Tetrahedron. Vol. 26, pp. 1043 to 1059. Pergamon Press 1970. Printed in Great Britain

STUDIES ON CONFORMATION AND REACTIVITY—VII*
THE SYNTHESIS AND TRANSANNULAR CYCLIZATION OF 2α-HYDROXY-5β-CHOLESTANE LEADING TO 2α,9α-EPOXY-5β-CHOLESTANE: A NEW FUNCTIONALIZATION REACTION AT 9C IN THE STEROID NUCLEUS†

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(*Received in Japan* 4 *August* 1969; *Received in the UK for publication* 14 *October* 1969)

Abstract—Previously unknown 2α-hydroxy-5β-cholestane (Va) was synthesized from cholest-4-en-3-one (VI) in five steps and in the overall yield of 15·7% via the intermediate 2α-hydroxycholest-4-en-3-one (VIII). Oxidation of Va with Jones reagent afforded the 2-oxo-5β system which exhibits a negative Cotton effect curve symmetrical to that of the already known 2-oxo-5α system. Treatment of Va with lead tetraacetate in benzene afforded 2α,9α-epoxy-5β-cholestane (VII) as the result of a new transannular cyclization reaction from 2C to 9C in the 5β-steroid series. The 2α,9α-epoxide (VII) was converted to the 9α,11α-epoxide (XVII) via the 9(11)-eno intermediate (XVI). Reductive cleavage of XVII with lithium ethylamine afforded the 2α,9α-dihydroxy-5β system (XVIII). The stereochemistry of the reactions was confirmed by both physical and chemical data. The results obtained provide successful and stepwise functionalizations at 9C and 11C in the 5β-steroid steries with 2α-hydroxy compounds as starting material.

INTRODUCTION

AN ORGANIC reaction of interest and value is the functionalization at an inactive C atom, namely the selective introduction of a desirable hetero function onto a certain C atom which is unreactive towards reagents under normal conditions. Such a reaction may take place only if it can be controlled regarding both electronic and steric factors of substrate and reagent. An efficient method for the success of the reaction may then be a sterically controlled intramolecular substitution reaction with a compound in which a reactive functional group and an inactive C atom are located closely enough, even transitorily, to enable the reaction to take place.

A number of such functionalization reactions with steroids as substrate have been reported in connection with the general objective of synthesizing modified steroid hormones. One of representative types has been the oxidative transannular cyclization of steroidal alcohols with lead tetraacetate or other oxidizing agents in non-polar solvents leading to various steroidal epoxides.[2–4] The cyclization reaction reported took place in the following direction, 11α → 1β, 11α → 1α‡, 2β → 19, 3α → 9α‡, 4α → 9α‡, 4β → 19, 6β → 19, 11β → 18 and → 19, and 20 → 18.

In a series of stereochemical investigations on the normal and abnormal ring opening of 4β,5-epoxy-3-oxo-steroids (I), we have prepared the 2α-hydroxy-4-en-3-oxo system (II) in the cholestane series.[5] The system in other steroid series has also been prepared.[6–8]

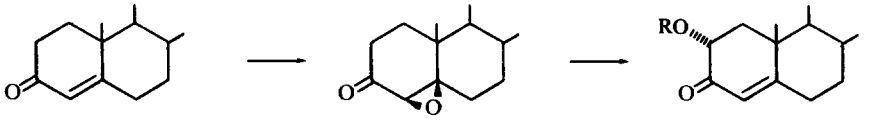
The system appeared useful starting material for the synthesis of previously unknown

* Part VI of this Series: A. Ishida, Y. Hiyoshi, T. Koga and M. Tomoeda, *Chem. Pharm. Bull. Tokyo* **17**, 355 (1969).

† Published in part as a communication[1] in 1965.

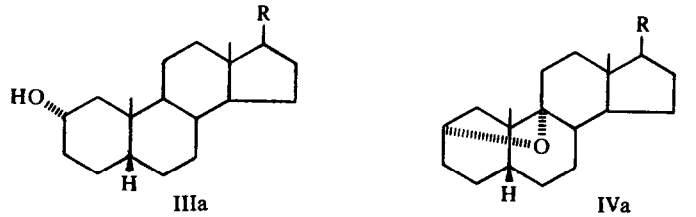
‡ These cyclizations took place in the 5β series.

2α-hydroxy-5β-steroids (IIIa), in which, as can be seen by inspection of the stereochemistry of the compound around A and B rings with the stereo model (IIIb), the position of and the distance between the 2α-alcohol and the 9-methine groups are sterically favoured to ring closure, forming a new steroidal 1,4-epoxide (IVa, b). Subsequent to a preliminary communication, the present paper describes the stereochemistry and the synthesis of 2α-hydroxy-5β-cholestane (Va) from cholest-4-en-3-one (VI), its successful transannular cyclization at 9C with lead tetraacetate leading to 2α,9α-epoxy-5β-cholestane (VII).



I II: R=H, Ac

CHART 1



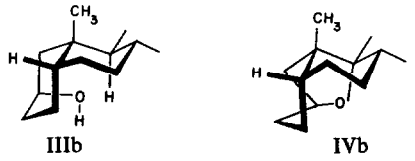


CHART 2

Synthesis of 2α-*hydroxy*-5β-*cholestane* (*Va*)

The starting material for the synthesis of Va, i.e. 2α-hydroxycholest-4-en-3-one (VIII),[5] was prepared from VI via 4β,5-epoxy-5β-cholestan-3-one (IX)[9] as described in a yield of 40·2%. When VIII was treated with ethanedithiol in glacial acetic acid using BF_3-etherate as catalyst, 2α-hydroxycholest-4-en-3-one ethylenethioketal (X), m.p. 163–165° was obtained in 86·6% yield. The IR and UV spectra supported the structure. The NMR spectrum of the compound shows a triplet at τ 6·65 with J = 2·7 c/s which could be assigned to the $-S-CH_2-CH_2-S-$ group at 3C. The NMR spectrum also shows a singlet at τ 4·52 due to the 4-vinylic hydrogen, and a broad doublet at τ 6·03 with a large J of 12 c/s assignable to the 2β-H of axial character.[10] The thioketal (X) was finally proved identical with a specimen prepared from 2α-acetoxy-cholest-4-en-3-one.[11]

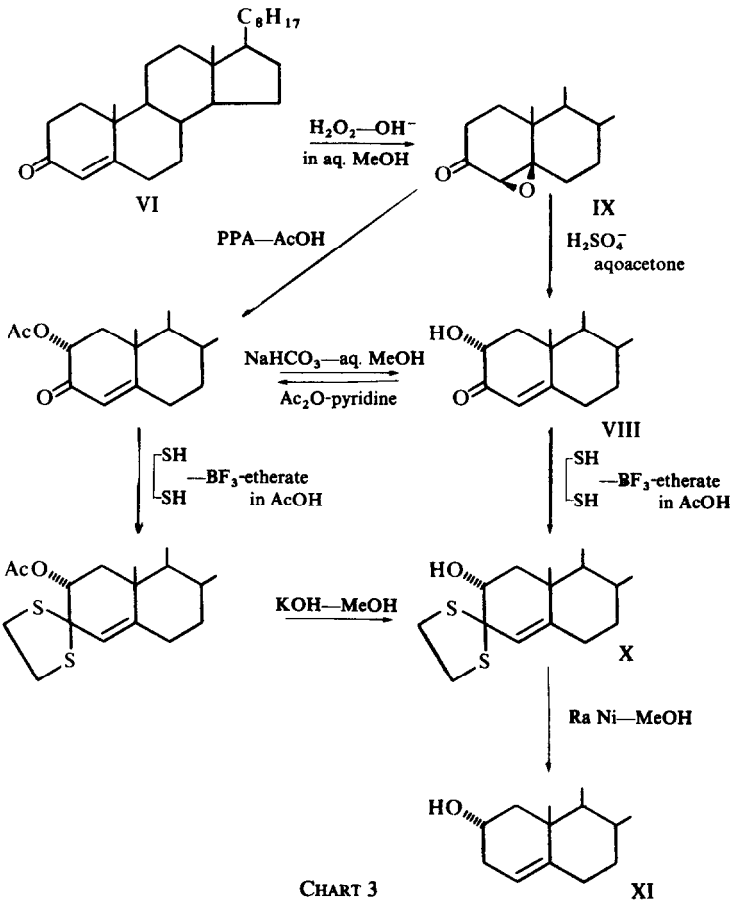


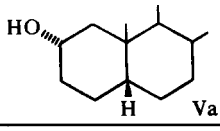
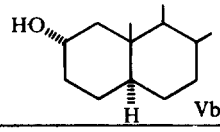
CHART 3

The thioketal (X) was then desulfurized followed by chromatography over neutral alumina to give 2α-hydroxycholest-4-ene (XI) in 81·9% yield. The m.p., 140·5–141·5°, and elemental analysis are in agreement with the expected molecular formula of $C_{27}H_{46}O$. The UV absorption spectrum shows λ_{max} 199 mμ (ε 7880) and the IR spectrum ν_{max} 1657 cm^{-1} which supports the 4-eno system. The 4-vinylic hydrogen appears in the NMR spectrum as a multiplet at τ 4·84. The NMR spectrum further shows a broad multiplet at τ 6·08 assignable to the 2β-hydrogen of axial character,[10] and a singlet at τ 8·93 due to the 19-Me group under a deshielding effect of the 4-eno group.[12] The spectroscopic evidence and the supporting information are in agreement with that reported.[11]

