Sodium Borohydride Reduction of 5α,6β-Dibromocholestan-3-one. A Simple Method for the Preparation of *epi*-Cholesterol

Yoram Houminer

Department of Organic Chemistry, The Hebrew University, Jerusalem, Israel

Received May 20, 1974

Usually, the sodium borohydride reduction of 3-keto steroids produces mainly the 3β-hydroxy isomer,[1] since hydride transfer to the carbonyl group proceeds preferentially from the less hindered side of the molecule, i.e., from the α side. Thus, reduction of cholestan-3-one in ethanol yields 89% cholestan-3β-ol and 5% cholestan-3α-ol,[2] and reduction of cholest-5-en-3-one in 2-propanol yields 83% cholesterol and 17% *epi*-cholesterol.[3] However, the presence of a substituent in the 5α position of the cholestane skeleton changes the stereochemical course of the reduction. For example, reduction of 5α-hydroxycholestan-3-one in methanol gives 67% 3α,5α-dihydroxycholestane and 33% 3β,5α-dihydroxycholestane.[4] Reduction of 5α,6α-dichlorocholestan-3-one in ether yields 56% of the corresponding 3α-hydroxy isomer and 44% of the 3β isomer.[5] It seems, therefore, that introduction of a large substituent in the 5α position of cholesterol could have been used as a tool for its isomerization to *epi*-cholesterol by, first, oxidation to the corresponding ketone, then sodium borohydride reduction, and finally removal of the 5α substituent.

For this purpose, 5α,6β-dibromocholestan-3β-ol seemed to be the most suitable substrate, since it is easily and quantitatively obtained from cholesterol,[6] it is oxidized smoothly to the ketone,[6] and the two bromine atoms can be easily removed by various methods. In addition, the steric effect of the 6β-bromo group on the reduction should be much smaller than that of the 5α-bromo group, since the latter is closer to the reaction center.

Reduction of 5α,6β-dibromocholestan-3-one (1) was studied both in ethanol and in 1,2-dimethoxyethane, and the results are given in Table I. In the two solvents treatment with a large excess of sodium borohydride affects both reduction of the carbonyl group and reductive elimination of the two bromine substituents, so that the two major products of the reaction are *epi*-cholesterol and cholesterol. Reaction pathways through which *epi*-cholesterol and cholesterol can be formed in the reduction of 1 are presented in the scheme. As the results in ethanol differ from those in 1,2-dimethoxyethane, we shall separate the discussion for each solvent. In ethanol, the relative amounts of

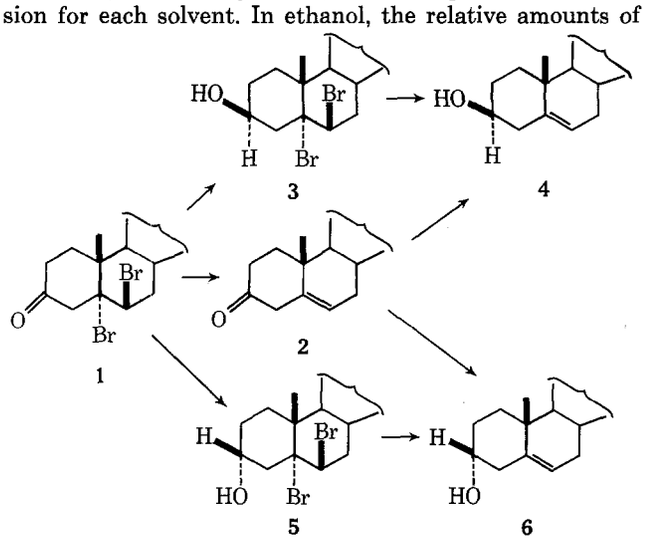
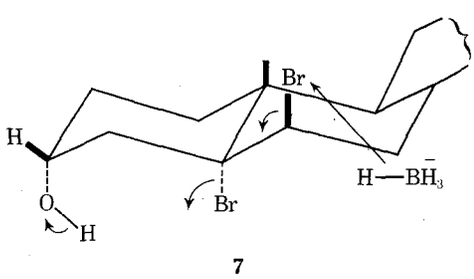


