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STUDIES IN ORGANIC SULPHUR COMPOUNDS—XVI[1]

SYNTHESIS AND REACTIONS OF STEROID EPISULPHIDES

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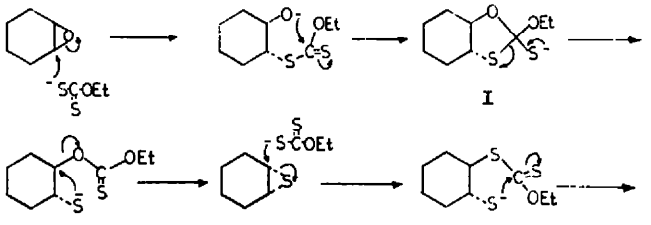
Abstract—Herein are described two general syntheses of episulphides as applied to steroids and involving α-hydroxy-xanthates and α-hydroxy-thiocyanates. The more precise stereochemistry in the synthetic sequences in steroids as compared to the hitherto investigated low mol. wt compounds serves to substantiate earlier proposed mechanisms of episulphide and trithiocarbonate formation. The stereochemical consequences of nucleophilic attack of episulphides are discussed in detail.

ALTHOUGH episulphides (thioepoxides, thiiranes) have been known and reported over forty years ago,[3,4] their chemistry, both in terms of synthesis and reactivity, has been limited largely to low molecular weight compounds. Recently,[5] there has been initiated the preparation of steroidal episulphides, and even more recently these episulphides have been the subject of wider investigation as to synthesis,[6–9] reactivity,[6,7,10] and optical rotatory dispersion-circular dichroism properties.[11]

Synthesis of steroidal episulphdes

The preparation of steroid episulphides in our laboratory has proceeded by two general methods: from α-hydroxy-xanthates and from α-hydroxy-thiocyanates. The initial studies of episulphide formation in this work involved the preparation of xanthate intermediates, substances similar to intermediate I which can be postulated in the

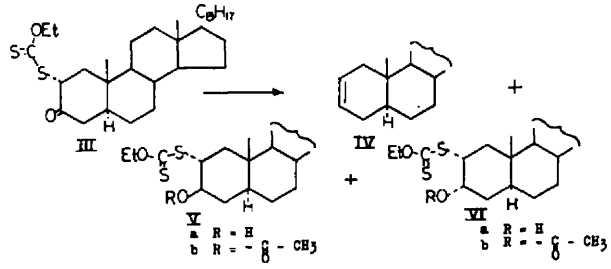


I

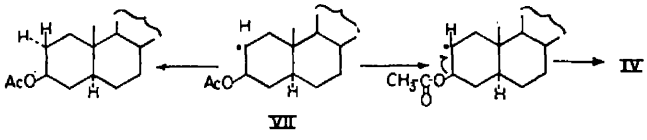
[1] For paper XV see D. A. Lightner and C. Djerassi, *Steroids* **2**, 583 (1963).
[2] Taken in part from the Ph.D. Dissertation (1963) of D. A. Lightner (Parke-Davis Fellow 1960–1961; N.I.H. Pre-doctoral Fellow 1961–1962; N.S.F. Pre-doctoral Fellow 1962–1963).
[3] M. Delépine, *Bull. Soc. Chim. Fr.* **27**, 740 (1920).
[4] H. Staudinger and J. Siegwart, *Helv. Chim. Acta* **3**, 833 (1920).
[5] K. Takeda, T. Komeno and J. Kawanami, *Chem Pharm. Bull. Tokyo* **8**, 621 (1960).
[6] D. A. Lightner and C. Djerassi, *Chem. & Ind.* 1236 (1962).
[7] K. Takeda and T. Komeno, *Chem. & Ind.* 1783 (1962).
[8] J. F. McGhie, W. A. Ross, F. J. Julietti, B. E. Grimwood, G. Usher and N. M. Waldron, *Chem. & Ind.* 1980 (1962).
[9] T. Kawasaki and E. Mosettig, *J. Org. Chem.* **27**, 1374 (1962).
[10] J. F. McGhie, W. A. Ross, F. J. Julietti, G. Swift, G. Usher, N. M. Waldron and B. E. Grimwood, *Chem & Ind.* 460 (1964).
[11] C. Djerassi, H. Wolf, D. A. Lightner and E. Bunnenberg; and K. Takeda, T. Komeno and K. Kuriyama, *Tetrahedron* **19**, 1547 (1963); D. E. Bays, R. C. Cookson, R. R. Hill, J. F. McGhie and G. E. Usher, *J. Chem. Soc.* 1563 (1964).

II

mechanism[12] of formation of episulphides which themselves act as intermediates in trithiocarbonate (II) formation. As has been heretofore described,[6] sodium borohydride reduction of cholestan-3-one-2α-ethylxanthate[13] (III) can lead directly to an intermediate of the type postulated in the mechanism of episulphide formation above and gave a mixture of three compounds which were separated by column chromatography on silica gel. The mixture gave the expected hydroxyxanthates (Va and VIa) as well as a large amount of Δ^2-cholestene (IV).



The formation of the latter was clearly unexpected, and its mode of formation has not been clearly established. Conversion of the hydroxy-xanthates to their respective acetates (Vb and VIb) and subsequent desulphurization with Raney nickel to the known 3β- and 3α-acetoxycholestanes, respectively, defined the stereochemistry at C-3 of Va and VIa. In addition, a small amount of Δ^2-cholestene (IV) was formed in each of the desulphurization reactions. This occurrence could have arisen conceivably from a desulphurized intermediate such as VII, a small amount of which loses acetate radical in the manner indicated as a side reaction, whereas, the main course is the capture of a hydrogen atom from the catalyst.



VII

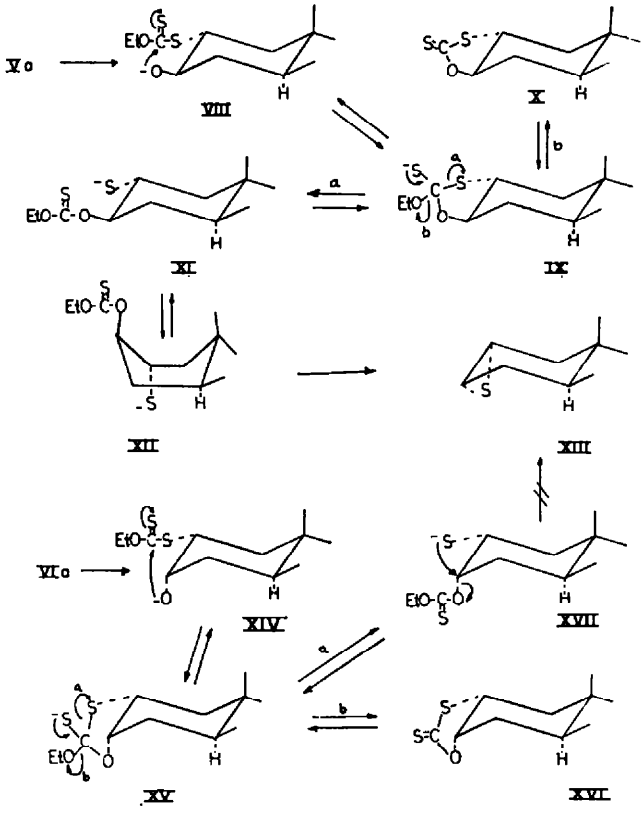
In the keto-xanthate (III) the configuration at C-2 was arbitrarily indicated as equatorial (α) due to the analogy of the sodium iodide in acetone reaction with 2α-bromocholestan-3-one in which the iodine in the resultant α-iodoketone possesses the equatorial (α) configuration at C-2.[14] That is, the expected product (β) of an S_N2 displacement of bromide underwent complete and facile epimerization under the mild (potassium ethylxanthate in anhydrous acetone) conditions of the displacement reaction. The indicated configuration at C-2 is correct, as can be predicted from the subsequent base-catalyzed reactions of the two hydroxy-xanthates,

[12] A. M. Creighton and L. N. Owen, *J. Chem. Soc.* 1024 (1960).
[13] C. Djerassi, M. Gorman, F. X. Markley and E. B. Oldenburg, *J. Amer. Chem. Soc.* **77**, 568 (1955).
[14] C. Djerassi, H. Wolf and E. Bunnenberg, *J. Amer. Chem. Soc.* **85**, 324 (1963).

and as was confirmed by an independent synthesis of cholestan-2α,3α-episulphide.[7] The perhaps obvious epimerization reaction of III afforded instead only rearranged products, whose structure has been discussed elsewhere.[1]

The interpretation of the previously postulated mechanism of episulphide formation seems to require diaxial opening of the epoxide and formation of the cyclic intermediate (I) in which the initially *trans*-diaxial moieties have become *trans*-diequatorial (by conformational flipping of the flexible cyclohexane ring). It might be expected that the steroid which has the diequatorial arrangement of hydroxyl and xanthate should give an episulphide. Base treatment of the hydroxy-xanthate (Va) led to the episulphide (XIII) and no cyclic dithiocarbonate (X); whereas, similar treatment of VIa gave only the cyclic dithiocarbonate (XVI) with no trade of episulphide. It is interesting to consider the stereochemical implications of the two reactions.

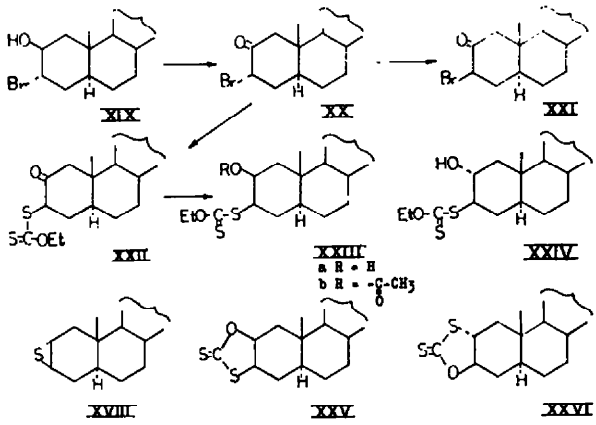
As indicated, the oxide ions (VIII) and (XIV) are formed by base abstraction of the hydroxylic proton. Presumably these species are in equilibrium with IX and XV respectively, the latter two being formed by nucleophilic attack of the oxide ion at the thione moiety of the xanthate group to give the cyclic intermediates. Collapse of such cyclic intermediates may proceed via either path (a) or path (b). As indicated, in path (b), ethoxide ion is lost and the cyclic dithiocarbonate (X and XVI) is formed. Alternatively, similar to the β-mercaptanol O-acetate rearrangement,[15] path (a) leads to the sulphide anion (XI and XVII).



