ON STEROIDS. CXLII.* 5,7-CYCLOSTEROIDS. VI.**

ACETOLYSIS OF 4α-METHANESULPHONYLOXY-5,7,β-CYCLO-5β-CHOLESTANE

J.FAJKOŠ and J.JOSKA

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

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Two unambiguous syntheses of 5,7β-cyclo-5β-cholestan-4α-ol as well as the acetolysis of its mesylate are described.

In our previous papers[1] we have been studying the solvolyses of the epimeric 3-methanesulfonyloxy derivatives of 5,7-cyclo steroids. The 3α-epimer derived from the 5β,7β-cyclo compound afforded under acetolytic condititons the 4,5-unsaturated B-nor derivative *XIX*. The formation of this compound was explained by conjugative stabilisation of the cation from $C_{(3)}$ to $C_{(4)}$ followed by participation with the cyclopropane ring. It seemed therefore interesting to study the behaviour of some 4-substituted methanesulphonyloxy derivatives of the 5β,7β-cyclo series under solvolytic conditions.

In this paper we describe the synthesis of 4α-methanesulphonyloxy-5,7β-cyclo-5β-cholestane (*XVIII*) and its solvolysis. The starting compound was the epoxide[2] *I* which was transformed to the mesylate *II*. In analogy with our previous findings[3] the cleavage of this epoxide with hydrogen bromide afforded next to the bromohydrin *III* the methanesulphonyloxy derivative *IV*. Its structure was proved by acetylation to the diester *VI* which in turn was obtained from the previously described[3] monoacetate *V* with methanesulphonyl chloride. Next step was the metal hydride reduction of the mesylate *IV*. By analogy[4,5] this reaction should lead to the 4α-hydroxy derivative *VII* which in fact was obtained in a very good yield and as the sole product. Its structure was proved by hydrogenation to the previously described[6] 4α-hydroxy derivative *XI*. Oxidation afforded the α,β-unsaturated ketone *X* which on reduction with lithium tri-tert-butoxyaluminium hydride yielded next to the ketone *XII* the alcohol *XI*. Attempts to prepare the methanesulphonyloxy derivative of this alcohol failed and the only compound isolated in quantitative yield was the olefin *XIII*.

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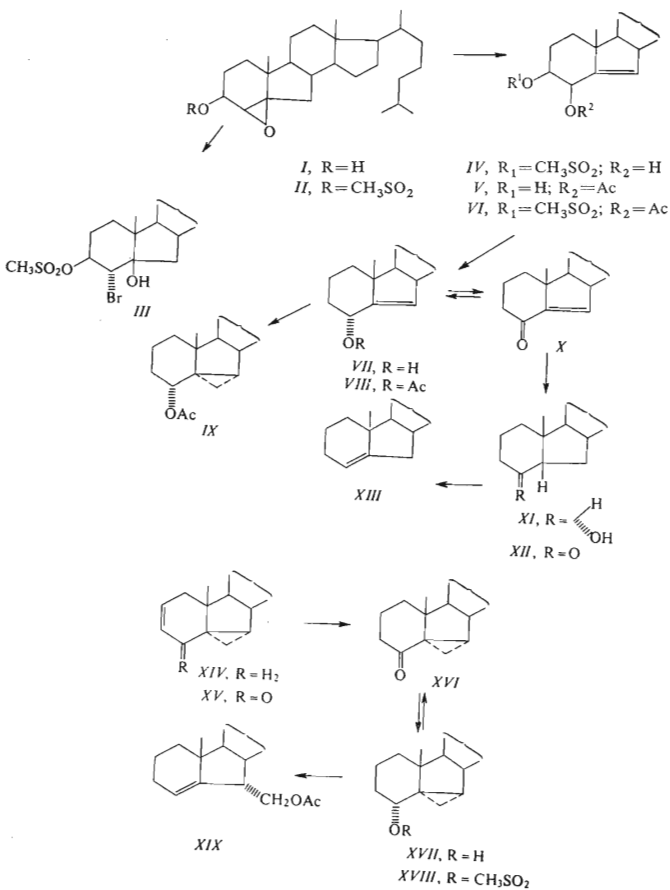
Unfortunately, the last step, the Simmons–Smith methylenation of the acetate *VIII* to the desired cyclo derivative *IX*, gave very low yields. We therefore underwent an alternative route which proved to by more successful: The olefin *XIV* was oxidised with tert-butyl chromate to give the unsaturated ketone *XV* which was hydrogenated



