REDUCTIVE DEBROMINATION OF DIBROMO STEROIDS*

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A number of vicinal dibromides of cholestane and androstane series afford the corresponding olefins when treated with silver salts in the presence of amines. Under these conditions diaxial bromohydrins yield epoxides. The preparative utilisability of this reaction is discussed in comparison with other methods.

Recently we reported on the reaction of vicinal dibromides with silver fluoride in the presence of water which leads to epoxides, hydroxy derivatives and fluoro bromides at room temperature[1]. In attempts to suppress the formation of by-products, silver perchlorate was used instead of fluoride and excess triethylamine was added to buffer the perchloric acid released during the reaction. This modification, hovewer, altered the course of the reaction considerably: thus 1α,2β-dibromo-5α-cholestane (*II*) was converted into 5α-cholest-1-ene (*III*) in 95% yield while epoxide *I* was not detected in the mixture. Similar transformations of vicinal dibromides have been accomplished by means of a variety of reagents (*e.g.* complex metal hydrides[2-5], metals[6-10], organometallics[11,12], salts of some metals[13-16], organic radicals[17], acetic and oxalic acid[18,19], alkoxides[20], sulfoxides[21], amines[22,23], trialkylphosphites[24], halides[25-27] and others[28-31]). The reaction could also be made by electrochemical methods[32,33]. In order to find out the scope and limitations of this reductive elimination we treated several dibromosteroids with silver salts in the presence of triethylamine (Table I). We found that in contrast to the treatment with metals, bromohydrins were not reduced to olefins but converted to epoxides. With the exception of fluoro bromides (*cf.* the treatment with lithium aluminum hydride[2]) olefins were produced from vicinal dihalides only. Qualitative comparison of dehalogenation rates in particular substrates shows the same trends as the rates of the nucleophilic substitution of these substrates[1]: the rates of secondary-tertiary dibromides are higher than those of disecondary dibromides (see Table I, entries *5*, *8* and the rest) the rates of diaxial dibromides (entries *2*, *8*) are higher than those of the diequatorial** ones (entries *3*, *31*) and the rates of bromo derivatives

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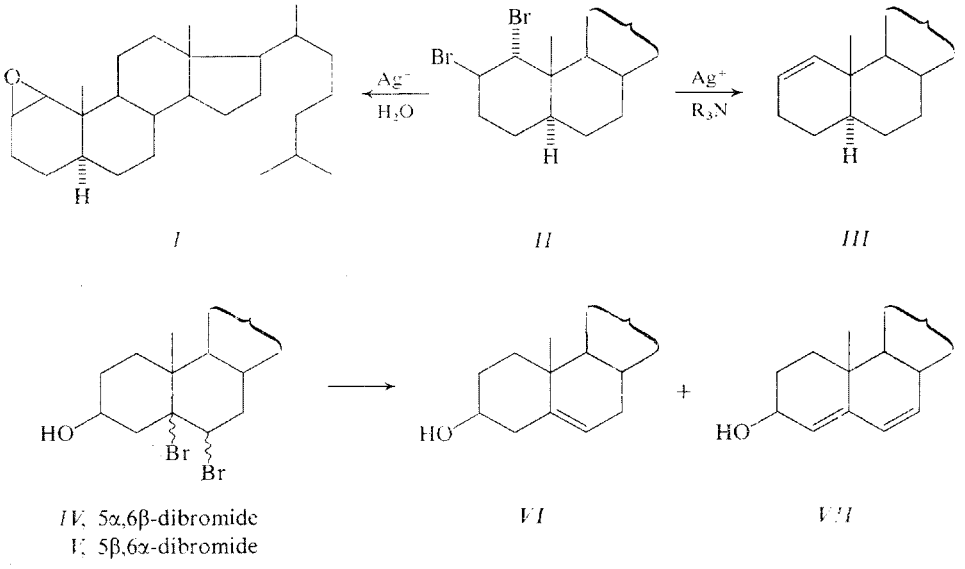
** *erythro*-3,4-Dibromononane gives rise to pure *trans*-3-nonene under the conditions used which brings further evidence that the reaction belongs among *anti*-elimination reactions[35].

