REACTION MECHANISM STUDIES

2. REDUCTIVE ELIMINATION OF 1,2-DIHALIDES WITH LITHIUM ALUMINUM HYDRIDE

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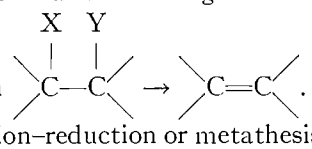
ABSTRACT

1,2-Dibromides and bromohydrin *p*-toluenesulphonates of favorable geometry are readily reduced by lithium aluminum hydride in good yield to the corresponding olefin. Small quantities of water are found to have a *temporary accelerating effect* on the reduction. The normal course of the reaction is a trans elimination, but when steric factors inhibit this, then substitution or *cis* elimination reactions may occur. It is shown that the *cis* elimination in the case of *cis*-1,2-dibromocyclohexane cannot involve reduction to the monobromide followed by dehydrobromination to the olefin. The reaction of some other 1,2-dihalides and related compounds with lithium aluminum hydride, and the reaction of a 1,2-dibromide with a number of other complex hydrides are reported.

A general scheme for the mechanism of the olefin-forming elimination reaction is proposed. The limits that this study places on the possible positions of the reductive elimination of 1,2-dibromides with lithium aluminum hydride within this general scheme are discussed.

The elimination reaction leading to the formation of an olefin may be expressed generally by the equation  . The conventional description of a reaction as either an oxidation–reduction or metathesis can be usefully applied to classify eliminations as oxidative (e.g. dehydrogenation, in which X, Y = H), reductive (e.g. X, Y = halogen) or metathetical (e.g. X = H, Y = halogen); correspondingly the formal reverse of each of these reactions would be reductive addition (e.g. hydrogenation), oxidative addition (e.g. addition of halogen), and metathetical addition (e.g. addition of hydrogen halide), respectively. Much study has been devoted toward an understanding of the metathetical addition and elimination reactions, but much less work has been carried out on the oxidative and reductive processes. Though some of the most commonly used examples of the latter group are heterogeneous phase reactions whose study is complicated by special problems, a substantial number of oxidative and reductive additions and eliminations take place in solution. Table I lists a number of conditions under which reductive elimination of dibromides has been reported to occur; the great majority of these, in fact, involve a homogeneous system.

Most of the work on the mechanism of homogeneous phase reductive eliminations that had been reported at the beginning of this study had been restricted to the reduction of 1,2-dibromides (and some related species) with alkali iodides.* But the number and variety of other reagents which could effect reductive elimination of 1,2-dibromides (see Table I) suggested the possibility that the mechanism of reaction of some of these reagents might be quite different from that of an alkali iodide. If this were the case it would not be possible to discover all the ramifications of the mechanism of the general reductive elimination reaction were the study to be restricted to the reduction induced by alkali iodides. Accordingly, we decided to investigate the reductive elimination with lithium

**While this work was in progress, an investigation of the reduction of similar compounds with mercaptides was reported (24).*

TABLE I

Reactions reported to result in the reductive elimination of 1,2-dibromides

Reaction conditions	Substrate	Product	Ref.
Sodium in liquid ammonia	*meso*-2,3-Dibromobutane	*cis*-2-Butene (50%) *trans*-2-Butene (50%)	1
Sodium iodide* in acetone	Ethylene dibromide	Ethylene	2
n-Propylmagnesium bromide in ether	*trans*-1,2-Dibromocyclohexane	Cyclohexene (plus cyclohexane)	3
Phenyllithium in ether	*trans*-1,2-Dibromocyclohexane	Cyclohexene (80%)	4
Di-*p*-tolylmercury in toluene	*meso*-Stilbene dibromide	*trans*-Stilbene	5
Trimethyl phosphite in toluene	*trans*-Dibenzoylethylene dibromide	*trans*-Dibenzoylethylene (92%)	6
Potassium cyclohexylphosphide in benzene	Ethylene dibromide	Ethylene (85%)	7
Pyridine at ~ 100°	*meso*-Stilbene dibromide	*trans*-Stilbene	8
Ethanol at 150°	*meso*-Stilbene dibromide	*trans*-Stilbene	9
Aniline at 130°	*meso*-Stilbene dibromide	*trans*-Stilbene	9
Acetic acid	*meso*-Stilbene dibromide	*trans*-Stilbene	10
Phenylhydrazine	*meso*-Stilbene dibromide	*trans*-Stilbene	10
Potassium hydrosulphide in ethanol	*meso*-Stilbene dibromide	*trans*-Stilbene	11
Sodium thiophenoxide in ethanol	*meso*-Stilbene dibromide	*trans*-Stilbene	12
Sodium benzenesulphinate in ethanol	*meso*-Stilbene dibromide	*trans*-Stilbene	12
Water at 170°	2,3-Dibromohexane	2-Hexene	13
Silver oxalate in xylene	*meso*-Stilbene dibromide	*trans*-Stilbene	14
Phenetole at 170°	*meso*-Stilbene dibromide	*trans*-Stilbene (25%)	15
Triphenylphosphine in ether	Methyl 1,2-dibromopropionate	Methyl acrylate (64%)	16
Tri-*n*-butyltin hydride in pentane	1,2-Dibromopropane	Propylene (81%)	17
Chromous chloride in acetone	Stigmasteryl acetate tetrabromide	Stigmasteryl acetate 22,23-dibromide (65%)	18
Ferrous chloride, potassium acetate, and acetic acid in ethanol	Cholesterol dibromide	Cholesterol (72%)	19
Dropping mercury electrode	Ethylene dibromide	Ethylene	20
Zinc* and alcohol	Ethylene dibromide	Ethylene	21
Magnesium in ether	Ethylene dibromide	Ethylene	22
Amorphous arsenic	Ethylene dibromide	Ethylene	23
Lithium aluminum hydride	See Table II		

*An important preparative reaction with numerous variations of conditions; the example quoted is one of the earlier illustrations of its use.

aluminum hydride. From what little was known of this reaction at the beginning of this study, it appeared that this reagent effects reductive elimination of 1,2-dibromides in high yield, but it is otherwise different from alkali iodides in its reactions with organic compounds. Though lithium aluminum hydride is a much-used reagent in organic synthesis, there are serious technical and theoretical problems associated with a study of its mechanism of action. To a considerable extent these have limited the present study. At the same time it is hoped that this work has contributed toward their eventual solution.

Scope of the Reductive Elimination with Complex Metal Hydrides

Previous reports of reduction of 1,2-dihalides with lithium aluminum hydride are listed in Table II. In most of these examples reductive elimination is the only observed course of reaction, though substitution predominates with the following substrates: 1,2-dibromoöctane, ethyl β-chloroethyl ether, and *trans*-1,4-dibromo-2-butene. These anomalies are given further comment in the discussion of the mechanism of the reaction.

Table III summarizes the results of a number of experiments designed to show the range of compounds reducible with lithium aluminum hydride. The rest of this paragraph offers some general conclusions that may be drawn from these data. All of the 1,2-dibromides

TABLE II

Previous work on reductions of dihalides with lithium aluminum hydride

Substrate	Product	Yield (%)	Reference
meso-Stilbene dibromide	*trans*-Stilbene	98	25
1,2,3,4-Tetrabromobutane	Butadiene	—	25
Styrene dibromide	Styrene	71	25
Ethyl 2,3-dibromo-3-phenylpropionate	Hydrocinnamyl alcohol	59	25
1,2-Dibromoöctane	1-Octene	17	25
	2-Bromoöctane	26	25
2,3-Diiodo-1-propanol	Allyl alcohol	—	25
trans-1,4-Dibromo-2-butene	*trans*-2-Butene	72	25
24,25-Dibromocholest-8-en-3β-ol (zymosterol dibromide)	Cholesta-8,24-dien-3β-ol (zymosterol)	91	26
Ethyl 2,3-dibromo-4,4,4-trifluorobutyrate	4,4,4-Trifluorocrotyl alcohol	50	27
3,4-Dihydro-3,4-dibromohexachloro-1,5-hexadiene	3,4-Dihydrohexachloro-1,3,5-hexatriene	99	28
7,8-Dibromo-1,2,5,6-dibenzocycloöctatriene	1,2,5,6-Dibenzocycloöctatetraene	93	29
Ethyl α,β-dichloroethyl ether	Ethyl β-chloroethyl ether	53	25
Cycloöctatetraene dibromide*	Cycloöctatriene	—	30
	Bicyclo[4.2.0]octa-2,4-diene	—	

*Reaction mixture also contained a small amount of sodium iodide.

listed in Table III gave the corresponding olefin, though in the case of *cis*-1,2-dibromocyclohexane the yield was low. Reductive elimination with formation of *trans*-stilbene took place fairly smoothly with all compounds derived from it including the meso dichloride. The two *trans*-2,3-dichlorocholestanes (I*d* and II*c*), however, both gave a remarkable mixture of products which included only small amounts of the reductive elimination product. It seems likely that the dichlorocholestanes are more representative of 1,2-dichlorides than *meso*-stilbene dichloride; in general, then, formation of the olefin from 1,2-dichlorides probably does not predominate over other possible reactions. A similar result was found with 2-fluorobromides; *trans*-stilbene was formed in good yield from the corresponding fluorobromide, but fluorocyclohexane was the only product obtained from *trans*-1-fluoro-2-bromocyclohexane. As expected, the two diaxial bromohydrin *p*-toluenesulphonates (I*b*) and (I*c*) both gave the corresponding olefin in high yield. Surprisingly, however, the diequatorial isomer II*b* yielded much the same complex mixture of products as that obtained from the dichlorocholestanes, whereas the *cis* isomer IV gave a fairly good yield of the olefin.