to the saturated ketone *XVI*. This compound was recently[7] prepared by oxidation of 5,7β-cyclo-5β-cholestan-4β-ol which was obtained on irradiation of 4,6-cholestadiene; the recorded melting point is in agreement with our determination but there is a striking difference in the optical rotation (ref.[7] −13·8° our finding −76°). On the other hand our data for the alcohol *XVII* are in good agreement with the literature[7]. Its mesylate *XVIII* was submitted to the acetolytic conditions as described[1] for the corresponding 3α-methanesulphonyloxy isomer. As expected the result of the reaction was identical for both the 3α- as well as for the 4α-isomer leading exclusively to the acetoxymethyl compound *XIX*. These results are in agreement with our[1] considerations.

EXPERIMENTAL

Melting points were determined on a Kofler block. Analytical samples were dried at 80°C/0·2 Torr. Optical measurements were carried out in chloroform with an error of ±1° unless otherwise stated. The infrared spectra were recorded on the Zeiss UR 10 spectrometer. The NMR spectra were recorded on Varian HA-100 instrument in deuteriochloroform with tetramethylsilane as internal reference. The identity of samples prepared by different routes was checked by mixture melting point determination, by thin-layer chromatography and by IR spectra. Light petroleum with b.p. 40—60°C was used.

3β-Methanesulphonyloxy-4β,5-epoxy-5β-B-norcholestane (*II*)

The epoxide[2] *I* (1 g) in pyridine (12 ml) was treated at 0°C with methanesulphonyl chloride (1·2 ml) and allowed to stand at room temperature for 6 h. The reaction mixture was decomposed with ice, diluted with water, and the product taken into ether. The ethereal solution was washed with dilute hydrochloric acid, a sodium hydrogen carbonate solution, water, dried, and evaporated. The residue on crystallisation from chloroform–methanol yielded 1·1 g of the mesylate *II*, m.p. 115°C (decomposition), $[\alpha]_D^{20}$ −19° (*c* 2·46). For $C_{27}H_{46}O_4S$ (466·7) calculated: 69·48% C, 9·94% H, 6·87% S; found: 69·31% C, 9·66% H, 6·49% S.

3β-Methanesulphonyloxy-4α-bromo-5β-B-norcholestan-5β-ol (*III*)

The epoxide *II* (1 g) in chloroform (100 ml) was agitated with 48% HBr (5 ml) at room temperature for 20 min. The reaction mixture was washed with water, a sodium hydrogen carbonate solution, water, dried and evaporated. The oily residue consisted according to the thin-layer chromatography of two components in about equal quantities. It was chromatographed on a silica gel column (150 g) in benzene–ether (19 : 1). Fractions containing the more lipophilic component were worked up and the residue was crystallised first from chloroform–methanol and then from ethyl acetate to yield 360 mg of the bromo derivative *III*, m.p. 143—144°C (decomposition), $[\alpha]_D^{20}$ +38° (*c* 1·76). For $C_{27}H_{47}BrO_4S$ (547·6) calculated: 59·21% C, 8·65% H, 14·60% Br, 5·85% S; found: 60·31% C, 8·39% H, 13·83% Br, 6·08% S.

