# REACTION OF 5,6-DIBROMOSTEROIDS WITH SILVER FLUORIDE IN THE PRESENCE OF WATER*

A. KASAL and A. TRKA

*Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, 166 10 Prague 6*

Received July 4th, 1973

On reaction of an aqueous silver fluoride solution with 5,6α-dibromo-5β-cholestan-3β-ol (*V*) and 5,6β-dibromo-5α-cholestan-3β-ol (*VI*) we obtained a mixture of products from the composition of which we judged the course of the single consecutive processes. We found that the transformation of dibromide *V* is initiated by $C_{(5)}$—Br ionisation and that it continues with reactions of the carbonium ion *VII*, while the transformation of dibromide *VI* is initiated predominantly by $C_{(5)}$—Br ionisation and to a lesser extent by $C_{(6)}$—Br ionisation, and it continues with the reactions of the carbonium ion *IX* and epibromonium ions *VIII* and *X*.

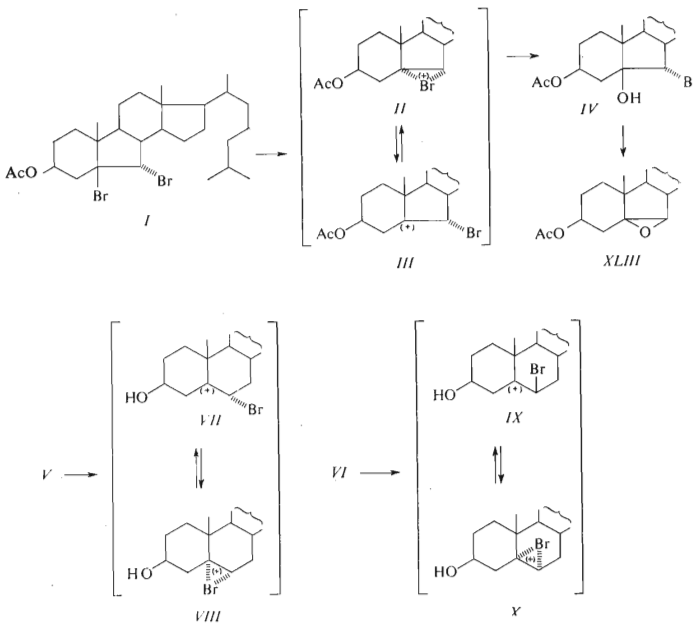
In 1877 Greene[1] published a report on the reaction of some metal oxides especially silver oxide, with vicinal dihalogenides, during which the formation of epoxides takes place. This reaction was later used successfully for substances which did not contain other sensitive groups[2], but little attention was given to the regioselectivity and stereochemistry of the reaction. In our previous paper[4] we indicated the formation of a single of the two possible epoxides during the transformation of the acetate of 5,6α-dibromo-B-nor-5β-cholestan-3β-ol (*I*) and we explained this reaction as a consequence of the preferential solvolysis of the tertiary bound bromine, as well as by the properties of the 5α,6α-epibromonium ion *II* and bromohydrin *IV*. We considered it as interesting to investigate the utilisability of this reaction with homologous 5,6α-dibromo-5β-cholestan-3β-ol (*V*) (ref.[4]) or with its isomer *VI* where the fate of single onium species *VII* and *VIII*, or also *IX* and *X*, is dependent on the effect of other conformational factors[5].

Under the effect of the original Greene reagent, silver oxide, on the isomeric dibromides *V* and *VI* very complex mixtures were obtained. The main product from the second of the reactions is substance *XI* of the composition $C_{27}H_{46}O_2$ (mass spectrum), which contains two double bonds (NMR). This fact, as well as the spectral data of tetrahydro derivative of substance *XI* indicate that the cleavage of some of the skeletal bonds took place during the reaction. Therefore, in further experiments we substituted silver oxide by silver fluoride which is free of the unwanted oxidative

* Part CLXIII in the series On Steroids; Part CLXII: This Journal *39*, 307 (1974).

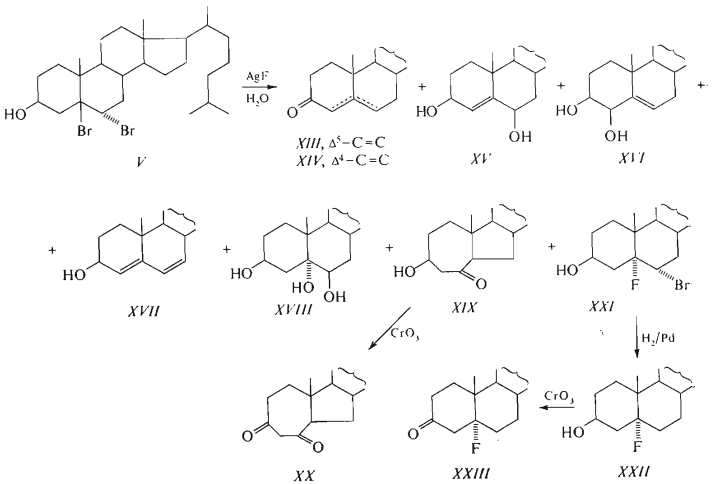
properties of the oxide. We checked the weak nucleophility of the fluoride ion in our previous work[3] where we used this technique without undesirable complications.