The quantity of lithium aluminum hydride consumed by the reduction of 1 mole of *meso*-stilbene dibromide and cholesterol dibromide (V) was estimated by iodometric titration of the unreacted hydride (31) to be 0.47 and 0.42 moles, respectively (see Experimental); this corresponds reasonably well with the equation

$$2\left(\rangle CBr—CBr\langle\right) + LiAlH_4 \longrightarrow 2\left(\rangle C{=}C\langle\right) + 2H_2 + [LiAlBr_4].$$

Gas (presumably hydrogen) is evolved in the reaction. The fate of the lithium, aluminum, and bromine atoms after the reduction has not been investigated, though a recent report on the reaction of lithium aluminum hydride with bromine suggests that the inorganic products may be LiBr and $LiAl_2Br_7$ (32).

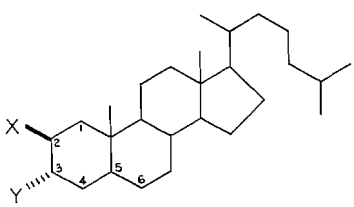
The reaction of 2β,3α-dibromocholestane (I*a*) with a number of other complex hydrides was briefly investigated. Unreacted starting material was the principal constituent of the product obtained from the following conditions: (*a*) sodium borohydride in methanol at

TABLE III

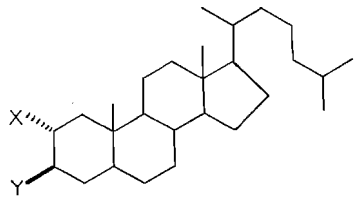
Reaction of lithium aluminum hydride with 1,2-dihalides and halohydrin *p*-toluenesulphonates

Substrate	Solvent	Temp.	Time (hours)	Product	Yield (%)
2β,3α-Dibromocholestane (I*a*) (diaxial)	Tetrahydrofuran	Reflux	1	Cholest-2-ene (III)	90
2α,3β-Dibromocholestane (II*a*) (diequatorial)	Tetrahydrofuran	Reflux	1	Cholest-2-ene (III)	88
trans-1,2-Dibromocyclohexane	Triglyme	25°	1	Cyclohexene	77
		then 100°	1	Cyclohexane	5
cis-1,2-Dibromocyclohexane	Triglyme	25°	1	Cyclohexene	26*
		then 100°	1	Bromocyclohexane	49*
meso-Stilbene dibromide	Tetrahydrofuran	Reflux	1	*trans*-Stilbene	95
dl-Stilbene dibromide	Tetrahydrofuran	(see Table IX)		*trans*-Stilbene *cis*-Stilbene } see Table IX	
meso-2,3-Dibromobutane	Ether	25°	1	*trans*-2-Butene	90
dl-2,3-Dibromobutane	Ether	25°	1	*cis*-2-Butene	86
trans-1-Fluoro-2-bromocyclohexane	Triglyme	25°	1	Fluorocyclohexane	45
		then 100°	1		
erythro-1,2-Diphenyl-2-bromoethyl fluoride	Tetrahydrofuran	25°	0.75	*trans*-Stilbene	86
2β-Bromocholestan-3α-yl *p*-toluenesulphonate (I*b*) (diaxial)	Tetrahydrofuran	Reflux	1	Cholest-2-ene	90
3α-Bromocholestan-2β-yl *p*-toluenesulphonate (I*c*) (diaxial)	Tetrahydrofuran	Reflux	1	Cholest-2-ene	93
2α-Bromocholestan-3β-yl *p*-toluenesulphonate (II*b*) (diequatorial)	Tetrahydrofuran	Reflux	1	Small amounts of: cholest-2-ene, cholestane, cholestan-2β-ol, cholestan-2α-ol, cholestan-3β-ol, cholestan-3α-ol, plus unidentified products	—
2α-Bromocholestan-3α-yl *p*-toluenesulphonate (IV)	Tetrahydrofuran	Reflux	0.5	Cholest-2-ene	75
meso-Stilbene dichloride	Tetrahydrofuran	25°	1	*trans*-Stilbene	75*
2β,3α-Dichlorocholestane (diaxial)	Tetrahydrofuran	Reflux	1	Starting material plus cholest-2-ene, cholestane, cholestan-2β-ol, cholestan-2α-ol, cholestan-3β-ol, cholestan-3α-ol	—
2α,3β-Dichlorocholestane (diequatorial)	Tetrahydrofuran	Reflux	1	Starting material (mainly), plus cholest-2-ene, cholestane, cholestan-2β-ol, cholestan-2α-ol, cholestan-3β-ol, cholestan-3α-ol	—
5α,6β-Dibromocholestan-3β-ol (V)	Tetrahydrofuran	Reflux	2	Cholesterol (VI)	97
erythro-1,2-Diphenyl-2-bromoethyl methyl ether	Tetrahydrofuran	Reflux	5	*trans*-Stilbene	45
2β-Chlorocholestan-3α-yl *p*-toluenesulphonate (I*c*)	Dioxane	Reflux	2	Mainly starting material	—

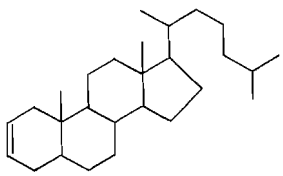
*Based on reacted starting material.



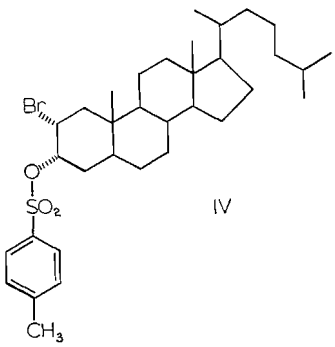
Ia X,Y = Br
Ib X = Br
Y = OSO_2–C_6H_4–CH_3
Ic X = OSO_2–C_6H_4–CH_3
Y = Br
Id X,Y = Cl
Ie X = Cl
Y = OSO_2–C_6H_4–CH_3



IIa X,Y = Br
IIb X = Br
Y = OSO_2–C_6H_4–CH_3
IIc X,Y = Cl



III



IV

room temperature, (*b*) commercial sodium "trimethoxyborohydride" in diglyme (diethylene glycol dimethyl ether) at room temperature, (*c*) lithium borohydride in ether or tetrahydrofuran under reflux, (*d*) lithium tri-*t*-butoxyaluminohydride in refluxing tetrahydrofuran, (*e*) diborane in diglyme at room temperature. With sodium borohydride in triglyme at 135°, sodium borohydride and aluminum chloride in diglyme at 100°, or lithium tri-*t*-butoxyaluminohydride in triglyme (triethylene glycol dimethyl ether) at 135°, neither starting material nor cholest-2-ene were isolated. Sodium "trimethoxyborohydride" in diglyme at 135° gave cholest-2-ene in 88% yield. Further work on some of these reactions will be described in a subsequent publication. Relevant to these observations is the recent report (17) that tri-*n*-butyltin hydride reduced certain 1,2-dibromides to the corresponding olefin (see Table I).

Rates of Reduction of Dibromides and Bromohydrin p-Toluenesulphonates

To gain further insight into the factors influencing the reductive elimination with lithium aluminum hydride, a study of the approximate rates of reduction of a number of dibromides and bromohydrin *p*-toluenesulphonates (tosylates) was initiated. The reaction was carried out in dry tetrahydrofuran at 0° in an atmosphere of oxygen-free, dry nitrogen under conditions designed to exclude water. Under these conditions the lithium aluminum

hydride solution, though slightly turbid, was found to maintain the same reducing power (as measured by titration with iodine) over a period of at least 3 months. The rate of the reductive elimination was followed by stopping the reaction with excess water and titrating the bromide ion formed in the reaction. It was found, however, that only the most approximate comparisons of relative rates could be made under these conditions. Individual runs for a certain reaction time using the same lithium aluminum hydride stock solution and the same specimen of the substrate were reasonably reproducible, but the same experiment with similar materials of different origin often gave results incompatible with those obtained previously. In addition, the extent of reaction for different reaction times, even when carried out on the same day with the same materials, did not correspond to any simple rate expression. (These results are discussed in greater detail elsewhere (33).)

