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PREPARATION, REACTIONS, PROTON MAGNETIC RESONANCE SPECTRA, AND DIPOLE MOMENTS OF 3-SUBSTITUTED 5α-CHOLESTAN-2α,5-*ANTI*-EPISULPHOXIDES

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Abstract- Oxidation of 3-substituted 5α-cholestan-2α,5-episulphides (**4a**, **4b**, **5**, **6a**, **6b**, **10a**, and **10b**) with *m*-chloroperbenzoic acid afforded the corresponding *anti*-sulphoxides (**7a**, **7b**, **8**, **9a**, **9b**, **11a**, and **11b**, respectively). Sulphinyl configurations have been assigned from chemical evidence and established by dipole-moments and NMR spectroscopy, 3β-Bromo-*anti*-sulphoxide **11a** with phenyl lithium was found to give cholesta-2,4-diene. A mechanism is discussed which involves the formation of 5-(S)-phenylsulphinyl-5α-cholest-2-ene as an incipient intermediate, followed by *syn*-elimination *via* a cyclic intramolecular mechanism. Anisotropic shielding effects and benzene-induced solvent shifts concerning the S → O bond introduced are discussed.

IN PREVIOUS papers,[1-3] we reported the oxidation of 5α-cholestan-2α,5-episulphide (**1**)[4] comprising a 7-thiabicyclo[2.2.1]heptane system, with various reagents leading to *anti*-oxide **2** and the *syn*-isomer **3**, bridge-top sulphoxides whose properties are significantly influenced by steric effects in the sulphur-bridged system. The thermodynamically more stable **2** was formed exclusively by reaction of **1** with peroxy reagents and the less stable **3** was formed stereoselectively only with t-butyl hypochlorite. We here present the preparation of a series of 3-substituted 5α-cholestan-2α,5-*anti*-episulphoxides and the determination of their sulphinyl configurations based on chemical conversions, NMR spectra, and dipole moments.

Oxidation of 3α-*exo*-hydroxy-, 3α-acetoxy-, 3β-*endo*-hydroxy-, 3β-acetoxy, and 3-oxo-5α-cholestan-2α,5-episulphides (**4a**, **4b**, **6a**, **6b**, and **5**, respectively)[4] with 1 molar equivalent of *m*-chloroperbenzoic acid[5] in CH_2Cl_2 afforded the corresponding sulphoxides (**7a**, **7b**, **9a**, **9b**, and **8**, respectively) as single products in high yield. The presence of the sulphinyl group in these compounds was readily established from their IR spectra which showed strong absorption at 1020–1060 cm^{-1}. An identical configuration at sulphur in all five sulphoxides was assigned on the basis of chemical interconversions involving no epimerization of the sulphinyl groups. It is noteworthy that the sulphinyl moiety in each of the compounds was unexpectedly stable under the reaction conditions employed. Acetylation of the hydroxy sulphoxides **7a** and **9a** with Ac_2O in pyridine gave the corresponding acetates (**7b** and **9b**), identical with the compounds produced by direct oxidation of **4b** and **6b**, respectively. $NaBH_4$ reduction of oxosulphoxide **8** in MeOH gave a mixture of **7a** and **9a**, separable only by prep TLC using an infinite developing method. Thus, acetylation of the mixture, followed by prep TLC readily gave the pure components, **7b** and **9b**, in a ratio of 29 to 1. On reduction of the 3-oxo function, product distribution favouring

† Deceased April 17, 1969.

