DESULFURATION OF STEROIDAL THIANS*

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The reaction of 4-thia-5-cholesten-3-one (*X*) with Raney nickel in protic medium affords alcohol *III*, while A-nor-5β-cholestan-3-one (*XXIII*), A-bisnor-2,5-secocholestane (*XXXI*) and the esters of the type *XVIII* are formed as by-products. When aprotic medium is used compounds *XXIII* and *XXXI* are the main products. During desulfuration with a less active Raney nickel the mentioned substances are accompanied by 5-unsaturated derivatives of the type *I*, *XIV* and *XXIX*. Optimum conditions for the preparation of either saturated alcohols of type *III* or of unsaturated esters of type *XIV* were found.

During the preparation of the seco derivatives of type *I* or *III* from 5-oxo-A-nor-3,5-secocholestan-3-oic acid (*VI*) the key intermediate is benzylthioenol ether *VIII* which is desulfurated and further reduced[1]. In this paper we describe desulfuration of 4-thia-5-cholesten-3-one[2] (*X*) which we considered a useful synthone for the realisation of the conversion of acid *VI* to alcohol *III*.

In preliminary experiments we found that the reaction of compound *X* with Raney nickel in methanol affords a mixture of alcohols *I* and *III* as the main product. It is known that the medium used for desulfuration can also have a substantial influence on the composition of the product[3,4]. While an alcohol as medium leads to saturated derivatives, acetone leads to unsaturated derivatives. The substitution of methanol by acetone during desulfuration of compound *X* did not give the corcorresponding alcohol *I* in useful yields. When the reduction was carried out in the higher-boiling cyclopentanone, transformation of compound *X* did take place, it is true, but the mixture was contaminated by an excessive amount of by-products. Nor did the use of higher boiling alcohols have any distinct effect on the ratio of saturated derivatives (^{1}H NMR spectroscopy) but we found that when a freshly prepared Raney-nickel in protic medium and in an inert atmosphere was used the saturated alcohol *III* is the main product of desulfuration. A model experiment with the unsaturated seco ester *XIV* has shown that under these conditions a saturation of the Δ^5-double bond takes place.

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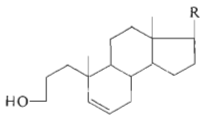
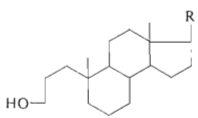
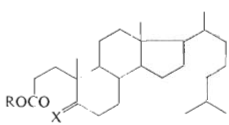
In the reaction mixtures after various modifications of the desulfuration procedure different amounts of by-products were present. One of them consisted of esters



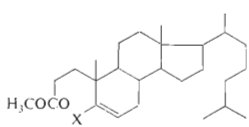
I, i-C_8H_{17}
II, R = OH



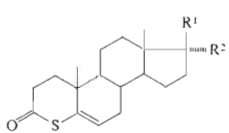
III, i-C_8H_{17}
IV, R = OH
V, R = $OCOC_6H_5$



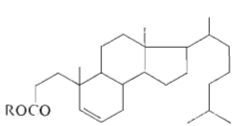
VI, R = H, X = O
VII, R = CH_3, X = S



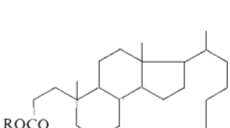
VIII, R = $SCH_2C_6H_5$
IX, R = SH



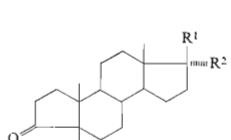
X, $R^1 = i$-C_8H_{17}, R^2 = H
XI, $R^1 = OCOC_6H_5$, R^2 = H
XII, $R^1 + R^2$ = O



XIII, R = H
XIV, R = CH_3
XV, R = C_2H_5
XVI, R = C_3H_7
XVII, R = $CH_2C_6H_5$



XVIII, R = CH_3
XIX, R = C_2H_5
XX, R = C_3H_7
XXI, R = $CH_2C_6H_5$
XXII, R = CH_2CH_2OH



XXIII, $R^1 = i$-C_8H_{17}, R^2 = H
XXIV, $R^1 + R^2$ = O
XXV, $R^1 = OCOC_6H_5$, R^2 = H

of the type *XVIII*, derived from alcohols in which the reduction was carried out. In the case of a less active catalyst these esters were accompanied by unsaturated esters of type *XIV*, while the degree of saturation of the Δ^5-double bond in these esters corresponded completely to the degree of saturation of the main product, alcohol

TABLE I

Yields (%) of products after desulfuration of 4-thia-5-cholesten-3-one (*X*) and its derivatives *VII*, *XXXVII* with Raney-nickel