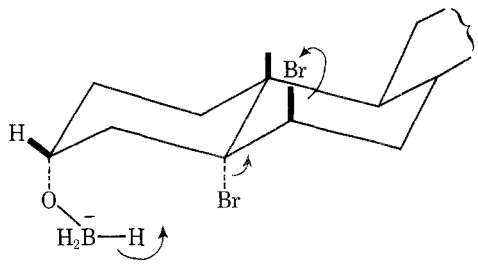
Table I
Reduction of 5α,6β-Dibromocholestan-3-one with a Large Excess of Sodium Borohydride

Solvent	Yield of *epi*-cholesterol, %	Yield of cholesterol, %
Ethanol	57	25
1,2-Dimethoxyethane	22	66

cholesterol (4) and *epi*-cholesterol (6) do not reflect the stereochemistry of the reduction of the carbonyl group in 1, since reductive elimination of the 5α,6β-dibromo grouping may proceed[7] parallel to the reduction of the carbonyl group. Indeed, the formation of cholesterol does not proceed via route 1 → 3 → 4, since 5α,6β-dibromocholestan-3β-ol (3) itself does not react with sodium borohydride under the same conditions in which ketone 1 is smoothly reduced to cholesterol and *epi*-cholesterol. Moreover, 3 could not be detected in the reaction mixture. Therefore, cholesterol is probably formed via route 1 → 2 → 4 in which reductive elimination takes place first to give cholest-5-en-3-one (2), which then undergoes further carbonyl reduction to cholesterol. In a careful examination of the reaction of 1 with 1 equiv of sodium borohydride, we could not detect any of 2. In this compound, the carbonyl group is less hindered and it is probably reduced much faster than any of the other compounds present in the reaction mixture. We observed also that with small amounts of sodium borohydride, because the overall reduction rate is low, several side reactions of 1 take place, such as hydrogen bromide elimination and substitution. No attempt was made to investigate these reactions in more detail.

In ethanol the yield of cholesterol is smaller than that of *epi*-cholesterol. This indicates that in 1 reductive elimination is slower than reduction of the carbonyl group. Moreover, route 1 → 2 → 6 cannot account for the formation of *epi*-cholesterol, since 2 is reduced mainly to the 3β-hydroxy isomer.[3] Therefore, *epi*-cholesterol is probably formed via route 1 → 5 →6 in which the carbonyl group of 1 is first reduced to give 5α,6β-dibromocholestan-3α-ol (5), which then undergoes reductive elimination to give 6. When 1 was treated with 1 equiv of sodium borohydride, we were able to detect by TLC one major intermediate which was converted to *epi*-cholesterol on further addition of sodium borohydride. Several attempts to isolate this intermediate failed since it decomposed during work-up. It is interesting to note that the same intermediate is detected by TLC in the bromination of *epi*-cholesterol, but here again no dibromide could be isolated. Therefore, although there is no direct evidence for the formation of 5, we believe that this must be the intermediate through which *epi*-cholesterol is formed in the reduction of 1. These results suggest that 5 is capable of undergoing a faster reductive elimination than 3. The reason for this behavior is not yet clear. It is, however, possible that the 3α-hydroxy group of 5 catalyzes the reaction by neighboring group participation either by hydrogen bonding with the 5α bromine as in 7, or by complex formation with reducing agent as in 8. Another





8

possibility is that steric interaction of the 3α,5α groups in **5** raises the energy of its ground state and is therefore responsible for the faster reductive elimination.

