WESTPHALEN REARRANGEMENT. MECHANISM OF FORMATION OF 5α-ACETOXY DERIVATIVES*

Pavel Kočovský[a], Václav Černý[a] and František Tureček[b]

[a] *Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, 166 10 Prague 6 and*
[b] *J. Heyrovský Institute of Physical Chemistry and Electrochemistry, Czechoslovak Academy of Sciences, 121 38 Prague 2*

Received May 25th, 1978

5α-Acetoxy derivatives formed as by-products in the course of Westphalen rearrangement of [5-^{18}O]-5-hydroxy-5α-cholestanes *Ia* and *Ib* are shown to preserve their ^{18}O content. This fact rules out previously proposed neighboring group participation of the 6β-substituent involving a 5β,6β-"onium" intermediate (*F*).

Westphalen rearrangement[1,2] of 5α-hydroxy steroids carrying an electron-withdrawing 6β-substituent is known[3] to occur in acetic anhydride under specific catalysis of sulfuric acid. The reaction has been demonstrated to proceed[3-5] via the acetyl sulfate *B* which then undergoes ionization to the carbocation *C* followed by 10β-methyl migration and 9α-proton abstraction to yield the Westphalen product *D*. Usually, the product is accompanied by the 5α-acetoxy derivative *F* and the 4,5-unsaturated steroid[3].

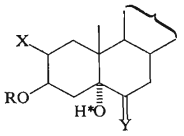
Kirk and Hartshorn[3-5] pointed out that a rough correlation exists between the ratio of the rearranged product to the 5α-acetoxy derivative and the ability of the 6β-substituent to participate as a nucleophilic neighboring group. With such a grouping at 6β-position the 5α-hydroxy steroids are more prone to form 5α-acetoxy derivatives. This is particularly true of the 6β-bromo, 6β-methoxy and 6β-azido derivatives[3-6]. Kinetic data also support the assumption of neighboring group participation. High reaction rates of 6β-bromo and particularly of 6β-methoxy derivatives are indicative of anchimeric assistance by the 6β-substituent. The good yields of the 5α-acetates from compounds bearing such 6β-groups were explained[3-6] by the formation of a cyclic 5β,6β-"onium" intermediate (*E*) opened by nucleophilic attack with acetic acid at $C_{(5)}$. This assumption is also in agreement with the behavior of the 6β-fluoro and 6β-cyano derivative (Table I). Both these derivatives react slowly and give no detectable amount of 5α-acetoxy derivatives (Table I). Whereas fluorine is known not to participate generally, the cyano group cannot act in this case as a participating group for steric reasons[6].

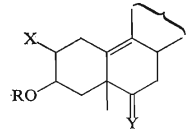
* Part CCXIII in the series On Steroids; Part CCXII: This Journal, in press.

TABLE I

6β-Substituent Effect on Rates and Products of Dehydration of 3β-Acetoxy-5-hydroxy-5α--cholestane Derivatives with $(CH_3CO)_2O$ — CH_3COOH — H_2SO_4

6β-Subst.	Relative rate	Products isolated, %			Ref.
		5β-CH_3-Δ^9	5-acetate	others	
CF_3CO_2	0·5	—	—	—	7
CN	0·8	41	—	—	6
F	1·0	81	0	2	4, 5
$C_6H_5CO_2$	5·8	—	—	—	7
CH_3CO_2	10·0	66	5	24 (Δ^4)	4, 5
Cl	44·0	72	5	22 (mixture)	4, 5
Br	>Cl	22	24	26	4, 5
I	>Br	0	37	51 (Δ^5 + Δ^4)	4, 5
CH_3O	3 300	38	40	10 (Δ^4)	4, 5
N_3	—	8	36	—	6
CH_3	—	0	0	100 (Δ^5)	3
H	—	0	1	65 (Δ^5)	3

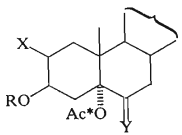


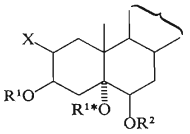


+ Other olefines

Ia, R = Bz, X = H, Y = 
Ib, R = Ac, X = AcO, Y = O

IIa, R = Bz, X = H, Y =  (53 %)
IIb, R = Ac, X = AcO, Y = O (29 %)





IIIa, R = Bz, X = H, Y =  (41 %)
IIIb, R = Ac, X = AcO, Y = O (65 %)

