# SYNTHESIS AND REARRANGEMENT REACTIONS OF 4α-BROMO-5β-CHOLESTANE-3β,5-DIOL 3-ACETATE

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*Summary*

The structure of the bromohydrin 4α-bromo-5β-cholestane-3β,5-diol 3-acetate (V), obtained by the addition of hypobromous acid to cholest-4-en-3β-ol 3-acetate, has been proved conclusively by an unequivocal synthesis from cholest-3-ene-5β-ol.

An equilibrium mixture (approx. 1:2) of (V) and the isomeric bromohydrin 5-bromo-5α-cholestane-3β,4β-diol 3-acetate (IV;R = Ac) [prepared[1] by the addition of HBr to 4β,5-epoxy-5β-cholestan-3β-ol 3-acetate (I; R = Ac)] resulted when either pure isomer was refluxed with a trace of mineral acid in an inert solvent.

The 4β-hydroxy-5α-bromo derivative (IV; R = Ac) can be acetylated or oxidized without rearrangement. Interestingly, under mild conditions of acetylation or oxidation, the isomeric bromohydrin (V) (having a tertiary 5β-hydroxyl) reacted with rearrangement to give 5-bromo-5α-cholestane-3β,4β-diol 3,4-diacetate (II; $R_1 = R_2 =$ Ac) or 5-bromo-5α-cholestan-4β-ol-3-one 4-acetate (VI), respectively.

The acetylation of (V) to (II; $R_1 = R_2 =$ Ac) does not proceed via equilibration of (V) with (IV; R = Ac) and acetylation of the latter. Rather, it has been shown that through participation of the 5β-hydroxyl, migration of the 3-acetate to the 4-position occurs with concomitant shift of the 4α-bromine to the 5α-position, displacement of the 5β-hydroxyl, and acetylation at C3. Evidence for this mechanism follows from the fact that treatment of (V) with benzoyl chloride in pyridine afforded a benzoate *different* from that (II; $R_1$ = Ac, $R_2$ = Bz) obtainable from (IV; R = Ac), and identical with the 3-benzoate 4-acetate (II; $R_1$ = Bz, $R_2$ = Ac) which was synthesized from 4β,5-epoxy-5β-cholestan-3β-ol 3-benzoate (I; R = Bz) via 5-bromo-5α-cholestane-3β,4β-diol 3-benzoate (IV; R = Bz). The proposed mechanism is supported by other evidence.

It is suggested that the oxidative rearrangement of (V) to (VI) proceeds by a mechanism similar to that which operates in the acylation–rearrangement reaction, differing only in oxidation rather than acylation at C3.

## I. INTRODUCTION

The present investigation was prompted by the observation that the physical constants [m.p. 143–145°C (decomp.), $[\alpha]_D$+18°] of 5-bromo-5α-cholestane-3β,4β-diol 3-acetate (IV; R = Ac), prepared[1] by the addition of hydrobromic acid to 4β,5-epoxy-5β-cholestan-3β-ol 3-acetate (1; R = Ac) were similar to those of the bromohydrin, m.p. 147°C (decomp.), $[\alpha]_D$+32° which had been prepared by the addition of hypobromous acid to cholest-4-en-3β-ol 3-acetate (III), and had been assigned the isomeric structure 4α-bromo-5β-cholestane-3β,5-diol 3-acetate (V).[2]

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[1] Fieser, L. F., Goto, T., and Bhattacharyya, B. K. (1960).—*J. Amer. Chem. Soc.* **82**: 1700.

[2] Collins, D. J. (1959).—*J. Chem. Soc.* **1959**: 3919.

To facilitate discussion, the bromohydrin (IV: R = Ac) prepared by the addition of hydrobromic acid to the epoxide (I; R = Ac) will be hereinafter referred to as the "HBr–epoxide" bromohydrin, and that obtained by reaction of the olefin (III) with hypobromous acid, as the "HOBr–olefin" bromohydrin.

In spite of evidence presented for structures (IV; R = Ac) and (V), for the HBr–epoxide, and HBr-olefin bromohydrins respectively, the possibility that both compounds may have *either* one of these structures made it desirable to make a direct comparison of the two bromohydrins. That they are in fact different, was shown by depression of their mixed melting point, and by their infrared spectra. However, further investigation has shown that the structural assignments, although correct in each case, were made fortuitously. Apart from consideration of the principle of diaxial fission of epoxides[3] the only evidence given for the structure of the HBr-epoxide bromohydrin (IV; R = Ac) was that acetylation gave the diacetate (II; $R_1 = R_2 = Ac$), indicating the presence of a secondary hydroxyl.[1] We have now found that the isomeric HOBr-olefin bromohydrin (V) can *also* be converted to the 3,4-diacetate (II; $R_1 = R_2 = Ac$) by reaction with acetic anhydride in pyridine overnight at room temperature. In fact, this reaction proceeds more rapidly and more cleanly than the acetylation of the 4β-axial hydroxyl of (IV; R = Ac); the latter reaction was incomplete after 24 hr at room temperature.

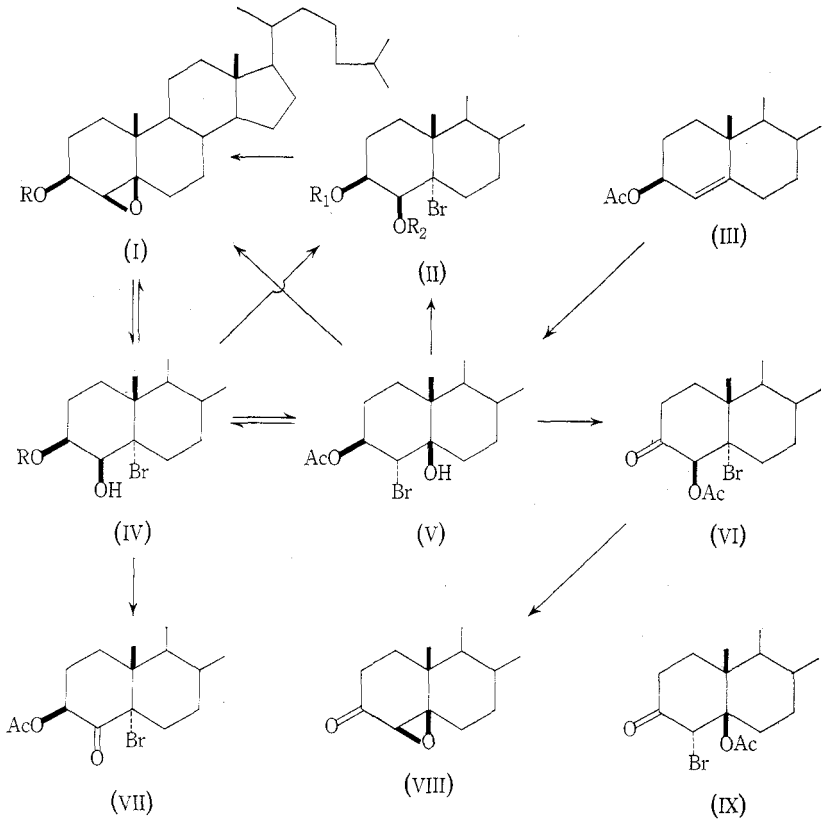
Apart from the demonstration that the hydroxyl group of (V) had to have the β-configuration, the main evidence for structure (V) for the HOBr–olefin bromohydrin was that it failed to react with chromic acid in acetone, indicating that the hydroxyl group was tertiary.[2] Re-examination of this reaction has shown that when the oxidation mixture is allowed to stand for the usual period of 10 min before being worked up, about 25% of unreacted bromohydrin can indeed be isolated. If, however, the reaction mixture is allowed to stand overnight at room temperature, the bromohydrin (V) is smoothly oxidized to a ketone (VI), m.p. 126–127°C (decomp., capillary), $[\alpha]_D +99 \cdot 2°$ which differed from the ketone (VII), m.p. 139–140·5°C, $[\alpha]_D +85 \cdot 4°$ obtained by brief chromic acid–acetone oxidation of the "HBr-epoxide bromohydrin" (IV).