The transformation of dibromide *V* under these conditions gave a mixture of products which we separated by chromatography on silica gel and of which we measured the mass, infrared, or also NMR spectra. We observed that the expected 5,6β-epoxy--5β-cholestan-3β-ol (*XII*) (ref.[6]) was absent in the reaction mixture. The main products were identified by direct comparison with authentic samples, as for example 5-cholesten-3-one[7] (*XIII*, 32%), 4-cholesten-3-one (*XIV*, 4%), 4-cholestene-3β,6β--diol[8] (*XV*, 20%), 5-cholestene-3β,4β-diol[9] (*XVI*, 19%), 4,6-cholestadien-3β-ol[10] (*XVII*, 2%), and 5α-cholestane-3β,5,6β-triol[11] (*XVIII*, 3%). Another product was identified as 3β-hydroxy-A-homo-B-nor-5α-cholestan-4a-one[12] (*XIX*, 2·4%) because on oxidation it gave authentic[12] β-diketone *XX*. The last isolated product was 5-fluoro-6α-bromo-5α-cholestan-3β-ol (*XXI*, 3·7%) the structure of which was demonstrat-



ed in the following manner: On hydrogenolysis fluoro alcohol[13] *XXII* was obtained which was transformed to fluoro ketone[13] *XXIII* by oxidation. Elimination of hydrogen fluoride from this ketone afforded cholestenone, indicating thus that unchanged cholestane skeleton remained in substances *XXI* and *XXIII*. The 5α-configuration of fluorine in substances *XXI* and *XXIII* was confirmed by the shape of the $C_{(19)}$--protons signals in the PMR spectra of these compounds (singlets). The 6α-configuration of the bromine atom in substance *XXI* is evident from the shape of the Br—C—H signal (multiplet, $J_{F,6\beta H} = 29$ Hz, $J_{6\beta H,7\alpha H} = 11{\cdot}5$ Hz, $J_{6\beta H,7\beta H} = 5{\cdot}5$ Hz).

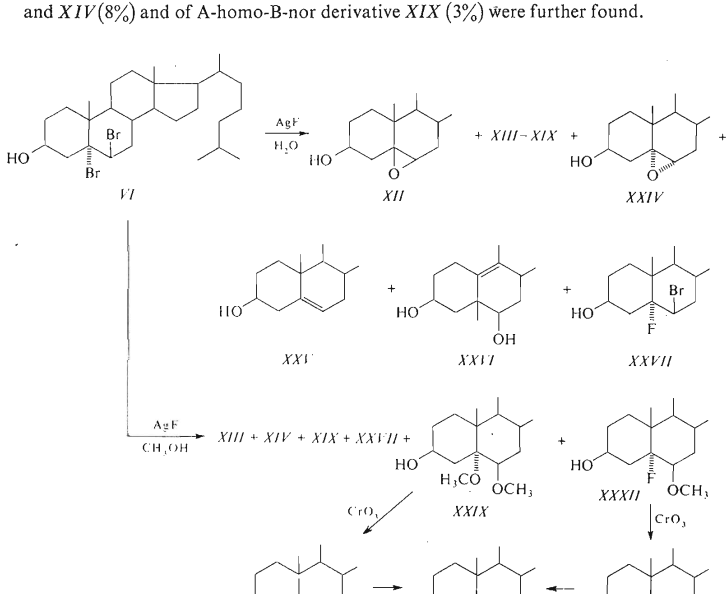
The transformation of dibromide *VI* under the effect of an aqueous silver fluoride solution afforded the expected 5,6α-epoxy-5α-cholestan-3β-ol[11] (*XXXIV*, 8%), but also the isomeric epoxide *XII* (15%). The by-products were mostly identical with the products of the preceding experiment: *XIII* and *XIV* (19%) *XV* (10%), *XVI* (10%), *XVII* (3%), *XVIII* (1%), and *XIX* (5%). In addition to this we also isolated cholesterol (*XXV*, 1%), Westphalen diol[14] (*XXVI* (1%), and instead of substance *XXI* the isomeric 5-fluoro-6β-bromo-5α-cholestan-3β-ol (*XXVII*, 15%) the structure of which was proposed on the basis of the PMR spectra (zero interaction of fluorine and $C_{(19)}$-protons, broad unresolved multiplet of the Br—C—H signal). This was confirmed by hydrogenolysis to the above prepared fluoro alcohol *XXII*. For the sake of




*V* *XIII*, $\Delta^5$-C=C *XIV*, $\Delta^4$-C=C *XV* *XVI* *XVII* *XVIII* *XIX* *XXI* *XX* *XXIII* *XXII*

comparison we also prepared the isomeric 5-bromo-6β-fluoro-5α-cholestan-3β-ol (*XXVIII*) by the standard addition[15] of bromide fluoride to cholesterol.

