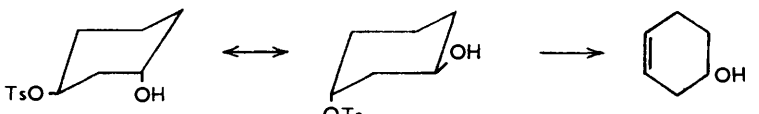
380. *Aspects of Stereochemistry. Part V.* Reactions of* cyclo*Hexane*-1 : 3-*diol Monoarenesulphonates with Alkali.*

By R. B. Clayton, H. B. Henbest, and Michael Smith.

At least four paths are available for the reaction of 1 : 3-diol monosulphonates with alkali. With monocyclic and steroid *cyclo*hexane-1 : 3-diol derivatives the course of the reaction is dependent on experimental conditions and the stereochemical arrangement of the reacting centres. Reasons are put forward for the exceptional formation of a 1 : 3-epoxy*cyclo*hexane system within a steroid molecule, and some of the reactions of this compound are described.

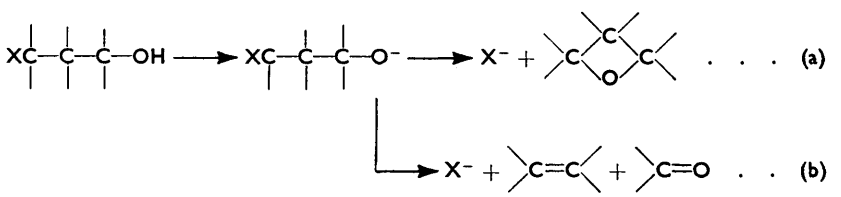
Before this work began no 1 : 3-epoxy*cyclo*alkane had been prepared. Cyclic epoxides are commonly produced by treatment of suitable halogenohydrins and related compounds with alkali : as a possible route to 1 : 3-epoxy*cyclo*hexane, *cyclo*hexane-*trans*-1 : 3-diol monotoluene-*p*-sulphonate (I) had earlier [1] been treated with sodium methoxide in methanol, but the only product obtained was *cyclo*hex-3-en-1-ol (II) in 80% yield. One



(IA) (IB) (II)

reason for the formation of the unsaturated alcohol could be a ready diaxial elimination of toluene-*p*-sulphonic acid from the less favourable conformation (IB) of the starting material. Consequently the reaction was re-investigated with a *trans*-diol monoester of the steroid series where ring inversion is impossible, and in this way a 1 : 3-epoxide was obtained [2] (see below).

To clarify subsequent discussion it may be noted that past and present results show that four types of reaction can take place between cyclic or acyclic 1 : 3-halogenohydrins and alkali. Two of these, epoxide formation (a) and fission into olefin and carbonyl compound [3] (b), depend on the formation of an intermediate anion,[4] whose powerful nucleophilicity provides the driving force for the intramolecular processes. [Conversely,



the fission of some 1 : 3-diols with strong acids [5] can be regarded as proceeding by a predominantly electrophilic process; the reaction may take place [6] *via* a transition state partaking of the character of the conjugate acid of the corresponding 1 : 3-epoxide.] For the intermediate anion, it will be shown that the choice between reaction paths (a) or (b)

* Part IV, preceding paper.

[1] Clarke and Owen, *J.*, 1950, 2103.

[2] Its preparation was first reported by Clayton and Henbest, *Chem. and Ind.*, 1953, 1315.

[3] This fission is one example of a more general carbon–carbon cleavage comprising reverse aldol, reverse Michael, etc., reactions : many examples, including the interesting fission of a 1 : 4-dihalide, have been collated by Grob and Baumann, *Helv. Chim. Acta*, 1955, **38**, 594.

[4] For some earlier observations with acyclic halogenohydrins, cf. Searles and Gortatowski, *J. Amer. Chem. Soc.*, 1953, **75**, 3030; Gaylord, Crowdle, Himmler, and Pepe, *ibid.*, 1954, **76**, 59.

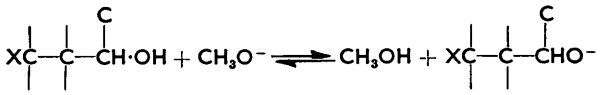
[5] English and Brutcher, *ibid.*, 1952, **74**, 4279.

[6] Zimmerman and English, *ibid.*, 1954, **76**, 2294.

depends on its structure and stereochemistry, variation of the external conditions (including type of alkali used) being expected to have relatively little effect on this choice.

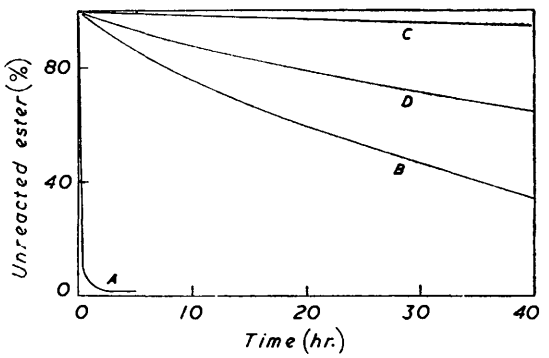
The other two reaction courses, elimination of acid (c_1 and c_2), and displacement of halide by a nucleophil (d), do not necessarily involve the hydroxyl group. As already mentioned, the elimination in *cyclo*hexane systems is more difficult when the sulphonic ester grouping is equatorial. Replacement (d) will be inhibited by steric factors such as increase of adjacent substitution and increased bulkiness of potential nucleophil.

On the other hand, reactions (a) and (b) should clearly be promoted by bases which efficiently generate the necessary intermediate anion. The formation of this anion by alkoxides in alcoholic solutions is an equilibrium process, which for given initial concentrations will be chiefly dependent on the relative acid strengths of the hydroxy-sulphonate and the solvent alcohol. As the acidities of alcohols decrease in the order primary, secondary, tertiary (p*K*'s of methyl, *iso*propyl, *tert.*-butyl alcohol, 16, 18, 19,

e.g., 

respectively [7]), a tertiary alkoxide in a tertiary alcohol should most completely generate the required anion of the starting material. It will be particularly disadvantageous to

Reaction of toluene-p-*sulphonates* (0·02M) *with alkali* (0·04M) *at* 50°. (*Unchanged ester was estimated spectrophotometrically*; *the pure ester has* $\lambda_{max.}$ 2250 Å; ε = 12,700.)



A, *Hydroxy-ester* (III) *and potassium* tert.-*butoxide in* tert.-*butyl alcohol.*
B, *Hydroxy-ester* (III) *and potassium methoxide in methyl alcohol.*
C, *Ester* (VIII) *and potassium* tert.-*butoxide in* tert.-*butyl alcohol.*
D, *Ester* (VIII) *and potassium methoxide in methyl alcohol.*

employ, for example, a primary alkoxide in a primary alcohol to produce an anion from a secondary (and even more so a tertiary) alcohol. The high yield of *cyclo*hexenol obtained previously from the monocyclic ester (I) by treatment with methoxide in methanol can be attributed to the non-formation of anion (see later) as well as to the possibility of conformational inversion to assist elimination.