IVa, R^1 = H, R^2 = CH_3, X = H
IVb, R^1 = H, R^2 = H, X = OH
Va, R^1 = CH_3, R^2 = CH_3, X = H
Vb, R^1 = CH_3, R^2 = CH_3, X = OCH_3

An obvious way how to verify the above mechanism of the 5α-acetate formation has been to investigate the behavior of a suitable steroid bearing a ^{18}OH grouping in the 5α-position. For this purpose, we chose the methoxy derivative *Ia* since this compound is a typical case for which neighboring group participation has been assumed[3-5]. In addition, we studied the 6-oxo derivative *Ib* as an example of another type of 6-substituted compound giving a good yield of the 5α-acetate[8].

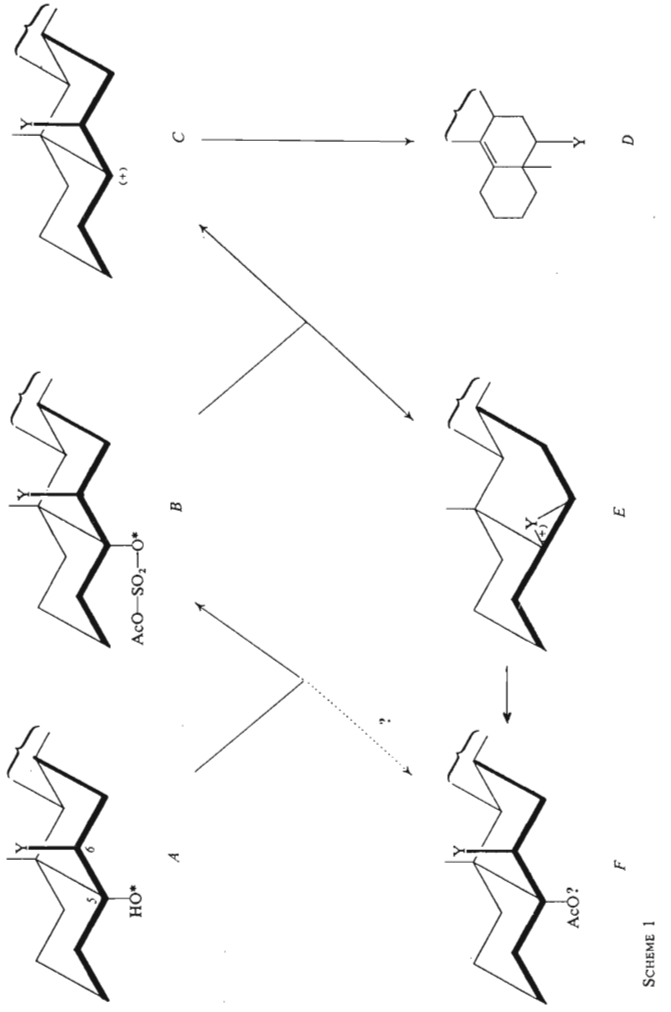
The compounds *Ia* and *Ib* were treated with acetic anhydride and potassium hydrogen sulfate under standard Westphalen dehydration conditions and the products were separated by chromatography with the intention of submitting them to mass spectrometric analysis. However, the 5α-acetoxy derivatives *IIIa* and *IIIb* are not suitable for mass spectrometric study because of the loss of the 5α-acetoxy group. This obstacle was circumvented by converting them to 5α-methoxy derivatives *Va* and *Vb*. This conversion was performed by lithium aluminum hydride reduction to hydroxy compounds *IVa* and *IVb* and subsequent methylation by sodium hydride–methyl iodide method.

Surprisingly, the mass spectrometric analysis revealed complete preservation of ^{18}O in the 5α-position (Table II). This result rules out any mechanism of the 5α-acetoxy derivative formation involving cleavage of the $C_{(5)}$—O bond. The 5α-acetoxy derivatives *IIIa* and *IIIb* cannot arise from the intermediary „onium" ion (*E*) by nucleophilic attack with acetic acid at $C_{(5)}$ as was believed to date. Formation of *IIIa, b* is thus due to simple acetylation of the 5α-hydroxyl group in *Ia* and *Ib*. This acetylation competes with the formation of the acetyl sulfate *B* and thus with the formation of the Westphalen compound *D*.