[15] L. W. C. Miles and L. N. Owen, *J. Chem. Soc.* 817 (1952).

The assumption that the xanthate is equatorial at C-2 means that the configuration of the hydroxyl and the xanthate moieties is *trans*(diequatorial) in V and *cis* in VI. The relative configurations are not changed in XI and XVII. Flipping ring A of XI into a boat leads to a *trans*-diaxial orientation (XII); whereas, XVII will still be *cis*(axial-equatorial) by the same conformational change. The thiolate XII is superbly in position for displacement (four-centred, planar)[16] at C-3. Such is not the case with XVII. Assuming the validity of the general rule of Barton[16] for elimination reactions of a type similar to that involved with XII and XVII, in which the four-centered transition state is ideally planar, only XII satisfies this requirement. Thus, on this basis, V should give the episulphide (XIII), and VI should give the cyclic dithiocarbonate (XVI), which exhibits the most favourable fusion (*cis*) for a five- to a six-membered ring. Inasmuch as the configuration of C-2 has been confirmed[7] unequivocally as equatorial (a), this reaction serves as another cogent instance of support of the Barton generalization.

Cholestan-2α,3α-episulphide (XIII) having been synthesized, it was desirable to obtain the 2β,3β-isomer (XVIII) by the same type of sequence.



Using a method analogous to the previously described xanthate procedure, Δ^2-cholestene (IV) was converted[17] to bromhydrin (XIX) by means of N-bromosuccinimide. Oxidation[17] of XIX with chromium trioxide in acetic acid gave bromo-ketone (XX). Hydrogen bromide-catalyzed epimerization of XX and subsequent column chromatography of the mixture of epimers at C-3 gave the bromo-ketones (XX and XXI) in a 56:44 mixture—indicating no particular preference for either configuration (axial or equatorial bromine) at C-3. Treatment of bromo-ketone XX with potassium ethylxanthate in acetone gave only one keto-xanthate (XXII) with the xanthate group in the equatorial position. Assuming an S_N2 displacement of bromide by the xanthate anion, the initially formed keto-xanthate is required to have the 3β-configuration (equatorial). If the epimeric equilibrium at C-3 in the case of the xanthates is similar to that of the bromides, and if epimerization had occurred, at least fifty per cent of the mixture would have to have the 3β (equatorial) configuration). Inasmuch as it was found experimentally that only one keto-xanthate is formed, it should have the 3β (equatorial) configuration.

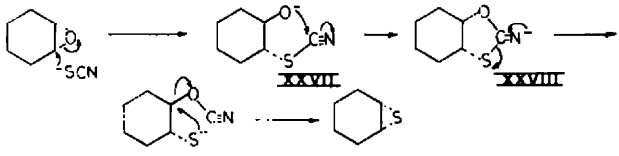
[16] D. H. R. Barton and R. Cookson, *Quart. Rev.* **10**, 44 (1956).
[17] T. Nakano, M. Hasegawa and C. Djerassi, *Chem. Pharm. Bull., Tokyo* **11**, 465 (1963).

Reduction of XXII with sodium borohydride in ethanol gave only one hydroxy-xanthate (XXIIIa) and only a trace of Δ^2-cholestene (IV). This observation is in direct contrast to the results of the reaction of cholestan-3-one-2α-ethyl-xanthate (III) with sodium borohydride in which approximately one third of the material isolated after the reduction was Δ^2-cholestene. Such a dichotomy (barring special intrinsic differences (e.g., the location of the keto group)) is consistent with the possibility that the olefin arises from an episulfide which was formed during the course of the reaction from the initial products of reduction of the keto group and any base generated by reaction of borohydride with solvent. This suggestion is supported by the observation that the reduction of cholestan-3-one-2α-ethylxanthate (III) gives a hydroxy-xanthate (Va) capable of being transformed by base into an episulphide; whereas, the single hydroxy-xanthate is not capable of generating an episulphide, as will be indicated subsequently. In addition, it has been shown that the reaction of sodium borohydride with cholestan-2α,3α-episulphide (XIII) generates Δ^2-cholestene (IV).

Sodium borohydride reduction of cholestan-2-one-3β-ethylxanthate (XXII) proceeded to give the axial alcohol (XXIIIa) to the exclusion of the possible equatorial product (XXIV). The configuration at C-2 was determined as before with conversion of XXIIIa to its acetate XXIIIb. Raney nickel desulphurization of XXIIIb gave cholestan 2β-ol acetate as well as a trace of Δ^2-cholestene, the latter observation being consistent with that observed earlier.

Base treatment of the *cis*-hydroxy-xanthate (XXIIIa) gave the cyclic dithiocarbonate (XXV) as expected from the *cis* arrangement of the xanthate and hydroxyl groups. Cholestan-2α(S),3β(O)-dithiocarbonate (XXVI), possessing the *trans*-diequatorial arrangement of oxygen and sulphur, was also synthesized (by reaction of thiophosgene and cholestan-2α-thiol-3β-ol[1]) for use in conjunction with our optical rotatory dispersion and circular dichroism studies of twisted chromophores. The episulphide (XVIII) would have been the product of the *trans* isomer (XXIV) which, unfortunately, was not formed in the reduction step.

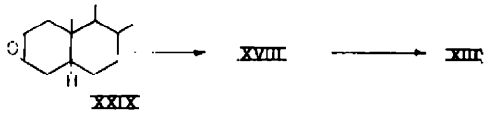
The second and more facile method formation involves the synthesis of a compound similar to the protonated form of an intermediate (XXVII) suggested[18] in the mechanism of formation of an episulphide from an epoxide by reaction with thiocyanate anion. The mechanism requires that the resultant episulphide will have a stereochemistry opposite to that of the starting epoxide. The most effective method of



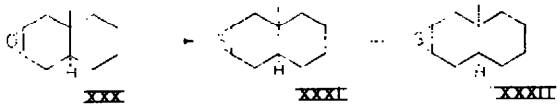
introducing thiocyanate into a steroid for purposes of episulphide formation is by opening an epoxide with thiocyanic acid.[5] Treatment of a steroid epoxide directly with potassium thiocyanate resulted in yields of episulphide which are markedly inferior to those of the less direct method of first opening with thiocyanic acid. Thus, cholestan-2α,3α-epoxide (XXIX), upon treatment with potassium thiocyanate, gave yields of cholestan-2β,3β-episulphide (XVIII) which were less than 15% and which

[18] E. E. van Tamelen, *J. Amer. Chem. Soc.* **73**, 3444 (1951).

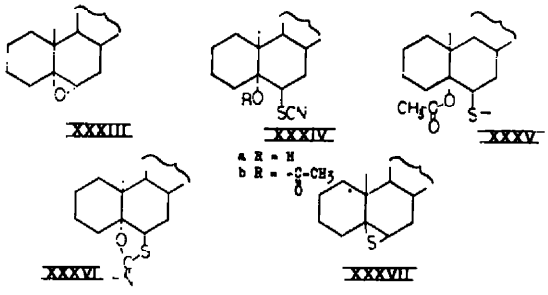
was contaminated by its α-epimer, probably arising from reaction of the initially formed episulphide with thiocyanate.



The surprising non-reactivity of the high molecular weight steroid differs noticeably from that of lower analogs,[18] although a compound of intermediate size gave yields of episulphide which were only somewhat better than that of the steroid. Thus, the bicyclic epoxide, (+)-*trans*-9-methyldecalin-2α,3α-epoxide (XXX) upon reaction with potassium thiocyanate in refluxing ethanol gave a 4:1 mixture of the episulphides (XXXI and XXXII) respective.



Opening of cholestan-5α,6α-epoxide XXXIII with thiocyanic acid in ether gave cholestan-5α-ol-6β-thiocyanate (XXXIVa). Treatment of XXXIVa with base resulted in the formation of the starting epoxide (XXXIII) only, demonstrating that when an intermediate of the type XXVIII is unobtainable during base treatment of an α-hydroxy thiocyanate, the oxide anion will displace thiocyanate and give an epoxide in a



manner analogous to the reaction of bromohydrins.[19] In the case of XXIVa, the 5α-hydroxyl is held rigidly axial, and any conformational twisting in ring B is insufficient to bring the two functional moieties in correct juxtaposition for formation of the cyclic intermediate (XXXVI). Nevertheless, functionalization of the tertiary alcohol as the acetate and subsequent base treatment preferentially hydrolyzed the thiocyanate moiety to furnish the sulphide anion (XXXV) which displaced acetate anion to form cholestan-5β,6β-episulphide (XXXVII). As required by the mechanism of formation, the episulphide (XXXVII) has a configuration opposite to that of the starting epoxide (XXXIII), and this can be substantiated by NMR measurements.[20] By the preceding general method a large number of steroidal episulphides[11] have been prepared both here and in Japan.[21]

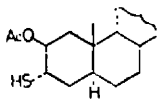
[19] L. F. Fieser and W.-Y. Huang, *J. Amer. Chem. Soc.* **75**, 4837 (1953).
[20] K. Tori, T. Komeno and T. Nakagawa, *J. Org. Chem.* **29**, 1136 (1964).
[21] K. Takeda T. Komeno, J. Kawanami, S. Ishihara, H. Kadokawa, H. Tokura and H. Itani, *Tetrahedron* **21**, 329 (1965).