Reactions of trans-*Hydroxy-sulphonates.*—(i) As an example of a compound with the ester grouping stabilised in an equatorial position, the steroid monotoluene-*p*-sulphonate (III) was prepared and treated in *tert.*-butyl alcohol with potassium *tert.*-butoxide (2 mol.). The reaction was rapid at 50° (Figure) with precipitation of potassium toluene-*p*-sulphonate: the only organic products identified were the crystalline 3α : 5α-epoxide (IV; 55%) and the liquid *seco*-ketone (V; 37%) [further reactions of all new steroid compounds are described towards the end of the paper]. By using a much larger amount of *tert.*-butoxide some 3α-*tert.*-butoxy-5α-alcohol (2%) was also obtained, the *cis*-disposition

[7] McEwen, *J. Amer. Chem. Soc.*, 1936, **58**, 1124.

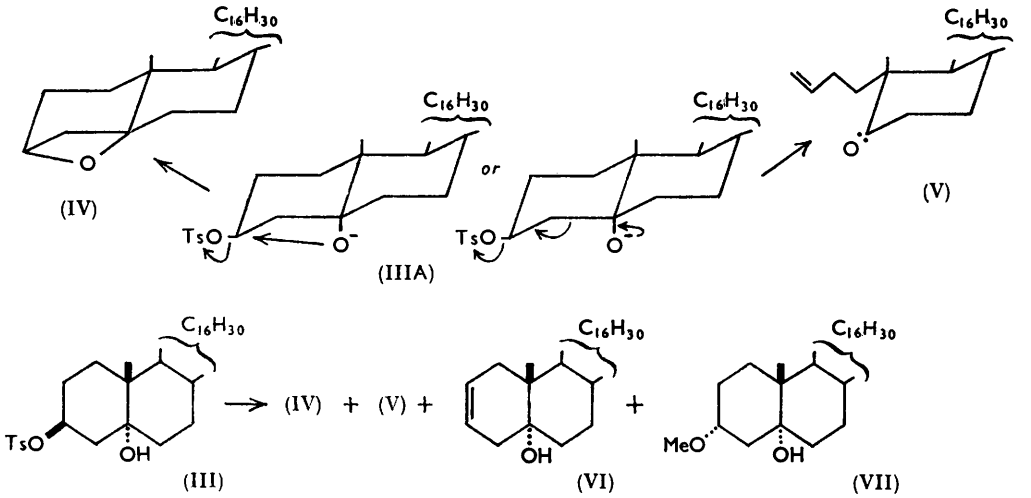
of groups being confirmed by the intramolecular hydrogen bonding revealed in the infrared spectrum.[8]

The reaction between the hydroxy-ester (III)[9] and potassium methoxide in methanol was much slower (Figure), giving a mixture of products corresponding to the four types of reactions (*a*)—(*d*). The greater rate of this reaction than that of the analogous 5-hydrogen compound under the same conditions (Figure) is due to the additional possibility of (rather inefficient) anion formation leading, as with the *tert.*-butoxide experiments, to the 3 : 5-epoxide and *seco*-ketone.

This discussion implies that the formation of epoxide and *seco*-ketone proceeds by first-order decomposition of the anion (IIIA), which is itself formed rapidly and reversibly from the starting materials:

$$(III) + Bu^tO^- \rightleftharpoons Bu^tOH + (IIIA) \longrightarrow (IV) + (V)$$

As *tert.*-butyl alcohol is the medium present in large excess, and as the acidity of the hydroxy-ester should only be comparable to that of this, the concentration of the intermediate anion will be small relative to the concentrations of hydroxy-ester and *tert.*-butoxide anion. As a close approximation, therefore, the reaction should be kinetically of the second order, the rate depending on [hydroxy-ester] and [Bu^tO^-]. This was the case for over 80% of the reaction.



Nace[10] has shown that the solvolysis of the 5α-hydrogen analogue (VIII) of the hydroxy-ester affords a mixture of olefin (see below) and 3α-methoxycholestane (X). As the rate of elimination from an equatorial toluene-*p*-sulphonate is essentially base-insensitive,[11] methanolysis of the hydroxy-ester (III) was performed in the expectation that the reactions of type (c) and (d) would now proceed with the exclusion of the reaction leading to epoxide and *seco*-ketone (the relatively weak base and nucleophil, sodium acetate, was added to buffer the solution against toluene-*p*-sulphonic acid produced in the reaction, 5α-hydroxy-steroids being dehydrated by acid). As expected, the experiment gave the hydroxy-olefin (VI) and methyl ether (VII), accompanied by a negligible amount

[8] Henbest and Lovell, *J.*, 1957, 1965.

[9] The corresponding methanesulphonates had earlier been treated with potassium hydroxide in methanol, *epi*cholesterol (25%) being isolated by an unspecified procedure; Plattner, Fürst, Koller, and Lang, *Helv. Chim. Acta*, 1948, **31**, 1455. No *epi*cholesterol could be detected in our product, and it seems likely that their material arose from the 3α : 5α-epoxide (22% in our experiment) during chromatography on alumina (see later).

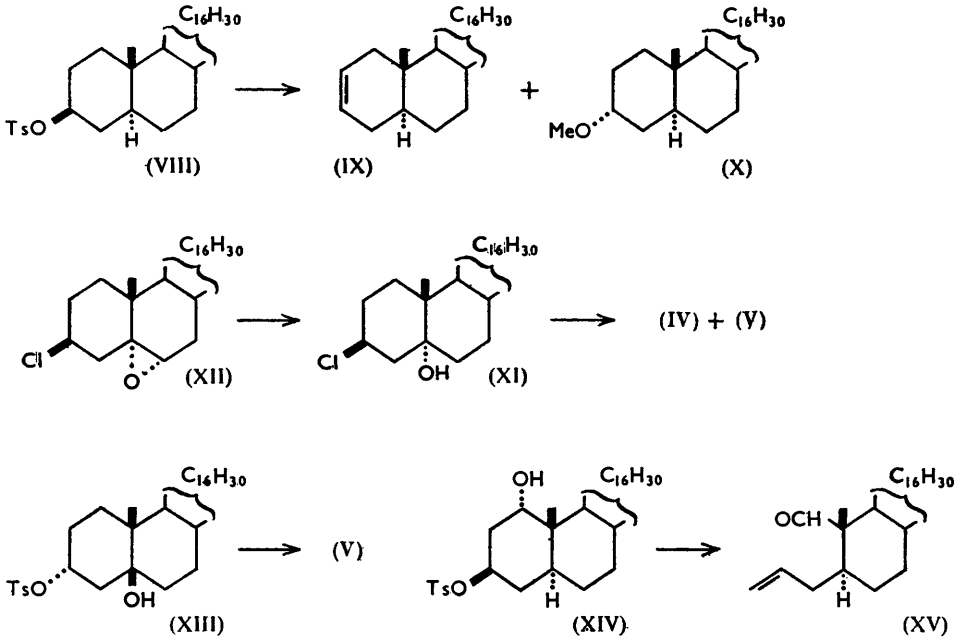
[10] Nace, *J. Amer. Chem. Soc.*, 1952, **74**, 5937.