TABLE II
Mass Spectrometric Data of Labeled Compounds

Compound	$M^{+\cdot}$	Content of ^{18}O (%)[a]
Ia	540	19·1 ± 2·2[b]
Ib	—	15·0[c]
Va	464	20·7 ± 1·3[d]
Vb	494	14·7 ± 2·3[d]
XIV	568	22·4 ± 2·7[e]
XVIII	508	19·6 ± 1·9[b]
XIX	524	20·5 ± 1·0[b]
XX	420	15·6 ± 1·8[d]

[a] All values were corrected for the natural abudance of ^{13}C, ^{18}O and ^{2}H; [b] in ions $(M-C_6H_5.CO_2H)^{+\cdot}$; [c] estimated from the content of ^{18}O in *XX*; [d] in ionized molecules; [e] in ions $(M-C_6H_5CO_2H-CH_3CO_2H)^{+\cdot}$.



SCHEME 1

The role of the 6β-substituent has to be reconsidered. Substituents having strong electron-withdrawing ability (CF_3CO_2, CN, F) decrease the total reaction rate (Table I). The extremely low rate of acetylation (if any) may be attributed to diminished electron density at the 5α-hydroxyl oxygen atom and the low rate of rearrangement may be due to destabilization of carbocation *C*.

As mentioned above, substituents with medium electron-withdrawing ability (CH_3O, N_3) are known to increase the total reaction rate. The assumption of a neighboring group effect *via* 5β, 6β-"ionium" intermediate (*E*) has been disproved by our experiments. The strong influence of the 6β-substituent upon the reaction rate thus remains to be explained. If we assume a throughspace interaction[9] of the methoxyl oxygen lone electron pairs with the $C_{(5)}$—O bond orbital leading to increased electron density at 5α-hydroxyl oxygen (Fig. 1), we can understand the increase in the rate of acetylation of the 5α-hydroxyl in the 6β-methoxy derivative *Ia*. The increase in the rate of rearrangement may be attributed to a lesser −I effect (as compared with the fluorine atom) of the methoxyl group. Similarly, the increase in the rate of acetylation of the 5α-hydroxyl in the 6-keto derivative *Ib* may be due to interaction of the π-electron system of the carbonyl group with the $C_{(5)}$—O bond orbital.

The model compounds were synthetized in the following manner. The 5β,6β-epoxide[10] *IX* was prepared from cholesteryl benzoate (*VI*) *via* the bromohydrin *VII* and short treatment of the latter with potassium hydrogen carbonate. Cleavage of the epoxide *IX* with water containing 24% of $H_2{}^{18}O$ and a drop of perchloric acid yielded four products. The major product was the desired diol *XIII* with 22·4% of ^{18}O (as indicated by mass spectrum of *XIV*). One of the minor products was the olefin *X* the structure of which was proved by acetylation to the known[11] compound *XI* prepared for comparison by thionyl chloride dehydration of the 5α-hydroxy derivative *VIII*. A further side product was the known[12] 6-ketone *XII* and the last product was the 5β,6α-diol *XVI* which could be oxidized to the 5β-hydroxy-6-oxo derivative *XVII*, known[13] in unlabeled form.

Direct methylation of the diol *XIII* failed and an indirect route to preparation of the 6β-methoxy derivative *Ia* had to be applied. The diol *XIII* was converted to the nitrate *XV*, which was cyclized in a mild alkaline medium to the epoxide *XVIII*.

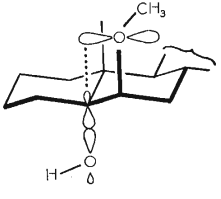


FIG. 1

Through Space Interaction of the 6β-Methoxyl Oxygen Lone Electron Pairs with the $C_{(5)}$—O Bond Orbital

Cleavage of the epoxide ring in this compound led to the desired methoxy derivative *Ia* which was accompanied by a small amount of the diol *XIII*.

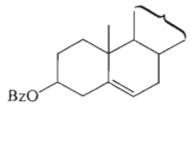
The second model compound, *Ib*, was prepared from the epoxide *XVIII* by oxidative cleavage to the hydroxy ketone *XIX* followed by saponification and conversion to the mesylate *XXI*, treatment of the latter with *sym*-collidine to furnish the olefin *XXII* and Woodward hydroxylation to *Ib*.