TABLE I

Preparation of Olefins from Dihalo Steroids[1]

Entry	Starting compound	Reagent	Reaction time h	Yield, %
1	1α,2β-dibromo-5α-cholestane	$AgNO_3 + (C_2H_5)_3N$	96	95
2	2β,3α-dibromo-5α-cholestane[a]	$AgNO_3 + (C_2H_5)_3N$	120	31
3	2α,3β-dibromo-5α-cholestane[b]	$AgNO_3 + (C_2H_5)_3N$	120	3·4
4	3α,4β-dibromo-5α-cholestane[c]	$AgNO_3 + (C_2H_5)_3N$	2 800	traces
5	4β,5-dibromo-5α-cholestane	$AgClO_4 + (C_2H_5)_3N$	0·5	96
6	2β-bromo-5α-cholestan-3α-ol[d,e]	Ag^o	1·5	0
7	2β-bromo-5α-cholestan-3α-ol[e]	$AgNO_3 + (C_2H_5)_3N$	1·5	0
8	5,6β-dibromo-5α-cholestan-3β-ol	$AgNO_3 + (C_2H_5)_3N$	0·5	95
9	5,6β-dibromo-5α-cholestan-3β-ol	$AgClO_4 + (C_2H_5)_3N$	0·5	94
10	5,6β-dibromo-5α-cholestan-3β-ol[f]	$AgOCOCH_3 + (C_2H_5)_3N$	0·5	95
11	5,6β-dibromo-5α-cholestan-3β-ol[g]	$AgBF_4 + (C_2H_5)_3N$	0·5	74
12	5,6β-dibromo-5α-cholestan-3β-ol[h]	$AgNO_3 + (C_2H_5)_2)NH$	14	66
13	5,6β-dibromo-5α-cholestan-3β-ol[i]	$AgNO_3 + C_6H_{11}NH_2$	20	70
14	5,6β-dibromo-5α-cholestan-3β-ol[j]	$AgNO_3 + NH_4OH$	96	28
15	5,6β-dibromo-5α-cholestan-3β-ol[k]	$AgNO_3$ + pyridine	70	less than 2%
16	5,6β-dibromo-5α-cholestan-3β-ol[l]	$AgNO_3$ + aniline	15	32
17	5,6β-dibromo-5α-cholestan-3β-ol[m]	Ag^o	2	95
18	5,6β-dibromo-5α-cholestan-3β-ol[n]	$(C_2H_5)_3N$	69	6
19	5,6β-dibromo-5α-cholestan-3β-ol[o]	$Ag_2O + (C_2H_5)_3N$	20	96
20	5,6β-dibromo-5α-cholestan-3β-ol	$Cu_2Cl_2 + (C_2H_5)_3N$	0·5	22
21	5,6β-dibromo-5α-cholestan-3β-ol	$Cu_2Cl_2 + (C_2H_5)_3N$	17	43
22	5,6β-dibromo-5α-cholestan-3β-ol	$CuCl_2 + (C_2H_5)_3N$	0·5	25
23	5,6β-dibromo-5α-cholestan-3β-ol[p]	$CuCl_2 + (C_2H_5)_3N$	22	86
24	5,6β-dibromo-5α-cholestan-3β-ol[p,w]	$HgCl + (C_2H_5)_3N$	17	77
25	5,6βdibromo-5α-cholestan-3β-ol[p]	$HgBr_2 + (C_2H_5)_3N$	3	99
26	5,6β-dibromo-5α-cholestan-3β-ol[h]	$ZnCl_2 + (C_2H_5)_3N$	72	70
27	5,6β-dibromo-5α-cholestan-3β-ol[h,r]	$KNO_3 + (C_2H_5)_3N$	72	70
28	5-fluoro-6β-bromo-5α-cholestan-3β-ol[40]	$AgNO_3 + (C_2H_5)_3N$	20	0
29	5-bromo-6β-fluoro-5α-cholestan-3β-ol[40,s]	$AgNO_3 + (C_2H_5)_3N$	96	0
30	5-bromo-6β-chloro-5α-cholestan-3β-ol	$AgClO_4 + (C_2H_5)_3N$	24	52
31	5,6α-dibromo-5β-cholestan-3β-ol[t]	$AgNO_3 + (C_2H_5)_3N$	18	43
32	6β,7α-dibromo-5α-cholestane[u]	$AgNO_3 + (C_2H_5)_3N$	70	10
33	16β,17α-dibromo-5α-androstane[v]	$AgNO_3 + (C_2H_5)_3N$	72	0