Reactions of steroidal episulphides

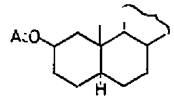
The reactions of episulphides as well as epoxides may be divided into two general types: reactions with bases and reactions with acids. The former category involves the well-known reactions at carbon by amines[22] as well as the reactions of strong nucleophilic reagents: thiocyanate,[18] xanthate,[12] hydride,[6,23] mercaptide,[8,24] etc. The reactions of this group of anions may be considered simply as nucleophilic attack at the carbon bearing the sulphur, with subsequent opening of the thiirane ring, cationic participation with sulphur being minimal before ring opening. With acids, the opposite effect is true. Thus, with a protonic acid, the sulphur or oxygen is first protonated, and this cyclic sulphonium or oxonium ion is opened by means of nucleophilic attack on a carbon of the acid anion, although it is conceivable that the protonated sulphonium or oxonium ion may first open in one direction, with subsequent attack of the resultant classical carbonium ion. Lewis acids, such as triphenylphosphine,[25] triethylphosphite,[25] and aluminum chloride (Experimental) have been observed to effect desulphurization, and the suggested mechanism involves electrophilic attack at sulphur by the Lewis acid. In addition, n-butyl lithium and phenyl lithium have been observed to cause desulphurization,[26] the suggested mechanism involving nucleophilic attack at sulphur rather than at carbon.

Lithium aluminum hydride treatment of an epoxide or episulphide can be envisaged as simple nucleophilic attack at carbon by hydride with or without prior coordination of the oxygen or sulphur to the reagent.

In connection with determining unambiguously the configuration of cholestan-2α, 3α-episulphide (XIII) as truly α and not β, it was expected that normal acetic acid opening of the thiirane ring, an operation analogous to the reaction of acetic acid with cholestan-2α,3α-oxide (XXIX) would afford the 2β-acetoxy-3α-mercaptan (XXXVIII) and that subsequent desulphurization would lead to cholestan-2β-ol



XXXVIII



XXXIX

acetate (XXXIX). Instead, no reaction occurred on mild heating, while with refluxing acetic acid, the only product of the reaction was Δ^2-cholestene (IV) and no trace of XXXVIII. A similar reaction with cholestan-2α,3α-oxide (XXIX) gave no olefin. Further investigations on the nature of this unique desulphurization reaction indicate that it is likely the high reaction temperature (boiling point of acetic acid is 118°) near the melting point (124–126°) of the episulfide which was the cause of the desulphurization. Indeed, heating the episulphide XIII under reflux in 2,2,4-trimethylpentane (boiling point 99°) gave little or no desulphurization; whereas, heating under reflux in 1-butanol (boiling point 117°) gave complete desulphurization for the same reaction time. In fact, simply heating the solid above its melting point in the absence of solvent gave desulphurization to Δ^2-cholestene (IV).

[22] R. L. Jacobs and R. D. Schuetz, *J. Org. Chem.* **26**, 3472 (1961).
[23] M. Mousseron, R. Jaques, M. Mousseron-Canet and R. Zagdoun, *Bull. Soc. Chim. Fr.* 1042 (1952).
[24] E. M. Meade and F. N. Woodward, *J. Chem. Soc.* 1894 (1948).
[25] R. E. Davis, *J. Org. Chem.* **23**, 1767 (1958).
[26] F. G. Bordwell, H. M. Andersen and B. M. Pitt, *J. Amer. Chem. Soc.* **76**, 1082 (1954).

Whereas reactions of steroid epoxides with lithium aluminium hydride give axial alcohols,[27] and cyclohexane episulphide has been shown[28] to give an 85% yield of cyclohexanethiol, the reduction of cholestan-2α,3α-episulphide (XIII) as well as cholestan-2β, 3β-episulphide (XVIII) under a variety of conditions with lithium aluminium hydride always gave only Δ^2-cholestene (IV). In addition, sodium borohydride treatment of cholestan-2α,3α-episulphide (XIII) in ethanol as well as other solvents under a variety of reaction conditions gave as the sole products varying amounts of Δ^2-cholestene (IV) and unreacted episulphide.

To test the validity of the reaction of lithium aluminium hydride with an episulphide other than a steroid, (+)-*trans*-9-methyldecalin-2β,3β-episulphide (XXXI) was reduced in a like manner to (+)-*trans*-9-methyloctalin-2 in 99% yield as determined by gas phase chromatography.

It is possible that the unusual reactive properties of these episulphides are due not only (or at all) to an intrinsic property of the compound itself, but perhaps at least to the nature of the lithium aluminium hydride. The major impurity in commercial (Metal Hydrides, Inc.) lithium aluminium hydride is aluminium chloride, or a chlorohydride, and it is a well known fact that the addition of aluminium chloride increases the electrophilic character of the hydride reagent.[28,29] Treatment of cholestan-2α,3α-episulphide (XIII) with aluminium chloride under the same reaction conditions as with lithium aluminium hydride led to a mixture of olefin and starting material even after a longer reaction period. Also, reaction at room temperature was imperceptibly slow, indicating that aluminium chloride as an impurity alone does not effect the desulphurization with lithium aluminium hydride, and that lithium aluminium hydride is necessary for the fast and complete reaction. Whether absolutely pure lithium aluminium hydride will effect desulphurization has not been determined; however, the results of Takeda,[7] in which cholestan-2α,3α-episulphide (XIII) reacts with lithium aluminium hydride to the extent of desulphurization but the β-episulphide gives largely cholestan-2β-thiol, may be consistent with a purer sample of hydride, but it may also indicate again that there are genuine differences in reactivity (both rate and type) between high molecular weight and low molecular weight episulphides.

The rather ubiquitous nature of olefin formation by episulphide under a variety of reactions and reaction conditions was completely unexpected. These unique properties of episulphides which proceeded to the exclusion of the "normal" reactions as compared with epoxides are also in marked contrast to the reactions of the low molecular weight episulphides.

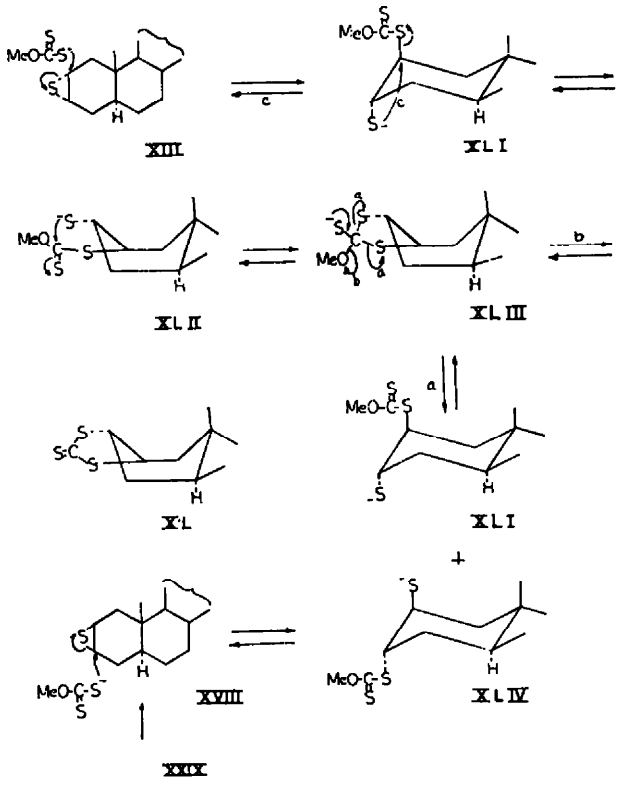
That steroid episulphides can react in some instances under nucleophilic conditions to give products other than olefins is indicated in their ability to react with potassium methylxanthate in refluxing methanol to give trithiocarbonates. Thus, cholestan-2α, 3α-episulphide (XIII) reacted to give cholestan-2β,3α-trithiocarbonate (XL). Such a reaction proceeds by nucleophilic attack at C-2 to give intermediate XLI, which can exist in equilibrium with a number of species. The obvious reaction back to an episulphide by this *trans* diaxial species is possible *via* path (c); alternatively, ring A may flip into a boat XLII to afford the diequatorial configuration of the functional

[27] For leading references see J. G. Phillips and V. D. Parker, *Steroid Reaction* (Edited by Carl Djerassi) Chap. 14. Holden-Day, San Francisco (1963).

[28] E. L. Eliel, *Rec Chem. Progress* 129 (1961).

[29] A. E. Petrarca and E. M. Emery, *Tetrahedron Letters* No. 10, 635 (1963).

groups, enabling the attack by mercaptide on the thione moiety of the xanthate group to give the cyclic intermediate (XLIII). Collapse of this species can occur either by

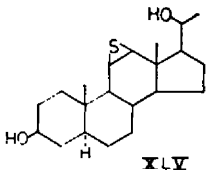


path (a) to regenerate the starting intermediate (XLI) or its isomer (XLIV), or by path (b) by loss of methoxide ion to give the trithiocarbonate (XL).

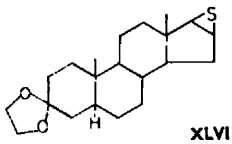
In a like manner, cholestan-2α,3α-oxide (XXIX) was converted to the same trithiocarbonate (XL) *via* cholestan-2β,3β-episulphide (XVIII). The formation of the intermediate episulphide (XVIII) is similar to the sequence mentioned earlier with cyclohexane oxide. The subsequent reaction of XVIII with xanthate gives compound XLIV, and the equilibrium pathway proceeds as before. Theory thus predicts that either epimeric episulphide should react to give the same trithiocarbonate, and this is borne out experimentally.

The foregoing mechanistic scheme requires that the ring in the steroid nucleus to which the trithiocarbonate group is joined be conformationally flexible enough to allow a boat conformation or at least allow the diaxial groups to approximate a diequatorial relationship. It is not surprising then, that 5α-pregnane-3β,20β-diol 11β,12β-episulphide (XLV) does not react at all,[30] and that cholestan-5β,6β-episulphide XXXVII gives only olefin and no trithiocarbonate. In ring C the incipient diaxial groups are clearly restrained to this configuration because of the inflexibility of the ring; whereas, in the case of cholestan-5β,6β-episulphide XXXVII, although there is a

[30] K. Takeda (Shionogi Research Laboratories, Osaka, Japan) private communication.



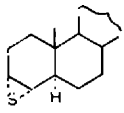
XLV



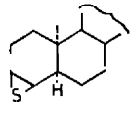
XLVI

limited conformational flexibility in ring B, no cyclic intermediate of the type IX can be formed, due to the strictly axial character of the 5α substituent. It may also be noted that 5α-androstan-3,3-ethylenedioxy-16β,17β-episulphide (XLVI) also does not react[30] to give a trithiocarbonate, although cyclopentane episulphide does give a trithiocarbonate.[31] The latter fact may be rationalized by the greater flexibility of cyclopentane episulphide over its steroid analog (XLVI), in which the five-membered ring is additionally *trans* fused to a six-membered ring.