We considered the substitution of water by its homologue, methanol, as a convenient modification of the preceding experiment. The main products were fluoro derivative *XXVII* (29%) and 5,6α-dimethoxy-5α-cholestan-3β-ol (*XXIX*, 26%). Its structure was proved by oxidation to dimethoxy ketone *XXX* by the decomposition of which the known 6β-methoxy-4-cholesten-3-one[16] (*XXXI*) was obtained. The molecular elipticity value for ketone **XXX** ($\Delta\varepsilon_{287} = 2{\cdot}19$) is indicative for the 5α-configuration of substances *XXX* and *XXIX*. Of monomethoxy derivatives we isolated 5-fluoro-6β-methoxy-5α-cholestan-3β-ol (*XXXII*, 17%) which was again correlated with substance *XXXI* by its oxidation and dehydrofluorination. The 5α-configuration of fluorine in substances *XXXII* and *XXXIII* is again confirmed by its PMR spectrum ($J_{F,19H} = 0$ Hz). In the reaction mixture a smaller amount of cholestenones *XIII* and *XIV* (8%) and of A-homo-B-nor derivative *XIX* (3%) were further found.




*VI* *XII* *XXIV*

*XXV* *XXVI* *XXVII*

*XXIX* *XXXII*

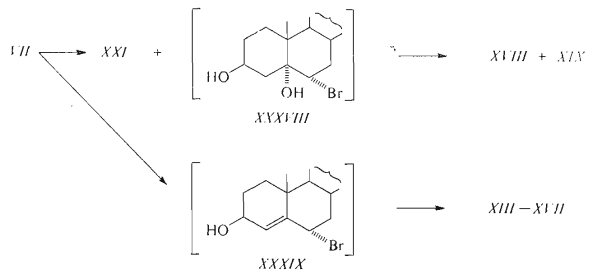
*XXX* *XXXI* *XXXIII*

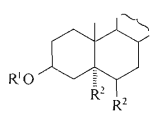
These experiments were completed by several model experiments which confirmed that the fluoro derivative *XXVII* is stable against the action of silver fluoride in methanol and that 6β-bromo-5α-cholestan-3β-yl-acetate[17] (*XXXIV*) resists the effect of this reagent in water, while 5-bromo-5α-cholestane-3β-yl acetate[17] (*XXXV*) smoothly afforded under standard conditions a mixture of 4- and 5-cholestene-3β--yl-acetates (*XXXVI* and *XXXVII*).

From these data and common ideas on the properties of carbonium and epibromonium ions it is possible to construe a picture of the fate of 5,6α-dibromide *V* in the course of the reaction: the fact that none of the two possible epoxides *XII* or *XXIV* could be found among the products is against the function of epibromonium ions in the process of the reaction. Moreover, the finding of *cis*-fluoro bromide *XXI* cannot be explained by the opening of epibromonium ions with fluoride anion, but by the interaction of this anion with carbonium ion *VII*. In this case a competitive reaction with another nucleophile present in the reaction should be expected, *i.e.* hydroxyl ion; the evidence for the fact that such a reaction took place under formation of *cis*-bromohydrin *XXXVIII* may be found in the presence of further products, A-homo-B-nor derivative *XIX* and triol *XVIII*. Further, the carbonium ion undergoes the elimination of a proton. Model experiments with bromo derivative *XXXV* indicated that 1,2-elimination takes place exclusively and that the unisolated product is 6α-bromo-4-cholesten-3β-ol (*XXXIX*) from which elimination products (ketone *XIII* and *XIV*, dienol *XVII*) as well as substitution products (diols *XV* and *XVI*) are formed. Cholestenone is also one of the products of chlorohydrin *XL* dehydration with potassium hydrogen sulfate in acetic anhydride, as carried out by Mishina[18]. In this case too the reaction is explained by the primary formation of the $C_{(5)}$-carbonium ion. The entering of the hydroxyl group into the positions 4β and 6β is not in contradiction with the results of related reactions; in the above mentioned paper Mishina described the isolation of 4β-hydroxy derivative *XLI*, while Petrow[19] prepared isomeric *XLII* by reacting dibromide *VI* with silver acetate. The solvolysis of allylic halogenides affords a mixture of 4β and 6β-hydroxycholestanes or their derivatives (ref.[20] and the references therein). These results, for the interpretation of which we in no case needed the existence of epibromonium ion *VII* as a prerequisite, contrasts with the situation in B-norsteroids. Different behaviour of dibromides *I* and *V* is probably due to the different geometry and thermodynamic stability of corresponding carbonium ions *III* and *VII*; while the first of them is derived from the thermodynamically more stable B-nor-5β-cholestane, the second is derived from the thermodynamically less stable 5β-cholestane and therefore it assumes a more suitable conformation[21] rapidly.