TABLE III
Analytical and Physical Data of Some Products

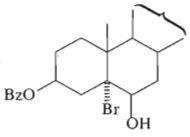
Compound	Formula (m.w.)	Calculated/Found		M.p., °C $[\alpha]_D^{20}$
		% C	% H	
IIa	$C_{35}H_{52}O_3$ (520·8)	80·72 80·56	10·06 9·93	157—158 +95°
IIb	$C_{31}H_{48}O_5$ (500·7)	74·36 74·32	9·96 9·78	oil −33°
IIIa	$C_{38}H_{56}O_5$ (592·9)	76·99 76·83	9·52 9·41	90—92 − 5°
IIIb	$C_{33}H_{52}O_7$ (560·8)	70·68 70·56	9·35 9·33	132—134 − 5°
Va	$C_{30}H_{54}O_3$ (462·8)	77·87 77·64	11·76 11·72	154—155 −23°
Vb	$C_{31}H_{56}O_4$ (492·8)	75·56 75·37	11·45 11·34	oil − 8°

TABLE IV
^{1}H-NMR Spectra of Some Products

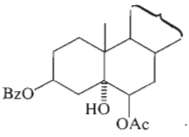
Compound	18-H	19-H	3α-H	6α-H
IIa	0·82	1·22	5·30 m	3·00 dd ($J_{6\alpha,7\alpha}$ = 5·5) ($J_{6\alpha,7\beta}$ = 10·0)
IIb	0·79	1·39	5·37 m	—
IIIa	0·69	1·18	5·00 m	4·20 m ($W_{1/2}$ = 6)
IIIb	0·65	1·03	5·00 m	—
Va	0·66	1·07	3·30 m	3·30 m
Vb	0·65	1·20	3·30 m	3·30 m



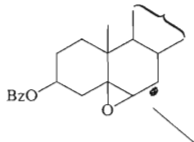
VI



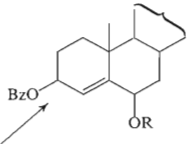
VII



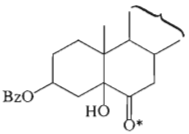
VIII



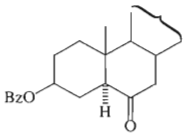
IX



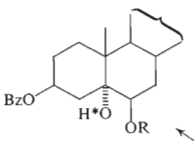
X, R = H
XI, R = Ac



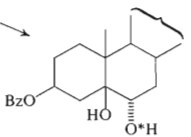
XVII



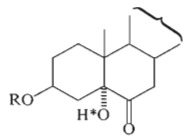
XII



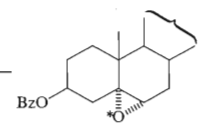
XIII, R = H
XIV, R = Ac
XV, R = NO_2



XVI

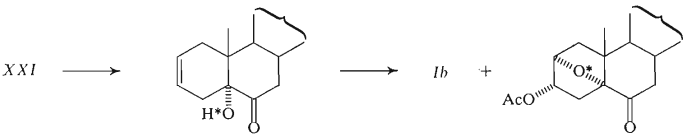


XIX, R = Bz
XX, R = H
XXI, R = Mes



XVIII

Ia



XXII *XXIII*

EXPERIMENTAL

Melting points were determined on a Kofler block. Analytical samples were dried at 50°C/0·2 Torr (26 Pa). Optical measurements were carried out in chloroform with an error of ±3°. The infrared spectra were recorded on a Zeiss UR 20 spectrometer in tetrachloromethane unless otherwise stated. The ^{1}H-NMR spectra were recorded on a Tesla B 476 instrument (60 MHz) in deuteriochloroform at 30°C with tetramethylsilane as internal reference. Chemical shifts are given in ppm. Apparent coupling constants were obtained from the first order analysis. The mass spectra were recorded on a JEOL JMS D-100 mass spectrometer using a direct inlet. ^{18}O contents were averaged over at least twenty scans. The identity of ^{18}O-containing ion species was checked by precise mass measurements in compounds *Va*, *XVIII* and *XIX*. The CD spectra were recorded on a Dichrographe II (Jouan-Roussel) in methanol. The identity of samples prepared by different routes was checked by mixture melting point determination, by thin-layer chromatography (TLC) and by IR and ^{1}H-NMR spectra. The identity of the structures of labeled and unlabeled compounds was checked by melting point determination, TLC and by comparison of their mass spectra. Usual work up of an ethereal solution means washing the solution with 5% aqueous hydrochloric acid, water, 5% aqueous potassium hydrogen carbonate solution, water, drying with sodium sulfate and evaporation of the solvent *in vacuo*.

