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THE REDUCTION OF *CIS*- AND *TRANS*-3β-HYDROXY--5,10-SECO-1(10) - CHOLESTEN-5-ONE AND THEIR ACETATES WITH COMPLEX METAL HYDRIDES*

by

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Investigations of cyclic systems have shown that their reactivity depends to a considerable extent on ring size (2). This difference in reactivity is ascribed to changes in the total internal strain (*I*-strain) associated with bond formation and bond cleavage at the reacting ring carbon (or other) atom in the rate determining step, whereby such strain changes are function of ring size (3). Thus, for example, in ten-membered cyclic systems reactions which proceed with a change of hybridization of the reacting ring (carbon) atom from sp^3 to sp^2 are favoured, because of considerable relief of bond angle strain and decrease in ("transannular" non-bonded) van der Waals compression, whereas, on the contrary, reactions involving $sp^2 \rightarrow sp^3$ hybridization change are associated with increase in total internal strain and are therefore retarded. Most data on these effects were obtained by studying reactions of known mechanism and kinetics on simple saturated cyclic systems (built of $—CH_2—$ units and reaction centres only). However, little is known on the influence of other functional groups present in such molecules on reactivity in processes involving both (above mentioned) types of hybridization change at the reacting center (4).

In the present work we have studied the reactivity of *cis*- and *trans*--3β-hydroxy-5,10-seco-1(10)-cholesten-5-one and their acetates (I and IV) (5) (i.e. modified steroid compounds containing instead of the two fused six-membered rings A and B the medium-sized *cis*- or *trans*-1(10)-cyclo--decen-5-one system) in the reduction whith the complex metal hydrides sodium borohydride and lithium aluminium hydride. This investigation was undertaken in order to establish if these two olefinic diastereomers (I and IV), which differ in configuration and conformation, behave differently, and if so to what degree, in metal hydride reductions, i.e. in reactions which involve a change of hybridization of carbon C—5 from sp^2 (trigonal carbonyl carbon) to sp^3 (tetrahedral carbinol carbon). Having in mind the fact that

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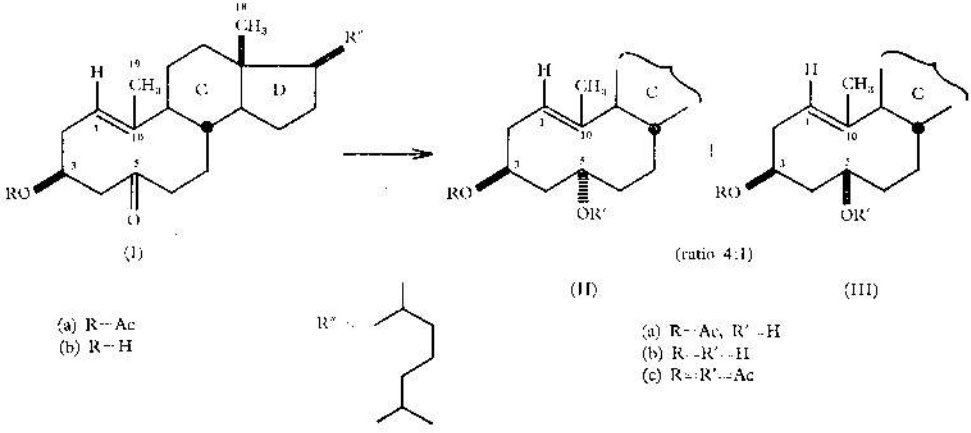
the mechanism of, and the steric requirements for, the reductions with complex metal hydrydes, as well as the relatively simple kinetics of the sodium borohydride reduction of the carbonyl group are known (6, 7, 8), we have studied both the stereochemical course and the kinetics of the metal hydride reductions of the isomeric seco-ketones (I) and (IV).

RESULTS

1. *Stereochemical Course of the Reductions*

(a) *Reductions of the cis-unsaturated seco-ketones (I).* — The sodium borohydride reduction of *cis*-3β-acetoxy-5,10-seco-1(10)-cholesten-5-one (Ia) in methanol or isopropanol solution affords, in nearly quantitative yield, a mixture of the two 5-epimeric alcohols with 5*S* (5α—OH) and 5*R* (5β—OH) configuration (IIa) and (IIa)*,**, in an approximate ratio of 4:1. The diastereomer with the 5*S* configuration (IIa), which is formed as the major reduction product, was isolated in a pure state after repeated crystallization from acetone (in a 60% crystallization yield)***.



The reduction of the 5-carbonyl group in the *cis*-seco-ketone (Ia) with lithium aluminium hydride in diethyl ether solution follows a similar stereochemical course, and the 5-epimeric 3β,5-diols with 5*S* and 5*R* configuration, (IIb) and (IIIb) respectively, were again obtained in a ratio of about 4:1.

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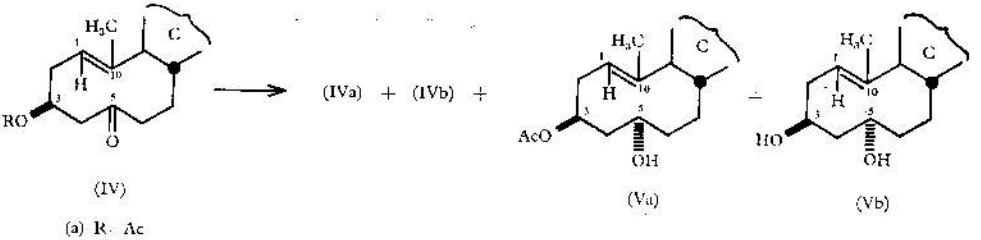
* The *S* and *R* configuration at C-5 in epimers (II) and (III), respectively, was tentatively determined on the basis of analysis and comparison of their NMR spectral data (9).