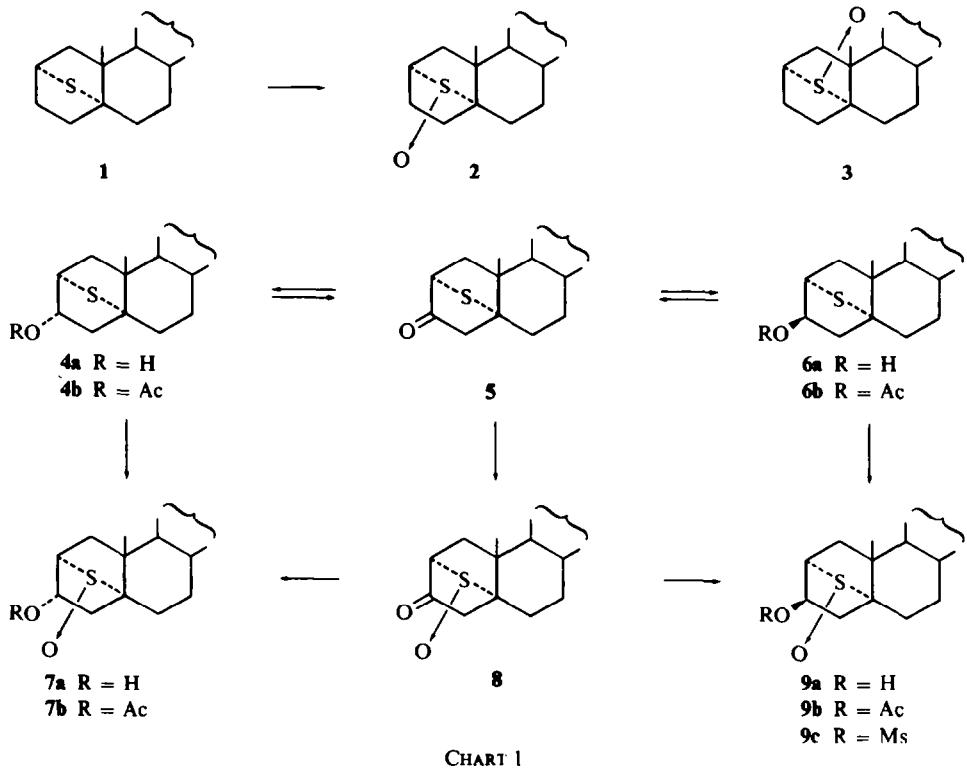


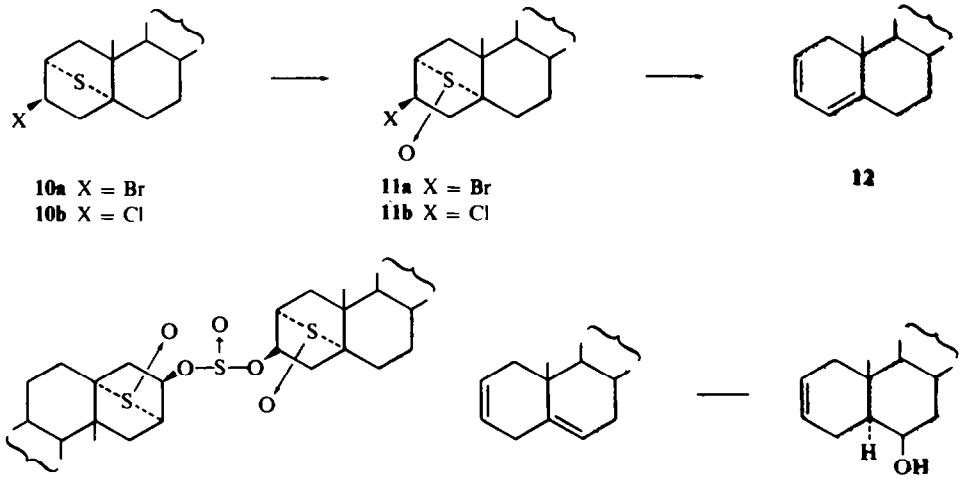
CHART 1

the α-*exo*-hydroxyl compound is more marked with the sulphoxide **8** than with the parent sulphide **5** (10:3).[4] This seems to suggest that the sulphinyl group in **8** significantly interferes with attack by reagent from the rear of the molecule. It will be shown later that an alternative interpretation, that sulphur participation with the carbonyl group in **5** is replaced in **8** by neighbouring group participation of the sulphinyl oxygen, a more dominant factor, can be discounted. Johnson *et al.*[5,6] pointed out that in oxidation of a sulphide to the diastereomeric sulphoxides, the distribution of the isomeric products produced is governed by the competing factors of thermodynamic control, steric approach control, and product development control. As already reported,[1-3] oxidation of **1** with *m*-chloroperbenzoic acid gave *anti*-sulphoxide **2** exclusively, and the equilibration between **2** and **3** with dinitrogen tetroxide showed their thermodynamical stabilities, **2** being preferred to **3**.* These observations led us to assume the *anti*-configuration of the sulphinyl groups for the sulphoxides in question. This assumption was supported by the fact that 3α-*exo*-hydroxy sulphoxide **7a** shows absorption due to an intramolecularly hydrogen-bonded hydroxyl group at 3467 cm^{-1} ($\Delta\nu$ = 163 cm^{-1})[7] in the IR spectrum determined in a 0·9 × 10^{-4} mole CCl_4 solution.

On the other hand, 3β-*endo*-bromo- and 3β-chloro-5α-cholestan-2α,5-episulphides (**10a** and **10b**) on oxidation with 1 molar equivalent of *m*-chloroperbenzoic acid

* The observed preference of **2** to **3** in their epimerization has been discussed in terms of the steric effects in the sulphur-bridged system; steric hindrance between the *syn*-sulphinyl oxygen and the 9α- or 7α-hydrogen in compound **3** was deduced from examination of a model (ref 1 and 3).

furnished the sulphoxides (**11a** and **11b**) as single products, respectively. The *anti*-configuration of their sulphinyl groups was assumed on the basis of evidence similar to that mentioned above. Since a reaction involving participation of sulphinyl-oxygen was demonstrated in 1962 by Leonard and Johnson[8] (reaction of 1-thiacyclooctan-5-one with perchloric acid to give 5-hydroxy-9-oxa-1-thioniabicyclo[3.3.1]nonane perchlorate) a number of papers dealing with such participation have appeared.[9] In all cases observed, the sulphinyl group in a molecule undergoing such reaction is located at a position γ or δ to the developing electron deficient centre formed by ejection of the departing group. In the present case, **11a** and its analogues have a sulphinyl group situated β to the carbon bearing the potentially removable group and the oxygen at the sulphur is spatially close to this carbon atom. Hence, the possibility that these compounds may undergo reaction involving such participation



10a X = Br
10b X = Cl

11a X = Br
11b X = Cl

12

13

16

17

CHART 2

of the sulphinyl–oxygen was of interest and was examined. However, kinetic studies[10] on the solvolysis of **11a** and its closely related compounds revealed no significant rate acceleration in **11a**, indicating that such participation is not likely. In addition, **11a** and its analogues were found to lack reactivity against some reagents. Thus, treatment of **11a** with $NaBH_4$ in DMF gave only starting material, neither **2** nor **3** being obtained; whereas the same treatment of **10a** resulted in reduction affording **1** in high yield.[4] Heating 3β-*endo*-mesyloxysulphoxide **9c**, derived from **9a** by mesylation under the usual conditions,*† with LiBr in DMF at 100° for 4 hr gave unchanged **9c**. Formation of **11a** and the syn-isomer of **7a** could not be detected On the other hand, attempted bromination of 3β-hydroxysulphoxide **9a** with PBr_3 resulted in deoxygenation of the sulphinyl group, yielding 3β-bromosulphide **10a**.

* It should be noted that this mesylation proceeded smoothly to give a high yield of **9c**, in contrast to the reaction of 3β-hydroxysulphide **6a** affording a water-soluble substance as the major product accompanied by a small amount of 3β-chlorosulphide **10b** (ref 4).

† Jones *et al.*, however, have reported that the reaction of phenyl- and methyl-sulphinyl steroids with MesCl gave rise to deoxygenation of the sulphinyl moieties yielding the corresponding sulphides (ref 11).

Chlorination of **9a** with $SOCl_2$ afforded the corresponding bisulphite (**13**) as sole crystalline product.

Consequently, correlation between these hydroxysulphoxides and halosulphoxides could not be made. The only successful conversion relating to the assignment of the configuration at sulphur in 3β-bromosulphoxide **11a** was the following. Treatment of **11a** with excess PhLi in dry ether furnished in 89% yield cholest-2,4-diene **12**, a homoannular diene, and not a heteroannular diene. It is reasonable to assume that the reaction initiated by nucleophilic attack of the phenyl anion on sulphur in an S_N2'-like or concerted manner,* proceeds with cleavage of the C_2—S bond, followed by extrusion of bromine, giving 5-phenylsulphinyl-5α-cholest-2-ene as intermediate which maintains the inherently asymmetric nature of the sulphur atom. Such a transient intermediate is reasonably considered to be unstable because of the presence of the bulky group at a tertiary and homoallylic position, and so to readily undergo *syn*-elimination *via* a cyclic intramolecular mechanism[13,14] to afford the diene. If the sulphinyl group in **11a** takes the *anti*-configuration, the formation of 5α-(S)†-phenylsulphinyl-2-ene as an intermediate would be expected. In this case, examination of molecular models show that the transition state (**14b**) leading to 2,5-diene is less favourable than the transition state (**14a**) leading to 2,4-diene **12** on account of the non-bonded interaction between the phenyl group and the 1α-, 7α-, and 9α-hydrogens in the former. Alternatively, assuming the *syn*-configuration at sulphur for **11a**, the formation of 5α-(R)-phenylsulphinyl-2-ene as an intermediate is expected. The transition state (**15a**) leading to 2,4-diene **12** is destabilized by steric compression between the phenyl group, the 1α-hydrogen, and the C_2–C_3 double bond; whereas the transition state (**15b**) leading to 2,5-diene **16** is unhindered. If dienes **12** and **16** are not interconvertible in the course of the reaction, then from the experimental results, this argument predicts the *anti*-configuration at sulphur for **11a**.

