THE SYNTHESIS OF 5,6-CYCLOPROPANOCHOLESTANES WITH OXYGEN FUNCTIONS IN POSITIONS 3 AND 7*

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The Simmons–Smith methylenation of the double bond in 3β-acetoxycholest-5-en-7-ols takes place selectively under formation of an adduct the configuration of which is determined by the configuration of the 7-hydroxyl group: 7β-alcohol *IV* gave 5β,6β-cyclopropane derivative *VI*, 7α-alcohol *V* gave 5α,6α-cyclopropane derivative *VIII*. On photochemically initiated cyclization of 3β-acetoxy-B-homo-5-en-7a-one (*XIII*) we obtained the product with an α-cyclopropane ring exclusively, *i.e.* 3β-acetoxy-5,6α-cyclopropano-5α-cholestan-7-one (*XII*).

During the study of the properties of steroidal cyclopropylcarbinols we were faced with the problem of the preparation of 5α,6α- and 5β,6β-cyclopropanocholestanes with oxygen functions in positions 3 and 7. The construction of such a skeleton could be attempted in two possible ways: by the attachement of the cyclopropane cycle to the well accessible Δ^5-7-ketone *I* on the one hand or by the cyclopropane ring closure in the known 3β-acetoxy-B-homo-5-cholesten-7a-one (*XIII*) by a procedure described in literature[1-4] on the other.

It was found that the application of Corey's reagent to 3β-acetoxy-5-cholesten-7-one (*I*) did not lead to the formation of 5,6-cyclopropane ring: the main component of the reaction mixture was the product of acetic acid elimination (*i.e.* cholesta-3,5-dien--7-one (*II*)), accompanied by the product of the addition of the cyclopropane ring to the position 3,4 (*III*).

If corresponding allylic alcohol *IV* or *V* is used as starting substance for the Simmons–Smith methylenation, which are resistant to the elimination of acetic acid under the conditions of Simmons–Smith reaction, the reaction takes place in high yields (about 70%). From literature it is known[5-10] that on Simmons–Smith methylenation of an allylic alcohol a compound is formed the cyclopropane ring of which has the same configuration as the hydroxyl group of the starting allylic alcohol. From 7α-alcohol *V* we obtained the adduct with the 5α,6α-cyclopropane ring, *i.e.* 3β-acetoxy-5,6α-cyclopropano-5α-cholestan-7α-ol (*VIII*) while from the 7β-alcohol *IV* we obtained the adduct with the 5β,6β-cyclopropane ring, *i.e.* 3β-acetoxy-5,6β-

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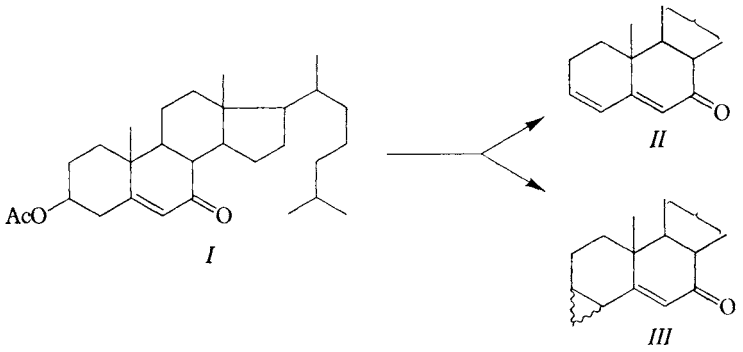
-cyclopropano-5β-cholestan-7β-ol (*VI*). The configurations of the adducts determined in this manner are in agreement with the data obtained from ^{1}H NMR spectra (Table I).



