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REDUCTIONS OF STEROIDAL HALOHYDRINS AND THEIR ESTERS BY TRI-n.BUTYLTIN HYDRIDE; SOME STEREOSPECIFIC 1,2-MIGRATIONS OF ACETOXY- OR BENZOXY-GROUPS

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Abstract - Six 5α-chloro- and one 5α-bromo-cholestane derivatives bearing hydroxy-, acetoxy- or benzoxy-groups in the 3β and 4β or 3β and 6β positions, 1, 3, 5, 6, 8, 10 and 12 have been hydrogenolysed with the title reagent to afford the corresponding reduced derivatives. The reduction of 4α-chloro-5β-cholestane-3β,5-diol 3-benzoate (14) and 3α-chloro-5α-cholestan-2β-ol acetate gave also the products of simple hydrogenolysis.

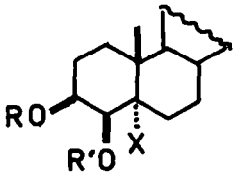
However, four examples of a stereospecific 1.2-migration of an acetoxy- or benzoxy-group from a tertiary to a secondary carbon have been found during the hydrogenolysis of 6β-chloro-(or 6β-bromo)-5α-cholestane-3β,5-diol diacetates 18, 19, 4β-bromo-5α-cholestane-3β,5-diol diacetate 22 and 4α-chloro-5β-cholestane-3β,5-diol 5-monobenzoate 24.

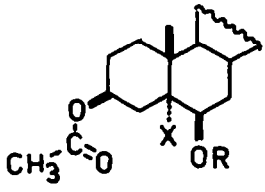
Radical chemistry has recently received much attention, it's growing importance in the synthesis of various products is documented in several reviews and papers [1]. Radical generation from alkyl halides with tri-n.butyltin hydride has long been recognized to be an efficient process [2]. In the outset of our work, very few examples of reduction of vicinal halohydrins and their esters by that means were known [3]. In a previous communication [4], we reported the reduction of steroidal halohydrins and their esters with four examples of a stereospecific 1.2-migration of an acyloxy-group from a tertiary to a secondary carbon. Since then, the properties of the radicals generated by halogen abstraction from various halohydrin-esters have been studied [5,6,7,8]. Now, we report the details of our preliminary communication.

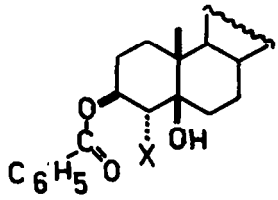
First, three simple diaxial chlorhydrins 1, 6 and 10 in the cholestane series were treated with a slight excess of tri-n.butyltin hydride in refluxing benzene with a catalytic amount of azo-bisisobutyronitrile. The compounds 6 and 10 were smoothly converted into the corresponding reduced products 7 and 11. However 1 gave, after two hrs reflux, the expected equatorial mono-acetate 2 with a small amount of the axial mono-acetate 4 which was formed probably through a thermal equilibration.

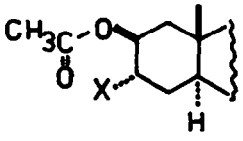
When treated in the same conditions, the four halohydrin-esters 3, 5, 8 and 12 gave the corresponding esters 4 (with a small amount of the equilibrated ester 2), 4, 9 and 13 respectively. As the halogen atom of the preceding halohydrin-esters was bound to a tertiary carbon, we also examined the reduction of some available secondary halogen derivatives.

4α-chloro-5β-cholestane-3β,5-diol 3-mono-benzoate 14 [9b] and 3α-chloro-5α-cholestan-2β-ol acetate 16 afforded the products of simple hydrogenolysis 15 and 17 respectively.









	R	R'	X
1	CH_3CO	H	Cl
2	CH_3CO	H	H
3	H	CH_3CO	Cl
4	H	CH_3CO	H
5	H	CH_3CO	Br
6	C_6H_5CO	H	Cl
7	C_6H_5CO	H	H
8	H	C_6H_5CO	Cl
9	H	C_6H_5CO	H