At first sight, it is surprising that cholestan-3α,4α- and 3β,4β-episulphides (XLVII and XLVIII), which are conformationally flexible in ring A, do not react to give any trithiocarbonate, but are recovered unchanged or partially desulphurized from the reaction mixture. There are some rather subtle stereochemical and conformational



XLVII

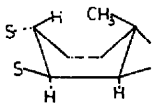
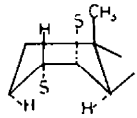
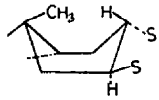
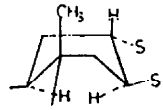
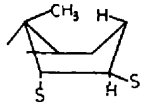
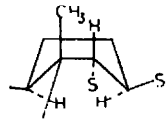


XLVIII

factors which apparently play an important role. In the case of the 3,4 substituted steroids several new stereochemical factors are introduced. For ring A in a boat, there are two possible conformations. In case (X) the bow and the stern are C-3 and C-10, and in this conformer there is a severe interaction between the 3β-H and the C-19 methyl group. This conformer may proceed through more staggered twist conformers to case (Y) in which the bow and the stern are C-2 and C-5. This latter conformer exhibits an H-H interaction between the 2α-H and the 5α-H, other than the usual boat eclipsing which is approximately equal in the two forms (X and Y). For the case of the 2,3-diaxial compound when ring A is in a boat, the atoms attached to C-2 and C-3 are in a sufficiently favourable position for ring formation in both (X) and (Y) and also in the intermediate twist forms. However, in the 1,2 and 3,4 diaxially substituted steroids there is only one favourable conformation of ring A suitable for ring fusion. Thus, for the 3,4 diaxial compound when ring A flips to a boat conformer only in case (X) are the vicinal substituents in close enough proximity for ring fusion. All intermediate twist forms force the vicinal substituents farther apart until they are at their farthest point in case (Y) and in which they are as nearly far apart as in the chair conformer where ring formation is impossible. The favourable positions for the 1,2 diaxially substituted steroid are reversed from its 3,4-isomer. Here case (Y) is more favourable.

It may then be predicted that the formation of a 1α,2β-trithiocarbonate would be possible (in case Y); whereas, a 3α,4β-trithiocarbonate would be energetically unfavourable in case (X) due to the 3β-H—19-CH_3 interaction, although the bonding

[31] S. M. Iqbal and L. N. Owen, *J. Chem. Soc.* 1030 (1960).

Points of Attachment of Sulphur Atoms	Conformer X	S–S distance	Conformer Y	S–S distance
3,4		3·2 Å		4·1 Å
2,3		3·2 Å		3·2 Å
1,2		4·1 Å		3·2 Å

Chair, *trans*-diaxial 4·4 Å
Chair, *cis* 3·2 Å

distance is favourable; and it would be impossible in case (X) because of the unfavourable bonding distance. The end result is that it should be extremely difficult, if not impossible, to form a five-membered cyclic derivative involving the 3α and 4β stereochemistry. These arguments account for the observation that treatment of the cholestan-3α,4α and 3β,4β-epoxides and episulphides does not lead to a 3α,4β-trithiocarbonate, but rather to olefin and decomposition products.* Moreover, these arguments also explain the inability to form the oxathiolane and dithiocarbonate of the 3α,4β-mercaptanol.[30] Presumably, however, a trithiocarbonate in case (X) should be easily formed in a 19-nor steroid.

It can be seen from the foregoing that steroidal episulphides can be synthesized easily from epoxides and also from bromoketones. It is also apparent that the better defined stereochemistry of the steroids has confirmed previously suggested[12] mechanisms of episulphide formation and has served additionally to detect the seemingly anomalous reactions of episulphides *per se* as well as those related to their particular conformational demands on the steroid ring system.

EXPERIMENTAL

The silica gel (200–300 mesh) used for column chromatography was procured from L. Light Co. Colnbrook, England. The silicic acid (100 mesh) for column chromatography was from Baker and Adamson. It was washed several times with water to remove the finer particles and activated at 125° for 8 hr.

All m.ps were taken in a capillary on a Thomas Hoover capillary melting point apparatus and are uncorrected unless otherwise indicated. The IR spectra were determined an a Perkin-Elmer model 421 spectrophotometer and the UV spectra were recorded on an Applied Physics model 14 spectro photometer. The optical rotatory dispersion measurements were performed by Mrs. Ruth Records with a Japan Spectroscopic Company automatically recording spectropolarimeter. The circular

* The reported[11] cholestan-3β,4α-trithiocarbonate is actually cholestan-2β,3α-trithiocarbonate (XL), which arose from a sample of cholestan-3α,4β-episulphide (XLVII) contaminated with its 2,3-isomer. Reaction of a very pure sample of XLVII gave no trithiocarbonate. In addition the reported[11] optical rotatory dispersion and circular dichrosim curves of XLVII should be oppositely signed.

dichroism measurements were obtained on a Baird-Atomic/Jouan Dichrograph. The mass spectra were determined by Drs. H. Budzikiewicz, J. M. Wilson and M. Ohashi on a Consolidated Electrodynamics Corp. mass spectrometer No. 21-103C by means of a direct inlet system[32] at 70 eV ionization voltage.

Cholestan-3-one-2α-ethyl xanthate (III)

2α-Bromocholestan-3-one[33] (7·10 g, 15·2 mmoles) was dissolved in 175 ml dry acetone and to this solution was added dropwise 2·6 g (16·2 mmoles) potassium ethyl xanthate in 90 ml acetone. The solution was stirred at room temp for 12 hr, during which time KBr precipitated. The mixture was evaporated to dryness under red. press. and to the resulting solid was added 100 ml n-hexane which dissolved the organic material. The insoluble was removed by filtration, and the hexane was removed under red. press. to give a light yellow solid (7·20 g). This solid was crystallized from chloroform–ethanol to give white needles, 5·10 g, m.p. 114–115°. A second crop of needles was obtained (0·60 g), m.p. 114–115°. The total yield was 5·70 g (74%) of pure keto xanthate; $[\alpha]_D^{23}$ −101° (*c* 0·015, $CHCl_3$); ν_{max} 1705, 1105, 1045, 587 cm.$^{-1}$ (KBr); log ϵ_{253}^{max} 1·74, log ϵ_{290}^{min} 1·67, log ϵ_{280}^{max} 4·03, log ϵ_{250}^{min} 3·10, log $\epsilon_{230}^{shoulder}$ 3·97, (dioxane); (Lit.[18] m.p. 116·5–118°, $[\alpha]_D^{25}$ −64·5°).

Sodium borohydride reduction of cholestan-3-one-2α-ethyl xanthate (III)

Cholestan-3-one-2α-ethyl xanthate (2·0 g, 3·95 mmoles) was added to 100 ml ethanol and enough ether was added to completely dissolve the solid. Sodium borohydride (90 gm, 2·36 mmoles) was added directly and the solution was stirred at room temp for 4 hr, after which time it was diluted with 200 ml ether, and the ether solution washed well with water and dried ($MgSO_4$). Evaporation of the ether gave 1·80 g sticky gum which was chromatographed on 85 g silicic acid. Hexane eluted 587 mg of Δ^3-cholestene (40%), which was homogeneous by chromatoplate (n-hexane). Crystallization from chloroform-ethanol gave long needles, m.p. 74–75°; $[\alpha]_D^{26}$ +68·5° (*c* 1·25, $CHCl_3$). A mixture m.p. with authentic Δ^3-cholestene gave 73–74°; (Lit.[34] m.p. 75°; $[\alpha]_D$ +70°). (Found: C, 87·21; H, 12·57. $C_{27}H_{46}$ requires: C, 87·49; H, 12·51%).

Benzene–hexane (1:1) gave 597 mg (30%) cholestan-3α-ol-2α-ethyl xanthate as an uncrystallizable oil, $[\alpha]_D^{27}$ −36° (*c* 2·45, $CHCl_3$); ν_{max} 3500, 1220, 1105, 1045, 555 cm.$^{-1}$ (KBr); log ϵ_{256}^{max} 3·87, log ϵ_{217}^{min} 3·57 (dioxane). The compound was analyzed as the acetate.

Ether–hexane (1:3) eluted 633 mg (32%) cholestan-3β-ol-2α-ethyl xanthate as an uncrystallizable oil, $[\alpha]_D^{23}$ −82° (*c* 0·95, $CHCl_3$); ν_{max} 3400, 1220, 1105, 1045, 545 cm^{-1} (KBr); log ϵ_{255}^{max} 1·88, log ϵ_{310}^{min} 1·64, log ϵ_{255}^{max} 4·08, log ϵ_{280}^{min} 3·08, log ϵ_{227}^{max} 3·69, log ϵ_{220}^{min} 3·21 (dioxane). (Found: C, 71·17; H, 10·27; S, 12·71. $C_{30}H_{52}O_2S_2$ requires: C, 70·81; H, 10·30; S, 12·60%).

Cholestan-3β-ol acetate 2α-ethyl xanthate (Vb)

To cholestan-3β-ol 2α-ethyl xanthate (242 mg, 0·475 mmoles) in 5 ml anhydrous pyridine was added 0·5 ml acetic anhydride. The solution was allowed to stand at room temp for 48 hr, whereupon it was diluted with ice water and extracted with methylene chloride. The methylene chloride layer was washed well with 1% HCl aq, water, and dried ($MgSO_4$). The methylene chloride was evaporated under red. press. to give 235 mg semi-solid material which was chromatographed on 30 g silicic acid. Elution with 2% ether–hexane gave 204 mg (78%) of the acetate, pure by chromatoplate (85% benzene–15% hexane). Crystallization from ethanol gave plates, m.p. 112–113°; $[\alpha]_D^{26}$ −66° (*c* 0·60, $CHCl_3$); ν_{max} 1734, 1220, 1103, 1042, 596 cm^{-1} (KBr); log ϵ_{257}^{max} 1·76, log ϵ_{227}^{min} 1·48, log ϵ_{261}^{max} 4·12, log ϵ_{247}^{min} 2·50, log $\epsilon_{228}^{shoulder}$ 3·91 (dioxane). (Found: C, 69·79; H, 9·99; S, 11·93. $C_{32}H_{54}O_2S_2$ requires: C, 69·77; H, 9·88; S, 11·64%).