Cholesta-2,4-diene (**12**) is isomerized to cholesta-3,5-diene[16] on treatment with mineral acid. Although **12**, as previously reported by Tsou,[17] was not fully characterized, Bowers *et al.*[18] have recently synthesized some pregna-2,5-diene derivatives by the Cornforth reaction[19] of the corresponding 2-en-5α,6α-epoxides, and have also observed that 2,5-dienes are isomerized with HCl to the corresponding 3,5-dienes and not to the 2,4-dienes. In our present work, we prepared cholesta-2,5-diene (**16**) in 80% yield by dehydration of 5α-cholest-2-en-6β-ol (**17**)[20] with $SOCl_2$ in pyridine.‡

Our compound, whose physical constants are slightly different from those reported by Tsou,[17] was characterized by its NMR spectrum and CD curve (Experimental). Treatment of 2,5-diene **16** thus obtained with excess PhLi under the same conditions as those employed in the reaction of **11a** afforded unchanged **16**. Accordingly, the *anti*-configuration should be assigned for **11a**; this is supported by NMR spectroscopy as discussed later. An attempt to obtain the diastereomeric sulphoxides of **11a** and **8**

* Similar nucleophilic attack by Grignard reagent on sulphur in thietane oxide has been postulated (ref 12).

† The sequence used in assigning configuration is O, Ph, C_5, pair of electrons (ref 15).

‡ Slow addition of **17** to a mixture of pyridine and $SOCl_2$ gave **12** in high yield. The usual procedure, where $SOCl_2$ is added to a solution of **17** in pyridine, provided less favourable, yielding **12** in 40% yield accompanied by bis-5α-cholest-2-en-6β-yl sulphite (**18**) in 53% yield. The structure of **18** was confirmed by reduction with LAH giving the parent 2-en-6β-ol (**17**) (Experimental).

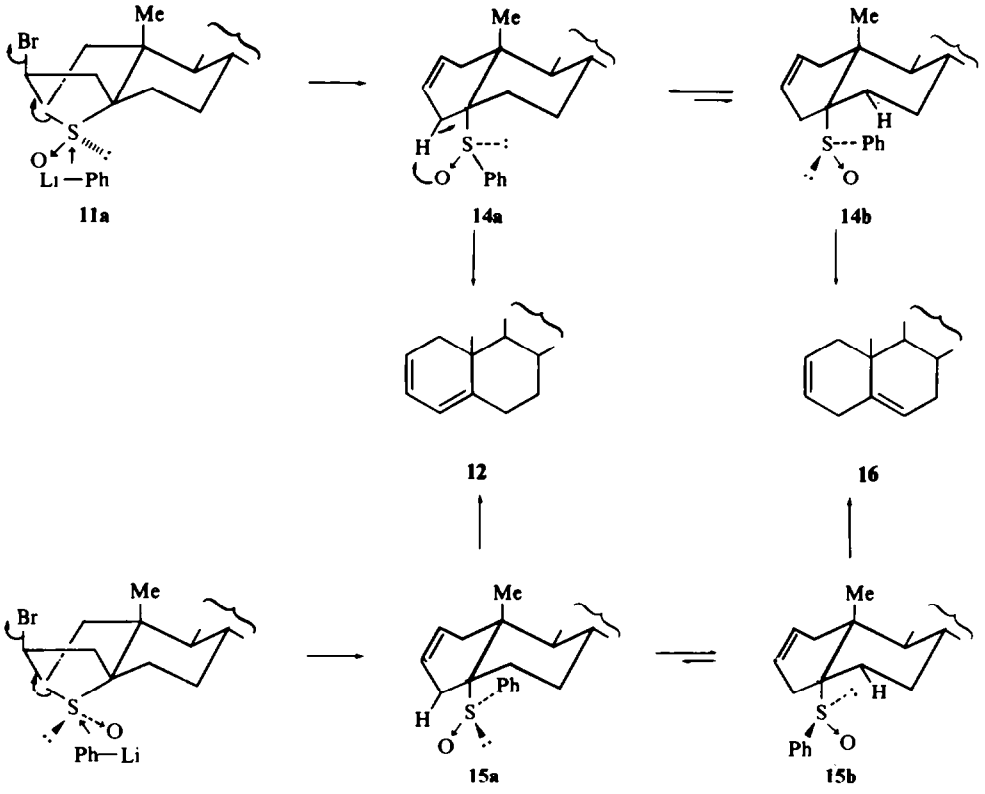


CHART 3

was carried out by t-butyl hypochlorite oxidation of **10a** and **5**, respectively; but an intractable mixture was obtained in each case, and no corresponding isomers were detected.

NMR *studies*

Applications of NMR spectroscopy to the assignment of the sulphinyl configurations of diastereomeric sulphoxides have been reported.[21–27] We have recently studied the NMR spectra of **1**, **2**, and **3**, in which the $H_{1\alpha}$, $H_{1\beta}$, and $H_{2\beta}$ signals were assignable as an ABX - - - system, though the $H_{3\alpha}$, $H_{3\beta}$, $H_{4\alpha}$, and $H_{4\beta}$ signals were not assignable owing to their overlapping with other methylene signals.[2,3] From a comparison of their $H_{1\alpha}$ and $H_{1\beta}$ chemical shifts, the configurations of their sulphinyl oxygens were determined[2] on the basis of the anisotropic shielding effects of an S → O bond.[21–27] The configurations were further confirmed[3] by the use of paramagnetic shifts induced by tris(dipivalomethanato)europium (III).[28]

In the 100 MHz NMR spectra of 3-substituted 5α-cholestan-2α,5-episulphides and their corresponding sulphoxides in $CDCl_3$ and C_6D_6, signals due to protons on their A-ring (an ABXYCD system) were assigned by using double and/or triple resonance techniques. The chemical shifts and coupling constants (J) obtained are summarized in Tables 1 and 2, respectively.

Also listed in Table 1 are the shift values of all assignable signals in $CDCl_3$ due to

TABLE 1. CHEMICAL SHIFT DATA ON 3-SUBSTITUTED 5α-CHOLESTAN-2α,5-EPISULPHIDES AND THEIR CORRESPONDING *anti*-SULPHOXIDES IN $CDCl_3$ (δ IN ppm DOWNFIELD FROM INTERNAL TMS) AND THE SHIELDING EFFECTS OF THE S → O BOND INTRODUCED (IN PARENTHESES)[a]

