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The Conversion of the 3-Chloro-2-butanols to the 2,3-Dichlorobutanes; Evidence for a Cyclic Chloronium Intermediate[1]

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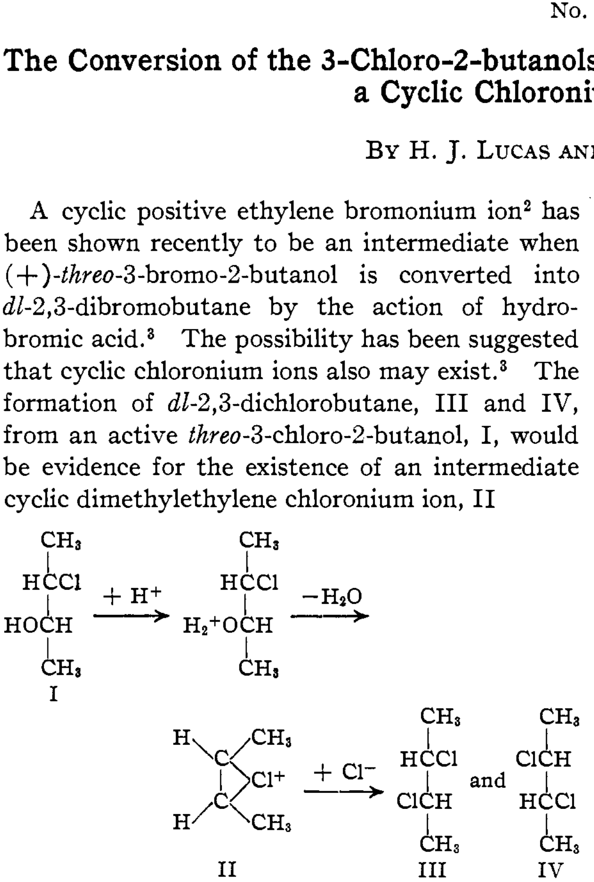
A cyclic positive ethylene bromonium ion[2] has been shown recently to be an intermediate when (+)-*threo*-3-bromo-2-butanol is converted into *dl*-2,3-dibromobutane by the action of hydrobromic acid.[3] The possibility has been suggested that cyclic chloronium ions also may exist.[3] The formation of *dl*-2,3-dichlorobutane, III and IV, from an active *threo*-3-chloro-2-butanol, I, would be evidence for the existence of an intermediate cyclic dimethylethylene chloronium ion, II



I

II

III

IV

However, the chlorohydrins of the 2-butenes cannot be converted to dichlorobutanes by the action of fuming hydrochloric acid or by zinc chloride–hydrochloric acid. They do not even react with fuming hydrobromic acid. Moreover, neither the 3-chloro-2-acetoxybutanes nor the 2,3-diacetoxybutanes yield dichlorides with fuming hydrochloric acid. The former yield the chlorohydrins, and the latter, mixtures of chlorohydrin and chloroacetate.

Thionyl chloride effected the change of (+)-*threo*-3-chloro-2-butanol to *dl*-2,3-dichlorobutane. Other reagents studied were phosphorus pentachloride, phosphorus trichloride, phosphorus trichloride and pyridine, and thionyl chloride and pyridine.

The Inactive 2,3-Dichlorobutanes and 3-Chloro-2-butanols.—Tentatively, configurations were assigned to the two pairs of compounds on the assumption that they are strictly comparable to the configurations of the bromo compounds[4] and that one stereoinversion accompanies the following changes: (1) the addition of chlorine or of hypochlorous acid to 2-butene; (2) the opening of the oxide ring of 2,3-epoxybutane by hydrogen chloride; (3) the formation of the oxide ring by the elimination of hydrogen chloride from 3-chloro-2-butanol. These changes are shown in Fig. 1. Here only one of the two forms of *dl* compounds are shown.

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[1] Presented at the June meeting of the Pacific Section, Am. Assoc. Adv. Sci., Pasadena, California, June 16 to 20, 1941.

[2] (a) Roberts and Kimball, THIS JOURNAL, **59**, 947 (1937); (b) Winstein and Lucas, *ibid.*, **60**, 843 (1938); (c) **61**, 1576 (1939).

[3] Winstein and Lucas, *ibid.*, **61**, 2845 (1939).

[4] The configurations of the 3-bromo-2-butanols[2c] are still provisional. The configurations of the 2,3-dibromobutanes assumed previously are now confirmed by obtaining one with optical activity. This result proves the correctness of the deductions regarding configurations of dibromobutanes from reaction rates studies: Dillon, Young and Lucas, *ibid.*, **52**, 1953 (1930); Young and Winstein, *ibid.*, **58**, 102 (1936); Young, Pressman and Coryell, *ibid.*, **61**, 1640 (1939).

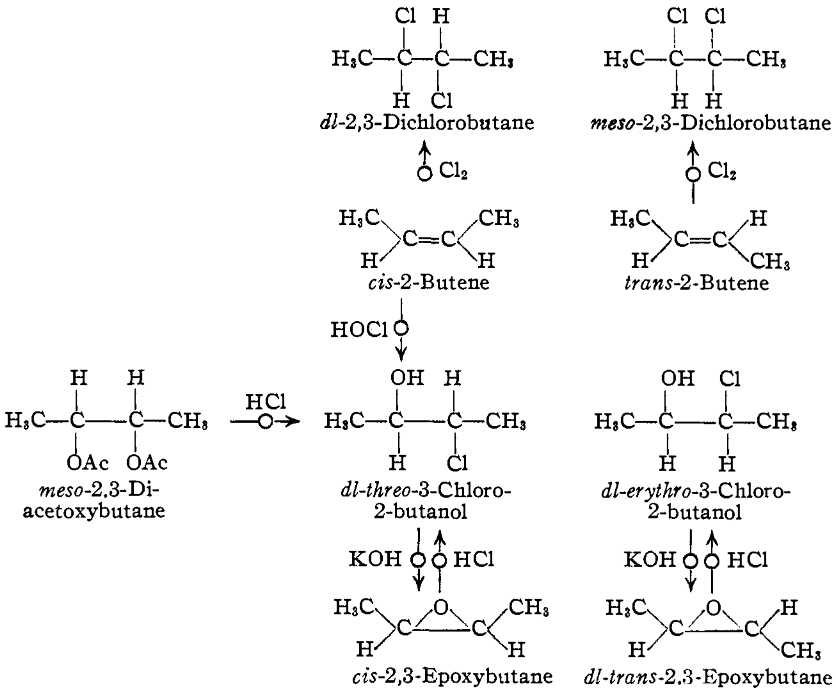

Fig. 1.

The configurations of the 2-butenes[5] and of the 2,3-epoxybutanes[6] are known. The assumed configurations of the 2,3-dichlorobutanes have been confirmed by obtaining one with optical activity, and relating this active form to the *dl* form by similarity in physical properties. The confirmation of the chlorohydrin configurations is not so satisfactory, but is believed to be adequate. It rests upon an explanation of some of the reactions of the chlorohydrins, as discussed later. Some physical properties of the inactive 2,3-dichlorobutanes are shown in Table I and of the 3-chloro-2-butanols in Table II.

The purity of the dichlorides may be open to discussion for it has been shown in the case of the two *dl*-2,3-dibromopentanes that when either of these is converted into the corresponding 2-pentene and then back to the same dibromide, about 2% of the inactive diasteromeric dibromide is present.[7] Although the conversion of each 2-butene to its dichloride was carried out at −20° and in diffused artificial light, conditions which were found to give the best yield and almost completely to eliminate the substitution reaction, the presence of some of the diastereoisomer is not excluded. However, each isomer was subjected to five fractional distillations through a Weston column[8] at 80 mm., and at a reflux ratio of 15 to 20. The physical properties did not change between the last two distillations. There was no evidence from the behavior on distillation that the other isomer was present in appreciable amounts.