[11] Winstein and Holness, *ibid.*, 1955, **77**, 5562.

of *seco*-ketone and epoxide. [In contrast to the 5α-hydrogen series, the methoxy-compound (VII) is eluted before the accompanying olefin (VI) owing to chelation in the former compound.] A related hydrolysis took place when the hydroxy-ester was adsorbed on to active (but damp) alumina, the olefinic alcohol (VI) and cholestane-3α : 5α-diol being subsequently eluted.

The methanolysis of cholestanyl toluene-*p*-sulphonate carried out by Nace was repeated to give cholestene (25%) and 3α-methoxycholestane (75%) : the ether : olefin ratio is higher in the 5-hydrogen than in the 5-hydroxyl series owing to hindrance to α-approach of solvent imposed by the axial 5α-hydroxy-group. This experiment was repeated as it had been suggested that the olefin formed is a mixture of equal parts of cholest-2- and -3-ene. However, the optical rotation of the product (confirmed by us) was close to that of the pure Δ^2-olefin (IX) and, moreover, we could detect no cholest-3-ene in the mixture by infrared measurements.[12] Thus, there is little doubt that the formation of the olefin is thermodynamically controlled (as in the 5-hydroxy-series). As expected, alkaline solvolysis of the 5-hydrogen-ester (VIII) was much slower in *tert.*-butyl alcohol than in methyl alcohol (Figure).

As an example of a 5α-hydroxycholestane with a different $C_{(3)}$-equatorial group for heterolysis, the 3β-chloro-compound (XI) was prepared by lithium aluminium hydride reduction of the 5 : 6-epoxide (XII). The reaction of the chloro-alcohol with potassium *tert.*-butoxide was much slower than that of the sulphonate (in agreement with their



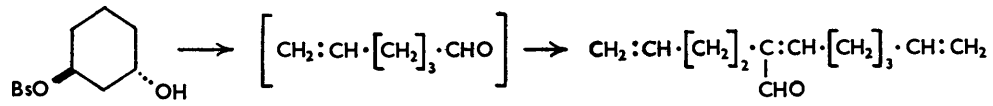
relative reactivities in simple S_N reactions); the epoxide and the *seco*-ketone were formed ultimately in the same proportion as before. With cholestane-3β : 5α-diol 3β-benzoate hydrolysis (regenerating diol) evidently proceeded rapidly relative to the formation of epoxide and *seco*-ketone, neither of which could be detected in the product.

(ii) The hydroxy-ester (XIII) of the coprostane series was treated with potassium *tert.*-butoxide in *tert.*-butyl alcohol. No 3β : 5β-epoxide was formed, the product being the pure *seco*-ketone (V). The rate of the reaction was similar to that of its isomer (III).

[12] Henbest, Meakins, and Wood, *J.*, 1954, 800.

(iii) Partial esterification of the secondary alcohol, cholestane-1α : 3β-diol, with toluene-*p*-sulphonyl chloride gave a monoester [assumed to be (XIV); cf. acetylation of the diol [13]], which with potassium *tert.*-butoxide afforded the *seco*-aldehyde (XV) as sole product. The reaction was much quicker than those of the 5-hydroxy-compounds, probably owing to the more acidic secondary 1-hydroxyl group's giving rise to a greater concentration of intermediate anion.

(iv) After completion of these experiments with steroids, monocyclic compounds were again investigated. The reaction between *cyclo*hexane-*trans*-1 : 3-diol mono-*p*-bromobenzenesulphonate (XVI; Bs = benzenesulphonyl) and potassium *tert.*-butoxide was complete in 30 min. at 30°. The only identifiable product was a $C_{(12)}$-unsaturated carbonyl com-

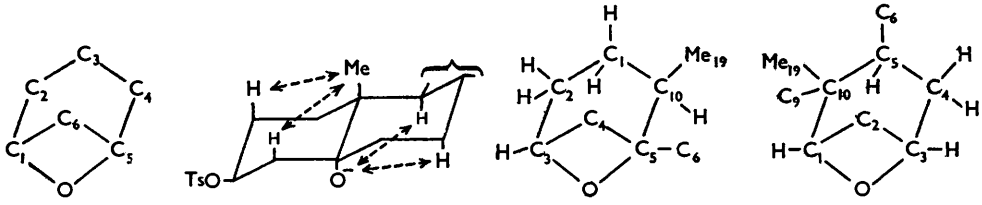


(XVI) (XVII) (XVIII)

pound, formulated as the aldehyde (XVIII) formed *via* aldol condensation of two molecules of the initial fission product (XVII) : condensation of *n*-butyraldehyde takes place under the same reaction conditions. No products as volatile as $C_{(6)}$-compounds (1 : 3-epoxy*cyclo*hexane or *cyclo*hex-3-en-1-ol) were detected by vapour-phase chromatography. Thus, as for the steroid disecondary compound (XIV), fission appears to be the only reaction taking place, the use of *tert.*-butoxide precluding formation of the *cyclo*hexenol obtained previously.

Thus, in reactions of types (a) and (b), proceeding *via* an intermediate anion, fission is the preferred reaction in the *cyclo*hexane series, an epoxide being (partially) formed in only one of the four systems studied. The difficulty in forming 1 : 3-epoxy*cyclo*hexanes may be due to the additional steric strains which have to be created : the four-membered oxide ring is approximately perpendicular to the remainder of the *cyclo*hexane ring which becomes altered so that atoms $C_{(1)}$ to $C_{(5)}$ (in XIX) become nearly coplanar and roughly in positions similar to those comprising a *cyclo*pentane ring. This distortion of the normal chair form of the *cyclo*hexane ring causes increased hydrogen eclipsing, especially in the $C_{(2)}$, $C_{(3)}$, and $C_{(4)}$ groups. Such eclipsing probably contributes largely to the greater heat of combustion per methylene group of *cyclo*pentane (158·7 kcal. mole^{-1}) than of *cyclo*hexane (157·4).[14]

It is left, therefore, to consider why some epoxide is formed from the hydroxy-ester (III). It is suggested that in this compound there are steric interactions of the solvated



(XIX) (XX) (XXI) (XXII)

(effectively large) oxygen atom and the angular methyl group with nearby axial CH groups (diagram XX), which help to force the $C_{(3)}$ atom towards the anion, thus assisting epoxide formation. The increased eclipsing in the region of $C_{(2)}$, $C_{(1)}$, and $C_{(10)}$ is counterbalanced by relief of strain during epoxide formation in the skew interactions indicated.