It was evident that whichever bromohydrin has the tertiary 5β-hydroxyl [structure (V)] was readily undergoing rearrangement under the mild conditions of acetylation and oxidation. Although the HOBr-olefin bromohydrin, which was the more slowly oxidized, probably had the tertiary hydroxyl [i.e. structure (V)], the fact that both bromohydrins could be acetylated, and oxidized, left their structures in doubt.

That no skeletal rearrangement had occurred during formation of (II; $R_1 = R_2 = Ac$) from either (IV; R = Ac) or (V) was shown by its rapid conversion with methanolic potassium hydroxide at room temperature to 4β,5-epoxy-5β-cholestan-3β-ol (I; R = H). Both bromohydrins (IV; R = Ac) and (V) upon treatment with Merck "Neutral" alumina, or with potassium acetate in refluxing methanol yielded 4β,5-epoxy-5β-cholestan-3β-ol 3-acetate (I; R = Ac). In fact, the treatment of the crude HOBr-olefin bromohydrin (V) with methanolic potassium acetate under reflux is the most convenient method of preparation of (I; R = Ac).

[3] Barton, D. H. R., and Cookson, R. C. (1956).—*Quart. Rev. Chem. Soc. Lond.* **10**: 44.

Further information on the structures of the isomeric bromohydrins (IV; R = Ac) and (V) could best be obtained from a study of the derived ketones. The ultraviolet spectrum of the ketone (VII), m.p. 139–140·5°C, obtained by oxidation of the HBr-epoxide bromohydrin (IV; R = Ac) showed $\lambda_{max.}$ (cyclohexane) 305 m$\mu$ (log $\epsilon$ 2·06), the bathochromic shift of the *R*-band being of the order expected for an axial bromoketone,* and consistent with structure (VII). The O.R.D. curve of (VII) showed a positive Cotton effect, confirming the assigned structure.




The ready conversion by methanolic potassium hydroxide at room temperature of the ketone derived from (V) to 4$\beta$,5-epoxy-5$\beta$-cholestan-3-one (VIII), ruled out the possibility that skeletal rearrangement had occurred during the oxidation of (V), and left only the structures (VI) and (IX) to be considered for the product of the latter reaction. It seemed unlikely that structure (IX), having a tertiary acetoxy group, would readily afford the epoxyketone (VIII) on mild base treatment. Moreover, the ready elimination of hydrobromic acid from the ketone derived from (V), upon simply refluxing it in methanol, favoured the $\beta$-bromoketone structure (VI). The O.R.D. curve showed a +ve Cotton effect, but the information derived from O.R.D.

* 5-Bromo-5$\alpha$-cholestan-4-one showed $\lambda_{max.}$ (EtOH) 307 m$\mu$ (log $\epsilon$ 2·1).[4]

[4] Shoppee, C. W., Howden, M. E. H., Killick, R. W., and Summers, G. H. R. (1959).—*J. Chem. Soc.* **1959**: 630.

measurements in this series is limited by the conformational mobility of ring A with its several axial substituents. The ultraviolet spectrum of (VI) showed $\lambda_{max.}$ (cyclohexane) 298 mμ (log ε 1·59) and although the bathochromic shift is less than that shown by (VII), the position of the maximum was not at a low enough wavelength to rule out the possibility of the axial α-bromoketone structure (IX). In any case, an α-axial acetoxy group could also be expected to cause some bathochromic shift of the *R*-band.[5]

An examination of the course of the reaction of cholest-4-en-3β-ol 3-acetate (III) with acetyl hypobromite suggested the possibility of an independent synthesis of the 4α-bromo-5β-acetoxyketone (IX), and thereby the settlement of the choice between structures (VI) and (IX) for the ketone derived from (V).

Although the reaction of acetyl hypobromite with several steroidal olefins has been studied,[6–8] there has been no report of the reaction of this reagent with $\Delta^4$-steroids. Assuming a 4α,5α-bromonium ion intermediate, the diaxial addition of acetyl hypobromite to (III) could produce one, or both of the isomeric bromodiacetates (II; $R_1 = R_2 =$ Ac) and (X); the 5β-acetoxy derivative (X) was expected to predominate. Treatment of the olefin (III) with *N*-bromoacetamide in glacial acetic containing anhydrous sodium acetate[cf.8] gave a complex mixture. It is interesting that the main product (25%) was the bromohydrin (V), which was readily isolated from the crude product through its insolubility in light petroleum. The amount of this material was not significantly reduced by the use of freshly fused anhydrous sodium acetate, and by the inclusion of acetic anhydride in the reaction mixture. Careful chromatography of the light petroleum mother liquors yielded 14% of the desired 3β,5β-diacetoxybromo derivative (X), m.p. 167–168°C, whose infrared spectrum was consistent with this structure, and differed from that of the isomeric 3β,4β-diacetate (II; $R_1 = R_2 =$ Ac). No trace of the latter compound could be detected in the reaction of (III) with acetyl hypobromite, but a small amount of another isomeric diacetoxybromo derivative, m.p. 154–157·5°C, $[\alpha]_D$ −2·8°, of unknown structure was formed. It is significant that although none of the 3,4-diacetate (II; $R_1 = R_2 =$ Ac) was isolated, about 11% of a halogen-free compound, identified as cholest-5-en-3β,4β-diol 4-acetate (XII), was obtained from the later fractions of the chromatogram. The known fact that the 3-acetoxy-4-hydroxy isomer of (XII) can be readily isomerized to the latter,[9] at first suggested that (XII) could have arisen from the bromohydrin (IV; R = Ac) [which may have been formed along with (V)] by successive dehydrobromination and acyl migration on alumina. This was ruled out by the fact that chromatography of the bromohydrin (IV; R = Ac) [and its isomer (V)] smoothly converted it to the epoxyacetate (I; R = Ac), and no trace of the glycol 4-monoacetate (XII) was detected. It seems most likely that (XII) arises via the intermediate (XI) formed in the acetyl hypobromite reaction mixture by rearrangement of (V). The formation of the intermediate (XI) is in line with the mechanisms proposed for the rearrangement of (V) during acetylation and oxidation (*vide infra*).

[5] Cookson, R. C., and Dandegaonker, S. H. (1955).—*J. Chem. Soc.* **1955**: 352.