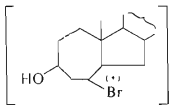
Among the products of transformation of dibromide *VI* substances *XIII* to *XVII* also occur. Their formation may be explained, similarly as in the preceding consideration, by a preferential $C_{(5)}$—Br ionisation, decomposition of the carbonium ion *IX* and further reactions of 6β-bromo-4-cholesten-3β-ol (*XLIV*). In addition

the ion *IX* may undergo Wagner–Meerwein rearrangement, as shown by one of the final products, the Westphalen diol *XXVI*. In addition to this group of substances the mixture contains all compounds which demonstrate the existence of epibromonium ions *VIII* and *X*, *i.e.* epoxides *XII* and *XXIV* and fluoro bromide *XXVII* (totally about 38%). The finding of epoxide *XII* proves that a part of the starting compound *VI* splits off first the bromide ion from the position $C_{(6)}$ forming 5α,6α-epibromonium ion *VIII* which undergoes diaxial opening with water to bromohydrin *XLV*, the precursor of epoxide *XII*, or with methanol to methoxy bromide *XLVI*, the precursor of methoxy fluoride *XXXII*. The alternative explanation of the formation

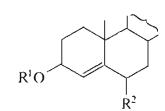


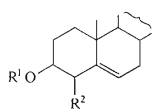

*XXVIII*, $R^1 = H$, $R^2 = Br$, $R^3 = F$
*XXXIV*, $R^1 = Ac$, $R^2 = H$, $R^3 = Br$
*XXXV*, $R^1 = Ac$, $R^2 = Br$, $R^3 = H$
*XLV*, $R^1 = H$, $R^2 = Br$, $R^3 = OH$
*XLVI*, $R^1 = H$, $R^2 = Br$, $R^3 = OCH_3$




*XLVII*




*XXXVI*, $R^1 = Ac$, $R^2 = H$
*XLIV*, $R^1 = H$, $R^2 = Br$




*XXXVII*, $R^1 = Ac$, $R^2 = H$
*XLI*, $R^1 = Ac$, $R^2 = OH$
*XLII*, $R^1 = H$, $R^2 = OAc$

of compound *XXXII* by methanolysis of fluoro bromide *XXVII* was excluded by model experiment. We consider that epibromonium ion *VIII* may also undergo a skeletal rearrangement leading to A-homo-B-norderivative *XIX via XLVII*. This opinion is supported by stereoelectronic requirements put on such a rearrangement[12] and by the analogy with the isomerisation of tirucallane[22]. If this view is correct then the preferential $C_{(6)}$—Br ionisation in dibromide *VI* is responsible for the formation of substances *XII* and *XIX* (about 20%), while other compounds are the results of processes initiated by $C_{(5)}$—Br ionisation.

Summarizing, it may be said that in all compared dibromides, *I*, *V* and *VI*, the reaction with silver fluoride is initiated by the splitting off of the bromide ion from the position 5; only in diaxial dibromide *VI* a sequence started by the splitting off of the secondary bound bromine from the position 6 competes with this process to a certain extent. The increase in reactivity of the last mentioned substituent is attributed to the antiparallel arrangement of both bromine atoms, that is suitable for the formation of epibromonium ion *VIII* in which 1,3-diaxial interactions of the $C_{6\beta}$-bromine with the substituents on carbon atoms $C_{(8)}$ and $C_{(10)}$ are eliminated.

## EXPERIMENTAL

The melting points were determined on a Kofler block and they are not corrected. Analytical samples were dried at room temperature at 0·2 Torr for 8 hours over phosphorus pentoxide. The infrared spectra were measured in tetrachloromethane unless stated otherwise, the ultraviolet spectra in ethanol, and circular dichroism and optical ratotation in chloroform and PMR spectra in deuteriochloroform. The identity of the samples obtained by various routes was proved by the comparison of their IR spectra and on the basis of mixture melting points. The aqueous solution of silver fluoride contained 2 g of substance per 1 ml of volume.

### Reaction of 5,6β-Dibromo-5α-cholestan-3β-ol with Silver Oxide

A solution of 500 mg of compound *VI* in 5 ml of tetrahydrofuran was shaken with a freshly prepared neutral silver oxide (approx. 1·3 g) for 15 minutes at room temperature. Chloroform (50 ml) was added to the reaction mixture and the solid material was separated by filtration. The filtrate was evaporated to dryness. Chromatography of the residue on 300 g of silica gel (10% of ether in benzene) afforded 85 mg of conjugated and unconjugated ketones and 157 mg of a mixture of cholesterol and a substance less polar than cholesterol. Preparative chromatography on a silica gel layer (10% of ether in benzene, triple development) gave 21 mg of cholesterol (*XXV*, 146—149°C, $[\alpha]_D^{20}$ −40° (*c* 1·1) and 125 mg of seco steroid *XI* (m.p. 97—99°C (ether), $[\alpha]_D^{20}$ −77° (*c* 1·2). IR spectrum: 3 600, 1 096, 1 044, 1 029, 1 665 $cm^{-1}$, PMR spectrum: 0·685 (s, 3H), 0·86 (d, J = 6 Hz), 0·915, (s, 3 H), 2·86 (bs, 1 H disappearing after addition of AcOD), 3·55 and 4·47 (d, $J_{gem}$ = 13 Hz, 1 + 1 H), 5·15 (bt, 1 proton), 5·59 (bd, 1 H) p.p.m.. For $C_{27}H_{46}O_2$ (402·6) calculated: 80·54% C, 11·52% H; found: 80·39% C, 11·57% H. Hydrogenation of compound *XI* (acetic acid, platinum oxide, 4 hours) afforded a mixture of about 6 substances of which 3 predominating are hydrocarbons $C_{27}H_{50}$ and two alcohols $C_{27}H_{50}O$ (mass spectra, IR spectra).

