury lamp at room temperature, 17β-benzoyloxy-A-nor-3-thia-estra-1,5(10)-diene (**3a**) was obtained in 39·1% yield as a colourless oil, probably through δ-hydrogen abstraction by the carbonyl group at C_4 with concomitant expulsion of acetaldehyde. Scale-up and use of internal irradiation lowered the yield of **3a** to 20·4%. Treatment of **3a** with LAH in ether furnished a crystalline 17-OH derivative (**3b**). In its NMR spectrum, two aromatic protons were observed at 3·24 and 3·06 τ as an AB quartet[7] (*J* 5·5 Hz).

The UV spectrum showed an absorption maximum at 236·5 mμ (ε 6340) analogous to that of 2,3-disubstituted thiophene.[9] Thus, **3b** was characterized as 17β-hydroxy-A-nor-3-thia-estra-1,5(10)-diene. The compound (**13b**) was also expected to be formed from photolysis of 17β-benzoyloxy-3-oxo-19-nor-5α-androstane-2α,5-sulphide (**1e**) by C_α bond fission, followed by hydrogen abstraction,[10] but in fact, irradiation of **1e** in benzene through a Pyrex filter for 1 hr gave **13b** and **3a** in 5·0 and 5·6% yield, respectively, accompanied by 40% of the starting material. Prolonged irradiation gave only **3a** as a product. Next, we examined the photolysis of 17β-acetoxy-3-oxo-19-nor-5α-androstan-2α,5-oxide (**2f**), which on irradiation in cyclohexane through a Pyrex filter for 1 hr afforded 5-formylmethyl-17β-acetoxy-A-nor-3-oxa-5β-ester-1-ene (**10b**) and the crystalline A-furano-steroid, 17β-acetoxy-A-nor-3-oxa-estra-1,5(10)-diene (**4c**) in 5·0 and 5·7% yield respectively, accompanied by 35% of recovered **2f**. The A-furano-steroid (**4c**) was obtained in an improved yield on prolonged irradiation. The structure was identified by comparison of the IR spectrum with that of an authentic sample synthesized by a separate route.* Although **10b** was not isolated in a pure state because of its instability, its IR spectrum showed absorption bands characteristic of an aldehyde and a vinyl ether, supporting the structure (**10b**).

EXPERIMENTAL

M.ps were measured on a Kofler hot-stage apparatus and are uncorrected. Optical Rotations were determined in 1% EtOH–$CHCl_3$ with a Perkin–Elmer Polarimeter, type 141. Unless otherwise stated, UV spectra were recorded with a Hitachi EPS-2 spectrophotometer and IR spectra in Nujol mulls by use of a Koken DS-201B spectrophotometer. NMR spectra were taken in $CDCl_3$ with a Varian A-60, TMS as internal standard. Mass spectra were observed with a Hitachi RMU-6 mass spectrometer (70 eV). For preparative TLC silica gel G or GF (E. Merck Co.) was used.

Fragmentation reactions with $Pb(OAc)_4$

(a) 3β-*Hydroxy*-5α-*cholestan*-2α,5-*oxide* (**2a**). A mixture of 600 mg (1·39 mM) of $Pb(OAc)_4$ and 200 mg (2·00 mM) of $CaCO_3$ in 5 ml of cyclohexane was refluxed with stirring for 30 min. To the boiling mixture, 140 mg (0·35 mM) of **2a** in 5 ml cyclohexane was added and the mixture was agitated under reflux for 30 min. After the excess $Pb(OAc)_4$ and $CaCO_3$ had been filtered off, the filtrate was concentrated to dryness under reduced pressure and the residual oil purified by preparative TLC (benzene–AcOEt = 15:1) to give two crystalline products, 103 mg (62·5%) of **5a** as the more mobile fraction and 20 mg (12·1%) of its 2α-epimer (**5b**) as the less mobile fraction. **5a** was recrystallized from acetone to give colourless crystals. m.p. 148–150°, $[\alpha]_D^{23}$ + 38·4 ± 1·5° (*c* = 0·515), $\nu_{max}^{CS_2}$ 2730, 1754, 1724, 1225, 1130, 1080, 1000, 970, 930 cm^{-1}. NMR (τ): 9·32 (s, 3, 13-Me), 9·09 (s, 3, 10-Me), 8·17, 7·53 (AB part of ABX, each 1, J_{AB} 14·0, J_{AX} 5·0, J_{BX} 6·5 Hz, 1α-H and 1β-H), 7·98 (s, 3, —OAc), 7·78, 7·18 (AB part of ABX, each 1, J_{AB} 15·0, J_{AX} 3·0, J_{BX} 2·5 Hz, 4-H), 3·68 (dd, 1, *J* 5·0, 6·5 Hz, 2α-H), 0·2 (dd, 1, *J* 3·0, 2·5 Hz, —CHO). (Found: C, 75·70; H, 10·48. $C_{29}H_{48}O_4$ requires C, 75·62; H, 10·72%).