3β-Methanesulphonyloxy-B-norcholest-5-en-4β-ol (*IV*)

Further elution of the chromatography from the foregoing experiment with the same solvent system afforded fractions with the polar component. Working up and crystallisation from methanol gave 460 mg of the derivative *IV*, m.p. 108°C, $[\alpha]_D^{20}$ −89° (*c* 1·57). For $C_{27}H_{46}O_4S$ (466·7) calculated: 69·48% C, 9·94% H, 6·87% S; found: 69·90% C, 10·01% H, 6·91% S.

3β-Methanesulphonyloxy-4β-acetoxy-B-norcholest-5-ene (*VI*)

a) *From* 3β-*methanesulphonyloxy*-B-*norcholest*-5-*en*-4β-*ol* (IV): The alcohol *IV* (500 mg) was acetylated with acetic anhydride (1·5 ml) in pyridine (2 ml) at room temperature for 20 h. The reaction mixture was decomposed with ice and the product extracted into ether. Usual working up and crystallisation from light petroleum afforded 410 mg of the diester *VI*, m.p. 116—117°C, $[\alpha]_D^{20}$ —114° (*c* 1·45). For $C_{29}H_{48}O_5S$ (508·7) calculated: 68·46% C, 9·51% H, 6·30% S; found: 68·31% C, 9·39% H, 6·15% S.

b) *From* 4β-*acetoxy*-B-*norcholest*-5-*en*-3β-*ol* (V): The alcohol[3] *V* (100 mg) in pyridine (2 ml) was treated at 0°C with methanesulphonyl chloride (0·15 ml) and allowed to stand at room temperature for 18 h. It was decomposed with ice, diluted with water, and the product extracted with ether. The ethereal solution was worked up as usual and evaporated. The residue on crystallisation from light petroleum afforded 72 mg of the diester *VI*, m.p. 115—117°C, $[\alpha]_D^{20}$ —112° (*c* 1·20), identical with the compound prepared under *a*.

B-Norcholest-5-en-4α-ol (*VII*)

a) *From* 3β-*methanesulphonyloxy*-B-*norcholest*-5-*en*-4β-*ol* (IV): The mesylate *IV* (600 mg) in tetrahydrofuran (60 ml) was refluxed with lithium hydride (600 mg) for 1 h. The reaction mixture was diluted with ether the excess hydride was decomposed with ethyl acetate and the solution was washed with dilute HCl a sodium hydrogen carbonate solution, water, dried and evaporated. The residue was chromatographed on a silica gel column (100 g) in benzene–light petroleum (1 : 1). Working up of the corresponding fractions and crystallisation from methanol–water afforded 380 mg of the alcohol *VII*, m.p. 134—136°C, $[\alpha]_D^{20}$ —121° (*c* 1·12); IR spectrum 1 630, 3 040, 3 595, 3 615 cm^{-1}. For $C_{26}H_{44}O$ (372·6) calculated: 83·80% C, 11·90% H; found: 83·70% C, 11·71% H.

b) *From* B-*norcholest*-5-*en*-4-*one* (X): The ketone *X* (110 mg) in tetrahydrofuran (3 ml) was treated with lithium tri-tert-butoxyaluminium hydride (300 mg) and allowed to stand at room temperature for 1 h. The reaction mixture was diluted with ether, the solution was washed with dilute HCl a sodium hydrogen carbonate solution, water, dried, and evaporated. The residue was chromatographed on a silica gel column (10 g) in benzene–light petroleum (1 : 1). Fractions containing the lipophilic component gave after working up and crystallisation from methanol 17 mg of the saturated ketone *XII*. Further elution with the same solvent mixture yielded fractions with the polar component. Working up and crystallisation from methanol gave 53 mg of the alcohol *VII*, m.p. 139—140°C, $[\alpha]_D^{20}$ —123° (*c* 1·15), identical with the compound prepared under *a*).