The 2α-hydroxy-4-eno compound (XI) was hydrogenated in ethanol with 20% Pt-charcoal. Chromatography of the crude product over silica gel afforded isomeric 2α-hydroxy-5β-cholestane (Va) and its 5α-isomer (Vb) in 55·1% and 25·5% yields respectively. Added to Va and Vb, a crystalline hydrocarbon, m.p. 72–73°, was obtained as the least polar product. The hydrocarbon did not show any characteristic absorption due to a functional group in its IR and UV spectra, and this suggested that it could be a further hydrogenated product, cholestane, but identification was not

carried out. Two isomeric alcohols, Va and Vb, were also obtained by catalytic hydrogenation in glacial acetic acid with 10% Pt-charcoal, but in different yields, i.e. 20·9% and 32·8% respectively. It was therefore concluded that catalytic hydrogenation in ethanol (neutral solvent) and acetic acid (acidic solvent) gives isomeric 5β and 5α systems in relative ratios of 2·2:1 and 1:1·6 respectively, and that catalytic hydrogenation in ethanol favours the formation of the desired 2α-hydroxy-5β system.

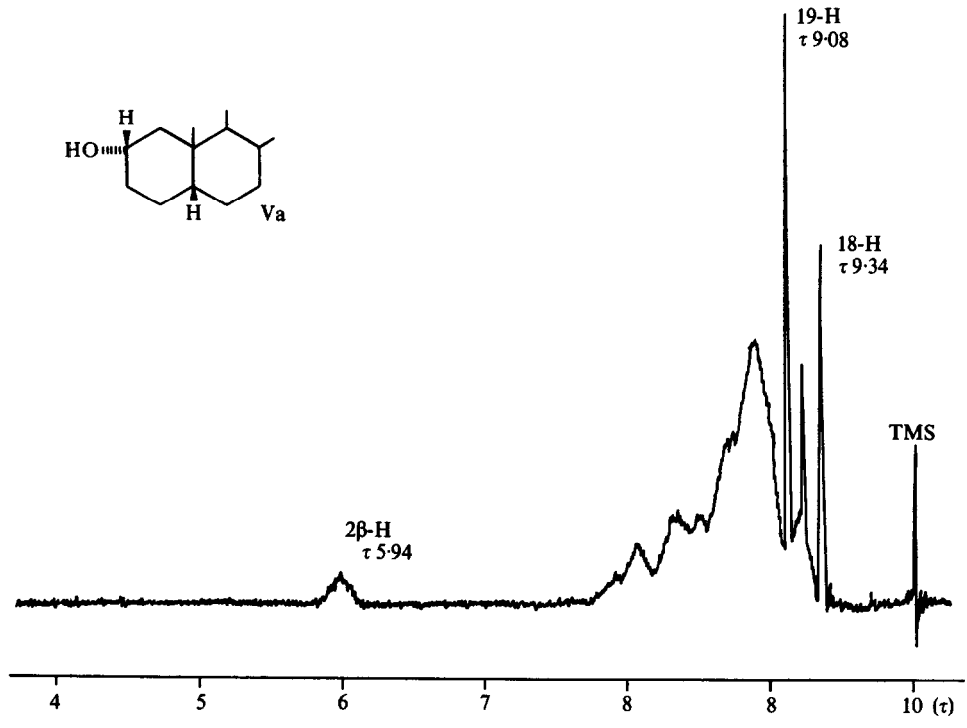
TABLE 1. CATALYTIC HYDROGENATION OF 2α-HYDROXYCHOLEST-4-ENE (XI) WITH PLATINUM–CHARCOAL AS CATALYST

Solvent (catalyst) \ Yield of product	 Va	 Vb	Relative ratio of Va:Vb
EtOH (20% Pt-C)	55·1%	25·5%	2·2:1
AcOH (10% Pt-C)	20·9%	32·8%	1:1·6

Confirmation of the structure and configuration of isomeric Va and Vb was carried out as follows: The 5β isomer (Va) was easily soluble in most polar and nonpolar solvents but was crystallized from a small volume of 99% ethanol under −10°, m.p. 106–107°.* The microanalysis was in agreement with the expected formula of $C_{27}H_{48}O$. Any absorption due to the 4-eno group was no longer present in the UV or IR spectra but only an absorption due to an OH group is present in the IR spectrum. The 5α isomer (Vb), crystallized from acetone, was proved as in the case of Va. Evidence for the assignment of α configuration at 2C of Va and Vb was provided by the NMR spectra. The NMR spectrum of Va shows a broad peak with the half width of 7 c/s at τ 5·94 due to the 2β-H while the spectrum of Vb shows a much broader peak with the half width of 23 c/s at τ 6·26 due to the same H. Therefore the 2β-H of Va is equatorial and that of Vb, axial,[10] and the configuration at 5C of Va should then be β and that of Vb, α. The assignment of these configurations in Va and Vb was supported by the fact that Va with the axial OH group is eluted faster from a chromatogram than Vb with the isomeric equatorial OH group.

Further evidence for the structure and configuration of Va and Vb was obtained as follows. Acetylation of Va and Vb with acetic anhydride in pyridine, followed by TLC, showed that acetylation of Va takes longer (87 hr) than Vb (17 hr), affording the corresponding acetates, XIIa and XIIb. This is apparently due to the axial 2α-OH group of Va and equatorial OH of Vb. XIIa shows in its NMR spectrum a broad peak with the half width of 7 c/s at τ 4·98 due to the 2β-H, while XIIb shows a much broader peak with the half width of 23 c/s at τ 5·17 due to the same H. The NMR evidence supports the assignment of configurations at 2C and 5C in V and XII.

* Fieser *et al.*[11] reported that the 5α isomer (Vb) was the only product isolated from the catalytic hydrogenation of XI in acetic acid.



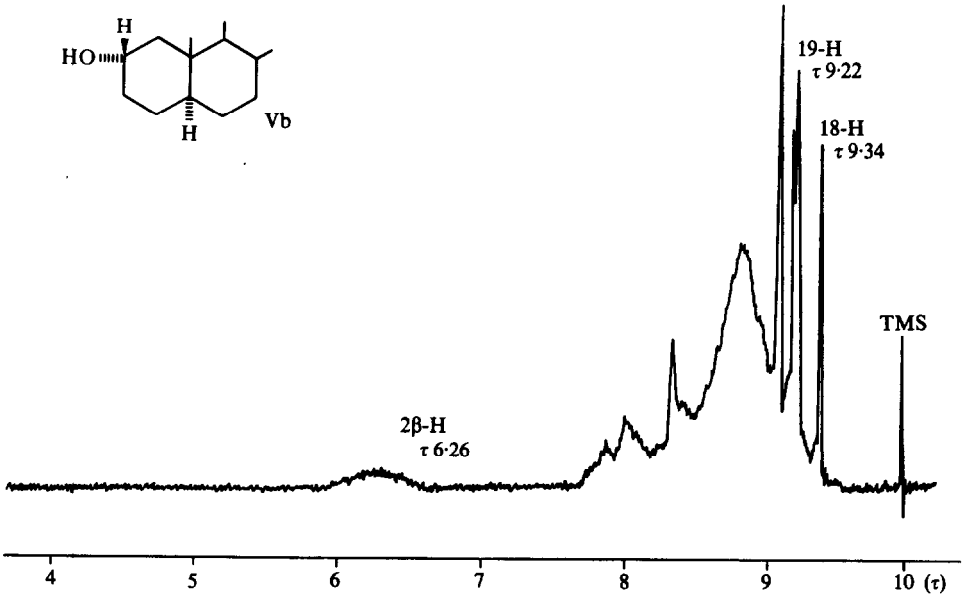


FIG. 1 NMR spectra of 2α-hydroxy-5β-(Va) and -5α-cholestane (Vb) in $CDCl_3$ at 60 Mc.