I *II* *III*

When crystallizing the 5α,6α-adduct *VIII* from methanol a very easy methylation of the 7α-hydroxy group takes place under formation of two compounds; according to IR and ^{1}H NMR spectra both substances contained in addition to the unchanged acetoxy group and the cyclopropane ring also a methoxy group (IR spectrum: 2 820, 1 079, 1 091, or, 2 820, 1 102, 1 190 cm^{-1}, respectively. ^{1}H NMR spectrum: a singlet of the methoxy group at 3·25 or 3·32 ppm, respectively). The lipophilic methyl ester was also prepared by methylation of the 7α-hydroxy group of the adduct *VIII* with diazomethane. We assign the lipophilic methyl ether the structure of 3β-acetoxy-7α-methoxy-5,6α-cyclopropano-5α-cholestane (*IX*), and the second methyl

TABLE I

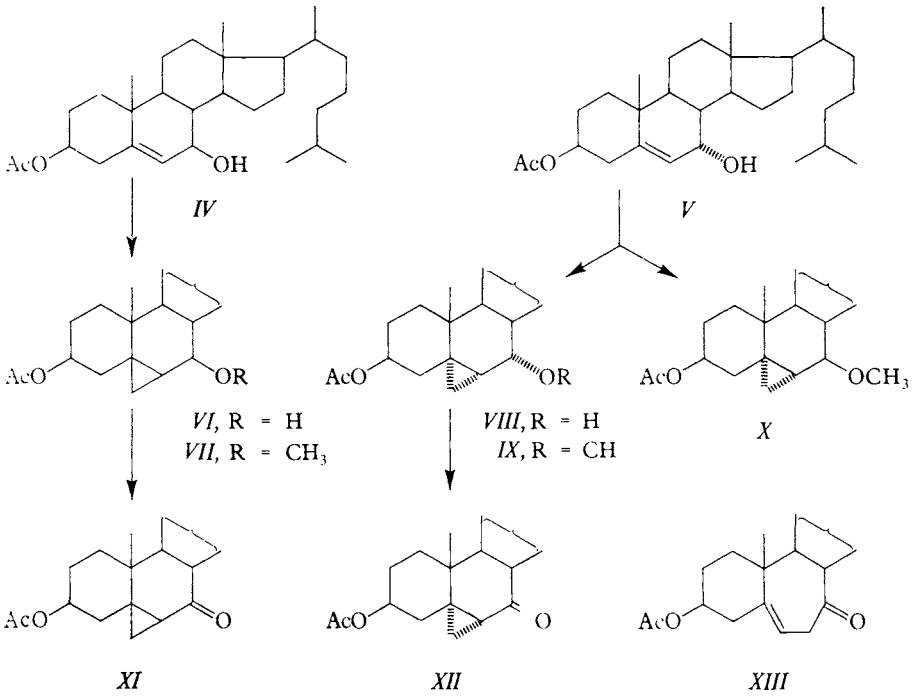
Signals of 19-protons in the ^{1}H NMR spectra (in ppm)

Compound	19-H	Δ
5α-Cholestan-7α-ol[10]	0·78	0·29
5α,6α-Cyclopropanocholestan-7α-ol[10]	1·07	
5α-Cholestan-7β-ol[10]	0·81	0·06
5β,6β-Cyclopropanocholestan-7β-ol[10]	0·87	
3β-Acetoxy-5α-cholestan-7α-ol[a]	0·81	0·28
3β-Acetoxy-5α,6α-cyclopropanocholestan-7α-ol (*VIII*)	1·09	
3β-Acetoxy-5α-cholestan-7β-ol[a]	0·84	0·05
3β-Acetoxy-5β,6β-cyclopropanocholestan-7β-ol (*VI*)	0·89	

[a] Calculated according to ref.[11].

ether the structure of 3β-acetoxy-7β-methoxy-5,6α-cyclopropano-5α-cholestane (*X*). On crystallization of the 5β,6β-adduct *VI* from methanol we did not observe a similar reaction, and we always obtained the pure product *VI* only. The etherification of the 7α-hydroxy group in adduct *VIII* during crystallization can be suppressed by carrying out crystallization very rapidly and using aqueous methanol or pure ethanol.