Although there are three skew interactions on the α-side of the coprostane hydroxy-ester (XIII) which might assist β-oxide formation, the bulky anion is now equatorial to

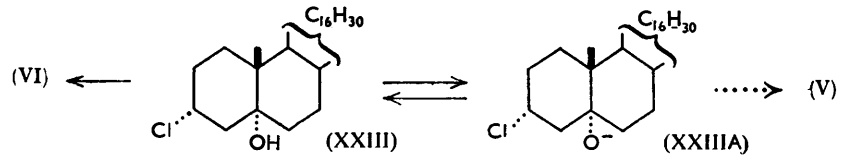
[13] Striebel and Tamm, *Helv. Chim. Acta*, 1954, **37**, 1094.
[14] Spitzer and Hofmann, *J. Amer. Chem. Soc.*, 1947, **69**, 211.

ring B and is only involved in one interaction (with the angular methyl group): these compressions are evidently not sufficient to promote oxide formation.

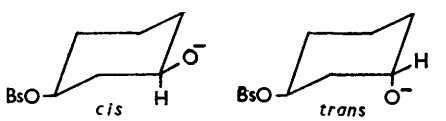
With the 1α-hydroxy-3β-ester (XIV) the interactions are very similar to those in the 5α-hydroxy-3β-ester (III) and yet no epoxide is produced. However, compared with either 5-hydroxy-compound, there is, with 1-hydroxy-ester, an additional factor preventing epoxide formation. Whereas in the linking of $C_{(3)}$ to the 5α-oxygen atom all the distortion is taken up in ring A (XXI), 1α : 3α-epoxide formation would involve simultaneous distortion of both linkages to ring B together with increased carbon eclipsing [$C_{(19)}$ methyl and $C_{(6)}$ methylene groups; see (XXII)].

The isolation of 3α : 5α-epoxycholestane is therefore probably exceptional as there are steric compressions sufficiently powerful to promote ring formation and yet the remainder of the molecule need not be greatly distorted. Formation of the 3α : 5α-epoxide may be compared with the ready solvolysis of cholesteryl toluene-*p*-sulphonate where participation of π-electrons from the 5 : 6-double bond can proceed to the extent of forming a covalent bond between $C_{(3)}$ and $C_{(5)}$.[15] In this reaction interactions between the angular methyl group and the axial hydrogen atom attached at $C_{(2)}$ and $C_{(4)}$ may again encourage movement of $C_{(3)}$ towards $C_{(5)}$ during the reaction. It would be interesting to carry out these reactions with steroids lacking the $C_{(19)}$ angular methyl group.

Stereochemistry of the Fission.—We have suggested [2] that the production of *seco*-ketone under such mild conditions from either of the 5-hydroxy-compounds (III) and (XIII) was a consequence of the parallel arrangement of the O–$C_{(3)}$ and the $C_{(4)}$–$C_{(5)}$ bond; this condition is also fulfilled in the *trans*-hydroxy-esters (XIV) and (XVI) where fission also occurs. The *cis*-chloro-alcohol (XXIII) with non-parallel Cl–$C_{(3)}$ and $C_{(4)}$–$C_{(5)}$ bonds was also treated with potassium *tert.*-butoxide. The only product isolated was cholest-2-en-5α-ol (VI), the infrared spectrum of the total product indicating that only a trace of *seco*-ketone was formed. It being assumed that some of the anion (XXIIIA) is generated under the experimental conditions, the result shows that fission does not occur when the bonds to be severed are in a (non-parallel) skew arrangement. The elimination observed was not especially rapid, its rate being similar to that of the conversion of the *trans*-isomer (XI) into epoxide and *seco*-ketone.



The rate of reaction of potassium *tert.*-butoxide with *cyclo*hexane-*cis*-1 : 3-diol mono-*p*-bromobenzenesulphonate was almost identical with that of the *trans*-isomer. Again the $C_{(12)}$ unsaturated aldehyde (XVIII) was obtained and no $C_{(6)}$-compounds were detected. For the fission the intermediate anions from the *cis*- and the *trans*-compound should be in the conformations shown (bonds to be broken being parallel).



The very close similarity between the two reactions shows that fission does not depend on the equatorial–axial arrangement of the bond to the anion. [Experiments with related acyclic hydroxy-esters will be reported later.]

Reactions of the New Steroid Compounds.—The 3α : 5α-epoxide (IV) with dilute acid

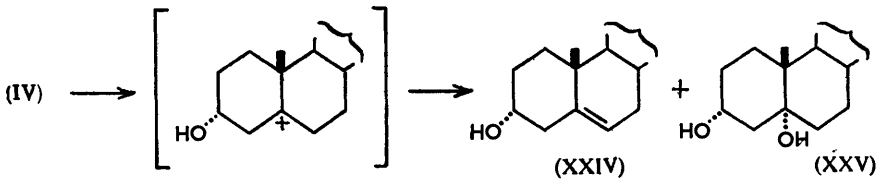
[15] Solvolysis of esters of the analogous 7β-hydroxy-Δ⁴-steroids leads to retention of configuraton at $C_{(7)}$ and no 5 : 7-*cyclo*steroid; cf. Shoppee, Summers, and Williams, *J.*, 1956, 1893.

gave a mixture of *epi*cholesterol (XXIV) and the 3α : 5α-diol (XXV), both of which could arise *via* a $C_{(5)}$ carbonium ion. Retention of configuration at $C_{(5)}$ in the formation of the diol is noteworthy, as the hydration of epoxides usually gives *trans*-diols. However, retention of configuration has been observed [15] in the formation of 5α : 8α-epoxides from 5α : 8α-diols, and it appears that the intermediate carbonium ions in these reactions are sufficiently long-lived before reaction with an external or an internal nucleophil.

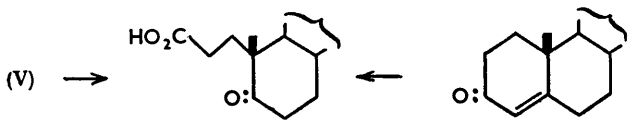
With boron trifluoride–ether complex in benzene the 3α : 5α-epoxide afforded a high yield of epicholesterol. Chromatographic alumina also seemed to act as a Lewis acid, for although the mixtures of epoxide and *seco*-ketone could be partially separated, isomerisation of the former to epicholesterol was very difficult to avoid. For the quantitative estimation of products, treatment with boron trifluoride followed by ready separation of *seco*-ketone and epicholesterol was used.