[a] 62% of the starting material was isolated; [b] 94% of the starting material was regenerated; [c] besides 90% of the starting compound, 0·6 mg of a product, identical in polarity with authentic 5α-cholest-3-ene, was isolated. On oxidation with 3-chloroperbenzoic acid, this compound yielded the same mixture of 3,4-epoxides as authentic 5α-cholest-3-ene; [d] the reaction was carried out with a suspension of porous silver in tetrahydrofuran under stirring. The reagent was prepared by reduction of an aqueous solution of silver nitrate with sodium borohydride; [e] all starting compound



Explanation to Table I

was converted into 2α,3α-oxido-5α-cholestane; [f] because of the low solubility of silver acetate in acetonitrile the reaction was performed under shaking; [g] the reaction was carried out in the absence of acetonitrile. The yield was lower than usual presumably because of difficulties in the isolation of the product (acetylation of the mixture was necessary in order to get rid of the ballast with similar polarity as cholesterol); [h] all the starting material was consumed; [i] because of difficulties in chromatographic separation the product was isolated after acetylation; [j] the reaction rate was reduced apparently by the insolubility of the complex; [k] all the starting dibromide was transformed to give a complex mixture of products; [l] 3β-hydroxy-4,6-cholestadiene (4%, λ_{max} 239 nm) and 5,6α-dibromo-5β-cholestan-3β-ol (18%) were isolated; [m] the reaction with porous silver was carried out under stirring in tetrahydrofuran; [n] 68% of the starting compound were recovered (see Experimental); [o] after two-hours' shaking the mixture was allowed to stand for 18 hours (see Experimental); [p] all the starting material was consumed. In the absence of amines a complex mixture of products was formed which contained no detectable amount of cholesterol; [r] m.p. of the raw cholesterol fraction from chromatography was 141—146°C, UV spectrum indicated contaminatiom with 3β-hydroxy-4,6-cholestadiene (3·8%); [s] the starting compound (50%) was recovered in addition to 6β-fluoro-5α-cholestane-3β,5-diol (45%, mass spectrum and IR spectrum proved identity with the authentic sample[41]); [t] all the starting compound was consumed, cholesterol was accompanied by other components; [u] 89% of the starting compound was recovered; [v] 97% of the starting compound was regenerated; [w] the raw cholesterol fraction from chromatography (m.p. 141—147°C) contained 2·2% of 3β-hydroxy-4,6-cholestadiene (UV spectrum).

(entry *8*) are higher than those of chloro derivatives (entry *30*). In contrast to the treatment with silver salts in the absence of amines[1,34,35], the reaction is independent of the nature of anion used; the presence of strong nucleophiles in the reaction medium does not change the product distribution (entries *8* to *11*). Therefore we mostly used silver nitrate in our preparative experiments, which is readily soluble in acetonitrile. The addition of triethylamine leaves the system quite homogenous though amorphous silver begins to precipitate later.

In our speculations about the likely course of the reaction we took into account earlier knowledge of the reductive debromination. Depending on the nature of the reagent used the reaction has been interpreted as an ionic[5] or radical one[18,36,37]. We found that even triethylamine slowly debrominates dibromide *IV* in the absence of silver salts: besides the starting material and its isomer (*V*) we isolated cholesterol (*VI*) slightly contaminated with 3β-hydroxy-4,6-cholestadiene (*VII*) and triethylammonium bromide which was also isolated as a product of the action of triethylamine upon bromine[38]. Acceleration of the reacction by the silver salt added seems to support the notion of the ionic nature of the reaction. On the other hand one has to consider the coordination of silver ions with triethylamine and the disproportionation[39] in Ag^+ and Ag^{++} derivatives. Model experiments with metallic silver in the absence of amine show that the reaction course and rate are comparable to those found when combining the two reagents (see entries *6* and *7*, or *8* and *17*). We assume that the treatment with silver salts in the presence of triethylamine may be understood as a reduction on behalf of triethylamine while silver salt serves in two ways: it is a source of highly reactive colloidal silver which is formed both directly by the disproportionation and indirectly by the reduction of argentic ions with triethylamine or its degradation products. Secondly, silver salts react with the halogen released and thus contribute to the completion of the reaction.

