REDUCTION OF SOME 3,6-CYCLO-A-NOR-3,5-SECO-6β-CHOLESTANES*

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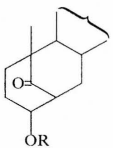
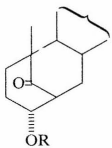
Reduction of 3- and 5-ketones with hydride reagents affords the products of the attack on the keto group from the least hindered side: in 3α-substituted 5-ketones (5*R*)-hydroxy derivatives are thus formed. The introduction of the 3β-substituent changes the reaction course. Meerwein–Ponndorf reduction of 5-ketones affords axial (5*S*)-alcohols. 5-Hydroxy 3-ketones are relatively stable in alkaline medium.

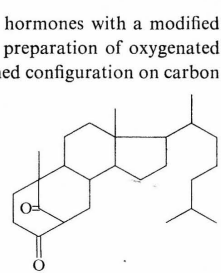
In connection with the study of the analogues of steroid hormones with a modified skeleton we were also interested in the possibility of the preparation of oxygenated derivatives of 3,6-cyclo-A-nor-3,5-secosteroids with a defined configuration on carbon



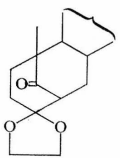
I, R = H
II, R = Bz
III, R = Ac



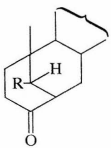
IV, R = H
V, R = Ac



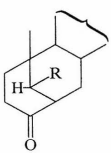
VI



VII



VIII, R = HO
IX, R = BzO



X, R = BzO
XI, R = HO

* Part CC in the series On Steroids; Part CIC: This Journal *43*, 336 (1978).

atoms 3 and 5. The substances of this type are accessible from epimeric 3-hydroxy 5-ketones[1] *I* and *IV*, or can be prepared directly on reduction of 4-oxa-5-cholesten--3-one[2]. From the four possible diols, however, only diol *XII* is known[1], and some properties – but not the structure – of one of the remaining 3 isomers are known.

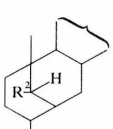
Reduction of hydroxy ketones *I* and *IV* always gave a mixture of diols which we separated by chromatography on silica gel (for the comparison of polarities see Table I). In this set of four substances the known diol *XIIa* was identified easily on the basis of its IR spectrum (intramolecular hydrogen bond). Partial acetylation of this diol gave predominantly monoacetate *XIIb* the structure of which was checked by oxidizing it to the known[3] acetoxy ketone *III*. Acetoxy alcohol *XIIb* was converted consecutively to acetoxy benzoate, hydroxy benzoate and keto benzoate, *i.e. XIIc*, *XIId* and *IX*, respectively. In view of the applied method of preparation the configuration at $C_{(5)}$ in compound *IX* remained the same as in compound *XIIa*, and therefore ketone *IX* was used in the correlation of the structures of other diols: we have found that diol *XIVa* can also be converted in the same manner to compound *IX*, while diols *XIIIa* and *XVa* afford isomeric keto benzoate *X*. It was found that the diol prepared according to the procedure of Japanese authors[2] is identical in all respects with diol *XIIIa*, which also confirms the speculative conclusion of Martin and coworkers[1] on the structure of this substance.

TABLE I

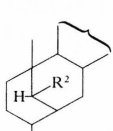
Chromatography on Silica Gel Thin Layer Survey of R_F Values

Substance	S_1[a]	S_2	S_3
VIII	—	0·58	0·02
IX	—	—	0·44
X	—	—	0·18
XI	—	0·61	0·02
XIIa	0·77	0·50	—
XIIIa	0·40	0·19	—
XIVa	0·38	0·17	—
XVa	0·52	0·26	—

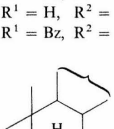
[a] S_1: 10% acetone in chloroform, triple development; S_2: 50% of chloroform in ether; S_3: benzene, double development.



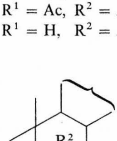
XIIa, R^1 = H, R^2 = HO
XIIb, R^1 = Ac, R^2 = HO
XIIc, R^1 = Ac, R^2 = BzO
XIId, R^1 = H, R^2 = BzO
XIIe, R^1 = Bz, R^2 = HO
XIIf, R^1 = Ac, R^2 = AcO
XIIg, R^1 = H, R^2 = AcO
XIIh, R^1 = Bz, R^2 = BzO



XIIIa, R^1 = H, R^2 = HO
XIIIb, R^1 = Ac, R^2 = HO
XIIIc, R^1 = Ac, R^2 = BzO
XIIId, R^1 = H, R^2 = BzO
XIIIe, R^1 = Bz, R^2 = HO
XIIIf, R^1 = Ac, R^2 = AcO
XIIIg, R^1 = H, R^2 = AcO



XIVa, R^1 = H, R^2 = HO
XIVb, R^1 = Ac, R^2 = HO
XIVc, R^1 = Ac, R^2 = BzO
XIVd, R^1 = H, R^2 = BzO
XIVf, R^1 = Ac, R^2 = AcO
XIVg, R^1 = H, R^2 = AcO