The epoxide was unaffected by boiling methanol containing potassium methoxide. It was not reduced by lithium aluminium hydride at room temperature, and this provided the basis for the most convenient method for isolating the pure epoxide, which could easily be separated by chromatography from the alcohol produced by reduction of the *seco*-ketone.

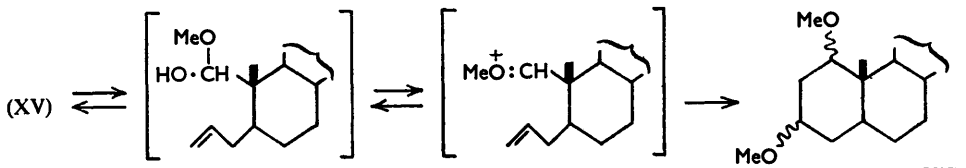
The structure of the *seco*-ketone was confirmed by its infrared absorption spectrum, by formation of a yellow 2 : 4-dinitrophenylhydrazone, and by ozonolysis to formaldehyde and the oxo-acid (XXVI), also produced [16] from cholest-4-en-3-one.



(XXIV) (XXV)



(XXVI)



(XXVII)

In contrast, the *seco*-aldehyde (XV) did not afford a dinitrophenylhydrazone in acidic methanol solution, being transformed instead into a colourless crystalline product, whose properties suggested a dimethoxycholestane structure : the same compound was produced in the absence of 2 : 4-dinitrophenylhydrazine. The colourless compound is probably one of the four possible 1 : 3-dimethoxy-compounds (XXVII) formed by a Prins reaction as suggested in the flow-chart. The non-formation of a 2 : 4-dinitrophenylhydrazone cannot be ascribed solely to hindrance imposed by the adjacent quaternary carbon group, as pivalaldehyde and pinacone readily give derivatives. Under the conditions wherein the presumed 1 : 3-dimethoxy-compound is formed, the *seco*-ketone (V) is almost

[16] Clayton, Henbest, and Jones, *J.*, 1953, 2015.

unaffected: ketones are generally less reactive than aldehydes, and the conformation of the alkyl side-chain in the *seco*-ketone may be less favourable for cyclisation than that in (XV).

From several of the experiments with the 5α-hydroxy-3-sulphonates an unsaturated alcohol with the same physical constants was obtained. This appears to be the pure Δ^2-5α-alcohol, and the presence of the Δ^3-5α-alcohol has not been detected. The structure is confirmed by (*a*) hydrogenation to cholestan-5α-ol, (*b*) formation of a single epoxide (2α : 3α) showing hydrogen bonding between the epoxy- and the hydroxy-groups, (*c*) lack of reactivity towards thionyl chloride under conditions where an allylic alcohol would be expected to give a chloro-compound (cf. conversion of a 5α-hydroxy-Δ^6-steroid into a 7α-chloro-Δ^5-compound [17]), and (*d*) optical-rotation evidence. As in the 5α-hydrogen series, elimination gives the more stable compound with the double bond opposite the bridge-head positions.

Experimental

Preparation of Sulphonic Esters.—cyclo*Hexane*-cis-1 : 3-*diol*. The diol (5 g.) and *p*-bromobenzenesulphonyl chloride (11 g.) were kept in pyridine (50 c.c.) at 0° for 24 hr. The product was isolated with chloroform, and then adsorbed from benzene–light petroleum (1 : 1; 250 c.c.) on to deactivated alumina (500 g.). Elution with the same solvent (1·5 l.) gave the *diester* (0·42 g.), needles (from ether), m. p. 115—117° (Found: C, 39·25; H, 3·3. $C_{18}H_{18}O_6S_2Br_2$ requires C, 39·0; H, 3·3%). Further elution with this mixture (0·5 l.) gave some oil (40 mg.), which was discarded. Elution with benzene–ether (1 : 1; 1 l.) afforded the *monoester* (12 g., 83%) as plates (from ether–light petroleum), m. p. 74—76° (Found: C, 42·8; H, 4·4. $C_{12}H_{15}O_4SBr$ requires C, 43·0; H, 4·5%).

cyclo*Hexane*-trans-1 : 3-*diol*. Similar treatment of the *trans*-diol gave the *diester* as plates (from ether), m. p. 154—155° (decomp.) (Found: C, 39·4; H, 3·4%), and the *monoester* (XVI), m. p. 60—61° (Found: C, 43·2; H, 4·6%).

Cholestane-3β : 5α-*diol*. The diol (1·7 g.) and toluene-*p*-sulphonyl chloride (1·7 g.) were kept in pyridine (20 c.c.) at 20° for 24 hr. The product was isolated with ether and chromatographed on deactivated alumina (100 g.). Elution with benzene afforded the ester (III) (2·3 g.) which crystallised from nitromethane as plates, m. p. 128—129° (decomp.), $[\alpha]_D$ −1° (Found: C, 73·2; H, 9·7. $C_{34}H_{54}O_4S$ requires C, 73·1; H, 9·75%). Ultraviolet absorption (in EtOH): $\lambda_{max.}$ 2250 Å; ε = 12,700. This compound was also obtained in a form with m. p. 143—145° (decomp.).

Cholestane-1α : 3β-*diol*. The diol (0·5 g.) and toluene-*p*-sulphonyl chloride (0·3 g.) were kept in pyridine (10 c.c.) at 20° for 24 hr. The product was isolated with ether, and then chromatographed on deactivated alumina (25 g.). Elution with benzene (200 c.c.) gave the 3β-*monoester* (XIV) (0·6 g., 85%) as prisms (from nitromethane), m. p. 135—137°, $[\alpha]_D$ +17·5° (Found: C, 73·4; H, 9·6. $C_{34}H_{54}O_4S$ requires C, 73·1; H, 9·75%). Ultraviolet absorption (in EtOH): $\lambda_{max.}$ 2250 Å; ε = 12,000.

Coprostane-3α : 5β-*diol*. The diol (1 g.) and toluene-*p*-sulphonyl chloride (1 g.) were kept in pyridine (5 c.c.) overnight at 20°. Isolation with and crystallisation from ether, gave the *ester* (XIII) (1·05 g., 75%) as prisms, m. p. 120—124°, $[\alpha]_D$ +36° (Found: C, 72·75; H, 9·55. $C_{34}H_{54}O_4S$ requires C, 73·1; H, 9·75%).

Reaction of 5α-*Hydroxycholestan*-3β-*yl Toluene*-p-*sulphonate* (III) *with Potassium* tert.-*Butoxide*.—Solutions of the ester (2 g.) in *tert.*-butyl alcohol (180 c.c.) and molar potassium *tert.*-butoxide (7 c.c.; 2 mol.) were mixed at 50° (potassium toluene-*p*-sulphonate began to precipitate almost immediately), and kept at 50° for 2 hr. The product (1·355 g., 98%) was isolated with ether.