5b was unstable and decomposed during recrystallization. $\nu_{max}^{CS_2}$ 2730, 1755, 1725, 1224, 1124, 1000 cm^{-1}. NMR (τ): 9·31 (s, 3, 13-Me), 9·11 (s, 3, 10-Me), 7·94 (s, 3, —OAc), 7·90 (d, 2, *J* 4·0 Hz, 1-H), 7·82, 7·50 (AB part of ABX, each 1, J_{AB} 14·5, J_{AX} 3·5, J_{BX} 2·2 Hz, 4-H), 3·76 (t, 1, *J* 4·0 Hz, 2β-H), 0·2 (dd, 1, *J* 3·5, 2·2 Hz, —CHO).

(b) 3α-*Hydroxy*-5α-*cholestan*-2α,5-*oxide* (**2b**). **2b** (140 mg) on the treatment as described above gave two crystalline products, 104 mg (63·1%) of **5a** and 24 mg (14·5%) of **5b**, identified by comparisons of their IR spectra with those of authentic samples.

(c) 3β-*Hydroxy*-5α-*cholestane*-2α,5-*sulphide* (**1a**). A mixture of 720 mg (1·62 mM) of $Pb(OAc)_4$, 240 mg (2·40 mM) of $CaCO_3$, and 180 mg (0·43 mM) of **1a** on the same treatment in cyclohexane followed by

* Di-isobutyl aluminum hydride reduction[11] of the conjugated enelactone (**18**) gave **4c** in high yield, ref. 12.

preparative TLC (benzene–AcOEt = 30:1) gave 93 mg (45·3%) of crystalline **11a** as the more mobile fraction and 53 mg of colourless oil, a mixture of the 2α-epimer of **11a** (**11b**) and **12**, as the less mobile fraction.

11a was recrystallized from acetone–MeOH to give an analytically pure sample as colourless crystals. m.p. 146·5–150°, $[\alpha]_D^{23}$ −46·8 ± 1·8° (*c* = 0·491), $\nu_{max}^{CS_2}$ 2730, 1742, 1721, 1228, 1015, 945 cm^{-1}; NMR (τ): 9·33 (s, 3, 13-Me), 9·02 (s, 3, 10-Me), 8·05, 7·35 (AB part of ABX, each 1, J_{AB} 14·5, J_{AX} 7·0, J_{BX} 8·0 Hz, 1α-H and 1β-H), 7·95 (s, 3, —OAc), 7·54, 7·13 (AB part of ABX, each 1, J_{AB} 15·0, J_{AX} 3·0, J_{BX} 2·5 Hz, 4-H), 3·95 (dd, 1, *J* 7·0, 8·0 Hz, 2α-H), 0·17 (dd, 1, *J* 3·0, 2·5 Hz, —CHO). (Found: C, 73·11; H, 10·36; S, 6·56. $C_{29}H_{48}O_3S$ requires C, 73·06; H, 10·15; S, 6·72%).