XVa, R^1 = H, R^2 = HO
XVb, R^1 = Ac, R^2 = HO
XVc, R^1 = Ac, R^2 = BzO
XVd, R^1 = H, R^2 = BzO
XVf, R^1 = Ac, R^2 = AcO
XVg, R^1 = H, R^2 = AcO

All the conversions mentioned were checked by ^{1}H-NMR spectroscopy (Table II). The shape of the doublet of the hydrogen at the position 5 was not as good a criterion for the differentiation of the $C_{(5)}$-epimeric hydroxy and acyloxy derivatives as the width of the multiplet of the $C_{(3)}$-proton for the determination of the configuration of the substituent in the position 3. In substances of the type *XII*, *XIII* and *XV* the coupling constant $J_{5,6}$ assumed the values from 2·5 to 2·7 Hz, while in substances of the type *XIV* it was 4·2 Hz. The long range interaction of the (5*R*)-proton with other ring B protons became evident in the doublet found for ketones *VIII* and *IX* and substances of the type *XIII* and *XV*. However, the increment for the benzoylation of the 5-hydroxy group proved to be a more reliable diagnostic tool: the chemical shift of the $C_{(18)}$-protons remained practically unchanged after bezoylation of the (5*S*)-hydroxy group in substances *XII* and *XIV*, while the benzoylation of the (5*R*)--hydroxy group in substances *XIII* and *XV* caused a clear down-field shift of the $C_{(18)}$--protons (0·12 ppm).

TABLE II

Characteristic Parameters of the ^{1}H-NMR Spectra

The spectra were measured on a Tesla 60 instrument in deuteriochloroform with tetramethylsilane as internal reference. Chemical shifts are given in δ-scale (ppm). The methyl groups in the side-chain, unless overlapped by other signals, displayed doublets at 0·86 ppm (6 protons) and 0·90 ± 0·01 ppm (3 protons).

Substance	19-H[a]	18-H[a]	3-H	5-H
I	0·98	0·61	4·22[b]	—
II	1·03	0·63	5·40[b]	—
IV	0·94	0·65	3·85[c]	—
VII	1·00	0·61	—	—
VIII	1·05	0·66	—	3·96[g]
IX	1·01	0·69	—	5·37[g]
X	1·05	0·78	—	5·16[h]
XI	1·09	0·68	—	3·59[i]
XIIa	0·98	0·65	3·76[f]	3·76[f]
XIIIa	1·00	0·68	3·73[f]	3·73[f]
XIVa	1·02	0·69	3·86[c]	3·75[e]
XVa	0·98	0·68	3·86[c]	3·11[d]
XIIb	0·99	0·65	4·85[b]	3·65[d]
XIIg	0·83	0·66	3·65[b]	5·21[d]
XIIIb	1·04	0·68	4·84[b]	3·65[d]
XIVb	0·91	0·65	5·15[c]	3·86[e]
XVb	0·99	0·69	4·76[c]	3·14[d]
XVg	0·87	0·70	3·80[c]	4·34[d]
XIIc	0·96	0·68	4·72[b]	5·11[d]
XIIf	0·87	0·66	4·67[b]	4·86[d]
XIIh	1·01	0·69	4·95[b]	5·18[d]
XIIIc	0·99	0·80	4·91[b]	5·19[d]
XIIIf	0·91	0·69	4·83[b]	4·92[d]
XIVc	0·88	0·69	5·14[c]	5·36[e]
XIVf	0·91	0·67	5·02[c]	5·09[e]
XVc	0·90	0·81	4·92[c]	4·69[d]
XVf	0·92	0·74	4·83[c]	4·43[d]
XIId	0·90	0·68	3·61[b]	5·44[d]
XIIe	1·02	0·66	5·11[b]	3·74[d]
XIIId	0·99	0·81	3·92[b]	5·30[d]
XIIIe	1·08	0·69	5·12[b]	3·80[d]
XIVd	0·87	0·69	4·06[c]	5·32[e]
XVd	0·94	0·81	3·88[c]	4·62[d]

[a] singlet, 3 protons; [b] multiplet, 1 proton, $W_{1/2}$ = 8—9 Hz; [c] multiplet, 1 proton, $W_{1/2}$ = 21 Hz; [d] doublet, 1 proton, J = 2·4—2·7 Hz; [e] doublet, 1 proton, J = 3·8 to 4·5 Hz; [f] overlapped signals; [g] broad doublet, $J_{5,6}$ = about 3 Hz; [h] doublet, $J_{5,6}$ = 4·0 Hz; [i] doublet, $J_{5,6}$ = 3·6 Hz.

A further technique useful fo the differentiation of the $C_{(5)}$-epimers is circular dichroism of corresponding benzoates (Table III): in accordance with Nakanishi's rule[4] (5*R*)- benzoates *X*, *XIIIc* and *XVc* display a positive Cotton effect of the π-π^* transition of the benzoate group at 228 nm, while the (5*S*)-benzoates *IX*, *XIIc* and *XIVc* show a negative Cotton effect.