	X	R
10	Cl	H
11	H	H
12	Cl	$COCH_3$
13	H	$COCH_3$

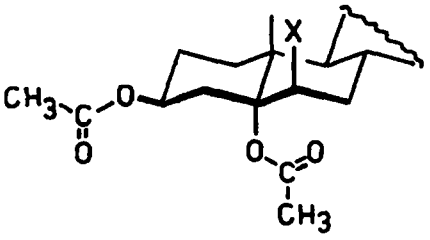
14 X = Cl
15 X = H

16 X = Cl
17 X = H

Table. Reduction of halohydrins and their esters with tri-n.butyltin hydride

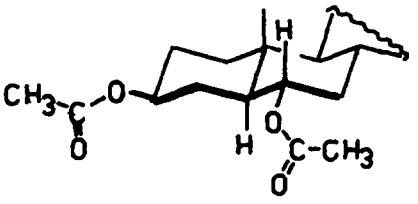
Substrate	Conditions (time of refluxing)	(Yields of isolated) products
1 [9b]	2 hrs	2 (54 %); 4 (10 %)
3 [9b]	5 hrs	4 (41 %); 2 (15 %)
5 [9b,c]	30 min	4 (54 %)
6 [9b]	1 hr	7 (78 %)
8 [9b]	2 hrs	9 (69 %)
10 [10]	6 hrs	11 (87 %)
12 [11]	6 hrs	13 (82 %)
14 [9b]	1 hr	15 (68 %)
16 [12]	30 min	17 (51 %)
18 [13]	1 hr	20 (63 %)
19 [14]	75 min	20 (59 %)
22	1 hr	23 (57 %)
24 [9b]	90 min	9 (63 %)

However, the reduction of 6β-chloro- or 6β-bromo-5α-cholestane-3β,5-diol diacetate 18 or 19 gave a single product which turned out to be the 3β,6α-diacetoxy-derivative 20 instead of the expected 5α-cholestane-3β,5-diol diacetate:



18 X = Cl
19 X = Br

$n.(C_4H_9)_3SnH$ →



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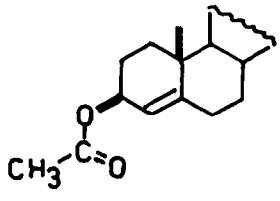
Treatment of 4-cholesten-3β-ol acetate 21 with N-bromoacetamide in glacial acetic acid containing anhydrous sodium acetate was reported to give two products to which the structures of 4α-bromo-5β-cholestane-3β,5-diol 3-acetate (25 %) and 4α-bromo-5β-cholestane-3β,5-diol diacetate (14 %) were assigned [15]. In our laboratory, the same reaction gave also two products (33 % and 8 %) with the same m.p. as reported [15]; however their structures must be revised, as 5 and 22. The halohydrin monoacetate was found to be identical with a previously obtained sample of 5 [9b] and the new 4β-bromo-diacetate 22 was well characterized by a doublet at δ 5.35 ppm (J = 4 Hz), the $C^{4\alpha}$-H being deshielded by the 5α-acetoxy group [16]. The structure of the 4β-bromo-diacetate 22 was ascertained through a mild alkaline hydrolysis into the 5-mono-acetate then a conversion of this cis-bromhydrin by hot methanolic potassium hydroxide into 4-cholesten-3-one.



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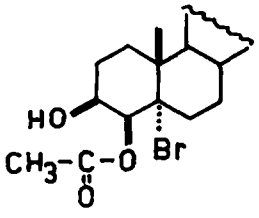

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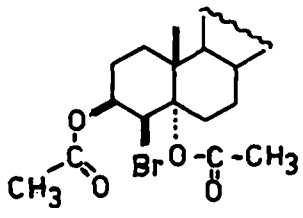

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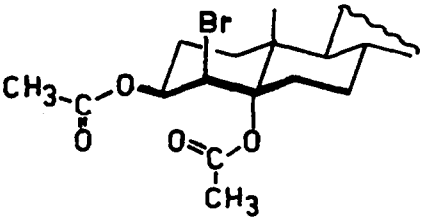
The reduction of 4β-bromo-5α-cholestane-3β,5-diol diacetate 22 with tri-n.butyltin hydride gave a single product which was found to be the 3α,4α-diacetoxy derivative 23; here also an 1.2-migration of the acetoxy group has occurred:



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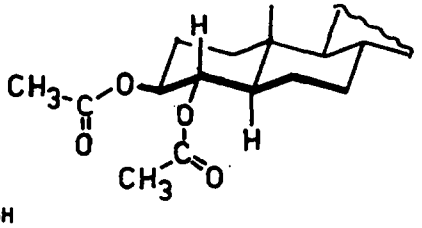
$n.(C_4H_9)_3SnH$ →