The most useful property of the dichlorobutanes which permits analysis of mixtures to be made is the dielectric constant, ϵ, which has been shown to be useful also in connection with dibromobutanes[6,9] and dibromopentanes.[7] This could be determined with an accuracy of 0.1%. In general, the condenser reading was used, however, rather than the dielectric constant. Here the accuracy was about 0.1% also.

The purity of the *dl-erythro* and *dl-threo*-3-chloro-2-butanols is believed to be high because: (1) there was no change in the boiling point or refractive index between the first and second redistillations at 80 mm. through a 60-cm. column of glass helices[10] at a reflux ratio of 20; (2) there was excellent agreement in the physical constants of the different preparations of the *threo*-chlorohydrin (Table II), prepared from *cis*-2,3-epoxybutane, from *meso*-2,3-diacetoxybutane, and from *cis*-2-butene, as indicated in Fig. 1; (3) the physical constants of the oxides prepared from the chlorohydrins were identical with those reported previously.[2c]

The opening or closing of the oxide ring by addition or elimination of hydrogen chloride is a clean-cut reaction, unaccompanied by the side reaction which results in the formation of the diastereomeric chlorohydrin. In this respect the reactions resemble those in which hydrogen bromide is similarly involved.[2c]

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[5] Brockway and Cross, THIS JOURNAL, **58**, 2407 (1936). The respective melting points, Kistiakowsky, Ruhoff, Smith and Vaughan, *ibid.*, **57**, 876 (1935), and rates of reaction with mercuric acetate, Thomas and Wetmore, *ibid.*, **63**, 136 (1941), are confirmatory.

[6] (a) Wilson and Lucas, *ibid.*, **58**, 2396 (1936); (b) Brockway and Cross, *ibid.*, **59**, 1147 (1937).

[7] Lucas, Schlatter and Jones, *ibid.*, **63**, 22 (1941).

[8] Weston, *Ind. Eng. Chem., Anal. Ed.*, **5**, 179 (1933).

[9] Winstein and Lucas, THIS JOURNAL, **61**, 1581 (1939).

[10] Wilson, Parker and Laughlin, *ibid.*, **55**, 2795 (1933); **56**, 1396 (1934); Roper, Wright, Ruhoff and Smith, *ibid.*, **57**, 954 (1935); Young and Jasaitis, *ibid.*, **58**, 377 (1936).

TABLE I

PHYSICAL PROPERTIES OF THE 2.3-DICHLOROBUTANES

	Source							
	Config.	$\alpha^{25}\text{D}$	Reagent	B. p., °C. at 80 mm.	$n^{25}\text{D}$	Condenser reading[25]	$\alpha^{25}\text{D}$	Configuration
Butene	*cis*		Cl_2	53.16^a	1.4409	179.5		*dl*
	trans		Cl_2	49.52^b	1.4386	163.3		*meso*
Chlorohydrin	*erythro*		$PCl_5 + CHCl_3$	50.5–53.0	1.4401	171.0		mixture
	erythro		$SOCl_2$ + Py	53.0–53.2	1.4410	179.2		*dl*
	erythro	+0.82^c	$SOCl_2$ + Py	53.0–53.2	1.4404	179.4	−3.80°	*dl* + (−)
	erythro		$SOCl_2$	48.5–49.0	1.4392	161.4		*meso*
	erythro	+0.82	$SOCl_2$	49.4–49.7	1.4385	164.1	−0.07°	*meso*
	erythro		PCl_3	53.1–53.4	1.4405	180.5		*dl*
	erythro	+0.27	PCl_3	53.0–53.4	1.4400	180.3	− .86°	*dl* + (−)
	threo	+1.10	$SOCl_2$ + Py		1.4395	8.68^d	+ .13	*meso* + (+)
	threo	−0.10	$SOCl_2$	53.0–53.4	1.4402	180.1	.00	*dl*
	threo	+1.10	$SOCl_2$	52.7–53.5	1.4411	9.79^d	− .10	*dl*

[a] B. p. 117.10° (746 mm.); d^{25}_4 1.1063; ϵ^{25} 9.761. [b] B. p. 113.14° (746 mm.); d^{25}_4 1.1023; ϵ^{25} 8.823. [c] All rotations were observed with sodium light in 1-dm. tube at 25°. [d] This is dielectric constant, ϵ.

TABLE II

PHYSICAL PROPERTIES OF *dl*-3-CHLORO-2-BUTANOLS

		B. p., °C., at				
Configuration	Source	30 mm.	748 mm.	d^{25}_4	$n^{25}\text{D}$	Oxide from,^{a} $n^{25}\text{D}$
erythro	*trans*-2,3-Epoxybutane	56.1	135.4	1.0610	1.4397	1.3705
threo	*cis*-2,3-Epoxybutane	52.0	130.8	1.0586	1.4386	1.3802
threo	*meso*-2,3-Diacetoxybutane	52			1.4386	1.3802
threo	*cis*-2-Butene	52			1.4386	1.3802

[a] Constants of pure oxides:[2c] b. p. (742 mm.), *cis* 59.7±0.05°; *trans* 53.5±0.05°; $n^{25}\text{D}$, *cis* 1.3802; *trans* 1.3705.

Reactions of the 3-Chloro-2-butanols.—The reagents were tried out first on the *dl-erythro* isomer, since this was available in larger quantity, from the oxide.[2c] With phosphorus pentachloride a mixture of *meso*- and *dl*-2,3-dichlorobutane is formed, while with phosphorus trichloride and pyridine, no dichloride. However, phosphorus trichloride, thionyl chloride and pyridine–thionyl chloride give only a single product. The yields are poor with the first two and satisfactory (about 70%) with the last. These three reagents therefore were satisfactory. They were tried next on the optically active *erythro*-chlorohydrin, and finally thionyl chloride was tried on the active *threo*-chlorohydrin. The results are shown in Table I.

The physical properties of the dichlorides obtained from the chlorohydrins agree well with those prepared from the butenes, with one exception, *viz.*, the dichloride from the reaction with phosphorus pentachloride, which yields a mixture. The condenser reading or the dielectric constant is the most useful figure. The values for dichlorides possessing optical activity show that the higher boiling 2,3-dichlorobutane has the *dl*- or *threo* configuration, and the lower boiling has the *meso* or *erythro* configuration.

The results with inactive and active forms of the chlorohydrins show that phosphorus trichloride or thionyl chloride in pyridine causes one inversion (or an odd number) and retention of optical activity, while thionyl chloride causes no inversion (or an even number), but loss of optical activity. Figure 2 shows the stereochemical relationships involved in these transformations, and Fig. 3, the steps in the reaction of active *threo* chlorohydrin with thionyl chloride. The formulas are not to be interpreted as showing the true configurations of the optically active forms.

The Cyclic Chloronium Intermediate.—The formation of *dl*-2,3-dichlorobutane III and IV, Fig. 3, from (+)-*threo*-3-chloro-2-butanol (+1.1°) by the action of thionyl chloride necessitates the assumption that a cyclic chloronium ion, II, is an intermediate. Loss of optical activity is not due to any racemizing action of thionyl chloride, for active 2,3-dichlorobutane is not racemized when heated with thionyl chloride for five hours at 100°, and the active chlorohydrin, I, is converted into an active ester, IA, which is the compound which decomposes to yield the dichloride. Moreover, a by-product of the reaction is a dibutyl sulfite, IB, which also possesses optical activity.