Previous investigators (34, 35) had reported that water exhibits a catalytic effect in the lithium aluminum hydride reduction of certain organic halides. It seemed not unreasonable that some of the difficulties described above might be due to traces of water being added with the organic substrate. To test this possibility, a small amount of water was added to the reaction mixture along with the substrate. A notable acceleration was observed, see Table IV, and also Table V experiments No. 1 vs. 9, and 5 vs. 7. However, when the same

TABLE IV

Effect of varying the amount of water added with the substrate in the reduction of *meso*-stilbene dibromide

Time (minutes)	Substrate (mmoles)	Water (mmoles)	$LiAlH_4$ solution* (conc.)	% Reaction of individual experiments	Average % reaction
1.5	0.37	None	0.124 *M*	43, 43, 45	44
1.5	0.37	0.72	0.121 *M*	56, 53, 54	54
1.5	0.37	1.44	0.121 *M*	62, 66, 59, 58	61
1.5	0.37	2.88	0.121 *M*	77, 75, 78	77

*In tetrahydrofuran, 60 ml.

amount of water was added to the lithium aluminum hydride solution and the mixture allowed to stand for 15 minutes *before* adding the dibromide, then the rate of reduction was accelerated only slightly (if at all) over the case in which no water was added: compare experiment 12 (Table V) with 1 and 9, or 8 with 7 and 5. Addition of water, therefore, has a *temporary accelerating effect.* The reproducibility of the above results was checked in two ways: (i) A portion of the first lithium aluminum hydride stock solution (A) was stored under nitrogen for 3 months at room temperature; this solution (B) gave essentially the same results as had been obtained earlier. (ii) A new stock solution (C) was prepared from a fresh lot of lithium aluminum hydride and also gave similar results (see Table V).

It was apparent at this stage that the temporary accelerating effect of water introduces a complication into any attempt to compare the rates of reduction of different organic substrates. In the hope of obtaining a reaction mixture of constant reducing power, water was added gradually and continuously by passing a constant stream of wet nitrogen through the reaction mixture. The results obtained by this procedure using *meso*-2,3-dibromobutane as substrate are recorded in experiments 14–24 (Table V). A plot of log (100 − % reaction) vs. time indicates that under these conditions the reaction is approximately first order in dibromide, indicating that the constant addition of water to a large excess of lithium aluminum hydride produces a reagent of at least roughly constant

TABLE V

Effect of added water and its mode of addition to the rate of reduction of *meso*-2,3-dibromobutane*

Expt. No.	Time (minutes)	Amount and mode of addition of H_2O	$LiAlH_4$ concentration†	% Reaction of individual experiments	Average % reaction
1	5	None	0.126 *M* (*C*)	5, 6, 6, 5	5
2	5	None	0.127 *M* (*B*)	5, 7	6
3	10	None	0.126 *M* (*C*)	7, 8, 8	8
4	60	None	0.126 *M* (*C*)	16, 16, 16	16
5	60	None	0.127 *M* (*A*)	15, 13, 16	15
6	60	None	0.127 *M* (*B*)	17, 12, 13	14
7	1.5	1.44 mmoles H_2O with substrate	0.127 *M* (*A*)	22, 23, 25	23
8	1.5	1.44 mmoles H_2O added to reagent; let stand for 15 minutes then substrate added	0.127 *M* (*A*)	6, 4, 5	5
9	2	1.44 mmoles H_2O with substrate	0.126 *M* (*C*)	29, 34, 33	32
10	2	1.44 mmoles H_2O with substrate	0.127 *M* (*B*)	28 (one run only)	(28)
11	2	1.44 mmoles H_2O with substrate	0.127 *M* (*A*)	31 (one run only)	(31)
12	5	1.44 mmoles H_2O added to reagent; let stand for 15 minutes then substrate added	0.126 *M* (*C*)	5, 8, 9	7
13	5	1.44 mmoles H_2O added to reagent; let stand for 15 minutes then substrate added	0.127 *M* (*B*)	13, 7, 9	10
14	3	N_2, saturated at 0° with H_2O, bubbled into reaction mixture at 6.6 cc/second	0.127 *M* (*A*)	14, 15, 14	14
15	5	N_2, saturated at 0° with H_2O, bubbled into reaction mixture at 6.6 cc/second	0.127 *M* (*A*)	22, 23, 25, 24, 23, 21, 23	23
16	5	N_2, saturated at 0° with H_2O, bubbled into reaction mixture at 6.6 cc/second	0.127 *M* (*B*)	20, 29, 21, 20, 22	22
17	5	N_2, saturated at 0° with H_2O, bubbled into reaction mixture at 6.6 cc/second	0.126 *M* (*C*)	19, 25, 23, 23, 21	22
18	7	N_2, saturated at 0° with H_2O, bubbled into reaction mixture at 6.6 cc/second	0.127 *M* (*A*)	32, 34	33
19	7	N_2, saturated at 0° with H_2O, bubbled into reaction mixture at 6.6 cc/second	0.127 *M* (*C*)	31, 29	30
20	10	N_2, saturated at 0° with H_2O, bubbled into reaction mixture at 6.6 cc/second	0.127 *M* (*A*)	42, 41, 43	42
21	10	N_2, saturated at 0° with H_2O, bubbled into reaction mixture at 6.6 cc/second	0.126 *M* (*C*)	46, 44, 43	44
22	15	N_2, saturated at 0° with H_2O, bubbled into reaction mixture at 6.6 cc/second	0.127 *M* (*A*)	58, 54, 58	57
23	15	N_2, saturated at 0° with H_2O, bubbled into reaction mixture at 6.6 cc/second	0.126 *M* (*C*)	58, 57	58
24	30	N_2, saturated at 0° with H_2O, bubbled into reaction mixture at 6.6 cc/second	0.127 *M* (*B*)	94, 96	95

*6.3×10^{-3} *M* in tetrahydrofuran at 0°.

†Letters *A*, *B*, and *C* designate the stock solution of lithium aluminum hydride. Solution *B* was a portion of stock solution *A* that had been allowed to stand under nitrogen for 3 months. Solution *C* was prepared in the same way as *A* from a different lot of lithium aluminum hydride (from the same supplier).

reducing power in which the rate of reaction depends only on the concentration of the substrate. The detailed kinetics of the reduction are, without doubt, considerably more complicated, but the reproducibility of the above results with different stock solutions of lithium aluminum hydride gives confidence that the rates of reduction obtained by this technique would be at least semiquantitatively valid, and hence useful for comparing different organic substrates. It should be noted at this point that the amount of water added was not sufficient to destroy any more than about 10 to 25% of the lithium aluminum hydride, i.e. that the molar ratio of hydride to substrate changed at most from 20 to about 15.

In Table VI are summarized the results of the kinetic experiments which were carried out by passing wet nitrogen (saturated with water vapor at 0°) through solutions of lithium

TABLE VI

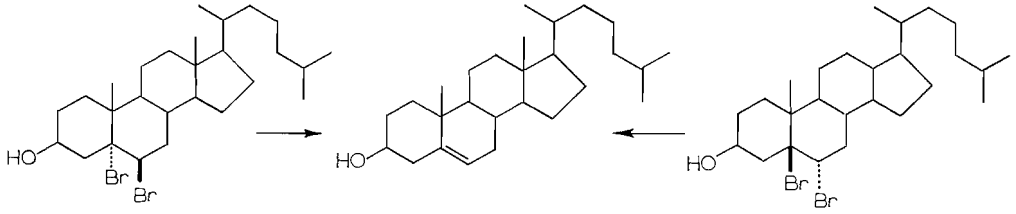
Lithium aluminum hydride reductions of 1,2-dibromides and bromohydrin *p*-toluenesulphonates with continuous addition of wet nitrogen at 0°

Substrate	Time (minutes)	% Reaction of individual experiments*	Approximate time for 20% reaction (minutes)	Isolation yield†
meso-Stilbene dibromide	1	75, 82	0.25	95
dl-Stilbene dibromide	1	21, 23	1.0	—
	1.5	28, 30		
meso-2,3-Dibromobutane	5	21, 24	5	90
dl-2,3-Dibromobutane	5	25, 21	5	86
2β,3α-Dibromocholestane (I*a*)	3.5	19	4	87
	3.75	21		
	4.0	23		
	15	70, 56		
2α,3β-Dibromocholestane (II*a*)	15	9, 11	30	85
	20	15		
	30	21, 23		
trans-1,2-Dibromocyclohexane	4	21, 21, 23	4	77
	15	55		
cis-1,2-Dibromocyclohexane	10	27, 29	—	26
	15	36		
2β-Bromocholestan-3α-yl *p*-toluenesulphonate (I*b*) (diaxial)	6	19	6	
	8	27		91
3α-Bromocholestan-2β-yl *p*-toluenesulphonate (I*c*) (diaxial)	5	36, 38	3	85
2α-Bromocholestan-3α-yl *p*-toluenesulphonate (IV)	15	20	15	74

*Concentrations: $LiAlH_4$, 0.128 *M*; substrate, 6.37×10^{-3} *M*; in tetrahydrofuran.
†After titration, the reaction mixture from one run was worked up in the same way that was used for that substrate to obtain the data in Table III. The numbers in the column give the percentage actually isolated of the quantity expected on the basis of the titration.

aluminum hydride and a variety of organic substrates in tetrahydrofuran. From these data it is readily apparent that those compounds reduce most readily in which the dihedral angle formed by the two carbons and the two leaving groups is 180°. In other words the preferred reaction is a trans elimination. Thus *meso*-stilbene dibromide reduces faster than *dl*-stilbene dibromide and the diaxial steroids reduce more readily than their diequatorial (or their cis) isomers. In most instances the rate differences were not very large, and with the 2,3-dibromobutanes there was no apparent rate difference at all. The products from the reduction of the 2,3-dibromobutanes, however, show that the reaction is strictly a trans elimination (see Table III). It is of interest that under the "anhydrous" conditions *meso*-2,3-dibromobutane apparently reduces slightly faster than the racemic isomer.