After having obtained the standards of individual diols and having elaborated the methods of their analysis we endeavoured to find the conditions for the preparation of individual isomers. The results of the reductions of the ketones with complex hydrides (Table IV) are in agreement with the idea of the aproach of the reagent mainly from the least hindered side[5]:in the absence of a bulky group in the position 3β the 5-keto group is reduced under formation of equatorial (5*R*)-hydroxy derivatives (entries *4*–*6*, *8*), while the introduction of a hydroxyl[6], benzoyloxy- or ethylenedioxy group into the axial 3β-position furthers the reverse approach of the hydride ion and thus the formation of the axial (5*S*)-alcohol (entries 1–3, *11*). During the reduction an intramolecular transfer of the hydride ion from the hydride reagent bound to the 3β-hydroxy group was not observed[7] (compare the yields of the substances of the type

TABLE III
Circular Dichroism of Some Benzoates

Substance[a]	Configuration of the benzoyloxy group	λ^b nm	Δε	λ^c nm	Δε
VIII	5*S*	—	—	291	+2·5[e]
IX	5*S*	228	−2·20	294	+4·00[e]
X	5*R*	227	+[d]	296	+1·00[f]
XI	5*R*	—	—	292	+2·4[f]
XIIc	5*S*	228[g]	−3·40	—	—
XIIe	3*R*	225	+1·80	—	—
XIIIc	5*R*	230	+1·13	—	—
XIVc	5*S*	226[h]	−2·76	—	—
XVc	5*R*	228	+2·68	—	—

[a] The curves were measured on a Dichrographe II (Jouan-Roussel) in methanol; [b] the wave-length of the intramolecular charge transfer transition of the benzoate group ($\pi \rightarrow \pi^*$); [c] wave-length of the $n \rightarrow \pi^*$ transition of the keto group; [d] owing to considerable noise in this region an accurate value could not be recorded; [e] Snatzke's acylation shift was +1·5, for the mirror image of the model Snatzke[3] gives the value −2·07; [f] acylation increment was −1·4, for the mirror image model Snatzke[3] gives the value +1·17; [g] In 3β-acetoxy derivative *XIIb* the measured value was $\Delta\varepsilon_{210}^{MeOH}$ + 0·09; [h] In 3α-acetoxy derivative *XIVb* the measured value was $\Delta\varepsilon_{210}^{MeOH}$ + 0·12 (compare with the circular dichroism of acetoxy steroids[10]).

TABLE IV

Reduction of Keto Derivatives *I*—*IX*

The reductions were carried out with excess reducing agent under nitrogen, the mixtures were cooled and decomposed by pouring into a stirred solution of sodium potassium tartrate. The yields of the products are based on the weights of the substances isolated

No	Ketone	Reagent	Solvent	Temperature °C	Time h	Products %
1	*I*	$LiAlH_4$	ether	35	1	*XIIa* (43) *XIIIa* (43)
2	*I*	$(i\text{-}PrO)_3Al$	toluene	111	20	*XIIa* (45) *XIIIa* (5) *XIVa* (41) *XVa* (3)
3	*II*	$(t\text{-}BuO)_3LiAlH$	ether	20	60	*II* (55), *XIIe* (25) *XIIIe* (18)
4	*IV*	$LiAlH_4$	ether	0	7	*XVa* (96)
5	*IV*	$LiAlH_4$	dioxane	102	2	*XIVa* (21) *XVa* (71)
6	*IV*	$(t\text{-}BuO)_3LiAlH$	ether	20	24	*XIVa* (20) *XVa* (75)
7	*IV*	$(i\text{-}PrO)_3Al$	toluene	111	18	*XIIa* (34) *XIIIa* (2) *XIVa* (54) *XVa* (3)
8	*V*	$(t\text{-}BuO)_3LiAlH$	dioxane	20	1	*XVb* (95)
9	*V*	$(i\text{-}PrO)_3Al$	toluene	111	18	*XIIa* (7) *XIVa* (69) *XVa* (17)
10	*VI*	$(t\text{-}BuO)_3LiAlH$	toluene–dioxane	0	0·5	*IV* (70)
11	*VII*	$(t\text{-}BuO)_3LiAlH$	toluene	111	1	*VIII* (85)
12	*VIII*	$LiAlH_4$	dioxane	102	1	*XIIa* (67) *XIVa* (33)
13	*IX*	$(t\text{-}BuO)_3LiAlH$	dioxane	20	2	*XIId* (95)
14	*X*	$(t\text{-}BuO)_3LiAlH$	ether	20	4	*XVd* (95)

XIII in entries *1* and *3*), but the conditions for the formation of such a complex had not been expressly modelled. Analogously, 3-ketones without a bulky (5*S*)-substituent (entries *10*, *14*) are reduced with tri-tert-butoxylithium aluminum hydride under

formation of equatorial 3α-alcohols and the introduction of the oxygen function into the position (5*S*) leads mainly to the formation of axial 3β-alcohols (entries *12*, *13*). Meerwein–Ponndorf reduction is known[8] to give mainly axial alcohols. Table IV (entries *2*, *7*, *9*) shows that the 5-keto group is reduced with aluminum isopropoxide in toluene mainly to the axial (5*S*)-alcohol, but the reaction mixture contains in all instances the products of preliminary $C_{(3)}$-equilibration that represents a further demonstration of the instability[3] of 3-hydroxy 5-ketones of this series in basic medium.