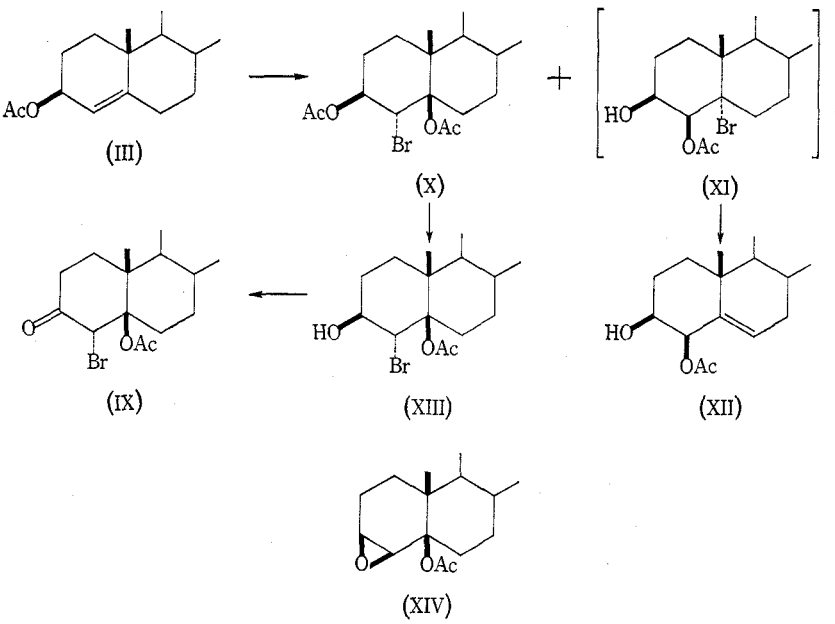
[6] Levine, S. G., and Wall, M. E. (1959).—*J. Amer. Chem. Soc.* **81**: 2826.

[7] Levine, S. G., and Wall, M. E. (1959).—*J. Amer. Chem. Soc.* **81**: 2829.

[8] Reimann, H., Oliveto, E. P., Neri, R., Eisler, M., and Perlman, P. (1960).—*J. Amer. Chem. Soc.* **82**: 2308.

[9] Petrow, V. A., Rosenheim, O., and Starling, W. W. (1943).—*J. Chem. Soc.* **1943**: 135.

Selective hydrolysis of the 3β,5β-diacetate (X) by brief treatment with 2% methanolic potassium hydroxide at room temperature afforded the bromohydrin (XIII), whose spectrum showed hydroxyl and acetate bands in the infrared, and whose physical properties differed from those of its isomers (IV; R = Ac) and (V). There was no evidence for 4β,5β-epoxide formation in the above reaction, and the 5β-acetoxy group of (X) and (XIII) is quite stable to mild alkali. Also the failure of (XIII) to be converted to the 3β,4β-oxide (XIV) upon treatment with base is interesting and possibly indicates an abnormal conformation of ring A in (XIII). The new bromohydrin (XIII) was readily oxidized with chromic acid–acetone to the 4α-bromo-5β-acetoxyketone (IX) whose ultraviolet spectrum [$\lambda_{max.}$ (cyclohexane) 313 mμ (log ε 2·00)] showed a large bathochromic shift compatible with its formulation as an axial α-bromoketone.

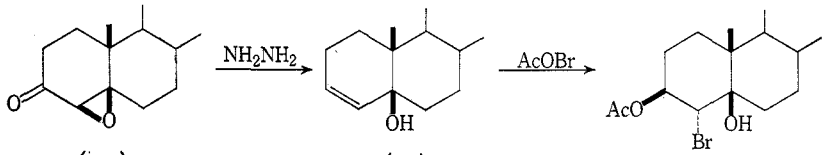



The fact that the ketone (IX), and the ketone, m.p. 117–122°C, derived by the oxidation of (V) were different indicates that the latter ketone has structure (VI).

To provide final proof of the structure (V) for the HOBr-olefin bromohydrin, an unequivocal synthesis from a compound already containing a 5β-hydroxyl was desirable. The recent discovery,[10] of a novel one-step synthesis of 5β-cholest-3-en-5-ol (XV) from the epoxyketone (VIII) by its reaction with hydrazine, made this relatively simple. Assuming the formation of a 3α,4α-bromonium ion intermediate, diaxial addition of acetyl hypobromite to (XV) should give the desired bromohydrin (V). On the other hand, examination of Dreiding models indicated that as a consequence of the A/B *cis*-ring junction in (XV), there may be less hindrance to the formation of a 3β,4β-bromonium ion, in which case the formation of the isomeric bromohydrin 3β-bromo-5β-cholestane-4α,5-diol 4-acetate may be preferred.

[10] Wharton, P. S., and Bohlen, D. H. (1961).—*J. Org. Chem.* **26**: 3615.

Nevertheless the reaction of the allylic alcohol (XV) with acetyl hypobromite *did* give some of the desired 4α-bromo-5β-cholestane-3β,5-diol 3-acetate, identical in all respects with the bromohydrin obtained by the addition of hypobromous acid to cholest-4-en-3β-ol 3-acetate (III), thus proving conclusively that this bromohydrin has structure (V).




(VIII) (XV) (V)

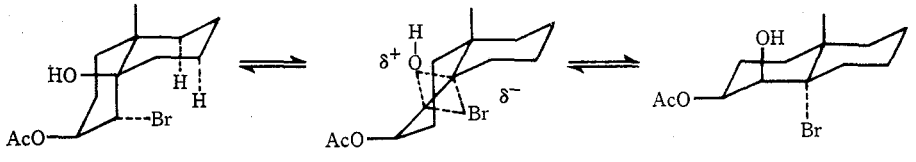
It may be mentioned here that the addition of HOBr to the $\Delta^4$-double bond of cholesta-4:6-diene-3-one also gives a 4α-bromo-5β-hydroxy derivative.[11]

## II. Mechanism and Stereochemistry

With the structure of the bromohydrin (V) established, attention was directed to the nature of its rearrangement reactions.

The possibility that (IV; R = Ac) is an intermediate in the rearrangement of (V) during oxidation and acetylation made it of interest to determine whether (V) could be isomerized to (IV) under conditions of mild acid catalysis. Such a rearrangement would be a special case of the generalized "diaxial→diequatorial" rearrangement,[12] but owing to the unique environment in the present instance, it would be a diaxial→diaxial 1,2-shift with respect to ring A.

When the bromohydrin (V) was refluxed in light petroleum with a trace of either perchloric acid, or of hydrobromic acid–acetic acid, an equilibrium mixture of the bromohydrins (IV; R = Ac) and (V) in a ratio of approximately 2:1 was obtained. Although equilibrium was obtained much more slowly, the same mixture resulted when the isomeric bromohydrin (IV; R = Ac) was similarly treated. This rearrangement presumably proceeds via the transition state (XVI) (cf. Barton and King[12]). The conformational driving force which displaces the equilibrium in favour of (IV; R = Ac) is probably largely due to the severe interaction of the 4α-bromine in (V) with hydrogen atoms of ring B irrespective of the comformation of ring A.