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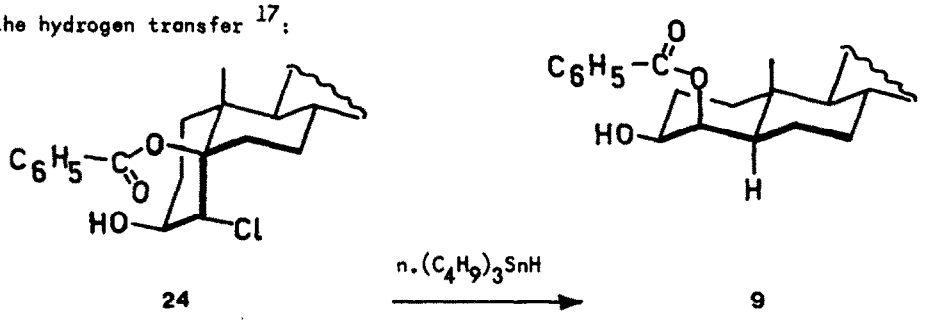
In a previous study, the treatment of 4-cholesten-3β-ol benzoate with hypochlorous acid afforded six products, one of which was the 4α-chloro-5β-cholestane-3β,5-diol 5-mono-benzoate 24, whose structure was determined by ^1H NMR spectroscopy and by chemical transformations [9b]. Treatment of this chlorhydrin-benzoate 24 with tri-n.butyltin hydride gave a

single product which was found to be identical with a sample of 5α-cholestane-3β,4β-diol 4-mono-benzoate 9. Thus the reduction of the chloro-compound 24 has occurred with a stereospecific 1.2-migration of the benzoxy-group and with an inversion at the C^5 carbon atom during the hydrogen transfer [17]:



24 9

The rearrangement of α-acyloxy radicals generated by various means is not unprecedented [18] and the mechanism has been discussed [8,19]. Our results show that this 1.2-migration of acyloxy groups has some stereospecific requirements and that caution must be taken for assigning structures to the hydrogenolysis products of halohydrin-esters.

EXPERIMENTAL

Melting points are uncorrected. The purity of the described products has been checked by thin layer chromatography (T.L.C.)(silica gel GF254 Merck); a solution of sulfuric acid and anisaldehyde in ethanol was used as spraying agent and the spots were visualised by heating to 110°C.

The I.R. spectra were recorded in KBr disks; the ^{1}H NMR spectra were recorded on a Varian 60 MC spectrometer; the width at half height (Wh/2) and the coupling constants (J) are given in Hz.

The starting halohydrins and their esters are known products and the corresponding references are given in the table. The halohydrin-diacetates 18 and 19 were prepared following a described procedure [20].

Preparation of 4β-bromo-5α-cholestane-3β,5-diol diacetate 22

The reaction of 4-cholesten-3β-yl acetate with N-bromoacetamide in glacial acetic acid containing anhydrous sodium acetate was conducted as reported [15]. Crystallisation of the crude product from ether:petroleum ether afforded 33% of 5-bromo-5α-cholestane-3β,4β-diol 4-monoacetate 5 mp_{dec} = 158-9°C (literature: mp = 148°C [9b]; 156-7°C [9c]). The filtrate was evaporated to dryness and adsorbed on preparative silica gel thin layers; after elution with cyclohexane : ethyl acetate (8:2), a fraction crystallised from acetone:methanol to give pure 4β-bromo-5α-cholestane-3β,5-diol diacetate 22 (8 %), mp = 167-8°C; IR = 1759, 1732, 1235, 1206, 1190, 1046 and 748 cm^{-1}; δ ^{1}H NMR ($CDCl_3$): 0.67 (s, $C^{18}H_3$); 1.34 (s, $C^{19}H_3$); 2.06 and 2.10 (2 s, 2 CH_3CO); 4.71-5.15 (m, Wh/2 = 20 Hz, C^3-H); 5.35 (d fine structure, J = 4 Hz, C^4-H).

Formation of 4-cholesten-3-one from bromo-diacetate 22

A solution of 4β-bromo-5α-cholestane-3β,5-diol diacetate (100 mg) in methanol (5 ml) and light petroleum (5 ml) was treated with 2 % methanolic potassium hydroxide (5 ml) and the two-phase solution was stirred at room temperature for 10 min. After several washings with water, the organic extract was dried (Na_2SO_4) and evaporated. The residue crystallised from acetone to afford 4β-bromo-5α-cholestane-3β,5-diol 5-monoacetate (65 mg) mp = 165°C; δ ^{1}H NMR ($CDCl_3$) : 0.68 (s, $C^{18}H_3$); 1.32 (s, $C^{19}H_3$); 2.08 (s, CH_3CO); 3.36-4.05 (m, Wh/2 = 22 Hz, C^3-H); 5.38 (d, J = 4 Hz, C^4-H).