[5^{18}O]-6β-Methoxy-5α-cholestane-3β,5-diol 3-Monobenzoate (*Ia*)

The epoxide *XVIII* (400 mg) was dissolved in dioxane (10 ml) and methanol (10 ml) and treated with *p*-toluenesulfonic acid (100 mg) at room temperature for 3 h. The mixture was diluted with ether and the solution was washed with water and 5% aqueous potassium hydrogen carbonate solution, dried and the solvent was evaporated. The residue was chromatographed on a silica gel column (40 g) using a mixture of light petroleum and ether (95 : 5) as eluent to yield the unreacted epoxide *XVIII* (120 mg), m.p. 169—170°C. Elution with a mixture of light pretroleum, ether and acetone (85 : 10 : 5) afforded as a lipophilic fraction the methoxy derivative *Ia* (180 mg), m.p. 140—142°C (authentic sample of the unlabeled compound had m.p. 143—144°C, $[\alpha]_D^{20}$ −15°), and, as a polar fraction, the diol *XIII* (55 mg), m.p. 266—227°C.

[5^{18}O]-2β,3β-Diacetoxy-5-hydroxy-5α-cholestan-6-one (*Ib*)

A solution of iodine (40 mg) in a mixture of 1,2-dimethoxyethane (0·2 ml) and acetic acid (0·3 ml) was added dropwise in the course of 30 min to a stirred solution of the olefin *XXII* (45 mg) in glacial acetic acid (2·6 ml) and 1,2-dimethoxyethane (0·4 ml) containing silver acetate (60 mg). Stirring was continued for an additional 30 min at room temperature and a solution of water (0·01 ml) in acetic acid (0·1 ml) was added; the temperature was raised to 90°C and stirring continued for 2 h. The mixture was passed through a column of sodium chloride, washed with chloroform

and the filtrate evaporated *in vacuo*. The residue was dried azeotropically with benzene and acetylated with acetic anhydride (0·2 ml) in pyridine (1 ml) at room temperature overnight. The mixture was decomposed with ice, the product was taken up in ether and the ethereal solution was worked up as usual. The residue was chromatographed on one preparative silica gel plate (20 × 20 cm) using double development with a mixture of benzene and ether (95 : 5) as eluent. The slower moving zone was collected, eluted with ether and the solvent was evaporated to yield *Ib* (31 mg), m.p. 182—183°C (mixture of acetone, methanol and water), the authentic sample of the unlabeled compound[14] had m.p. 182—183°C.

5,6β-Epoxy-5β-cholestan-3β-ol 3-Benzoate (*IX*)

The cholesteryl benzoate *VI* (5 g) was dissolved in dioxane (200 ml) and water (20 ml) and treated with 70% perchloric acid (1·3 ml) and N-bromoacetamide (1·45 g) for 1·5 g at room temperature. The mixture was then diluted with water and the product extracted with ether. The ethereal solution was washed with water, a 5% aqueous potassium hydrogen carbonate solution, water, dried and the solvent evaporated to yield the crude bromohydrin *VII* (4 g), used without purification for the following step. The crude *VII* (4 g) was dissolved in a mixture of acetone (30 ml), methanol (30 ml) and water (5 ml) and refluxed with a 5% aqueous potassium hydrogen carbonate solution (5 ml) for 3 min. The mixture was cooled, treated with ether and water, the ethereal layer was washed with water, dried and the solvent was evaporated. The residue was chromatographed on a silica gel column (200 g) using a mixture of light petroleum and benzene (70 : 30) as eluent. Corresponding fractions were collected and evaporated to yield *IX* (1·8 g), which on crystallization from a mixture of acetone, methanol and water gave the pure β-epoxide *IX* (1·1g), m.p. 174—175°C, $[\alpha]_D^{20}$ +10° (*c* 2·1) in accordance with the literature[10]. ^{1}H-NMR spectrum: 0·65 (3 H, s, 18-H), 1·05 (3 H, s, 19-H), 3·12 (1 H, d, J = 3 Hz, 6α-H), 5·00 (1 H, m, 3α-H).