Under the "anhydrous" conditions also, 5α,6β-dibromocholestan-3β-ol (V), in which the bromine atoms are diaxial, apparently reduces more than 40 times faster than its di-equatorial isomer (VII).



V VI VII

For those compounds in which the dihedral angle of 180° is not readily formed, trans elimination may require extra activation energy, and other reactions, especially cis elimination and substitution, may compete. An example is the reduction of *dl*-stilbene dibromide, which at −10° in tetrahydrofuran gives 5% *cis*-stilbene (the trans elimination product) and 95% *trans*-stilbene (formally, at least, the product of a cis elimination). At higher temperatures a higher proportion of the cis isomer is formed. *cis*-Stilbene is gradually isomerized to *trans*-stilbene under the reaction conditions but the rate is too slow to account for the quantity of *trans*-stilbene produced in these reductions. In addition it was found that 1,2-diphenylethyl bromide yields no *trans*-stilbene under the conditions of the reaction; this clearly demonstrates that this reduction, unlike some cis reductions with sodium iodide (36), cannot be rationalized by a two-step process of initial substitution by one equivalent of the reducing agent followed by a trans elimination. The experiments do not exclude the possibility that under the reaction conditions the *dl*-stilbene dibromide rearranges to the *meso* isomer which is then rapidly reduced; the rearrangement of *dl*-stilbene dibromide above its melting point is well-known (37) but the likelihood of a rapid rearrangement at −10° seems small.

A second compound which undergoes cis elimination is *cis*-1,2-dibromocyclohexane which yields cyclohexane together with a larger amount of the monosubstitution product, bromocyclohexane. *cis*-1,2-Dibromocyclohexane is an apparently stable compound with no tendency to isomerize to the trans isomer; preliminary isomerization followed by trans elimination would seem very unlikely indeed. Again the possibility of substitution followed by metathetical elimination is excluded by the observation that bromocyclohexane yields no cyclohexene under the conditions of the reaction. In the sense that the reaction cannot be reasonably interpreted as involving a preliminary transformation followed by a trans elimination, the formation of cyclohexene from *cis*-1,2-dibromocyclohexane evidently must be regarded as a "true" cis elimination; further mention of this will be made in the discussion of the mechanism.

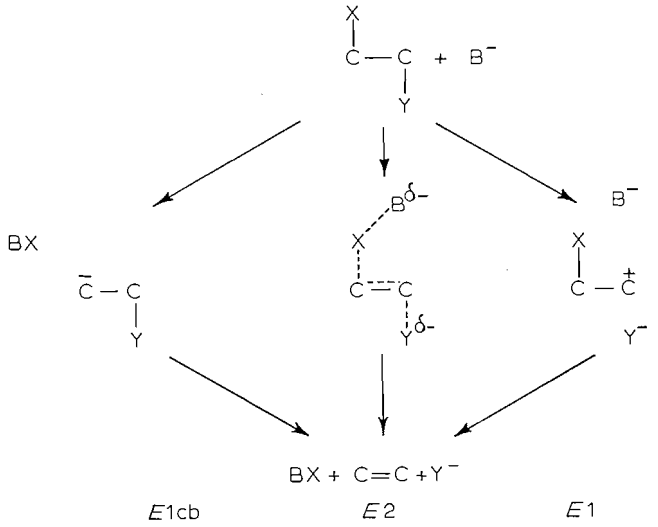
The reductive elimination of 2α-bromocholestan-3α-yl tosylate (IV), in which the bromine and tosyloxy groups are cis, would also appear to be a true cis elimination for the following reasons. Displacement of the bromine by hydride followed by dehydrohalogenation of the resultant tosylate (cholestan-3α-yl tosylate) is excluded because the latter compound does not give cholest-2-ene (III) under the reaction conditions. The alternative substitution–metathetical elimination pathway, which would require the intermediacy of 2α-bromocholestane, would seem extremely unlikely in view of the lack of olefin obtained from bromocyclohexane.

Referring again to Table VI, another point of interest is the fact that the two diaxial

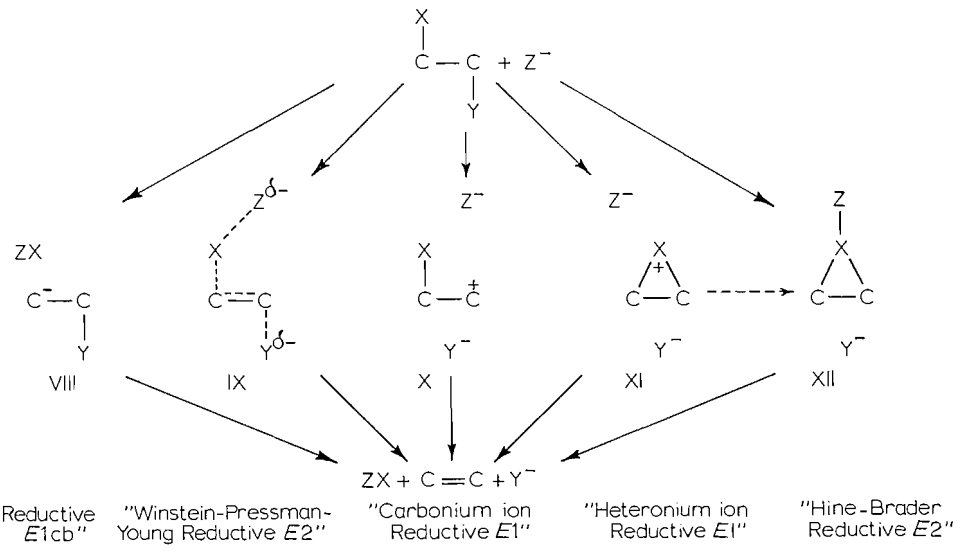
bromohydrin tosylates (I*b*) and (I*c*) reduce at about the same rate as the corresponding dibromide (I*a*). In this respect the reduction with lithium aluminum hydride differs from that with sodium iodide. With the latter reagent Cristol *et al.* (36) found that *trans*-2-bromocyclohexyl tosylate reduced about 20 times faster than *trans*-1,2-dibromocyclohexane.

Discussion of Mechanism

It would seem natural, in attempting to determine the mechanism of a reductive elimination reaction, to make use of the concepts which have been developed for the metathetical processes. Extension of the mechanisms of metathetical elimination to reductive



METATHETICAL ELIMINATION MECHANISMS



POSSIBLE REDUCTIVE ELIMINATION MECHANISMS

SCHEME 1

elimination is in some respects not trivial and some amplification is required at this point. In scheme 1 are set down the three mechanisms, which, together with mechanisms intermediate in character between these extremes, are currently regarded (38, 39) as describing all ionic metathetical eliminations which lead to the formation of olefins. Underneath are extensions which have been or may be made to apply to ionic reductive elimination. The arrangement in scheme 1 is such that between each mechanism and the one adjacent to it, one can easily visualize a continuous range of hybrid or "in between" processes. The five typical mechanisms shown, together with the hybrid mechanisms, constitute a continuous band or spectrum of reaction pathways. This scheme, though discussed here specifically with respect to reductive elimination, is probably general for all eliminations; the somewhat more restricted scheme for metathetical eliminations probably just reflects the inability of hydrogen to form species such as XI and XII, together with the fact that most of the work on metathetical eliminations has been carried out on compounds in which X = H.

At least three of the five reductive elimination mechanisms have been proposed previously. In 1939, Winstein, Pressman, and Young put forward (40) the mechanism involving species IX (scheme 1) to rationalize the observed kinetic and stereochemical data for the reduction of 1,2-dibromides with sodium iodide; since then it has been usual for most authors to discuss the mechanism of other reductive eliminations in terms of this process. Hine and Brader, however, put forward another reductive *E*2 mechanism (proceeding via species XII in scheme 1) for the reaction of dibromides with iodides (41); their chief point in favor of this mechanism is that it allows the halogenation and dehalogenation reactions to proceed via the same species (though, of course, in the reverse sequence). The "reductive *E*1cb" mechanism has been suggested (1) for the reduction of 1,2-dibromides with bivalent metals.* (The designation "reductive *E*1cb" is used in this discussion in order to show the parallel with the metathetical reaction; the literal significance of the term is lost, however, since the intermediate anion (VIII) is not the conjugate base of the starting material.)

To complete this mechanistic scheme it is apparently necessary to postulate mechanisms involving *both* the carbonium and "heteronium" ions, (X) and (XI) respectively, since depending on the nature of the substituent X and on the substitution of the carbon bearing Y, heterolysis of the starting material may lead to either of the extreme species and presumably also to a range of cations of intermediate character. It has recently been reported that an episulphonium salt is reduced to the corresponding olefin with sodium iodide (42). It is attractive to regard this reduction either as representing an example of the second stage of the "heteronium ion *E*1 reaction" (XI → olefin, directly), or alternatively as proceeding first to the Hine–Brader intermediate, as indicated by the dotted arrow, followed by olefin formation (i.e. XI → XII → olefin).