Starting compounds	Medium[a]	*I*, *III*	*XIV*–*XXII*	*XXIII*	*XXVII*	*XXXI*
X	methanol	56	15	12	6	9
X	ethanol	55	12	14	12	6
X	propanol	54	10	19	10	6
X	tert-butanol	29	0	15	5	48
X	ethylene glycol	43	36	14	2	4
X	benzyl alcohol	43	13	19	3	
X	heptane, methanol[b]	65	6	17	3	12
X	toluene[c]	0	0	22[d]	0	40[d]
X	acetone[e]	19	0	38	4	31
VII	methanol[e]	0	99	0	0	0
XXXVIII	methanol[c]	93	2	2	0	2

[a] All the reactions, with the exception of that in benzyl alcohol and ethylene glycol were carried out under reflux in corresponding alcohol, under stirring and under nitrogen. The reaction temperature in the case of benzyl alcohol or ethylene glycol was 100°C, the reaction time 20 h. The yields are based on the weight of the products isolated (chromatography on silica gel thin layers with a mixture of 5% of ether in light petroleum); content of alcohol *XXVII* in addition to alcohol *III* was determined after completed oxidation to a mixture of ketone *XXIII* and the corresponding acid. Unless otherwise stated the products do not contain the Δ^5 double bond. Raney-nickel was prepared according to ref.[13] and it was kept under methanol. Under "freshly prepared" a material is meant, not older than 8 days. The substitution of methanol by another solvent was carried out by stirring the precipitate after decantation for 10 min with a 10-fold volume of the new solvent, the supernatant was poured off after sedimentation, and the operation was repeated twice more. [b] Since heptane and methanol are partly immiscible, the substitution of methanol by heptane, carried out as under *a* did not eliminate methanol sticking to the Raney-nickel surface. [c] The substitution of methanol by toluene was carried out as under *a*, and the mixture was then heated at 80°C for 18 h under nitrogen, in order to set the absorbed hydrogen free, and the reaction was then carried out in this solvent. [d] The low yields were checked in repeated experiments; the material was lost probably by oxidation of the steroid to the carboxylic acid which remained bound to Raney-nickel. [e] The compounds formed do not contain an observable (by ^{1}H NMR) amount of the saturated derivatives *III*, *XVIII* or *XXXI* (see Experimental).

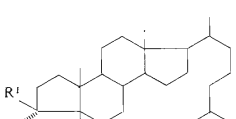
III. The yields of these esters amounted up to 35%, but in tert-butanol this type of by-product did not appear at all (Table I).

As a further by-product A-nor-5β-cholestan-3-one (*XXIII*) was formed which was identified on the basis of the agreement of its IR spectrum with the spectrum of an authentic sample[5]. The most polar component of the mixture was hydroxy derivative *XXVII* which was found usually merely in the products of the reaction with active Raney-nickel. Oxidation of this alcohol gave 5β-ketone *XXIII*, but compound *XXVII* differed from the known[6] 3β-hydroxy derivative *XXVI* and therefore the structure of A-nor-5β-cholestan-3α-ol was assigned to it.

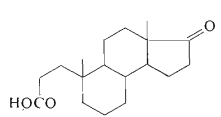
The most lipophilic product was hydrocarbon $C_{25}H_{46}$ (*XXXI*), sometimes accompanied (when a less active reducing agent was used) by olefin $C_{25}H_{44}$ (*XXIX*). The structure of both hydrocarbons was proposed on the basis of an analysis of the ^{1}H NMR and the mass spectra of analogous products obtained by desulfuration of the androstane derivative *XI*.

Similar results were also obtained when derivatives *XI* and *XII* were desulfurated, but the substances obtained gave spectra which could be interpreted more easily: Thus, for example, the ^{1}H NMR spectrum of the saturated bisnor-derivative *XXXIII* displayed a three-proton triplet of protons in the position 2 in addition to the singlets of the angular methyl groups. This finding, together with the finding of important fragments $[M-C_2H_5]^+$ in the mass spectra contributed to the formulation of the structures of products *XXXXI* to *XXXIII* in which only the ethyl group bound to the tertiary $C_{(10)}$ atom remained of the original A ring. The position of the double bond in unsaturated bisnor-derivatives *XXIX* and *XXX* was proved in the following manner: the olefinic product was epoxidated with *m*-chloroperbenzoic acid and the mixture of epoxides formed was reduced with lithium aluminum hydride. The mixture formed was oxidized according to Jones. Thus diketones *XXXIV* and *XXXV* were formed which contain a cyclopentanone and a cyclohexanone ring (IR spectra).