These experiences may be utilized for the synthesis of (5*R*) and (5*S*)-hydroxy derivatives. The easiest way of preparation of (5*S*)-hydroxy compounds consists in a one-step reduction of 4-oxa-5-cholesten-3-one[9] with tri-tert-butoxylithium aluminum hydride in boiling toluene; a probable intermediate of this reaction is 3β(tri-tert-butoxylithium aluminoxy) 5-ketone which is further reduced with excess reagent mainly to the diol of type *XIIa*. For the preparation of (5*R*)-alcohols the reduction of 3α-substituted 5-ketones under the conditions given in entry 4 is most suitable.

Alkaline hydrolysis of benzoyloxy derivatives *IX* and *X* affords alcohols *VII* and *XI* without a substantial equilibration (analyzed by thin-layer chromatography on silica gel after rebenzoylation). Hence, it is evident that in contrast to 3-hydroxy 5-ketones of this series[1] 5-hydroxy 3-ketones are relatively stable in alkaline medium and in the absence of oxygen.

EXPERIMENTAL

The melting points were determined on a Kofler block and they are not corrected. Optical rotations and IR spectra were measured in chloroform unless stated otherwise. The analytical samples were dried over phosphorus pentoxide (50°C, 0·2 Torr). The ether used for reductions was distilled with lithium aluminum hydride shortly before use. Preparative thin layer chromatography on silica gel or alumina was carried out on 20 × 20 cm plates (layer thickness 1·7 mm), and the load was 20 to 60 mg of substance per plate. Detection was carried out under the UV lamp after spraying with a 2% methanolic solution of morin. The substances were eluted with ether.

3,3-Ethylenedioxy-3,6-cyclo-A-nor-3,5-seco-6β-cholestan-5-one (*VII*)

A solution of 218 mg of diketone[1] *V* and 100 mg of *p*-toluenesulfonic acid hydrate in 50 ml of benzene was refluxed with 5 ml of ethylene glycol. Water was eliminated continually by means of a Dean-Stark adapter. After 6 h the mixture was diluted with benzene, washed with a saturated potassium hydrogen carbonate solution and water, dried over anhydrous sodium sulfate, and evaporated with 2 drops of pyridine. The product was chromatographed on a thin layer of alumina in benzene. The main product (152 mg) was crystallized from methanol at −70°C, m.p. 97 to 101°C, $[\alpha]_D^{20}$ +1° (*c* 0·9); IR spectrum 1 710, 1 110, 1 085 cm^{-1}. For $C_{28}H_{45}O_3$ (430·5) calculated: 78·09% C, 10·77% H; found: 77·80% C, 10·68% H.

(5*S*)-5-Hydroxy-3,6-cyclo-A-nor-3,5-seco-6β-cholestan-3-one (*VIII*)

a) Reduction of compound *VII*: 90 mg of ketal *VII* were refluxed with 200 mg of tri-tert-butoxylithium aluminum hydride in 10 ml of toluene for 1 h. The mixture was cooled and poured into an aqueous solution of sodium potassium tartrate, the aqueous solution was extracted with benzene and the combined organic extracts were dried by filtration through a layer of sodium sulfate. The filtrate was evaporated in a vacuum and the residue heated at 85°C in the presence of 4 ml of 75% aqueous acetic acid for 3 h. After evaporation of the acetic acid in a vacuum the product was dissolved in chloroform, dried over sodium sulfate, concentrated and crystallized from a mixture of chloroform and heptane. M.p. 184–186°C, $[\alpha]_D^{20}$ +49° (*c* 0·9, CHC_3). For $C_{26}H_{44}O_2$ (288·6) calculated: 80·30% C, 11·40% H; found: 79·96% C, 11·34% H.

b) Hydrolysis of compound *VIII*: 46 ml of benzoate *VIII* were refluxed with a solution of 200 mg of potassium hydroxide in 0·6 ml of water, 4 ml of methanol and 1 ml of benzene, under nitrogen. After 1 h the mixture was concentrated to 1 ml, diluted with a saturated sodium chloride solution in water, and extracted continually with ether. The extract was dried over sodium sulfate, evaporated, and the residue dissolved in chloroform, filtered through a layer of sodium sulfate, and concentrated to a small volume. After addition of heptane a substance crystallized out which was identical with the sample prepared under *a*). Rebenzoylation of the crystalline product gave a benzoate identical with compound *VIII*.

(5*R*)-5-Hydroxy-3,6-cyclo-A-nor-3,5-seco-6β-cholestan-3-one (*XI*)

Benzoyloxy ketone *X* (40 mg) was hydrolysed under the conditions used for compound *IX*. Crystallization of the crude product from chloroform–heptane mixture gave 24 mg of compound *XI*, m.p. 176–178°C, $[\alpha]_D^{20}$ +45° (*c* 0·8). For $C_{26}H_{44}O_2$ (388·8) calculated: 80·30% C, 11·40% H; found: 80·17% C, 11·38% H. Rebenzoylation of the crystalline product gave a benzoate identical with compound *XI*.