Compound	3-Substituent	H_{18}	H_{19}	$H_{1\alpha}$	$H_{1\beta}$	$H_{2\beta}$	H_3	$H_{4\alpha}$	$H_{4\beta}$	OAc
1[b]	none(S)	0·64	0·92	1·85	1·31	3·61				
2[b]	none(SO)	0·66	1·01	1·78	1·29	3·42				
(2 - 1)		(+0·02)	(+0·09)	(−0·07)	(−0·02)	(−0·19)				
3[b]	none(SO)	0·67	1·10	2·84	1·79	3·28				
(3 - 1)		(+0·03)	(+0·18)	(+0·99)	(+0·48)	(−0·33)				
4a	α-OH(S)	0·65	0·85	1·87	1·18	3·45	3·93	1·26	2·53	
7a	α-OH(SO)	0·65	0·95	1·76	1·07	3·63	1·26	2·21	2·60	
(7a - 4a)		(0·00)	(+0·10)	(−0·11)	(−0·11)	(+0·18)	(+0·21)	(+0·95)	(+0·07)	
4b	α-OAc(S)	0·65	0·89	1·87	1·30	3·57	4·87	1·60	2·55	2·04
7b	α-OAc(SO)	0·64	0·97	1·78	1·28	3·66	5·09	2·49	2·49	2·05
(7b - 4b)		(−0·01)	(+0·08)	(−0·09)	(−0·02)	(+0·09)	(+0·22)	(+0·89)	(−0·06)	(+0·01)
6a	β-OH(S)	0·65	1·05	1·71	2·04	3·37	4·53	2·03	2·02	
9a	β-OH(SO)	0·65	1·13	1·55	2·01	3·48	4·85	2·39	1·93	
(9a 6a)		(0·00)	(+0·08)	(−0·16)	(−0·03)	(+0·11)	(+0·32)	(+0·36)	(−0·08)	
6b	β-OAc(S)	0·66	1·02	1·77	1·82	3·65	5·18	2·13	1·98	2·03
9b	β-OAc(SO)	0·65	1·09	1·63	1·72	3·75	5·55	2·57	2·01	2·07
(9b - 6b)		(−0·01)	(+0·07)	(−0·14)	(−0·10)	(+0·10)	(+0·37)	(+0·44)	(+0·03)	(+0·04)
10a	β-Br(S)	0·66	1·06	1·82	2·20	3·61	4·61	2·27	2·27	
11a	β-Br(SO)	0·65	1·14	1·73	2·06	3·57	4·89	2·65	2·27	
(11a-10a)		(−0·01)	(+0·08)	(−0·09)	(−0·14)	(−0·04)	(+0·28)	(+0 38)	(0·00)	
5	C=O(S)	0·66	0·99	2·13	1·63	3·60	—	2·42	2·64	
8	C=O(SO)	0·66	1·07	2·09	1·55	3·83		2·78	2·58	
(8 - 5)		(0·00)	(+0·08)	(−0·04)	(−0·08)	(+0·23)		(+0·36)	(−0·06)	

[a] Plus sign denotes a downfield shift.
[b] Taken from ref 2 and 3.

TABLE 2. COUPLING CONSTANT DATA ON 3-SUBSTITUTED 5α-CHOLESTAN-2α.5-EPISULPHIDES AND THEIR CORRESPONDING *anti*-SULPHOXIDES IN $CDCl_3$ (Hz)

Compound	3-Substituent	^2J		^3J						^4J	
		1α,1β	4α,4β	2β,1α	2β,1β	2β,3α	2β,3β	3,4(*cis*)	3,4(*trans*)	1α,3α	2β,4α
4a	α-OH(S)	(−)13·0	(−)14·0	4·6	0·5			6·5	2·5	—	0·5
7a	α-OH(SO)	(−)14·2	(−)15·0	4·5		—	0·6	7·5	3·2	—	
4b	α-OAc(S)	(−)13·1	(−)13·9	5·0	1·0	—	0·6	7·0	3·5	—	
7b	α-OAc(SO)	(−)14·2	(−)14·2	4·2	1·0	—		7·4	5·0		
6a	β-OH(S)	(−)12·9	(−)13·5	4·0	1·2	4·0	—	9·0	3·1		0·8
9a	β-OH(SO)	(−)14·5	(−)14·5	3·5		3·5	—	9·0	2·0		
6b	β-OAc(S)	(−)12·4	(−)13·4	3·6	1·0	3·6	—	9·0	3·0	1·0	
9b	β-OAc(SO)	(−)14·4	(−)14·6	3·0	1·2	3·0	—	9·5	2·0	1·0	0·5
10a	β-Br(S)	(−)13·0	(−)14·0	4·0	0·7	4·0	—	9·5	4·0	2·0	
11a	β-Br(SO)	(−)14·6	(−)15·0	4·0	1·0	4·0	—	10·0	3·0	1·5	
5	C=O(S)	(−)13·3	(−)18·0	4·8	0·6	—	—	—	—	—	<0·5
8	C=O(SO)	(−)14·4	(−)18·4	4·2	1·0	—	—	—	—	—	<0·5

oxidation of the sulphides. As previously described,[2,3] the $H_{1\alpha}$ of *syn* **3** resonates at a field lower by 0·99 ppm than that of the parent sulphide (**1**); this fact indicates the *syn*-axial proximity[21–27] of the proton to the sulphinyl oxygen. In contrast, the $H_{1\alpha}$ of *anti* **2** showed a small upfield shift of 0·07 ppm, obviously caused by the shielding effect due to the acetylenic-type magnetic anisotropy of the S—O bond.[23–27] As seen from Table 1, conversion of the sulphides to the corresponding sulphoxides gives rise to both deshielding ($+0{\cdot}34 \backsim +0{\cdot}95$ ppm) of the $H_{4\alpha}$ and shielding ($-0{\cdot}04 \backsim -0{\cdot}16$ ppm) of the $H_{1\alpha}$, this fact being in accord with structures containing sulphinyl oxygen of *anti*-configuration at sulphur. The observed shift values for the $H_{4\alpha}$ signals vary widely from compound to compound. This variation may be ascribed to the effects of geometrical changes in their A-ring by introduction of the sulphinyl oxygen. The shift values for the $H_{4\alpha}$ signals can apparently be classified into two groups; values of $+0{\cdot}89 \backsim +0{\cdot}95$ ppm for the *exo*-substituted sulphoxides and lower values of $+0{\cdot}34 \backsim +0{\cdot}44$ ppm for the *endo*-substituted sulphoxides. These results suggest that the steric compression between the *exo*-substituents and the oxygen atom in the former and that between the *endo*-substituents and the C_{10}-Me in the latter may be responsible for the effects. Recently, the lone-pair electrons of sulphur, like those of nitrogen,[29] have been noted to cause shielding of vicinal protons and methyl protons located in an *anti*-parallel arrangement to the lone-pair electrons of sulphur in NMR spectral studies of penicillin sulphoxide derivatives.[25c,26] This effect might also be taken into account in the present cases. However, the shift values of the $H_{2\beta}$ signals for all the compounds except the bromo derivative show less shielding of the vicinal $H_{2\beta}$ due to oxidation. Here also, deformation of the A-ring may be responsible for the results.