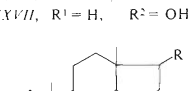
The formation of individual products can be interpreted as a consequence of the primary formation of diradical *XXXVI* which undergoes a series of competing reactions, such as *a*) reduction to unsaturated and saturated alcohol of type *III*, *b*) intramolecular combination of the diradical and reduction under formation of A-nor--derivatives *XXIII* and *XXVII* (see analogous contractions of sulfur-containing heterocycles under the effect of Raney nickel[7,8]), *c*) intermolecular combination of the diradical with the medium, under formation of unsaturated up to saturated esters of type *XVIII*, *d*) decarbonylation to A-bis-nor-2,5-seco derivative of type *XXIX* or *XXXI*. A-Nor-5β-cholestan-3α-ol (*XXVII*) is evidently a product of subsequent hydrogenation of the corresponding ketone *XXIII*: a model experiment showed that under the conditions of desulfuration the 3-ketone *XXIII* is converted almost exclusively to 3α-hydroxy derivative *XXVII* (a hydrogenation of the same compound in acetic acid catalysed by platinum, or a reduction with complex hydrides affords predominantly 3β-hydroxy derivative *XXVI*).



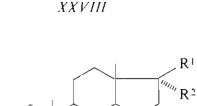
XXVI, $R^1 = OH$, $R^2 = H$
XXVII, $R^1 = H$, $R^2 = OH$



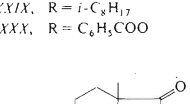
XXVIII



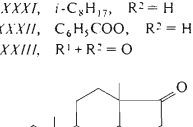
XXIX, $R = i\text{-}C_8H_{17}$
XXX, $R = C_6H_5COO$



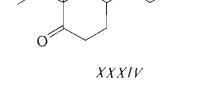
XXXI, $i\text{-}C_8H_{17}$, $R^2 = H$
XXXII, C_6H_5COO, $R^2 = H$
XXXIII, $R^1 + R^2 = O$



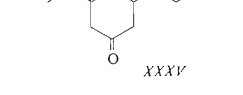
XXXIV



XXXV



XXXVI



XXXVII

XXXVIII

The assumption of the intervention of diradical *XXXVI* in the process of desulfuration of compound *X* is also in agreement with the results of the desulfuration carried out in various media (Table I): when Raney-nickel freed of hydrogen[9,10] is

used in aprotic solvent process *d* is favoured, while in alcohol as medium proces *a* is more favoured, and – with the exception of a tertiary alcohol – also process *c*. Process *b* seems little affected by reaction conditions.

Since a similar distribution of products also occurred in the desulfuration of hydroxy derivative *XXXVII*, and since the 3-oxo group in compound *X* is easily reducible[2], it could be assumed that under the effect of Raney-nickel the hydrogenation of the 3-oxo group woud take place first, followed by the splitting off of the sulfur atom, under formation of diradical *XXXVIII*. However, we found that the yields of alcohol *III* after desulfuration of hydroxy derivative *XXXVII* are repeatedly substantially higher at the expense of other products (*XIV*, *XXIII* and *XXXI*), than during the transformation of the 3-oxo derivative *X*; the mechanism, initiated by the reduction of the 3-oxo group cannot thus explain by itself the qualitative and the quantitative composition of the product but, the simultaneous operation of this mechanism, parallel with the route leading *via* the diradical *XXXVI*, cannot be excluded.

Since it was found that the route leading *via* the intermediate carrying the radical in the position 3 (*XXXVI*) leads to a considerable amount to undesirable products we converted substance *X*, using sodium methoxide, to thioxo derivative *VII* quantitatively. The ^{1}H NMR spectrum of this substance shows that a rapid equilibrium is attained in solution between the thioxo and the enethiol form (*VII* and *IX*), which – as in other thioxocyclohexanes[11] – has the equilibrium constant close to 1. The thioxo derivative *VII* is an unstable compound, but the opening of the thiapyran ring and the desulfuration of compound *VII* with Raney-nickel or aluminum amalgam[12,13] can be carried out in one step straight to the unsaturated ester *XIV*. Therefore, from the preparative point of view, the thienol lactones of type *X* can be recommended for the synthesis of either unsaturated esters (*via* the thioxo esters of type *VII*) or saturated alcohols (fresh Raney-nickel and 3-oxo derivatives of type *X* or better *XXXVII*) while other types of desulfuration (lithium in ammonia, tributyltin hydride, aluminum amalgam) give lower yields.

EXPERIMENTAL

The melting points were determined on a Kofler block and they are not corrected. Samples for analysis were dried at 20°C/26 Pa for 6 h. Optical rotation was measured in chloroform, the infrared spectra in tetrachloromethane, unless stated otherwise. The CD spectra were recorded on a Dichrographe II (Jouan-Roussel) in methanol, the mass spectra on a Jeol JMS D-100 spectrometer, operating at 14–75 eV. Mixtures were separated by thin-layer chromatography on silica gel. Raney-nickel was prepared according to ref.[13] and under methanol. If the reaction was carried out in another alcohol, the Raney nickel suspension was introduced into a reaction flask, the methanol was decanted, the required alcohol was added (about a 10-fold amount) and the alloy was stirred in an inert atmosphere for 5 min. The supernatant was poured off and the whole operation was repeated twice more. When a suspension in toluene had to be prepared, the washing was carried out with toluene and then the suspension was heated at 80°C for 20 h in an inert atmosphere in order to eliminate the adsorbed hydrogen.