Treatment of this 5-monoacetate (25 mg) with refluxing 2 % methanolic potassium hydroxide for 90 min afforded after the usual work up with ether, a crude product which was chromatographed on a silica gel thin layer (cyclohexane : ethyl acetate, 7:3). A crystalline fraction (9 mg) was found to be 4-cholesten-3-one (mp, mixed mp, TLC, IR and UV).

General procedure for the reductions with tri-n.butyltin hydride

To a solution of halogeno-compound (0.5 mmol) in anhydrous benzene (10 ml) tri-n.butyltin hydride (0.6 mmol) and a very small amount of azo-bisisobutyronitrile were added. The mixture was heated at reflux during the time indicated in the table. After evaporation of the solvent under reduced pressure, the crude material was worked up as follows :

- the reduction of 5-chloro-5α-cholestane-3β,4β-diol 3-monoacetate 1 gave two products which were separated by preparative thin layer chromatography (cyclohexane:ethyl acetate, 8:2): 5α-cholestane-3β,4β-diol 3-monoacetate 2 (the least polar) had mp = 194-196°C (acetone) (literature [21]: mp = 197-9°C); IR : 3612, 3482, 1730, 1719 and 1272 cm^{-1}; δ ^1H NMR ($CDCl_3$): 0.65 (s, $C^{18}H_3$); 1.05 (s, $C^{19}H_3$); 2.08 (s, CH_3CO); 3.72-3.91 (m, Wh/2 = 7 Hz, C^4-H); 4.50-4.94 (m, Wh/2 = 21 Hz, C^3-H); and 5α-cholestane-3β,4β-diol 4-monoacetate 4 identical (TLC, IR) with a sample obtained through reduction of 5-chloro-5α-cholestane-3β,4β-diol 4-monoacetate.
- the reduction of 5-chloro-5α-cholestane-3β,4β-diol 4-monoacetate 3 gave after preparative thin layer chromatography the 5α-cholestane-3β,4β-diol 4-monoacetate 4 (polar fraction) as a major product, mp = 159-161°C (acetone) (literature [21]: mp = 163-4°C); IR : 3450, 3410 (sh), 1738, 1721, 1258 and 1238 cm^{-1}; δ ^1H NMR ($CDCl_3$): 0.65 (s, $C^{18}H_3$); 0.99 (s, $C^{19}H_3$); 2.10 (s, CH_3CO); 3.50-3.90 (m, Wh/2 = 20 Hz, C^3-H); 5.02-5.17 (m, Wh/2 = 7 Hz, C^4-H); and 5α-cholestane-3β,4β-diol 3-monoacetate 2, mp = 183-4°C, identical (TLC and IR) with the sample obtained above.
- the reduction of 5-bromo-5α-cholestane-3β,4β-diol 4-monoacetate 5 gave after two crystallisations from acetone and chromatography of the mother liquors, the 5α-cholestane-3β,4β-diol 4-monoacetate mp = 157-158°C identical (mixed mp, TLC and IR) with the sample obtained above.
- the reduction of 5-chloro-5α-cholestane-3β,4β-diol 3-monobenzoate 6 gave after crystallisation from methylene chloride the 5α-cholestane-3β,4β-diol 3-monobenzoate 7, mp = 239-240°C (literature : mp = 250-251°C [25]; 242-246°C [26]); IR : 3530, 3490 (sh); 1719, 1695, 1601, 1585, 1284 and 711 cm^{-1}; δ ^1H NMR ($CDCl_3$): 0.66 (s, $C^{18}H_3$); 1.10 (s, $C^{19}H_3$); 3.88-4.06 (m, Wh/2 = 8 Hz, C^4-H); 4.72-5.24 (m, Wh/2 = 25 Hz, C^3-H); 7.42-7.63 and 7.93-8.28 (2 m, 5H); $C_{34}H_{52}O_3$.
- the reduction of 5-chloro-5α-cholestane-3β,4β-diol 4-monobenzoate 8 gave after crystallisation from acetone the 5α-cholestane-3β,4β-diol 4-monobenzoate 9, mp = 167-9°C; IR : 3455, 3415 (sh); 1718, 1691, 1602, 1582, 1281, 1272 and 705 cm^{-1}; δ ^1H NMR ($CDCl_3$): 0.65 (s, $C^{18}H_3$); 1.16 (s, $C^{19}H_3$); 3.58-4.03 (m, Wh/2 = 21 Hz, C^3-H); 5.26-5.45 (m, Wh/2 = 7 Hz, C^4-H); 7.40-7.65 and 7.99-8.20 (2 m, 5H); $C_{34}H_{52}O_3$.
- the 5-chloro-5α-cholestane-3β,6β-diol 3-monoacetate 10 was reduced to 5α-cholestane-3β,6β-diol 3-monoacetate 11, mp = 158°C (acetone:methanol), (literature [21]: mp = 144°C); IR : 3555, 3460 (sh), 1720, 1259, 1246 and 1022 cm^{-1}; δ ^1H NMR ($CDCl_3$): 0.69 (s, $C^{18}H_3$); 1.05 (s, $C^{19}H_3$); 2.05 (s, CH_3CO); 3.80 (narrow m, C^6-H); 4.75 (large m, C^3-H). This monoacetate gave after acetylation the corresponding 3β,6β-diacetate identical (mp, mixed mp, TLC and IR) with a sample obtained below.
- the reduction of 5-chloro-5α-cholestane-3β,6β-diol diacetate 12 gave 5α-cholestane-3β,6β-diol diacetate 13, mp = 138-139°C (methanol), (literature [21]: mp = 139°C).
- 4α-chloro-5β-cholestane-3β,5-diol 3-monobenzoate 14 was reduced to 5β-cholestane-3β,5-diol 3-monobenzoate 15 which was isolated through crystallisation, mp = 140-143°C (acetone); $[\alpha]_D$ +55°C (c = 1.00); IR : 3530, 3468, 1730, 1716, 1606, 1588, 1278, 1266 and 699 cm^{-1}; δ ^1H NMR ($CDCl_3$): 0.67 (s, $C^{18}H_3$); 1.01 (s, $C^{19}H_3$); 2.29 (d fine structure, J = 3.5 Hz, C^4-H); 2.57 (d fine structure, J = 3.5 Hz, C^4-H); 5.35-5.59 (m, Wh/2 = 8 Hz, C^3-H); 7.39-7.64 and 7.90-8.14 (2 m, 5H); $C_{34}H_{52}O_3$. This monobenzoate 15 was identical (mp, mixed