The chloronium intermediate, II, accounts for

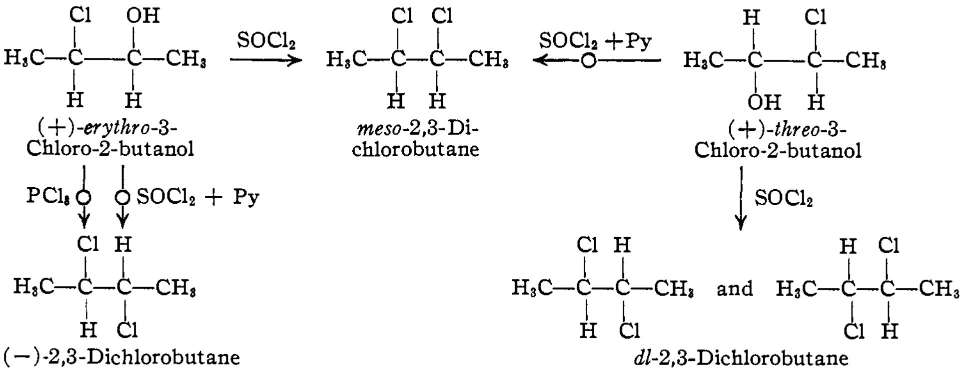

Fig. 2.

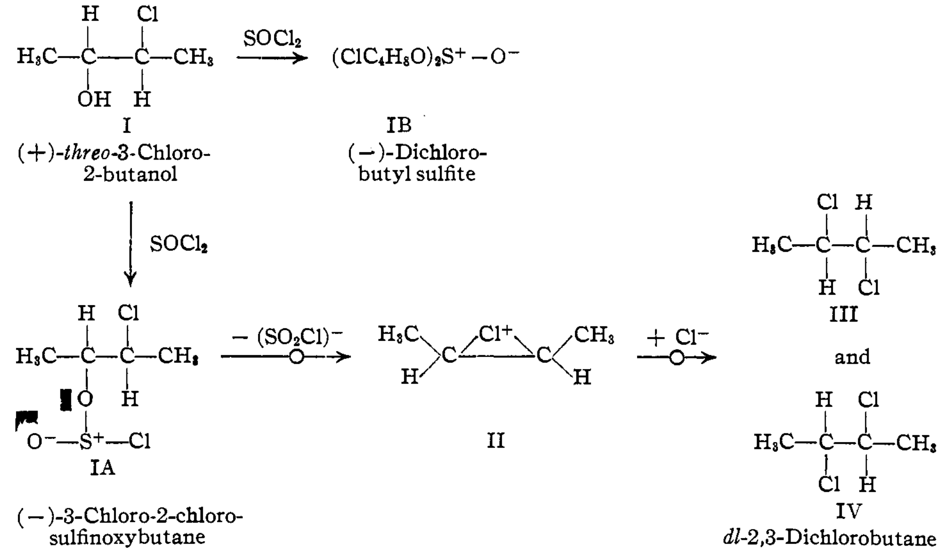

Fig. 3.

equal amounts of III and IV, and for the absence of any *meso* dichloride. Since II is inactive by internal compensation, products formed from it would be expected to be inactive. The formation of II may be explained as the result of a simultaneous loss of the negative ion SO_2Cl^- and attack at the back side of the carbon atom by the chlorine atom attached to the neighboring carbon atom. One inversion accompanies this change. The cyclic intermediate then reacts with chloride ion (or with SO_2Cl^-), which attacks the back side of one of the secondary carbon atoms. If III is the product, one carbon atom of the original chlorohydrin has been inverted twice. If IV is the product, each secondary carbon atom has been inverted once. Thus, the two steps involved in the decomposition of the chlorosulfinoxy compound to the dichloride are typical exchange reactions, the first intramolecular, the second intermolecular. They conform with the usual picture of bimolecular exchange reactions.[11]

When thionyl chloride in pyridine, or phosphorus trichloride reacts, the *trans* chloronium ion is not an intermediate, otherwise there would be zero or an even number of inversions. Actually, the formation of (−)-2,3-dichlorobutane from (+)-*erythro*-3-chloro-2-butanol by the action of these two reagents indicates: (1) one inversion (or an odd number); (2) retention of optical activity; and (3) a change in the sign of rotation. In these reactions, therefore, thionyl chloride in

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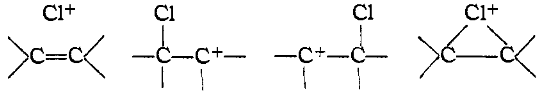
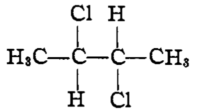
(11) (a) Meer and Polanyi, *Z. physik. Chem.*, **19B**, 164 (1932); (b) Olson, *J. Chem. Phys.*, **1**, 418 (1933). However, Ingold, *et al.*, *J. Chem. Soc.*, 1011 (1940), consider that formation of the cyclic bromonium ion[2,3] belongs to the S_N1 type, since it is essentially a two-stage process involving the preliminary ionization of one of the bromine atoms of 2,3-dibromobutane. The configuration of the intermediate cation is preserved by the α-bromine atom. The symmetry of the system converts through resonance, what would have been a dipole with one covalent and one electrostatic bond, into a ring with two equivalent bonds which are partly covalent and partly electrostatic.

pyridine, and phosphorus trichloride, behave as they do with methylphenylcarbinol[12] and other hydroxy compounds.[13] Since in the present case little or no *meso* dichloride is formed, the reaction takes place essentially with inversion and without any racemization on the carbon atom attacked. To explain the inversion, it probably is correct to say that in the case of thionyl chloride and pyridine, the attack on the back side of the carbon atom is made by chloride ion resulting from the presence of pyridine hydrochloride in the reaction mixture,[14] rather than by the chlorine atom on the adjacent carbon atom.

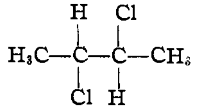
The butylene chloronium ions are stabilized by resonance among four different structures, analogous to the bromonium,[3] silver[15a] and mercury[15b] complexes





$H_3C-\overset{Cl}{\underset{H}{C}}-\overset{H}{\underset{Cl}{C}}-CH_3$

and



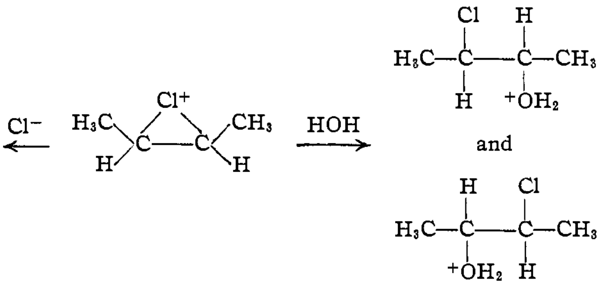
$H_3C-\overset{H}{\underset{Cl}{C}}-\overset{Cl}{\underset{H}{C}}-CH_3$

As in the bromonium complex, the contribution of the cyclic structure is so great that the configuration is stabilized. Thus, at least in the case of the butenes, the reaction follows a single path.

On the above basis, the carbon-to-chlorine bond in the cyclic intermediate possesses a much larger amount of ionic character than does the usual carbon-to-chlorine bond. The bond is broken only when a nucleophilic reagent approaches from the back side of the carbon atom, not the front. The explanation of this mechanism has been made on the basis of dipole interactions.[11] It seems from the behavior of the intermediate that the greater the ionic character of a carbon-to-chlorine bond, the greater is the tendency for attack at the back rather than at the front of the carbon atom. Presumably this is due to the greater orienting effect of the dipole. It may well be that in the dipole character of the bond being broken, and in the variations of this due to changing conditions, lies an explanation of some of the stereochemical differences observed in exchange reactions.

The concept of a cyclic chloronium ion is of value in the interpretation of the course of other reactions connected with this work, besides the ones just discussed. These are: (1) *trans* addition of chlorine to 2-butene; and (2) *trans* addition of hypochlorous acid to 2-butene, by the action of *t*-butyl hypochlorite. The first step in each case is the formation of the cyclic intermediate without inversion, the *cis* intermediate from *cis*-2-butene, the *trans* intermediate from *trans*-2-butene.[16] The next step is attack with inversion at the back side of one of the secondary carbon atoms, in (1) by chloride ion, in (2) by a solvent molecule, which in this case is water. The products from *cis*-2-butene are *dl-threo*-2,3-dichlorobutane and *dl-threo*-3-chloro-2-butanol, respectively. The *trans* isomer yields the *erythro* compounds.