(d) *3α-Hydroxy-5α-cholestane-2α,5-sulphide* (**1b**). **1b** (180 mg) on the same treatment as described above gave 122 mg (68·2%) of crystalline **1c** as the most mobile fraction, 53 mg (25·9%) of crystalline **11a** as the middle fraction, and 11 mg of colourless oil, a mixture of **11b** and **12**, as the least mobile fraction. **1c** and **11a** were identified by comparisons of the IR spectra with those of authentic samples.

(e) *17β-Benzoyloxy-3β-hydroxy-19-nor-5α-androstane-2α,5-sulphide* (**1d**). To a stirred and refluxed mixture of 800 mg (1·81 mM) of $Pb(OAc)_4$ and 250 mg (2·50 mM) $CaCO_3$ in 8 ml cyclohexane, 175 mg (0·43 mM) of **1d** in 1·2 ml of pyridine was added and the mixture was stirred under reflux for 5 min. After the $Pb(OAc)_4$ and $CaCO_3$ had been filtered off, the filtrate was washed successively with dil HCl, Na_2CO_3 aq, and water and dried over Na_2SO_4. Evaporation of the solvent afforded 180 mg of an oil, which was purified by preparative TLC (benzene–AcOEt = 15:1) to give two oily products, 74 mg (37·3%) of **11c** as the more mobile fraction and 29 mg (14·4%) of the 2α-epimer **11d** as the less mobile one. **11c**, $\nu_{max}^{CCl_4}$ 2720, 1745, 1725, 1600, 1275, 1222, 1175, 1115, 1070, 1025, 1015 cm^{-1}; NMR (τ): 9·09 (s, 3, 13-Me), 8·00 (s, 3, —OAc), 7·44, 7·13 (AB part of ABX, each 1, J_{AB} 15·5, J_{AX} 3·0, J_{BX} 2·0 Hz, 4-H), 5·17 (m, 1, 17α-H), 3·88 (dd, 1, *J* 6·5, 8·0 Hz, 2α-H), 2·58 (m, 3, arom-H), 2·05 (m, 2, arom-H), 0·23 (dd, 1, *J* 3·0, 2·0 Hz, —CHO). **11d**, $\nu_{max}^{CCl_4}$ 2720, 1745, 1725, 1600, 1275, 1221, 1175, 1115, 1070, 1025 cm^{-1}. NMR (τ): 9·06 (s, 3, 13-Me), 7·99 (s, 3, —OAc), 7·56, 7·23 (AB part of ABX, each 1, J_{AB} 15·5, J_{AX} 3·0, J_{BX} 2·0 Hz, 4-H), 5·13 (m, 1, 17α-H), 3·95 (t, 1, *J* 3·0 Hz, 2β-H), 2·55 (m, 3, arom-H), 2·00 (m, 2, arom-H), 0·22 (dd, 1, *J* 3·0, 2·0 Hz, —CHO).

Pyrolysis of the fragmentation products

(a) *2β-Acetoxy-5-formylmethyl-A-nor-3-thia-5β-cholestane* (**11a**). A soln of 100 mg of **11a** in 1 ml xylene was heated at 150° for 10 min and concentrated to dryness under reduced pressure. The residual oil was purified by preparative TLC (benzene) to afford 70 mg (80·0%) of **13a** as a colourless oil; $[\alpha]_D^{23}$ +213·9 ± 4·8° (*c* = 0·505), $\nu_{max}^{CS_2}$ 2750, 1720, 703 cm^{-1}; NMR (τ): 9·32 (s, 3, 13-Me), 8·93 (s, 3, 10-Me), 7·76, 7·20 (AB part of ABX, each 1, J_{AB} 15·5, J_{AX} 2·5, J_{BX} 3·5 Hz, 4-H), 4·42, 3·98 (AB, each 1, *J* 6·5 Hz, 1-H and 2-H), 0·25 (dd, 1, *J* 3·5, 2·5 Hz, —CHO).