** The orientation (α or β) of the substituents in the ten-membered ring is formally defined with respect to the spatial position of the methyl carbon C-18 when the ten-membered ring has the hypothetical planar conformation, whereby an α-substituent is on the opposite side and a β-substituent on the same side of the ring.

*** Since both epimeric 5-alcohols (IIa) and (IIIa) have the same R_f value when subjected to thin layer chromatography on silica gel, the purity of the reduction products and their ratio was controlled after conversion to the corresponding diacetates (IIc) and (IIIc), which showed different R_f values on chromatoplates.

The same ratio of diols (IIb) and (IIIb) was observed in the sodium borohydride reduction of *cis*-3β-hydroxy-5,10-seco-1(10)-cholesten-5-one (Ib) in methanol or isopropanol solution.

(b) *Reductions of the trans-unsaturated seco-ketones (IV).* — The reduction of *trans*-3β-acetoxy-5,10-seco-1(10)-cholesten-5-one (IVa) with sodium borohydride in dioxane-methanol or in isopropanol is more stereospecific than the reduction of the corresponding *cis*-isomer (Ia) (see above), and of the two possible 5-epimeric alcohols (with 5*S* and 5*R* configuration) only one diastereomer, having the 5*S* configuration (Va and its hydrolysis product Vb)*, was obtained from the reduction mixture. However, in this case, in addition to *trans*-3β-acetoxy-5,10-seco-1(10)-cholesten-5α-ol (Va) which is formed in 53% yield, other products were also isolated, such as unreacted starting ketone (IVa) in 15% yield**, its 3-saponified derivative (IVb) in 3% yield, and the 3β,5α-diol (Vb) [resulting from hydrolysis of the 3β-acetate group in the initially produced 3β-acetoxy-5α-ol (Va)] in 11% yield. (These products were separated and isolated by chromatography on a SiO_2-column.).



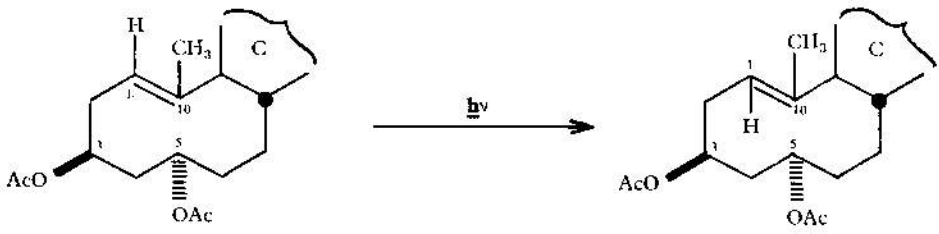
It was found that the lithium aluminium hydride reduction of the *trans*-seco-ketone (IVa) in diethyl ether solution, and the sodium borohydride reduction of *trans*-3β-hidroxy-5,10-seco-1(10)-cholesten-5-one (IVb) in methanol or isopropanol solution are also highly stereospecific, whereby in both cases *trans*-5,10-seco-1(10)-cholestene-3β,5α-diol (Vb) is formed in practically quantitative yield.

The correlation of configuration at C—5 between the *cis*-olefinic 5--alcohol (IIa and/or IIb), obtained as major product in the reductions of the *cis*-seco-5-ketone (Ia and Ib), and the *trans*-olefinic 5-alcohol (Va and/or Vb), produced stereospecifically in the reductions of the *trans*-seco-5-ketone (IVa and IVb), was achieved by photochemical isomerization of the 1,10--double bond. Namely, by UV-irradiation of the *cis*-unsaturated 3β,5-diacetate (IIc), obtained by O-acetylation of alcohol (IIa) or (IIb), a product was formed which proved identical with the 3β,5-diacetate (Vc) prepared

* According to thin layer chromatography, the corresponding epimer with the 5*R* (i.e. 5β-OH) configuration was formed only in traces. [For tentative configuration assignment at C-5 see ref. (9)].

** These reductions were not carried out to completion, because of considerable hydrolysis of the 3β-acetate group.

from the *trans*-unsaturated 5-alcohol (Va) or (Vb). In this way, it was established that alcohols (II) and (V) are olefinic *cis-trans* diastereomers and that they have the same configuration at C—5, which, according to NMR studies, is very probably *S* (i.e. 5α-OH) (9).



(IIc) (Vc)

$\Delta^{1(10)}$-*cis* $\Delta^{1(10)}$-*trans*

2. *Kinetic Measurements*

The kinetics of the reductions of *cis*- and *trans*-3β-hydroxy-5,10-seco--1(10)-cholesten-5-one (Ib) and (IVb) with sodium borohydride were followed by applying the procedure of Brown *et al.* (6). Solutions of the *cis*- and *trans*-seco-ketone (Ib) and (IVb) in isopropanol were mixed with sodium borohydride dissolved in the same solvent, and heated in a thermostat at 35° ±0.2°*. The amount of unreacted sodium borohydride was determined at regular time intervals by titration, using the potassium iodate method (10). It was found that the sodium borohydride reductions of *cis*- and *trans*-3β-hydroxy-5,10-seco-1(10)-cholesten-5-one (Ib) and (IVb) are analogous to those of ketones containing authentic steroid systems (8) and that they correspond to second-order kinetics. The rate constants, k_2, given in Table I, indicate that the *cis*-isomer (Ib) is reduced by means of sodium borohydride about 10 times faster than the *trans*-isomeric ketone (IVb).