Table 2 shows that the magnitudes of various *J*-values observed for the compounds examined correspond well to those so far reported for compounds containing the bicyclo[2.2.1]heptane system.[30] Systematic changes in the *J*-values are seen with the change from the episulphides to the corresponding sulphoxides; these changes can also be ascribed to both geometrical and electronic changes due to introduction of the sulphinyl oxygen. It may be of interest that the vicinal $J_{3,4(trans)}$ values are positively and negatively changed by oxidation in the 3α- and 3β-substituted series, respectively, while the vicinal $J_{3,4(cis)}$ values are positively changed in both series.

Table 3 shows the benzene-induced solvent shifts,[31] $\Delta = \delta(C_6D_6) - \delta(CDCl_3)$, for the assignable protons in the compounds studied. In the geometry of benzene–sulphoxide collision complexes, it has been proposed and demonstrated that the dipole axis of the S → O bond is located along the six-fold axis of symmetry of the benzene system with the sulphur nearest to and the oxygen farthest away from the S → O group.[25a] In keeping with expectation based on this concept,[32] large solvent-shift values ($\Delta = -0{\cdot}31 \backsim -0{\cdot}80$ ppm) of the signals due to the $H_{1\alpha}$ and $H_{1\beta}$, situated on the opposite side to the oxygen of the S → O group, were obtained in all *anti*-sulphoxides examined except the 3β-hydroxysulphoxide **9a**.

In order to exclude other substituent effects on Δ values, the differences of Δ values between the sulphides and the corresponding sulphoxides, $\dot{\Delta} = \Delta(SO) - \Delta(S)$, were calculated and are listed in Table 4, where the effects of benzene interacting solely with the S → O bond must be separated. In fact, the $\dot{\Delta}$ values for all assignable protons in the *anti*-isomers are close to one another in each column. Here also, the values for the 3β-hydroxy compound pair are quite different from those for the

TABLE 3. BENZENE-INDUCED SOLVENT SHIFTS [$\Delta = \delta(C_6D_6) - \delta(CDCl_3)$] OBSERVED IN 5α-CHOLESTAN-2α,5-EPISULPHIDE DERIVATIVES (IN ppm)[a]

Compound	3-Substituent	H_{18}	H_{19}	$H_{1\alpha}$	$H_{1\beta}$	$H_{2\beta}$	H_3	$H_{4\alpha}$	$H_{4\beta}$
1	none(S)	+0·03	−0·13	+0·04	−0·20	−0·18	[b]	[b]	[b]
2	none(SO)	−0·06	−0·37	−0·45	−0·54	−0·49	[b]	[b]	[b]
3	none(SO)	+0·02	−0·29	+0·02	−0·41	−0·50	[b]	[b]	[b]
4a	α-OH(S)	−0·01	−0·27	−0·23	−0·35	−0·17	−0·15	−0·04	−0·23
7a	α-OH(SO)	−0·11	−0·51	−0·65	−0·67	−0·36	−0·17	+0·06	−0·33
4b	α-OAc(S)	−0·03	−0·28	−0·19	−0·27	−0·04	−0·02	+0·08	−0·13
7b	α-OAc(SO)	−0·10	−0·47	−0·62	−0·62	−0·33	−0·17	+0·19	−0·30
6a	β-OH(S)	0·00	−0·02	−0·05	+0·06	−0·27	−0·29	−0·04	−0·04
9a	β-OH(SO)	+0·03	−0·06	−0·24	+0·10	−0·07	+0·23	+0·25	+0·20
6b	β-OAc(S)	−0·01	−0·09	−0·13	−0·03	−0·05	+0·16	−0·02	−0·07
9b	β-OAc(SO)	−0·07	−0·26	−0·45	−0·32	−0·28	+0·24	+0·13	−0·21
10a	β-Br(S)	−0·04	−0·10	−0·15	[b]	−0·31	−0·18	−0·27	−0·09
11a	β-Br(SO)	−0·11	−0·30	−0·54	−0·31	−0·54	+0·05	−0·07	−0·27
5	C=O(S)	−0·06	−0·39	−0·42	−0·36	−0·18	—	−0·14	−0·28
8	C=O(SO)	−0·14	−0·59	−0·80	−0·66	−0·42	···	+0·01	−0·41

[a] Plus sign denotes a downfield shift.
[b] Not assignable.

TABLE 4. THE DIFFERENCE IN BENZENE-INDUCED SOLVENT SHIFT VALUES BETWEEN 5α-CHOLESTAN-2α,5-EPISULPHIDES AND THEIR CORRESPONDING SULPHOXIDES. [$\dot{\Delta} = \Delta(SO) - \Delta(S)$] (IN PPM)[a]

Compound to be compared	H_{18}	H_{19}	$H_{1\alpha}$	$H_{1\beta}$	$H_{2\beta}$	H_3	$H_{4\alpha}$	$H_{4\beta}$
2 - 1	−0·09	−0·24	−0·49	−0·30	−0·31	[b]	[b]	[b]
3 - 1	−0·01	−0·16	−0·02	−0·21	−0·32	[b]	[b]	[b]
7a - 4a	−0·10	−0·24	−0·42	−0·32	−0·19	−0·02	+0·10	−0·10
7b - 4b	−0·07	−0·19	−0·43	−0·35	−0·29	−0·15	+0·11	−0·17
9a - 6a	+0·03	−0·04	−0·19	+0·04	+0·20	+0·52	+0·29	+0·24
9b - 6b	−0·06	−0·17	−0·32	−0·29	−0·23	+0·08	+0·15	−0·14
11a - 10a	−0·07	−0·20	−0·39	[b]	−0·23	+0·23	+0·20	−0·18
8 - 5	−0·08	−0·20	−0·38	−0·30	−0·24	—	+0·15	−0·13

[a] Plus sign denotes a downfield shift.
[b] Not assignable.

other pairs. This result cannot immediately be explained, but a type of specific solvation by benzene molecules for the 3β-hydroxy derivative **9a** would be suggested.

However, the Δ and $\dot{\Delta}$ values for $H_{1\alpha}$ of *syn* **3** are very small, indicating the *syn*-configuration of its S → O bond. It is suggested that the benzene-induced solvent-shift rule proposed for a C=O group[33] can also be applied to an S → O group; namely, a downfield shift (a positive $\dot{\Delta}$ value) is observed for a proton situated at the frontside (the oxygen side) of a plane perpendicular to the S → O bond through the S-atom, and an upfield shift is observed for a proton at the opposite side (Fig 1).