Reaction of 5,6α-Dibromo-5β-cholestan-3β-ol (*V*) with Silver Fluoride

A solution of 1·6 g of compound *V* in 20 ml of tetrahydrofuran was stirred with 3 ml of aqueous silver fluoride solution under nitrogen and exclusion of light. After one hour's stirring the mixture was diluted with 100 ml of chloroform and the liquid part was decanted from the precipitate of inorganic substances which was extracted with an additional portion of chloroform. The combined organic extracts were washed with water, dried over sodium sulfate and evaporated *in vacuo* to dryness. The residue was introduced in benzene onto a column of silica gel (120 ml) and then eluted rapidly with 10% ether in benzene. Gradually the following fractions were eluted: 5-Cholesten-3-one (*XIII*, 359 mg), m.p. 126–129°C, $[\alpha]_D^{20}$ −3° (*c* 1·1); IR spectrum: 1719 and 3030 $cm^{-1}$; PMR spectrum: 0·71 (s, 3 H); 0·875 (d, $J$ = 6 Hz, 6 H); 0·92 (d, $J$ = 6 Hz, 3 H); 1·17 (s, 3 H); 2·69 + 3·14 (d, 1 + 1 H, $J_{gem}$ = 17 Hz) p.p.m.; 4-Cholesten-3-one (*XIV*, 45 mg), m.p. 80–82°C, $[\alpha]_D^{20}$ +88° (*c* 0·9), IR spectrum: 1620 and 1680 $cm^{-1}$, PMR spectrum 0·72 (s, 3 H), 0·87 (d, $J$ = 6·1 Hz, 6 H), 0·91 (d, $J$ = 6·2 Hz, 3 H), 1·18 (s, 3 H), 5·71 (bs, 1 H), p.p.m.; 4,6-Cholestadien-3β-ol (*XVII*, 22 mg), m.p. 110–113°C (acetone), UV spectrum: $\varepsilon_{240}$ 27560; 5-Fluoro-6α-bromo-5α-cholestan-3β-ol (*XXI*, 53 mg), m.p. 68–71°C (methanol, $[\alpha]_D^{20}$ +10° (*c* 0·9); PMR spectrum: 0·65 (s, 3 H), 0·86 (d, $J$ = 6 Hz, 6 H), 0·89 (d, $J$ = 6 Hz, 3 H), 1·01 (s, 3 H). 2·70 (mt, 1 H), 3·98 (mt, 1 H), 4·22 (doublet of quartets, $J$ = 29, 11·5, 5·5 Hz, 1 H), p.p.m.; for $C_{27}H_{46}BrFO$ (485·6) calculated: 66·78% C, 9·55% H, 16·46% Br, 3·91% F; found: 66·65% C, 9·70% H, 16·19% Br, 3·90% F. By elution with 20% ether in benzene the following compounds were eluted gradually: 3β-Hydroxy-A-homo-B-nor-5α-cholestan-4a-one (*XIX*, 28 mg), m.p. 145–148°C (methanol), $[\alpha]_D^{20}$ +20° (*c* 0·8); mass spectrum: $M^+/e$ 402; IR spectrum 1695 and 3600 $cm^{-1}$ ($CHCl_3$); PMR spectrum: 0·655 (s, 3 H); 0·86 (d $J$ = 6 Hz, 6 H); 0·91 (d, $J$ = 6 Hz, 3 H); 1·15 (s, 3 H); 2·35 (bs, disappears after addition of AcOD); 2·5–2·8 (mt, 2 H); 3·55–3·90 (mt, 1 H) p. p. m.; CD (cyclohexane): $\Delta\varepsilon_{298}$ +1·41; for $C_{27}H_{46}O_2$ (402·6) calculated: 80·54% C, 11·52% H, found: 80·40% C, 11·60% H; 5-Cholestene-3β,4β-diol (*XVI*, 225 mg) m.p. 176–177°C (dichloromethane–heptane, $[\alpha]_D^{20}$ −60° (*c* 0·9), IR spectrum ($CHCl_3$): 3610, 3555, 3430, 1660, 1630, 1053 and 962 $cm^{-1}$. A mixture of methanol (15%) in ether eluted: 4-Cholestene-3β,6β-diol (*XV*, 240 mg), m.p. 255–260°C (benzene), $[\alpha]_D^{20}$ +9° (*c* 0·6); for $C_{27}H_{46}O_2$ (402·6) calculated: 80·54% C, 11·52% H; found: 80·48% C, 11·37% H; 5α-Cholestane-3β,5,6β-triol (*XVIII*, 35 mg), m.p. 240–245°C (methanol); for $C_{27}H_{48}O_3$ (420·7) calculated: 77·09% C, 11·50% H; found: 76·80% C, 11·62% H.