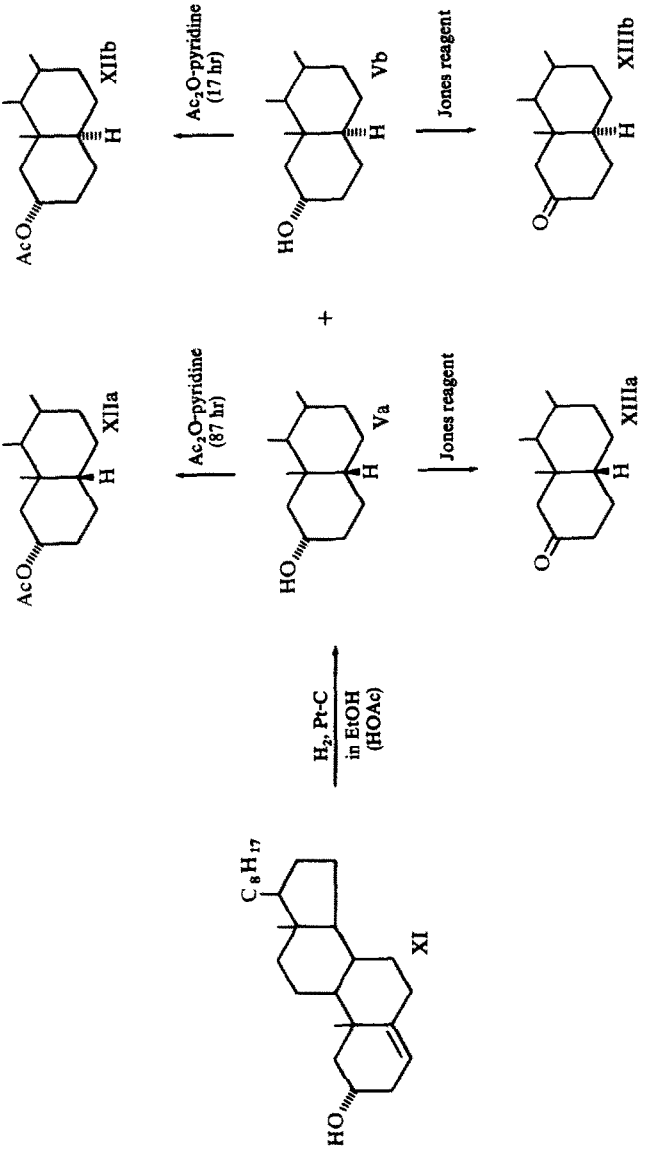

C8H17
XI
H2, Pt-C
in EtOH
(HOAc)
HO
AcO
H
XIIa
Ac2O-pyridine
(87 hr)
Va
Jones reagent
XIIIa
+
Ac2O-pyridine
(17 hr)
Vb
Jones reagent
XIIIb

CHART 4

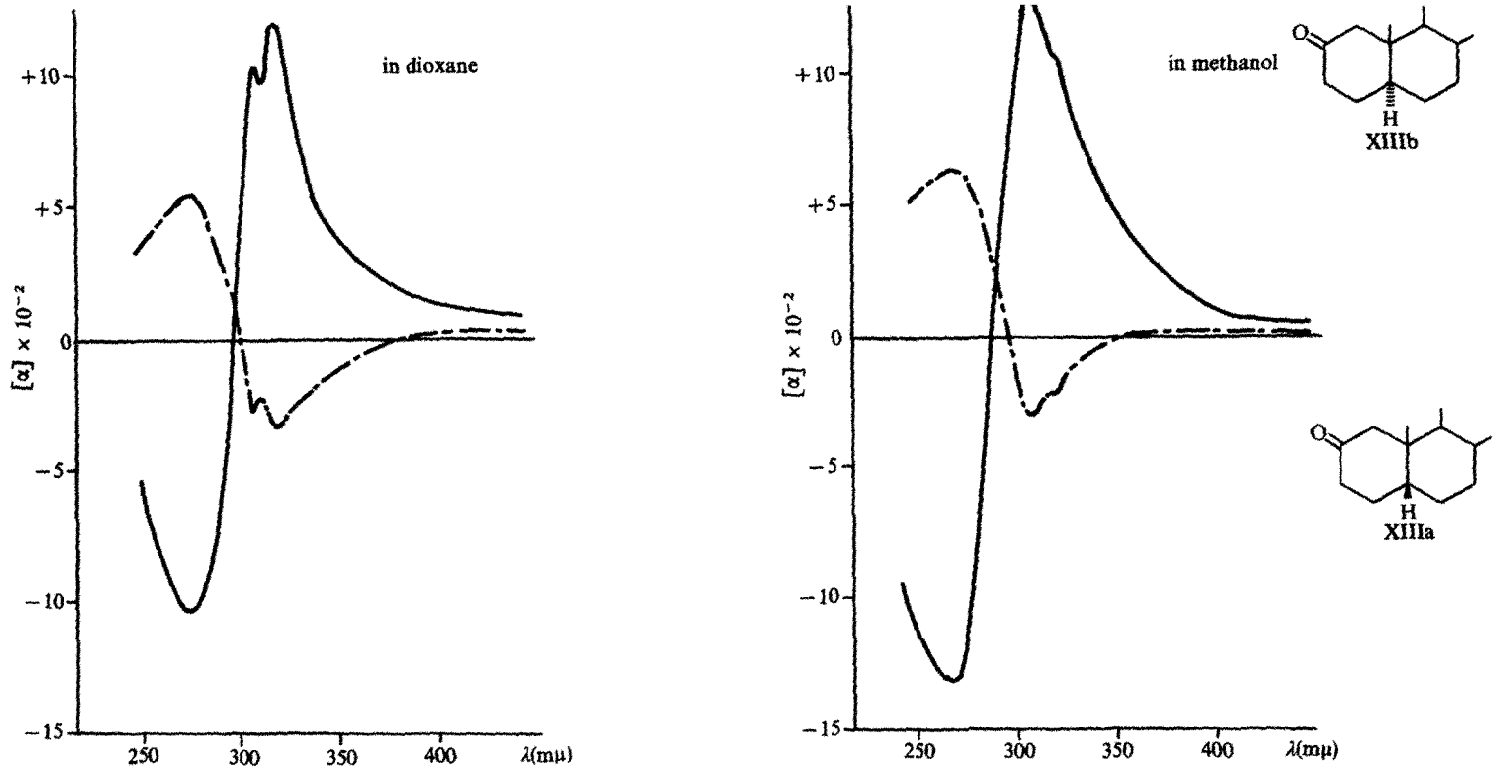


FIG. 2 ORD curves of 2-oxo-5β-(XIIIa) (— · — · —) and -5α-cholestane (XIIIb) (———) in dioxane and in methanol solution.

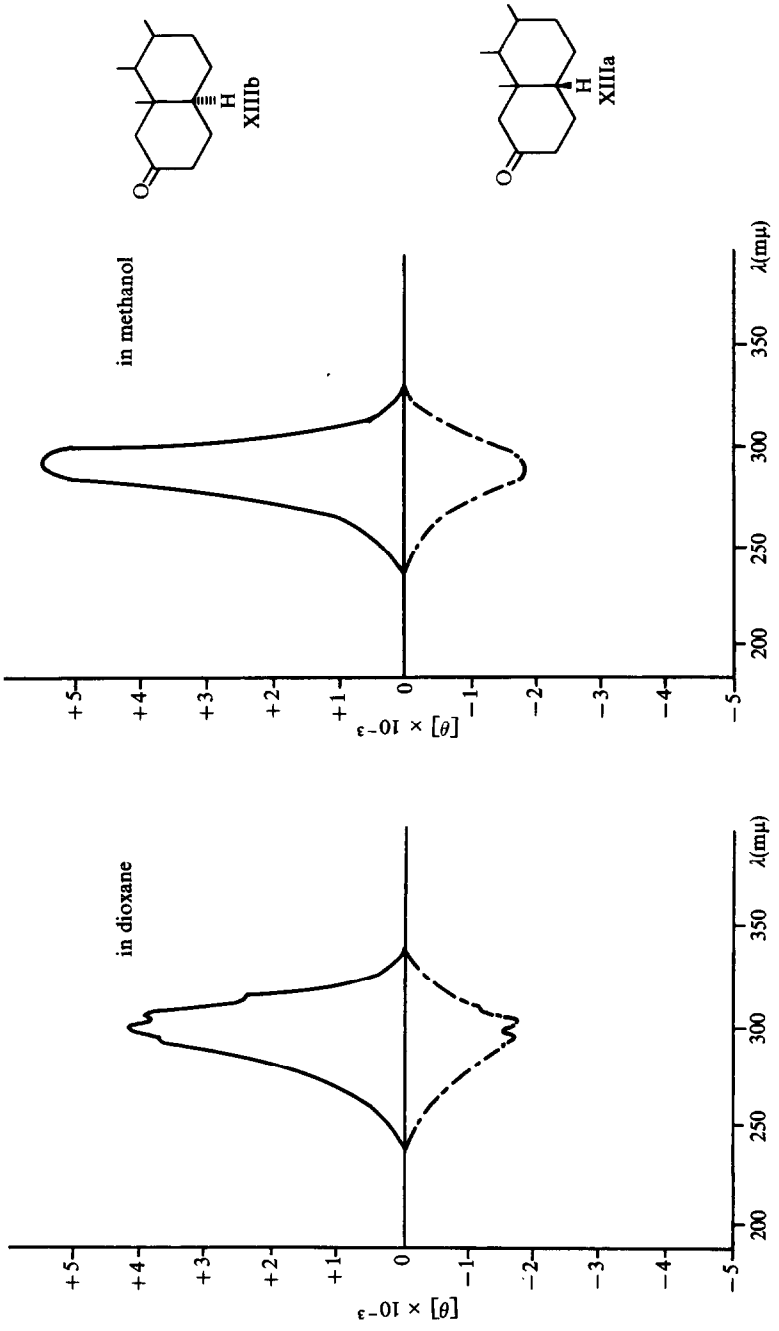


FIG. 3 CD curves of 2-oxo-5β-(XIIIa) (—·—·—) and -5α-cholestane (XIIIb) (———) in dioxane and in methanol solution.