(b) *A mixture of 2α-acetoxy-5-formylmethyl-A-nor-3-thia-5β-cholestane* (**11b**) *and 2-acetoxy-5-acetoxymethyl-A-nor-3-thia-5β-cholestane* (**12**). A soln of 175 mg of the oily product obtained in the fragmentation reaction of **1a**, in 2 ml of xylene, was heated at 150° for 30 min. The products were purified by preparative TLC (benzene) to afford 50 mg of **13a** as the more mobile fraction and 65 mg of oily **14** as the less mobile one; $\nu_{max}^{CS_2}$ 1744, 1230, 1030, 700 cm^{-1}; NMR (τ): 9·32 (s, 3, 13-Me), 8·92 (s, 3, 10-Me), 7·93 (s, 3, —OAc), 5·72, 6·04 (AB, each 1, *J* 11·0 Hz, 4-H), 4·41, 4·03 (AB, each 1, *J* 6·5 Hz, 1-H and 2-H). A soln of 38 mg of the oily product obtained in the fragmentation reaction of **1b**, in 1 ml of xylene, was treated as described above. Purification of the products afforded 20 mg of **13a** and 2 mg of **14**, identified by their IR spectra.

(c) *2β-Acetoxy-17β-benzoyloxy-5-formylmethyl-A-nor-3-thia-5β-estrane* (**11c**), *and its 2α-epimer* (**11d**). A soln of 58 mg of **11c** in 1 ml of xylene was heated at 160° for 25 min and the products were purified by preparative TLC (benzene–AcOEt = 30:1) to give 38 mg (74·5%) of **13b**. Recrystallization from n-hexane–ether gave analytically pure **13b** as colorless crystals. m.p. 113·5–114·5°, $[\alpha]_D^{26}$ +97·9 ± 2·4° (*c* = 0·571), $\nu_{max}^{CCl_4}$ 3020, 2700, 1723, 1599, 1273, 1175, 1116, 1080, 1025 cm^{-1}; NMR (τ): 9·00 (s, 3, 13-Me), 7·71, 7·31 (AB part of ABX, each 1, J_{AB} 15·5, J_{AX} 3·0, J_{BX} 2·5 Hz, 4-H), 5·20 (m, 1, 17α-H), 4·21, 3·90 (AB part of ABX, each 1, J_{AB} 6·0, J_{AX} 3·2 Hz, $J_{BX} \approx 0$, 1-H and 2-H), 2·60, 2·07 (m, 5, —OBz), 0·33 (dd, 1, *J* 3·0, 2·5 Hz, —CHO). (Found: C, 73·40; H, 7·50; S, 7·78. $C_{25}H_{30}O_3S$ requires: C, 73·15; H, 7·37; S, 7·81%).

Pyrolysis of 50 mg of **11d** as described above afforded 30 mg (68·9%) of **13b** identified by its IR spectrum.

Bromination of 2β-acetoxy-5-formylmethyl-3-oxa-5β-cholestane (**5a**)

To a stirred and cooled soln of 190 mg of **5a** in 10 ml of dry THF, 160 mg of $PhMe_3N\,Br_3$ was added portionwise. The resulting orange soln was stirred for 10 min at room temp to give a yellow ppt and then poured into ice water. The deposited white crystals were collected by filtration, washed with water, dissolved

in CH_2Cl_2–ether and dried over anhydrous Na_2SO_4. Preparative TLC (benzene–AcOEt = 5:1) of 200 mg of the crude product gave 100 mg (48·5%) of white crystals. Recrystallization from ether gave analytically pure **6** as colourless crystals. m.p. 178·5–179·5°, $[\alpha]_D^{23}$ +5·9 ± 0·9° (*c* = 0·509), ν_{max} 3500, 3420, 1288, 1269, 1214, 1159, 1134, 1115, 1067, 1041, 966, 951, 924, 896, 883, 841, 745 cm^{-1}; MS: *m/e* 478 (0·8%), *m/e* 480 (0·8%) $[M^+—H_2O]$, *m/e* 375 (100%) $[(M—OH)—C{\equiv}CBr)]^+$. NMR (τ): 9·33 (s, 3, 13-Me), 8·91 (s, 3, 10-Me), 6·45, 5·05 (AB part of ABX, each 1, J_{AB} 13·0, $J_{AX} \approx 0$, J_{BX} 2·5 Hz, —OH and C<u>H</u>OH), 5·76 (d, 1, *J* 2·5 Hz, C<u>H</u>Br), 4·56 (dd, 1, *J* 5·8, 2·0 Hz, 2-H). (Found: C, 64·95; H, 9·22; Br, 16·13. $C_{27}H_{45}O_3Br$ requires: C, 65·16; H, 9·12; Br, 16·06%).