Cleavage of 5,6β-Epoxy-5β-cholestan-3β-ol 3-Monobenzoate (*IX*)

The epoxide *IX* (1 g) was dissolved in dioxane (20 ml), a solution of 24% $H_2{}^{18}O$ in $H_2{}^{16}O$ (0·1 ml) and 70% perchloric acid (a drop) in dioxane (5 ml) was added, and the solution was set aside for 3 h at room temperature (the reaction was checked by TLC). The mixture was diluted with ether, the ethereal solution was washed with water, a 5% aqueous potassium hydrogen carbonate solution, water, then dried and the solvent evaporated. The residue was chromatographed on a silica gel column (100 g) using a mixture of light petroleum and ether (95 : 5) as eluent to yield the ketone *XII* (57 mg) identical with the authentic sample, m.p. 170—171°C (in accordance with the literature[12]) as a most lipophilic fraction. Elution with a mixture of light petroleum and ether (90 : 10) yielded the olefin *X* (65 mg), m.p. 141—142°C. Elution with a mixture of light petroleum, ether and acetone (90 : 5 : 5) afforded the diol *XVI* (226 mg), m.p. 163 to 164°C. Elution using a mixture of light petroleum, ether and acetone (80 : 10 : 10) gave the diol *XIII* (640 mg), m.p. 229—231°C (mixture of acetone, methanol and water). The authentic sample of the unlabeled compound[15] had m.p. 230—231°C.

4-Cholestene-3β,6β-diol 3-Benzoate 6-Acetate (*XI*)

a) *From 5α-cholestane-3β,5,6β-triol 3-benzoate 6-acetate*[15] (VIII): The hydroxy derivative *VIII* (100 mg) was dissolved in pyridine (2 ml), and treated with thionyl chloride (0·1 ml) at 0°C for 1 h. The mixture was decomposed with ice, the product was taken up in ether and the ethereal solution worked up as usual. The residue was crystallized from a mixture of acetone, methanol and water to yield *XI* (27 mg), m.p. 128—130°C, $[\alpha]_D^{20}$ —13° (*c* 5·4), literature[11] gives m.p. 128 to

132°C, $[\alpha]_D^{20}$ −25°. ^{1}H-NMR spectrum: 0·73 (3 H, s, 18-H), 1·20 (3 H, s, 19-H), 2·00 (3 H, s, CH_3COO), 5·30 (1 H, m, $W_{1/2}$ = 7 Hz, 6α-H), 5·50 (1 H, m, W = 11 Hz, 3α-H), 5·70 (1 H, m, $W_{1/2}$ = 4 Hz, 4-H).

b) *From 4-cholestene-3β,6β-diol 3-monobenzoate* (*X*): The alcohol *X* (30 mg) was acetylated with acetic anhydride (0·2 ml) in pyridine (2 ml) at room temperature overnight, the mixture was decomposed with ice, the product was taken up in ether and the ethereal solution was worked up as usual. The residue was crystallized from a mixture of acetone, methanol and water to yield *XI* (11 mg), m.p. 127—130°C, $[\alpha]_D^{20}$ −15° (*c* 1·8).

[5^{18}O]-5α-Cholestane-3β,5,6β-triol 3-Benzoate, 6-Acetate (*XIV*)

The diol *XIII* (300 mg) was acetylated with acetic anhydride (0·5 ml) in pyridine (2 ml) at room temperature overnight. The mixture was decomposed with ice, the product was extracted with ether and the ethereal solution worked up as usual. The residue was crystallized from ethanol to yield *XIV* (210 mg), m.p. 166—167°C. The authentic unlabeled sample[15] had m.p. 164—165°C. Mass spectrum shows the presence of the ^{16}O-containing compound (77·6%) and the labeled ^{18}O-compound *XIV* (22·4)%.

[5^{18}O]-5α-Cholestane-3β,5,6β-triol 3-Benzoate, 6-Nitrate (*XV*)

A solution of the diol *XIII* (700 mg) in chloroform (20 ml) was introduced into a reagent prepared from acetic anhydride (6 ml) and 65% nitric acid (1·4 ml) at −30°C. The mixture was stirred at −40 to −10°C for 4 h, poured into ice and neutralized with a 5% aqueous potassium hydrogen carbonate solution and solid sodium carbonate. The product was taken up in ether, the ethereal solution was washed with a 5% aqueous potassium hydrogen carbonate solution, water, dried and the solvent evaporated to yield the nitrate *XV* (650 mg), m.p. 188—189°C (mixture of acetone, methanol and water). An authentic sample of the unlabeled compound prepared by the same manner[15] had m.p. 188—190°C.