15

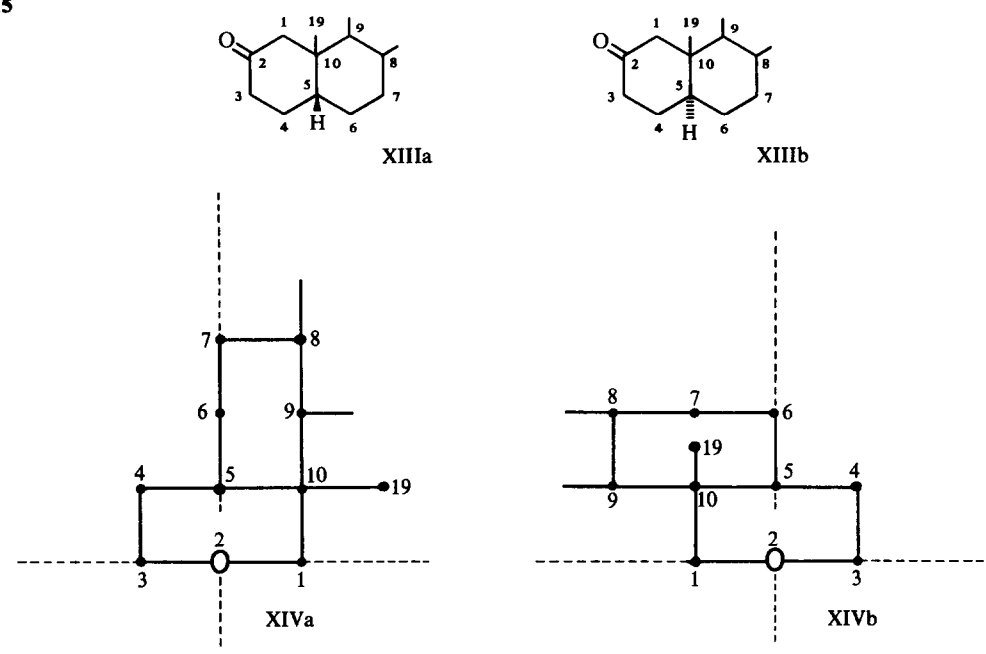


FIG. 4 Octant projection formulae of rings A and B of 2-oxo-5β-(XIIIa) and -5α-(XIIIb) steroid series.

The 5β and 5α configurations of Va and Vb were further proved as follows. Oxidation of Va and Vb with Jones reagent followed by chromatography over silica gel or neutral alumina gave their corresponding 2-oxo derivatives, i.e. the previously unknown 2-oxo-5β system (XIIIa), m.p. 87·5–88° and the previously known 2-oxo-5α system (XIIIb),[13] m.p. 131·5–132° in 94% and 92% yields respectively. Microanalyses and other physical properties supported their structures, and particularly those of XIIIb were in agreement with the literature.[13] The NMR spectrum of XIIIa shows a singlet peak due to the 19-Me group at τ 8·93 a lower field than that of XIIIb or τ 9·23, supporting the 5β configuration for XIIIa. Furthermore, XIIIa and XIIIb show in their ORD and CD curves negative and positive Cotton effects respectively as are shown in Figs 2 and 3. The negative sign of Cotton effects shown by XIIIa, in contrast to the positive sign of Cotton effects shown by XIIIb,[14, 15] can be understood by applying the Octant rule[16] to the cyclohexanone system of the A ring in the compound, as visualized in the Octant projection formulae* XIVa for XIIIa and XIVb for XIIIb (Fig. 4).

The overall yield of Va from VIII was now found to be 15·7%.

Transannular cyclization of Va *with lead tetraacetate leading to* 2α-9α-*epoxy*-5β-*cholestane*

Oxidation of Va with lead tetraacetate (two equivs) was followed by TLC and was almost complete in 5 hr. Chromatography of the crude product over silica gel afforded

* The Octant projection formulae were derived from possible conformations of the compounds with the A or cyclohexanone ring in the preferred chair form.

2α,9α-epoxy-5β-cholestane (VII) in 51·9% yield. A small amount of the starting material (Va) (1·8%) was recovered, and the 2-oxo derivative (XIIIa) was isolated as a minor product (3·4%). The structure of the 2α,9α-epoxide (VII), colourless needles, m.p. 46–47·5°, was supported by microanalysis and also by the IR spectrum showing an absorption at 1103 cm^{-1} due to the C—O—C bond in the compound. The NMR spectrum exhibits a broad doublet (J = 7 c/s) at τ 5·85 with the half width of 9 c/s due to the equatorial 2β-H[10] and a singlet at τ 8·97 due to the 19-Me group under the deshielding effect of the 2α,9α-epoxy function.

Oxidation of Vb, isomeric at 5C to Va, with lead tetraacetate was carried out analogously. Epoxidation at 9C was not observed, and the only product isolated apart from starting material (40·0%) was the corresponding acetate (XIIb; 6·5% yield).

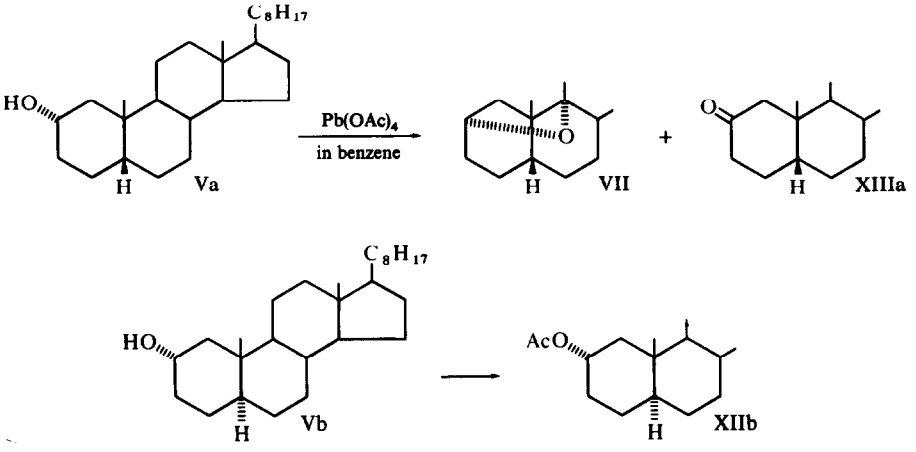


CHART 5

It was anticipated that acid-catalyzed epoxide fission of VII might lead to a new synthesis of 9α-hydroxy-steroids. The epoxide (VII) was treated with a mixture of acetic anhydride-BF_3-etherate followed by chromatography over silica gel giving two colourless oily products, XV and XVI. They resisted crystallization but were proved to be homogeneous by TLC. Chromatographically the less polar XV shows $[\alpha]_D$ −88·2° and absorptions at λ 211 mμ (ε 3870) in the UV spectrum and ν 1667 cm^{-1} in the IR spectrum suggesting the presence of a double bond. The presence of a vinylic hydrogen was not supported by NMR, so that the location of a double bond in the compound was assumed to be 8(9) or 8(14). An intensity lower than ε 5000 in the UV absorption due to the double bond and the appearance of signals in the NMR spectrum due to 18- and 19-Me groups at τ 9·29 and τ 9·00 respectively, suggested the location of the double bond to be 8(9) and not 8(14).[12, 17] The NMR spectrum further shows a multiplet with the half width of 9 c/s at τ 5·13 due to the equatorial 2β-H.[10] The evidence suggested the structure of XV to be 2α-acetoxy-5β-cholest-8(9)-ene, but further confirmation was not carried out.

The second and chromatographically more polar product XVI shows $[\alpha]_D$ + 19·2° and absorptions due to a double bond at λ 211 mμ (ε 3630) and ν 1647 cm^{-1} in the UV