Cholestan-3α-ol acetate 2α-ethyl xanthate (VIb)

Cholestan-3α-ol-2α-ethyl-xanthate (268 mg, 0·525 mmoles) was acetylated in the same manner to give 235 mg solid which was easily crystallized from ethanol to give 211 mg (73%) shiny plates, m.p. 160–161° $[\alpha]_D^{26}$ +5·4° (*c* 1·00, $CHCl_3$); ν_{max} 1738, 1220, 1103, 1045, 598 cm^{-1} (KBr); log ϵ_{255}^{max} 1·73, log ϵ_{235}^{min} 1·47, log ϵ_{280}^{max} 4·09, log ϵ_{247}^{min} 2·69, log $\epsilon_{228}^{shoulder}$ 3·86 (dioxane). (Found: C, 69·48; H, 9·77; S, 11·57. $C_{32}H_{54}O_2S_2$ reqiures: C, 69·77; H, 9·88; S, 11·64%).

[32] J. F. Lynch, J. M. Wilson, H. Budzikiewicz and C. Djerassi, *Experientia* **19**, 211 (1963).
[33] L. F. Fieser and X. A. Dominguez, *J. Amer. Chem. Soc.* **75**, 1704 (1953).
[34] R. B. Turner, W. R. Meador and R. E. Winkler, *J. Amer. Chem. Soc.* **79**, 4122 (1957).

Raney nickel desulfurization of cholestan-3α-ol acetate 2α-ethyl xanthate (VIb)

Cholestan-3α-ol acetate 2α-ethyl xanthate (50 mg, 0·091 mmoles) was dissolved in 25 ml ethanol and to this solution was added 1·0 g freshly prepared W-4 Raney Ni.[35] This mixture was heated under reflux for 2 hr. After cooling and filtering through Celite to remove the Ni, the ethanol was evaporated to give 38 mg oily material. Attempted crystallization of the oil from ethanol gave 12 mg crystalline starting material. The remaining 26 mg oil was separated by preparative plate chromatography, using 85% benzene–15% hexane. By this procedure there was isolated 10 mg (25%) cholestan-3α-ol acetate. Crystallization from methanol gave material m.p. 94–96°. A mixture m.p. with authentic cholestan-3α-ol acetate gave 93–95°. The compound had the same R_f value (0·45) as authentic material, which was different from that (0·48) of cholestan-3β-ol acetate on chromatoplate (85% benzene–15% hexane). In addition, there was isolated 4 mg of a non-polar substance, Δ^2-cholestene. Crystallization from methanol gave small needles, m.p. 70–71°. Its identification as Δ^2-cholestene was authenticated by a mixture m.p. (70–72°) with genuine Δ^2-cholestene.

Raney nickel desulphurization of cholestan-3β-ol acetate 2α-ethyl xanthate (Vb)

Cholestan-3β-ol acetate 2α-ethyl xanthate (50 mg, 0·091 mmoles) was treated exactly as above to give 30 mg crude material upon evaporation of the ethanol. This material was chromatographed on 30 g silica gel, using gradient elution. Pure benzene was added to a reservoir of n-hexane (150 ml) in a gradient manner, taking 20 ml fractions. Fractions 8 and 9 gave 16 mg (40%) cholestan-3β-ol acetate, m.p. 105–106°. The compound, upon admixture with authentic cholestan-3β-ol acetate, gave m.p. 106–107°, and it had an R_f value (0·48) identical to that of authentic material. In addition, fractions 1 and 2 contained 4 mg Δ^2-cholestene.

Cholestan-2α,3α-episulphide (XIII)

(a) *By sodium borohyride treatment of cholestan-3β-ol-2α-ethyl xanthate* (Va). Cholestan-3β-ol-2α-ethyl xanthate (100 mg, 0·197 mmoles) was dissolved in 25 ml absolute ethanol, and to this solution was added excess $NaBH_4$ (10 mg, 0·263 mmoles). After 2 days at room temp the solution was diluted with water and extracted with n-hexane. The hexane solution was washed well with water, dried ($MgSO_4$) and evaporated to give 78 mg oil. This oil was chromatographed on 12 g silicic acid. Elution with n-hexane gave 53 mg (73%) pure solid material which was crystallized from methylene chloride–methanol to give crystals of cholestan-2α,3α-episulfide, m.p. 123–125°; $[\alpha]_D^{27}$ +39° (*c* 0·656, $CHCl_3$); ν_{max} 587 cm^{-1} (KBr); $\log \epsilon_{265}^{max}$ 1·55, $\log \epsilon_{240}^{min}$ 1·28 (isooctane); (Lit.[7] m.p. 123–125°; $[\alpha]_D$ +39°). No Δ^2-cholestene was detected. (Found: C, 80·40; H, 11·35; S, 8·07. $C_{27}H_{46}S$ requires: C, 80·52; H, 11·51; S, 7·97%).

(b) *By sodium ethoxide treatment of cholestan-3β-ol-2α-ethyl xanthate* (Va). To cholestan-3β-ol-2α-ethyl xanthate (570 mg, 1·12 mmoles) in 25 ml ethanol was added 10 ml of a solution of sodium ethoxide prepared from 100 mg Na and 10 ml ethanol. The solution was allowed to stand at room temp for 2 days, whereupon it was poured into water and extracted with ether. The ether extract was washed well with water until the washings were no longer basic. After drying, the ether was evaporated to give an oil which was chromatographed on 40 g silicic acid. Elution with n-hexane gave 325 mg (72%) of the episulphide. Crystallization from methylene chloride–methanol gave crystals, m.p. 123–125°. No Δ^2-cholestene was isolated or detected.

Cholestan-2α(S),3β(O)-dithiocarbonate (XVI)

(a) *By sodium borohydride treatment of cholestan-3α-ol-2α-ethyl xanthate* (VIa). Cholestan-3α ol-2α-ethyl-xanthate (28 mg, 0·055 mmole) was dissolved in 4 ml ethanol and to this solution was added excess $NaBH_4$ (15 mg, 0·39 mmoles). After 4 days at room temp, a slight precipitate had formed. The total mixture was diluted with water and extracted with ether. The ether solution was washed well with water until the washings were neutral, dried ($MgSO_4$) and evaporated to give 20 mg oil. Crystallization from chloroform–methanol gave 15 mg (59%) white solid (cholestan-2α(S),3α(O)-dithiocarbonate), m.p. 195–197°; $[\alpha]_D^{28}$ + 108° (*c* 0·72, $CHCl_3$); ν_{max} 1205, 1176, 1045 cm^{-1} (KBr); $\log \epsilon_{375}^{max}$ 1·87, $\log \epsilon_{327}^{min}$ 0·89, $\log \epsilon_{288}^{max}$ 4·22, $\log \epsilon_{250}^{min}$ 3·00, $\log \epsilon_{229}^{max}$ 3·68, $\log \epsilon_{220}^{min}$ 3·65 (dioxane). No Δ^2-cholestene was detected. (Found: C, 72·66; H, 10·13; S, 13·82. $C_{28}H_{46}OS_2$ requires: C, 72·66; H, 10·02; S, 13·86%).

[35] H. Adkins and A. A. Pavlic, *J. Amer. Chem. Soc.* **68**, 1471 (1946).

(b) *By sodium ethoxide treatment of cholestan-3α-ol-2α-ethyl xanthate (VIa).* To cholestan-3α-ol-2α-ethyl xanthate (316 mg, 0·620 mmoles) in 15 ml ethanol was added 10 ml sodium ethoxide solution made by dissolving 100 mg Na in 10 ml ethanol. After 1 hr a copious white precipitate appeared. After 4 days at room temp, the precipitate was filtered and washed well with ice-cold methanol–water (1:1) and dried to give 170 mg (60%) solid cholestan-2α(S),3α(O)-dithiocarbonate. Recrystallization from chloroform–methanol gave 150 mg cyclic xanthate, m.p. 195–197°.

An additional amount of material was obtained by working up the ethanolic solution and chromatographing the resultant oil on silicic acid to yield 66 mg solid, m.p. 194–196°. The combined yield was 216 mg (75%).

Cholestan-2-one-3β-ethyl xanthate (XXII)

To XX (1·03 g, 2·22 mmoles) in 35 ml acetone was added 0·40 g (2·5 mmoles) potassium ethyl xanthate and the solution was stirred at room temp for 2·5 hr. The acetone was removed under red. press. and the organic material extracted from the solid residue with 50 ml n-hexane. Filtration and evaporation of the hexane gave 980 mg crude solid keto-xanthate. Crystallization from chloroform–ethanol gave 740 mg (66%) needles, m.p. 107–109°. An additional 200 mg keto-xanthate was obtained by chromatography of the mother liquor residue on silica gel. The total yield was 940 mg (84%). A chromatoplate of the original crude solid (85% benzene–15% hexane) revealed only two spots—starting material and product—indicating that epimerization of the initially formed keto-xanthate had not occurred. The keto-xanthate had $[\alpha]_D^{27}$ −13° (*c* 1·41, $CHCl_3$), ν_{max} 1700, 1215, 1145, 1045, 588 cm^{-1} (KBr); log ϵ_{254}^{max} 1·75, log ϵ_{287}^{min} 1·50, log ϵ_{279}^{max} 4·06,l og ϵ_{250}^{min} 2·74, log ϵ_{223}^{max} 3·90, log ϵ_{220}^{min} 3·86 (dioxane). (Found: C, 70·93; H, 10·06; S, 12·64. $C_{30}H_{52}O_2S_2$ requires: C 70·81; H, 10·30; S, 12·60%).