It should be emphasized that the possible reductive elimination mechanisms in scheme 1 are put forward in the hope of creating some order in the study of these transformations. Some of the mechanisms, though plausible, are nonetheless quite speculative. To our knowledge, in no case has *any* of the five mechanisms been established beyond question. It is in the context of this primitive state of the knowledge of these reactions that the following discussion of the lithium aluminum hydride reduction must be viewed.

Of the five mechanisms in scheme 1, two may be readily excluded for the reductive

**These authors do not draw a clear distinction between the "reductive E1cb" and the "Winstein–Pressman–Young reductive E2" mechanisms, but their discussion of the non-stereospecific reduction of the stilbene dibromides and related compounds is, in effect, in terms of the E1cb mechanism.*

elimination with lithium aluminum hydride. Neither the "reductive *E*1cb" mechanism nor the "carbonium ion reductive *E*1" mechanism satisfactorily accounts for the observed predominance of trans elimination and hence cannot be important routes for the reduction. The available data do not allow any definite conclusions to be drawn concerning the other three reductive elimination mechanisms. The "heteronium ion reductive *E*1" and, perhaps more particularly, the "Hine–Brader reductive *E*2" mechanisms might be expected to be strictly trans eliminations,* so that any scheme involving either of these would probably require the postulation of one of the other mechanisms to explain the cis eliminations. On the other hand it has recently been proposed (43, 44) that the metathetical *E*2, reaction takes place most readily when the leaving groups and the carbons to which they are directly attached form a dihedral angle of either 0° or 180°. If the geometrical requirements for the "Winstein–Pressman–Young *E*2" reaction are the same, then it by itself would account for all of the reductive eliminations described in this paper. The fact that the cis elimination is somewhat slower than the trans would be regarded simply as a reflection of the extra energy required for the compound undergoing cis elimination to achieve the totally eclipsed conformation (44). The ability of the "Winstein–Pressman–Young *E*2" mechanism to account for all of the observed elimination products is an attractive feature favoring this possibility, but it cannot be regarded as conclusive evidence.

There does not appear to have been any previous mention of the "heteronium ion reductive *E*1" mechanism,† and lest it be dismissed too lightly it is perhaps worth pointing out that such a mechanism fits readily into the pattern of the reactions of lithium aluminum hydride with organic halides generally. It was early recognized (25) that *substitution* at a saturated carbon with lithium aluminum hydride was a nucleophilic attack on carbon by a hydride ion or its complex equivalent. In addition it has been clearly shown that the displacement in simple secondary bromides and tosylates is predominantly a S_N2 reaction (45). Nonetheless there are a number of cases in which it seems likely that the reaction proceeds via a S_N1 mechanism. Corey and co-workers (46) have observed that the products formed in the reduction of cholesteryl tosylate are not compatible with a S_N2 process but are readily accounted for by assuming that the homoallylic carbonium ion is an intermediate. Other phenomena more readily explained by a S_N1 rather than a S_N2 mechanism are: (i) the high reactivity of triphenylmethyl chloride (25), (ii) the formation of rearranged products from 2-phenyl-3-pentyl tosylate (47), 7-chloronorbornadiene (35, 48), and 1-bromo-7-norbornanone (49) as well as cholesteryl tosylate (46, 50). In addition it may be noted that the tropylium ion is reduced to tropilidene (51), showing that an undoubted carbonium ion can, in fact, be reduced to the hydrocarbon with lithium aluminum hydride.

**This expectation rests on two assumptions: (i) that the formation of the intermediates XI and XII involves displacement of Y^- with inversion of configuration, and (ii) that no geometrical isomerization takes place before or during reduction of the intermediate (XI or XII) to the olefin. It is reasonable to expect that these assumptions would be valid in most instances, but it is possible to imagine exceptions, especially with the "heteronium ion E1" reaction; to the extent that such exceptions are plausible in the present instance, then the force of the argument favoring the "Winstein–Pressman–Young E2" mechanism is diminished. The distinction that is being drawn at this point is that there are* real *cis eliminations in a reaction which is believed to be analogous to the "Winstein–Pressman–Young E2" reduction, whereas any cis eliminations in the other two eliminations are, at present, hypothetical.*

†NOTE ADDED IN PROOF: *Such a mechanism, as we have belatedly discovered, has, in fact, been proposed by J. W. Cornforth, R. H. Cornforth, and K. K. Mathew (J. Chem. Soc. 112 (1959)). Specifically these authors suggest that a three-membered ring iodonium is an intermediate in the reduction of iodohydrins to olefins by means of a mixture of stannous chloride and phosphorus oxychloride in pyridine. The data in this admirable paper are not sufficient to establish the mechanism rigorously (they would fit equally well with the "Hine–Brader reductive E2" mechanism, for example), and at the moment the proposal would appear to be best described as an attractive and reasonable suggestion.*

Ionization of a 1,2-dibromide or bromohydrin tosylate is believed to lead to a bromonium ion (52, 53). Such an ion, in principle, could be attacked by hydride either at carbon or bromine; the former would lead to formation of the monobromide, the latter to the olefin (which reaction is, of course, simply the "heteronium ion *E*1" reduction of scheme 1). Such a direct reduction of a bromonium ion to an olefin is not implausible and finds parallel in the formation of olefins by the reduction of episulphides with lithium aluminum hydride (54) or triethyl phosphite (55), and also the reduction, referred to above, of an episulphonium ion with sodium iodide (42). It is perhaps of interest that the bromonium ion mechanism can account for the formation of 2-bromoöctane (as well as 1-octene) from 1,2-dibromoöctane (see Table II). In this case since one of the carbons of the bromonium ion is primary, attack on that carbon might be expected to be an important reaction path. (Another rationalization of the formation of 2-bromoöctane is mentioned below.)

To sum up this discussion of the three stereospecific mechanisms in scheme 1, it appears that attractive cases may be made for both the "Winstein–Pressman–Young *E*2" and the "heteronium ion *E*1" mechanisms but there is no reason to fault the "Hine–Brader *E*2" mechanism. The possibility either of two or more concurrent mechanisms* or of a hybrid or "in between" mechanism exists but does not warrant discussion until more data are obtained.

Another question raised by this study is the cause of the temporary accelerating effect of water. A priori it is conceivable that reaction of water with lithium aluminum hydride produces a reagent of greater reducing power than lithium aluminum hydride itself. But it has been reported that the lithium alkoxyaluminohydrides in general are weaker reducing agents than lithium aluminum hydride (57); this is in agreement with our finding that lithium tri-*t*-butoxyaluminohydride does not react with 2β,3α-dibromocholestane in refluxing tetrahydrofuran. Eliel and Prosser (34) have called attention to this point in connection with the effect of added water and alcohols in the reduction of chlorohydrins, and have concluded that the accelerating effect in their system may be due to the formation of a more active Lewis acid in the mixture. Such a Lewis acid could accelerate these reactions by adding onto the halide (or tosylate) group to give an easily heterolyzed complex. Such a process would fit in with any of the mechanisms in scheme 1, it would simply mean that the Y groups would be complexed leaving groups rather than the original halide or tosylate functions. A preliminary complexing with a Lewis acid is probably necessary for either the *E*1 or the S_N1 reactions with lithium aluminum hydride (assuming that they exist), since most halides or tosylates do not ionize spontaneously and rapidly in the solvents used for these reactions. Aluminum hydride has been suggested as the active Lewis acid facilitating the formation of an ionic intermediate (58), but the complex of aluminum hydride with tetrahydrofuran is apparently stable under the conditions of our study (59, 60) and therefore is a poor candidate to explain the comparatively short lifetime of the accelerating effect observed in our case. The present data are consistent with the possibility that the accelerating effect of water is due to an hydroxyaluminohydride ($Al(OH)_nH_{4-n}$) which rapidly disproportionates, reacts with solvent, and (or) polymerizes. The inorganic products formed in the reaction do not show any noticeable catalytic activity: a solution of lithium aluminum hydride in which *meso*-stilbene dibromide had been completely reduced showed no greater reactivity than one that had had no stilbene dibromide added to it.

**It has recently been suggested that reduction of ethylene dibromide with sodium iodide in acetone involves* both *the "Winstein–Pressman–Young E2" and the "Hine–Brader E2" mechanisms (56).*

Among the data in Tables II and III are a number of cases in which direct displacement of halogen by hydride predominates over reductive elimination. These are, in particular, the reactions of (*a*) 1,2-dibromoöctane, in which the displaced bromine is primary, (*b*) *trans*-1,4-dibromo-2-butene, in which the displaced bromine is allylic, and (*c*) ethyl β-chloroethyl ether, in which the displaced chlorine is on the same carbon as the ether oxygen; in each of these cases the relatively fast displacement is easily rationalized in terms of known properties of the S_N2 reaction. The cycloöctatetraene dibromide reduction is readily explained if it is assumed that the reduction proceeds through the monocyclic valence tautomer, in which both bromine atoms are allylic. The formation of bromocyclohexane from *cis*-1,2-dibromocyclohexane presumably reflects the ability of displacement to compete with reductive elimination when steric factors retard the latter reaction.