*Determination of epoxides in mixtures by gas chromatography*: The ratio of isomers *XII*, *XXIV*, *XIX* and *XVI* which partly overlap in chromatography on silica gel were determined by gas chromatography of corresponding trimethylsilyl derivatives (Perkin Elmer F11) using a glass column (2 m, diameter 4 mm) packed with Gas Chrom Q (100–120 mesh) wetted with 3% QF1 (temperature 230°C, carrier gas nitrogen, 17·5 ml/min). The mother liquors after crystallisation of compounds *XVI* and *XIX* did not display peaks due to trimethylsilyl derivatives of *XII* or *XXIV*.

*Determination of epoxide* XII *in the mixture after reduction to* 5β-*cholestane*-3β,5β-*diol*: The thermal lability of the trimethylsilyl derivative of substance *XII* threw doubt on the reliability of the GLC results; therefore the sample under investigation was reduced by two hours refluxing with lithium aluminium hydride in tetrahydrofuran. From the mixture the zone corresponding to 5β-cholestane-3β,5-diol was isolated, which was obtained under identical conditions from authentic epoxide *XII* in 40% yield. The mother liquors after substances *XVI* and *XIX* from the preceding experiment do not afford any 5β-cholestane-3β-diol.

A-Homo-B-nor-5α-cholestane-3,4a-dione (*XX*)

Hydroxy ketone *XIX* (30 mg) was oxidized by Jones'[23] method at 20°C for 3 minutes. The product was extracted with ether and purified by thin-layer chromatography, m.p. 145–146°C; IR spectrum: 1722 and 1700 $cm^{-1}$, UV spectrum (ethanol with KOH): $\varepsilon_{293} = 20000$. IR spectrum measured in chloroform is identical with that of an authentic specimen[12].

5-Fluoro-5α-cholestan-3β-ol (*XXII*)

*a*) A solution of substance *XXI* (30 mg) in 3 ml of methanol was hydrogenated at room temperature and atomospheric pressure on 30 mg Adams catalyst. After 5 hours the reaction mixture was worked up and the product purified by thin-layer chromatography on silica gel (10% of ether in benzene), m.p. 124 and 132–134°C (ethanol), $[\alpha]_D^{20}$ +20° (*c* 1·1). For $C_{27}H_{47}FO$ (406·6) calculated: 79·73% C, 11·65% H, 4·67% F; found: 79·50% C, 11·69% H, 4·70% F. *b*) Fluoro bromide *XXVII* (180 mg) in 5 ml of ether and 5 ml of methanol was hydrogenated at room temperature on 5% $Pd/CaCO_3$ (150 mg) for 8 hours. The product was separated from the residue of the starting material by chromatography on silica gel and crystallisation from methanol. M.p. 133–134°C, undepressed on admixture with the sample prepared under *a*).

5-Fluoro-5α-cholestan-3-one (*XXIII*)

Hydroxy derivative *XXII* (10 mg) was oxidized according to Jones and the product purified by thin layer chromatography on silica gel with 15% of ether in benzene, and crystallisation from heptane, 149–151°C, $[\alpha]_D^{20}$ +37° (*c* 0·7). IR spectrum ($CHCl_3$): 1715, 1423, 1415, 1126 $cm^{-1}$. $\Delta\varepsilon$ + 0·86 at 290 nm. PMR spectrum: 0·66 (s, 3 H); 0·84 (d, $J$ = 6 Hz, 6 H); 0·89 (d, $J$ = = 6 Hz, 3 H); 1·12 (s, 3 H); 2·36 (mt, 2 H) p.p.m.. For $C_{27}H_{45}FO$ (404·6) calculated: 80·14% C, 11·21% H, 4·70% F; found: 80·06% C, 11·29% H, 4·61% F.

4-Cholesten-3-one (*XIV*)

Fluoro ketone *XXIII* (20 mg), was refluxed with pyridine (5 ml) for 40 minutes and after evaporation of the solvent the product was chromatographed on a thin layer of silica gel with 20% ether in benzene mixture. The product (12 mg) after crystallisation from acetone at −60°C had m.p. 82–85°C, the IR spectrum was identical with that of an authentic sample.