Cholestan-2β-ol acetate 3β-ethyl xanthate (XIIIb)

Cholestan-2β-ol-3β-ethyl-xanthate (90 mg, 0·177 mmoles) was acetylated in the usual manner and purified by chromatography to give 50 mg (51%) acetoxy-xanthate. Crystallization from chloroform–ethanol yielded crystals, m.p. 162–163°; $[\alpha]_D^{25}$ +68° (*c* 1·02, $CHCl_3$); ν_{max} 1731, 1238, 1204, 1102, 1040, 1020, 598 cm^{-1} (KBr); log ϵ_{253}^{max} 1·81, log ϵ_{285}^{min} 1·63, log ϵ_{279}^{max} 4·11, log ϵ_{247}^{min} 2·84, log ϵ_{234}^{max} 3·87, log ϵ_{217}^{min} 3·84 (dioxane).

Desulphurization of a 25 mg sample in the previously described manner led to 13 mg (67%) cholestan-2β-ol acetate. Crystallization from ether–methanol gave cyrstals m.p. 79–80°; $[\alpha]_D^{25}$ +26° (*c* 0·50, $CHCl_3$); (Lit.[35] m.p. 78°; $[\alpha]_D$ +27°). The earlier chromatography fraction contained a nonpolar substance which was tentatively identified as Δ^5-cholestene.

Cholestan-2β(O),3β(S)-dithiocarbonate (XXV)

Cholestan-2β-ol-3β-ethyl xanthate (113 mg, 0·222 mmoles) was added to 15 ml ethanol and to this solution was added 5 ml sodium ethoxide solution made by dissolving 100 mg Na in 15 ml ethanol. After a few min, delicate crystals began to form in the solution. Within 1 hr a copious precipitate had formed and, after 14 hr at room temp, the solid was filtered and washed well with cold ethanol to afford 95 mg (92%) white crystals. Recrystallization from methylene chloride–methanol gave crystals m.p. 170–172°; $[\alpha]_D^{25}$ +5·5° (*c* 0·62, $CHCl_3$); ν_{max} 1200, 1166, 1047, 1030 cm^{-1} (KBr); log ϵ_{272}^{max} 1·91, log ϵ_{287}^{min} 1·31, log ϵ_{282}^{max} 4·25, log ϵ_{250}^{min} 3·19, log ϵ_{282}^{max} 3·69, log ϵ_{216}^{min} 3·37 (dioxane). (Found: C, 72·25; H, 10·02; S, 13·61. $C_{28}H_{46}OS_2$ requires: C, 72·66; H, 10·02; S, 13·86%).

Cholestan-2α(S),3β(O)-dithiocarbonate (XXVI)

To a solution of 62 mg (0·15 mmoles) cholestan-3β-ol-2α-thiol in 60 ml dry benzene was added 0·1 ml thiophosgene (K and K Laboratories, Inc., Jamaica, N.Y.) and the solution allowed to stand at room temp for 1 hr. After this time, the benzene solution was poured into a 250 ml beaker containing 75 ml sat. $NaHCO_3$ aq and the mixture rapidly stirred in the open beaker in the hood until the benzene had evaporated. The insoluble organic residue was extracted with ether, the ether layer washed well with water, dried ($MgSO_4$) and evaporated to give 60 mg crude yellow oil. This oily mixture was separated, using a preparative chromatoplate (methylene chloride) to yield 30 mg (42%) dithiocarbonate, after crystallization from n-pentane, m.p. 114–116°; $[\alpha]_D$ + 127° (*c* 1·28, $CHCl_3$); ν_{max} 1190, 1149, 1045 cm^{-1} ($CHCl_3$); λ_{280}^{max} log ε 1·89, λ_{305}^{min} log ε 1·86, λ_{282}^{max} log ε 4·15,

λ_{347}^{min} log ε 3·21, λ_{247}^{max} log ε 3·72, λ_{227}^{max} log ε 3·47 (dioxane). (Found: C, 72·52; H, 9·99; S, 14·13. $C_{28}H_{46}OS_2$ requires: C, 72·66; H, 10·02; S, 13·86%).

Cholestan-2β,3β-episulphide (XVIII)

Cholestan-2α,3α-oxide[25] (215 mg, 0·556 mmoles) and 255 mg (2·63 mmoles) KCNO in 10 ml ethanol were heated under reflux for 42 hr. After cooling, the solution was diluted with water and extracted with ether. The ether layer washed well with water and dried ($MgSO_4$). Evaporation of the ether gave 200 mg crude oil. Chromatography on 20 g silica gel with n-hexane gave 14 mg Δ^2-cholestene (fractions 2–5), m.p. 71–72°; which showed no depression upon admixture with authentic material. Thin-layer chromatography of a sample of the starting epoxide (85%) benzene–15% hexane) indicated no Δ^2-cholestene. Fractions 10–14 yielded 34 mg (15%) cholestan-2β,3β-episulphide. Crystallization from methylene chloride–methanol afforded white crystals, m.p. 113–115°; $[\alpha]_D^{27}$ +43° (*c* 0·583, $CHCl_3$); ν_{max} 590 cm^{-1} (KBr); log ϵ_{246}^{max} 1·58, log ϵ_{240}^{min} 1·31 (isooctane); (Lit.[6,7] m.p. 120–122°; $[\alpha]_D$ +40·6°). A mixture m.p. with cholestan-2α,3α-episulphide was depressed to 93–105°. Further elution with 6% ether–hexane produced 140 mg recovered epoxide. (Found: C, 80·35; H, 11·31; S, 8·00. $C_{27}H_{46}S$ requires: C, 80·52; H, 11·51; S, 7·97%).

Other reaction conditions were attempted, but as shown below, they resulted in the same or poorer yield of episulphides.

Molar ratio of epoxide to KSCN	Solvent	Reaction time	Reaction temp	Yield
1:2	methanol	120 hr	reflux	6%
1:2	ethanol	112 hr	reflux	7%
1:10	ethanol	72 hr	reflux	10%
1:1	1-propanol	48 hr	reflux	15%
1:1	DMSO	36 hr	90°	0%

(+)-*trans*-9-*Methyldecalin-2α,2α-oxide* (XXX)

To a solution of 925 mg (6·05 mmoles)(+)-9-methyloctalin-2[26] in 50 ml ether was added 1·2 equivs *p*-nitroperbenzoic acid.[27] The solution was allowed to stand at room temp for 16 hr, whereupon it was washed well with 10% Na_2CO_3 aq, water and dried ($MgSO_4$). Chromatography of the resultant oil on 66 g silica gel gave 190 mg unreacted olefin and 747 mg (93% based on reacted olefin) of the oily epoxide; $[\alpha]_D^{29}$ +25° (*c* 1·12, $CHCl_3$). The substance was homogeneous by thin-layer chromatography (85% benzene—15% hexane) and gas-phase chromatography (phenyl diethylamine succinate column, 185°, 28 lbs N_2, 39 ml/min H_2 on Wilkin's Hi-Fi). The α-configuration follows from the course of the $LiAlH_4$ reaction.[26] (Found: 79·75; H, 10·61. $C_{11}H_{18}O$ requires: C, 79·48; H, 10·91%).

(+)-trans-9-*Methyldecalin-2β,3β-episulphide* (XXXI)

(+)-*trans*-9-Methyldecalin-2α,3α-oxide (240 mg, 1·44 mmoles) was allowed to react with excess (1·00 g, 10·3 mmoles) KCNO in refluxing ethanol for 22 hr. The ethanol solution was cooled and poured into cold water. This mixture was subsequently extracted with ether end the ether layer was washed well with water, dried ($MgSO_4$) and evaporated at red. press. to give 210 mg oil. This oil was chromatographed on 25 g silica gel, using n-pentane. Fractions 1–3 gave 23 mg olefin and fractions 9–13 97 mg (37%) episulphide. The unreacted epoxide was eluted with 4% ether–pentane. The episulphide was shown to be pure on chromatoplate (n-hexane), but on gas-phase chromatography, using a PDEAS column at 175°, it exhibited two peaks in a ratio of 4:1. The larger peak corresponds to the β-episulphide; whereas, the smaller one probably represents the α-episulphide. The mixture of episulphides had $[\alpha]_D^{26}$ +11° (*c* 0·91, $CHCl_3$). (Found: C, 72·54; H, 10·06; S, 17·44. $C_{11}H_{18}S$ requires: C, 72·47; H, 9·95; S, 17·59%).

Cholestan-5α-ol-6β-thiocyanate (XXXIVa)

To cholestan-5α,6α-oxide[28] (2·5 g, 6·5 mmoles) was added 100 ml ethereal solution of thiocyanic acid. The thiocyanic acid solution was prepared as follows: to KCNO (24 g, 0·246 mmoles) in a

[25] A. Fürst and P. A. Plattner, *Helv. Chim. Acta.* **32**, 275 (1949).
[26] Carl Djerassi and J. E. Gurst, *J. Amer. Chem. Soc.* **86**, 1755 (1964).
[27] M. Vilkas, *Bull. Soc. Chim. Fr.* 1401 (1959).
[28] R. E. Ireland, T. I. Wrigley and W. G. Young, *J. Amer. Chem. Soc.* **80**, 4604 (1958).

500 ml separatory funnel was added a small amount of water and ice to dissolve the salt. One hundred ml ether was then added with subsequent addition of 30 ml H_3PO_4 (85%) in small portions with shaking. Final shaking left a clear, deep pink ether layer and a nearly colorless aqueous layer which was discarded. The ether layer was washed with a small portion of water and dried ($MgSO_4$). The reaction mixture was allowed to stand at room temp for 3 days. The ether solution was then washed with 10% Na_2CO_3 aq, water, then dried and evaporated. The resulting solid was crystallized from chloroform–methanol to yield 2·3 g (79%) needles, m.p. 119–120°. Recrystallization gave 1·9 g needles, m.p. 119–120°; $[\alpha]_D^{25}$ −74° (*c* 1·015, $CHCl_3$); ν_{max} 3440, 2150, 962, 951, 917, 805, 719, 723, 714 cm^{-1} (KBr). (Found: C, 75·44; H, 10·64; S, 7·28. $C_{28}H_{47}NOS$ requires: C, 75·45; H, 10·63; S, 7·19%).