The reduction of **1** in ethanol is undoubtedly a very useful method for the preparation of *epi*-cholesterol. Several other more complicated procedures have been described in the literature[8] but none which gives a higher yield of *epi*-cholesterol. The method could also be used for the isomerization of other compounds having similar structure. For example, we propose the transformation of 3β,17β-dihydroxyandrost-5-ene into 3α,17β-dihydroxyandrost-5-ene.

In 1,2-dimethoxyethane the yield of cholesterol is much higher than that of *epi*-cholesterol. The effect of the solvent on the stereochemistry of the sodium borohydride reduction of 3-keto steroids is small.[2] Indeed, we find that reduction of 5α,6β-dichlorocholestan-3-one in ethanol yields the two isomers of 3-hydroxy-5α,6β-dichlorocholestane in the same ratio that is obtained in 1,2-dimethoxyethane.[9]

Therefore, we believe that in 1,2-dimethoxyethane, reductive elimination in **1** is faster than the reduction of the carbonyl group and this is the reason why a larger amount of cholesterol is formed. This suggestion is supported by the observation that 5α,6β-dibromocholestan-3β-ol itself undergoes smooth reductive elimination in 1,2-dimethoxyethane.

Experimental Section

All melting points were determined with a Fisher-Johns apparatus. Optical rotations were taken for solutions in chloroform with a Perkin-Elmer Model 141 polarimeter. Both qualitative and preparative TLC was carried out on silica gel G plates eluted with light petroleum (bp 60–80°) containing 10% acetone. 5α,6β-Dibromocholestan-3β-ol and 5α,6β-dibromocholestan-3-one were prepared according to the method of Fieser et al.[6] The dibromo ketone was dried in vacuo over sodium hydroxide. Absolute ethanol (Riedel-DeHaen) was used. 1,2-Dimethoxyethane (B. D. H.) was eluted through a column of alumina and then distilled from sodium.

Sodium Borohydride Reduction of 5α,6β-Dibromocholestan-3-one. In Ethanol. A suspension of the dibromo ketone (1.00 g) in absolute ethanol (100 ml) was treated with a large excess of sodium borohydride (0.50 g), and the mixture was stirred at room temperature for 3 hr. During this period hydrogen was evolved and all the material dissolved. Acetic acid was added to destroy the excess of sodium borohydride and after dilution with water the product was extracted with ether. The solution was washed with water, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The residue was separated by TLC to give pure *epi*-cholesterol (410 mg, 57%), mp 141–142° (from ethanol), $[\alpha]_D$ −41° (*c* 0.25) (lit.[8] mp 142–143°, $[\alpha]_D$ −42°). The material is identical with authentic *epi*-cholesterol by mixture melting point, ir, and TLC. Also isolated was pure cholesterol (180 mg, 25%), mp 148–149° (from ethanol), $[\alpha]_D$ −39° (*c* 0.50), identical with an authentic sample by mixture melting point, ir, and TLC.

In 1,2-Dimethoxyethane. The dibromo ketone (1.00 g) in 1,2-dimethoxyethane (100 ml) was treated with sodium borohydride (0.50 g), and the solution was stirred at room temperature for 6 hr. During this period hydrogen was evolved and a precipitate of sodium bromide was separated. Acetic acid was added to destroy the excess of sodium borohydride. The solution was evaporated under reduced pressure to a volume of 20 ml, then diluted with water and work-up was continued as above. Separation by TLC gave pure *epi*-cholesterol (158 mg, 22%) and pure cholesterol (475 mg, 66%). Both products were shown to be identical with authentic samples by mixture melting point, ir, and TLC.

Treatment of 5α,6β-Dibromocholestan-3β-ol with Sodium Borohydride. In Ethanol. The dibromide (1.00 g, mp 115–116° from methanol–ethyl acetate) in ethanol (100 ml) and ether (20 ml) was treated with sodium borohydride (0.50 g) and the solution was stirred at room temperature for 3 hr. TLC indicated no change. Work-up as above and recrystallization from methanol–ethyl acetate gave 890 mg of the starting material, mp 116–117°, and no depression on mixture melting point. When the reaction was carried out under the same conditions for 24 hr, a small amount of cholesterol could be detected by TLC, together with small amounts of other unidentified products.