TABLE I

Rate constants (k_2) for sodium borohydride reductions of *cis*-3β-hydroxy--5,10-seco-1(10)-cholesten-5-one (Ib) and *trans*-3β-hydroxy-5,10-seco-1(10)--cholesten-5-one (IVb) in isopropanol solution at 35°

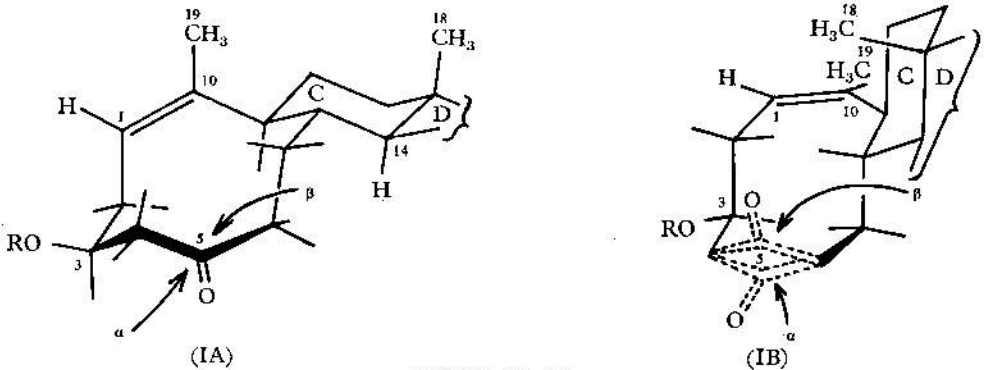
Substrate	Rate constant k_2[a] (in *liters/mole-sec*)	Relative rate
cis-Isomer (Ib)	6.2×10^{-3}	10
trans-Isomer (IVb)	6.4×10^{-4}	1

a) Mean value of two separately performed kinetic experiments

* Under these conditions, over a 24 hour reaction period, neither diol (Ib) nor diol (IVb) exhibited any tendency towards reaction of the 3-hydroxyl group with the reducing agent (which would result in the evolution of molecular hydrogen).

DISCUSSION

The data obtained on the stereochemical course of the reductions of the *cis*- and *trans*-seco-ketones (I) and (IV) with sodium borohydride and lithium aluminium hydride, and on the kinetics of the sodium borohydride reductions of these compounds, suggest that molecules of the isomeric ketones (I) and (IV), although containing the steroid residue ring system C and D, have nevertheless conformations resembling those of simple *cis*- and *trans*-5-cyclodecenone cyclic systems (5,11). The fact that both the sodium borohydride and the lithium aluminium hydride reductions of the *cis*-seco-ketones (Ia) and (Ib) afford mixtures containing an approximately equal ratio of 5*S* (i. e. 5α-OH) to 5*R* (i. e. 5β-OH) alcohol (II : III = about 4 : 1), indicates that these reactions are not dependent on the steric characteristics of the used reducing agent (7, 12). By inspection of models it can be seen (Scheme 1) that the proposed stable conformation for the *cis*-1(10)-



$\triangle^{1(10)}$-*cis*-5-ketone

Scheme 1

-cyclodecen-5-one system (IA) (5,11)* allows approach of the reagent to the carbonyl (C-5) carbon atom from both sides (α and β)**, but that, because of the presence of the steroid residue (rings C and D), attack from the β side to give the epimeric alcohol with the 5*S* configuration (II), should be preferred (as experimentally confirmed; see above)***. Other conformations of the seco-steroid ketone (I) containing the *cis*-1(10)-cyclodecen-5--one system, such as those illustrated on Scheme 1 by (IB) (5,11), should

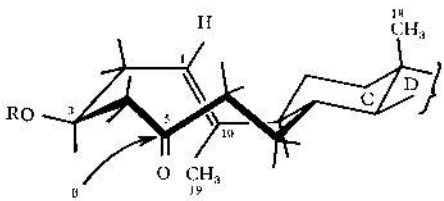
* By slight changes in the relative orientation of the bond plane of the trigonal (sp^2-hybridized) C-5 carbonyl carbon in conformation (IA, Scheme 1), different distances (and therefore non-bonded interactions) between the hydrogens on C-4 and C-7, and the hydrogens on C-2, C-6, C-9 and C-14, may be attained (11). Conformation (IA), as drawn here, represents a compromise and is probably the energetically most favourable form of the *cis*-isomer (I).

** Approach from the „β" side means that the reagent attacks the 5-carbonyl group from the side in which the angular methyl carbon C-18 is located when the ten--membered ring has the hypothetical planar conformation. The opposite side is called the „α" side.

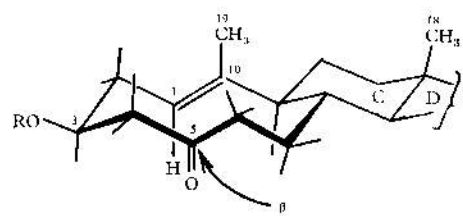
*** On the basis of data available, it is not possible to discuss in detail and predict the importance of the influence of thermodynamic factors in the transition state or intermediate products on the outcome of this and other reductions studied in the present work,

be less stable. In these conformations, preferential attack (α or β) would mainly depend on the relative orientation of the bond plane of the trigonal (C-5) carbonyl carbon.