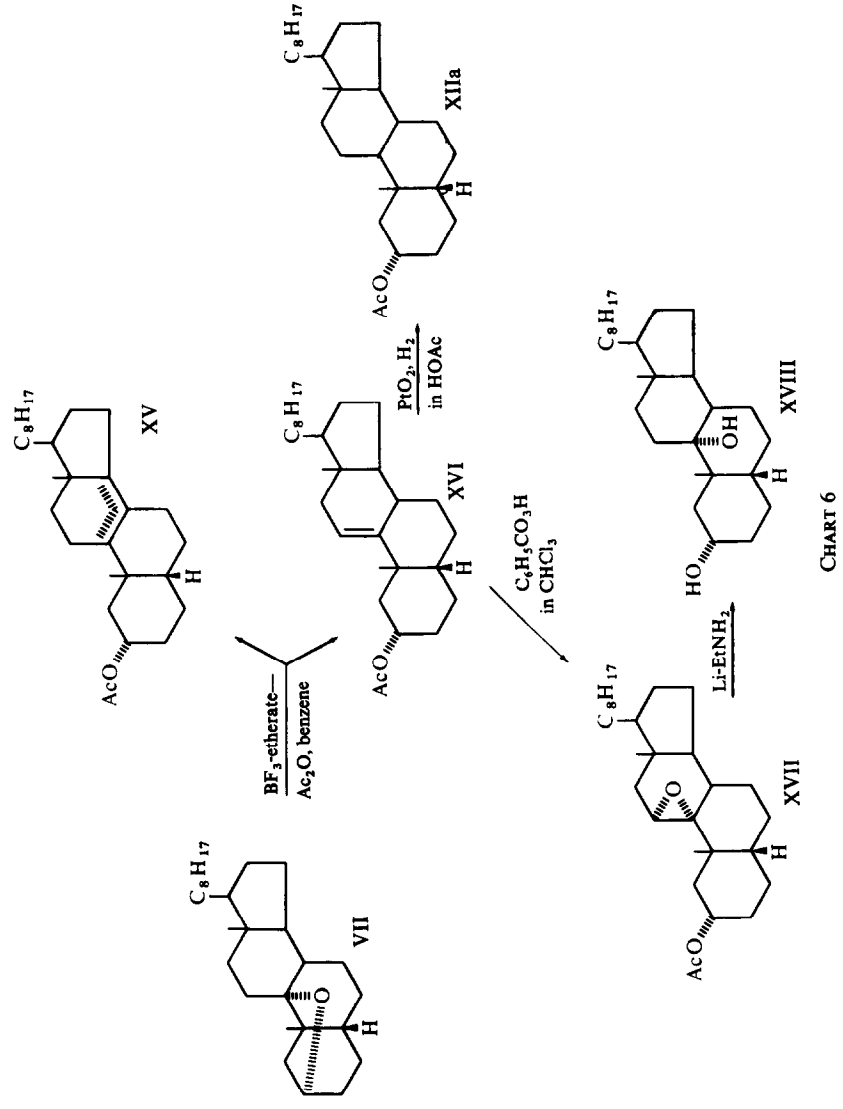

C8H17
XV
AcO
H
BF3-etherate—
Ac2O, benzene
C8H17
VII
O
H
C8H17
XVI
AcO
H
PtO2, H2
in HOAc
C8H17
XIIa
AcO
H
C6H5CO3H
in CHCl3
C8H17
XVII
O
H
AcO
Li-EtNH2
C8H17
XVIII
OH
H
HO

CHART 6

and IR spectra respectively. The IR spectrum further shows an absorption at ν 3049 cm^{-1} assignable to a vinylic hydrogen. Presence of a vinylic hydrogen was further supported by NMR spectroscopy, its spectrum showing a multiplet centred at τ 4·61. As the peaks due to the 18- and 19-Me groups in the NMR spectrum appear at τ 9·41 and τ 8·91 respectively, the location of the double bond must be 9(11).[12] The NMR spectrum shows a broad peak at τ 5·01 due to the 2β-H. Presence of an acetate group was supported both by IR and NMR spectra. The evidence suggested the structure of XVI to be 2α-acetoxy-5β-cholest-9(11)-ene. This was confirmed by catalytic hydrogenation of XVI with platinum oxide in glacial acetic acid to XIIa. It was therefore concluded that the transannular oxidation reaction did not cause any rearrangement or configurational change of the skeleton of Va.

The 9(11)-eno compound (XVI) was oxidized with perbenzoic acid in chloroform to give 2α-acetoxy-9α, 11α-epoxy-5β-cholestane (XVII) in 80·2% yield. Microanalysis of the 9α, 11α-epoxide (XVII), m.p. 118·5–119·5° and $[\alpha]_D$ −61·0°, supported the expected molecular formula of $C_{29}H_{48}O_3$. The IR spectrum shows ν 1727 cm^{-1} and 900 cm^{-1} due to an acetate and a C—O—C groups respectively. The NMR spectrum shows, in addition to a broad peak at τ 5·19 due to the 2β-H, a doublet of J = 5 c/s at τ 7·09 due to the 11β-epoxide hydrogen. The fact that the epoxy function has the α configuration was supported by NMR in that the epoxide causes a deshielding effect towards the 19-Me group appearing at τ 8·83 whereas this is not the case with the 18-Me group appearing at τ 9·34.[12]

The 9α,11α-epoxide (XVII) was then treated with lithium in ethylamine followed by chromatography over silica gel which caused the reductive epoxide fission at 11C and hydrolysis of the 2α-acetate group affording 2α,9α-dihydroxy-5β-cholestane (XVIII) in 75·1 % yield. The diol (XVIII), m.p. 208–209°, had an empirical formula of $C_{27}H_{48}O_2$ supported by microanalysis. The IR spectrum shows ν 3205 and 3127 cm^{-1} probably due to two OH groups, however, the NMR spectrum shows a single peak at τ 6·05 due to methine group bearing an OH function, which could be assigned to the 2β-hydrogen. This suggested that the epoxide fission did not take place at 9C but at 11C. The NMR spectrum further shows a peak at τ 8·94 due to the 19-Me group under the deshielding effect of the 9α-OH function and a peak at τ 9·34 due to the 18-Me group being not influenced by the 9α-OH function.[12] The evidence was further support for the assignment of the α-configuration of the epoxide function in XVII, and provided proof that epoxidation of the 9(11)-eno system in the 5β-steroid prefers to take place from the α-side.

DISCUSSION

It was anticipated that the previously unknown 2α-hydroxy-5β-steroid, if synthesized, might have a close proximity around the 2α-O and 9α-H atoms leading to a ring closure between these functions under conditions generating an oxygen cation at 2C. The desired system (Va) in the cholestane series could be synthesized with success from cholest-4-en-3-one (III) in five steps, and its successful transannular cyclization with lead tetraacetate led to a new steroidal tetrahydrofurane or the 2α,9α-epoxide (VII). Acidic epoxide fission of the 2α,9α-epoxide (VII) gave 2α-acetoxy 8(9) (XV) and -9(11)- (XVI) -eno compounds, the 9(11)-eno isomer (XVI) of which was then converted to the 2α,9α-diol (XVIII) via the intermediacy of the 9α,11α-epoxide (XVII). The successful and step-wise functionalization reactions at 9C and 11C with 2α-

hydroxy-5β-steroids as starting material, thus established, could be applied to other steroid systems with somewhat different stereochemical environments and with unique biological activities. Results will be reported elsewhere.

Meanwhile, oxidation of Va with Jones reagent afforded the previously unknown 2-oxo-5β system (XIIIa) showing a negative Cotton effect in both ORD and CD curves, exactly symmetrical to that of the previously known 2-oxo-5α system with positive sign (Figs 2 and 3). Much weaker intensities of the negative Cotton effect curves of the 2-oxo-5β system (XIIIa) compared with those of the positive Cotton effect curves of the 2-oxo-5α system* (XIIIb), could be due to different steric environments around the 2-oxo group of these compounds as visualized in their Octant projection formulae XIVa and XIVb. Further experiments should be necessary to understand the exact nature of the phenomenon in question.

EXPERIMENTAL

M.ps were taken on a Kofler-type hot plate, and are uncorrected. $[\alpha]_D$ Refers to $CHCl_3$, UV absorption spectra to 95% EtOH, and IR spectra to nujol unless otherwise stated. NMR spectra were run on a Varian Associated A-60 high resolution spectrometer with $CDCl_3$ as solvent, and the intensities or peak areas were measured by the integrater.

2α-Hydroxycholest-4-en-3-one (VIII)

Compound VIII was prepared by H_2SO_4-catalyzed abnormal ring opening of IX,[9] derived from VI.[5] The overall yield of VIII from VI was 40·2%; colourless needles, m.p. 147–148°; $[\alpha]_D^{14}$ +82° (*c* 0·98); λ_{max} mμ (ε): 243 (11,900); ν_{max} cm^{-1}: 3346 (m) (OH), 1675 (s) (C=O), 1612 (w) (C=C).

2α-Hydroxycholest-4-en-3-one ethylenethioketal (X)

To a soln of VIII (13·0 g) in 312 ml glacial AcOH, 19·5 ml ethanedithiol and 19·5 BF_3-etherate were successively added and the mixture kept at room temp for 15 min when colourless needles began to separate. The reaction was complete in 8 hr (TLC). The mixture was diluted with 90 ml MeOH, poured into ice-water, and the deposited colourless crystals were filtered off, washed with water, and dried *in vacuo*, m.p. 154–159°, wt. 14·6 g. Recrystallization from a mixture of acetone–ether gave X as colourless needles, m.p. 163–165°, wt. 13·4 g (86·6% yield). $[\alpha]_D^{24}$ +116·4° (*c*, 1·04); λ_{max}^{hexane} mμ (ε): 253 (750); ν_{max} cm^{-1}: 3481 (m) (OH), 1645 (w) (C=C); NMR τ: 4·52 (1 proton, s) (4-H), 6·03 (1 proton, d, J = 12 c/s) (2β-H), 6·65 (4 protons, t, J = 2·7 c/s) (—S—CH_2—CH_2—S—), 9·01 (3 protons, s) (19-H), 9·34 (3 protons, s) (18-H). The needles were identical with a specimen of X prepared from 2α-acetoxycholest-4-en-3-one.[11] Their IR and UV spectra were superposable.