In 1,2-Dimethoxyethane. The dibromide (0.50 g) in 1,2-dimethoxyethane (50 ml) was treated with sodium borohydride (0.25 g) and the solution was stirred at room temperature for 6 hr. During this period hydrogen was evolved and a precipitate of sodium bromide was separated. TLC indicated a clean reaction, with one product having the same R_f as cholesterol. Work-up as above and recrystallization from ethanol afforded pure cholesterol (300 mg, 83%), mp 149°, $[\alpha]_D$ −39°, ir identical with that of authentic sample.

Registry No.—**1**, 2515-09-5; **3**, 1857-80-3; **4**, 57-88-5; **6**, 474-77-1; sodium borohydride, 16940-66-2.

References and Notes

(1) L. F. Fieser and M. Fieser, "Steroids", Reinhold, New York, N.Y., 1959, pp 268–271.
(2) O. R. Vail and D. M. S. Wheeler, *J. Org. Chem.*, **27**, 3803 (1962).
(3) O. H. Wheeler and J. L. Mateos, *Can. J. Chem.*, **36**, 1049 (1958).
(4) M. Akhtar and S. Marsh, *J. Chem. Soc. C*, 937 (1966). The authors give these values in their Experimental Section. However, in their results the reverse numbers are presented. To overcome this difficulty we have repeated their experiment in ethanol and obtained 41% 3β,5α-dihydroxycholestane and 59% 3α,5α-dihydroxycholestane.
(5) R. Jacquesy and J. Levisailes, *Bull. Soc. Chim. Fr.*, 396 (1966); 1649 (1967).
(6) L. F. Fieser, "Organic Syntheses", Collect. Vol. IV, Wiley, New York, N.Y., 1963, p 197.
(7) J. F. King, A. D. Allbutt, and R. G. Pews, *Can. J. Chem.*, **46**, 805 (1968).
(8) P. A. Plattner, A. Furst, F. Koller, and W. Lang, *Helv. Chim. Acta*, **31**, 1455 (1948); K. D. Bingham, T. M. Blaiklock, R. C. B. Coleman, and G. D. Meakins, *J. Chem. Soc. C*, 2330 (1970), and references cited therein.
(9) Y. Houminer, unpublished results.

Reduction of Organomercurials by Sodium Dithionite[1]

John A. Todhunter and Douglas L. Currell*

Department of Chemistry, California State University, Los Angeles, Los Angeles, California 90032

Received August 26, 1974

The reduction of alkyl and aryl mercurials by various reducing agents such as magnesium,[2] sodium stannite,[3] metal hydrides,[4] and hydrazine[5] is well known. The types of reduction products are illustrated by the following equation.

$$\text{R-Hg-X} \xrightarrow{(H)} \underset{\mathbf{1}}{\text{R-H}} \text{ or } \underset{\mathbf{2}}{\text{R-Hg-R}} \text{ and Hg(0)}$$

The "symmetrization" product, **2**, is produced most often upon reduction with magnesium, sodium stannite, or hydrazine while product **1** is produced by reaction with metal hydrides.

Dithionites are powerful reducing agents as indicated by the couples below.

$$HS_2O_4^- + 2H_2O \longrightarrow 2H_2SO_3 + H^+ + 2e \quad E^\circ_{298} = 0.23 \text{ V}$$

$$S_2O_4^{2-} + 4OH^- \longrightarrow 2SO_3 + 2H_2O + 2e \quad E^\circ_{298} = 1.4 \text{ V}$$

Oxidants such as silver ion, iodine, iodate, permanganate, cupric ion, hydrogen peroxide, nitrous acid, molecular oxygen, and organic dyes are all reduced.[6]