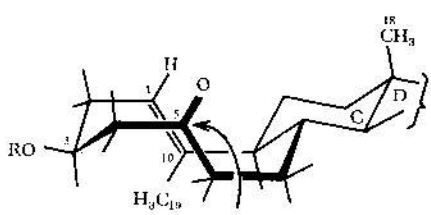
On the other hand, from the high stereospecificity of the sodium borohydride and lithium aluminium hydride reductions of the *trans*-seco-ketones (IVa) and (IVb), it follows that in this case the reducing agent can approach the carbonyl (C-5) carbon atom only from one side. Examination of models corresponding to the stable conformations of the *trans*-1(10)-cyclodecen-5-one system (Scheme 2; forms IVA, IVB and IVC) (5, 11, 13, 14) reveals that



(IVA)



(IVB)



(IVC)

$\Delta^{1(10)}$-*trans*-5-ketone

Scheme 2

all these conformations allow attack of the reagent mainly from one side, this being the β side in conformations (IVA) and (IVB) (whereby alcohol V with the 5*S* conformation would be formed), and the α side in conformation (IVC) (which would result in the formation of the epimeric 5-alcohol with the 5*R* configuration). Since the metal hydride reductions of the *trans*--seco--ketones (IVa) and (IVb) furnish almost exclusively the epimeric alcohol with the 5*S* configuration (V), it appears highly probable that ketone (IV) reacts in one or both of the former conformations, i. e. (IVA) and/or (IVB) (or in another similar conformation allowing β-attack with formation of the 5*S* alcohol).

The proposed conformations for the *cis*-unsaturated 5-ketone (IA and perhaps IB, Scheme 1) and the *trans*-unsaturated isomer (IVA and IVB, Scheme 2) can also explain the kinetic data of the sodium borohydride reductions of these compounds (see Table 1). If the reaction was dependent

only on ring size, one would expect the reduction rates to be approximately equal for both olefinic diastereomers. However, since their reactivity towards sodium borohydride is different, whereby the *cis*-unsaturated ketone (I) is reduced about 10 times faster than the *trans*-isomer (IV) (Table 1), it follows that the reaction rate must be chiefly influenced by the 1(10)-cyclodecen-5-one ring conformation(s) in the seco-ketone undergoing reduction, and that, in the absence of other factors, that isomer will be more difficultly reduced in which the change of hybridization from sp^2 to sp^3 on the C-5 carbon attacked is associated with higher increase in total internal strain in the transition state. This is clearly the case with the *trans*-seco-ketone IV (conformations IVA and IVB, Scheme 2), in which steric crowding in the transition state for metal hydride reduction will be considerably greater (because the oxygen at C-5 is "pushed" inside of the ten-membered ring)* than in the relatively flat molecules of the *cis*-seco-ketone I (conformation IA and eventually IB, Scheme 1). This assumption is supported by the fact that when the 5-epimeric alcohols (IIa) and (Va) are oxidized with chromic anhydride in the two-phase system ether-water (a reaction which involves $sp^3 \rightarrow sp^2$ hydridization change of the reacting C-5 carbon atom), the rate ratio is opposite, namely the oxidation of the *trans*-alcohol (Va) to the *trans*-ketone (IVa) proceeds considerably faster (more than 10 times) than the conversion of the *cis*-alcohol (IIa) to the corresponding *cis*-ketone (Ia).

It should also be noted that the steric course of the sodium borohydride and lithium aluminium hydride reductions of ketones (I) and (IV) does not depend on whether the 3β-substituent is an acetoxy or a hydroxy group.

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EXPERIMENTAL**

All m. ps are uncorrected. Optical rotations were measured in $CHCl_3$. IR spectra were recorded on a Perkin-Elmer Infracord instrument, Model 337. NMR spectra were obtained at 100 MHz with a Varian HA-100 spectrometer, in $CDCl_3$ solutions (5%) using tetramethylsilane as internal standard; chemical shifts are reported in δ (ppm) values (abbreviations: *s* for singlet, *d* for doublet, *m* for multiplet). The separation of products was controlled by thin layer chromatography, which was carried out on silica gel G (Stahl) with benzene-ethyl acetate (9:1 or 7:3); the detection was effected with 50% H_2SO_4.

Reductions of cis-3β-hydroxy-5,10-seco-cholest-1(10)-en-5-one acetate (Ia)

1A. *Sodium borohydride reduction of (Ia) in methanol solution.* — A solution of 1 *g* of the *cis*-acetoxy-seco-ketone (Ia) (5) in methanol (400 *ml*) was cooled to 5° and treated with sodium borohydride (2 *g*). After stirring for one hour at 5° the reduction was completed, and the reaction mixture was diluted with water, acidified with 10% sulfuric acid and extracted with ether. The ethereal layer was washed with water, saturated aqueous

* Obviously, by a change of the ten-membered ring conformation, in the once formed C-5 alcohol (V) the 5α-hydroxy group will addopt a more favourable relative spatial orientation (9).

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sodium bicarbonate, water, dried over anh. magnesium sulfate and evaporated to dryness in vacuo, leaving a mixture of the epimeric alcohols (IIa) and (IIIa). After four crystallizations of this mixture from acetone, pure cis-3β,5α-*dihydroxy*-5,10-*seco-cholest*-1(10)-*ene* 3-*acetate* (IIa) was obtained (595*mg*; 59.4%), m.p. 173–174°, $[\alpha]_D^{20} = +30° \pm 2°$ ($c = 0.64$); IR (KBr): ν_{max} – 3462, 1711, 1270 cm^{-1}, and IR (CH_2Cl_2): ν_{max} = 3640, 1735, 1235 cm^{-1}; NMR: δ = 0.70 (CH_3-18, *s*), 0.86 (CH_3-26 and CH_3-27, *d*), 0.90 (CH_3-21, *d*), 1.68 (CH_3-19, *d*), 2.01 (CH_3COO at C-3, *s*), 3.72, 5.22 and 5.36 (three protons, at C-5, C-1 and C-3, multiplets). (Found: C, 77.92; H, 11.25%. $C_{29}H_{50}O_3$ requries C, 77.97; H, 11.28%).