A-Homo-3-oxa-5α-cholest-4-en-2α,5-oxide (**7**)

A mixture of 60 mg of **6** and 400 mg of Zn dust in 15 ml of ether–AcOH (10:1) was stirred at room temp for 2·5 hr. After the Zn dust had been filtered off, the filtrate was concentrated and the product purified by preparative TLC (benzene–AcOEt = 15:1) to give 20 mg (42%) of white crystals. Recrystallization from MeOH gave pure **7** as colourless crystals. m.p. 125·5°, $[\alpha]_D^{23}$ +30·4 ± 1·7° (*c* = 0·418), ν_{max} 3070, 1628, 1210, 1203, 1060, 990, 960, 932, 875, 797, 720 cm^{-1}; NMR (τ): 9·33 (s, 3, 13-Me), 8·96 (s, 3, 10-Me), 8·11, 7·81 (AB part of ABX, each 1, J_{AB} 14·0, J_{AX} 2·0, J_{BX} 5·5 Hz, 1-H), 5·23 (d, 1, *J* 6·0 Hz, vinyl-H), 4·44 (dd, 1, *J* 5·5, 2·0 Hz, 2-H), 3·83 (d, 1, *J* 6·0 Hz, =C<u>H</u>—O). (Found: C, 81·09; H, 10·95. $C_{27}H_{44}O_2$ requires: C, 80·95; H, 11·07%).

A-Homo-4a-bromo-4-oxo-3-oxa-5α-cholestan-2α,5-oxide (**8**)

A mixture of 90 mg of **6** and 350 mg of CrO_3 in 3 ml of pyridine was stirred at 0° for 4 hr, and worked up in the usual way to give 77 mg of white crystals. Recrystallization from acetone gave 70 mg (78%) of **8** as colourless crystals. m.p. 198° (dec), $[\alpha]_D^{23}$ +40·8 ± 1·9° (*c* = 0·431); ν_{max} 1764, 1217, 1185, 1069, 991, 971, 932, 850 cm^{-1}; CD (isooctane) $[\theta]$ (mμ): O (295), −1757 (260), −1654 (250), −7441 (219), −3721 (210); NMR (τ): 9·33 (s, 3, 13-Me), 8·91 (s, 3, 10-Me), 8·08, 7·65 (AB part of ABX, each 1, J_{AB} 15·0, $J_{AX} \approx 0$, J_{BX} 5·5 Hz, 1-H), 5·60 (s, 1, C<u>H</u>Br), 4·17 (d, 1, *J* 5·5 Hz, 2-H). (Found: C, 65·61; H, 8·67; Br, 16·17. $C_{27}H_{43}O_3Br$ requires: C, 65·44; H, 8·75; Br, 16·12%).

A-Homo-4-oxo-3-oxa-5α-cholestan-2α,5-oxide (**9**)

(a) A mixture of 60 mg of **8** and 600 mg of Zn dust in 6 ml of ether–AcOH (1:1) was stirred at room temp for 3 hr and worked up in the usual way to give 45 mg of white crystals. Recrystallization from pentane gave 35 mg (69·5%) of **9** as colourless crystals, m.p. 177–178°, $[\alpha]_D^{23}$ +48·9 ± 1·7° (*c* = 0·530), ν_{max} 1757, 1228, 1143, 1068, 998, 987, 966, 937, 833, 775 cm^{-1}; CD (isooctane) $[\theta]$ (mμ): O (260), −4300 (231), O (205); MS: *m/e* 416 (90%) $[M^+]$; NMR (τ): 9·33 (s, 3, 13-Me), 8·94 (s, 3, 10-Me), 8·18, 7·64 (AB part of ABX, each 1, J_{AB} 14·0, J_{AX} 1·2, J_{BX} 5·5 Hz, 1-H), 7·57, 7·27 (AB q, each 1, J_{AB} 18·5 Hz, C<u>H</u>$_2$—CO), 4·26 (br d, 1, *J* 5·5 Hz, 2-H). (Found: C, 77·72; H, 10·68. $C_{27}H_{44}O_3$ requires: C, 77·93; H, 10·66%).