4α-Acetoxy-B-norcholest-5-ene (*VIII*)

The alcohol *VII* (1 g) in pyridine (5 ml) was acetylated with acetic anhydride (3 ml) at room temperature for 18 h. The reaction mixture was decomposed with ice and the product isolated with ether. Usual working up and crystallisation from ether–methanol gave 910 gm of the acetate *VIII*, m.p. 85—86°C, $[\alpha]_D^{20}$ —64° (*c* 1·84). For $C_{28}H_{46}O_2$ (414·6) calculated: 81·10% C, 11·18% H; found: 81·46% C, 11·52% H.

4α-Acetoxy-5,7β-cyclo-5β-cholestane (*IX*)

a) *From* 4α-*acetoxy*-B-*norcholest*-5-*ene* (VIII): 0,5% Zinc–copper couple was prepared from zinc dust (5 g; Baker Analyzed Reagent), cupric acetate monohydrate in acetic acid. The couple

was added in a 100 ml autoclave to a solution of the acetate *VIII* (1 g) and diiodiomethane (4·1 ml) and heated to 100°C for 7 h. After additional 18 h at room temperature the reaction mixture was diluted with ether and poured into 5% $NaHCO_3$ (200 ml). The ethereal layer was separated, washed with dilute hydrochloric acid, a sodium hydrogen carbonate solution, a sodium sulphite solution, water, dried and evaporated. The residue was chromatographed over silica gel (80 g) in light petroleum–30% benzene. The fractions containing the starting acetate and the cyclosteroid were combined, evaporated, and dissolved in ether (20 ml). The ethereal solution was treated with a solution of perphthalic acid (600 mg) in ether (8 ml) and allowed to stand at room temperature for 20 h. The reaction mixture was diluted with ether, the excess peracid was extracted into a sodium carbonate solution and the ethereal solution was worked up. The residue (620 mg) was chromatographed on a silica gel column (80 g) in light petroleum–30% benzene. Fractions containing the lipophilic cyclosteroid were combined, evaporated and the residue crystallised from methanol to yield 130 mg of the cyclo derivative *IX*, m.p. 128–130°C, $[\alpha]_D^{20}$ +15° (*c* 1·01); IR spectrum 1030, 1247, 1378, 3010, 3065 cm^{-1}. For $C_{29}H_{48}O_2$ (428·7) calculated: 81·25% C, 11·29% H; found: 81·17% C, 11·21% H.

b) *From* 5,7β-*cyclo*-5β-*cholestan*-4-*one* (XVI): The ketone *XVI* (1 g) in acetic acid (40 ml) was hydrogenated on Adams' catalyst (100 mg) for 30 min. The reaction mixture was diluted with ether, the catalyst was filtered off and the filtrate evaporated to dryness under reduced pressure. The residue was dissolved in pyridine (5 ml) and acetylated with acetic anhydride (4 ml) for 20 h at room temperature. Usual working up gave an oil which was chromatographed over silica gel (100 g) in benzene to yield 650 mg of the crude product. Crystallisation from methanol afforded 580 mg of the acetate *IX*, m.p. 129–131°C, $[\alpha]_D^{20}$ +17° (*c* 1·08).

c) *From* 5,7β-*cyclo*-5β-*cholestan*-4α-*ol* (XVII): The alcohol *XVII* (80 mg) was acetylated with acetic anhydride (0·3 ml) in pyridine (0·4 ml) for 20 h at room temperature. Usual working up and crystallisation from methanol afforded 58 mg of the acetate *IX*, m.p. 128–129°C, $[\alpha]_D^{20}$ +16·5° (*c* 1·33).

B-Norcholest-5-en-4-one (*X*)

The alcohol *VII* (200 mg) in acetone (40 ml) was treated with Jones' reagent (1 ml) and set aside for 20 min. The excess oxidising agent was removed with methanol (2 ml), the reaction mixture was removed with methanol (2 ml), the reaction mixture was diluted with water (200 ml), and the product extracted with ether. The ethereal solution was washed with water, a sodium hydrogen carbonate solution, dried, and evaporated. The residue was chromatographed on a silica gel column (20 g) in light petroleum–benzene (1 : 1). Working up of the corresponding fraction and crystallisation from methanol yielded 65 mg of the ketone *X*, m.p. 116–118°C, $[\alpha]_D^{20}$ –108° (*c* 1·35); IR spectrum 1597, 1682, 3045 cm^{-1}; UV spectrum λ_{max} 257 nm (log ε 4·01). For $C_{26}H_{42}O$ (370·6) calculated: 84·26% C, 11·42% H; found: 83·98% C, 11·18% H.