The mother liquors from these crystallizations, containing the 5β-epimeric alcohol (IIIa), were combined and evaporated (in vacuo) to dryness; the residue (about 400 *mg*) was acetylated with acetic anhydride (5 *ml*) in pyridine solution (10 *ml*). The white solid obtained after working up the reaction mixture in the usual way was chromatographed on 16 *g* of silica gel (0.20 – 0.05). The first benzene eluate afforded 168 *mg* (15.3%) of cis-3β,5β-*dihydroxy*-5,10-*seco-cholest*-1(10)-*ene diacetate* (IIIc), which was purified by two crystallizations from methanol (yield 120 *mg*, i.e. 10.9%), m.p. 78°, $[\alpha]_D^{20} = +36° \pm 3°$ ($c = 0.40$); IR (KBr): ν_{max} = 1738, 1735, 1240 cm^{-1}; NMR: δ = 0.72 (CH_3-18, *s*), 0.86 (CH_3-26 and CH_3-27, *d*), 0.91 (CH_3-21, *d*), 1.71 (CH_3-19, *d*), 2.01 and 2.03 (two CH_3COO, at C-3 and C-5, singlets), 4.95, 5.12 and 5.30 (three protons, at C-3, C-5 and C-1, multiplets). (Found: C, 76.07; H, 10.51%. $C_{31}H_{52}O_4$ requires: C, 76.18; H, 10.72%).

Further elution with benzene gave a mixture (56 *mg*) of both 5-epimeric diacetates (IIc) and (IIIc). By elution with benzene-ether (98:2) cis-3β,5α-*dihydroxy*-5,10-*seco-cholest*-1(10)-*ene diacetate* (IIc) was obtained (179 *mg*) in 16.3% yield (bringing the total yield of 5*S*-epimer II to 75.7%), which after crystallization from methanol (yield of pure product 120 *mg*, i.e. 10.9%) melted at 86–87°, $[\alpha]_D^{20} = +52° \pm 2°$ ($c = 0.58$); IR (KBr): ν_{max} = 1740, 1248, 1235 cm^{-1}; NMR: δ = 0.72 (CH_3-18, *s*), 0.85 (CH_3-26 and CH_3-27, *d*), 0.89 (CH_3-21, *d*), 1.69 (CH_3-19, *d*), 2.03 and 2.06 (two CH_3COO, at C-3 and C-5, singlets), 4.83, 5.28 and 5.38 (three protons, at C-3, C-5 and C-1, multiplets) (Found: C, 76.02; H, 10.89%. $C_{31}H_{52}O_4$ requires: C, 76.18; H, 10.72%).

Hydrolysis of cis-3β,5β-*dihydroxy*-5,10-*seco-cholest*-1(10)-*ene diacetate* (IIIc.). – Diacetate (IIIc) (100 *mg*) in 10 *ml* of 5% methanolic potassium hydroxide was left overnight at room temperature, then poured into water and extracted with ether. The ethereal layer was washed with water, dried over anh. magnesium sulfate and evaporated (in vacuo) to dryness. Crystallization of the remaining product from acetone afforded 74 *mg* (89.4%) of cis-3β,5β-*dihydroxy*-5,10-*seco-cholest*-1(10)-*ene* (IIIb), m.p. 192–193°, $[\alpha]_D^{20} = +13° \pm 2°$ ($c = 1.0$); IR (KBr): ν_{max} = 3340 cm^{-1}. (Found: C, 80.29; H, 11.82%. $C_{27}H_{48}O_2$ requires: C, 80.14; H, 11.96%).

Hydrolysis of cis-3β,5α-*dihydroxy*-5,10-*seco-cholest*-1(10)-*ene diacetate* (IIc). – Diacetate (IIc) (100 *mg*) was hydrolysed in the same way (as IIIc), giving, after crystallization from acetone, 76 *mg* (91.8%) of cis-3β,5α-*dihydroxy*-5,10-*seco-cholest*-1(10)-*ene* (IIb), m.p. 157–158°, $[\alpha]_D^{20} = +17° \pm 2°$ ($c = 0.59$); IR (KBr): ν_{max} = 3380 cm^{-1}. (Found: C, 80.02; H, 12.18%. $C_{27}H_{48}O_2$ requires: C, 80.14; H, 11.96%).

1B. *Sodium borohydride reduction of (Ia) in isopropanol solution.* – A solution of 1 *g* of the *cis*-acetoxy-seco-ketone (Ia) in isopropanol (200 *ml*) was reduced with sodium borohydride (2 *g*) at room temperature for about 5 hours. The reaction mixture was worked up as described in section 1A, leaving a white solid which was chromatographed on 40 *g* of silica gel (0.20 – 0.05). Benzene eluted a complex mixture (96 *mg*) which was not further investigated. Benzene-ether (90:10 and 85:15) eluates afforded a mixture of 5-epimeric alcohols (IIa) and (IIIa) (740 *mg*), out of which, after four crystallizations from acetone, 520 *mg* (51.8%) of pure *cis*-3β,5α-dihydroxy-5,10-seco-cholest-1(10)-ene 3-acetate (IIa), m.p. 173–174°, was obtained.