(V) (XVI) (IV)

The ease with which this isomerization occurs in the presence of acid, necessitates careful removal of traces of perchloric acid from the crude bromohydrin (V), before attempting its recrystallization.

[11] Bruckner, K., Hampel, B., and Johnsen, U. (1961).—*Chem. Ber.* **94**: 1225.
[12] Barton, D. H. R., and King, J. F. (1958).—*J. Chem. Soc.* **1958**: 4398.

The intermediate (XVI) may be very similar to the transition state involved in the addition of hydrobromic acid to the epoxide (I; R = Ac) which reaction produces mainly the bromohydrin (IV; R = Ac) readily isolated because of its sparing solubility in acetone.

There are four possible mechanisms for the conversion of (V) to the 3,4-diacetate (II; $R_1 = R_2 = Ac$) with acetic anhydride in pyridine, they are:

(1) That the equilibrium (V)⇌(XVI)⇌(IV; R = Ac) is set up in the acetylation mixture, and that esterification of (IV; R = Ac) produces (II; $R_1 = R_2 = Ac$).

(2) That 3→5 *trans*-esterfication results in the formation of the 5β-acetoxy derivative (XIII), which then undergoes acetylation of the 3-hydroxyl group and a 4⇄5 rearrangement [analogous to the rearrangement of (V)→(IV; R = Ac)].

(3) That direct nucleophilic attack of the acylating species occurs at C4 with concomitant migration of the bromine atom to the 5α-position, and displacement of hydroxyl ion from C5.

(4) That the 3β-acetate group participates in a concerted intramolecular *trans*-esterification–displacement reaction in which the 5β-hydroxyl participates to promote attack of the 3-acetate group on C4 with the formation of a 3,4-*ortho*-ester type intermediate, and migration of the bromine to the 5α-position. Evidence presented below shows that this is the preferred mechanism.

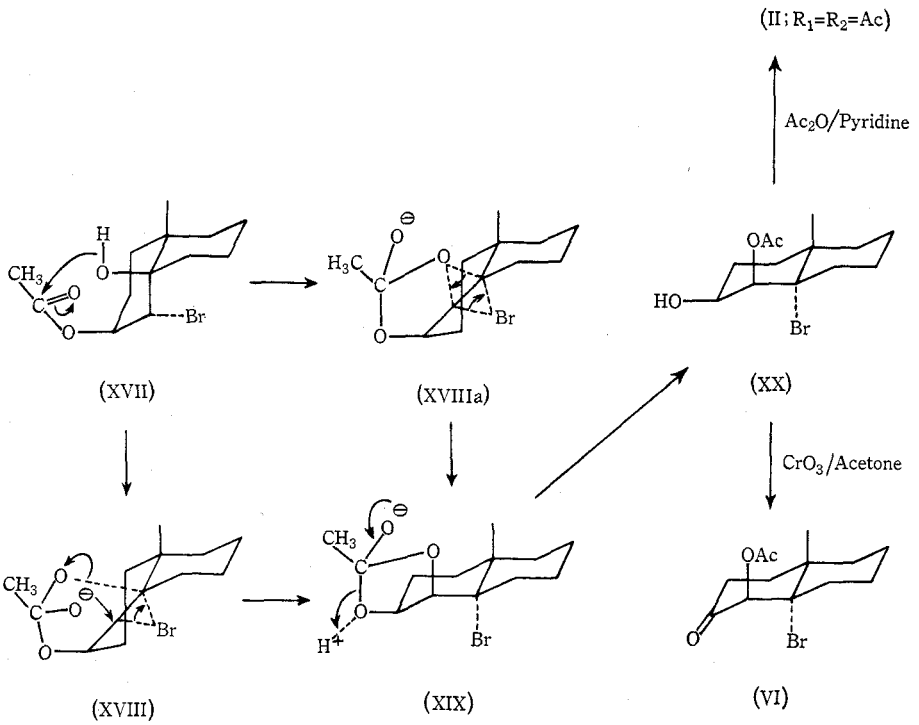
Mechanism (1) seemed unlikely since acetylation of (V) proceeds more rapidly and more cleanly than the acetylation of (IV; R = Ac). If the first step in the conversion of (V) to (II; $R_1 = R_2 = Ac$) involved isomerization to (IV; R = Ac), the acetylation of (V) should be at least as slow as, if not slower than, the simple acetylation of (IV; R = Ac). Mechanism (2) could be ruled out since acetylation of the postulated intermediate (XIII) gave the 3β,5β-diacetate (X) without rearrangement of the latter to (II; $R_1 = R_2 = Ac$). Mechanism (3) appeared unlikely since most bromohydrins can be acetylated without complications. Thus, by elimination, mechanism (4) was the favoured one.

The proximity in space of the 3β-acetate and the 5β-hydroxyl group (1 : 3 diaxial) could readily permit the reaction sequence (XVII)→(XVIII)→(XIX). The postulated intermediate 3β,5β-*ortho*-ester may rearrange via transition states (XVIII) or (XVIIIa) to the 3β,4β-*ortho*-ester intermediate (XIX), which could undergo preferential fission of the 3-equatorial ester linkage* to give (XX), acetylation of which would afford (II; $R_1 = R_2 = Ac$).

Further evidence for the latter mechanism was very simply obtained by the formation of mixed esters from the bromohydrins (IV; R = Ac) and (V). If mechanism (4) operates, benzoylation of (V) should give the 3-benzoate (II; $R_1 = Bz$, $R_2 = Ac$), whereas if any of the mechanisms (1), (2), or (3) are correct, benzoylation of (V) should afford the 4-benzoate (II; $R_1 = Ac$, $R_2 = Bz$), also obtainable directly from (IV; R = Ac). In fact, the bromohydrins (IV; R = Ac) and (V) *did give different isomeric benzoates*. Confirmation that the benzoylation of (V) gave the 3-benzoate

* Preferential fission of the *ortho*-ester intermediate (XIX) at the 3-equatorial oxygen, finds a parallel in the observed rearrangement of cholest-5-en-3β,4β-diol 3-acetate to the corresponding 4-monoacetate (XI).[9]

(II; $R_1$ = Bz, $R_2$ = Ac), was obtained by an independent synthesis of the latter from 4β,5-epoxy-5β-cholestan-3β-ol 3-benzoate (I; R = Bz) by addition of HBr to give the bromohydrin (IV; R = Bz) and acetylation of the 4β-hydroxyl to give (II; $R_1$ = Bz, $R_2$ = Ac), identical in all respects with the product obtained by the direct benzoylation of (V). This provides strong evidence in favour of mechanism (4) for the acylation of (V) to (II; $R_1 = R_2$ = Ac).