The intermediate oxonium compound arising from the action of water yields the neutral chlorohydrin by loss of a proton. Other solvent molecules can act like water, as for example ethyl alcohol, phenol, acetic acid, etc.[17] The intermediate oxonium compound can pass by loss of a proton to the neutral chloroether, chloroacetate, etc. Thus the phenomena associated with additions of chlorine or of hypochlorous acid to 2-butene, *i. e.*, *trans* addition and absence of the other diastereomer, are best accounted for on the basis of the cyclic chloronium intermediate, analogous to the bromonium compound.[2]



A mechanism involving an intermediate carbonium ion[18] in the reactions does not seem probable, because "racemization" at the positively charged carbon atom would give rise to a mixture,

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(12) Kenyon, Phillips and Taylor, *J. Chem. Soc.*, 382 (1931).

(13) (a) Frankland and Gainer, *ibid.*, 105 (1914); (b) Levene and Mikeska, *J. Biol. Chem.*, **59**, 45 (1924); (c) McKenzie and Tredhope, *ibid.*, **62**, 551 (1924); (d) Kenyon, Lipscomb and Phillips, *J. Chem. Soc.*, 415 (1930).

(14) Gerrard, *ibid.*, 218 (1940).

(15) (a) Winstein and Lucas, THIS JOURNAL, **60**, 636 (1938); (b) Lucas, Hepner and Winstein, *ibid.*, **61**, 3102 (1939).

(16) Bartlett and Tarbell, THIS JOURNAL, **58**, 466 (1936); **59**, 407 (1937), have demonstrated the existence of intermediate positive ions containing a halogen atom when bromine reacts with stilbene, or when chlorine or bromine reacts with dimethylmaleic or dimethylfumaric acid. Bromine intermediate ions have been formulated as cyclic compounds.[2]

(17) Irwin and Hennion, *ibid.*, **63**, 858 (1941).

(18) There is no evidence for the stable existence of carbonium ions: Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 68.

in which both *erythro* and *threo* isomers would be present. If the behavior of the butenes is typical of olefins in general, then any reagent which may donate a "positive" or electrophilic chlorine atom,[17] as, for example, chlorine, hypochlorous acid, *t*-butyl hypochlorite,[17] monochlorourea[19a] or N,N-dichlorobenzenesulfonamide[19b] probably forms first a cyclic chloronium ion, rather than a carbonium ion.

Configurations of the Chlorohydrins.—If the chlorohydrin configurations were the opposite of those assumed, then (1) the conversion of (+)-*threo*-3-chloro-2-butanol, *i. e.*, the higher boiling isomer to (−)-2,3-dichlorobutane by thionyl chloride and pyridine or by phosphorus trichloride, would be accompanied by retention of optical activity and zero or an even number of inversions; and (2) the conversion of (+)-*erythro*-3-chloro-2-butanol to the racemic dichloride by thionyl chloride alone would be accompanied by loss of activity and an odd number of inversions. Since equal amounts of the (+) and (−) forms of the dichloride are formed in (2), the *cis* chloronium ion must be an intermediate, for an active *trans* chloronium ion would give rise to active dichloride. On this basis, therefore, it would be necessary to assume zero inversion in the formation of the *cis* intermediate from an *erythro* chlorohydrin, for there would be an odd number of inversions in the over-all reaction (2), and one inversion presumably accompanies the conversion of the *cis* intermediate to the *dl* dichloride. In the formation of the *cis* intermediate it would be necessary for the chlorine atom on the adjacent carbon atom to swing over into the position occupied by the oxygen atom. This hardly seems likely, in view of the known cases where molecular rearrangements are possible only when the migrating group can attack the back side of a carbon atom.[20]

In (1) phosphorus trichloride or thionyl chloride and pyridine would have to give retention of activity and an even number of inversions, whereas usually one inversion, with more or less racemization, accompanies the reactions of these reagents.[12,13] Thus, the products are more easily accounted for on the basis of the assumed configurations of the chlorohydrin.

Inversions.—One inversion definitely accompanies the addition of chlorine to each of the isomeric 2-butenes. Therefore, *trans* addition of chlorine to the double bond in these hydrocarbons must be regarded as proven. Also, on the basis of the above configurations of the chlorohydrins, one inversion accompanies the addition of hypochlorous acid to 2-butene, the addition of hydrogen chloride to 2,3-epoxybutane, the reaction of the 3-chloro-2-butanols with potassium hydroxide, with phosphorus trichloride, and with thionyl chloride and pyridine.

Two inversions are associated with the reaction of the 3-chloro-2-butanols with thionyl chloride.

The clean-cut nature of each of the above reactions, leading in general to a pure compound uncontaminated by the diastereomeric form, and accompanied by an inversion at each step, indicates that it proceeds *via* simultaneous attack and removal, without the formation of a carbonium ion.

Experimental

Especially pure *cis*-**2-butene** was prepared from recrystallized *meso*-2,3-butanediol, m. p. 34.45–34.55° (100%?), through the steps, *meso*-2,3-diacetoxybutane, *dl*-2,3-dibromobutane and *cis*-2-butene,[6a] for the preparation of the *dl*-dichloride. This butene was considered to be pure, for the properties of the *dl*-2,3-dibromobutane made from it, *viz.*, b. p. 76.3–76.4° (50 mm.); $n^{25}\text{D}$ 1.5124, agree so well with values reported previously[20] that it was considered better than 99.5% pure *dl*-2,3-dibromobutane.

A much larger quantity of *cis*-2-butene (11.6 moles) was prepared from 1167 g. (13.1 moles) of slightly less pure glycol, m. p. 33.90–34.15° (99.5%) for conversion to chlorohydrin.

trans-**2-Butene** was prepared by a similar series of reactions from recrystallized *dl*-2,3-diacetoxybutane, m. p. 41.9–42.1° (cor.).[6a] The properties of the *meso*-2,3-dibromobutane, *viz.*, b. p. 73.2–73.3° (50 mm.), $n^{25}\text{D}$ 1.5092, agree well with those given elsewhere.[20,6a]

cis- and *trans*-**2,3-epoxybutanes** used for preparing chlorohydrins were available from a stock on hand, the same as described previously.[20]

2,3-Dichlorobutanes.—Addition of chlorine to the 2-butene was carried out in diffused artificial light, by passing each gas separately into an all glass reaction tube, 35 × 200 mm., equipped with mercury-sealed stirrer, "dry-ice" reflux condenser[21] (both attached by means of standard taper joints), and two inlet tubes, each extending to within 60 mm. of the bottom. The vessel was surrounded by a cooling bath at −20°. The butene passed through a water wash bottle and a drying tube packed with calcium chloride. The chlorine from a cylinder passed through concentrated sulfuric acid. The rates of flow were six to seven bubbles per second. The reaction product acts as a common solvent for the olefin and halogen. Reaction takes place in the liquid phase, which was kept slightly greenish in color with a slight excess of chlorine. The dry-ice condenser is necessary to reflux butene and chlorine. The

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(19) (a) Detouef, *Bull. soc. chim.*, **31**, 102 (1922); (b) Likhosherstov, *et al.*, *J. Gen. Chem.* (U. S. S. R.), **8**, 370 (1938); *C. A.*, **32**, 5369 (1938).

(20) Bartlett and Pöckel, THIS JOURNAL, **59**, 820 (1937); Bartlett and Bavley, *ibid.*, **60**, 2416 (1938).

(21) Reference 6a, p. 2398.

mercury-sealed stirrer prevents local "hot-spots" in the reactor.