The reduction of the *trans*-2,3-dichlorocholestanes leads to cholest-2-ene, together with roughly the same amount of what appears to be cholestane, and a smaller amount of a mixture consisting of all four of the 2- and 3-cholestanols in approximately equal proportions. The surprising formation of the cholestanol mixture would appear to result from displacement of chlorine by hydroxide or oxygen bound in some form to aluminum. The most likely source of the oxygen is hydrolyzed reagent though the ratio of mixed cholestanols to other materials in the product is not sensitive to the extent of hydrolysis of the reagent: carrying out the reaction with carefully dried apparatus and solvent gives the same mixture as that obtained in the presence of wet nitrogen. It is not difficult to devise a scheme which accounts for the cholestanols being formed, but it is not particularly obvious why the four isomers should be formed in similar quantities. A similar mixture of cholestanols is also formed in low yield from 2α-bromocholestan-3β-yl tosylate. With this compound the hydroxyl group in the products might conceivably arise by S—O fission of the ester, but the similarity of the composition of the mixture of cholestanols to that obtained from the dichlorocholestanes suggests that they arise by a similar mechanism. Experiments are now being carried out which, it is hoped, will provide evidence as to the origin of the cholestanol mixture.

EXPERIMENTAL

Infrared spectra were obtained using Beckman IR-5 or IR-7 spectrophotometers equipped with sodium chloride optics; all values quoted for the frequencies of infrared maxima were determined with the IR-7 instrument. Melting points, which were determined on a Kofler hot stage, and boiling points are uncorrected. Optical rotations refer to chloroform solutions at room temperature ($c \sim 1.0$). The refractive indices were determined with a thermostatically controlled Bausch and Lomb refractometer. Thin-layer chromatography was carried out using Camag Kieselgel D5 or DF5. Petroleum ether, unless otherwise specified, refers to the fraction of boiling range 35–60°. All glassware used for rate measurements and the distillation of solvents was dried at 200° or more for not less than 2 hours.

The tetrahydrofuran used in this study was Fisher Certified Reagent refluxed for not less than 4 hours with lithium aluminum hydride and then distilled. Triglyme was purified as previously described (61). Dioxane was purified by the method of Vogel (62) and stored under dry nitrogen; it was tested for peroxides before use and if these were found present, it was redistilled from lithium aluminum hydride. The benzene for the iodometric titrations was BDH "Analar" grade refluxed over calcium hydride and distilled. Mallinckrodt "ether anhydrous analytical reagent" was used in reductions without further purification.

2β,3α-Dibromocholestane

Prepared from cholest-2-ene as described by Alt and Barton (63); m.p. 123–124°, $[\alpha]_D$ +76°; reported m.p. 123–124°, $[\alpha]_D$ +76°.

2α,3β-Dibromocholestane

Prepared from 2β,3α-dibromocholestane as described by Alt and Barton (63); m.p. 143–145°, $[\alpha]_D$ −29°; reported m.p. 144–145°, $[\alpha]_D$ −29°.

2β,3α-Dichlorocholestane

Prepared from cholest-2-ene as previously described (63); m.p. 105–108°, $[\alpha]$ +61°; reported m.p. 108–112°, $[\alpha]$ +63°.

2α,3β-Dichlorocholestane
Prepared from cholest-2-ene as previously described (63); m.p. 148–150°, $[\alpha]_D$ −4°; reported m.p. 150–152°, $[\alpha]_D$ −7°.

5α,6β-Dibromocholestan-3β-ol
Prepared as previously described by Fieser (64). Recrystallization from ether – petroleum ether gave a product m.p. 115–117°, $[\alpha]_D$ −45°; reported m.p. 112–114°, $[\alpha]_D$ −44° (65).

5β,6α-Dibromocholestan-3β-ol
The following procedure was found to be more convenient than that of Barton and Miller (65). 5α,6β-Dibromocholestan-3β-ol (3.5 g) was refluxed in spectroscopic grade carbon tetrachloride (100 ml) for 24 hours. About 60 ml of the solvent was removed *in vacuo* and the solution was then diluted rapidly with methanol. The first crop of crystals was unchanged starting material. Further dilution with methanol furnished, after recrystallization from ether–methanol, 5β,6α-dibromocholestan-3β-ol (1.3 g), m.p. 141–143°, $[\alpha]_D$ +45°; reported m.p. 143°, $[\alpha]_D$ +47°.

2β-Chlorocholestan-3α-ol
Prepared from 2α,3α-epoxycholestane as previously described (63); m.p. 118–121°, $[\alpha]_D$ +40°; reported m.p. 118–120°, $[\alpha]_D$ +39°.

2α-Bromocholestan-3α-ol
Prepared by reduction of 2α-bromocholestan-3-one with sodium borohydride as previously described (66); m.p. 116–118°, $[\alpha]_D$ +36°; reported m.p. 117–118°, $[\alpha]_D$ +33°.

2α-Bromocholestan-3α-yl p-Toluenesulphonate
Prepared from the alcohol in the usual way (61); recrystallized four times from acetone, m.p. 237–240°, $[\alpha]_D$ +40°. Calc. for $C_{34}H_{53}O_3SBr$: C, 65.68; H, 8.59; S, 5.16; Br, 12.85%. Found: C, 65.74; H, 8.45; S, 4.97; Br, 13.02%.

2β-Chlorocholestan-3α-yl p-Toluenesulphonate
Prepared from the alcohol in the usual way (61); recrystallized four times from acetone, m.p. 182–183°, $[\alpha]_D$ +46°. Calc. for $C_{34}H_{53}O_3SCl$: C, 70.73; H, 9.25; S, 5.55; Cl, 6.14%. Found: C, 71.20; H, 8.91; S, 5.59; Cl, 5.91%.

2β-Bromocholestan-3α-yl p-Toluenesulphonate
Prepared as previously described (67), m.p. 168–170°, $[\alpha]_D$ +49°; reported m.p. 168–170°, $[\alpha]_D$ +49°.

3α-Bromocholestan-2β-yl p-Toluenesulphonate
Prepared as previously described (61), m.p. 174–177°, $[\alpha]_D$ +49°.

2α-Bromocholestan-3β-yl p-Toluenesulphonate
Prepared as previously described (61), m.p. 135° and around 165°, $[\alpha]_D$ −38.5°.

Derivatives of 1,2-Diphenylethane
meso-Stilbene dibromide: crystallized from toluene, m.p. 237°. *dl*-Stilbene dibromide: m.p. 113–114°. *meso*-Stilbene dichloride: m.p. 191–193°. *dl*-1,2-Diphenylethanol: m.p. 65–67°. *dl*-1,2-Diphenylethyl bromide: prepared by the method of Curtin and Kellom (68): n_D^{20} 1.6015. *erythro*-1,2-Diphenyl-2-bromoethyl fluoride: prepared by Dr. J. Newton (69): m.p. 104–105°. *erythro*-1,2-Diphenyl-2-bromoethyl methyl ether: prepared as described by Bartlett and Tarbell (70): m.p. 117–120°.

Derivatives of Butane
(a) meso-2,3-Dibromobutane.—*trans*-2-Butene (99 mole % minimum, supplied by Phillips Petroleum Company, Special Products Division, Bartlesville, Oklahoma) was bubbled slowly into an ether solution (150 ml) of bromine (16 g) cooled in a dry-ice and carbon tetrachloride bath, until the solution became colorless. The reaction mixture was then poured into water and extracted with ether. The ether extract was washed with dilute sodium sulphite solution, dilute potassium bicarbonate solution, and water, and dried over sodium sulphate. Removal of the solvent and distillation of the residue gave after a small forerun, *meso*-2,3-dibromobutane (8.0 g); b.p. 72–73° (51 mm); n_D^{20} 1.5120; reported b.p. 72.7–72.9° (50 mm), n_D^{20} 1.5116 (71).
(b) dl-2,3-Dibromobutane.—This compound was prepared from *cis*-2-butene (99.97 mole % minimum supplied by Phillips Petroleum Company, Special Products Division, Bartlesville, Oklahoma) by the same procedure as described above for *meso*-2,3-dibromobutane; b.p. 72.5–73.5° (50 mm), n_D^{20} 1.5143; reported b.p. 75.6–75.8° (50 mm), n_D^{20} 1.5147 (71).

Derivatives of Cyclohexane
(*a*) *trans*-1,2-Dibromocyclohexane was prepared by the addition of bromine to cyclohexene in carbon tetrachloride as previously described (72); n_D^{25} 1.5507; reported n_D^{25} 1.5507 (73).

(*b*) *cis*-1,2-Dibromocyclohexane was prepared by the free radical addition of hydrogen bromide to 1-bromocyclohexene as described by Goering *et al.* (74). Recrystallization from pentane gave the product, m.p. 6–8°; reported m.p. 9–10°.

(*c*) *trans*-1-Bromo-2-fluorocyclohexane was supplied by Mr. F. H. Dean (69), n_D^{20} 1.4820; b.p. 88–90° (84 mm).