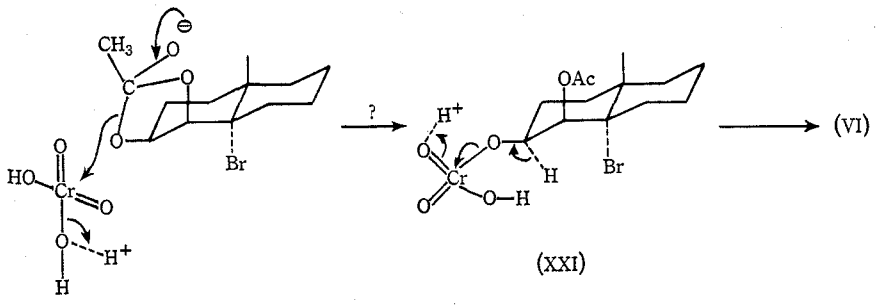



It should be noted that 5β-cholestane-3β,5-diol 3-acetate failed to undergo transacetylation when treated with acetic anhydride in pyridine; thus, the combined presence of a 4α-bromine atom and a 5β-hydroxyl group is necessary to promote the participation of the 5β-hydroxyl group in this reaction.

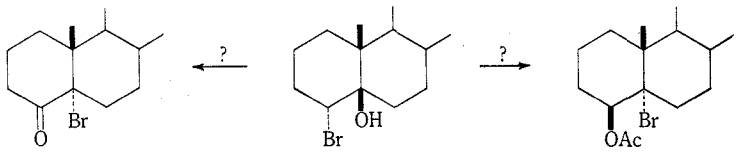
The mechanism of formation of the ketone (VI) obtained by the mild oxidation of (V) is also interesting. It is unlikely that this reaction proceeds by initial isomerization of (V) to (IV; R = Ac) followed by 3→4 *trans*-acetylation, and oxidation at C3, since (IV; R = Ac) is rapidly oxidized to (VII) under these conditions. Similarly, simple 3→5 *trans*-acetylation to give the 5β-acetoxy-3β-alcohol (XIII) can be ruled out as the first step, since it has already been shown that (XIII) is rapidly oxidized to the 5β-acetoxyketone (IX); moreover, the latter ketone was not isomerized to (VI) by treatment overnight with the chromic acid–acetone reagent.

It is likely therefore, that the above reagent catalyses the sequence (XVII)→(XVIII)→(XIX) and that the latter is then oxidized to (VI). Although it is easier to think in terms of the free 3-alcohol (XX) as an intermediate it is reasonable to suppose that the intermediate (XIX) may be directly involved in a nucleophilic attack

on chromic acid to give the intermediate chromate ester (XXI), or at least, that this reaction may compete to some extent with temporary accession of a proton to the 3-oxygen, and subsequent removal upon oxidation to the ketone.



(XIX) (XXI) (VI)



(XXIII) (XXII) (XXIV)

Although a detailed examination has not been carried out, it seems reasonable that the oxidative rearrangement of (V) to (VI) should proceed by a mechanism similar to that which is strongly indicated for the rearrangement which occurs during the acylation of (V).

From the mechanistic point of view, it would be interesting to determine whether the oxygen of the 5-hydroxyl of (V) becomes the acyl, or the alcoholic oxygen of the 4-acetate, and hence distinguish between the possible intermediates (XVIII) and (XVIIIa) respectively, in the formation of (II; $R_1 = R_2 =$ Ac) and (VI).

It had been hoped to obtain further information on the mechanism of these reactions by synthesizing the simple bromohydrin (XXII), to see if it would rearrange to (XXIII) or (XXIV) under oxidizing or acylating conditions respectively. However several attempts to prepare (XXII) by the addition of hypobromous acid to cholest-4-ene failed to give a crystalline bromohydrin.* In any case it has clearly been shown that the 3-acetate group is directly involved in the acylation and oxidation of (V). With respect to the interaction of the 5$\beta$-hydroxyl and 3$\beta$-acetate in the rearrangement reactions of (V), it is relevant to quote the observations of Henbest and Lovell[14]

* It appears that the course of addition of hypohalous acids to $\Delta^4$-steroids unsubstituted at C3 may differ from their addition to the 3$\beta$-acetoxyolefin (III), since Heusler *et al.*[13] have reported that the addition of hypochlorous acid to androst-4-en-17-one gave the secondary alcohol 5-chloro-5$\alpha$-androstan-4$\beta$-ol-17-one. Even so, the latter may have arisen by isomerization of 4$\alpha$-chloro-5$\beta$-androstan-5-ol-17-one, which had been formed initially.

[13] Heusler, K., Kalvoda, J., Wieland, P., Anner, G., and Wettstein, A. (1962).—*Helv. Chim. Acta* **45**: 2575.

[14] Henbest, H. B., and Lovell, B. J. (1957).—*J. Chem. Soc.* **1957**: 1965.

and of Kupchan *et al.*[15,16] on the facilitation of ester hydrolysis by a neighbouring hydroxyl group; the present case is one of acyl migration assisted by both a neighbouring hydroxyl group and a neighbouring bromine. The rearrangement reactions of (V) are unusual examples of neighbouring group participation, and may be described as the mutually assisted migration of three reactive groups, resulting from their relative stereochemical, and sequential attachment to three contiguous carbon atoms at a conformationally appropriate site of a "rigid" system.

## III. Experimental

Unless stated otherwise melting points were determined on a Kofler block and are uncorrected. Rotations refer to chloroform solutions. Ultraviolet spectra were measured with a Unicam SP500 spectrophotometer. Infrared spectra were recorded by a Perkin–Elmer model 221 spectrophotometer. Optical rotatory dispersion measurements were carried out with a Rudolph recording spectropolarimeter. Light petroleum refers to the fraction, b.p. 40–60°C. Microanalyses were carried out by the C.S.I.R.O. and University of Melbourne Microanalytical Laboratory, Melbourne.

(*a*) *5-Bromo-5α-cholestane-3β,4β-diol 3-Acetate* (*IV; R = Ac*).—A solution of 4β,5-epoxy-5β-cholestan-3β-ol 3-acetate (160 mg) in acetone (7·5 ml) was treated with aq. HBr (0·32 ml of 46–48% w/v) at room temperature for 30 min, during which time the bromohydrin crystallized out. The mixture was kept for 2 hr at 0°C, then the product was collected [150 mg, m.p. 152–154°C (decomp.)]. Recrystallization from acetone gave leaflets of 5-bromo-5α-cholestane-3β,4β-diol 3-acetate, m.p. 154–155·5°C (decomp.), $[\alpha]_D$+20° (*c*, 1·00), $\nu_{max.}$ (Nujol) 3400, 1709, 1266 cm$^{-1}$; ($CCl_4$) 3602, 1752, 1224 cm$^{-1}$. (Fieser, Goto, and Bhattacharyya[1] quote m.p. 143–145°C (decomp.), $[\alpha]_D$+18°).

Acetylation of (IV; R = Ac) with acetic anhydride in pyridine for 2 days at room temperature (the reaction was incomplete after 24 hr) gave the 3,4-diacetate (II; $R_1 = R_2 =$ Ac). Recrystallization from methanol gave plates, m.p. 151–152°C, $[\alpha]_D$+26° (*c*, 1·42), $\nu_{max.}$ (Nujol) 1748, 1233, 1211 cm$^{-1}$. (Lit.[1] m.p. 148·5–150·5°C, $[\alpha]_D$+24°.) Treatment of (IV; R = Ac) with benzoyl chloride in pyridine gave *5-bromo-5α-cholestane-3β,4β-diol 3-acetate 4-benzoate* (II; $R_1$ = Ac, $R_2$ = Bz) which crystallized from methanol as plates, m.p. 129–131°C, $[\alpha]_D$+50·1° (*c*, 1·10), $\nu_{max.}$ (Nujol) 1754, 1733, 1269, 1218 cm$^{-1}$ (Found: C, 68·7; H, 8·7%. Calc. for $C_{36}H_{53}O_4Br$: C, 68·7; H, 8·5%).