(5*S*)-5-Benzoyloxy-3,6-cyclo-A-nor-3,5-seco-6β-cholestan-3-one (*IX*)

a) *Oxidation of hydroxy derivative* XIId: Hydroxy derivative *XIId* (120 mg) was dissolved in 4 ml of dichloromethane and 4 ml of acetone, and Jones's reagent was added under stirring. After 3 min reaction at room temperature the mixture was poured into a solution of potassium hydrogen carbonate. the product was extracted with ether, the extract washed with a saturated sodium chloride solution, dried over sodium sulfate and evaporated to dryness. Crystallization from ethanol gave 110 mg of ketone *IX*, m.p. 198–200°C, $[\alpha]_D^{20}$ +56° (*c* 1·4); IR spectrum: (CCl_4): 1715 cm^{-1} (3-keto group), 1724, 1272 cm^{-1} (benzoyloxy group). For $C_{33}H_{48}O_3$ (492·7) calculated: 80·44% C, 9·82% H; found: 80·31% C, 9·80% H.

b) *Oxidation of hydroxy derivative* XIVd: Compound *XIV* (37 mg) was oxidized under the conditions described sub *a*). The product of oxidation was chromatographed on a thin layer. After crystallization from ethanol it melted at 198–200°C, undepressed in admixture with the sample prepared sub *a*).

c) *Benzoylation of compound* VIII: Hydroxy derivative *VIII* (20 mg) was reacted with 0·06 ml of benzoyl chloride in 0·1 ml of pyridine. After 5 h reaction the mixture was poured into a solution of potassium carbonate, the product was extracted with benzene, the extract washed with a potassium carbonate solution and water, and dried over sodium sulfate. After evaporation of the solvent the product was chromatographed on a thin layer of silica gel and crystallized from methanol. The melting point and the mixture melting point with the sample prepared sub *a*) were identical.

(5*R*)-5-Benzoyloxy-3,6-cyclo-A-nor-3,5-seco-6β-cholestan-3-one (*X*)

a) *Oxidation of hydroxy derivative* XIIId: Compound *XIIId* (150 mg) was oxidized according to Jones at room temperature. After 3 min reaction time the mixture was poured into a solution of potassium hydrogen carbonate and the product extracted with ether. The extract was washed with a saturated sodium chloride solution, dried over sodium sulfate and concentrated. The product was purified by thin layer chromatography on silica gel (128 mg), but it still resisted attempts at crystallization. $[\alpha]_D^{20}$ +7° (*c* 1·4), IR spectrum (CCl_4): 1715 cm^{-1} (3-keto group), 1722, 1270 cm^{-1} (benzoyloxy group).

b) *Oxidation of hydroxy derivative* XVd: Substance *XVd* (180 mg) was oxidized according to procedure *a*). After purification by thin-layer chromatography on silica gel (in benzene, double development) the product had identical IR spectrum to that of the sample prepared under *a*).

3β-Benzoyloxy-3,6-cyclo-A-nor-3,5-seco-6β-cholestan-5-one (*II*)

Hydroxy derivative *XIIe* (80 mg) was oxidized with Jones's reagent in 3 ml of dichloromethane and 3 ml acetone. After 5 min standing at room temperature the mixture was worked up as in the preparation of compound *IX*. Crystallization from acetone afforded 58 mg of ketone *II*, identical with an authentic sample[3].

(5*S*)-3β-5-Dihydroxy-3,6-cyclo-A-nor-3,5-seco-6β-cholestane (*XIIa*)

From a solution of 180 mg of 4-oxa-5-cholesten-3-one[9] in 35 ml of toluene 10 ml of solvent were evaporated and tri-tert-butoxylithium aluminum hydride (500 mg) was added to the boiling solution and the mixture refluxed for 2 g. After cooling the solution was washed with a solution of sodium potassium tartrate and water, dried over sodium sulfate, and crystallized directly from a mixture of acetone and heptane. Yield 103 mg of diol *XIIa*, m.p. 216–218°C (ref.[1] gives 200–202°C), $[\alpha]_D^{20}$ +22° (*c* 1·1; pyridine); IR spectrum: 3625, 1026 cm^{-1}; in tetrachloromethane: 3520, 3649, 3625 cm^{-1}. For $C_{26}H_{46}O_2$ (390·6) calculated: 78·95% C, 11·85% H: found: 78·81% C, 11·66% H.

Partial Benzoylation of Diol *XIIa*

Diol *XIIa* (101 mg) was submitted to reaction with 0·1 ml of benzoyl chloride in 1·5 ml pyridine at room temperature. After half-an-hour's standing the reaction mixture was decomposed and worked up. The product was separated by thin-layer chromatography on silica gel (30% of light petroleum in benzene). The non-polar component is (5*S*)-3β,5-dibenzoyloxy-3,6-cyclo--A-nor-3,5-seco-6β-cholestane (*XIIf*, 28 mg); m.p. 180–181°C (ethanol), $[\alpha]_D^{20}$ +64° (*c* 0·9); IR spectrum: 1712, 1280 cm^{-1}. For $C_{40}H_{54}O_4$ (598·8) calculated: 80·22% C, 9·14% H; found: 80·07% C, 8·91% G. The more polar component is composed of (5*S*)-3β-benzoyloxy-3,6--cyclo-A-nor-3,5-seco-6β-cholestan-5-ol (*XIIe*, 63 mg), m.p. 161–163°C (ethanol); $[\alpha]_D^{20}$ +53° (*c* 0·9); IR spectrum: 1710, 1713, 1275, 3595 cm^{-1}. IR spectrum (CCl_4): 3605 cm^{-1}. For $C_{33}H_{50}O_3$ (494·7) calculated: 80·11% C, 10·19% H; found: 79·93% C, 10·07% H.