[6^{18}O]-3β-Benzoyloxy-5-hydroxy-5β-cholestan-6-one (*XVII*)

The diol *XVI* (35 mg) was dissolved in dichloromethane (3 ml) and oxidized with Corey's oxidant (80 mg) at room temperature for 2 h. The mixture was then passed through a column of aluminum oxide, the solvent was evaporated and the residue was crystallized from aqueous acetone to afford *XVII* (18 mg), m.p. 168—169°C, $[\alpha]_D^{20}$ +23° (*c* 1·6) in accordance with the literature[16]. ^{1}H-NMR spectrum: 0·78 (3 H, s, 18-H), 1·46 (3 H, s, 19-H), 5·40 (1 H, m, $W_{1/2}$ = 10 Hz, 3α-H). CD spectrum: $\Delta\varepsilon_{296}$ = −2·62 (methanol).

[5^{18}O]-5,6α-Epoxy-5α-Cholestan-3β-ol 3-Benzoate (*XVIII*)

The nitrate *XV* (600 mg) was dissolved in a mixture of dioxane (7 ml) and methanol (10 ml) and refluxed with a 5% aqueous potassium hydrogen carbonate solution for 2 min. The mixture was then cooled, diluted with ether and the ethereal solution was washed with water, dried and evaporated to yield *XVIII* (430 mg), m.p. 169—170°C (aqueous acetone). The unlabeled compound prepared by the same manner[15] had m.p. 168—169°C.

[5^{18}O]-3β-Benzoyloxy-5-hydroxy-5α-cholestan-6-one (*XIX*)

The epoxide *XVIII* (120 mg) was dissolved in a mixture of acetone (3 ml) and dioxane (2 ml), and the solution of chromium trioxide (100 mg) in water (0·3 ml) was added over a period of 5 min.

The mixture was stirred for 30 min at room temperature, then diluted with ether, the solution was washed with water, a 5% aqueous potassium hydrogen carbonate solution, water, dried, and the solvent was evaporated to yield the hydroxy ketone *XIX* (115 mg), m.p. 233—235°C (mixture of acetone, dioxane, methanol and water), authentic sample of the unlabeled compound prepared in the same manner[16] had m.p. 236—237°C.

[5^{18}O]-3β,5-Dihydroxy-5α-cholestan-6-one (*XX*)

A solution of the benzoate *XIX* (110 mg) and potassium hydroxide (100 mg) in methanol (10 ml) and acetone (5 ml) was refluxed for 30 min. Water was added to the solution, the product was extracted into ether, the ethereal solution was washed with water, dried and evaporated to yield *XX* (94 mg), m.p. 229—231°C (ether). The authentic sample of the unlabeled compound prepared by the same method[16] had m.p. 230—232°C.

[5^{18}O]-3β-Methanesulfonyloxy-5-hydroxy-5α-cholestan-6-one (*XXI*)

A solution of the diol *XX* (60 mg) in pyridine (2 ml) was treated with methanesulfonyl chloride (0·2 ml) at 0°C for 30 min. The mixture was decomposed with ice, the product was taken up in ether and the ethereal solution was worked up as usual to yield *XXI* (61 mg), m.p. 143—145°C (mixture of acetone, methanol and water). The authentic sample of the unlabeled compound[16] had m.p. 147—148°C.

[5^{18}O]-5-Hydroxy-5α-cholest-2-en-6-one (*XXII*)

The mesylate *XXI* (60 mg) in *sym*-collidine (2 ml) was refluxed under nitrogen for 30 min. The mixture was cooled, diluted with water and a 5% aqueous hydrochloric acid solution, the product was extracted with ether and the ethereal solution was worked up as usual. The residue was chromatographed on one preparative silica gel plate (20 × 20 cm) using a mixture of light petroleum and ether (90 : 10) as eluent to yield *XXII* (46 mg), m.p. 138—140°C (mixture of acetone, methanol and water). The authentic sample of the unlabeled compound[16] had m.p. 140 to 141°C.

[2^{18}O]-2α,5-Epoxy-3α-acetoxy-5α-cholestan-6-one (*XXIII*)

The lipophilic zone from the chromatography of the mixture of Woodward addition products to the olefin *XXII* gave by elution and evaporation of the solvent epoxide *XXIII* (11 mg), m.p. 85—87°C. The authentic sample of the unlabeled compound[14] had m.p. 86—87°C.