Elution with ether gave a mixture of the 5-epimeric 3β,5-diols (IIb) and (IIIb) (120 *mg*), which was combined with the mother liquors of the above crystallizations and acetylated with acetic anhydride-pyridine (see 1A). The resulting mixture of diacetates (IIc) and (IIIc) was chromatographed on SiO_2 as described in section 1A, affording: 164 *mg* (14.9%) of *cis*-3β,5β-dihydroxy-5,10-seco-cholest-1(10)-ene diacetate (IIIc), m.p. 78° (from MeOH); a mixture (72 *mg*) of both 5-epimeric diacetates (IIc) and (IIIc); and 183 *mg* (16.6%) of *cis*-3β,5α-dihydroxy-5,10-seco-cholest-1(10)-ene diacetate (IIc), m.p. 86–87° (from methanol) (The total yield of 5*S* epimer II being therefore in this reduction 68.4%).

2. *Lithium aluminium hydride reduction of (Ia).* — A mixture of the *cis*-acetoxy-seco--ketone (Ia) (300 *mg*) and lithium aluminium hydride (75 *mg*) in dry ether (30 *ml*) was stirred and heated for one hour. After working up as usual, the mixture of reduction products, i.e. of the 5-epimeric diols (IIb) and (IIIb) (272 *mg*, 100%), was acetylated with acetic anhydride in pyridine solution (see 1A). The resulting mixture (326 *mg*) of the diacetates (IIc) and (IIIc) was subjected to chromatography on silica gel (0.20—0.05) as described above (section 1A), whereby the following products were separated: 52 *mg* (15.8%) of *cis*-3β,5β-dihydroxy-5,10-seco-cholest-1(10)-ene diacetate (IIIc); a mixture of both diacetates (IIc) and (IIIc); and 234 *mg* (71.8%) of *cis*-3β, 5α-dihydroxy-5, 10-seco-cholest-1(10)-ene diacetate (IIc).

Reductions of cis-3β-hydroxy-5,10-seco-cholest-1(10)-en-5-one (Ib)

3A. *Sodium borohydride reduction of (Ib) in methanol solution.* — A solution of 201 *mg* of *cis*-hydroxy-seco-ketone (Ib) (5) in methanol (100 *ml*) was treated with sodium borohydride (400 *mg*) at room temperature for 2 hours. After isolation, the mixture of reduction products was acetylated (with acetic anhydride-pyridine) and chromatographed on silica gel (see 1A) to give: 42 *mg* (17.2%) of *cis*-3β,5β-dihydroxy-5,10-seco--cholest-1(10)-ene diacetate (IIIc), m.p. 78° (from methanol); a mixture of the 5-epimeric diacetates (IIc) and (IIIc); and 163 *mg* (66.8%) of *cis*-3β,5α-dihydroxy-5,10-seco--cholest-1(10)-ene diacetate (IIc), m.p. 86° (from metanol).

3B. *Sodium borohydride reduction of (Ib) in isopropanol solution.* — The *cis*-hydroxy--seco-ketone (Ib) (201 *mg*) in isopropanol (100 *ml*) was reduced with sodium borohydride (400 *mg*) at room temperature for 5 hours, then worked up, acetylated (with acetic anhydride-pyridine) and chromatographed on SiO_2 (see 1A and 1B), affording: 39 *mg* (16%) of *cis*-3β,5β-dihydroxy-5,10-seco-cholest-1(10)-ene diacetate (IIIc), a mixture of both diacetates (IIc) and (IIIc); and 159 *mg* (65.2%) of *cis*-3β,5α-dihydroxy-5,10-seco-cholest--1(10)-ene diacetate (IIc).

Reductions of trans-3β-hydroxy-5,10-seco-cholest-1(10)-en-5-one acetate (IVa)

4A. *Sodium borohydride reduction of (IVa) in dioxan-methanol solution.* — To a stirred solution of 2 *g* of the *trans*-acetoxy-seco-ketone (IVa) (5,12) in dioxan (300 *ml*) and methanol (30 *ml*), cooled at 5°, sodium borohydride (4 *g*) was added portionwise. The mixture was stirred at 5° for a further 10 hours, and then diluted with water, acidifid with 10% sulfuric acid and extracted with ether. The ethereal layer was washed with water, saturated aqueous sodium bicarbonate, water, dried over anh. magnesium sulfate and evaporated to dryness (in vacuo), giving a mixture (about 2 *g*) which was chromatographed on 60 *g* of silica gel (0.20 – 0.05).

Elution with benzene-ether (95:5) afforded 391 *mg* (19.5%) of the starting ketone (IVa), which was recrystallized from acteone-methanol (yield 305 *mg*, i.e. 15.2%), m.p. 136° [lit. m.p. 136° (5)].

From benzene-ether (85:15) eluates 1.15 *g* (57.9%) of trans-3β,5α-*dihydroxy*-5, 10-*seco-cholest*-1(10)-*ene* 3-*acetate* (Va) was isolated, which was purified by crystallization from acetone-methanol (yield 1.06 *g*, i.e. 52.8%), m.p. 134—136°, $[\alpha]_D^{20} = -16° \pm 2°$ ($c = 0.42$); IR (KBr): $\nu_{max} = 3510, 1708, 1260\ cm^{-1}$, and IR ($CH_2Cl_2$): $\nu_{max} = 3620, 3500, 1732, 1235\ cm^{-1}$; NMR: $\delta = 0.73$ (CH_3-18, *s*), 0.85 (CH_3-26 and CH_3-27, *d*), 0.89 (CH_3-21, *d*), 1.72 (CH_3-19, *d*), 2.03 (CH_3COO at C-3, *s*), 3.94, 4.92 and 5.18 (three protons, at C-5, C-1 and C-3, multiplets). (Found: C, 77.79; H, 11.37%. $C_{29}H_{50}O_3$ requires: C, 77.97; H, 11.28%).