2α-Hydroxycholest-4-ene (XI)

To a soln of X (4·0 g) in 300 ml MeOH, ca. 40 g Rabey Ni,[19] deactivated by refluxing in AcOEt and acetone for 15 min each, was added and the suspension was refluxed for 5 min. Concentration of the filtrate *in vacuo* gave colourless crystals, m.p. 106–122°, wt. 3·25 g. The crystals were chromatographed over 130 g neutral alumina (Woelm, grade III) when elution with 5·91. 4:1 light petroleum–benzene afforded XI as colourless needles, m.p. 132–137°, wt. 2·654 g (81·9% yield). Recrystallization from MeOH gave sample, m.p. 140·5–141·5°. (Found: C, 83·77; H, 12·01. Calc. for $C_{27}H_{46}O$: C, 83·87; H, 11·99%); $[\alpha]_D^{22}$ +79·2° (*c*, 0·99); λ_{max} mμ (ε): 199 (7880); ν_{max} cm^{-1}: 3263 (m) (OH), 1657 (w) (C=C); NMR τ: 4·84 (1 proton, m) (4-H), 6·08 (1 proton, m) (2β-H), 8·93 (3 protons, s) (19-H), 9·32 (3 protons, s) (18-H). Fieser and Romero[11] carried out the desulfurization of X with Raney Ni in acetone to give XI in a yield less than 25%.

Catalytic hydrogenation of XI-*formation of* 2α-*hydroxy*-5β- (Va) *and* -5α- (Vb) -*cholestanes*

(a) *Catalytic hydrogenation in* 99% EtOH. XI (5·0 g) in 200 ml 99% EtOH was hydrogenated with 2·5 g 20% Pt-C at 10°. After 557 ml H_2 was absorbed, the catalyst was filtered off, and the filtrate was concentrated *in vacuo* to give colourless needles, m.p. 77–91°, wt. 4·9 g. They were chromatographed over 150 g

* Similar results were reported, for instance, with 3-oxo-5α- and -5β-cholestanes.[14b, 18]

silica gel (Kanto Chemical Co.) when elution with 400 ml light petroleum gave colourless prisms, m.p. 69–71°, wt. 684 mg. Recrystallization from 99% EtOH gave sample, m.p. 72–73°; IR spectrum: no absorption due to functional group—probably cholestane but further confirmation of the structure was not carried out.

Further elution with 1·41. 2:1 light petroleum–benzene gave Va as colourless needles, m.p. 104–105·5°, wt. 2·771 g (55·1%). Recrystallization from a small amount of 99% EtOH (< −10°) gave sample, m.p. 106–107°. (Found: C, 83·38; H, 12·60. $C_{27}H_{48}O$ requires: C, 83·43; H, 12·45%); $[\alpha]_D^{18}$ +29·6° (*c*, 0·98): λ_{max} transparent above 210 mμ; ν_{max} cm^{-1}: 3347 (m) (OH); NMR τ: 5·94 (1 proton, m) (2β-H), 9·08 (3 protons, s) (19-H), 9·34 (3 protons, s) (18-H).

Further elution with 1·61. benzene gave Vb as colourless needles, m.p. 177–181°, wt. 1·280 g (25·5% yield). Recrystallization from acetone gave sample of m.p. 182·5–183°. (Found: C, 83·56; H, 12·45. Calc. for $C_{27}H_{48}O$: C, 83·43; H, 12·45%); $[\alpha]_D^{22}$ +25·4° (*c*, 1·03); λ_{max}: transparent above 210 mμ; ν_{max} cm^{-1}: 3260 (m) (OH); NMR τ: 6·26 (1 proton, m) (2β-H), 9·22 (3 protons, s) (19-H), 9·34 (3 protons, s) (18-H).

(b) *Catalytic hydrogenation in glacial acetic acid.* XI (100 mg) in 20 ml glacial AcOH was hydrogenated with 50 mg 10% Pt-C at 21°. After absorption of H_2 ceased, the catalyst was filtered off, and water (10 ml) was added to the filtrate to give colourless crystals. These were filtered off, washed with sat. $NaHCO_3$ aq and water, and dried *in vacuo*, m.p. 95–134°, wt. 95 mg. They were chromatographed over 4·8 g neutral alumina (Woelm, grade III) and elution with 5·0 ml light petroleum gave a colourless oily substance, wt. 11 mg; ν_{max}: no absorption due to functional group. This substance was not further investigated.

Further elution with 30 ml light petroleum gave Va as colourless needles, m.p. 103–105°, wt. 21 mg (20·9%). Recrystallization from 99% EtOH gave sample, m.p. 106–107°, alone and on admixture with a specimen of Va obtained above. Their IR spectra were superposable, ν_{max} cm^{-1}: 3348 (m) (OH).

Further elution with 70 ml 4:1 light petroleum–benzene gave Vb, m.p. 179–181°, wt. 33 mg (32·8% yield). Recrystallization from acetone gave sample, m.p. 182–183°, alone and on admixture with a specimen of Vb obtained above. Their IR spectra were superposable, ν_{max} cm^{-1}: 3260 (m) (OH).

2α-*Acetoxy*-5β-*cholestane* (XIIa)

To a soln of Va (200 mg) in 2·0 ml pyridine, 2·0 ml Ac_2O was added dropwise in the cold and the mixture kept at room temp; it was complete in 87 hr (TLC). The mixture was poured into ice-water to deposit an oily product which was extracted into $CHCl_3$. The $CHCl_3$ layer was washed with dil H_2SO_4, water, sat $NaHCO_3$ aq and water, and dried (Na_2SO_4). Concentration of the filtrate *in vacuo* gave an oily product, wt. 218 mg. This was chromatographed over 22 g silica gel (Kanto Chemical Co.) when elution with 90 ml 2:1 light petroleum–benzene gave XIIa as colourless needles, m.p. 57·5–58·5°, wt. 202 mg (91·2% yield). Recrystallization from 99% EtOH gave sample, m.p. 58·5–59·5°. (Found: C, 80·81; H, 11·66. $C_{29}H_{50}O_2$ requires: C, 80·87; H, 11·70%); $[\alpha]_D^{25}$ +7·9° (*c*, 1·01); ν_{max} cm^{-1}: 1738 (s) (OAc); NMR τ 4·98 (1 proton, m) (2β-H), 7·95 (3 protons, s) (2α-$OCOCH_3$), 9·07 (3 protons, s) (19-H), 9·34 (3 protons, s) (18-H).

2α-*Acetoxy*-5α-*cholestane* (XIIb)

To a soln of Vb (200 mg) in 5·0 ml pyridine, 2·5 ml Ac_2O was added dropwise in the cold and the mixture kept at room temp; it was complete in 17 hr (TLC). The mixture was poured into ice-water depositing XIIb as colourless needles. The needles were filtered off, washed with dil H_2SO_4, water, sat $HaHCO_3$ aq and water, and dried *in vacuo*, m.p. 85–87°, wt. 214 mg (96·6% yield). Recrystallization from 95% EtOH gave sample, m.p. 86·5–87·5°. (Found: C, 80·96; H, 11·67. Calc. for $C_{29}H_{50}O_2$: C, 80·87; H, 11·70%); $[\alpha]_D^{24}$ −4·0° (*c*, 1·01); ν_{max} cm^{-1}: 1736 (s) (OAc); NMR τ: 5·17 (1 proton, m) (2β-H), 8·01 (3 protons, s) (2α-$OCOCH_3$), 9·17 (3 protons, s) (19-H), 9·36 (3 protons, s) (18-H).

2-*Oxo*-5β-*cholestane* (XIIIa)

To a soln of Va (200 mg) in 20 ml acetone, 0·4 ml Jones reagent[20] was added dropwise; the temp of the mixture was maintained at 20°. The reaction was complete in 30 min (TLC), when the brown mixture was diluted with water and extracted into $CHCl_3$. The $CHCl_3$ layer was washed with water, and dried (Na_2SO_4). Concentration of the filtrate *in vacuo* gave colourless crystals, m.p. 74–79°, wt. 198 mg. They were chromatographed over 20 g silica gel (Kanto Chemical Co.) when elution with 300 ml 1:2 light petroleum–benzene gave XIIIa as colourless needles, m.p. 87–88°, wt. 186 mg (93·5% yield). Recrystallization from aqueous EtOH gave colourless plates, m.p. 88·5–89°. (Found: C, 83·71; H, 12·01. $C_{27}H_{46}O$ requires: C, 83·87; H, 11·99%); $[\alpha]_D^{25}$ +20·5° (±5°) (*c*, 0·205 in dioxan); ORD (*c*, 0·205 in dioxan) $[\alpha]^{25}$ (mμ): −354° (317) (trough), −210° (310) (peak), −234° (307) (trough), 0° (302), +542° (274) (peak); ORD (*c*, 0·320 in MeOH) $[\alpha]^{20}$

(mμ): 263° (306) (trough), 0° (295) +621° (268) (peak); CD (*c*, 0·305 in dioxan) $[\theta]^{20}$ (mμ): −1068 (310) (shoulder), −1738 (301) (negative max), −1615 (297), −1715 (293); CD (*c*, 0·320 in MeOH) $[\theta]^{20}$ (mμ): 1793 (291) (negative max); λ_{max} mμ (ε): 284 (33) (C=O); ν_{max} cm^{-1}: 1712 (s) (C=O); NMR τ: 8·93 (3 protons, s) (19-H), 9·37 (3 protons, s) (18-H).