On photochemically initiated cyclization[1-4] of β,γ-unsaturated B-homo-ketone *XIII* we obtained a mixture which contained in addition to the starting compound about 10% of a product identical with the oxidation product of 7α-hydroxy compound *VIII*, *i.e.* 3β-acetoxy-5,6α-cyclopropano-5α-cholestan-7-one (*XII*).



From the experiments mentioned it follows that for the synthesis of 5,6-cyclo propanocholestanes with oxygen functions in positions 3 and 7 both the Simmons–Smith methylenation of the double bond in 7-alcohols *IV* and *V* and the photochemically initiated cyclization of β,γ-unsaturated B-homo-ketone *XIII* may be used. The first method is more advantageous from the point of view of the accesssibility of the starting substances, reaction time and yield. Moreover, both isomers, α- and β-cyclopropane products, may be obtained by Simmons–Smith methylenation.

EXPERIMENTAL

The melting points were determined on a Kofler block and they are not corrected. Optical measurements were carried out in chloroform, with a $\pm 3°$ error. The infrared spectra were measured on a Zeiss UR 20 spectrophotometer, in tetrachloromethane, unless stated otherwise. The UV spectrum was measured on a CF 4 spectrometer in ethanol. The ^{1}H NMR spectra were measured on a Tesla B 476 (60 MHz) spectrometer, or a Varian HA 100 (100 MHz) instrument, in deuteriochloroform with tetramethylsilane as internal reference, unless stated otherwise. The chemical shifts are given in δ-scale. The symbol *W* means the width of the signal at half of its height. The spectra were interpreted as 1st order spectra. The mass spectra were recorded on an AEI MS 902 spectrometer. The identity of the samples prepared was checked by mixture melting point determinations, thin-layer chromatography (TLC), infrared and ^{1}H NMR spectra. Ther term "conventional work-up" of the solutions means that the organic phase into which the product was extracted was washed with 5% hydrochloric acid, water, 5% potassium hydrogen carbonate solution and water, drying over sodium sulfate, filtration off of the drying agent and evaporation of the solvent in a vacuum. If light petroleum was used, it was the fraction with b.p. 40 to 62°C.

Cholesta-3,5-dien-7-one (*II*)

Corey's reagent[12] (trimethyloxosulfonium iodide, 2 g) was added to dimethyl sulfoxide (20 g) and the mixture was stirred under nitrogen until the iodide was dissolved. A sodium hydride (0·4 g) solution in dimethyl sulfoxide (2·5 ml) was added dropwise to the above solution and the mixture stirred under nitrogen for 24 h. After pouring into water the product was extracted with ether and the extract submitted to the conventional work-up. The residue was chromatographed on silica gel (100 g, light petroleum–ether 33 : 1). The combined fractions with the lipophilic product yielded 280 mg of dienone *II*, m.p. 111–113°C, $[\alpha]_D^{20}$ −30° (*c* 1·1), in agreement with literature[10].

3ξ,4ξ-Cyclopropanocholest-5-en-7-one (*III*)

a) *From* 3β-*acetoxycholest*-5-*en*-7-*one* (I): continuing the chromatography from the preceding experiment a more polar product, *III*, was obtained in 390 mg yield, m.p. 139–140 °C (methanol–chloroform), $[\alpha]_D^{20}$ −198° (*c* 1·6). IR spectrum: 1 668, 1 623 (C=C—C=O), 3 015, 3 080 (double bond, cyclopropane) cm^{-1}. ^{1}H NMR spectrum: 0·43 (dd, J = 5 Hz, J' = 5 Hz, cyclopropane protons), 0·69 (s, 18-H), 0·86 (d, J = 5·5 Hz, 26-H and 27-H), 0·91 (d, J = 5 Hz, 21-H), 1·12 (s, 19-H), 5·85 (s, 6-H). For $C_{28}H_{44}O$ (386·7) calculated: 84·78% C, 11·18% H; found: 84·74% C, 11·03% H.

b) *From cholesta*-3,5-*dien*-7-*one* (II): In the same manner as described in the preparation of compound *II* dienone *II* (0·2 g) was treated with Corey's reagent. Yield, 102 mg of product *III*, m.p. 136–138°C.