The above procedure was found to give less substitution,[22] as evidenced by evolution of hydrogen chloride, than any of a number of modifications. Thus, the substitution reaction became more important if the temperature was higher, if the butene was in excess, if the gas flow was increased, or especially if the illumination was more intense. In sunlight, even at temperatures below 0°, substitution was quite pronounced, and the yield of product calculated as dichloride was as high as 107%. Actually, the product contained much trichlorobutane (23%) and some higher chlorinated material (about 15%).

From 11.2 g. of *cis*-2-butene there was obtained in two hours 22.1 g. of crude dichloride which after washing repeatedly with 1 *M* potassium carbonate until neutral to litmus and drying over potassium carbonate, gave 20.4 g. of product distilling at 52.5–54.5° (80 mm.); yield of distilled dichloride was 80.5%. The dichloride was redistilled five times. The boiling point, refractive index, and condenser reading did not change between the fourth and fifth distillations.[23]

From 8.75 g. of *trans*-2-butene, there was obtained by a similar procedure 12.1 g. (63% yield) of distilled *meso*-2,3-dichlorobutane, b. p. 49.0–50.5° (80 mm.). After being subjected to five distillations, the boiling point, refractive index and condenser reading did not change between the fourth and fifth distillations.[23]

dl-erythro-**3-Chloro-2-butanol.**—To 250 ml. (3 moles) of C. P. concentrated hydrochloric acid maintained at 5° or lower, was added with vigorous stirring, 144 g. (2 moles) of *trans*-2,3-epoxybutane during the course of one hour. Stirring was continued for forty minutes longer. The solution was poured over 138 g. (1 mole) of solid potassium carbonate. The oil was decanted from the resulting paste, which was filtered. The solid was washed with isopropyl ether and the filtrate was extracted with three successive portions, 40 ml. each of isopropyl ether. The oil phase, the ether extracts, and ether washings were combined and after shaking with anhydrous potassium carbonate, the liquid was subjected to distillation through a 60-cm. column of glass helices with a reflux ratio of about 10. The *dl-erythro*-chlorohydrin, b. p. 55.9–56.1° (30 mm.), weighed 181 g. (82.5% yield).

For determination of physical properties, 20 g. of this chlorohydrin was redistilled twice through the Weston column. The boiling point and refractive index did not change between the first and second redistillations.[24]

dl-threo-**3-Chloro-2-butanol; from the** *cis*-**Oxide.**—Similarly, from 18 g. (0.25 mole) of *cis*-2,3-epoxybutane was obtained 20.8 g. (77% yield) of chlorohydrin, b. p. 51.6–52.1° (30 mm.). This material was redistilled three times through the Weston column. The boiling point and refractive index did not change between the second and third redistillations.[24]

From *cis*-**2-Butene.**—In a 3-necked 1-liter flask equipped with mercury sealed stirrer, dropping funnel and "dry-ice" condenser[21] and surrounded by ice was placed 55 g. (0.98 mole) of *cis*-2-butene and 600 ml. of an aqueous solution containing 48 ml. of glacial acetic acid and 14 ml. of concentrated sulfuric acid. The sulfuric acid was needed as catalyst, and the acetic acid to dissolve 2-butene. More was not desirable, because of possible side reactions forming acetate and sulfate, respectively (see also ref. 17). Under vigorous agitation 106 g. (0.98 mole) of fresh *t*-butyl hypochlorite was added dropwise under the surface of the liquid during two hours time. A test with potassium iodide showed the absence of hypochlorite. The emulsion was broken by the addition of a small amount of sodium bicarbonate. After separation of the oil phase the aqueous layer was extracted twice with isopropyl ether (50 ml.) which was cooled in "dry-ice" to crystallize out trimethylcarbinol and water, from which the liquid was poured off. The ether and chlorohydrin were combined, neutralized and dried with potassium carbonate, and distilled at 30 mm. The yield of *dl-threo*-3-chloro-2-butanol was 66 g. (61%). The constants of *cis*-2,3-epoxybutane prepared from 10 g. of redistilled chlorohydrin[24] agree well with those reported previously.[2c] Since the oxide is pure, the chlorohydrin is also. Thus 2-butene and *t*-butyl hypochlorite give only a single *dl*-chlorohydrin, not a mixture of inactive diastereomers.

The chlorohydrin could not be prepared by the action of N-chloroacetamide on 2-butene in the presence of water, sulfuric acid and acetic acid, as was done for the bromohydrin, using N-bromoacetamide.[2c] No product could be isolated even when the reaction mixture was sealed and allowed to stand at room temperature for a day. In one case the reaction mixture was sealed in an ampoule. After standing at room temperature for twelve hours, it exploded.

From *meso*-**2,3-Diacetoxybutane.**—In 1100 g. of C. P. hydrochloric acid (Baker 38%) was dissolved 756 g. (4.30 moles) of *meso*-2,3-diacetoxybutane, prepared by the acetylation[6a] of *meso*-2,3-butanediol, m. p. 34.1° (99.5% pure). It was found that 1 drop of concd. sulfuric acid was a sufficient amount of catalyst for 2 moles of glycol. After about one hour at 50 to 60° a little more catalyst could be added. Hydrogen chloride was passed into the mixture at −10° until the gain in weight was 415 g., equivalent to a total of 22.8 moles of hydrogen chloride. The liquid was sealed in two 1-liter ampoules and allowed to stand at room temperature for ninety hours.

The ampoules were opened, and the contents were poured, during vigorous stirring, onto 2 kg. of technical sodium bicarbonate. The solid was removed by filtration and washed with 1 liter of isopropyl ether, which was used for extracting the aqueous phase. It was combined with the chlorohydrin phase. The solution was neutralized by stirring with bicarbonate solution, then cooled by "dry-ice," and filtered through a Büchner funnel filled with "dry-ice" to remove ice crystals. Distillation gave 200 g. (43%) of *dl-threo*-3-chloro-2-butanol.[24] Also some *dl-threo*-3-chloro-2-acetoxybutane was obtained; 89 g. (13.5%), b. p. 70–72.5° (30 mm.).

Some of the redistilled chlorohydrin was converted into the *cis* oxide, having $n^{25}D$ 1.3802, which is identical with

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[22] Stewart and Hanson, THIS JOURNAL, **53**, 1121 (1931); Stewart and Weidenbaum, *ibid.*, **57**, 2036 (1935); **58**, 98 (1936); Stewart, Dod and Stenmark, *ibid.*, **59**, 1765 (1937), have pointed out that the substitution reaction is favored by an excess of the olefin; Groll, Hearne, Rust and Vaughan, *Ind. Eng. Chem.*, **31**, 1239 (1939), found much substitution to accompany the reaction of 2-butene and chlorine at 20°.

[23] Physical constants are given in Table I.

[24] Physical constants are given in Table II.

other values. Thus the purity of this oxide indicates that the chlorohydrin prepared from the diacetate is pure.

If the reaction mixture is heated to 60° while the hydrogen chloride is being pumped off, the yield of chlorohydrin can be increased at the expense of the chloroacetate. If potassium carbonate replaces sodium bicarbonate, the recovery of the product is less satisfactory since potassium chloride dissolves in the ether solution of the chlorohydrin.

Partial Resolution of the Chlorohydrins.—The method of Wegler was followed[25] but was improved by using chloroform as the solvent, for then the higher concentration allowed the reaction to proceed at 50°. It was noted that under identical conditions the *erythro*-chlorohydrin was acetylated 81% of the amount expected while the *threo* reacted only 15–20%.

To a solution of 79 g. (0.17 mole) of brucine and 37.2 ml. (0.39 mole) of freshly distilled acetic anhydride in 200 ml. of chloroform was added 86 g. (0.79 mole) of *dl*-*erythro*-3-chloro-2-butanol. The mixture warmed spontaneously to 50° and was kept there for five hours. After cooling the brucine was extracted with four successive portions of 6 *N* hydrochloric acid, 125 ml. each, and the acid washings extracted with isopropyl ether to recover any chlorohydrin. The chlorohydrin and chloroacetate were recovered as usual, and separated from each other by fractional distillation at 30 mm. The chlorohydrin weighed 34.8 g. (81% recovery)[26]; α +0.82°; and the *dl*-*erythro*-3-chloro-2-acetoxybutane, 48 g. (0.32 mole); b. p. 70–73° (30 mm.), α −3.37°.