Elution with ether afforded 80 *mg* (4.4%) of *trans*-3β-hydroxy-5,10-seco-cholest--1(10)-en-5-one (IVb), which was purified by crystallization from methanol (yield 55 *mg*, i.e. 3.0%), m.p. 160° [lit. m.p. 158°(5)].

Methanol eluted 217 *mg* (11.4%) of trans-3β,5α-dihydroxy-5,10-seco-cholest--1(10)-ene (Vb), m.p. 153° (from methanol), $[\alpha]_D^{20} = -12° \pm 2°$ ($c = 2.0$); IR (KBr): $\nu_{max} = -3330\ cm^{-1}$. (Found: C, 76.62; H, 11.75. $C_{27}H_{48}O_2 \cdot H_2O$ requires C, 76.72; H, 11.92%).

4B. *Sodium borohydride reduction of (IVa) in isopropanol solution.* — A mixture of the *trans*-acetoxy-seco-ketone (IVa) (900 *mg*) and sodium borohydride (2 *g*) in iso-

propanol (200 *ml*) was stirred at room temperature for 42 hours. It was worked up and chromatographed on SiO_2 as described above (see 4A), affording: 68 *mg* (7.6%) of starting ketone (IVa); 257 *mg* (28.4%) of *trans*-3β,5α-dihydroxy-5,10-seco-cholest-1(10)-ene 3-acetate (Va); and 430 *mg* (52.2%) of *trans*-3β,5α-dihydroxy-5,10-seco-cholest-1(10)-ene (Vb).

5. *Lithium aluminium hydride reduction of (IVa).* — The *trans*-acetoxy-seco-ketone (IVa) (300 *mg*) was reduced with lithium aluminium hydride (75 *mg*) in dry ether (30 *ml*), whereby the mixture was stirred and heated to reflux for one hour. After working up as usual, a nearly quantitative yield (280 *mg*) of crude *trans*-3β,5α-dihydroxy-5,10-seco-cholest-1(10)-ene (Vb) was obtained, which was purified by crystallization from methanol (yield 256 *mg*, i.e. 93.8%), m.p. 153°.

Acetylation of trans-3β,5α-dihydroxy-5,10-seco-cholest-1(10)-ene (Vb). — Acetylation of the *trans*-diol (Vb) (250 *mg*) with acetic anhydride in pyridine at room temperature gave 278 *mg* (92.0%) of trans-3β,5α-*dihydroxy*-5,10-*seco-cholest*-1(10)-*ene diacetate* (Vc), m.p. 95—96° (from acetone-methanol), $[\alpha]_D^{25} = -18° \pm 2°$ ($c=2$); IR (KBr): $\nu_{max} = 1755, 1732, 1255\ cm^{-1}$; NMR: $\delta = 0.78$ (CH_3-18, *s*), 0.85 (CH_3-26 and CH_3-27, *d*), 0.89 (CH_3-21, *d*), 1.76 (CH_3-19, *d*), 1.99 and 2.02 (two CH_3COO, at C-3 and C-5, singlets), 5.10 and 5.40 (three protons, at C-3, C-5 and C-1, multiplets). (Found: C, 76.05; H, 10.55%. $C_{31}H_{52}O_4$ requires: C, 76.18; H, 10.72%).

Reductions of trans-3β-hydroxy-5,10-seco-cholest-1(10)-en-5-one (IVb)

6A. *Sodium borohydride reduction of (IVb) in methanol solution.* — A solution of 201 *mg* of the *trans*-hydroxy-seco-ketone (IVb) (5) in methanol (100 *ml*) was treated with sodium borohydride (400 *mg*) at room temperature for 15 hours. After working up as usual (see 1A), a quantitative yield (200 *mg*) of *trans*-3β,5α-dihydroxy-5,10-seco-cholest-1(10)-ene (Vb) was obtained, which was purified by crystallization from methanol (yield 184 *mg*, i.e. 91.1%), m.p. 153°.

6B. *Sodium borohydride reduction of (IVb) in isopropanol solution.* — The *trans*-hydroxy-seco-ketone (IVb) (201 *mg*) in isopropanol (100 *ml*) was reduced with sodium borohydride (400 *mg*) at room temperature (36 hours), affording 176 *mg* (87.1%) of *trans*-3β,5α-dihydroxy-5,10-seco-cholest-1(10)-ene (Vb), m.p. 153° (from methanol).

Isomerization of cis-3β,5α-dihydroxy-5,10-seco-cholest-1(10)-ene diacetate (IIc) into the corresponding trans-isomer (Vc)

A solution of the *cis*-3β,5α-diacetate (IIc) (200 *mg*) in 200 *ml* of anh. benzene was irradiated with a high pressure mercury lamp *Q* 81 (Hanau) for 14 hours at room temperature. The solvent was removed in vacuo and the residue chromatographed on silica gel (0.20 – 0.05). Elution with benzene gave 16 *mg* (8%) of *trans*-3β,5α-dihydroxy-5,10-seco-cholest-1(10)-ene diacetate (Vc), which was identified by m.p. and mixed m.p. determination and by comparison of spectral data (with an authentic sample; see above). By elution with benzene-ether (98:2) 123 *mg* (61.5%) of unchanged starting *cis*-3β,5α-diacetate (IIc), m.p. 85°, was recovered.