This theory is supported by model experiments in which silver ions were replaced by other ones which are able to form complexes with amines and undergo one-electron redox reactions (see entries *20* to *25*): both cuprous and cupric, mercurous and mercuric salts cause rather fast transformation of dibromide *IV* into cholesterol provided that triethylamine is present. On the other hand reaction rates are low when zinc and potassium salts are used as catalyst (entries *26* and *27*).

Triethylamine seems to be the most and pyridine the least suitable for the reaction of the tested set of amines, which may be connected with their respective basicity, ability to form complexes, or stability towards oxidation.

EXPERIMENTAL

The melting points were determined on a Kofler block and they are not corrected, UV spectra were measured in ethanol, ^{1}H-NMR spectra in deuteriochloroform on a Varian HA-100 instrument, mass spectra on AEI MS 902 spectrometer. Reductive debromination was carried out

by treatment of 50 mg of dihalosteroid in 1 ml tetrahydrofuran with a solution or suspension of silver perchlorate, nitrate, oxide, acetate or tetrafluoroborate in acetonitrile (1 ml) and amine (0·4 ml). The reaction was monitored by two-dimensional chromatography on a thin layer of silica gel using ligroin (deoxysteroids) or 10% ether in benzene (oxygenated steroids). The reaction mixture was worked up as usual, see the examples given below. The yields shown in Table I are based on weighing of the olefins isolated.

5α-Cholest-1-ene (*III*)

A solution of silver nitrate (150 mg) in acetonitrile (1 ml) and triethylamine (0·4 ml) was added to a solution of 1α,2β-dibromo-5α-cholestane[1] (*II*, 50 mg), and the mixture was allowed to stand at room temperature for 96 hours. The reaction mixture was diluted with chloroform (about 30 ml), washed with water and dried over anhydrous sodium sulfate. The residue after evaporation was purified by chromatography on a thin layer of silica gel (ligroin; detection in UV light after spraying with a solution of morin in methanol). The zone of R_F 0·85 was eluted with ether yielding the compound *III* (35 mg), m.p. 68—70°C, unchanged after crystallization from ether and ethanol; $[\alpha]_D^{20}$ +16°, *c* 0·9). (reference[39] records the values 68—70°C and +12·5°); ^{1}H-NMR spectrum: 0·67 (s, 3 H), 0·85 (s, 3 H,) 0·87 (d, J = 6 Hz, 6 H), 0·91 (d, J = 6 Hz, 3 H), 5·50 (mt, 1 H) and 5·85 (dt, J = 10 and 2 Hz) p.p.m.

5-Cholesten-3β-ol (*VI*)

a) A suspension of mercuric bromide (412 mg) in acetonitrile (2 ml) and tetrahydrofuran (2 ml) was mixed with triethylamine (0·8 ml) and a solution of 5,6β-dibromo-5α-cholestan-3β-ol (103 mg) in tetrahydrofuran (1 ml). After shaking all the components dissolved and the solution was allowed to stand at room temperature for 3 hours. The mixture was diluted with chloroform (60 ml), washed with water, dried over sodium sulfate and evaporated. The residue (160 mg) was shaken up in benzene (50 ml) and hot water (50 ml), the benzene extract was dried and evaporated. Purification of the residue on silica gel (20% ether in benzene) afforded the product (*VI*), m.p. 149—151°C (72 mg), undepressed on admixture of an authentic sample.

b) A solution of silver nitrate (150 mg) in acetonitrile (1 ml) and aniline (0·4 ml) was added to a solution of 5,6β-dibromo-5α-cholestan-3β-ol (48 mg) in tetrahydrofuran (1 ml) and allowed to stand at room temperature for 20 hours. The mixture was diluted with ether (50 ml), washed successively with dilute hydrochloric acid, water and potassium hydrogen carbonate solution, and dried over sodium sulfate. Chromatography on a silica gel thin layer with 10% ether in benzene afforded cholesterol (12·3 mg) contaminated with 11% of the dienol *VII* (λ_{max} = 239 nm, characteristic detection after spraying with sulfuric acid) and dibromide *V* (8·8 mg, IR spectrum, characteristic decomposition during two-dimensional chromatography on silica gel thin layer.