From 85 g. (0.78 mole) of *dl*-threo-3-chloro-2-butanol, 85 g. (0.19 mole) of brucine, 38 ml. (0.40 mole) of acetic anhydride and 200 ml. of chloroform, which likewise warmed spontaneously to 50°, were obtained by the same procedure, 36 g. (0.332 mole) of chlorohydrin, α −0.10°, n^{25}D 1.4360; approximately 23 g. (0.15 mole) of *dl*-*threo*-3-chloro-2-acetoxybutane, b. p. 60–72° (30 mm.), but not purified by subsequent distillation; n^{25}D 1.4330; α −0.05°.

The poor results with the *threo*-chlorohydrin may have been due to the fact that it is easily racemized when distilled at 30 mm. In the following adsorption method better resolution was realized, due in part to the fact that the chlorohydrin could be obtained pure by distillation at room temperature, thus minimizing racemization.

To a solution of 200 g. (1.84 moles) of *dl*-*threo*-3-chloro-2-butanol in 1 liter of ligroin (b. p. 28–30°) was added in small portions and with vigorous stirring 350 g. (0.89 mole) of Merck brucine. The alkaloid, only slightly soluble in such a mixture, is a powerful adsorbent for the chlorohydrin. The first portions of the solid became gluey, but the rest of the brucine remained in suspension as a loose, fine powder. Stirring was continued for thirty minutes. The ligroin solution was filtered rapidly with minimum loss of solvent by evaporation. The solvent was removed at reduced pressure through a 60-cm. column of glass helices, keeping the boiler temperature below 25°. The chlorohydrin was distilled from a 200-ml. Claisen flask at room temperature and 1 to 2 mm. It was collected in a receiver cooled by dry-ice; weight, 61 g. (0.56 mole); n^{25}D 1.4372; α +1.10°.

The brucine left on the filter was washed with 500 ml. of isopropyl ether. The ether washings were concentrated as above, yielding 47 g. (0.43 mole) of chlorohydrin; n^{25}D 1.43; α +0.89. Recovery of chlorohydrin was 54%.

***cis*-2,3-Epoxybutane from Active *threo*-Chlorohydrin.**—To a solution of 50 g. of reagent potassium hydroxide in 25 ml. of water at 90–95° in a 3-necked flask provided with a dropping funnel, stirrer and condenser, was added during vigorous stirring 7.0 g. (0.054 mole) of active *threo*-3-chloro-2-butanol (α +1.10°).

The oxide distilled out as formed (5 g., 75%) and was collected in a receiver cooled by a mixture of "dry-ice" and isopropyl ether. The oxide was allowed to stand at room temperature for six hours in contact with reagent potassium hydroxide pellets to destroy any unchanged chlorohydrin, and distilled off from the hydroxide into a "dry-ice" trap. The ice crystals were removed by pouring the cold liquid through glass wool. The filtrate was clear at −77°; b. p. 59.0–60.0° (745 mm.); n^{25}D 1.3798; α +0.25°. These values show that 4.1% of the *trans* oxide is present (see Table II).

The *erythro* chlorohydrin which gave rise to this *trans* oxide, which is responsible for the rotation of +0.25°, must have been formed while the *threo* chlorohydrin was in contact with brucine during the resolution. The *threo* chlorohydrin originally was better than 99.5% pure, as shown by the properties of the oxide prepared from it.[24] This last result shows that ring closure to form the oxide from the chlorohydrin is a clean-cut reaction. On the basis of the assumed configuration of the chlorohydrin, it goes with 100% inversion of configuration.

Phosphorus Pentachloride and *dl*-*erythro*-3-Chloro-2-butanol.—To a refluxing solution of 160 g. (0.78 mole) of c. p. phosphorus pentachloride in 400 ml. of U. S. P. chloroform, was added dropwise over a period of thirty-five minutes, 21.7 g. (0.2 mole) of the chlorohydrin. The mixture was refluxed for two hours, cooled, the excess solid chloride filtered off, the filtrate reduced to 125 ml. by slowly distilling chloroform through an efficient column, then more phosphorus pentachloride removed by filtration, then more distillation, and finally, the residue was poured onto 150 g. of ice, with vigorous stirring for one hour. During this time potassium carbonate was added in portions until the chloroform layer was neutral to litmus. The product was worked up as before, giving 11.1 g. (42.7%) of dichloride.[23]

Thionyl Chloride and *erythro*-Chlorohydrin.—To 53.5 g. (0.45 mole) of refluxing thionyl chloride, b. p. 74.5–75.0° (uncor.), was added dropwise, during the course of ninety minutes, 32.7 g. (0.3 mole) of *dl*-*erythro*-3-chloro-2-butanol. The solution was refluxed for three hours, then heated on a steam-bath for another three hours until no more sulfur dioxide resulting from the decomposition of the chlorosulfite ester IA, was noticeable. The mixture was poured onto 100 g. of ice, neutralized with solid potassium carbonate, washed, dried and distilled through the Weston column, giving 6.1 g. (16% yield) of dichloride.[23] This was essentially pure *meso* dichloride. The impurity was not the *dl*-dichloride, otherwise both the refractive index and condenser reading would have been high. Only the former was high.

When 21.7 g. (0.2 mole) of (+)-*erythro*-3-chloro-2-butanol. α +0.82°, was converted by the method above to

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[25] Wegler, *Ann.*, **506**, 77 (1933).

[26] All rotations, α, are the values observed with sodium light at 25° in 1-dm tubes.

dichloride, the product after redistillation weighed 3.96 g. (15.7% yield). The properties[23] show that it was essentially pure *meso* dichloride, for although the condenser reading was high by 0.8, the refractive index was low by only 0.0001.

Thionyl Chloride and Active *threo*-Chlorohydrin.—By a similar procedure, 21.7 g., (0.2 mole) of *threo*-3-chloro-2-butanol, (α −0.10°) gave 4.4 g. (17.4% yield) of 2,3-dichlorobutane.[23] This was essentially pure *dl*-dichloride, for the condenser reading was 0.6 high, and the refractive index 0.0007 low. The impurity probably is not the *meso* isomer. The low initial rotation of the chlorohydrin raises some doubt regarding the value of this experiment. However, since the active dichloride probably has a much higher rotation than the active chlorohydrin, it would seem that the zero rotation of the dichloride obtained here really is significant.

To 35.7 g. (0.3 mole) of refluxing water white thionyl chloride, b. p. 76.0–76.5°, was added dropwise 21.7 g. (0.20 mole) of *threo*-3-chloro-2-butanol (+1.10°). The mixture was boiled for ten minutes, cooled, and examined for optical activity; α −9.06, weight 43.4 g. The mixture was heated on a steam-bath for five hours, during which time sulfur dioxide was evolved slowly. The dichloride was isolated as described above. It was washed in the cold with 80% sulfuric acid, then with concd. sulfuric acid, and redistilled at 1 to 2 mm., giving 5.2 g. (20% yield).[23] This was essentially pure *dl*-2,3-dichlorobutane, for the dielectric constant was only 0.03 high, and the refractive index, 0.002 high. Any *meso* dichloride would have lowered these values.

A by-product of the reaction, the sulfite of 3-chloro-2-butanol, IB, was isolated in 6 g. yield: b. p. 85–87° (0.1–0.2 mm.); n^{25}D 1.4667; α −11.29°; ε, 12.42.

Anal. Calcd. for $C_8H_{16}Cl_2O_3S$: C, 36.5; H, 6.1; S, 12.1; Cl, 27.0. Found: C, 36.0; H, 6.15; S, 11.1; Cl, 27.2.