(b) A soln of 60 mg of **5a** in 1 ml of collidine was heated at 160° for 5 hr and poured into ice water. The ether extract was worked up in the usual way to give 40 mg of brown oil. Preparative TLC (benzene–AcOEt = 15:1) of the crude product gave 10 mg (20%) of crystalline **9** identified by IR spectrum and TLC.

5-Hydroxyethyl-A-nor-3-thia-5β-cholest-1-ene (**16**)

To a cooled soln of 160 mg of **13a** in 2 ml of MeOH–ether (1:1) was added 9 mg of $NaBH_4$. The soln was stirred at 0° for 10 min and worked up in the usual way to give 170 mg of crude crystals, which were purified by preparative TLC (benzene–AcOEt = 15:1), affording 140 mg (87%) of **16** as white crystals. Recrystallization from MeOH gave an analytically pure sample as colourless crystals, m.p. 98·5–100°, $[\alpha]_D^{23}$ +206·1 ± 5·0° (*c* = 0·490), ν_{max} 3348, 3060, 3040, 1603, 1578, 1059, 1040, 827, 772, 748, 704, 667 cm^{-1}; NMR (τ): 9·33 (s, 3, 13-Me), 8·93 (s, 3, 10-Me), 6·22 (t, 2, *J* 6·5 Hz, C<u>H</u>$_2$—OH), 4·42, 4·07 (AB q, each 1, *J* 6·2 Hz, 1-H and 2-H). (Found: C, 77·20; H, 11·11; S, 7·50. $C_{27}H_{46}OS$ requires: C, 77·45; H, 11·08; S, 7·66%).

Bis-(5-hydroxyethyl-A-nor-3-thia-5β-cholest-1-ene) sulphite (**17**)

To a cooled soln of 130 mg of **16** in 2 ml of pyridine was added 0·06 ml of $SOCl_2$. The resulting yellow soln was stirred at 0° for 30 min and worked up in the usual way to give 110 mg (80·4%) of **17** as white crystals. Recrystallization from acetone gave an analytically pure sample as colourless crystals, m.p. 132–134°, $[\alpha]_D^{23}$ +234·8 ± 5·7° (*c* = 0·485), ν_{max} 3080, 1580, 1565, 1204, 968, 889, 843, 708 cm^{-1}; NMR (τ): 9·33 (s, 6, 13-Me), 8·93 (s, 6, 10-Me), 5·84 (t, 4, *J* 7·0 Hz, C<u>H</u>$_2$—OSO—), 4·46, 4·26 (AB q, each 2, *J* 6·4 Hz, 1-H and 2-H). (Found: C, 73·26; H, 10·31; S, 10·90. $C_{54}H_{90}O_3S_3$ requires: C, 73·41; H, 10·27; S, 10·89%).

5-Hydroxymethyl-A-nor-3-thia-5β-cholest-1-ene (**15**)

To a soln of 65 mg of **14** in 1 ml of dioxan, 0·4 ml of 2N–KOH–MeOH and one drop of water were added. The soln was heated on a water-bath for 5 min and worked up in the usual way to give 58 mg (98·5%) of **15** as white crystals. Recrystallization from MeOH gave an analytically pure sample as colourless crystals, m.p. 98–100°, $[\alpha]_D^{23}$ +209·8 ± 4·7° (c = 0·529), ν_{max} 3534, 3454, 3080, 3060, 1580, 1565, 1070, 1057, 1021, 982, 960, 938, 789, 755, 710 cm^{-1}; NMR (τ): 9·33 (s, 3, 13-Me), 9·00 (s, 3, 10-Me), 6·78, 6·34 (AB q, each 1, J 11·0 Hz, CH_2—OH), 4·34, 4·13 (AB q, each 1, J 6·0 Hz, 1-H and 2-H). (Found: C, 77·02; H, 11·11; S, 7·86. $C_{26}H_{44}OS$ requires: C, 77·16; H, 10·96; S, 7·93%).