Recently, Engler and Laszlo[34] have proposed a new concept of the aromatic-solvent induced shift, introducing the notion of a time-averaged cluster of solvent molecules around a polar functional group; they described how solvent shifts can be expressed

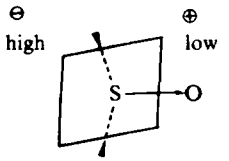


FIG 1

as product functions of a site-factor term for the various proton groups within the solute, and of a solvent parameter. According to this new method, we estimated the site-factors for **2** and **3**, using Dreiding models and putting a point-dipole on the oxygen of their S → O groups, by the equation $(1-3\cos^2\theta)\cdot r^{-3} \times 10^3$, where r is the distance between the point-dipole and a relevant proton and θ is the angle formed by this vector and the S → O bond. For **2**, the site factors are −24·2, −11·2, −15·2, and −5·4 for $H_{1\alpha}$, $H_{1\beta}$, $H_{2\beta}$, and 10-Me, respectively; for **3**, they are +42·8, +3·9, −15·2, and −0·6, respectively. In the former case, the site factors estimated correspond well to the Δ or $\dot{\Delta}$ values for each proton. However, in the latter case, deviation between the site factors and the Δ or $\dot{\Delta}$ values is quite apparent, particularly for $H_{1\alpha}$ and $H_{1\beta}$. This result implies that the formation of a cluster of benzene molecules around the S → O bond might be hindered by the steric effect of the C_7-methyne, C_9-methyne and the C-11 methylene moieties in the solute.

Dipole moments

In order to confirm the configurations at sulphur for the sulphoxides prepared in this paper, their dipole moments were determined in benzene solutions at 25°: the results obtained are summarized in Table 5 together with those of the parent sulphides. Since the structural parameters of the molecule of a 7-thiabicyclo[2.2.1]heptane 7-oxide system have not been elucidated,* the theoretical values were roughly calculated from the appropriate parameters measured directly from Dreiding models. The observed value (1·66D) for 5α-cholestan-2α,5-episulphide (**1**) is in good agreement with those for other sulphides; 1·78D for thietane, 1·90D for thiolane, 1·71D for thiane, and 1·59D for dialkyl sulphide.[36] Hence, assuming an angle of 61·5° between the S → O dipole and the C–S–C plane, a group moment of 1·60D for the C–S–C group, and a moment of 3·00D for the S → O group, we obtained a calculated value of 4·02D for the unsubstituted sulphoxides **2** and **3**; this value is consistent with the observed values of 4·23 and 3·96D, respectively. The observed value of 5·36D for 3-oxo-sulphoxide **8** is also in accord with the value of 5·09D calculated for the *anti*-form and quite different from the value of 3·04D similarly calculated for the *syn*-form by using a group moment of 2·76D for the C=O group. As can be realized from the models, the value of 3·30D calculated for *anti*-3β-bromosulphoxide by using a group moment of 2·00D for the C-Br group is identical with the value calculated for the *syn*-isomer, though it is consistent with the observed value of 3·56D. Similarly, that the observed value for 3α-*exo*-hydroxysulphoxide **7a** is significantly larger than the value for the *endo*-isomer (**9a**) can be expected in the *anti*-sulphoxide and not in the *syn*-isomer (Fig 2).

* Recently, the geometrical arrangement of 7-thiabicyclo[2.2.1]heptane itself has been determined by gas electron diffraction (ref 35).

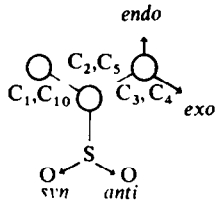


FIG 2

TABLE 5. DIPOLE MOMENTS (μ) OF THE SULPHOXIDES IN BENZENE (ε_1 = 2·2724) SOLUTIONS AT 25°

Compound	α	β	$P_{2\infty}$	d_1	MR_D	μ(D)
1	0·93	0·136	186·6118	0·873222	123·732	1·66
2	4·86	0·170	498·45419	0·873417	125·123	4·23
3	4·29	0·176	452·5099	0·873511	125·123	3·96
7a	6·05	0·176	613·93389	0·873276	126·648	4·85
7b	3·10	0·171	409·2846	0·873665	136·015	3·61
9a	2·87	0·161	356·06205	0·873538	126·648	3·30
9b	6·88	0·168	758·3189	0·873619	136·015	5·44
5	2·93	0·133	350·58101	0·873330	123·741	3·28
8	7·38	0·173	720·0086	0·873402	125·132	5·36
11a	2·90	0·220	398·9120	0·873466	132·887	3·56

Furthermore, in the conversion of 3β-hydroxysulphoxide **9a** to its acetate **9b**, an increase of 2·14D in the dipole moment was observed; whereas the change from 3α-hydroxysulphoxide **7a** to the acetate **7b** results in a decrease of 1·24D in the moment. These facts can be rationalized only in compounds possessing the *anti*-configuration at sulphur, assuming the preferred conformation of the acetoxyl groups[37] as shown in Chart 4.

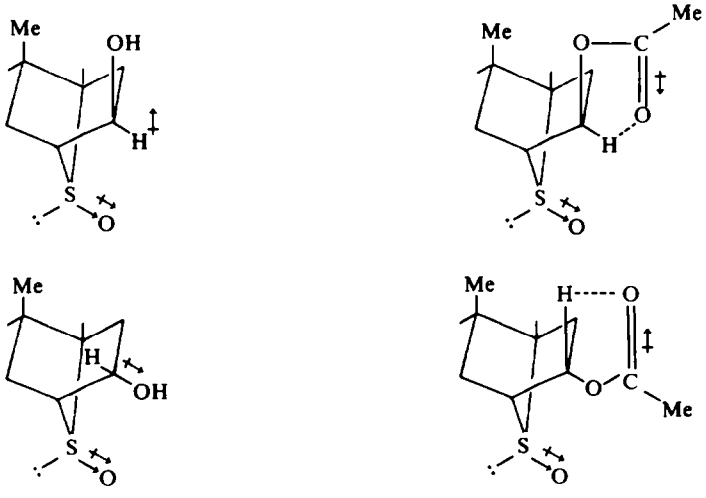


CHART 4

EXPERIMENTAL

M.ps were measured on a Kofler hot-stage apparatus and are uncorrected. Optical Rotations were determined with a Perkin–Elmer Polarimeter, type-141. Unless otherwise stated, IR spectra were recorded on Nujol mulls with a Koken DS-201B spectrophotometer. For prep TLC, silica gel G (Merck Co.) was used as an adsorbent.

General procedure for the oxidation of 3-substituted 5α-cholestan-2α,5-episulphides with m-chloroperbenzoic acid. To a cooled and stirred solution of 200 mg of 3-substituted 5α-cholestan-2α,5-episulphide in 2 ml of CH_2Cl_2 was added 1·1 molar equivalents of *m*-chloroperbenzoic acid. After stirring for 1 hr at room temp, the mixture was poured into cold Na_2CO_3 aq. and extracted with CH_2Cl_2. The extract was washed with water and dried (Na_2SO_4). After evaporation of solvent, the crude sulfoxide was purified by prep TLC.

3α-*Hydroxy*-5α-*cholestan*-2α,5-anti-*episulphoxide* (**7a**) was obtained from **4a** in 57·8% yield and recrystallized from n-pentane, m.p. 154–154·5°; $[\alpha]_D^{23}$ +47·4 ± 2·1° (*c* = 0·409); ν_{max}: 3366, 1054, 1035, 1020 cm^{-1}. (Found: C, 73·75; H, 10·59; S, 7·36. Calc. for $C_{27}H_{36}O_2S \cdot 1/4H_2O$: C, 73·85; H, 10·67; S, 7·30%).