Cholestan-5α-ol acetate 6β-thiocyanate (XXXIV)

Cholestan-5α-ol-6β-thiocyanate (510 mg, 1·14 mmoles) and 120 mg *p*-toluenesulphonic acid were dissolved in 25 ml isopropenyl acetate and this solution was heated under reflux for 10 hr. The solution was cooled and the solvent removed at red. press. The residue was dissolved in ether and this solution was washed well with water, dried ($MgSO_4$), and evaporated. The residue was chromatographed on 40 g silica gel, using gradient elution. To a 250 ml reservoir of n-hexane was added 150 m each of 5% and 10% ether-n-hexane, then 250 ml 15% ether-n-hexane, all in a dropwise gradient manner while taking 20 ml fractions off the column. Fractions 15–18 gave 440 mg (79%) pure acetate, m.p. 130–131°, $[\alpha]_D^{25}$ −60·6° (*c* 1·10, $CHCl_3$); ν_{max} 2150, 1728, 1230, 1010, 935, 745 cm^{-1} (KBr). (Found: C, 73·70; H, 10·25; S, 6·39. $C_{30}H_{49}NO_2S$ requires: C, 73·90; H, 10·13; S, 6·57%).

Cholestan-5β,6β-episulphide (XXXVII)

5α-Acetoxycholestan-6β-thiocyanate (296 mg, 0·61 mmoles) was dissolved in a small amount of ether and to this solution was added 20 ml ethanolic KOH (3%). The solution was warmed on the steam bath for 45 min, after which time it was cooled, diluted with water, and extracted with ether. The ether layer was washed well with water, dried ($MgSO_4$), and evaporated. Chromatography of the resultant oil on 40 g of silica gel, using n-hexane, led to 186 mg (76%) cholestan-5β,6β-episulphide, m.p. 71–72°; $[\alpha]_D^{27}$ −12·6° (*c* 0·88, $CHCl_3$); ν_{max} 735, 690 cm^{-1} (KBr); $\log \epsilon_{302}^{max}$ 2·11; $\log \epsilon_{245}^{min}$ 1·99 (dioxane). (Found: C, 80·37; H, 11·64; S, 7·71. $C_{27}H_{46}S$ requires: C, 80·52; H, 11·51; S, 7·97%).

Cholestan-3α-ol-4α-thiocyanate

Cholestan-3α,4α-oxide[39] (390 mg, 1·0 mmole) was allowed to react with 25 ml of a solution of thiocyanic acid in ether (prepared as previously described for cholestan-5α-ol-6β-thiocyanate) for 3 days at room temp. The ether solution was washed with 10% Na_2CO_3 aq, water, dried ($MgSO_4$), and evaporated to give 430 mg foam, which was chromatographed on 46 g silica gel, using gradient elution. To a 300 ml reservoir of n-hexane was added 150 ml each of 5%, 10%, and 15% ether–hexane, 200 ml 20% ether–hexane and 100 ml 50% ether–hexane, in a gradient manner, taking 25 ml fractions. Fractions 35–39 gave 300 mg (67%) pure hydroxy-thiocyanate. Crystallization from hexane gave needles, m.p. 167–169°; $[\alpha]_D^{29}$ +25° (*c* 1·22, $CHCl_3$); ν_{max} 3460, 2150, 1030, 990, 945, 750 cm^{-1} (KBr). (Found: C, 75·61; H, 10·54; S, 7·10. $C_{28}H_{47}NOS$ requires: C, 75·45; H, 10·63; S, 7·19%).

Cholestan-3α-ol-methanesulphonate 4β-thiocyanate

To cholestan-3α-ol-4β-thiocyanate (358 mg, 0·81 mmoles) in 6 ml pyridine at 0° was added 1 ml methanesulphonyl chloride and this reaction mixture was allowed to stand at 5° for 16 hr. The dark mixture was poured into cold water and extracted with 4:1 ether–methylene chloride. The organic layer was washed well with water, 5% HCl aq, 10% Na_2CO_3 aq, water, dried ($MgSO_4$) and evaporated at red. press. Crystallization from n-hexane gave 346 mg shiny plates, m.p. 160–161°; $[\alpha]_D^{25}$ −10·2° (*c* 0·96, $CHCl_3$); ν_{max} 2150, 1350, 1160, 934, 900, 760, 745, 665 cm^{-1} (KBr). (Found: C, 66·39; H, 9·39; S, 12·14. $C_{29}H_{49}NO_3S_2$ requires: C, 66·49; H, 9·43; S, 12·24%).

Cholestan-3β,4β-episulphide (XLVIII)

Cholestan-3α-ol methanesulphonate 4β-thiocyanate (110 mg, 0·21 mmoles) in a small amount of ether was added dropwise to a boiling solution of KOH (3%) in methanol. The episulphide

[39] A. Fürst and R. Scotoni, *Helv. Chim. Acta* 36, 1332 (1953).

precipitated from the solution. After cooling to −15°, the episulfide was removed by filtration to give 58 mg (68·5%) material, m.p. 134–135°; $[\alpha]_D^{21}$ +62° (*c* 0·94, $CHCl_3$). The mother liquor was diluted with ether, washed well with water, dried ($MgSO_4$) and evaporated. The resultant crude solid was chromatographed on 3 g Woelm Act. II neutral alumina. Hexane eluted an additional 15 mg pure episulphide, bringing the total yield to 73 mg (86%); ν_{max} 592 cm^{-1}(KBr); $\log \epsilon_{239}^{max}$ 1·98, $\log \epsilon_{247}^{min}$ 1·79 (dioxane); $[\alpha]_D^{21}$ +62°. (Found: C, 80·60; H, 11·70; S, 7·77. $C_{27}H_{47}S$ requires: C, 80·52; H, 11·51; S, 7·97%).

Acetic acid treatment of cholestan-2α,3α-episulphide (XIII)

A solution of cholestan-2α,3α-episulphide (225 mg, 0·56 mmoles) in 10 ml glacial acetic acid was warmed at 100° for 2 hr. After cooling, the solution was added to cold water and extracted with ether. The ether layer was washed well with 10% $NaHCO_3$ aq, with water, and dried ($MgSO_4$). Evaporated of the ether at red. press. afforded 200 mg solid material which contained no acetate peak in the IR; however, the spectrum was identical to that of the starting episulphide.

The material was then heated under reflux in acetic acid (10 ml) for 5 hr and worked up as above. Evaporation of the ether gave a solid material which again had no acetate peak in the IR; however, this spectrum was different from that of the starting material. A chromatoplate (n-hexane) indicated no episulphide and only a material which moved with the solvent front. Chromatography on 50 g silicic acid with n-hexane gave 180 mg (87%) of Δ^3-cholestene, m.p. 70–71°, and undepressed on admixture with authentic material.

Acetic acid treatment of cholestan-2α,3α-oxide (XXIX)

Cholestan-2α,3α-oxide (229 mg, 0·59 mmoles) was added to 3 ml glacial acetic acid and heated on the steam bath for 2·5 hr. After cooling, the solution was diluted with water and extracted with ether. The ether layer was washed well with 10% Na_2CO_3 aq and water. After drying ($MgSO_4$) and evaporation of the solvent, a chromatoplate (n-hexane) was run on the resultant oil, which indicated no Δ^3-cholestene.

The reaction was repeated again with a fresh sample of epoxide and heated under reflux for 5 hr in glacial acetic acid. A chromatoplate (n-hexane) again indicated no Δ^3-cholestene.

Heat-induced extrusion of sulphur from cholestan-2α,3α-episulphide (XIII)

Cholestan-2α,3α-episulphide (2 mg, 0·005 mmole) was heated at 130° for 1 hr. A chromatoplate (n-hexane) indicated that the material contained a trace amount of starting material as well as a substance moving with the solvent front. Crystallization from methanol gave 1 mg Δ^3-cholestene, m.p. 70–71°. A mixture m.p. with authentic material gave no depression.

Acetic acid treatment of (+)-trans-*9-methyldecalin-2β,3β,episulphide* (XXXI)

To 5 ml glacial acetic acid was added 11 mg (0·060 mmoles) (+)-*trans*-9-methyldecalin-2β,3β-episulphide and the solution was heated under reflux for 6 hr. After cooling, water was added to the reaction mixture, followed by an ether extraction. The ether layer was washed well with 10% Na_2CO_3 aq and with water. After drying ($MgSO_4$), the ether was evaporated at red. press. and the resultant oil was chromatographed on 10 g silica gel. Elution with n-pentane gave 8 mg oil having acetate bands in the IR. This material was not further investigated.

Aluminum chloride treatment of cholestan-2α,3α-episulphide (XIII)

Cholestan-2α,3α-episulphide (10 mg, 0·025 mmoles) was dissolved in 2 ml ether and to this solution was added a mixture of 100 mg (0·83 mmoles) of anhydrous $AlCl_3$ in 8 ml anhydrous ether. The reaction mixture was allowed to stand at room temp for 2 hr with no apparent decomposition, as indicated by a chromatoplate (n-hexane). An additional 5 hr at room temp also caused no apparent decomposition. Heating this mixture under reflux for 3 hr, however, gave some decomposition. The mixture was diluted with ether, washed well with water, dried ($MgSO_4$) and evaporated Chromatography of the resultant soild on 3 g silicic acid yielded 3 mg (33%) Δ^3-cholestene, m.p. 71–72°, and 6 mg unreacted episulphide with n-hexane as eluent.

Repetition of this experiment, except with 10 ml 1:1 tetrahydrofuran–ether mixture as solvent and heating under reflux for 3 hr, produced upon similar work-up 4 mg (44·5%) Δ^3-cholestene m.p. 71–72°, and 5 mg unreacted episulphide.

Lithium aluminum hydride treatment of cholestan-2α,3α-episulphide (XIII)

Cholestan-2α,3α-episulphide (10 mg, 0·025 mmoles) was dissolved in 5 ml ether and to this solution was added 10 mg (0·263 mmoles) $LiAlH_4$. The solution was heated under reflux for 5 hr. The excess $LiAlH_4$ was destroyed by the addition of sat Na_2SO_4 aq. The ether was filtered and dried ($MgSO_4$). Evaporation of the ether gave 8 mg material which, on a chromatoplate (n-hexane), showed only a minute trace of starting material and a large spot (Δ^2-cholestene) moving with the solvent front. Crystallization of the material from ether–methanol gave 7 mg (76%) Δ^2-cholestene, m.p. 73–74°. A mixture m.p. with authentic material showed 72–74°.