General procedure for photolysis

The reaction was run with a 450 W high pressure Hg arc lamp with a Pyrex filter under a steady argon stream. Adequate water cooling was provided to maintain the soln at room temp. After irradiation, solvent was removed under reduced pressure and the residue was purified by preparative TLC.

(a) *Photolysis of* 17β-*benzoyloxy-5-formylmethyl-A-nor-3-thia-5β-estr-1-ene* (**13a**). A soln of 280 mg of **13a** in 400 ml of cyclohexane was irradiated for 35 min. Preparative TLC (benzene–cyclohexane = 2:1) gave 52 mg (20·4%) of **3a** as colourless oil; $\nu_{max}^{CCl_4}$ 3020, 1723, 1600, 1310, 1274, 1170, 1115, 1070, 1025, 990 cm^{-1}.

3a on treatment with 50 mg of LAH in 1 ml of dry ether at room temp gave 36 mg of **3b** as white crystals. Recrystallization from n-hexane gave analytically pure **3b** as colourless crystals, m.p. 147–148°, $[\alpha]_D^{26}$ +75·2 ± 4·1° (c = 0·278), ν_{max} 3500, 1265, 1205, 1135, 1070, 1020, 1007, 880, 840, 750, 695 cm^{-1}, λ_{max}^{EtOH} 236·5 mμ (ε 6340); MS: *m/e* 262 (100%) [M^+]; NMR (τ): 9·27 (s, 3, 13-Me), 8·75 (s, 1, OH), 6·35 (m, 1, 17α-H), 3·24, 3·06 (AB q, each 1, J 5·5 Hz, 1-H and 2-H). (Found: C, 73·03; H, 8·73; S, 12·08. $C_{16}H_{22}OS$ requires: C, 73·23; H, 8·45; S, 12·22%).

External irradiation of 43 mg of **13a** in 25 ml of cyclohexane for 6 hr gave 15 mg (39·1%) of **3a** accompanied by 5 mg of starting material.

(b) *Photolysis of* 17β-*benzoyloxy-3-oxo-19-nor-5α-androstane-2α,5-sulphide* (**1e**). A soln of 100 mg of **1e** in 400 ml of benzene was irradiated for 1 hr. Preparative TLC (benzene) gave 5 mg (5·6%) of oily **3a** as the most mobile fraction, 5 mg (5·0%) of crystalline **13b** as the middle fraction, and 40 mg of recovered **1e** as the least mobile fraction, each identified by their IR spectra.

(c) *Photolysis of* 17β-*acetoxy-3-oxo-19-nor-5α-androstan-2α,5-oxide* (**2f**). A soln of 200 mg of **2f** in 400 ml of cyclohexane was irradiated for 25 min. Preparative TLC (cyclohexane–AcOEt = 4:1) gave 10 mg (5·7%) of crystalline **4c** as the most mobile fraction, 10 mg (5·0%) of oily **10b** ($\nu_{max}^{CCl_4}$ 2720, 1725, 1598, 1240, 1150, 1130, 1045, 1025 cm^{-1}) as the middle fraction and 70 mg of recovered **2f** as the least mobile fraction. Recrystallization of **4c** from n-hexane afforded an analytically pure sample, m.p. 118–119°, $[\alpha]_D^{24}$ 28·7 ± 0·7° (c = 0·951); λ_{max}^{EtOH} 223 mμ (ε 4800). ν_{max} 3162, 3106, 1734, 1627, 1505, 1241, 1036, 898, 725 cm^{-1}; NMR (τ): 9·16 (s, 3, 13-Me), 7·96 (s, 3, OAc), 5·37 (t, 1, 17α-H), 3·77 (d, 1, J 2·0 Hz, 1-H), 2·76 (d, 1, J 2·0 Hz, 2-H).

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