(*b*) *Preparation of 4α-Bromo-5β-cholestane-3β,5-diol 3-Acetate* (*V*).—(i) As previously described.[2]

(ii) cf. Method of Henbest and Wilson.[17] To a cold solution of cholest-4-en-3β-ol 3-acetate (1·0 g) in 5% water–t-butanol (50 ml) was added a solution of *N*-bromosuccinimide (0·5 g) in the same solvent (30 ml). The solution was cooled in an ice-bath and 1N $HClO_4$ (2 ml) added with stirring. After 2 hr the mixture was poured into water, and the precipitate was collected, washed, and dried. Trituration with light petroleum gave a solid (400 mg), m.p. 130–135°C (decomp.). Recrystallization from light petroleum gave pure 4α-bromo-5β-cholestane-3β,5-diol 3-acetate (220 mg), m.p. 150–153°C (decomp.), m.p. (capillary) 146–147°C (decomp.), $[\alpha]_D$+32° (*c*, 1·13), $\nu_{max.}$ (Nujol) 3541, 1740, 1250 cm$^{-1}$; ($CCl_4$) 3600, 1745, 1216 cm$^{-1}$.

(*c*) *Action of Acylating Agents on 4α-Bromo-5β-cholestane-3β,5-diol 3-Acetate* (*V*).—(i) *Acetic Anhydride–Pyridine.* The bromohydrin (200 mg) in pyridine (2 ml) was treated with acetic anhydride (0·5 ml) overnight at room temperature. Two recrystallizations of the product from methanol gave 5-bromo-5α-cholestane-3β,4β-diol 3,4-diacetate as laths, m.p. 153–154·5°C, $[\alpha]_D$+26°(*c*, 1·42), $\nu_{max.}$ 1748, 1233, 1211 cm$^{-1}$ (Found: C, 65·7; H, 8·8%. Calc. for $C_{31}H_{51}O_4Br$: C, 65·6; H, 9·1%).

[15] Kupchan, S. M., Slade, P., and Young, R. J. (1960).—*Tetrahedron Letters* **24: 22.**

[16] Kupchan, S. M., Slade, P., Young, R. J., and Milne, G.N.A.(1962).—*Tetrahedron* **18: 499.**

[17] Henbest, H. B., and Wilson, R. A. L. (1959.—*J. Chem. Soc.* **1959:** 4136.

Identity of this diacetate with 5-bromo-5α-cholestane-3β,4β-diol 3,4-diacetate obtained as in (*a*) was established by m.p., mixed m.p., and i.r. spectra. 4α-Bromo-5β-cholestane-3β,5-diol 3-acetate was unaffected by treatment with anhydrous pyridine at room temperature for 24 hr.

The 3,4-diacetate (100 mg) was refluxed with 2% methanolic KOH (15 ml) for 1·5 hr. The solution was concentrated *in vacuo*, water added, and the product isolated with ether. Recrystallization from aq. methanol gave 4β,5-epoxy-5β-cholestan-3β-ol, m.p. 95–96°C, undepressed on admixture with an authentic specimen. A similar result was obtained when the reaction was carried out at room temperature for 30 min.

(ii) *Benzoyl Chloride–Pyridine.* Treatment of the bromohydrin (V) with benzoyl chloride in pyridine at room temperature, and crystallization of the product from methanol gave fine needles of *5-bromo-5α-cholestane-3β,4β-diol 3-benzoate 4-acetate* (II; $R_1$ = Bz, $R_2$ = Ac), m.p. 166–169·5°C, $[\alpha]_D$+36° (*c*, 1·00), $\nu_{max.}$ (Nujol) 1745, 1718, 1267, 1222 cm$^{-1}$ (Found: C, 69·0; H, 8·6%. Calc. for $C_{36}H_{53}O_4Br$: C, 68·7; H, 8·5%).

(*d*) *Equilibration of 4α-Bromo-5β-cholestane-3β,5-diol 3-Acetate (V) and 5-Bromo-5α-cholestane-3β,4β-diol 3-Acetate (IV; R = Ac).*—(i) 4α-Bromo-5β-cholestane-3β,5-diol 3-acetate (30 mg) was refluxed 1·5 hr in light petroleum (15 ml) containing HBr–acetic acid (2 drops of 45% w/v). The cooled solution was diluted with ether, washed with water, dried ($Na_2SO_4$), and evaporated. The white powdery residue, m.p. 130–138°C (decomp.), showed $\nu_{max.}$ (Nujol) 3541, 3400, 1740, 1709 cm$^{-1}$. Integration of the areas under the hydroxyl and acetate bands showed the product to be a mixture of 5-bromo-5α-cholestane-3β,4β-diol 3-acetate and 4α-bromo-5β-cholestane-3β,5-diol 3-acetate in a ratio of approximately 2:1.

The same equilibrium mixture was obtained when a solution of the bromohydrin (V) (30 mg) in light petroleum containing 1 drop of 70% $HClO_4$ was refluxed for 1 hr. The bromohydrin underwent extensive decomposition when heated at reflux for 1 hr with glacial acetic acid.

(ii) Treatment of 5-bromo-5α-cholestane-3β,4β-diol 3-acetate (IV) (30 mg) with 1 drop of HBr–acetic acid in light petroleum (15 ml) at reflux for 10 hr resulted in the same equilibrium mixture as obtained in (i) from the isomeric bromohydrin (V).

(*e*) *Conversion of 5-Bromo-5α-cholestane-3β,4β-diol 3-Acetate (IV;R = Ac) to 4β,5-Epoxy-5β-cholestan-3β-ol 3-Acetate (VIII).*—(i) *By "Neutral" Alumina.* The bromohydrin (100 mg) was adsorbed onto Merck grade I "Neutral" alumina (8·0 g) from benzene solution. Elution with benzene gave 4β,5-epoxy-5β-cholestan-3β-ol 3-acetate (70 mg) which crystallized from methanol as needles, m.p. 90–92·5°C, identified by mixed m.p. and by its i.r. spectrum. Elution with ether afforded 20 mg of the bromohydrin.

(ii) *By Potassium Acetate.* A solution of the bromohydrin (100 mg) in 5% methanolic potassium acetate (10 ml) and dioxan (1·0 ml) was refluxed 3 hr. The cooled solution was poured into water and the product isolated with ether. Recrystallization from methanol gave 50 mg of the epoxyacetate (I; R = Ac), m.p. 89–91°C, identified by mixed m.p. and by its i.r. spectrum.