One portion (0·41 g.) in dry benzene (25 c.c.) was treated with freshly distilled boron trifluoride–ether complex (0·5 c.c.) for 15 min. at 20° in order to isomerise the 3 : 5-epoxide to epicholesterol (see below). The product was isolated with ether and chromatographed on deactivated alumina (25 g.). Elution with light petroleum (200 c.c.) gave 4 : 5-seco*cholest*-3-*en*-5-*one* (V) (155 mg., 37%) as an oil, $[\alpha]_D$ +37°, n_D^{20} 1·5036 (Found: C, 83·65; H, 12·0. $C_{27}H_{46}O$ requires C, 83·85; H, 12·0%). Infrared absorption (in CS_2): bands at 1700 (ketone).

[17] Cf. Turner, *J. Amer. Chem. Soc.*, 1950, **72**, 579.

3040, 1637, and 910 cm.$^{-1}$ (vinyl group). Further elution of the chromatogram with ether (100 c.c.) gave *epi*cholesterol (220 mg., 53%) as plates (from methanol), m. p. 140—142°, $[\alpha]_D$ −37° (lit. values : m. p. 141·5°, $[\alpha]_D$ −35°).

The second portion (0·945 g.) in dry ether (50 c.c.) was treated with lithium aluminium hydride (150 mg.) for 30 min. at 20°. The product was isolated with ether and chromatographed on deactivated alumina (50 g.). Elution with light petroleum (300 c.c.) afforded 3α : 5α-*epoxycholestane* (IV) (530 mg., 55%), as needles (from acetone), m. p. 82—86°, $[\alpha]_D$ +59° (Found : C, 84·0; H, 11·95. $C_{27}H_{46}O$ requires C, 83·85; H, 12·0%). This compound showed no appreciable absorption in the ultraviolet region; in the infrared region it showed a single strong band at 890 cm.$^{-1}$. Further elution of the chromatogram gave 4 : 5-*seco*cholest-3-en-5-ol (380 mg., 39%) as a gum, which was dissolved in acetone (50 c.c.) and oxidised with 8N-chromic acid solution (0·5 c.c.) at 20° for 15 min. Isolation with ether and filtration through alumina afforded 4 : 5-*seco*cholest-3-en-5-one (260 mg.), $[\alpha]_D$ +38°; the infrared spectrum was identical with that of the material obtained directly from the fission.

In an earlier experiment in which a much larger proportion of potassium *tert.*-butoxide was used, a small amount (2%) of 3α-tert.-*butoxycholestan*-5α-*ol* was also isolated (by chromatography). This compound crystallised from methanol as needles, m. p. 94—95°, $[\alpha]_D$ +11° (Found : C, 80·5; H, 12·0. $C_{31}H_{56}O_2$ requires C, 80·8; H, 12·25%). The infrared absorption spectrum demonstrated the existence of chelation in the compound.

The *seco*-ketone (V) was characterised as its 2 : 4-*dinitrophenylhydrazone*, yellow needles (from ethanol), m. p. 145—150° (with change of form) (Found : C, 70·0; H, 9·0. $C_{33}H_{50}O_4N_4$ requires C, 69·95; H, 8·9%). Ultraviolet absorption (in EtOH) : $\lambda_{max.}$ 2640 Å; ε = 23,400.

Reactions of 3α : 5α-*Epoxycholestane*.—Freshly distilled boron trifluoride–ether complex (0·1 g.) was added to the epoxide (1 g.) in dry benzene (10 c.c.), the resulting clear solution then being kept at 20° for 15 min. The product was isolated in the usual way and crystallised from methanol yielding *epi*cholesterol (XXIV) (0·8 g.) as plates, m. p. 141—143°, $[\alpha]_D$ −45° (Found : C, 84·1; H, 12·2. Calc. for $C_{27}H_{46}O$: C, 83·85; H, 12·0%). Acetylation gave *epi*cholesteryl acetate, m. p. 83—86°, $[\alpha]_D$ −12° (literature values for the alcohol, m. p. 141·5°, $[\alpha]_D$ −35° : for the acetate, m. p. 84—85°, $[\alpha]_D$ −12·5°).

The epoxide (125 mg.) in ethanol (8 c.c.) containing concentrated hydrochloric acid (50 mg.) was kept at 20° for 30 min. The product was isolated with ether and chromatographed on deactivated alumina (10 g.). Light petroleum eluted unchanged epoxide (40 mg.), m. p. 70—80° (impure). Light petroleum–benzene (9 : 1) eluted *epi*cholesterol (50 mg.), m. p. and mixed m. p. 140—142° (from methanol), $[\alpha]_D$ −43°. Ether–methanol (9 : 1) eluted cholestane-3α : 5α-diol (XXV) (20 mg.), flat needles (from ethyl acetate), m. p. 202—204°, $[\alpha]_D$ +16° (Found : C, 80·1; H, 11·8. Calc. for $C_{27}H_{48}O_2$: C, 80·15; H, 12·0%) (lit. values for the 3α : 5α-diol, m. p. 199°, $[\alpha]_D$ +17°).

Ozonolysis of the seco-*Ketone* (V).—The ketone (0·4 g.) in ethyl acetate (30 c.c.) was treated at −70° with a saturated (at −70°) solution of ozone in ethyl acetate until a slight blue colour persisted. The solution was shaken with ferrous sulphate solution, separated, and evaporated to give a gum that was dissolved in alcoholic ammoniacal silver nitrate solution and kept at 20° overnight. The acidic product (0·11 g.) was isolated with ether and crystallised from methanol to yield the oxo-acid (XXVI), m. p. 154·5—156°, $[\alpha]_D$ +35° (Found : C, 77·5; H, 11·0. Calc. for $C_{26}H_{44}O_3$: C, 77·2; H, 11·0%). A specimen prepared by ozonolysis of cholest-4-en-3-one had the same physical constants (including infrared spectrum).

In another experiment the ketone (0·28 g.) was dissolved in acetic acid (10 c.c.) and ozonised oxygen passed through the solution for 2 hr. The solution was steam-distilled into dimedone solution to yield the formaldehyde derivative (70 mg.), which after crystallisation from aqueous methanol had m. p. and mixed m. p. 192—193°.