Lithium Aluminum Hydride Stock Solutions

Lithium aluminum hydride (Metal Hydrides Inc.) sufficient to give an approximately 0.8 ± 0.2 *M* solution was placed in a Soxhlet extractor and extracted with anhydrous tetrahydrofuran. The stock solution was then attached to the burette assembly as in Fig. 1. The molarity of the stock solution was determined by the addition of excess standardized iodine in anhydrous benzene, followed by back titration with sodium thiosulphate as described by Felkin (31).

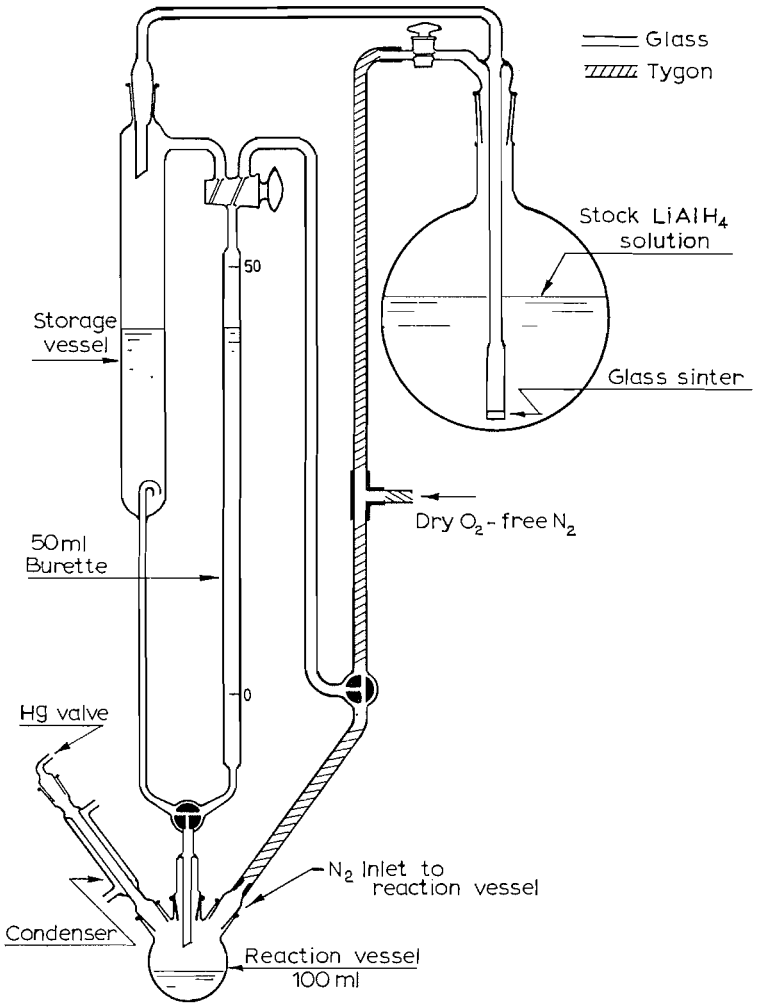


FIG. 1.

Procedure for the Determination of the Stoichiometry

Anhydrous tetrahydrofuran (approx. 150 ml) was distilled under a nitrogen atmosphere into a three-necked flask (300 ml) containing the dibromide (approx. 8 mmoles) and fitted with reflux condenser, magnetic stirrer, and drying tube. The flask was quickly transferred from the distillation assembly to the burette containing the stock solution of lithium aluminum hydride (see Fig. 1), and excess hydride added. After the

addition of the hydride was complete, the reaction mixture was refluxed for 1 hour in the *meso*-stilbene dibromide experiments and 2 hours in the 5α,6β-dibromocholestan-3β-ol experiments. The active hydride remaining after reduction was titrated with a standardized solution of iodine in benzene (31). Blank experiments with stilbene and cholesterol, respectively, were carried out to determine the amount of hydride lost during the operations. For these experiments both the 5α,6β-dibromocholestan-3β-ol and the cholesterol were recrystallized from ether – petroleum ether and carefully dried. The results are recorded in Table VII.

After the iodine titration, the reaction mixture was poured into water and extracted with ether. The ether extract was washed with dilute sodium sulphite solution, dilute sulphuric acid, and water, dried over sodium sulphate, and the solvent evaporated. The olefin was then recrystallized from ether–ethanol. The yields are summarized in Table VII.

General Procedure for Rate Measurements with Lithium Aluminum Hydride (Tables IV to VI)

(a) The Reaction

The glassware was heated in an oven (minimum temperature 200°) for not less than 4 hours before use. A three-necked, round-bottomed flask (100 ml) equipped with condenser, magnetic stirrer, stopper, and nitrogen inlet tube was quickly assembled and heated with a Bunsen burner flame while dry nitrogen was passed through the apparatus. When the apparatus had cooled to room temperature, the stopper was quickly removed and the substrate (0.366 mmole) and tetrahydrofuran (50 ml) added to the reaction vessel under positive nitrogen pressure. The reactants were cooled in an ice bath to 1±1°. The reaction vessel was quickly transferred from the ice bath to the burette assembly (see Fig. 1) and lithium aluminum hydride (7.32 mmoles) in tetrahydrofuran added. The reduction was stopped by pouring the reaction mixture into water (150 ml). In the kinetic experiments in which water was initially present before the addition of lithium aluminum hydride, the water was mixed with the anhydrous tetrahydrofuran. In all other experiments involving addition of water, nitrogen saturated with water vapor by passage through an ice–water trap was bubbled into the reaction vessel at a constant flow rate. The flow rate (6.6 ml/second) was measured with a burette (50 ml) as a soap bubble flow meter.

(b) Method of Bromide Ion Analysis

The reaction mixture, after being quenched with water, was acidified with glacial acetic acid (approx. 20 ml). The amount of bromide ion was then determined by potentiometric titration with *N*/10 silver nitrate using an Electronic Instruments Ltd. (Surrey, England) Model 23A pH meter, and the following electrode system: silver electrode in contact with the bromide ion solution, with a calomel reference cell in a separate beaker and connected to the titration vessel through an ammonium nitrate bridge. To inhibit gumming of the silver electrode by the organic precipitate, benzene (ca. 50 ml) was added to the titration mixture. Under the titration conditions the organic substrates do not react with silver nitrate. A blank titration of the hydrolyzed reagent showed the presence of a small amount of halide ion (presumably lithium chloride); the quantity of silver nitrate consumed by the hydrolyzed reagent was determined before each run and was subtracted from the titer of that run.

Reaction of Lithium Aluminum Hydride with Water

The following experiments were carried out to measure the amount of lithium aluminum hydride (or active hydride) destroyed by bubbling moist nitrogen into the solution under the conditions described in the above section. In two experiments wet N_2 (saturated at 0°) was bubbled into the mixture at the rate of 6.6 ml/second for an interval and the mixture then titrated immediately with I_2 in benzene. In the other two experiments a quantity of water equal to that calculated to have been added in the wet N_2 experiments was added directly and the mixture allowed to stand for the same length of time as the N_2 had been bubbled in and the mixture then titrated with I_2 in benzene. The results are summarized in Table VIII.

Reaction of Lithium Aluminum Hydride with 1,2-Dihalides and Related Compounds (Table III)

General Procedure

A number of the reactions gave a crystalline product in good yield. In each of these cases, the substrate (ca. 50 mg) was refluxed for 1 hour in 1.0 *M* lithium aluminum hydride (ca. 4 ml). The reaction mixture was poured into water and extracted with ether. The ether extract was washed with dilute sulphuric acid and water, dried with sodium sulphate, and the solvent evaporated. Recrystallization gave a product which was identified by melting point, infrared spectrum, and where useful, optical rotation. The yields are summarized in Table III.

Other reactions are described individually below.

(a) 2α-Bromocholestan-3β-yl p-Toluenesulphonate.—Examination of the reaction product by thin-layer chromatography gave the following results: tile 1 (petroleum ether) indicated only trace amounts of cholestane and cholest-2-ene (identified by authentic samples run on the same tile); tile 2 (petroleum ether – benzene, 1:1) established the absence of starting material; tile 3 (benzene–ether, 3:1) showed the presence of not less than 10 products, four of which appeared to be the 2- and 3-hydroxycholestanes by their R_f values.