Desulfuration of 4-Thia-cholesten-3-one (*X*)

a) 50 mg of compound *X* were stirred and heated with a suspension of Raney-nickel in excess in boiling methanol (30 ml) under nitrogen. After 20 h nickel was filtered through a layer of diatomaceous earth, the organic components were washed out with hot methanol and toluene, then concentrated and applied on a silica gel thin layer. After development with 10% ether in light petroleum the following compounds were isolated, in the order of increasing polarity: A-Bisnor-2,5-secocholestane (*XXXI*, 3·5 mg); IR spectrum: no absorption in the region of OH or C=O groups; mass spectrum: 346 *m/z* ($C_{25}H_{46}$), 317 *m/z* (base peak, $C_{25}H_{46}$—C_2H_5).

TABLE II

^{1}H NMR spectra of some A-norsteroids. The Spectra were measured in deuteriochloroform, using tetramethylsilane as internal standard, on a Tesla 60 instrument. Chemical shifts are given in ppm (δ-scale)

Compound	18-H[a]	19-H[a]	Further signals
I	0·67	0·89	0·85[b], 3·50[c], 5·29[d], 5·60[e]
III	0·64	0·84	0·85[b], 3·60[c]
VII	0·66	1·08	0·85[b], 3·64[a]
IX	0·66	1·08	0·85[b], 3·64[a], 2·65[f], 5·92[g]
XIV	0·67	0·90	0·85[b], 3·62[a], 5·23[d], 5·62[e]
XV	0·67	0·90	0·85[b], 1·23[c], 4·09[h], 5·25[d], 5·61[e]
XVI	0·67	0·90	0·85[b], 4·00[i], 5·26[d], 5·62[e]
XVII	0·67	0·90	0·85[b], 5·08[j], 5·23[d], 5·62[e], 7·37[k]
XVIII	0·63	0·85	0·85[b], 3·63[a]
XIX	0·63	0·85	0·85[b], 4·09[h]
XX	0·64	0·85	0·85[b], 4·00[c]
XXI	0·63	0·83	0·85[b], 4·55[l], 5·06[m], 7·32[k]
XXII	0·63	0·90	0·85[b], 3·53[n]
XXIII	0·66	1·14	0·85[b]
XXV	0·93	1·16	4·79[o], 7·47[p], 8·05[p]
XXVI	0·66	0·96	0·85[b], 4·29[r]
XXVII	0·64	0·96	0·85[b], 4·27[s]
XXVIII	0·86	0·89	—
XXIX	0·68	0·86	0·85[b], 5·28[d], 5·59[e]
XXXI	0·66	0·82	0·85[b]
XXXIII	0·86	0·86	0·75[t]

[a] Singlet, 3 H; [b] doublet, J = 6 Hz, 6 H; [c] triplet, J = 6·5 Hz, 2 H; [d] broad doublet, J = 10 Hz, 1 H; [e] doublet of doublets, J = 10 and 4 Hz, 1 H; [f] broad singlet, 0·5 H; [g] doublet, J = 5 Hz, 0·5 H; [h] quartet, J = 7 Hz, 2 H; [i] triplet, J = 7 Hz, 2 H; [j] singlet, 2 H; [k] singlet, 5 H; [l] triplet, J = 3 Hz, 1 H; [m] singlet, 1 H; [n] multiplet, 4 H; [o] triplet, J = 8 Hz, 1 H; [p] multiplet (aromatic protons), [r] multiplet, $W_{1/2}$ = 16 Hz, 1 H; [s] multiplet, $W_{1/2}$ = 20 Hz, 1 H; [t] triplet, J = 6·5 Hz, 3 H.

