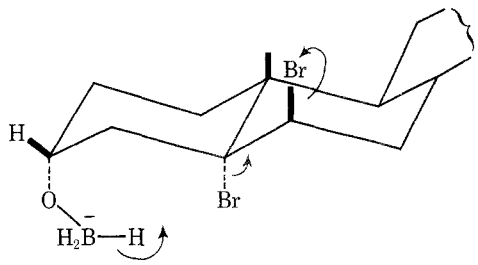

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possibility is that steric interaction of the 3α,5α groups in **5** raises the energy of its ground state and is therefore responsible for the faster reductive elimination.

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.

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Reduction of Organomercurials by Sodium Dithionite[1]

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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]

We have studied the reaction products and stoichiometry in the reduction of *p*-chloromercuribenzoic acid (PMB) by sodium dithionite in aqueous ethanol. The stereochemical course of the reaction was investigated in the reduction of *exo-cis*-3-hydroxy-2-norbornylmercuric chloride according to the method of Traylor and Baker.[7]

Experimental Section

Reduction of *p*-Chloromercuribenzoic Acid. Sodium dithionite (0.3 g, 1.7×10^{-3} mol) was added to a suspension of *p*-chloromercuribenzoic acid[8] (0.43 g, 1.2×10^{-3} mol) in absolute ethanol under a nitrogen atmosphere, after which the mixture was vigorously stirred for 2 hr and then refluxed gently for 1 hr. The mixture was filtered to remove elemental mercury, the pH was adjusted to pH 7, and the filtrate was concentrated to one-third of the original volume. The filtrate was acidified to pH 4 with dilute HCl. The white precipitate which formed was identified as bis(*p*-carboxyphenyl)mercury, 0.27 g (99.5%), mp >300°. The product was identified by determination of its equivalent weight through titration with standard sodium hydroxide solution as 222 ± 8 (expected value 220), and through identity of its infrared spectrum with that of bis(*p*-carboxyphenyl)mercury prepared[9] by symmetrization of *p*-chloromercuribenzoic acid with sodium stannite. The pK_a values as determined from the titration curve were 3.0 ± 0.2 for pK_1 and 6.4 ± 0.1 for pK_2. Yield of the elemental mercury in several experiments was 46–48% of the mercury contained in the starting material.

Attempts to reduce bis(*p*-carboxyphenyl)mercury with sodium dithionite under the conditions described for the reduction of *p*-chloromercuribenzoic acid were unsuccessful and resulted in recovery of 98% of the starting material. When the reduction of *p*-chloromercuribenzoic acid was carried out in the presence of styrene, no polymerization of the styrene was observed, which indicated an absence of free-radical intermediates.

Reduction of *exo-cis*-3-Hydroxy-2-norbornylmercuric Chloride. To 2.4647 g (0.007 mol) of *exo-cis*-3-hydroxy-2-norbornylmercuric chloride (prepared according to Traylor and Baker[7]) dissolved in 50 ml of absolute ethanol was added 2.44 g (0.014 mol) of sodium dithionite. The reaction was allowed to proceed at ambient temperature in a covered beaker equipped with a magnetic stirrer. The solution gradually turned from clear to gray. The mixture was stirred for 24 hr and then it was refluxed gently for 30 min to decompose the excess dithionite. The metallic mercury which formed was filtered out along with inorganic salts not soluble in ethanol. Evaporation of the filtrate yielded 1.49 g (100%) of a white powder, di-*cis-exo*-3-hydroxy-2-norbornylmercury, mp 150–153° dec (lit.[7] mp 152–152.5°). Recrystallization from ether raised the melting point to 152–153°. The infrared spectrum of a CCl_4 solution of the product showed a sharp peak at 3601 cm^{-1} indicative of a cis-exo geometry.[7] The product was quantitatively cleaved back to the pure starting material by the action of $HgCl_2$, a procedure known[7] not to alter the stereochemistry, thus confirming the cis-exo geometry.

Results

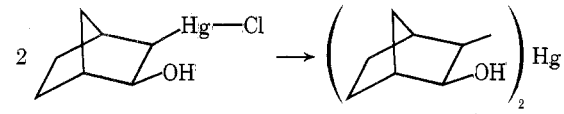
It was found that sodium dithionite is capable of effecting the quantitative reduction of both alkyl and aryl organomercurials, with the notable exception of bis(*p*-carboxyphenyl)mercury. The product of reduction is the symmetrization product of the ligand which is bonded through carbon to mercury.

The stoichiometry of the reduction process was found to be

$$2R\text{-}Hg\text{-}X + Na_2S_2O_4 \longrightarrow R\text{-}Hg\text{-}R + Hg(0) + 2NaCl + 2SO_2$$

as determined by quantitative determinations of the amount of R–Hg–R and metallic mercury produced, the observation that the dithionite sulfur is converted to sulfur dioxide (or sulfite), and the ability to obtain quantitative conversion of starting material to product with less than a 1:1 ratio of dithionite to oxidant (when O_2 is eliminated from the system). NaCl formation is observed even in nonaqueous systems not treated with HCl; therefore, it is formed as a product of the reaction. Its stoichiometry and that of SO_2 are assigned to fit the observed stoichiometry of the other reagents and were not directly determined.

The reduction is found to conserve the geometry about the carbon bonded to mercury as determined by the results of the reduction of the 3-hydroxy-2-norbornylmercuric chloride system



which was found to proceed with 100% retention of configuration at both carbons as determined by the method of Traylor and Baker.[7]

When the reduction by dithionite was carried out in the presence of styrene, the styrene remained unchanged, indicative of a nonradical mechanism. Further, the reaction proceeded in the presence of molecular oxygen (although a considerable amount of the reductant was lost by reaction with oxygen, accounting for the observed decrease in the amount of dithionite needed to effect reduction in the absence of oxygen).

Discussion

The reduction of organomercurials by sodium dithionite can best be interpreted as proceeding via a two-electron reduction scheme. Two known cases believed to involve two-electron reductions of organomercurials are symmetrization by magnesium metal and symmetrization by the action of hydrazine. In both cases the following mechanism has been proposed.[10]

$$RHgX + 2e \longrightarrow RHg^- + X^- \quad (1)$$

$$RHg^- + RHgX \longrightarrow RHgHgR + X^- \quad (2)$$

$$RHgHgR \longrightarrow R\text{—}Hg^-\text{—}R \longrightarrow RHgR + Hg(0) \quad (3)$$

(with Hg^+)

The ease of reduction of R–Hg–X when X is halogen and the absence of reaction when X is *p*-carboxyphenyl suggest that the transition state of the rate-determining step of the reaction involves breaking the Hg–X bond. Apparently the reduction proceeds readily only when X can produce a stable anion.

The stereochemical result is consistent with the two-electron mechanism, since reduction by dithionite is found to proceed with 100% retention of configuration. This result does not completely rule out a radical mechanism, however, since the reduction of the same stereoisomer used herein with sodium borohydride has been shown to proceed with greater than 95% retention[11] even though the mechanism is believed to proceed via free radicals.[12]

Registry No.—PMB, 59-85-8; BCM, 2013-22-1; $Na_2S_2O_4$, 7775-14-6.

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