The same reaction proceeded in like manner but at a slower rate at room temp (6 hr) and at −15°, to yield 50% of the olefin, the remainder of the material being episulphide.

Cholestan-2α,3α-episulphide (20·5 mg, 0·051 mmoles) was dissolved in a solution of tetrahydrofuran and this was added to a solution of 6 mg $LiAlH_4$ in 3 ml ether. The mixture was heated under reflux for 1·5 hr. Ice and dil. HCl aq (5%) were added, followed by an ether extraction. The layer was washed with 10% Na_2CO_3 aq, water and dried ($MgSO_4$). Evaporation of the ether gave 18·2 mg material. Crystallization from ether–methanol afforded 15·2 mg needles (Δ^2-cholestene), m.p. 70–71°, mixture m.p. with authentic material, 70–72°. Chromatography of the remaining 3 mg on silica gel produced an additional 2 mg Δ^2-cholestene, bringing the total yield to 17·2 mg (91%). Further elution gave approximately 1 mg starting material.

Lithium aluminum hydride treatment of cholestan-2β,3β-episulphide (XIX)

Cholestan-2β,3β-episulphide (13 mg, 0·032 mmoles) was dissolved in 10 ml ether and to this solution was added 10 mg (0·263 mmoles) $LiAlH_4$. The solution was allowed to stand at room temp for 3·5 hr, after which time the excess $LiAlH_4$ was destroyed with sat. NH_4Cl aq and filtered. The ether was washed with water, dried ($MgSO_4$) and evaporated to give 11 mg soild, which, on chromatoplate (n-hexane), showed a trace of episulphide and a large spot in the solvent front. The material was crystallized from ether–methanol yielding 10 mg (84%) needles (Δ^2-cholestene), m.p. 70–71°. A mixture m.p. with authentic Δ^2-cholestene gave 70–72·5°. Essentially the same results were encountered in ether–tetrahydrofuran solution (1 hr reflux).

Lithium aluminum hydride treatment of (+)-trans-9-*methyldecalin-2β,3β-episulphide* (XXXI)

(+)-*trans*-9-Methyldecalin-2β,3β-episulphide (10 mg, 0·055 mmoles) was dissolved in 5 ml ether and allowed to react with 5 mg $LiAlH_4$ for 20 hrs at room temp. Excess $LiAlH_4$ was destroyed with sat. Na_2SO_4 aq. The ether was filtered, washed with water, dried ($MgSO_4$) and evaporated at red. press. to give 7 mg oil. A chromatoplate (n-hexane) showed that there were only minute traces of material having an R_f value smaller than that of the olefin (which moved with the solvent front), and larger than that of the reactants (R_f: 0·85). No other material was detectable. Gas-phase chromatography on a PDEAS column at 175° detected the olefin, which had an identical retention time to that of authentic material. The olefin was present as 99% of the reaction mixture. The remaining 1% was represented by two small peaks (seen with a very large injection of sample) with a smaller retention time than that of the episulphides. The olefin had $[\alpha]_D^{26}$ +69° (*c* 0·565, $CHCl_3$) while the authentic olefin[26] showed $[\alpha]_D^{27}$ +69·5°.

Sodium borohydride treatment of cholestan-2α,3α-episulphide (XIII)

Cholestan-2α,3α-episulphide (5 mg, 0·012 mmoles) was dissolved in 2 ml ethanol and to this solution was added 3 mg (0·079 mmoles) $NaBH_4$. The solution was allowed to stand at room temp for 12 hr, after which time it was diluted with water and extracted with ether. The ether layer was washed well with water, dried ($MgSO_4$) and evaporated. A chromatoplate (n-hexane) indicated mostly unreacted starting material as well as a spot moving with the solvent front. Isolation of this latter material gave 1 mg (22%) needles from methanol, m.p. 71–72°. A mixture m.p. with authentic Δ^2-cholestene was 71–73°. Sodium borohydride in isopropyl alcohol gave essentially the same results.

Cholestan-2β,3α-trithiocarbonate (XL)

To a solution of 200 mg (0·52 mmoles) cholestan-2α,3α-oxide in 1 ml CS_2 was added a solution of 0·25 g KOH in 8 ml ethanol. The reaction mixture was heated under reflux for 5 hr, after which time the mixture was evaporated to dryness and extracted with n-pentane. Chromatography of the pentane-soluble material on a preparative chromatoplate, using 15 % benzene–85% hexane as eluent,

gave 7 mg (2·8%) of a yellow compound (small plates from pentane), m.p. 131–133°. The trithiocarbonate had $[\alpha]_D^{25}$ +51° (*c* 0·57, $CHCl_3$); ν_{max} 1099, 1047, 855 cm^{-1} (KBr); log ϵ_{455}^{max} 1·94, log ϵ_{400}^{min} 1·07, log ϵ_{318}^{max} 4·27, log $\epsilon_{310-300}^{shoulder}$ 4·22–4·33, log ϵ_{270}^{min} 2·91, log $\epsilon_{235}^{shoulder}$ 3·34 (dioxane). (Found: C, 70·40; H, 9·88; S, 19·88. $C_{28}H_{46}S_3$ requires: C, 70·23; H, 9·68; S, 20·09%). The remaining material from the chromatoplate was unreacted epoxide with traces of olefin and epoxide.

Repeating the above procedure with 40 mg (0·1 mmoles) cholestan-2α,3α-episulphide gave 18·5 mg (39%) yellow trithiocarbonate, m.p. 133–135°, mixture m.p. with the above material, 132–134°.

Attempted synthesis of cholestan-3α,4β-trithiocarbonate

Cholestan-3β,4β-episulphide (XLVIII) or 3α,4α-episulphide (XLVII) 13 mg, 0·032 mmoles) was dissolved in 1 ml CS_2 and to this solution was added methanolic KOH (10 ml methanol and 3 KOH pellets). The solution was heated under reflux for 16 hr, cooled and diluted with water and ether. The ether layer was washed well with water, dried ($MgSO_4$) and evaporated. The colourless residue gave 9 mg (75%) Δ^5-cholestene, m.p. 72–73° upon crystallization from ether–methanol. The olefin m.p. was undepressed upon admixture with authentic material.[40] There was also evidence for unreacted starting material (chromatoplate: n-hexane), but no trithiocarbonate.

A similar experiment with cholestan-3α,4α-oxide[39] led to no reaction.

Attempted synthesis of 5α-androstan-17β-ol acetate 3α,4β-trithiocarbonate

5α-Androstan-17β-ol acetate 3β,4β-episulphide[21] (20 mg, 0·057 mmoles) was dissolved in 1 ml CS_2 and to this solution was added methanolic KOH (10 ml methanol and 3 KOH pellets). This mixture was heated under reflux for 24 hr, cooled and diluted with ether. The ether was washed well with water and dried ($MgSO_4$). The colourless ether solution was evaporated at red. press. to give a a mixture of 5α-Δ^5-androsten-17β-ol and its acetate as well as a trace of unreacted episulphide (thin-layer chromatography: 100% methylene chloride).

This mixture was acetylated in 1 ml pyridine with 0·1 ml acetic anhydride at room temp for 6 hr. The solution was diluted with ether, washed well with water dried and evaporated. The resultant solid was crystallized from ether–methanol to give 15 mg (82%) crystalline 5α-Δ^5-androsten-17β-ol acetate, m.p. 110–112° (Lit. 110–112°, $[\alpha]_D^{20}$ +39°).

Attempted synthesis of androstan-17β-ol acetate 3α,4β-trithiocarbonate

To a solution of 10 mg (0·04 mmoles) androstan-17β-ol acetate 3β,4β-episulphide[21] in 10 ml dimethyl sulphoxide was added 50 mg (0·31 mmoles) potassium ethylxanthate and the mixture was allowed to stand at room temp for 2 days. The reaction mixture was diluted with ether and washed well with water. The ether layer was dried ($MgSO_4$) and evaporated to give 9 mg mixture of starting material and saponified starting material, but no trithiocarbonate.

An additional experiment was performed, using the same amounts of material as above, but with heating on the steam bath for 14 hr. Work-up as before gave only 5α-Δ^5-androsten-17β-ol which was acetylated to 5α-Δ^5-androsten-17β-ol acetate, m.p. 110–112°. No trithiocarbonate was detected.

Attempted synthesis of cholestan-5α,6β-trithiocarbonate

Cholestan-5β, 6β-episulphide (50 mg, 0·124 mmoles) was dissolved in 1 ml CS_2 and to this solution was added methanolic KOH (8 ml methanol and 0·15 g KOH). The mixture was heated under reflux for 18 hr, cooled and diluted with ether. The ether was washed well with water and dried ($MgSO_4$). This colourless ether solution was evaporated to yield a mixture of starting material and Δ^5-cholestene (thin-layer chromatography: 25% benzene–75% hexane).

(+)-trans-9-*Methyldecalin-2β,3α-trithiocarbonate*

A solution of (+)-*trans*-9-methyldecalin-2α,3α-oxide (125 mg, 0·75 mmoles) in 1 ml CS_2 and ethanolic KOH (0·25 g KOH in 8 ml ethanol) was heated under reflux for 3 hr. Evaporation of the solvent gave a residue which was extracted with ether. Evaporation of the ether and chromatography of the yellow solid on 10 g silicic acid gave 15 mg (19%) yellow trithiocarbonate, m.p. 194–196° (crystallized from pentane); $[\alpha]_D^{26}$ +33·9° (*c* 0·62, $CHCl_3$); ν_{max} 1093, 1053, 1045, 850 cm^{-1} log ϵ_{454}^{max} 1·94, log ϵ_{385}^{min} 1·06, log ϵ_{317}^{max} 4·24, log $\epsilon_{310-300}^{shoulder}$ 4·20–4·11, log ϵ_{287}^{min} 3·05, log ϵ_{227}^{max} 3·46, log ϵ_{218}^{min} 3·38 (dioxane). (Found: C, 54·93; H, 7·27; S, 32·22. $C_{12}H_{16}S_3$ requires: C, 55·76; H, 7·02; S, 37·22%).

[40] L. Caglioti, G. Cainelli, G. Maina and A. Selva, *Gazz. Chim. Ital.* **92**, 309 (1962).