5β-B-Norcholestan-4α-ol (*XI*)

The unsaturated alcohol *VII* (300 mg) in acetic acid (30 ml) was hydrogenated under the presence of Adams' catalyst (80 mg) for 1 h. The reaction mixture was diluted with ether, the catalyst was filtered off, the filtrate was washed with water and a sodium hydrogen carbonate, dried and evaporated. The residue was chromatographed over silica gel (50 g) in light petroleum–30% benzene. Working up of the corresponding fractions and crystallisation from methanol–water gave 140 mg of the alcohol *XI*, m.p. 76–78°C, $[\alpha]_D^{20}$ +4° (*c* 1·12) identical with the authentic sample[6].

5β-B-Norcholestan-4-one (*XII*)

The alcohol *XI* (60 mg) in acetone (3 ml) was treated at room temperature with Jones' reagent (0·1 ml). After 5 min the excess chromic acid was removed with methanol (0·5 ml), the reaction mixture was diluted with ether and the ethereal solution was washed with water a sodium hydrogen carbonate solution, water, dried, and evaporated. The residue on crystallisation from methanol gave 22 mg of the ketone *XII*, m.p. 84–85°C, $[\alpha]_D^{20}$ +66° (*c* 1·06) identical with the sample described[6] previously.

B-Norcholest-4-ene (*XIII*)

A solution of the alcohol *XI* (160 mg) in pyridine (3 ml) was treated at 0°C with methanesulphonyl chloride. The mixture was kept at 0°C for 2 h, decomposed with ice, diluted with water, and the product taken into ether. The ethereal solution was washed dilute hydrochloric acid, a sodium hydrogen carbonate solution, water, dried, and evaporated. The residue on crystallisation from methanol–ether afforded 120 mg of the olefin *XIII*, m.p. 64–66°C, $[\alpha]_D^{20}$ −13° (*c* 1·81); NMR spectrum: 5·23 (s, 4-H). For $C_{26}H_{44}$ (356·6) calculated: 87·56% C, 12·44% H; found: 87·79% C, 12·30% H.

5,7β-Cyclo-5β-cholest-2-en-4-one (*XV*)

The olefin[1] *XIV* (1 g) in tetrachloromethane (8 ml), acetic acid (2 ml) and acetic anhydride (0·5 ml) was treated with tert-butyl chromate (10 ml) containing 200 mg of chromic acid), acetic acid (2 ml) and acetic anhydride (0·5 ml). The reaction mixture was heated to 65°C for 26 h under stirring. The excess chromic acid was removed with 10% oxalic acid (40 ml), stirred for 1 h at room temperature, water was added, and the product was extracted into ether. The ethereal solution was washed with water, a sodium hydrogen carbonate solution, water, dried, and evaporated. The residual oil was chromatographed on a silica gel column (100 g) in benzene. Fractions containing the unsaturated ketone were combined, evaporated and the residue crystallised from methanol to yield 380 mg of the ketone *XV*, m.p. 131°C, $[\alpha]_D^{20}$ −71° (*c* 1·41), IR spectrum: 1640, 1680 cm^{-1}. For $C_{27}H_{42}O$ (382·6) calculated: 84·75% C, 11·07% H; found: 84·57% C. 11·21% H.