3α-*Acetoxy*-5α-*cholestan*-2α,5-anti-*episulphoxide* (**7b**) was obtained from **4b** in 63·5% yield and recrystallized from acetone. M.p. 159–161°; $[\alpha]_D^{24}$ +54·8 ± 1·0° (*c* = 0·977); ν_{max}: 1730, 1278, 1067, 1057, 1042 cm^{-1}. (Found: C, 73·26; H, 10·19; S, 6·81. Calc. for $C_{29}H_{48}O_3S$: C, 73·06; H, 10·15; S, 6·73%).

3-*Oxo*-5α-*cholestan*-2α,5-anti-*episulphoxide* (**8**) was obtained from **5** in 78·2% yield and recrystallized from n-pentane. M.p. 108–110°; $[\alpha]_D^{23}$ −93·6 ± 2·9° (*c* = 0·454); ν_{max}: 1760, 1057, 1046 cm^{-1}. (Found: C, 75·10; H, 10·28; S, 7·62. Calc. for $C_{27}H_{44}O_2S$: C, 74·94; H, 10·25; S, 7·41%).

3β-*Hydroxy*-5α-*cholestan*-2α,5-anti-*episulphoxide* (**9a**) was obtained from **6a** in 91·3% yield and recrystallized from acetone. M.p. 217–219°; $[\alpha]_D^{23}$ +73·6 ± 2·1° (*c* = 0·546); ν_{max}: 3374, 3300, 1025 cm^{-1}. (Found: C, 73·75; H, 10·53; S, 7·54. Calc. for $C_{27}H_{46}O_2S \cdot 1/4H_2O$: C, 73·85; H, 10·67; S, 7·30%).

3β-*Acetoxy*-5α-*cholestan*-2α,5-anti-*episulphoxide* (**9b**) was obtained from **6b** in 82·5% yield and recrystallized from ether-n-pentane. M.p. 127·5–129·5°; $[\alpha]_D^{23}$ +62·9 ± 2·3° (*c* = 0·448); ν_{max}: 1761, 1236, 1065, 1042, 1022 cm^{-1}. (Found: C, 73·33; H, 10·10; S, 6·88. Calc. for $C_{29}H_{48}O_3$: C, 73·06; H, 10·15; S, 6·73%).

3β-*Bromo*-5α-cholestan-2α,5-anti-*episulphoxide* (**11a**) was obtained from **10a** in 75·5% yield and recrystallized from MeOH. M.p. 94–95°; $[\alpha]_D^{22}$ +79·9 ± 2·2° (*c* = 0·536); ν_{max}: 1056 cm^{-1}. (Found: C, 65·08; H, 9·14; S, 6·59; Br, 15·98. Calc. for $C_{27}H_{45}OSBr$: C, 65·17; H, 9·12; S, 6·44; Br, 16·06%).

3β-*Chloro*-5α-*cholestan*-2α,5-anti-*episulphoxide* (**11b**) was obtained from **10b** in 70·2% yield and recrystallized from MeOH. M.p. 91·5–92°; $[\alpha]_D^{23}$ +79·5 ± 2·1° (*c* = 0·567); ν_{max}: 1060 cm^{-1}. (Found: C, 71·85; H, 10·23; S, 6·83; Cl, 7·83. Calc. for $C_{27}H_{45}OSCl$: C, 71·56; H, 10·01; S, 7·08; Cl, 7·82%).

Reduction of 3-oxo-5α-cholestan-2α,5-anti-episulphoxide (**8**). A mixture of 220 mg (0·51 mM) of **8** and 35 mg (0·92 mM) of $NaBH_4$ in 5 ml of MeOH was stirred at room temp for 1·5 hr then poured into ice water. Extraction with CH_2Cl_2 and work-up in the usual way yielded 192 mg of a mixture of epimeric alcohols ($\nu_{max}^{CS_2}$: 3460, 1150, 1095–1010, 945, 735 cm^{-1}), which was treated with 2 ml of Ac_2O and 3 ml of pyridine at room temp overnight. After usual work-up, the products were separated by prep TLC, developing with benzene–AcOEt (1:1). The more mobile fraction afforded 6 mg (2·5%) of **9b**. The less mobile fraction gave 172 mg (71·8%) of **6b**. These compounds were identified with authentic samples by m.m.p., IR spectra comparison, and TLC.

3β-*Mesyloxy*-5α-*cholestan*-2α,5-anti-*epilsulphoxide* (**9c**). A mixture of 200 mg of **9a** and 400 mg of MesCl in 6 ml of pyridine was allowed to stand for 2 hr at room temp then poured into ice water. Extraction with CH_2Cl_2 and work-up in the usual way gave 202 mg of product. Recrystallization from acetone afforded 167 mg (71·6%) of **9c**. M.p. 210–211°; $[\alpha]_D^{23}$ +50·0 ± 0·9° (*c* = 1·021); ν_{max}: 1352, 1168, 1056, 998, 973, 946, 914, 853, 818 cm^{-1}; NMR (δ): 0·67 (s, 3, 13-Me), 1·04 (s, 3, 10-Me), 3·04 (s, 3, OMs), 3·79 (m, 1, $W_{\frac{1}{2}}$ = 10·5 Hz, 2β-H), 5·46 (m, 1, $W_{\frac{1}{2}}$ = 18 Hz, 3α-H). (Found: C, 65·68; H, 9·44; S, 12·47. Calc. for $C_{28}H_{48}O_4S_2$: C, 65·58; H, 9·44; S, 12·51%).

Reaction of 3β-hydroxy-5α-cholestan-2α,5-anti-episulphoxide (**9a**). (a) With PBr_3. A mixture of 66 mg of **9a** and 150 mg of PBr_3 in 5 ml of dry benzene was refluxed with stirring for 30 min. Work-up in the usual way afforded 60 mg of **10a**, m.p. 88–89°, which was identified with an authentic sample by m.m.p. and IR spectrum comparison.

(b) With $SOCl_2$. To a cooled solution of 22 mg of **9a** in 1 ml of pyridine was added 30 mg of $SOCl_2$. The resulting mixture was stirred for 1 hr at 5–10°, then poured into ice-water. Extraction with ether–CH_2Cl_2 (4:1) and work-up in the usual way gave 20 mg of product. Purification by prep TLC, followed by recrystallization from acetone afforded 10 mg of a sulphite (**13**). M.p. 222–224°; $\nu_{max}^{CS_2}$: 1210, 1200, 1059, 885, 870, 740 cm^{-1}. (Found: C, 70·74; H, 9·95; O, 8·86; S, 10·45. Calc. for $C_{54}H_{90}O_5S_3$: C, 70·85; H, 9·91; O, 8·74; S, 10·51%).