The small negative rotation of the dichloride can be explained as due to the presence of a small amount of IB. This calculates to be 0.77% from the refractive index, 0.88% from the rotation, and 1.2% from the dielectric constant. From the amounts of thionyl chloride and IB present in the crude monobutyl chlorosulfite (−9.06°), 1A free of thionyl chloride and of 1B, is calculated to have a rotation of *ca.* −10°.

Both (−)- and (+)-*threo*-3-chloro-2-butanol yield *dl*-2,3-dichlorobutane with thionyl chloride.

Attempted Racemization of (−)-2,3-Dichlorobutane.—A mixture of active 2,3-dichlorobutane (−3.74°) and 4 g. of thionyl chloride was sealed in a test-tube and heated at 100° for five hours. The polarimeter readings[26] before and after heating were −1.41 and −1.36°, respectively.

Phosphorus Trichloride and *erythro*-Chlorohydrin.—To 20.0 g. (0.185 mole) of *dl-erythro*-3-chloro-2-butanol, with agitation and cooling, was added during the course of thirty-five minutes 8.6 g. (0.062 mole) of freshly distilled phosphorus trichloride, b. p. 73.5–75.0°. The mixture was heated for three hours on a steam-bath and then fractionally distilled, yielding 3.7 g. (20%) of crude dichloride, 49–54° (80 mm.). This was washed carefully with 1 *M* potassium carbonate solution, dried with anhydrous potassium carbonate and redistilled.[23] The product was essentially pure *dl*-dichloride, for the refractive index was low by 0.0004 and the condenser reading high by 1.0. The impurity probably was a trace of moisture, or of acid.

By a similar procedure 19.0 g. (0.175 mole) of active *erythro*-3-chloro-2-butanol (α +0.27°) gave 4.1 g. (17.5%) of dichlorobutane.[23] This was essentially a mixture of the (−) and *dl*-dichloride, for the condenser reading was 0.7 high, and the refractive index 0.0009 low.

When the molar ratio of trichloride to chlorohydrin was two, no dichloride was formed.

Thionyl Chloride, Pyridine and *erythro*-Chlorohydrin.—To 32.7 g. (0.3 mole) of *dl-erythro*-3-chloro-2-butanol, dissolved in 53 g. (0.67 mole) of freshly distilled Merck reagent pyridine, b. p. 115.5–116°, was added dropwise 59 g. (0.6 mole) of thionyl chloride. The dark orange reaction mixture was kept well agitated with mechanical stirring to break up the solid mass of pyridine hydrochloride as fast as it formed. Stirring was continued for twenty minutes after the addition was complete. The mixture was placed upon a steam-bath and heated for three hours. There were two colored liquid phases (the pyridine phase was the darker) and a solid phase. After standing overnight the upper liquid phase (dichlorobutane) was poured off, the lower phase was diluted with an equal volume of water, and extracted twice with isopropyl ether. The oil phase and ether extracts were combined, washed four times with 6 *N* hydrochloric acid to remove pyridine, washed with water, dried with potassium carbonate and distilled, yielding 23.8 g. (63% yield) of dichloride, b. p. 52.9–53.4 (80 mm.). This was redistilled twice.[23] The product was essentially pure *dl*-2,3-dichlorobutane, for the refractive index was 0.0001 high and the condenser reading 0.3 low.

Following the above procedure, 10.8 g. (0.1 mole) of active *erythro*-3-chloro-2-butanol, α +0.82°, gave 5.5 g. (43% yield) of 2,3-dichlorobutane.[23] This was a mixture of (−) and *dl*-2,3-dichlorobutane, free of the *meso* isomer, for although the refractive index was 0.005 low, the condenser reading was only 0.1 low.

Thionyl Chloride, Pyridine and *threo*-Chlorohydrin.—To 23.8 g. (0.20 mole) of thionyl chloride cooled to 5°, was added dropwise 10.8 g. (0.10 mole) of (+)-*threo*-3-chloro-2-butanol (+1.07°). Hydrogen chloride was evolved copiously. After addition of 10 ml. of pyridine, the mixture was heated for two hours at 95°. The product, worked up as above, weighed 3.1 g. (24% yield).[23] The properties show that this is essentially *meso*-2,3-dichlorobutane contaminated with a small per cent. of (+)-*threo*-2,3-dichlorobutane, which was formed from the small amount of *erythro*-chlorohydrin known to be present.

Phosphorus Trichloride, Pyridine and *erythro*-3-Chloro-2-butanol.—When to 27.6 g. (0.2 mole) of phosphorus trichloride was added with cooling and vigorous stirring, 10.8 g. (0.1 mole) of *erythro*-3-chloro-2-butanol in 15.8 g. (0.2 mole) of pyridine followed by heating at 50° for one hour, then pouring onto ice, no dichlorobutane could be recovered from the reaction mixture. Even when the heating time at 50° was lengthened to six hours, no product could be isolated.

Behavior of 3-Chloro-2-butanol and 3-Chloro-2-acetoxybutane with Hydrochloric and Hydrobromic Acids.—It was found that no dichloride appeared to be formed from a chlorohydrin, which was a mixture of the inactive *erythro* and *threo* forms, by the action of 46% aqueous hydrochloric acid at room temperature (in an ampoule) for four days. The hydrochloric acid concentration was increased by passing in dry hydrogen chloride until at −20° large colorless needles, presumably a hydrate of hydrochloric acid, separated. Standing at room temperature for ten days resulted in no change in the solution other than darkening. From the reaction mixture, no dichlorobutane could be obtained. Instead, 47% of the original chlorohydrin was recovered.

With concd. hydrochloric acid containing one mole of zinc chloride per mole of acid, at 100° for ninety minutes, slight amount of oil formation was noted, and a considerable amount of darkening. No dichloride could be isolated, however.

When 15.1 g. (0.1 mole) of *active*-3-chloro-2-acetoxybutane was sealed off with 128 g. of 65% hydrobromic acid and allowed to stand for five days, no reaction was noticeable except the development of an orange color, even though under these conditions 3-bromo-2-acetoxybutane reacts readily.[20] No second phase resulted when heated at 80° for three hours, or at 100° for one hour. Likewise, no chlorobromobutane could be isolated when 2 ml. of mixed chlorohydrin (*erythro* and *threo*) was heated for three hours at 100° in a sealed tube with 10 ml. of 60% hydrobromic acid.

From the failure of the chlorohydrin and chloroacetate to yield dihalides, it is evident that chlorine on an adjacent carbon atom decreases the reactivity of the alcohol more than bromine does.

Measurement of Condenser Readings and Calculation of Dielectric Constants.—A new small measuring cell, having a volumetric capacity of 1.2 ml. was constructed for use with the set-up used in making measurements of dielectric constants.[27] This cell resembles a miniature "thermos" bottle, with an inlet tube at the bottom and an outlet tube at the top. The walls of the inside of the annular space were platinized in such a way that the outer platinum film shielded the inner film for 8 to 10 mm. at the top and completely at the bottom. This was done to minimize "end effects." Before the cell was put together, the surfaces were covered with platinum, and contact made with leads, as follows: first, the platinum leads were welded to small pieces of thin platinum foil, then the foil was firmly bonded to the glass surface to be coated by heating the glass in an oxygen–gas flame, then pressing the foil onto the glass surface with a carbon rod. The entire surface, glass and foil, was then platinized before the cell was finally put together.

For calibration, the following were used as standards: air, carbon tetrachloride, benzene, chlorobenzene, ethyl bromide, and ethylene dichloride. These liquids were carefully purified.

It was found that the expression relating the capacitance of the cell to the dielectric constant of the fluid in the cell was of the form

$$\epsilon = A(R - B)/[1 - C(R - B)]$$

where R is the corrected condenser reading, A is 0.05529, B is 7.198, and C is 0.0001394. These values, calculated by Mr. R. M. Noyes of this Laboratory, lead to dielectric constants which agree within 0.1% of the literature values of the liquids used in the calibration.