2-Oxo-5α-cholestane (XIIIb)

To a soln of XIIb (200 mg) in 30 ml acetone, 0·4 ml Jones reagent[20] was added dropwise; the temp of the mixture was maintained at 25°. The reaction was complete in 30 min (TLC), when the brown mixture was diluted with water and extracted into $CHCl_3$. The $CHCl_3$ layer was washed with water, and dried (Na_2SO_4). Concentration of the filtrate gave colourless crystals, m.p. 117–126°, wt. 194 mg. They were chromatographed over 20 g neutral alumina (Woelm, grade III) when elution with 60 ml 4:1 light petroleum–benzene gave XIIIb as colourless needles, m.p. 130·5–132°, wt. 182 mg (91·5%). Recrystallization from MeOH gave colourless plates, m.p. 131·5–132°. (Found: C, 83·52; H, 11·94. Calc. for $C_{27}H_{46}O$: C, 83·87; H, 11·99%); $[\alpha]_D^{24}$ +41·8° (±5°) (*c*, 0·199 in dioxan); ORD (*c*, 0·199 in dioxan) $[\alpha]^{24}$ (mμ): +1220° (318) (peak), +987° (312) (trough), +1017° (310) (peak), 0° (296), −1037° (277) (trough); ORD (*c*, 0·20 in MeOH) $[\alpha]^{20}$ (mμ): +1268° (308) (peak), 0° (291), −1314° (269) (trough); CD (*c*, 0·190 in dioxan) $[\theta]^{20}$ (mμ): +2160 (313) (sh), +3840 (303), +3750 (300), +4125 (295) (positive max), +3590 (289); CD (*c*, 0·20 in MeOH) $[\theta]^{20}$ (mμ): +5468 (290) (positive max); λ_{max} mμ (ε): 286 (36) (C=C); ν_{max} cm^{-1}: 1709 (s) (C=O); NMR τ: 9·23 (3 protons, s) (19-H), 9·34 (3 protons, s) (18-H).

Transannular cyclization reaction of Va *with lead tetraacetate*

Formation of 2α,9α-epoxy-5β-cholestane (VII). To a soln of Va (660 mg, 1·7 mmole) in 15 ml anhyd benzene, 1·518 g (3·4 mmole) lead tetraacetate was added, and the mixture refluxed for 7 min when a colourless solid began to precipitate. The reaction was followed by TLC, and was complete in 5 hr. After cooling, the reaction mixture was diluted with ether and washed with water when a brown solid precipitated. The ethereal layer was separated, dried (Na_2SO_4), and concentrated *in vacuo* to give a yellow oily residue, wt. 741 mg. This was chromatographed over 75 g silica gel (Kanto Chemical Co.) when elution with 200 ml 4:1 light petroleum–benzene gave VII as colourless needles, m.p. 45·5–46°, wt. 341 mg (51·9% yield). Recrystallization from 99% EtOH gave sample, m.p. 46–47·5°. (Found: C, 84·07; H, 11·80. $C_{27}H_{46}O$ requires: C, 83·87; H, 11·99%); $[\alpha]_D^{21}$ −4·0° (*c*, 0·99); λ_{max}: transparent above 210 mμ; ν_{max} cm^{-1}: no OH absorption, but 1103 (m) (C—O—C); NMR τ 5·85 (1 proton, d, J = 7 c/s) (2β-H), 8·97 (3 protons, s) (19-H), 9·33 (3 protons, s) (18-H).

Further elution with 160 ml 1:1 light petroleum–benzene gave a colourless oil, wt. 77 mg. After TLC over 20 g Kiesel Gel G (Merck Co.) and elution with 19:1 benzene–ether gave Va as colourless needles, m.p. 103–104·5°, wt. 12 mg (1·8% yield). Recrystallization from 99% EtOH gave sample, m.p. 104–105·5°, alone and on admixture with a sample of Va. Their IR spectra were superposable, ν_{max} cm^{-1}: 3348 (m) (OH).

Further elution with 120 ml 1:2 light petroleum–benzene gave XIIIa as colourless crystals, m.p. 87–88°, wt. 22 mg (3·4% yield). Recrystallization from aqueous EtOH gave colourless plates, m.p. 88·5–89°, alone and on admixture with a sample of XIIIa. Their IR spectra were superposable, ν_{max} cm^{-1}: 1712 (m) (C=O); λ_{max} mμ (ε): 284 (32) (C=O).

Treatment of Vb *with lead tetraacetate*

Formation of XIIb. To a soln of Vb (500 mg, 1·3 mmole) in 12 ml anhyd benzene, 1·150 g (2·6 mmole) lead tetraacetate was added and the mixture refluxed for 4 min when a brown solid began to precipitate. The mixture continued to reflux for 5 hr, and was worked up as in the case of Va to give pale yellow crystals of m.p. 115–147°, wt. 519 mg. They were chromatographed over 155 g silica gel (Kanto Chemical Co.) when elution with 180 ml 2:1 light petroleum–benzene gave XIIb as colourless needles, m.p. 79·5–83°, wt. 45 mg. Recrystallization from 99% EtOH gave sample, m.p. 86–87°, alone and on admixture with a sample of XIIb, wt. 36 mg (6·5% yield). Their IR spectra were superposable, ν_{max} cm^{-1}: 1736 (s) (OAc).

Further elution with 660 ml 19:1 benzene–ether gave colourless needles, m.p. 166–177·5°, wt. 242 mg. They were rechromatographed over 80 g neutral alumina (Woelm, grade III) when elution with 300 ml 1:3 light petroleum–benzene gave Vb of colourless needles as the recovered starting material, m.p. 177–181°, wt. 201 mg (40·0% yield). Recrystallization from acetone gave sample of m.p. 181·5–182·5°, alone and on admixture with a sample of Vb. Their IR spectra were superposable, ν_{max} cm^{-1}: 3261 (m) (OH).

Ring opening of VII *with acetic anhydride-boron trifluoride etherate*

Formation of 2α-acetoxy-5β-cholest-8(9)-ene (XV) *and 2α-acetoxy-5β-cholest-9(11)-ene* (XVI). To a soln of VII (400 mg) in 1·6 ml anhyd benzene, a mixture of 4·0 ml Ac_2O and 0·01 ml BF_3-etherate was added and the reaction mixture kept at room temp; it was complete in 30 min (TLC). The mixture was poured into ice-water depositing a colourless oil which was extracted into light petroleum. This layer was washed with sat $NaHCO_3$ aq and water, and dried (Na_2SO_4). Concentration of the filtrate gave a colourless oil, wt. 439 mg. This was chromatographed over 132 g silica gel (Kanto Chemical Co.) when elution with 130 ml 1:2 light petroleum–benzene gave non-crystalline XV, wt. 103 mg (23·2% yield); $[\alpha]_D^{29}$ −88·2° (*c*, 1·02); λ_{max} mμ (ε): 211 (3870) (C=C); ν_{max}^{liquid} cm^{-1}: 1737 (s) (OAc), 1667 (shoulder) (m) (C=C); NMR τ: 5·13 (1 proton, m) (2β-H), 7·94 (3 protons, s) (2α-$OCOCH_3$), 9·00 (3 protons, s) (19-H), 9·29 (3 protons, s) (18-H). Tortelli–Jaffé colour test[21]: negative. The compound was not further investigated.

Further elution with 300 ml 1:2 light petroleum–benzene gave non-crystalline XVI, wt. 289 mg (65·1% yield); $[\alpha]_D^{29}$ +19·2° (*c*, 0·99); λ_{max} mμ (ε): 211 (3630) (C=C); ν_{max}^{liquid} cm^{-1}: 3049 (m) (>C=CH—), 1735 (s) (OAc), 1647 (w) (C=C); NMR τ: 4·61 (1 proton, m) (11-H), 5·01 (1 proton, m) (2β-H), 7·99 (3 protons, s) (2α-$OCOCH_3$), 8·91 (3 protons, s) (19-H), 9·41 (3 protons, s) (18-H). Tortelli–Jaffé colour test: negative.

Catalytic hydrogenation of XVI

Formation of XIIa–XVI (100 mg) was dissolved in 5·0 ml glacial AcOH, and hydrogenated with 215 mg $PtO_2 \cdot H_2O$ at 23°. After absorption of H_2 ceased, the catalyst was filtered off, and the filtrate concentrated *in vacuo* followed by addition of water to deposit a colourless oil. The oil was extracted into ether, and the ethereal layer was washed with sat $NaHCO_3$aq and water, and dried (Na_2SO_4). Concentration of the filtrate *in vacuo* gave a colourless oil, wt. 98 mg. This was chromatographed over 10 g silica gel (Kanto Chemical Co.) when elution with 50 ml 2:1 light petroleum–benzene gave XIIa as colourless needles, m.p. 57–58°, wt. 82 mg (81·4% yield). Recrystallization from 99% EtOH gave sample, m.p. 59–59·5°, alone and on admixture with a sample of XIIa. Their IR spectra were superposable, ν_{max} cm^{-1}: 1738 (s) (OAc); $[\alpha]_D^{31}$ +7·5° (*c*, 1·01).