3β-Acetoxy-5,6α-epoxy-5α-cholestane

a) A solution of 3β-acetoxy-6β-bromo-5α-cholestan-5-ol[1] (8 mg) in tetrahydrofuran (0·5 ml) was mixed with a solution of silver nitrate (100 mg) in acetonitrile (0·8 ml) and triethylamine (0·2 ml). Within 1 hour all the starting material was converted into 3β-acetoxy-5,6α-epoxy--5α-cholestane: no cholesteryl acetate was detected in the product (chromatography on a thin layer of silica gel with 10% ether in benzene).

b) The same starting material as above (9 mg) was stirred with 35 mg of porous silver in 0·25 ml tetrahydrofuran (porous silver was prepared from an aqueous solution of silver nitrate and sodium

borohydride). Within an hour half the starting material was converted into the epoxide, no other steroidal material was detected by thin layer chromatography.

c) The bromohydrin (8 mg) was stirred with porous silver (50 mg) in tetrahydrofuran (0·25 ml) and triethylamine (0·1 ml). Within 15 minutes all the starting material was transformed into the corresponding epoxide, no other steroidal compound was detected in the product (on silica gel thin layer chromatography).

Reaction of Silver Oxide with Triethylamine

A suspension of silver oxide (100 mg) in triethylamine (0·3 ml) was allowed to stand at room temperature for 24 hours. Within this period the test tube was covered with a silver mirror. Gas liquid chromatography of the supernatant revealed the presence of triethylamine only. Mass spectrometry also indicates the presence of acetic acid ($M^+/e = 60$) and carbon dioxide ($M^+/e = 44$).

Reaction of 5,6β-Dibromo-5α-cholestan-3β-ol with Triethylamine

A solution of dibromide *IV* (60 mg) in tetrahydrofuran (1·5 ml) and triethylamine (0·35 ml) was allowed to stand at room temperature for 69 hours. Crystals, formed during the reaction, were removed by filtration and washed with ether, m.p. 255°C (6 mg). For $C_6H_{15}N.HBr$ (182·1) calculated: 39·57% C, 8·86% H, 43·88% Br; found: 39·77% C, 8·85% H, 43·59% Br. The mother liquors were submitted to chromatography on a thin layer of silica gel, which yielded compound *V* (10 mg), compound *IV* (41 mg), and 2·7 mg of cholesterol contaminated (4%) with 3β-hydroxy--4,6-cholestadiene (λ_{max} 239 nm).

Consumption of Silver Salts in Reductive Elimination

a) Dibromide *IV* (139 mg) was added to a solution of silver nitrate (156 mg) in acetonitrile (1 ml), tetrahydrofuran (1·5 ml) and triethylamine (0·5 ml). The mixture was shaken for 15 minutes in darkness and submitted to centrifugation; the deposit was washed with tetrahydrofuran and dried, the weight of silver bromide being 89 mg (100·6 mg of silver bromide would prove the consumption of 2 equivalents of the silver salt by 1 equivalent of the dibromide, provided that the reaction was carried to completion and the silver bromide was completely insoluble in the reaction medium).

b) Silver nitrate (300 mg) was dissolved in 2 ml of acetonitrile, 3 ml of tetrahydrofuran and 0·8 ml of triethylamine. Concentration of this basic solution was estimated by titration with 0·1M-KBr (51·8 mg of $AgNO_3$ in 1 ml). 150 mg of the dibromide *IV* was added to 3·8 ml of the basic solution and the mixture was shaken for 10 minutes. The reaction mixture was titrated analogously and the result (25·5 mg of $AgNO_3$ in 1 ml) showed that 150 mg of the dibromide had consumed 99·7 mg of silver nitrate.

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