Partial Acetylation of Diol *XIIa*

a) Diol *XIIa* (102 mg) was acetylated at room temperature with a solution of 0·3 ml of acetic anhydride in 1·5 ml of pyridine. After 6 h standing at 20°C the mixture was worked up and the

product separated by thin-layer chromatography on silica gel (25% of ether in benzene). The polar component consists of the starting diol *XIIa* (46 mg), while the non-polar component consists of (5*S*)-3β-acetoxy-3,6-cyclo-A-nor-3,5-seco-6β-cholestan-5-ol (*XIIb*, 42 mg), m.p. 130–132°C (acetone, heptane), $[\alpha]_D^{20}$ +42°C (*c* 1·1); IR spectrum: 1738, 1244, 1024, 3590, 957 cm^{-1}. For $C_{28}H_{48}O_3$ (432·7) calculated: 77·72% C, 11·18% H; found: 77·61% C, 11·16% H.

b) Diol *XIIa* (114 mg) was refluxed with 50 ml of 90% acetic acid for 5 h. The mixture was evaporated and separated chromatographically on a thin layer of silica gel (20% of ether in benzene). Individual components, in the order of increasing polarity, are these: diacetate *XIIf* (19 mg), 3-acetate *XIIb* (22 mg), (5*S*)-5-acetoxy-3,6-cyclo-A-nor-3,5-seco-6β-cholestan-3β-ol (*XIIg*, 28 mg), m.p. 100–102°C (ethanol), $[\alpha]_D^{20}$ +10° (*c* 1·1); for $C_{28}H_{48}O_3$ (432·7) calculated: 77·72% C, 11·18% H; found: 77·48% C, 11·25% H; diol *XIIa* (53 mg).

(5*S*)-3β-Acetoxy-5-benzoyloxy-3,6-cyclo-A-nor-3,5-seco-6β-cholestane (*XIIc*)

A mixture of 92 mg of acetate *XIIb* and 0·2 ml of benzoyl chloride in 0·3 ml of pyridine was allowed to stand at room temperature for 20 h and worked up. The product was crystallized from ethanol, m.p. 160–162°C (85 mg), $[\alpha]_D^{20}$ +16° (*c* 1·5); IR spectrum (CCl_4): 1720, 1733, 1287, 1255 cm^{-1}. For $C_{35}H_{52}O_4$ (536·8) calculated: 78·31% C, 9·77% H; found: 78·01% C, 9·66% H.

(5*S*)-5-Benzoyloxy-3,6-cyclo-A-nor-3,5-seco-6β-cholestan-3β-ol (*XIId*)

Acetate *XIIc* (131 mg) was heated with a solution of 0·123 ml of hydrochloric acid in 6·5 ml methanol and 0·65 ml of chloroform at 37°C for 28 h. The mixture was diluted with 10 ml of chloroform, 2 ml were evaporated under reduced pressure, and the rest diluted with benzene, washed with water, dried over sodium sulfate and evaporated. After crystallization from ethanol the substance melts at 207–209°C (102 mg), $[\alpha]_D^{20}$ +9° (*c* 1·4); IR spectrum: 1710, 1715, 1270, 3605 cm^{-1}. For $C_{33}H_{50}O_3$ (494·7) calculated: 80·11% C, 10·19% H; found: 80·20% C, 10·27% H.

(5*R*)-3,6-Cyclo-A-nor-3,5-seco-6β-cholestan-3β,5-diol (*XIIIa*)

a) 4-Oxa-5-cholesten-3-one (210 mg) was dissolved in 3 ml of diethylene glycol and mixed with about 200 mg of lithium aluminum hydride. After 20 h standing at room temperature the mixture was added dropwise into a solution of 5% of hydrochloric acid in saturated sodium chloride solution (100 ml) and the separated product was filtered off and chromatographed on a thin layer of silica gel (with a 1 : 1 chloroform–ether mixture). The main product (80 mg) was crystallized from aqueous acetone, m.p. 140–144°C, $[\alpha]_D^{20}$ +8° (*c* 0·9) (ref.[2] gives 147°C and $[\alpha]_D^{20}$ +9·6°). For $C_{26}H_{46}O_2$ (390·6) calculated: 78·95% C, 11·85% H; found: 78·67% C, 11·59% H.

b) Substance *I* (45 mg) was mixed with 5 ml of ether in an apparatus provided with a reflux condenser and a two-neck adapter. Lithium aluminum hydride was introduced into the side arm of the adapter, the apparatus was rinsed and filled with nitrogen, and the ethereal solution was refluxed. After 2 h during which the hydride was washed into the reaction mixture by refluxing ether the mixture was worked up and the product separated by thin-layer chromatography to a non-polar component (diol *XIIa*, 20·9 mg) and a polar component (diol *XIIIa*, 20·8 mg) which had the same properties as authentic samples.