Reaction of 5α-*Hydroxycholestan*-3β-*yl Toluene*-p-*sulphonate with Potassium Methoxide*.—Solutions of the steroid (2·7 g.) in methanol (250 c.c.) and molar potassium methoxide solution (10 c.c.) were mixed and heated under reflux for 24 hr. The product was isolated with ether and chromatographed on alumina (200 g.). Elution with light petroleum–benzene (3 : 2; 800 c.c.) gave an oil (*A*) (455 mg.), $[\alpha]_D$ +40°, whose infrared spectrum indicated a mixture of the 3α : 5α-epoxide (IV) and the *seco*-ketone (V). Further elution with the same mixture afforded an oil (*B*) (73 mg.), $[\alpha]_D$ +25°, whose infrared spectrum indicated a mixture of *seco*-ketone and 3α-methoxycholestan-5α-ol. Elution with light petroleum–benzene (1 : 1; 1 l.) gave 3α-*methoxycholestan*-5α-*ol* (VII) (540 mg.), needles (from aqueous acetone), m. p. 91—93°,

$[\alpha]_D$ +12·5° (Found: C, 80·5; H, 12·05. $C_{28}H_{50}O_2$ requires C, 80·3; H, 12·0%). Elution with benzene–ether (4 : 1; 1·2 l.) gave *cholest-2-en-5α-ol* (VI) (555 mg.), needles (from aqueous methanol), m. p. 93—95°, $[\alpha]_D$ +52° (Found: C, 83·8; H, 11·85. $C_{27}H_{46}O$ requires C, 83·9; H, 12·0%). Ether–methanol (49 : 1; 1 l.) eluted epicholesterol (150 mg.), m. p. 139—141°, $[\alpha]_D$ −38°. Fraction (*A*) was treated with boron trifluoride–ether complex in benzene and the product chromatographed, giving the *seco*-ketone (183 mg.) and *epi*cholesterol (260 mg.). The physical properties of fraction (*B*) showed that it was a mixture of equal amounts of the *seco*-ketone and the methoxy-alcohol. The yields of the four products are thus estimated to be: 3α : 5α-epoxide (22%), *seco*-ketone (12%), methoxy-alcohol (29%), and cholest-2-en-5α-ol (30%).

From the rotations of cholestane, cholestan-5α-ol, and cholest-2-ene, that of cholest-2-en-5α-ol can be estimated as about +52°, in good agreement with the value obtained. Further reactions of the unsaturated alcohol are given below.

*Methanolysis of 5α-Hydroxycholestan-3β-yl Toluene-*p*-sulphonate.*—The steroid (720 mg.) and potassium acetate (1 g.) were heated under reflux in methanol (100 c.c.) for 24 hr. The product was isolated with ether, and then chromatographed on alumina (50 g.). Elution with benzene (300 c.c.) gave 3α-methoxycholestan-5α-ol (150 mg.; 28%), needles (from acetone), m. p. 91—92°, $[\alpha]_D$ +13°. Elution with ether (450 c.c.) afforded cholest-2-en-5α-ol (240 mg.; 48%), m. p. 93—95°, $[\alpha]_D$ +53° (from aqueous methanol). The infrared spectrum of the reaction product showed that the 3α : 5α-epoxide and the *seco*-ketone had not been formed in any significant quantity.

*Treatment of 5α-Hydroxycholestan-3β-yl Toluene-*p*-sulphonate with Alumina.*—The steroid (1 g.) was adsorbed on active alumina (100 g.). Elution with benzene gave a small amount of oil (discarded). Benzene–ether (19 : 1; 1 l.) eluted cholest-2-en-5α-ol (0·4 g.; 58%), m. p. 93—95°, $[\alpha]_D$ +53° (from aqueous methanol). Elution with ether–methanol (49 : 1; 400 c.c.) gave cholestane-3α : 5α-diol (0·1 g.; 15%), m. p. 196—199°, $[\alpha]_D$ +19° (from aqueous methanol).

Reaction of 3β-Chlorocholestan-5α-ol with Potassium tert.*-Butoxide.*—M-Potassium *tert.*-butoxide (0·8 c.c., 2 mol.) was added to a solution of the steroid (156 mg.) in *tert.*-butyl alcohol (20 c.c.), the mixture being heated under reflux for 8 hr. The product was an oil (137 mg.; 96%) whose infrared spectrum showed it to be a mixture of the 3α : 5α-epoxide and the 4 : 5-*seco*-ketone in the same proportion as obtained from the toluene-*p*-sulphonate.

5α-Hydroxycholestan-3β-yl Benzoate.—Cholestane-3β : 5α-diol (0·5 mg.) was treated with benzoyl chloride (0·3 c.c.) in pyridine (10 c.c.) for 30 min. at 20°. The *benzoate* (0·54 g.) crystallised from methanol as needles, m. p. 157°, resolidifying to plates, m. p. 179°, $[\alpha]_D$ +14° (Found: C, 80·45; H, 10·3. $C_{34}H_{54}O_3$ requires C, 79·95; H, 10·7%). The benzoate (0·51 g.) in *tert.*-butyl alcohol (50 c.c.) was treated with M-potassium *tert.*-butoxide (2 c.c.), the mixture being heated under reflux for 3·5 hr. Isolation in the usual way gave cholestane-3β : 5α-diol (0·39 g.), m. p. 220—222°.

*Reaction of 5β-Hydroxycoprostan-3α-yl Toluene-*p*-sulphonate* (XIII) *with Potassium* tert.*-Butoxide.*—The reaction was carried out as described for the cholestane isomer, except that the reaction time was 1 hr. The product appeared to consist only of the *seco*-ketone (V), $[\alpha]_D$ +38°, with infrared absorption identical with those of previous pure samples. The same 2 : 4-dinitrophenylhydrazone was also prepared.

*Reaction of 1α-Hydroxycholestan-3β-yl Toluene-*p*-sulphonate* (XIV) *with Potassium* tert.*-Butoxide.*—The steroid (0·28 g.) in *tert.*-butyl alcohol (25 c.c.) was treated with M-*tert.*-butoxide (1 c.c.) for 30 min. at 50°. Isolation in the usual way gave 1 : 2-seco*cholest-2-en-1-al* (0·19 g.; 98%) as an oil, $[\alpha]_D$ +16°. This was adsorbed on neutral alumina and eluted with light petroleum: the infrared spectra (in CS_2) of successive fractions were identical with that of the crude material, with peaks at 2655 and 1715 (aldehyde), 3050, 1635, 990, and 910 cm.$^{-1}$ (vinyl group). A satisfactory analysis was not obtained on the small sample available (Found: C, 82·4; H, 11·8. $C_{27}H_{46}O$ requires C, 83·9; H, 12·0%). Treatment of the aldehyde with a 5% solution of sulphuric acid in methanol at 20° for 24 hr. gave a *compound* (probably a 1 : 3-dimethoxycholestane), m. p. 70—75°, $[\alpha]_D$ +23° (Found: C, 80·15; H, 11·85. $C_{29}H_{52}O_2$ requires C, 80·5; H, 12·1%). This compound gave no colour with tetranitromethane and showed no end absorption in the ultraviolet region. In the infrared region the compound showed a peak at 1090 cm.$^{-1}$, but no hydroxyl or carbonyl bands.