Methyl A-nor-3,5-secocholestan-3-oate (*XVIII*, 12·1 mg); IR spectrum: 1 741, 1 199, 1 170, 1 160 cm^{-1}; mass spectrum: 404 m/z ($C_{27}H_{48}O_2$); for $C_{27}H_{48}O_2$ (404·6) calcualted: 80·14% C, 11·96% H; found: 80·26% C, 11·81% H. A-Nor-5β-cholestan-3-one (*XXIII*, 4·4 mg), m.p. 76 to 79°C (methanol, lit.[5] gives 79—80°C); circular dichroism, $[\Theta]_{308} + 11\,350°$, lit.[5] gives + 11 900°. A-nor-3,5-secocholestan-3-ol (*III*, 22 mg); IR spectrum is identical with that of an authentic specimen. A-Nor-5β-cholestan-3α-ol (*XXVII*, 4 mg); IR spectrum is identical with that of a sample prepared from authentic A-nor-5β-cholestan-3-one (see below).

b) Procedure as under *a*) in boiling ethanol. The distribution of the products was the same, except for the content of ester *XIX* (12%), the analytical values of which agree with the structure of ethyl ester of A-nor-3,5-secocholestan-3-oic acid, $[\alpha]_D^{20} + 13°$ (*c* 1·1). IR spectrum: 1 741, 1 730 (sh), 1 190, 1 178, 1 167 cm^{-1}). For $C_{28}H_{50}O_2$ (418·7) calculated: 80·32% C, 12·04% H; found: 80·07% C, 12·21% H.

c) When the reaction is carried out in boiling propanol the propyl ester of A-nor-3,5-secocholestan-3-oic acid (*XX*, 10%) was isolated, $[\alpha]_D^{20} + 14°$ (*c* 1·0). IR spectrum: 1 740, 1 730 (sh), 1 190, 1 176, 1 156 cm^{-1}). For $C_{29}H_{52}O_2$ (432·7) calculated: 80·49% C, 12·11% H; found: 80·41% C, 11·89% H.

d) The reaction was carried out in benzyl alcohol at 100°C, the mixture was worked up as in the preceding cases, the residue was concentrated on a rotatory evaporator. In addition to the standard yields of compounds *XXX*, *XXIII*, *III* and *XXVII*, benzyl ester of A-nor-3,5-secocholestan-3-oic acid (*XXI*, 13%) was also isolated, $[\alpha] + 16$ (*c* 1·2). IR spectrum: 1 741, 1 710 (sh), 1 154, 697 cm^{-1}. For $C_{33}H_{52}O_2$ (480·8) calculated: 82·44% C, 10·90% H; found: 82·04% C, 10·40% H.

e) In a similar manner 4-thia-5-cholesten-3-one (*X*; 107 mg) and an excess of Raney-nickel in 10 ml of ethylene glycol, when stirred at 100°C under nitrogen, gave 14 mg of A-nor-5β-cholestan-3-one *XXIII*, 43 mg of A-nor-3,5-secocholestan-3-ol (*III*) and 41 mg of 2-hydroxyethyl ester of A-nor-3,5-secocholestan-3-oic acid (*XXII*), $[\alpha]_D^{20} + 14°$ (*c* 1·0). IR spectrum: 3 630 (OH, (OH, group), 1 743, 1 180, 1 166 ($COOCH_3$) cm^{-1}. For $C_{28}H_{50}O_3$ (434·7) calculated: 77·36% C, 11·59% H; found: 76·97% C, 11·56% H.

f) On reaction with a less active Raney-nickel, even without nitrogen, the proportion of the products was the same, with the difference that the esters of type *XVIII* and bisnor derivatives of type *XXXI* were accompanied by 20 to 80% unsaturated compounds of type *XIV* and *XXIX*, respectively, while the degree of unsaturation was the same in both products from the same mixture (integration of the ^1H NMR spectra and mass spectra).

A-Nor-5β-cholestan-3α-ol (*XXVII*)

a) 80 mg of A-nor-5β-cholestan-3-one (*XXIII*) were stirred with a suspension of an excess of Raney-nickel in tert-butanol (30 ml) under nitrogen at 60°C. After 60 h the mixture was worked up as in the preceding cases and the product was separated on a thin-layer of silica gel to the following components (given in the order of decreasing polarity): A-nor-5β-cholestan-3α-ol (*XXVII*, 26 mg), m.p. 92—93°C and 105—106°C (methanol), $[\alpha]_D^{20} + 46$ (*c* 1·7); IR spectrum ($CHCl_3$): 3 625, 3 615, 1 066, and 1 045 cm^{-1}; for $C_{26}H_{46}O$ (374·6) calculated: 83·35% C, 12·38% H; found: 83·17% C, 12·29% H. A-Nor-5β-cholestan-3β-ol (*XXVI*, 4 mg); IR spectrum is identical with that of an authentic sample. A-Nor-5β-cholestan-3-one (*XXIII*, 45 mg), identical with the starting compound according to the mixture melting point.

b) 90 mg of ketone *XXIII* were reduced at 0°C with an excess of lithium aluminum hydride in 1 ml of tetrahydrofuran. After 30 min the mixture was decomposed with dilute hydrochloric acid, the product was extracted with chloroform and separated on silica gel thin layers with 10% of ether in benzene; the required substance represents a polar admixture (8 mg), while the main fraction (73 mg) is identical with authentic 3β-hydroxy-A-nor-5β-cholestane (*XXVI*, ref.[6]). When sodium triethylborohydride was used the 3α-hydroxy derivative could not be detected in the product and the 3β-alcohol *XXVI* was the sole product.