(b) 2β,3α-Dichlorocholestane.—In addition to a strong hydroxyl band at 3620 cm^{-1}, only unreacted starting

TABLE VII

Stoichiometry experiments

	Dibromide added (mmoles)	$LiAlH_4$ added (mmoles)	$LiAlH_4$ consumed in experiment (mmoles)	$LiAlH_4$ consumed by blank (mmoles)	Net $LiAlH_4$ consumed by reduction (mmoles)	$LiAlH_4$ consumed per mole of dibromide (mmoles)	Yield of olefin (%)
meso-Stilbene dibromide	9.71	12.00	5.67	1.15	4.52	0.47	95
	9.64	11.00	5.69	1.20	4.49	0.47	91
$5\alpha,6\beta$-Dibromocholestan-3β-ol	8.07	11.70	6.05		3.55	0.44	95
	8.10	11.70	5.85	2.50	3.35	0.41	97

TABLE VIII

Reaction of $LiAlH_4$ in water

Time (minutes)	Number of runs	Amount of water (mmoles) added and method of addition	$LiAlH_4$ (mmoles)	I_2 (mmoles) titer	$LiAlH_4$ (mmoles) destroyed
0	1	0	7.32	14.6	(0.0)
15*	3	1.62† in wet N_2	7.32	12.5	1.06
30*	3	3.34† in wet N_2	7.32	10.9	1.86
15‡	2	1.62 added directly	7.32	12.1	1.26
30‡	2	3.34 added directly	7.32	10.4	2.10

*Length of time the wet N_2 was bubbled through the mixture.
†Calculated from the volume of N_2 and the saturated vapor pressure of water at 0°.
‡Time elapsed between water addition and I_2 titration.

material could be identified from the infrared spectrum (IR-7) of the reaction product. Thin-layer chromatography gave the following results: tile 1 (petroleum ether) showed, by comparison of the R_f values of authentic samples, the presence of unreacted starting material, cholestane and cholest-2-ene but none of the diequatorial isomer, 2α,3β-dichlorocholestane; tile 2 (benzene–ether, 3:1) showed, by comparison of the R_f values of authentic samples, the presence of the following alcohols, cholestan-2β-ol, cholestan-2α-ol, cholestan-3β-ol, and cholestan-3α-ol.

(c) 2α,3β-Dichlorocholestane.—The reaction product consisted mainly of unreacted starting material. Examination of the thin-layer chromatograms gave the same results as described for 2β,3α-dichlorocholestane with the exception that the six identifiable products were produced in lesser amounts.

(d) cis-1,2-Dibromocyclohexane.— *cis*-1,2-Dibromocyclohexane (3.5 g), lithium aluminum hydride (1.5 g), and anhydrous triglyme (80 ml) were placed in a three-necked, round-bottomed flask equipped with a nitrogen inlet and a reflux condenser. The condenser was connected to a trap cooled in liquid nitrogen. After wet nitrogen was passed through the reaction mixture at room temperature for 1 hour, the temperature was raised to 100° to distil off the volatile fraction (0.27 g) which was found by vapor-phase chromatography to contain 63% of cyclohexene. The reaction mixture was poured into wet ether to destroy the unreacted lithium aluminum hydride and the ether extract washed with dilute sulphuric acid and water, dried over sodium sulphate, and the solvent evaporated. The residue (1.90 g) was analyzed by vapor-phase chromatography and was found to consist of bromocyclohexane, 51%, and unreacted dibromide 49%. These results are equivalent to the following yields: cyclohexane, 26%, and bromocyclohexane, 49%, based on reacted *cis*-1,2-dibromocyclohexane.

(e) trans-1,2-Dibromocyclohexane.—Following the procedure and method of analysis as outlined for the cis isomer, *trans*-1,2-dibromocyclohexane (28 g) and lithium aluminum hydride (7.5 g) in anhydrous triglyme (100 ml) gave cyclohexane (0.5 g, 5%) and cyclohexene (7.3 g, 77%).

(f) meso-2,3-Dibromobutane.—Following the procedure outlined for *cis*-1,2-dibromocyclohexane, *trans*-2-butene was identified as the principal product of the reduction of *meso*-2,3-dibromobutane by comparison of the infrared spectrum (IR-7) with that of an authentic sample. From the absorption bands in the 2800–3000 cm^{-1} region and at 960 cm^{-1} and the lack of absorption at 975 cm^{-1} it was established that *cis*-2-butene was not produced in appreciable amounts if at all. In a separate experiment, the yield of *trans*-2-butene, isolated as the dibromide, was 90%.

(g) dl-2,3-Dibromobutane.—Following the procedure outlined for *cis*-1,2-dibromocyclohexane, *cis*-2-butene was identified as the principal product of the reduction of *dl*-2,3-dibromobutane by comparison of the infrared spectrum (IR-7) with that of an authentic sample. From the absorption bands in the 2800–3000 cm^{-1} region and at 975 cm^{-1}, and the lack of absorption at 960 cm^{-1}, it was established that *trans*-2-butene was not produced in appreciable amounts if at all. In a separate experiment, the yield of *cis*-2-butene, isolated as the dibromide, was 86%.

(h) 1-Fluoro-2-bromocyclohexane.—Following the procedure outlined in (*d*) 1-fluoro-2-bromocyclohexane (3 g), lithium aluminum hydride (1.5 g), and anhydrous triglyme (100 ml) gave fluorocyclohexane (0.8 g, 45%), identified by comparison of the infrared spectrum with an authentic sample and by retention time upon vapor-phase chromatography.

(i) meso-Stilbene Dichloride.—*meso*-Stilbene dichloride (400 mg) was reacted with lithium aluminum hydride (500 mg) in anhydrous tetrahydrofuran (50 ml) for 1 hour at room temperature. Wet nitrogen (as above) was bubbled gently into the solution during the reaction. Isolation of product as in the general procedure and recrystallization of the crude material from benzene–ethanol gave unreacted *meso*-stilbene dichloride (77 mg). Evaporation of the mother liquors and recrystallization from ethanol gave *trans*-stilbene (200 mg), 75% yield based on reacted dichloride.

(j) erythro-1,2-Diphenyl-2-bromoethyl Methyl Ether.—*erythro*-1,2-Diphenyl-2-bromoethyl methyl ether (300 mg) was refluxed for 5 hours in 1.0 *M* lithium aluminum hydride solution (25 ml). Work-up as in the general procedure and recrystallization from ether–methanol gave *trans*-stilbene (45%). Evaporation of the

mother liquors yielded an oil (85 mg) which gave a negative Beilstein test and had an infrared spectrum resembling that of the starting material; this material was not further investigated.

(k) erythro-1,2-Diphenyl-2-fluoroethyl Bromide.—*erythro*-1,2-Diphenyl-2-fluoroethyl bromide (300 mg) was reacted with 1.0 *M* lithium aluminum hydride in tetrahydrofuran solution (15 ml) for 45 minutes at room temperature while wet nitrogen was bubbled gently into the solution. Isolation of the product as in the general procedure and recrystallization from ether–methanol gave *trans*-stilbene (166 mg, 86%).

(l) dl-Stilbene Dibromide.—*dl*-Stilbene dibromide (50 mg) or *cis*-stilbene (35 mg) was reacted with 1.0 *M* lithium aluminum hydride (2.0 ml) in tetrahydrofuran as listed in Table IX. The reaction mixture was

TABLE IX

Reaction of $LiAlH_4$ in tetrahydrofuran with *dl*-stilbene dibromide and *cis*-stilbene

Compound	Time (hours)	Temp.	Product (±10%)
dl-Stilbene dibromide	24	−10°	5% *cis*-, 95% *trans*-stilbene
dl-Stilbene dibromide	24	25°	50% *cis*-, 50% *trans*-stilbene
dl-Stilbene dibromide	1	Reflux	65% *cis*-, 35% *trans*-stilbene
dl-Stilbene dibromide	0.5	25°	55% *cis*-, 45% *trans*-stilbene
cis-Stilbene	1	Reflux	70% *cis*-, 30% *trans*-stilbene
cis-Stilbene	24	25°	40% *cis*-, 60% *trans*-stilbene
cis-Stilbene	48	−10°	95% *cis*-, 5% *trans*-stilbene
cis-Stilbene	0.5	25°	95% *cis*-, 5% *trans*-stilbene

poured into water and extracted with ether. The ether extract was washed with dilute sulphuric acid, dilute potassium bicarbonate, water, dried, and the solvent evaporated. The relative amounts of *cis*- and *trans*-stilbene were determined by comparison of the intensities of the infrared absorption bands at 925 cm^{-1} (cis) and 962 cm^{-1} (trans) with those of authentic mixtures. The results are summarized in Table IX.

Reaction of Lithium Aluminum Hydride with Bromocyclohexane

Bromocyclohexane (10 g) and lithium aluminum hydride (5 g) in anhydrous triglyme (75 ml) were reacted under the same conditions as described for *cis*-1,2-dibromocyclohexane. Cyclohexane (0.6 g) was isolated from the liquid nitrogen trap and identified by infrared spectroscopy and vapor-phase chromatography. Cyclohexene was not detected by either method of analysis. The reaction mixture, worked up as previously described, yielded unreacted starting material (5 g).

Reaction of Lithium Aluminum Hydride with Cholestan-3α-yl p-Toluenesulphonate

This compound was reacted with lithium aluminum hydride under identical conditions as described for 2α-bromocholestan-3α-yl *p*-toluenesulphonate. The infrared spectrum of the product indicated little, of any, loss of the tosylate group. Thin-layer chromatography showed the absence of cholest-2-ene and that the reaction product was mostly unreacted starting material.

Reaction of Lithium Aluminum Hydride with dl-1,2-Diphenylethyl Bromide

dl-1,2-Diphenylethyl bromide (600 mg) was added to a solution of lithium aluminum hydride (600 mg) in tetrahydrofuran. The mixture was allowed to stand for 1 hour at room temperature, and then worked up by pouring into water and extracting with ether. The extracts were washed with water, dried with Na_2SO_4, and the solvent evaporated giving dibenzyl (385 mg); m.p. after recrystallization 49–52°. Thin-layer chromatography of the crude product of a second experiment, carried out in the same way, showed the absence of either starting material or any *trans*-stilbene.

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