3β-Acetoxy-5,6β-cyclopropano-5β-cholestan-7β-ol (*VI*)

A mixture of 0·7% Cu in Zn (Cu–Zn couple) was prepared by adding Zn-dust into a solution of cupric acetate monohydrate (120 mg) in acetic acid (5 ml) at 50–60°C and shaking the mixture until decolorized. Another 5 ml of acetic acid were added and the sedimented zinc decanted by 8 additions of ether (10 ml each). Ether (20 ml) was then added to the Cu–Zn couple and the mixture stirred under dropwise addition of diiodomethane (4·6 ml) and the mixture was then refluxed under stirring and under nitrogen for 2 h. 3β-Acetoxycholest-5-en-7β-ol (*IV*) (1·5 g, m.p. 111–113°C) (ref.[13]) dissolved in 60 ml of ether was then added and the mixture refluxed under

nitrogen and stirring for 20 min, poured into a saturated aqueous solution of potassium hydrogen carbonate and extracted with ether. After conventional work-up the residue was chromatographed on silica gel (100 g, light petroleum–ether 7 : 1) and adduct *VI* obtained (1·12 g). It was crystallized from methanol after cooling at −40 to −80°C. M.p. 70–72°C, $[\alpha]_D^{20}$ +34° (*c* 1·9). Mass spectrum: *m/z* 458 (M), 440 (M − H_2O), 398 (base peak, M − $HOCOCH_3$), 380 (M − H_2O − $HOCOCH_3$). IR spectrum: 3 605, 1 021 (hydroxyl), 3 075 (cyclopropane), 1 736, 1 247, 1 033 (acetate) cm^{-1}. ^1H NMR spectrum: −0·02 to 0·27 and 0·40 to 0·60 (2 mts, cyclopropane protons), 0·62 (s, 18-H), 0·85 (d, *J* = 5·5 Hz, 26-H and 27-H), 0·88 (d, *J* = 5 Hz, 21-H), 0·89 (s, 19-H), 1·99 (s, 3β-acetate), 3·63 (mt, *W* = 12·5 Hz, 7α-H), 4·90 (mt, *W* = 18 Hz, 3α-H). For $C_{30}H_{50}O_3$ (458·7) calculated: 78·55% C, 10·99% H; found: 78·14% C, 10·92% H.

3β-Acetoxy-7β-methoxy-5,6β-cyclopropano-5β-cholestane (*VII*)

A diazomethane solution (10 ml, 137 mg of diazomethane) in ether was added to a solution of 7β-alcohol *VI* (350 mg) in ether (15 ml), followed by a few grains of anhydrous aluminum chloride, and the mixture was allowed to stand at room temperature for 5 min. Then another grain of aluminum chloride was added and after 30 min the mixture was poured into water and worked up with ether in the conventional manner. Yield, 350 mg of an oil which was purified by column chromatography on silica gel (30 g, light petroleum–ether 19 : 1) to give 290 mg of non-crystallizing methoxy derivative *VII*, $[\alpha]_D^{20}$ +31° (*c* 1·2). IR spectrum: 3 095, 3 075, 3 040 (cyclopropane), 2 820, 1 099 (methoxy group), 1 738, 1 248, 1 032, 1 024 (acetate), cm^{-1}. ^1H NMR spectrum: 0·00–0·27 and 0·39–0·59 (2 mts, cyclopropane protons), 0·62 (s, 18-H), 0·86 (d, *J* = 5·5 Hz, 26-H and 27-H), 0·88 (s, 19-H), 2·00 (s, 3β-acetate), 3·18 (mt, *W* = 15 Hz, 7α-H), 4·95 (mt, *W* = 27 Hz, 3α-H). For $C_{31}H_{52}O_3$ (472·7) calculated: 78·76% C, 11·09% H; found: 78·62% C, 11·21% H.