Reaction of 5,6β-Dibroms-5α-cholestan-3β-ol (*VI*) with Silver Fluoride

*a*) Dibromide *VI* (1·2 g) in 20 ml of tetrahydrofuran was stirred at 0°C with 3 ml of aqueous silver fluoride under nitrogen for one hour. The reaction mixture was mixed with 100 ml of chloroform and the extract was decanted from the precipitated inorganic material which was washed with additional portions of chloroform. The combined chloroform extract was washed with water, dried over sodium sulfate, concentrated, and chromatographed on a silica gel column (10% of ether in benzene). The following compounds were eluted gradually: 5-Cholesten-3-one (*XIII*, 140 mg); 4-cholesten-3-one (*XIV*, 22 mg); 4,6-cholestadien-3β-ol (*XVII*, 25 mg); 5-fluoro-6β-bromo-5α-cholestan-3β-ol (*XXVII*, 160 mg), m.p. 133°C (ethanol); $[\alpha]_D^{20}$ −30° (*c* 1·0) PMR spectrum: 0·71 (s, 3 H); 0·87 (d, $J$ = 6 Hz, 6 H); 0·91 (d, $J$ = 5·9 Hz, 3 H); 1·33 (s, 3 H); 3·91 (mt, 1 H), 4·09 (mt, 1 H) p.p.m.. For $C_{27}H_{46}BrFO$ (485·6) calculated: 66·78% C, 9·55% H, 16·46% Br, 3·91% F; found: 66·74% C, 9·57% H, 16·28% Br, 3·86% F. 5-Cholesten-3β-ol (*XXV*, 11 mg). Elution with a mixture of 20% of ether in benzene afforded: 3β-Hydroxy-A-homo-B-nor-5α--cholestan-4a-one (*XIX*, 44 mg), 5-cholestane-3β,4β-diol (*XVI*, 89 mg), 5,6α-epoxy-5α-chole-

stan-3β-ol (*XXIX*, 70 mg), 5,6β-epoxy-5β-cholestan-3β-ol (*XII*, 133 mg). Using ether and then ether with methanol 5β-methyl-19-nor-9-cholestene-3β-6β-diol (*XXVI*, 8 mg), m.p. 109—111°C, 4-cholestene-3β,6β-diol (*XV*, 85), and 5α-cholestane-3β,5,6β-triol (*XVIII*, 10 mg) were eluted consecutively. *b*) A solution of 1·54 g of dibromide *VI* in 15 ml benzene and 30 ml methanol was stirred at room temperature and under nitrogen for 72 hours in the presence of finely powdered silver fluoride (3 g). Inorganic material was filtered off, the filtrate evaporated *in vacuo* to dryness and the residue separated on a silica gel column (120 g with 10% of ether in benzene. The following fractions were obtained: 5-Cholestan-3-one (*XIII*, 40 mg), 4-cholesten-3-one (*XIV*, 40 mg), 5-cholesten-3-ol (*XXV*, 9 mg), 5-fluoro-6β-bromo-5α-cholestan-3β-ol (*XXVII*, 345 mg). 5-Fluoro-6β-methoxy-5α-cholestan-3β-ol (*XXXII*, 187 mg), m.p. 133—135°C (acetone and heptane), $[\alpha]_D^{20}$ −22° (*c* 1·1); IR spectrum ($CHCl_3$): 3600, 1097 and 1039 $cm^{-1}$; PMR spectrum: 0·64 (s, 3 H), 0·83 (d, $J$ = 6 Hz, 6 H), 0·86 (d, $J$ = 5·9 Hz, 3 H), 1·02 (s, 3 H), 3·14 (mt, 1 H), 3·27 (s, 3 H), 3·93 (mt, 1 H) p.p.m.. For $C_{28}H_{49}FO_2$ (436·7) calculated: 77·01% C, 11·31% H, 4·35% F; found: 76·90% C, 11·28% H, 4·30% F. 5,6β-Dimethoxy-5α-cholestan-3β-ol (*XXIX*, 292 mg), m.p. 155—158°C, $[\alpha]_D^{20}$ −6° (*c* 1·1); IR spectrum: 3610, 1037, 1080, 1096 $cm^{-1}$. For $C_{29}H_{52}O_3$ (449·7) calculated: 77·62% C, 11·68% H; found: 77·48% C, 11·59% H. 3β-Hydroxy-A-homo-B-nor-5α-cholestan-4a-one (*XIX*, 43 mg).

5-Fluoro-6β-methoxy-5α-cholestan-3-one (*XXXIII*)

Hydroxy derivative *XXXII* (30 mg) was oxidised according to Jones and the product was purified chromatographically on a silica gel thin-layer with 10% of ether in benzene, m.p. 90—91°C (methanol), $[\alpha]_D^{20}$ +8° (*c* 1·3); PMR spectrum: 0·705 (*c*, 3 H), 0·87 (d, $J$ = 6 Hz, 6 H), 0·91 (d, $J$ = 6 Hz, 3 H), 1·18 (s, 3 H). 3·11 (mt, 1 H), 3·29 (s, 3 H) p.p.m.. For $C_{28}H_{47}FO_2$ (434·7) calculated: 77·37% C, 10·90% H, 4·37% F; found: 77·40% C, 10·93% H, 4·12% F.