c) 36 mg of ketone *XXIII* were hydrogenated on platinum (200 mg of Adams catalyst) in acetic acid (5 ml) at room temperature. After 2 h the mixture was separated to: A-nor-5β-cholestan-3α-ol (*XXVII*, 5·9 mg), A-nor-5α-cholestan-3β-ol (2 mg), which was oxidized according to Jones to authentic A-nor-5α-cholestan-3-one then A-nor-5β-cholestan-3β-ol (*XXVI*, 18·2 mg), identical with an authentic sample (IR spectrum), and the starting ketone *XXIII* (10 mg).

Desulfuration of 17β-Benzoyloxy-4-thia-5-androsten-3-one (*XI*)

a) 15 ml of a suspension of Raney-nickel were rinsed with cyclopentanone and the suspension was stirred with another portion of the same solvent at 85°C for 30 min. A solution of benzoate *XI* (395 mg) in cyclopentanone (about 5 ml) was added to the mixture and the stirring was continued for another 20 h. After working up of the mixture the following compounds were identified: 17β-Benzoyloxy-2,5-seco-5-androstane (*XXX*, 70 mg), m.p. 133—135°C (methanol); IR spectrum: 1 724, 1 257 (benzoyloxy group), 1 660, 1 635 (C=C group) cm^{-1}; mass spectrum: 352 *m/z* ($C_{24}H_{32}O_2$), 323 *m/z* (base, peak) $M^+ - C_2H_5$; for $C_{24}H_{32}O_2$ (352·5) calculated: 81·77% C, 9·67% H; found: 81·50% C, 9·44% H. 17β-Benzoyloxy-A-nor-5β-cholestan-3-one (*XXV*, 31 mg), m.p. 152—154°C (methanol), $[\alpha]_D^{20}$ +150 (*c* 0·9); IR spectrum: 1 711, 1 280 (benzoyloxy group), 1 731 (oxo group) cm^{-1}; mass spectrum: 380 *m/z* ($C_{25}H_{32}O_3$), 258 *m/z* ($M^+ - C_6H_5COOH$). The more polar components represented a poorly separable mixture which was not further analysed.

b) 45 mg of compound *XI* were reacted with Raney-nickel in methanol at boiling temperature. After 18 h 17β-benzoyloxy-A-nor-3,5-secoandrostan-3-ol (*V*, 25 mg) was isolated as the main product, m.p. 95—97°C (methanol), $[\alpha]_D^{20}$ +55° (*c* 0·9), IR spectrum: 1 720, 1 275 (benzoyloxy group), 3 635 (OH) cm^{-1}. Mass spectrum: 384 *m/z* (M^+).

A-Bisnor-2,5-secoandrostane-5,17-dione (*XXXIV*) and A-bisnor-2,5-secoandrostane-6,17-dione (*XXXV*)

Derivative *XXX* (20 mg) was epoxidated with *m*-chloroperbenzoic acid (100 mg) in 1,5 ml of chloroform at room temperature. After 20 h the mixture was diluted with ether, washed with potassium carbonate and the epoxides were reduced by boiling with lithium aluminum hydride (about 100 mg) in tetrahydrofuran (5 ml). After 2 h the mixture was worked up, the product was oxidized according to Jones and separated to 2 components using 10% ether in benzene as solvent (on thin layers of silica gel). The more polar component (*XXXIV*, 3 mg), m.p. 175—176°C, had a mass spectrum compatible with the structure of A-bisnor-2,5-secoandrostane-5,17-dione; 262 *m/z* ($C_{17}H_{26}O_2$) and 233 ($M^+ - C_2H_5$); $\Delta\varepsilon_{299}$ +2·52. The more lipophilic component (*XXXV*, m.p. 84—86°C, 3·5 mg) had a similar mass spectrum, but the molecular peak loses a CO group instead of the ethyl radical (234 *m/z*, base peak). IR spectrum displays the presence of 2 methylene groups activated by the keto group on the six-membered ring, which is compatible with the structure of A-bisnor-2,5-secoandrostane-6,17-dione, $\Delta\varepsilon_{297}$ +3·42.