Attempted reaction of 3β-*bromo*-5α-*cholestan*-2α,5-anti-*episulphoxide* (**11a**). (a) With $NaBH_4$. A mixture of 30 mg of **11a** and 30 mg of $NaBH_4$ in 1·5 ml of DMF was stirred at room temp overnight and then warmed at 60° for 4 hr. Work-up in the usual way afforded 28 mg of unchanged **11a**.

(b) With KOAc. A mixture of 30 mg of **11a** and 30 mg of KOAc in 2 ml of AcOH was heated at 100° for 4 hr. Work-up in the usual way gave 24 mg of **11a**.

Reaction of 3β-*bromo*-5α-*cholestan*-2α,5-anti-*episulphoxide* (**11a**) *with phenyl lithium*. PhLi ether solution was prepared from 365 mg (52·2 mM) of Li and 3·14 g (20·0 mM) of bromobenzene in 15 ml of dry ether under N_2. To 1·5 ml (*ca.* 2 mM) of the cooled PhLi ether solution was added a solution of 155 mg (0·31 mM) of **11a** in 2 ml of dry ether. The resulting mixture was stirred at 0° for 1 hr then poured into ice water. The ether extract was worked up in the usual way to give 100 mg of a colourless oil, which was crystallized from MeOH. Recrystallization from ether–MeOH afforded 91 mg (89%) of cholest-2,4-diene (**12**) as colourless needles. M.p. 67–68·5°; $[\alpha]_D^{23}$ +170·1 ± 2·1° (*c* = 1·023) (Reported m.p. 68·5°; $[\alpha]_D$ +169°);[38] ν_{max}: 3040, 1596, 687 cm^{-1}; λ_{max}^{EtOH} nm (ε): 274·5 (5300), 266·5 (5680); NMR (δ): 0·69 (s, 3, 13-Me), 0·93 (s, 3, 10-Me), 5·57 (m, 1, 4-H), 5·67 (m, 2, 2-H and 3-H). (Found: C, 87·54; H, 12·04. Calc. for $C_{27}H_{44}$: C, 87·97; H, 12·03%).

Reaction of 6β-hydroxy-5α-*cholest*-2-*ene* (**17**) *with thionyl chloride*. (a) To a cooled solution of 250 mg of **17** in pyridine (3 ml) was added $SOCl_2$ (150 mg). The mixture was stirred (0°, 1 hr) then poured into ice water. Ether extraction and work-up afforded 240 mg of product, showing 2 spots on TLC. The mixture was separated by prep TLC, developed with cyclohexane. The more mobile fraction afforded 95 mg (39·9%) of cholesta-2,5-diene (**16**), which recrystallized from acetone. M.p. 62·5–63·5°; $[\alpha]_D^{22}$ −31·7 ± 1·4° (*c* = 0·504) (Lit.[17] m.p. 74°; $[\alpha]_D$ −25°); ν_{max}: 3030, 1665, 1002, 829, 796 cm^{-1}; CD (MeOH): $[\theta]_{219}$ +329, $[\theta]_{200}$ −23,060; NMR (δ): 0·69 (s, 3, 13-Me), 0·99 (s, 3, 10-Me), 5·40 (m, 1, $W_{\frac{1}{2}}$ = 9·0 Hz, 6-H), 5·62 (m, 2, $W_{\frac{1}{2}}$ = 5·0 Hz, 2-H and 3-H). (Found: C, 88·09; H, 11·98. Calc. for $C_{27}H_{44}$: C, 87·97; H, 12·03%). This compound was treated with 1 ml of PhLi–ether (above) at 0° for 1 hr. Work-up as for the conversion (**11a** → **12**) gave 16 mg of unchanged **16**, identified by IR and CD comparison.

The polar fraction gave 140 mg (52·9%) of bis 5α-cholest-2-en-6β-yl sulphite (**18**) which recrystallized from acetone, m.p. 168–169; $[\alpha]_D^{22}$ +47·4 ± 1·8° (*c* = 0·492); ν_{max}: 3020, 1190, 877, 851, 757 cm^{-1}; NMR (δ): 0·71 (s, 6, 13 and 13′-Me), 0·92 (s, 6, 10 and 10′-Me), 4·48 (m, 1, $W_{\frac{1}{2}}$ = 7·0 Hz, 6α-H),* 4·68 (m, 1, $W_{\frac{1}{2}}$ = 6·0 Hz, 6′α-H),* 5·60 (m, 4, $W_{\frac{1}{2}}$ = 5·0 Hz, 2-H, 2′-H, 3-H and 3′-H). (Found: C, 78·89; H, 11·02; S, 4·39. Calc. for $C_{54}H_{90}O_3S$: C, 79·16; H, 11·07; S, 3·91%). Reduction of this sulphite (**18**) with LAH in ether–THF (1:1) at room temp for 1 hr afforded 6β-hydroxy-5α-cholest-2-ene (**17**) in good yield, identified by TLC and IR comparison.

(b) To a cooled and vigorously stirred solution of $SOCl_2$ (3 ml) in pyridine (6 ml), a solution of 700 mg of **17** in pyridine (15 ml) was added dropwise at 0° over 2 hr. After stirring for an additional 30 min, the mixture was poured into ice–water and the deposited solid washed successively with 5% HCl, Na_2CO_3 aq and water, and dried (Na_2SO_4). Evaporation of solvent afforded 620 mg of crystals. Recrystallization from acetone gave 495 mg of pure **16**. Purification of the mother liquor by prep TLC (cyclohexane) provided 40 mg of **16** (combined yield 80·3%).

NMR *spectral measurement*. NMR spectra were taken with a Varian A-60A spectrometer (60 MHz spectra), calibrated by the usual side-band method; and/or a Varian HA-100 spectrometer operating at a 100 MHz field in the frequency-swept and TMS-locked mode (100 MHz spectra). Calibration of the 100 MHz spectra was made by using a Hewlett-Packard HP-5212A electronic counter. Accuracies of chemical shifts and coupling constants are within δ ±0·01 ppm and ±0·1 Hz, respectively. The spectra were measured on about 5–8% (w/v) solutions of samples in $CDCl_3$ and C_6D_6 containing TMS. Proton magnetic double and triple resonance experiments were carried out with the HA-100 spectrometer and two Hewlett-Packard HP-200ABR audio-oscillators in frequency-swept operation.

Dipole moment determination. Dielectric constants were measured by means of a heterodyne beat apparatus provided with a platinum cell. For each solute, determinations were made on solutions of three different concentrations. Graphical plots of both the dielectric constant and the density of solutions against the concentration in weight per cent, gave linear dependence within experimental errors. The slopes of these straight lines were evaluated by the least-squares method and the molar polarization of the solute was calculated by a method similar to that introduced by Halverstadt and Kumler,[40] but densities were used instead of specific volumes.

* It is interesting to note that the NMR spectrum of **18** showed nonequivalence of the 6α-proton attached to the same carbon as the sulphite group. This may originate from molecular asymmetry, and similar phenomena have recently been observed (ref 39).

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