(*f*) *Conversion of 4α-Bromo-5β-cholestane-3β,5-diol 3-Acetate (V) to 4β,5-Epoxy-5β-cholestan-3β-ol 3-Acetate (VIII).*—(i) The bromohydrin (220 mg) in benzene was adsorbed onto grade I Merck "Neutral" alumina (15 g), and the column allowed to stand for 2 days. Elution with 2% to 8% ether–benzene, and recrystallization of the combined residues (100 mg) gave 4β,5-epoxy-5β-cholestan-3β-ol 3-acetate, m.p. 90–91°C, undepressed on admixture with an authentic specimen. Elution with ether and crystallization of the product (80 mg) from methanol gave unchanged bromohydrin, m.p. 152–154°C (decomp.), identified by its i.r. spectrum.

(ii) Treatment of the bromohydrin (100 mg) with 5% methanolic potassium acetate (10 ml) at reflux for 3hr, and crystallization of the product from methanol afforded 4β,5-epoxy-5β-cholestan–3β-ol 3-acetate, m.p. 87–89°C, identified by mixed m.p., and by its i.r. spectrum.

(*g*) *Oxidation of 5-Bromo-5α-cholestane-3β,4β-diol 3-Acetate (IV; R = Ac).*—A solution of the bromohydrin (100 mg) in acetone (10 ml) was treated with 8N chromic acid solution[18] (0·35 ml) at room temperature. After 10 min, excess of reagent was decomposed with methanol and the mixture was poured onto ice-water. Ether extraction, and crystallization of the product from

[18] Bowden, K., Heilbron, I. M., Jones, E. R. H., and Weedon, B. C. L. (1946).—*J. Chem. Soc.* **1946**: 39.

methanol gave *5-bromo-5α-cholestan-3β-ol-4-one 3-acetate* (VII) as needles (55 mg), m.p. 139–140·5°C, $[\alpha]_D$ +85·4° (*c*, 1·09), $\lambda_{max.}$ (cyclohexane) 305 mμ (ε 115), $\nu_{max.}$ (Nujol) 1761, 1735, 1226 cm$^{-1}$ (Found: C, 66·8; H, 9·0%. Calc. for $C_{29}H_{47}O_3Br$: C, 66·5; H, 9·0%).

(*h*) *Oxidation of 4α-Bromo-5β-cholestane-3β,5-diol 3-Acetate.*—A solution of the bromohydrin (100 mg) in acetone (15 ml) was treated with 8N chromic acid solution (0·45 ml) and the mixture was allowed to stand overnight at room temperature. The excess of reagent was decomposed with methanol and the product isolated in the usual way. Trituration with cold methanol gave crystals (73 mg), m.p. (capillary) 125–126°C (decomp.). Recrystallization from aq. acetone gave needles of *5-bromo-5α-cholestan-4β-ol-3-one 4-acetate* (VI), m.p. 117–122°C, m.p. (capillary) 126–127°C (decomp.), $[\alpha]_D$ +99·2° (*c*, 1·08), $\lambda_{max.}$ (cyclohexane) 298 mμ (ε 39), $\nu_{max.}$ (Nujol) 1766, 1730, 1224 cm$^{-1}$, R.D. in dioxan: (*c*, 0·106), $[\phi]_{500}$ +113°, $[\phi]_{400}$ +264°, $[\phi]_{345}$ (infl.) +679°, $[\phi]_{326}$ +1040°, $[\phi]_{310}$ (infl.) + 566° (Found: C, 66·2; H, 8·8%. Calc. for $C_{29}H_{47}O_3Br$: C, 66·5; H, 9·0%).

A suspension of the above bromoketone (100 mg) in 2% methanolic KOH (3 ml) was shaken for 20 min at room temperature. During the first 5 min the mixture became homogeneous, and after 10 min a crystalline solid had separated. Filtration and recrystallization of the product from chloroform–methanol gave prisms of 4β,5-epoxy-5β-cholestan-3-one (30 mg), m.p. 119–120°C, identified by mixed m.p. and by its i.r. spectrum.

(*i*) *Reaction of Acetyl Hypobromite with Cholest-4-en-3β-ol 3-Acetate.*—To a stirred solution of cholest-4-en-3β-ol 3-acetate (3·44 g) and anhydrous sodium acetate (16·0 g) in glacial acetic acid (160 ml) at room temperature, was added *N*-bromoacetamide (1·2 g). A crystalline solid soon began to separate. After 40 min the mixture was poured onto ice and allowed to stand for 2 hr. The solid precipitate was collected, dissolved in ether, and the ether solution was washed with water, dried ($Na_2SO_4$), and evaporated. Trituration of the residue with light petroleum gave a solid 1·07 g), m.p. 150–153°C (decomp.), which was identified as 4α-bromo-5β-cholestane-3β,5-diol 3-acetate by mixed m.p. and by its i.r. spectrum. The filtrate from this was concentrated and adsorbed onto Merck grade I "Neutral" alumina (90 g). Elution with 20% benzene–light petroleum gave crude starting material (530 mg). Elution with 50% and 70% benzene–light petroleum gave a solid (610 mg). Several recrystallizations of this from methanol afforded needles of *4α-bromo-5β-cholestane-3β,5-diol 3,5-diacetate* (X), m.p. 167–168°C, $[\alpha]_D$ +16·9° (*c*, 1·07), $\nu_{max.}$ (Nujol) 1758, 1738, 1274, 1232, 1210, 1194 cm$^{-1}$ (Found: C, 65·7; H, 9·1%. Calc. for $C_{31}H_{51}O_4Br$: C, 65·6; H, 9·1%).

A solution of the foregoing diacetate (30 mg) in light petroleum (15 ml) containing 1 drop of HBr–acetic acid (45% w/v) was refluxed for 1 hr. The crystalline product, m.p. 165–167°C, was shown to be starting material (mixed m.p. and i.r. spectrum).

A portion (150 ml) of the 1% ether–benzene eluate afforded a solid (120 mg) which crystallized from methanol as laths, m.p. 152–155°C (frothing). Two further recrystallizations gave the pure *diacetoxybromo compound*, m.p. 154–157·5°C, $[\alpha]_D$ −2·8° (*c*, 1·09), $\nu_{max.}$ (Nujol) 1738, 1272, 1241, 1224 cm$^{-1}$ (Found: C, 65·6; H, 9·1%. Calc. for $C_{31}H_{51}O_4Br$: C, 65·6; H, 9·1%). Non-identity of this with 5-bromo-5α-cholestane-3β,4β-diol 3,4-diacetate was shown by depression of the mixed m.p. and by its i.r. spectrum.

Elution with 50% ether–benzene (50 ml) and with ether (150 ml) yielded a solid (380 mg), which upon crystallization from methanol afforded plates of cholest-5-en-3β,4β-diol 4-acetate, m.p. 164–166·5°C (capillary), $[\alpha]_D$ −90·1° (*c*, 1·14), $\nu_{max.}$ 3475, 1742 cm$^{-1}$ [Petrow, Rosenheim, and Starling[9] quote m.p. 164–165°C, $[\alpha]_D^{24}$ −88·8°]. To confirm this identification, the foregoing glycol monoacetate (90 mg) was refluxed for 30 min with 2% methanolic KOH (5 ml). Crystallization of the product from acetone gave prisms of cholest-5-en-3β,4β-diol, m.p. 175–177°C, undepressed on admixture with an authentic specimen.

The use of freshly fused anhydrous sodium acetate and inclusion of acetic anhydride (80 ml) in the acetyl hypobromite reaction mixture failed to reduce significantly the amount of the bromohydrin (V) formed.