Chromic acid oxidations

Oxidation of cis-3β,5α-dihydroxy-5,10-seco-cholest-1(10)-ene 3-acetate (IIa). — To a solution of the *cis*-acetoxy-seco-5α-alcohol (IIa) (100 *mg*) in ether (10 *ml*), chromic anhydride (500 *mg*) in water (10 *ml*) was added at room temperature and the resulting mixture was stirred efficiently for 24 hours, affording after chromatography on SiO_2: 92 *mg* (92.4%) of *cis*-3β-hydroxy-5,10-seco-cholest-1(10)-en-5-one acetate (Ia), and 6 *mg* (6%) of unchanged starting alcohol (IIa).

Oxidation of trans-3β,5α-dihydroxy-5,10-seco-cholest-1(10)-ene 3-acetate (Va). — When treated with CrO_3 for two hours (as above), the *trans*-acetoxy-seco-5α-alcohol (Va) (100 *mg*) was converted quantitatively to the corresponding ketone, i.e. *trans*-3β-hydroxy-5,10-seco-cholest-1(10)-en-5-one acetate (IVa).

Kinetic studies of the sodium borohydride reductions of the 3β-hydroxy-seco-5-ketones of the $\Delta^{1(10)}$-cis series (Ib) and $\Delta^{1(10)}$-trans series (IVb)

Material. — Sodium borohydride was recrystallized from diglyme (15). Isopropanol was dried over calcium sulfate and distilled through a fractionating column.

Rate measurements (6). — A standardized 0,005 *M* solution of sodium borohydride in isopropanol (100 *ml*) was placed in a reaction flask with a long narrow neck, which was immersed in a thermostat maintained at 35° ± 0.2.° The ketone (Ib and IVb) (804 *mg*, 0.002 mole) was added to the borohydride solution with vigorous stirring. At appropriate time intervals 10 *ml* aliquots of the reaction mixture were withdrawn, added to a 0.1202 *N* potassium iodate solution (25 *ml*) containing 2 *g* of potassium iodide, followed by the addition of 10 *ml* of 5 *N* sulfuric acid, and the libreated iodine was titrated with 0.1 *N* aqueous sodium thiosulfate (10). The rate constants k_2 were obtained from the rate data by using the following equation:

$$k_2 = \frac{2.303}{t(a-4b)} \log \frac{b\,(a-2x)}{a\,(b-x)}$$

where a is the initial molar concentration of ketone (Ib or IVb), b is the initial molar concentration of sodium borohydride, and x is the amount of sodium borohydride consumed at time t. The results are shown in Table I.

SUMMARY

The sodium borohydride and lithium aluminium hydride reductions of *cis*- and *trans*-3β-hydroxy-5,10-seco-1(10)-cholesten-5-one and their acetates have been studied. It was found that the *cis*-unsaturated ketones with both reducing agents afford a mixture of 5-epimeric alcohols in an approximate ratio of 5*S*:5*R*=4:1, whereas the reductions of the *trans*-isomeric ketones are more stereospecific, resulting in almost exclusive formation of the corresponding *trans*-unsaturated 5*S*-alcohols. According to kinetic measurements of the sodium borohydride reductions, *cis*-3β-hydroxy-5,10-seco-1(10)-cholesten-5-one is reduced about 10 times faster than *trans*-3β-hydroxy-5,10-seco-1(10)-cholesten-5-one. Possible conformations of the *cis*- and *trans*-1(10)-cyclodecen-5-one ring system in the 5,10-seco-steroids used as substrates are discussed, which might account for the stereochemical course and kinetics of these reductions.

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ИЗВОД

РЕДУКЦИЈА *CIS*- И *TRANS*-3β-ХИДРОКСИ-5,10-СЕКО-1(10)-ХОЛЕСТЕН-5-ОНА И ЊИХОВИХ 3-АЦЕТАТА ПОМОЋУ КОМПЛЕКСНИХ МЕТАЛНИХ ХИДРИДА

ОД

МИХАИЛА Љ. МИХАИЛОВИЋА, МИРОСЛАВА Ј. ГАШИЋА, ИВАНА ЈУРАНИЋА И ЉУБИНКЕ ЛОРЕНЦ

Проучаване су редукције *cis*- и *trans*-3β-хидрокси-5,10-секо-1(10)-холестен-5-она и њихових 3-ацетата (I односно IV) помоћу натријум-

-борхидрида и литијум-алуминијум-хидрида. При томе је нађено да *cis*-незасићени кетони (I) дају са оба редукциона средства смесу 5-епимерних алкохола (II и III) у приближно истом односу од $5S:5R=4:1$, а да су код *trans*-изомерних кетона (IV) обе редукције стереоспецифичније, тј. да се углавном добивају одговарајући *trans*-незасићени 5*S*-акохоли (V). На основу кинетичких мерења натријум-борхидридних редукција, утврђено је да *cis*-3β-хидрокси-5,10-секо-1(10)-холестен-5-он (Ib) реагује око 10 пута брже од диастереомерног *trans*-секо-кетона (IVb). Предложене су конформације *cis*- и *trans*-1(10)-циклодецен-5-онског прстенастог система у проучаваним 5,10-секо-стероидним кетонима (схеме 1 и 2), које су у сагласности са стереохемијским током и кинетичким резултатима ових редукција.

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