Epoxidation of XVI *with perbenzoic acid*

Formation of 2α-acetoxy-9α,11α-epoxy-5β-cholestane (XVII). To a soln of XVI (277 mg, 0·65 mmole) in 3·0 ml $CHCl_3$, 9·5 ml $CHCl_3$ soln of perbenzoic acid (containing 267·6 mg or 1·94 mmole of the peracid) was added in the cold and the mixture kept at room temp in dark; the reaction was complete in 17 hr (TLC). The amount of the peracid consumed was found to be 92·7 mg (1·04 equiv to XVI) by titration of the remaining amount in the mixture with 0·1 N $Na_2S_2O_3$. The mixture was washed with sat Na_2SO_3aq, water, sat $NaHCO_3$aq and water, and dried (Na_2SO_4). Concentration of the filtrate *in vacuo* gave colourless crystals, m.p. 109·5–115°, wt. 268 mg. They were chromatographed over 81 g silica gel (Kanto Chemical Co.) when elution with 420 ml 1:4 light petroleum–benzene gave XVII as colourless needles, m.p. 118–119·5°, wt. 231 mg (80·2% yield). Recrystallization from MeOH gave sample, m.p. 118·5–119·5. (Found: C, 78·34; H, 10·92. $C_{29}H_{48}O_3$ requires: C, 78·32; H, 10·88%); $[\alpha]_D^{22}$ −61·0° (*c*, 1·05); λ_{max}: transparent above 210 mμ; ν_{max} cm^{-1}: 1727 (s) (OAc), 900 (m) (C—O—C); NMR τ: 5·19 (1 proton, m) (2β-H), 7·09 (1 proton, d, J = 5 c/s) (11β-H), 7·99 (3 protons, s) (2α-$OCOCH_3$), 8·83 (3 protons, s) (19-H), 9·34 (3 protons, s) (18-H).

Reductive ring opening of XVII *with lithium–ethylamine*

Formation of 2α-9α-dihydroxy-5β-cholestane (XVIII). To a soln of XVII (300 mg) in 30 ml $EtNH_2$, 330 mg Li was added in small pieces at 0°; the colour of the mixture turned to dark blue in 8 min and then to pink in 2 hr. The mixture was kept at room temp until almost all $EtNH_2$ evaporated. Addition of water to the residue in the cold deposited colourless crystals, which were extracted into ether. The ethereal layer was washed with water, and dried (Na_2SO_4). Concentration of the filtrate *in vacuo* gave pale yellow needles, m.p. 207–214°, wt. 282 mg. They were chromatographed over 90 g silica gel (Kanto Chemical Co.) when elution with 210 ml 19:1 benzene–ether gave XVIII as colourless needles, m.p. 208·5–209·5°, wt. 205 mg (75·1% yield). Recrystallization from acetone gave sample, m.p. 208–209°. (Found: C, 79·90; H, 12·22. $C_{27}H_{48}O_2$ requires: C, 80·14; H, 11·96%); $[\alpha]_D^{26}$ +25·1° (*c*, 1·00); λ_{max}: transparent above 210 mμ; ν_{max} cm^{-1}: 3205 (m), 3127 (m) (OH); NMR τ: 6·05 (1 proton, m) (2β-H), 8·94 (3 protons, s) (19-H), 9·34 (3 protons, s) (18-H).

Acknowledgement—We are deeply indebted to Dr. K. Sasaki of the Research Laboratories of Shionogi and Co. for valuable suggestions on the stereochemistry of epoxidation of the 9(11)-eno system in the steroid nucleus, to the Research Laboratories of Shionogi and Co. for a part of ORD measurements, and also to the

Research Laboratories of Takeda Chemical Industries, for the NMR spectra. We are also indebted to Mr. Y. Itatani of the Faculty of Pharmaceutical Sciences, Kanazawa University, for the microanalyses, and to Miss N. Fukushima of our laboratory for skilled technical assistance.

REFERENCES

[1] M. Tomoeda and T. Koga, *Tetrahedron Letters* 3231 (1965).
[2] C. Djerassi (Ed.), *Steroid Reactions*. p. 327. Holden-Day, San Francisco (1963), and Refs cited.
[3] K. B. Wiberg (Ed.), *Oxidation in Organic Chemistry*, Part A, p. 321. Academic Press, New York (1965).
[4] [a] R. Ledger and J. McKenna, *Chem. & Ind.* 1662 (1963);
[b] K. Heusler and J. Kalvoda, *Tetrahedron Letters* 1001 (1963);
[c] G. Volpp and Ch. Tamm, *Helv. Chim. Acta* **46**, 219 (1963);
[d] J. Kalvoda, K. Heusler, G. Anner and A. Wettstein, *Ibid.* **46**, 1017 (1963);
[e] J. Kalvoda, K. Heusler, H. Ueberwasser, G. Anner and A. Wettstein, *Ibid.* **46**, 1361 (1963);
[f] J. Kalvoda, K. Heusler, Ch. Meystre, P. Wieland and G. Anner, *Gazz. Chim. Ital.* **93**, 140 (1963);
[g] R. Kwok and M. E. Wolff, *J. Org. Chem.* **28**, 423 (1963);
[h] J. F. Bagli, P. E. Morand and R. Gaudry, *Ibid.* **28**, 1207 (1963);
[i] R. M. Moriarty and T. D. D'Silva, *Ibid.* **28**, 2445 (1963);
[j] D. Hauser, K. Heusler, J. Kalvoda, K. Schaffner and O. Jeger, *Helv. Chim. Acta* **47**, 1961 (1964);
[k] M. Akhtar and M. M. Pechet, *J. Am. Chem. Soc.* **86**, 265 (1964);
[l] M. Akhtar and D. H. R. Barton, *Ibid.* **86**, 1528 (1964);
[m] K. Heusler, *Tetrahedron Letters* 3975 (1964);
[n] D. H. R. Barton, A. L. J. Beckwith and A. Goosen, *J. Chem. Soc.* 181 (1965);
[o] R. M. Moriarty and T. D. D'Silva, *Tetrahedron* **21**, 547 (1965).
[5] M. Tomoeda, M. Ishizaki, H. Kobayashi, S. Kanatomo, T. Koga, M. Inuzuka and T. Furuta, *Ibid.* **21**, 733 (1965).
[6] B. Camerino, B. Pattelli and A. Vercellone, *J. Am. Chem. Soc.* **78**, 3540 (1956).
[7] P. L. Julian, V. Georgian and H. C. Printy, *U.S. Pat.* 2,910,487 (1959).
[8] A. Kowitz, *Brit. Pat.* 839,376 (1960).
[9] [a] P. A. Plattner, H. Heusser and A. B. Kulkarni, *Helv. Chim. Acta* **31**, 1822 (1948);
[b] M. Legrand, R. Viennet and J. Caumartin, *C.R. Acad. Sci., Paris* **253**, 2378 (1961).
[10] L. M. Jackman, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry* p. 84. Pergamon Press, London (1959).
[11] L. F. Fieser and M. A. Romero, *J. Am. Chem. Soc.* **75**, 4716 (1953).
[12] N. S. Bhacca and D. H. Williams. *Applications of NMR spectroscopy in Organic Chemistry* p. 13. Holden-Day, San Francisco (1964).
[13] [a] A. Fürst and P. A. Plattner, *Helv. Chim. Acta* **32**, 275 (1949);
[b] L. Ruzicka, P. A. Plattner and M. Furrer, *Ibid.* **27**, 524 (1944).
[14] [a] C. Djerassi, W. Closson and A. E. Lippman, *J. Am. Chem. Soc.* **78**, 3163 (1956);
[b] C. Djerassi and W. Klyne, *J. Chem. Soc.* 2390 (1963).
[15] K. M. Wellmann, R. Records, E. Bunnenberg and C. Djerassi, *J. Am. Chem. Soc.* **86**, 492 (1964).
[16] W. Moffit, R. B. Woodward, A. Moscowitz, W. Klyne and C. Djerassi, *Ibid.* **83**, 4013 (1961).
[17] P. Bladon, H. B. Henbest and G. W. Wood, *J. Chem. Soc.* 2737 (1952).
[18] [a] C. Djerassi and W. Closson, *J. Am. Chem. Soc.* **78**, 3761 (1956);
[b] C. Djerassi, H. Wolf and E. Bunnenberg, *Ibid.* **84**, 4552 (1962).
[19] R. Mozingo, *Org. Syn.*, Collective Vol. III, p. 181 (1955).
[20] [a] K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.* 39 (1946);
[b] P. Bladon, J. M. Fabian, H. B. Henbest, H. P. Koch and G. W. Wood, *Ibid.* 2407 (1951).
[21] L. F. Fieser and M. Fieser, *Steroids* p. 114. Reinhold, New York (1956).