mp, IR and ^{1}H NMR) with a sample prepared through benzoylation of 5β-cholestane-3β,5-diol [21].

- 3α-chloro-5α-cholestan-2β-ol acetate 16 was reduced into 5α-cholestan-2β-ol acetate 17 which was isolated through direct crystallisation and chromatography of the mother liquors, mp = 73-6°C (literature [22]: mp=78°C); IR : 1738, 1239 and 1018 cm^{-1}; δ ^{1}H NMR ($CDCl_3$): 0.65 (s, $C^{18}H_3$); 0.92 (s, $C^{19}H_3$); 2.02 (s, CH_3CO); 4.96 - 5.20 (m, Wh/2 = 8 Hz, C^2-H).
- the reduction of 6β-chloro-5α-cholestane-3β,5α-diol diacetate 18 afforded after crystallisation and chromatography of the mother liquors, 5α-cholestane-3β,6α-diol diacetate 20 with mp, mixed mp, IR and ^{1}H NMR identical with those of the sample obtained below.
- 6β-bromo-5α-cholestane-3β,5-diol diacetate 19 was reduced to a crude product which was purified by crystallisation (methanol) and chromatography of the mother liquors to afford a single product: 5α-cholestane-3β,6α-diol diacetate 20, mp 105-106°C (literature [23]: mp = 106-107°C); IR : 1737, 1729, 1245 and 1034 cm^{-1}; δ ^{1}H NMR (C_6D_6): 0.58 (s, $C^{18}H_3$); 0.98 (s,$C^{19}H_3$); 1.72 and 1.75 (2 s, 2 CH_3CO); 4.53-5.20 (m, Wh/2 = 20 Hz, C^3-H and C^6-H).
- the reduction of 4β-bromo-5α-cholestane-3β,5-diol diacetate 22 afforded after crystallisation from acetone:methanol 5α-cholestane-3β,4α-diol diacetate 23, mp = 160-161°C; IR : 1741, 1248, 1228, 1060 and 1040 cm^{-1}; δ ^{1}H NMR ($CDCl_3$): 0.66 (s, $C^{18}H_3$); 0.91 (s, $C^{19}H_3$); 2.00 and 2.02 (2 S, 2 CH_3CO); 4.40-5.33 (m, Wh/2 = 42 Hz, C^3-H), 4.64-5.05 (m, Wh/2 = 20 Hz, C^4-H; this compound was found to be identical (mixed mp, IR and ^{1}H NMR) with an authentic sample [24,23b].
- 4α-chloro-5β-cholestane-3β,5-diol 5-monobenzoate 24 was reduced to give a product which crystallised from acetone, mp = 160-163°C which was found to be identical (TLC, IR and ^{1}H NMR) with the sample of 5α-cholestane-3β,4β-diol 4-monobenzoate 9 obtained above.

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