Acetylation of Diol *XIIIa*

Diol *XIIIa* (75 mg) was acetylated with acetic anhydride (0·5 ml) in pyridine (2 ml) at room temperature. After 8 h the mixture was worked up and the product chromatographed on a silica gel thin layer (with 10% of ether in benzene, double developemnt). Individual components, in the order of increasing polarity, were the following: diacetate *XIIIf* (18 mg), m.p. 160°C, $[\alpha]_D^{20}$ +80° (*c* 0·9), identical with an authentic specimen[2]; (5*R*)-3β-acetoxy-3,6-cyclo-A-nor-3,5-seco-6β-cholestan-5-ol (*XIIIb*, 43 mg), m.p. 126—129°C (methanol, water), $[\alpha]_D^{20}$ +23° (*c* 1·1); for $C_{28}H_{48}O_3$ (432·7) calculated: 77·72% C, 11·18% H; found: 77·50% C, 11·07% H; (5*R*)-5-acetoxy-3,6-cyclo-A-nor-3,5-seco-6β-cholestan-3β-ol (*XIIIg*, 2 mg), m.p. about 100 to 105°C (methanol); IR spectrum (KBr): 1738, 1722, 1264, 1241, 1050, 1031 cm^{-1}; dihydroxy derivative *XIIIa* (20 mg).

(5*R*)-3β-Acetoxy-5-benzoyloxy-3,6-cyclo-A-nor-3,5-seco-6β-cholestane (*XIIIc*)

Hydroxy derivative *XIIIb* (37 mg) was benzoylated with 0·1 ml of benzoyl chloride in 0·3 ml of pyridine. The product was chromatographed on a silica gel thin layer in benzene, $[\alpha]_D^{20}$ +22° (*c* 0·9). For $C_{35}H_{52}O_4$ (536·8) calculated: 78·31% C, 9·77% H; found: 78·21% C, 9·82% H.

(5*R*)-5-Benzoyloxy-3,5-cyclo-A-nor-3,5-seco-6β-cholestan-3β-ol (*XIIId*)

Acetate *XIIIc* (30 mg) was hydrolysed under the conditions used for the preparation of compound *XIId*. The product was chromatographed on a thin layer of silica gel (10% of ether in benzene, double development); m.p. 50—53°C (heptane, —70°C), $[\alpha]_D^{20}$ +8° (*c* 1·1). For $C_{33}H_{50}O_3$ (494·7) calculated: 80·11% C, 10·19% H; found: 79·86% C, 10·06% H.

(5*R*)-3β-Benzoyloxy-3,6-cyclo-A-nor-3,5-seco-6β-cholestan-5-ol (*XIIIe*)

A mixture of diol *XIIIe* and 0·1 ml of benzoyl chloride in 1 ml of pyridine was allowed to react for 30 minutes and then worked up. The product was chromatographed on a thin layer of silica gel in 25% ether in benzene. Monobenzoate *XIIIe* (68 mg) was crystallized from a mixture of chloroform and methanol, m.p. 138—139°C, $[\alpha]_D^{20}$ +28° (*c* 1·5). For $C_{33}H_{50}O_3$ (494·7) calculated: 80·10% C, 10·19% H; found: 80·01% C, 10·26% H.

(5*S*)-3,6-Cyclo-A-nor-3,5-seco-6β-cholestane-3α,5-diol (*XIVa*)

Ten ml of solvent were distilled off from a solution of 130 mg of hydroxy ketone *IV* in 100 ml of toluene and aluminum isopropoxide (850 mg) was then added to the mixture. This was refluxed for 20 h, cooled and diluted with chloroform, washed with dilute hydrochloric acid and water, dried over sodium sulfate and concentrated. Chromatography of the product on a silica gel thin layer (chloroform–ether 1 : 1) afforded 70 mg of (5*S*)-3,6-cyclo-A-nor-3,5-seco-6β-cholestan-3α,5-diol (*XIVe*), m.p. 201—203°(chloroform, heptane), $[\alpha]_D^{20}$ +42° (pyridine, *c* 1·1). For $C_{26}H_{46}O_2$ (390·6) calculated: 78·95% C, 11·85% H; found: 78·66% C, 11·59% H. Elution of further zones gave 44 mg of diol *XIIa*, 3 mg of diol *XVa* and 4 mg of diol *XIIIa*.

(5*S*)-3α-Acetoxy-3,6-cyclo-A-nor-3,5-seco-6β-cholestan-5-ol (*XIVb*)

A mixture of diol *XIVa* (50 mg) and acetic anhydride (0·5 ml) in 2 ml of pyridine was allowed to react at 0°C for 18 h and at 20°C for 6 h and the product chromatographed on a thin layer of silica gel (10% of ether in benzene, double development). The main product (40 mg, from

methanol) melted at 178—179°C, $[\alpha]_D^{20}$ +19° (*c* 1·1). For $C_{28}H_{48}O_3$ (432·7) calculated: 77·72% C, 11·18% H; found: 77·60% C, 11·09% H.

(5*S*)-3α,5-Diacetoxy-3,6-cyclo-A-nor-3,5-seco-6β-cholestane (*XIVf*)

The non-polar by-product from the preceding experiment (10 mg) was crystallized from ethanol. M.p. 135—137°C, $[\alpha]_D^{20}$ +54° (*c* 1·0). For $C_{30}H_{50}O_4$ (474·7) calculated: 75·90% C, 10·62% H; found: 75·91% C, 10·58% H.