*Methanolysis of Cholestan-3β-yl Toluene-*p*-sulphonate* (VIII).—The steroid (0·2 g.) in dry methanol (25 c.c.) was heated under reflux for 72 hr., the product then being isolated and chromatographed on alumina. Pentane (20 c.c.) eluted cholest-2-ene (34 mg., 25%), m. p. 72—74°,

$[\alpha]_D$ +65° (from acetone). Further elution with pentane (50 c.c.) gave 3α-methoxycholestane (114 mg., 75%), m. p. 63—66°, $[\alpha]_D$ +20° (from acetone). The infrared spectrum of the hydrocarbon fraction gave no indication of cholest-3-ene. Pure cholest-2-ene has $[\alpha]_D$ +66°, pure cholest-3-ene $[\alpha]_D$ +56°.

Reaction of 3α-*Chlorocholestan*-5α-*ol* (XXIII) *with Potassium* tert.-*Butoxide*.—M-Potassium *tert.*-butoxide (2 c.c.) was added to the steroid (0·42 g.) in *tert.*-butyl alcohol (50 c.c.) and the mixture heated under reflux for 16 hr. The product (0·28 g.) was chromatographed on alumina (30 g.), the only crystalline product being cholest-2-en-5α-ol (0·21 g., 55%), m. p. and mixed m. p. 94—95°. The infrared spectrum of the total product showed the presence of only a trace of ketonic material.

Reactions of Cholest-2-*en*-5α-*ol* (VI).—*Hydrogenation*. The steroid (50 mg.) in ethyl acetate (10 c.c.) was shaken with hydrogen in the presence of Adams's catalyst (50 mg.) for 16 hr Crystallisation of the product from aqueous methanol afforded cholestan-5α-ol, m. p. 101—103°, $[\alpha]_D$ +16°. This was identical with a sample (m. p. 101—103°; $[\alpha]_D$ +17°) prepared by reduction with lithium aluminium hydride of pure 5α : 6α-epoxycholestane.

Thionyl chloride. The steroid (47 mg.) in dry ether at 0° was treated with thionyl chloride (0·1 c.c.). The solution was kept at 20° for 1 hr., and the product, after crystallisation from acetone, gave starting material (33 mg.), m. p. and mixed m. p. 92—94°.

Peracid. Solutions of the steroid (0·34 g.) in dry ether (10 c.c.) and monoperphthalic acid in ether (3 c.c.; 1·2N-solution) were mixed and then kept at 20° for 3 hr. Crystallisation of the product from methanol afforded 2α : 3α-*epoxycholestan*-5α-*ol* (0·28 g.) as plates, m. p. 144—145°, $[\alpha]_D$ +32° (Found: C, 80·3; H, 11·45. $C_{27}H_{46}O_2$ requires C, 80·5; H, 11·5%). The position and intensity of the OH band at 3500 cm.$^{-1}$ were similar to those of peaks given by other 3α : 5α-dioxy-compounds.[8] Reduction of the epoxide with lithium aluminium hydride gave cholestane-3α : 5α-diol, m. p. and mixed m. p. 196—198°.

Reaction of cyclo*Hexane*-cis-1 : 3-*diol Mono*-p-*bromobenzenesulphonate with Alkali*.—M-Potassium *tert.*-butoxide (35 c.c., 2 mol.) was added to a solution of the ester (5·65 g.) in *tert.*-butyl alcohol (110 c.c.), and the pale yellow solution was then kept at 30° under nitrogen for 45 min. Isolation with ether gave a yellow oil [1·4 g.; 100% based on formation of (XVIII)], which was distilled at 10^{-4} mm.:

Fraction	Bath temp.	Wt. (mg.)	n_D^{21}	$E_{1\,cm.}^{1\%}$ at 2290 Å
1	80°	200	1·4790	465
2	80—110	50	1·4850	400
3	110—115	500	1·4940	127
4	115—135	50	1·4962	—

There was a brown polymeric residue (*ca.* 0·5 g.). The declining intensities at $\lambda_{max.}$ (2290 Å in EtOH) were paralleled in the infrared region by a decrease in the intensities of the aldehyde bands (2700 and 1690 cm.$^{-1}$) relative to the vinyl bands (910 and 990 cm.$^{-1}$). The later fractions also showed an increasing amount of hydroxylic material (bands at 3530 and 3600 cm.$^{-1}$). [2-Ethylhex-2-en-1-al showed ultraviolet absorption (in pentane) $\lambda_{max.}$ 2250 Å (ε = 19,200).]

Fraction 1 was converted into the 2 : 4-*dinitrophenylhydrazone* which was purified chromatographically (0·25 g.) followed by several crystallisations from methanol, giving red needles, m. p. 115—116° (Found: C, 60·3; H, 6·4. $C_{18}H_{22}O_4N_4$ requires C, 60·3; H, 6·2%). Ultraviolet absorption (in $CHCl_3$): $\lambda_{max.}$ 3790 Å (ε = 29,200). The absorption of the derivative of the related 2-ethylhex-2-en-1-al has been given (in $CHCl_3$) as: $\lambda_{max.}$ 3850 Å (ε = 27,000).

Reaction of the trans-*Ester* (XVI) *with Alkali*.—Solutions of the ester (2 g.) in *tert.*-butyl alcohol (250 c.c.) and M-potassium *tert.*-butoxide (80 c.c., 2 mol.) were mixed and then kept at 30° under nitrogen for 45 min. Isolation with ether gave a yellow oil (2·7 g.; 95% based on formation of XVIII) which was fractionated at 10^{-4} mm. in 4 fractions, leaving much polymeric residue. Fraction 1 gave a good yield of the same 2 : 4-dinitrophenylhydrazone, m. p. 115—116°, as was obtained from the *cis*-ester. The infrared absorptions of each subsequent fraction were very similar to those of the corresponding fractions from the *cis*-ester.

Attempted Detection of C_6-*Compounds from the Hydroxy*cyclo*hexyl Bromobenzenesulphonates*.—A solution of each ester (40 mg.) in *tert.*-butyl alcohol (0·5 c.c.) was treated with M-potassium *tert.*-butoxide (0·15 c.c.; 2 mol.) at 20° for 1 hr. Potassium *p*-bromobenzenesulphonate quickly separated and the solution became lemon-yellow. Some of each solution was introduced into a vapour-phase chromatography unit with a column (temp. 118°) packed with Johns Manville

Celite 545 impregnated with di-*n*-nonyl phthalate. No C_6-compound could be detected in either reaction solution : the C_6-compounds present in a dilute solution of 1 : 2-epoxy*cyclo*hexane and *cyclo*hex-3-en-1-ol in *tert.*-butyl alcohol were readily detected by chromatography under these conditions.

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