5,7β-Cyclo-5β-cholestan-4-one (*XVI*)

a) *From* 5,7β-*cyclo*-5β-*cholest*-2-*en*-4-*one* (XV): The unsaturated ketone *XV* (150 mg) in ethanol (25 ml) was hydrogenated over 5% $Pd/CaCO_3$ catalyst (200 mg) for 3 h. The reaction mixture was diluted with ether, the catalyst was filtered off, the filtrate was washed with dilute hydrochloric acid, a sodium hydrogen carbonate solution, water, dried, and evaporated. Crystallisation from methanol yielded 106 mg of the ketone *XVI*, m.p. 152–153°C, $[\alpha]_D^{20}$ −76° (*c* 1·25); literature[7] records m.p. 152–153°C, $[\alpha]_D^{31}$ −13·8°. For $C_{27}H_{44}O$ (384·6) calculated: 84·31% C, 11·53% H; found: 84·19% C, 11·39% H.

b) *From* 5,7β-*cyclo*-5β-*cholestan*-4α-ol (XVII): The alcohol *XVII* (90 mg) in acetone (2·5 ml) was treated at room temperature with Jones' reagent (0·15 ml) and allowed to stand for 30 min. Methanol was added, the mixture diluted with ether and the ethereal solution washed with water and sodium hydrogen carbonate, dried and evaporated. Crystallisation from methanol gave 65 mg of the ketone *XVI*, m.p. 154–155°C, $[\alpha]_D^{20}$ −79° (*c* 1·21), identical with the sample prepared as under *a*).

5,7β-Cyclo-5β-cholestan-4α-ol (*XVII*)

The ketone *XVI* (900 mg) in tetrahydrofuran (30 ml) was treated with lithium tri-tert-butoxyaluminium hydride (2 g) and allowed to stand at room temperature for 2 hours. The reaction mixture was diluted with ether, washed with dilute hydrochloric acid, a sodium hydrogen carbonate solution, water, dried, and evaporated. The residue was chromatographed on a silica gel column (100 g) in light petroleum–benzene (1 : 1). Working up of the corresponding fractions and crystallisation from methanol–water gave 530 mg of the alcohol *XVII*, m.p. 130—132°C, $[\alpha]_D^{20}$ −20° (*c* 2·55) in agreement with the literature[7]. For $C_{27}H_{46}O$ (386·6) calculated: 83·87% C, 11·99% H; found: 83·69% C, 11·90% H.

4α-Methanesulphonyloxy-5,7β-cyclo-5β-cholestane (*XVIII*)

The alcohol *XVII* (360 mg) in pyridine (4 ml) was treated at 0°C with methanesulphonyl chloride (0·7 ml) and set aside at room temperature for 18 h. The reaction mixture was decomposed with ice, diluted with water, and the product isolated with ether. Usual working up and crystallisation from chloroform–methanol gave 340 mg of the mesylate *XVIII*, m.p. 129°C, $[\alpha]_D^{20}$ +24° (*c* 1·16). For $C_{28}H_{48}O_3S$ (464·7) calculated: 72·36% C, 10·41% H, 6·90% S; found: 72·23% C, 10·22% H, 6·38% S.

6α-Acetoxymethyl-B-norcholest-4-ene (*XIX*)

The mesylate *XVIII* (180 mg) in acetic acid (2·5 ml) and acetic anhydride (0·25 ml) was refluxed with anhydrous sodium acetate (200 mg) for 6 h. The reaction mixture was decomposed with water, the product extracted into ether, and the ethereal solution was washed with a sodium hydrogen carbonate solution, water, dried, and evaporated. The residues was chromatographed over silica gel (35 g) in light petroleum. The corresponding fractions were combined, and evaporated leaving 125 mg of the acetate *XIX*, oil, $[\alpha]_D^{20}$ −42° (*c* 1·06), identical with the compound prepared previously[1].

The analyses were carried out in the Analytical Laboratory of this Institute by Mr V. Štěrba, Mrs E. Šipová, and Mrs E. Sýkorová under the direction of Dr J. Horáček. The IR spectra were recorded by Mrs S. Vašíčková under the direction of Dr J. Smolíková.

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