(*j*) *4α-Bromo-5β-cholestane-3β,5-diol 5-Acetate* (*XIII*).—A solution of 4α-bromo-5β-cholestane-3β,5-diol 3,5-diacetate (300 mg) in methanol (15 ml) and light petroleum (15 ml) was treated with 2% methanolic KOH (15 ml), and the two phase solution was shaken at room temperature for 15 min. After several washings with water the organic extract was dried ($Na_2SO_4$) and evaporated.

Trituration of the residue with light petroleum gave a solid (250 mg). Recrystallization from acetone afforded *4α-bromo-5β-cholestane-3β,5-diol 5-acetate* as leaflets, m.p. 167–170°C (decomp.), $[\alpha]_D$ +54·7° (*c*, 0·73), $\nu_{max.}$ (Nujol) 3565, 1740, 1264, 1231, 1214 $cm^{-1}$ (Found: C, 66·4; H, 9·4%. Calc. for $C_{29}H_{49}O_3Br$; C, 66·3; H, 9·4%).

Reacetylation of the bromohydrin (XIII) with acetic anhydride in pyridine afforded 4α-bromo-5β-cholestane-3β,5-diol 3,5-diacetate identified by mixed m.p. and its i.r. spectrum.

Treatment of the bromohydrin (XIII) with refluxing 2% methanolic KOH for 2 hr afforded a noncrystalline, unidentified αβ-unsaturated ketone whose i.r. spectrum showed no hydroxyl, but bands at 1678, 1618 $cm^{-1}$, and very broad bands at 1095 and 1008 $cm^{-1}$.

A solution of the bromohydrin (30 mg) in benzene (10 ml) was treated with 2 drops of HBr–acetic acid (45% w/v) and refluxed 1 hr. The crystalline product was shown to be unchanged starting material (mixed m.p. and i.r. spectrum).

The bromohydrin (50 mg) was recovered unchanged after refluxing for 2·5 hr with 5% methanolic potassium acetate (10 ml).

(*k*) *4α-Bromo-5β-cholestan-5-ol-3-one 5-Acetate* (*IX*).—A solution of 4α-bromo-5β-cholestane-3β,5-diol 5-acetate (XIII) (190 mg) in acetone (40 ml) was treated at room temperature with 8N chromic acid solution (0·5 ml). After 10 min methanol (1 ml) was added, and the product isolated in the usual way. Crystallization from methanol afforded *4α-bromo-5β-cholestan-5-ol-3-one 5-acetate* (IX) as platelets (150 mg), m.p. 108–109·5°C, $[\alpha]_D$ −6·3° (*c*, 1·28), $\lambda_{max.}$ (cyclohexane) 313 mμ (ε 101), $\nu_{max.}$ (Nujol) 1733, 1239, 1222, 1194 $cm^{-1}$ (Found: C, 66·8; H, 9·0%. Calc. for $C_{29}H_{47}O_3Br$: C, 66·5; H, 9·1%).

The same bromoketone was obtained when the reaction mixture was kept overnight at room temperature; i.e. no rearrangement of the initially formed product takes place in the reaction medium.

(*l*) *Experiments on 5β-Cholestane-3β,5β-diol 3-Acetate.*—(i) Treatment of the glycol monoacetate with acetic anhydride in pyridine gave no indication of the formation of a diacetate by *trans*-esterification.

(ii) The glycol monoacetate (80 mg) in acetone (10 ml) was treated overnight with 8N chromic acid solution (0·4 ml). The i.r. spectrum of the crude product, isolated in the usual way, showed that there had been virtually no reaction.

(*m*) *Preparation of 5β-Cholest-3-en-5-ol* (*XV*).(cf. Wharton and Bohlen[10]).—A mixture of 4β,5-epoxy-5β-cholestan-3-one (1·0 g) in hydrazine hydrate (100%; 5 ml) was heated to 90°C during 10 min, then heated at 118°C for 15 min. The cooled solution was poured onto ice-water and the product isolated with ether. The gum was dissolved in light petroleum and chromatographed on B.D.H. alumina. Elution with 2% and 4% ether–benzene, and recrystallization of the solid (300 mg) from aq. methanol gave the pure alcohol (XV), m.p. 94–96°C, $[\alpha]_D$ +97° (*c*, 1·07), $\nu_{max.}$ ($CCl_4$) 3484 $cm^{-1}$. Lit.[10] m.p. 89–91°C, $[\alpha]_D$ +98°.

(*n*) *Reaction of 5β-Cholest-3-en-5-ol with Acetyl Hypobromite.*—To a stirred solution of the allylic alcohol (250 mg) and anhydrous sodium acetate (1·3 g) in glacial acetic acid (13 ml) was added *N*-bromoacetamide (90 mg), and the mixture kept at room temperature (with stirring) for 1 hr. Addition of ice-water gave a precipitate which was isolated with ether.

The gummy product was dissolved in a small volume of light petroleum and kept overnight in the refrigerator. The crystalline product (14 mg), m.p. 147–148°C (decomp., capillary), was shown to be identical (mixed m.p. and i.r. spectra) with 4α-bromo-5β-cholestane-3β,5-diol 3-acetate (V) prepared as in (*a*).

(*o*) *Preparation of 5-Bromo-5α-cholestane-3β,4β-diol 3-Acetate 4-Benzoate from 4β,5-Epoxy-5β-cholestan-3β-ol 3-Benzoate.*—Treatment of 4β,5-epoxy-5β-cholestan-3β-ol with benzoyl chloride in pyridine at room temperature gave the *benzoate* (I; R = Bz), which crystallized in prisms from methanol, m.p. 111–113°C, $[\alpha]_D$ −18·6° (*c*, 1·02), $\nu_{max.}$ (Nujol) 1712, 1266 $cm^{-1}$ (Found: C, 80·6; H, 10·5%. Calc. for $C_{34}H_{50}O_3$: C, 80·6; H, 10·0%).

The above epoxybenzoate (211 mg) in acetone (10 ml) was treated with aq. HBr (0·42 ml of 46–48% w/v) with stirring. The reaction mixture deposited a precipitate almost immediately. After 0·5 hr the product was collected (196 mg). Two recrystallizations from acetone gave

*5-bromo-5α-cholestane-3β,4β-diol 3-benzoate* (IV; R = Bz) as fine matted needles, m.p. 176–177°C (decomp.), $[\alpha]_D$ +22·6° (*c*, 1·02), $\nu_{max.}$ ($CCl_4$) 3636, 1727 $cm^{-1}$(Found: C, 69·6; H, 9·0%. Calc. for $C_{34}H_{51}O_3Br$: C, 69·5; H, 8·8%).

Acetylation of the foregoing bromohydrin with acetic anhydride in pyridine at room temperature gave 5-bromo-5α-cholestane-3β,4β-diol 3-benzoate 4-acetate (II; $R_1$ = Bz, $R_2$ = Ac), m.p. 167–169°C, which was identical (mixed m.p. and i.r. spectrum) with the mixed ester obtained by benzoylation of 4α-bromo-5β-cholestane-3β,5-diol 3-acetate (V).

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