Treatment of 5α-Hydroxy Derivatives *Ia* and *Ib* with a Mixture of Acetic Anhydride and Potassium Hydrogen Sulfate

Powdered potassium hydrogen sulfate (20 mg) was added to a stirred solution of 5α-alcohol (30 mg) in acetic anhydride (0·5 ml) and acetic acid (1 ml) at 90°C, and the mixture was stirred for 30 min at the same temperature. The solution was poured onto ice and pyridine, the product was extracted with ether and the ethereal solution was worked up as usual. The residue was chromatographed on one silica gel plate (10 × 20 cm) using a mixture of light petroleum and ether (85 : 15). Corresponding zones were collected and eluted with ether. The yields of products prepared from unlabeled compounds by the same manner in larger scale experiments are given in Scheme 1. The physical data of products obtained from labeled and unlabeled compounds are given in Tables II—IV.

Hydride Reduction of the 5α-Acetates *IIIa* and *IIIb*

The 5α-acetate (15 mg) was dissolved in ether (2 ml) and reduced with lithium aluminum hydride (20 mg) at room temperature overnight. The mixture was decomposed with water, and a 5% aqueous hydrochloric acid solution, the product was taken up in ether and the ethereal solution was worked up as usual. The residue was chromatographed on one silica gel plate (8 × 8 cm) using a mixture of light petroleum, ether and acetone (60 : 20 : 20) as eluent. Corresponding zones were collected, eluted with ether and evaporated. The yields of products were about 8—10 mg.

Methylation of the Alcohols *IVa* and *IVb*

The hydroxy derivative (5 mg) was dissolved in 1,2-dimethoxyethane (0·5 ml), sodium hydride (10 mg) and methyl iodide (0·05 ml) were added and the mixture was set aside at room temperature for 10 h. The excess of hydride was decomposed with water and a 5% aqueous hydrochloric acid solution, the product was taken up in ether and the ethereal solution was worked up as usual. The residue was chromatographed on one silica gel plate (8 × 8 cm) using a mixture of light petroleum, ether and acetone (80 : 10 : 10) as eluent. Corresponding zones were collected and eluted with ether. The yields of products were in the range of 3—4 mg. The physical data of the products are given in Table III and IV.

The authors thank Drs Z. Arnold and Z. Havlas for their interest and valuable discussions. The analyses were carried out in the Analytical Laboratory of this Institute (head Dr J. Horáček). The IR *spectra were recorded by Mrs K. Matoušková and Mr P. Formánek and interpreted by Dr S. Vašíčková.* ^{1}H-NMR *spectra were recorded by Mrs J. Jelínková.*

REFERENCES

1. Westphalen T.: Ber. Deut. Chem. Ges. *48*, 1064 (1915).
2. Lettré N., Müller M.: Ber. Deut. Chem. Ges. *70*, 1947 (1937).
3. Kirk D. N.: Hartshorn M. P.: *Steroid Reaction Mechanism.* Elsevier, Amsterdam 1968.
4. Blunt J. W., Hartshorn M. P., Jones F. W., Kirk D. N.: Tetrahedron Lett. *1964*, 1399.
5. Blunt J. W., Fischer A., Hartshorn M. P., Jones F. W., Kirk D. N., Yoong S. W.: Tetrahedron *21*, 1567 (1965).
6. Marples B. A., O'Callaghan B. M., Scottow J. L.: J. Chem. Soc., Perkin Trans. 1, *1974*, 1026.
7. Kirk D. N.: Tetrahedron *31*, 1299 (1975).
8. Kočovský P., Černý V.: This Journal *42*, 2415 (1977).
9. Hoffmann R.: Accounts Chem. Res. *4*, 1 (1971).
10. Coleby B., Keller M., Weiss J.: J. Chem. Soc. *1954*, 66.
11. Spring F. S., Swain G.: J. Chem. Soc. *1941*, 83.
12. Barton D. H. R., Cox J. D.: J. Chem. Soc. *1948*, 783.
13. Heilborn I. M., Jones E. R. H., Spring F. S.: J. Chem. Soc. *1937*, 801.
14. Kočovský P., Černý V.: This Journal *42*, 163 (1977).
15. Kočovský P., Černý V.: This Journal *41*, 2620 (1976).
16. Kočovský P., Černý V.: This Journal *42*, 155 (1977).
17. Collins D. J., Hobbs J. J., Sternhell S.: Austr. J. Chem. *16*, 1030 (1963).

Translated by the author (V. Č.).