3β-Acetoxy-5,6α-cyclopropano-5α-cholestan-7α-ol (*VIII*)

Using the same procedure as in the preparation of *VI* 3β-acetoxy-cholest-5-en-7α-ol (*V*) (m.p. 137–139°C, $[\alpha]_D^{20}$ −84·5°) (ref.[13]) was submitted to Simmons–Smith methylenation. The only modification of the procedure was that after the addition of olefin *V* the mixture was refluxed under nitrogen and stirring for 120 min. After a similar work-up and chromatography of the residue on silica gel (300 g, light petroleum–ether 7 : 3) 1·06 g of product were obtained, which was crystallized from aqueous methanol to give 955 mg of adduct *VIII*, m.p. 153–153·5°C, $[\alpha]_D^{20}$ −87° (*c* 2·3). IR spectrum: 3 605, 1 021 (hydroxyl), 3 075 (cyclopropane), 1 736, 1 247, 1 033 (acetate) cm^{-1}. ^1H NMR spectrum: 0·18 (mt, cyclopropane protons), 0·60 (s, 18-H), 0·84 (d, *J* = 5·5 Hz, 26-H and 27-H), 0·89 (d, *J* = 5·0 Hz, 21-H), 1·09 (s, 19-H), 1·98 (s, 3β-acetate), 4·10 (mt, *W* = 15 Hz, 7β-H), 4·80 (mt, *W* = 22·5 Hz, 3α-H). For $C_{30}H_{50}O_3$ (458·7) calculated: 78·55% C, 10·99% H; found: 78·60% C, 11·17% H.

3β-Acetoxy-7α-methoxy-5,6α-cyclopropano-5α-cholestane (*IX*)

a) 7α-Alcohol *VIII* (1·2 g) was dissolved in boiling methanol and the solution was allowed to stand at room temperature for 2 h. After crystallization of the 7α-alcohol *VIII* and filtration the mother liquors contained a lipophilic product. If 7α-alcohol *VIII* was allowed to stand in methanol solution for 14 days, the resulting solution no longer contained the 7α-alcohol, but only lipophilic products. These lipophilic products were separated by chromatography on silica gel (150 g, light petroleum–ether 19 : 1). The working up of the fractions with the more lipophilic product gave 0·9 g of dry residue which was crystallized from methanol to give 610 mg of pure *IX*, m.p. 96–97°C, $[\alpha]_D^{20}$ −109° (*c* 1·4). IR spectrum: 3 085 (cyclopropane), 2 820, 1 079, 1 091

(methoxy group), 1 738, 1 246, 1 032 (acetate) cm^{-1}. ^1H NMR spectrum: 0·12 to 0·41 (mt, cyclopropane protons), 0·60 (s, 18-H), 0·86 (d, $J = 6$ Hz, 26-H and 27-H), 1·10 (s, 19-H), 2·01 (s, 3β-acetate), 3·25 (s, 7-methoxy group), 3·48 (mt, $W = 13$ Hz, 7β-H), 4·91 ($W = 22·5$ Hz, 3α-H). For $C_{31}H_{52}O_3$ (472·7) calculated: 78·76% C, 11·09% H; found: 79·05% C, 10·75% H.

b) A diazomethane solution in ether (5 ml) was added to a solution of 102 mg of 7α-alcohol *VIII* in ether (10 ml) and the mixture was allowed to react. After working up in the same manner as in the preparation of methyl ether *VII* and purification on a silica gel column (25 g, light petroleum–ether 19 : 1) 88 mg of methyl ether *IX* were obtained, m.p. 96–97°C, $[\alpha]_D^{20}$ −106° (*c* 1·1).