Desulfuration of 4-Thia-5-androstene-3,17-dione (*XII*)

a) Compound *XII* (123 mg) was heated with a suspension of Raney-nickel in tert-butanol at 80°C in an inert atmosphere. After 20 h the mixture was worked up as in the preceding cases and the product was oxidized according to Jones. The mixture was poured into an aqueous sodium chloride solution, the product was extracted with ethyl acetate, washed with water and concentrated in a vacuum. The residue was separated by thin layer chromatography (in 20% ether in benzene) to: 17-Oxo-A-nor-3,5-secoandrostan-3-oic acid (*XXVIII*, 24 mg), m.p. 176 to 177°C (lit.[4] gives the same value). A-Nor-5β-androstane-3,17-dione (*XXIV*, 17 mg); IR spectrum ($CHCl_3$): 1 736, 1 410 cm^{-1}, mass spectrum: 274 *m/z* ($C_{18}H_{26}O_2$), 256 *m/z* ($M^+ - H_2O$), 246 *m/z* ($M^+ - H_2O - CH_3$); m.p. 128–129°C (lit.[15] gives 127–129°C). A-Bisnor-2,5-seco-androstan-17-one (*XXXIII*, 49 mg), m.p. 72–73°C (methanol), $[\alpha]_D^{20}$ +82° (*c* 1·2); Circular dichroism (methanol) $\Delta\varepsilon_{297}$ +3·0; IR spectrum: 1 745, 1 408 cm^{-1}. For $C_{17}H_{28}O$ (248·4) calculated: 82·20% C, 11·36% H; found: 82·26% C, 11·41% H.

b) A solution of 4-thia-5-androstene-3,17-dione (*XII*, 36 mg) in 1 ml of ether was added to a solution of 520 mg of crystalline nickel-II chloride in 1 ml of methanol, and a cooled (0°C) solution of 245 mg of sodium borohydride in 6 ml of methanol was added to the mixture dropwise and under stirring and under nitrogen. After 20 h the mixture was concentrated in a vacuum, diluted with a saturated sodium chloride solution in water and the product was extracted with ethyl acetate. The product was purified by thin-layer chromatography on silica gel thin layers (with 50% ether in benzene). The only fluorescing band of organic material (detection with morin in UV light) at $R_F = 0{\cdot}5$, was eluted with ether (yield, 19·7 mg) and the product was identified by ^1H NMR spectrometry as the known[14] A-nor-3,5-secoandrostane-3,17β-diol (*IV*). The crude product (10 mg) was oxidized according to Jones, the mixture was poured into an aqueous sodium chloride solution and extracted with ethyl acetate. Then the product was separated by thin layer chromatography to 17-oxo-A-nor-3,5-seconadrostan-3-oic acid (*XXVIII*, 7·9 mg, mass spectrum: M^+ 292 *m/z*) and A-nor-5β-androstane-3,17-dione (*XXIV*, 0·1 mg).

Desulfuration of 4-Thia-5-cholesten-3α-ol (*XXXVII*)

Hydroxy derivative *XXXVII* (52 mg) was added to a suspension of Raney-nickel in tert-butanol and the mixture was stirred at 80°C under nitrogen. After 40 h the mixture was worked up as in the preceding cases and the product was separated by means of thin-layer chromatography on silica gel, using 10% of ether in benzene for elution. The following substances were isolated and identified by comparison with standards: 3α-hydroxy derivative *XXVII* (2 mg), saturated 3,5-seco-alcohol *III* (36 mg), A-norketone *XXIII* (2·5 mg) and A-bisnor derivative *XXXI* (5 mg).

Methyl 5-Thioxo-A-nor-3,5-secocholestan-3-oate (*VII*)

a) 4-Thia-5-cholesten-3-one (*X*) (40 mg) was dissolved in 1 ml of benzene and sodium methoxide in methanol (1 ml of a 1% solution) was added to it. After 5 min the mixture was diluted with 30 ml of cooled (0°C) ethyl acetate and washed twice with icy water. The solution was rapidly filtered through a layer of sodium sulfate and the filtrate evaporated in a vacuum. The total time of working up was shorter than 6 min. The checking of the purity by thin layer chromatography on silica gel (using 8% of ether in light petroleum) showed: the starting compound *X* gives a spot at R_F 0·60, product *VII* a dark spot (UV light) at R_F 0·73, and a trace of a polar impurity (about 4%) at R_F 0·30. Two-dimensional chromatography shows that on running on silica

gel the thioxo compound *VII* is decomposed to a mixture of compounds of which ester *VI* and lactone *X* were identified. Attempts at chromatographic purification led to complex mixtures. The crude compound had a ^{1}H NMR spectrum which is interpretable as a mixture of tautomers *VII* and *IX* in a 1 : 1 ratio. A checking of the sample after the recording of the spectrum confirms that the quality of the sample did not deterioate appreciably during the measurement.

b) Compound *X* (50 mg) was dissolved in 0·5 ml of chloroform and 5 ml of methanol, the solution was acidified with 0·1 ml of hydrochloric acid and allowed to stand under nitrogen for 20 h. The solution was concentrated *in vacuo*, diluted with light petroleum, the organic phase was washed with water, dried and evaporated. Thin-layer chromatography demonstrated the formation of thioxo ester *VII*, as under *a*), and the mixture contained about 20% methyl ester of acid *VI* as impurity.