5,6β-Dimethoxy-5α-cholestan-3-one (*XIX*)

Hydroxy derivative *XXIX* (328 mg) was oxidised according to Jones and the product purified chromatographically on silica gel. Benzene eluted the main product (170 mg), m.p. 152—154°C (light petroleum, $[\alpha]_D^{20}$ +7° (*c* 1·5); IR spectrum: 1714, 1098 and 1075 $cm^{-1}$; $\Delta\varepsilon$ +2·16 at 288 nm: PMR spectrum: 0·71 (s, 3 H), 0·88 (d, $J$ = 6 Hz, 6 H), 0·92 (d, $J$ = 6 Hz, 3 H), 1·27 (s, 3 H), 3·01 (s, 3 H), 3·26 (s, 3 H), 3·24 (mt, 1 H), 3·00 (d, $J$ = 15·5 Hz, 1 H) p.p.m. For $C_{29}H_{30}O_3$ (4 46·7): calculated: 77·97% C, 11·28% H; found: 80·18% C, 11·40% H. 6β-Methoxy-4-cholesten-3-one (*XXXI*, 74 mg) and another unsaturated methoxy ketone (3 mg) represent the by-products of the reaction.

6β-Methoxy-4-cholesten-3-one (*XXXI*)

*a*) A solution of substance *XXXIII* (40 mg) in 0·3 ml of benzene was introduced onto a column of alumina (act. II, 1 g) and after 2 hours standing the organic material was eluted with ether. After purification by thin-layer chromatography the product melts at 113—115°C (methanol, 21 mg), $[\alpha]_D^{20}$ +41° (*c* 0·9); PMR spectrum: 0·73 (s, 3 H), 0·865 (d, $J$ = 6 Hz, 6 H), 0·91 (d, $J$ = 6 Hz, 3 H); 1·28 (s, 3 H), 3·175 (s, 3 H), 3·64 (t, $J_1 = J_2$ = 3 Hz, 1 H), 5·77 (s, 1 H) p.p.m. For $C_{28}H_{46}O_2$ (414·6) calculated: 81·10% C, 11·18% H; found: 81·02% C, 11·25% H. *b*) A solution of substance *XXX* (17 mg) in 5 ml of acetic acid was refluxed for 90 minutes. After evaporation of the solvent the product was chromatographed on a silica gel thin layer with 20% ether in benzene and crystallised from methanol; m.p. 113—115°C (4 mg), undepressed on admixture

with the sample prepared under *a*). IR spectrum is identical with the spectrum of the substance prepared under *a*).

*We thank Dr B. A. Marples for the spectrum of authentic A-homo-B-nor-5α-cholestane-3,4a-dione. For technical assistance our thanks are due to Miss M. Kopecká and for the measurement and the interpretation of the spectra to Dr M. Buděšinský, Dr J. Smolíková, Dr V. Lukeš, Mrs H. Pilařová and Mr P. Formánek.*

REFERENCES

1. Greene H.: Compt. Rend. *85*, 624 (1877).
2. Rigaudy J., Nédélec L.: Bull. Soc. Chim. France *1960*, 400.
3. Kasal A.: This Journal *37*, 3095 (1972).
4. Barton D. H. R., Miller E.: J. Am. Soc. *72*, 1066 (1960).
5. Hasegawa A., Sable H. Z.: J. Org. Chem. *31*, 4161 (1966).
6. Baxter R. A., Spring F. S.: J. Chem. Soc. *1943*, 613.
7. Fieser L. F.: J. Am. Chem. Soc. *75*, 5421 (1953).
8. Petrow V. A., Rosenheim O., Starling W. W.: J. Chem. Soc. *1938*, 677.
9. Rosenheim O., Starling W. W.: J. Chem. Soc. *1937*, 377.
10. Schmutz J., Schaltegger H., Sanz M.: Helv. Chim. Acta *34*, 1111 (1950).
11. Fürst A., Koller F.: Helv. Chim. Acta *30*, 1454 (1947).
12. Jones J. G. Z., Marples R. A.: J. Chem. Soc. *1968C*, 2698.
13. Barnes C. S., Djerassi C.: J. Am. Chem. Soc. *84*, 1962 (1962).
14. Snatzke G., Fehlhaber H. W.: Ann. *676*, 188 (1964).
15. Bowers A.: J. Am. Chem. Soc. *81*, 4107 (1959).
16. Julia S., Decouvelaere B., Eugelmann F.: Bull. Soc. Chim. France *1966*, 2277.
17. Shoppee C. W., Lack R.: J. Chem. Soc. *1960*, 4864.
18. Mishina J. S.: J. Org. Chem. *27*, 2807 (1962).
19. Petrow V. A., Rosenheim O., Starling W. W.: J. Chem. Soc. *1943*, 135.
20. Ireland R. E., Wrigley T. J., Young W. C.: J. Am. Chem. Soc. *80*, 4604 (1958).
21. Hornish R. E.: Dissertation Abstr. Int. B. *31*, 5878 (1971).
22. Halsall T G., Weston R. J.: Chem. Comun. *1972*, 1212.
23. Bowden K., Heilbron J. M., Jones E. R. H., Weedon C.: J. Chem. Soc. *1949*, 39.

Translated by Ž. Procházka.