(5*S*)-3α-Acetoxy-5-benzoyloxy-3,6-cyclo-A-nor-3,5-seco-6β-cholestane (*XIVc*)

Acetate *XIVb* (28 mg) was benzoylated as in the preparation of *XIIc*. Crystallization of the product from methanol afforded benzoate *XIVc*, m.p. 190—191°C (20 mg), $[\alpha]_D^{20}$ +30° (*c* 1·9). For $C_{35}H_{52}O_4$ (536·8) calculated: 78·31% C, 9·77% H; found: 78·22% C, 9·86% H.

(5*S*)-5-Benzoyloxy-3,6-cyclo-A-nor-3,5-seco-6β-cholestan-3α-ol (*XIVd*)

Acetate *XIVc* (106 mg) was hydrolysed under the conditions employed for the preparation of compound *XIId*. Purification of the product by thin-layer chromatography on silica gel afforded 96 mg of substance which after crystallization from dichloromethane and heptane melted at 186—188°C, $[\alpha]_D^{20}$ +43° (*c* 1·2). For $C_{33}H_{50}O_3$ (494·7) calculated: 80·11% C, 10·19% H; found: 79·90% C, 10·17% H.

(5*R*)-3,6-Cyclo-A-nor-3,5-seco-6β-cholestan-3α,5-diol (*XVa*)

Lithium aluminum hydride was added in two portions (about 30 mg, and after 1 h another 50 mg) under stirring to a solution of 109 mg of hydroxy ketone *IV* in 6 ml of ether at 0°C, kept under nitrogen. After 7 h the solution was carefully poured into an aqueous solution of sodium potassium tartrate and the product was extracted with chloroform. The extract was dried over sodium sulfate and concentrated. The residue (109 mg) melted at 180—182°C, and the melting point remained unchanged after crystallization from aqueous methanol, $[\alpha]_D^{20}$ +9° (chloroform + + 10% methanol, *c* 1·0). For $C_{26}H_{46}O_2$ (390·6) calculated: 78·95% C, 11·85% H; found: 78·70% C, 11·81% H.

(5*R*)-3α-Acetoxy-3,6-cyclo-A-nor-3,5-seco-6β-cholestan-5-ol (*XVb*)

a) Compound *V* (180 mg) was reduced with 360 mg of tri-tert-butoxylithium aluminum hydride in 6 ml of dioxane at room temperature. After 1 h stirring the mixture was poured into a solution of sodium potassium tartrate and the product extracted with chloroform. Crystallization of the product from a mixture of acetone and heptane afforded 139 mg of compound *XVb*, m.p. 155—157°C, $[\alpha]_D^{20}$ +37° (*c* 0·8); IR spectrum: 1722, 1255, 1026, 3625 cm^{-1}; IR spectrum (CCl_4): 1740, 1725 (shoulder), 1242, 1025, 3630 cm^{-1}. For $C_{28}H_{48}O_3$ (432·7) calculated: 77·72% C, 11·18% H; found: 77·69% C, 11·26% H.

b) A mixture of diol *XVa* (273 mg) and acetic anhydride (0·9 ml) in pyridine (4·5 ml) was acetylated at 0°C for 20 h and then worked up. Thin-layer chromatography on silica gel (in 20% ether in benzene) afforded 167 mg of acetate *XVb*, 18 mg of acetate *XVg*, 61 mg of diol *XVa* and 30 mg of diacetate *XVf*.

(5*R*)-3α,5-Diacetoxy-3,6-cyclo-A-nor-3,5-seco-6β-cholestane (*XVf*)

Acetylation of diol *XVa* (50 mg) with acetic anhydride (0·2 ml) in pyridine at room temperature (18 h) gave diacetate *XVf*, m.p. 94–98°C (aqueous ethanol) $[\alpha]_D^{20}$ +10° (*c* 0·9). For $C_{30}H_{50}O_4$ (474·7) calculated: 75·90% C, 10·62% H; found: 75·97% C, 10·81% H.

(5*R*)-3α-Acetoxy-5-benzoyloxy-3,6-cyclo-A-nor-3,5-seco-6β-cholestane (*XVc*)

A mixture of 140 mg of acetate *XVb* and 0·15 ml of benzoyl chloride in 0·3 ml of pyridine was allowed to react at 35°C for 6 h and then worked up and the product chromatographed on a thin layer of silica gel (8% of ether in benzene). Crystallization from methanol afforded 92 mg of product, m.p. 116–118°C, $[\alpha]_D^{20}$ +35° (*c* 1·3). For $C_{35}H_{52}O_4$ (536·8) calculated: 78·31% C, 9·77% H; found: 78·30% C, 9·65% H.

(5*R*)-5-Benzoyloxy-3,6-cyclo-A-nor-3,5-seco-6β-cholestan-3α-ol (*XVd*)

a) Acetate *XVc* (77 mg) was hydrolysed as in the preparation of compound *XIId* and the product was chromatographed on a thin layer. $[\alpha]_D^{20}$ +5° (*c* 1·0). For $C_{33}H_{50}O_3$ (494·7) calculated: 80·11% C, 10·19% H; found: 80·26% C, 10·12% H.

b) Ketone *X* (101 mg) was reduced with tri-tert-butoxylithium aluminum hydride (300 mg) in 2 ml of ether at room temperature. After 4 h standing the mixture was worked up and chromatographed on a thin layer. The product (89 mg) had identical IR spectrum as a sample prepared as under *a*).

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