Methyl A-nor-3,5-seco-5-cholesten-3-oate (*XIV*)

4-Thia-5-cholesten-3-one (*X*, 40 mg) was dissolved in 1 ml of toluene, 1 ml of sodium methoxide (1% solution in methanol) was added and after 6 min this solution was added to an excess of Raney-nickel in methanol (about 1 ml of Raney-nickel and a total of 5 ml of methanol). The mixture was heated at 50°C and stirred under nitrogen, then worked up as in the preceding cases. The product was purified by thin-layer chromatography on silica gel (using 7% of ether in light petroleum for development), the yield of compound *XIV* mas 37 mg, mass spectrum: 402 m/z ($C_{27}H_{46}O_2$). IR spectrum was identical with the spectrum of an authentic sample.

Ethyl A-nor-3,5-seco-5-cholesten-3-oate (*XV*)

In a similar manner 50 mg of compound *X* and sodium ethoxide (1%) gave ethyl ester *XV* (46 mg), $[\alpha]_D^{20}$ −1° (*c* 1·6); IR spectrum: 3 070, 3 015, 1 661 (C=C), 1 741, 1 183 (ethoxycarbonyl) cm^{-1}. For $C_{28}H_{50}O_2$ (418·7) calculated: 80·32% C, 12·04% H; found: 80·06% C, 11·86% H.

Propyl A-nor-3,5-seco-5-cholesten-3-oate (*XVI*)

Similarly, compound *X* (99 mg) and sodium propoxide gave propyl ester *XVI* (89 mg), $[\alpha]_D^{20}$ 0° (*c* 2·0); IR spectrum: 3 070, 3 015, 1 661 (C=C), 1 742, 1 183 (propoxycarbonyl) cm^{-1}. For $C_{29}H_{52}O_2$ (432·7) calculated: 80·49% C, 12·11% H; found: 80·29% C, 12·01% H.

Benzyl A-nor-3,5-seco-5-cholesten-3-oate (*XVII*)

Methyl ester *XIV* (62 mg) was dissolved in 1 ml of chloroform and 5 ml of benzyl alcohol, the solution was acidified with 0·1 ml of hydrochloric acid and allowed to stand for 48 h. The solution was diluted with 20 ml of chloroform, washed with a potassium hydrogen carbonate solution and water, dried over sodium sulfate and concentrated under reduced pressure first on a water bath and finally in a Wood metal bath (150°C). The product was purified on silica gel thin layers, yield of compound *XVII* was 61 mg, $[\alpha]_D^{20}$ −7° (*c* 1·4); IR spectrum: 1 662 (C=C), 1 742, 1 154, 698 (benzyloxycarbonyl) cm^{-1}. For $C_{33}H_{50}O_2$ (478·7) calculated: 82·79% C, 10·53% H; found: 82·52% C, 10·71% H.

REFERENCES

1. Jones D. N., Lewton D. A., Msonthi J. D., Taylor R. J. K.: J. Chem. Soc., Perkin Trans. 1, *1974*, 2637.

2. Kasal A.: This Journal, in the press.
3. Kitagawa I., Kamigauchi Z., Yonetani K., Yoshihara M.: Chem. Pharm. Bull. *28*, 2403 (1980).
4. Spero G. B., McIntosh A. V., jr, Levin R. H.: J. Amer. Chem. Soc. *70*, 1907 (1948).
5. Fuchs B., Loeventhal H. J. E.: Tetrahedron *11*, 199 (1960).
6. Shoppee C. W., Sly J. C. P.: J. Chem. Soc. *1959*, 345.
7. Sheradsky T., Zbaida D.: J. Org. Chem. *45*, 2165 (1980).
8. Muthuramu K., Ramamurthy V.: J. Chem. Soc., Chem. Commun. *1980*, 243.
9. Pfenninger J., Henberger C., Graf W.: Helv. Chim. Acta *63*, 2328 (1980).
10. Hauptmann H., Wladislaw B.: J. Amer. Chem. Soc. *72*, 707 (1950).
11. Mayer R.: Sulfur Org. Inorg. Chem. *3*, 325 (1972).
12. Pascali V., Umani-Ronchi A.: J. Chem. Soc., Chem. Commun. *1973*, 351.
13. Billica H. R., Adkins H.: Org. Syn. Coll. Vol. *3*, 176 (1955).
14. Kasal A.: This Journal *45*, 2541 (1980).
15. Camerino B., Valcavi V.: Gazz. Chim. Ital. *93*, 723 (1963).

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