It was found that the condenser readings and consequently the dielectric constants of the isomeric inactive 2,3-dichlorobutanes could be determined with an accuracy of about 0.1%, using the small cell. However, the main difficulty was working up and purifying the small amounts of material, 3 or 4 g. in some cases, for then complete elimination of traces of impurities as for example, water or hydrochloric acid, was sometimes not accomplished. These tend to lower the refractive index and raise the condenser reading. However, the purification of the products was in general satisfactory, for usually both of these values would not be high. Generally, if one was high, the other was low.

The plot of condenser reading against composition of mixtures of the *dl*- and *meso*-2,3-dichlorobutanes is essentially linear, but that of dielectric constant against condenser reading is not linear. From these the composition of any mixture could be obtained. The values used are shown in Table III.

TABLE III

CONDENSER READINGS OF MIXTURES OF *meso* AND *dl*-2,3-DICHLOROBUTANES

meso by weight, %	Corrected condenser reading^{25}	ϵ^{25}
0	179.5	9.761
23.87	175.6	9.535
45.1	172.2	9.338
61.6	169.7	9.193
100	163.3	8.823

Summary

The inactive 2,3-dichlorobutanes and inactive 3-chloro-2-butanols have been prepared. The configurations of the former have been established by obtaining the higher boiling with optical activity, hence it has the *threo* configuration. The higher boiling chlorohydrin is assigned the *erythro* configuration.

trans-Addition of chlorine to the olefin bond in 2-butene is established.

An even number of inversions and loss of optical activity accompanies the reaction of thionyl chloride with the 3-chloro-2-butanols. The reaction proceeds *via* a cyclic dimethylethylene chloronium ion.

An odd number of inversions, and retention of optical activity accompanies the reaction of phosphorus trichloride and of thionyl chloride in pyridine with the 3-chloro-2-butanols.

The concept of the cyclic chloronium ion is useful in accounting for *trans* addition of chlorine and of hypochlorous acid to the 2-butenes, and for the purity of the resulting dichlorides and chlorohydrins.

The formation of a pure compound, essentially uncontaminated by any of the diastereomer in the reactions, 2-butene with chlorine, 2-butene with

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(27) Wood and Dickinson, THIS JOURNAL, **61**, 3259 (1939).

t-butyl hypochlorite, 2,3-epoxybutane with hydrochloric acid, 2,3-diacetoxybutane with hydrochloric acid, 3-chloro-2-butanol with thionyl chloride, with thionyl chloride and pyridine, with phosphorus trichloride, and with potassium hydroxide, is best accounted for on the basis of removal of one atom (or radical) with simultaneous attack at the back side of the carbon atom by a nucleophilic reagent. In some cases the attack is intramolecular, leading to the formation of a cyclic compound, in other cases the attack is intermolecular. All evidence is opposed to the concept of a carbonium ion as an intermediate.

When a carbon-to-chlorine bond possesses considerable ionic character, replacement of the chlorine atom by an electron donating reagent takes place by attack on the opposite side of the carbon atom with inversion, rather than at the front without inversion.

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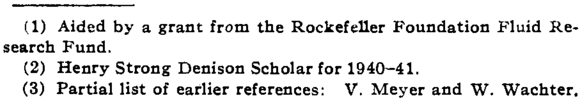
[CONTRIBUTION FROM DEPARTMENT OF PHYSIOLOGICAL CHEMISTRY, SCHOOL OF MEDICINE, THE JOHNS HOPKINS UNIVERSITY]

o-Iodosobenzoic Acid, a Reagent for the Estimation of Cysteine, Glutathione, and the Substituent Sulfhydryl Groups of Certain Proteins[1]

BY LESLIE HELLERMAN, FRANCIS P. CHINARD[2] AND PAULINE A. RAMSDELL

During some thirty years past, there has appeared only occasional reference to the aryl iodoso, iodoxy, and related compounds,[3] a group of considerable theoretical interest. The importance of this group for valence studies is reflected in an electronic representation of iodosobenzene, $C_6H_5\!:\!\overset{\cdot\cdot}{\underset{\dot{+}}{\mathrm{I}}}\!:\!\overset{\cdot\cdot}{\underset{\ddot{-}}{\mathrm{O}}}\!:$. Functioning as donor, this may add a proton, forming presumably the ion, $(C_6H_5IOH)^+$,[4] but there exist also the well-characterized dichloride, $(C_6H_5ICl)^+Cl^-$ and diacetate, $[C_6H_5I(OCOCH_3)]^+(OCOCH_3)^-$.

The better known simple iodoso compounds, functioning as "powerful" oxidizing agents, ordinarily are reduced *practically* irreversibly. This characteristic and the stability, observed in this study, of a slightly alkaline solution of certain salts of the readily available *o*-iodosobenzoic acid suggested a new approach to the troublesome problem of the estimation of cysteine and certain of its derivatives. This is based upon a reaction which has been found to proceed under proper conditions according to the process



$$2\,{}^-OOC{-}CH(NH_3^+){-}CH_2SH + C_6H_4(COO^-)IO \longrightarrow \begin{array}{l} {}^-OOC{-}CH(NH_3^+){-}CH_2S \\ \qquad\qquad\qquad\qquad\quad | \\ {}^-OOC{-}CH(NH_3^+){-}CH_2S \end{array} + IC_6H_4COO^- + H_2O$$

The following is representative of the analytical method now developed.

Estimation of Cysteine Hydrochloride.—*o*-Iodosobenzoic acid, purchased on the market, was purified by solution in a small excess of chilled potassium hydroxide solution (2 *N*), filtration, and recovery by treatment of the alkaline solution with carbon dioxide.[5] The acid was washed with water and dried in a vacuum over phosphorus pentoxide. An approximately 0.02 *N* solution was prepared by addition to the reagent of a slight excess of normal potassium hydroxide and dilution to volume. Standardization was done iodometrically with the use of the relation $RIO + 2I^- + 2H^+ \rightarrow RI + I_2 + H_2O$.

A high-grade specimen of cysteine hydrochloride which had been shown by independent analysis to contain a little free cysteine and no more than a trace of cystine was made up to be *by weight*, 0.01039 *N* (uncor.). The sulfhydryl content was estimated as follows. To 5 ml. of molar phosphate buffer[6] of *p*H 7 (K_2HPO_4, 117.7 g. plus KH_2PO_4, 44.1 g., made to 1000 ml.) was added 10.00 ml. of *o*-iodosobenzoate (0.01812 *N*), after which 10.00 ml. of the cysteine hydrochloride was added to the mixture. After thirty seconds, there was added to this reaction mixture an acidified solution of potassium iodide (0.5 to 1 g. dissolved in 1.5 ml. of water and then treated with 5 ml. of *N* hydrochloric acid immediately before use). The liberated iodine was titrated at once with standard thiosulfate. In six successive titrations, the excess

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(2) Henry Strong Denison Scholar for 1940–41.

(3) Partial list of earlier references: V. Meyer and W. Wachter, *Ber.*, **25**, 2632 (1892); C. Willgerodt, *ibid.*, **25**, 3494 (1892); **26**, 1802 (1893); **27**, 2326 (1894); P. Askenasy and V. Meyer, *ibid.*, **26**, 1354 (1893); V. Meyer, *ibid.*, **26**, 2118 (1893); C. Hartmann and V. Meyer, *ibid.*, **27**, 1592 (1894).

(4) Iodoxybenzene hydrogen sulfate, $(C_6H_5IO_2H)^+(HSO_4)^-$, has been crystallized, I. Masson, *Proc. Roy. Inst. Gt. Brit.*, **30**, 99–122 (1937).

(5) *Cf.* A. S. Loevenhart and W. E. Grove, *J. Pharmacol. and Exp. Therap.*, **3**, 101 (1911).

(6) A. A. Green, THIS JOURNAL, **55**, 2331 (1933).