3β-Acetoxy-7β-methoxy-5,6α-cyclopropano-5α-cholestane (*X*)

Working up of the fractions containing the more polar product from chromatography in the preparation of methyl ether *IX* according to procedure *a*) gave 0·35 g of product which when crystallized from methanol gave 183 mg of methyl ether *X*, m.p. 97–98°C, $[\alpha]_D^{20}$ −13° (*c* 1·1). IR spectrum: 3 070 (cyclopropane), 2 820, 1 102, 1 090 (methoxy group), 1 738, 1 246, 1 032 (acetate) cm^{-1}. ^1H NMR spectrum: 0·05 to 0·55 (mt, cyclopropane protons), 0·64 (s, 18-H), 0·86 (d, $J = 5·5$ Hz, 26-H and 27-H), 1·13 (s, 19-H), 2·1 (s, 3β-acetate), 3·12 (mt, $W = 11$ Hz, 7α-H), 3·32 (s, 7β-methoxy group), 4·82 (mt, $W = 27$ Hz, 3α-H). For $C_{31}H_{52}O_3$ (472·7) calculated: 78·76% C, 11·09% H; found: 79·20% C, 10·74% H.

3β-Acetoxy-5,6β-cyclopropano-5β-cholestan-7-one (*XI*)

Jones's reagent was added to a solution of 7β-alcohol *VI* (360 mg) in acetone (10 ml) until the brownish coloration persisted. After 5 min standing at room temperature methanol was added (0·5 ml) and after another 5 min standing the mixture was poured into water, extracted with ether and the extract washed with water, potassium hydrogen carbonate (10%) and water, then dried over sodium sulfate and evaporated. The residue was crystallized from methanol to give 212 mg of ketone *XI*, m.p. 115–116°C, $[\alpha]_D^{20}$ −27° (*c* 2·1). Mass spectrum: *m/z* 456 (M), 441 (M − CH_3), 396 (M − $HOCOCH_3$), 381 (M − CH_3 − $HOCOCH_3$), IR spectrum: 3 090, 3 015 (cyclopropane), 1 740, 1 246, 1 026 (acetate), 1 694 (carbonyl in conjugation with cyclopropane) cm^{-1}. ^1H NMR spectrum: 0·64 (s, 18-H), 0·86 (d, $J = 6$ Hz, 26-H and 27-H), 0·92 (d, $J = 5·5$ Hz, 21-H), 1·10 (s, 19-H), 1·98 (s, 3β-acetate), 4·94 (mt, $W = 18$ Hz, 3α-H). For $C_{30}H_{48}O_3$ (456·7) calculated: 78·90% C, 10·59% H; found: 79·10% C, 10·44% H.

3β-Acetoxy-5,6α-cyclopropano-5α-cholestan-7-one (*XII*)

a) A solution of alcohol *VIII* (150 mg) in acetone (10 ml) was oxidized with Jones's reagent in the same manner as in the preceding section. After similar work-up and crystallization from methanol, 89 mg of ketone *XII* were obtained, m.p. 127–129°C, $[\alpha]_D^{20}$ +15° (*c* 0·9). IR spectrum: 3 080, 3 010 (cyclopropane), 1 736, 1 244, 1 036 (acetate), 1 687 (carbonyl in conjugation with the cyclopropane ring) cm^{-1}. UV spectrum: $\lambda_{max} = 293$ nm (log $\varepsilon = 2·19$). ^1H NMR spectrum: 0·67 (s, 18-H), 0·86 (d, $J = 6$ Hz, 26-H and 27-H), 0·91 (d, $J = 5·5$ Hz, 21-H), 1·05 (s, 19-H), 1·99 (s, 3β-acetate), 4·76 (mt, $W = 28$ Hz, 3α-H). For $C_{30}H_{48}O_3$ (456·7) calculated: 78·90% C, 10·59% H; found: 79·11% C, 10·60% H.

b) A solution of B-homo-ketone *XIII* (1 g) in acetone (15 ml) in a Pyrex flask filled with nitrogen was irradiated with a Hanovia lamp (500 W) for 4 h. The mixture was evaporated and the residue chromatographed on a silica gel column (100 g, benzene–ether 99 : 1). In addition to 707 mg of compound *XIII* ketone *XII* (101 mg) was also obtained, m.p. 128·5–129·5°C (methanol), $[\alpha]_D^{20}$ +14° (*c* 0·9).

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