termined, an increase in buffer concentration caused no increase in rate, indicating no general catalysis at least for the acetate–acetic acid buffer.

To convert semicarbazide predominantly into its salt requires a *p*H of about 2. Efforts were made to study the rate of reaction in this *p*H range by adding acid from a micro buret at a rate sufficient to keep the *p*H at 2.2 (in which case the acid added is a measure of the semicarbazide formed) following the procedure of earlier work.[5] Evidence showed however that the cyanic acid was decomposing with little semicarbazide being formed, and this approach was not carried further.

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(5) Gilbert, THIS JOURNAL, **51**, 3394 (1929).

Summary

1. The formation of semicarbazide from hydrazine cyanate takes place readily at room temperature.

2. Increase in ionic strength reduces the velocity of reaction in a manner which agrees with the postulate that the rate determining process is the reaction between the hydrazine and cyanate ions.

3. The reaction reaches an equilibrium far to the side of formation of semicarbazide.

4. Quantitative results are presented on the velocity constants of the reaction at 15 and 25°, the equilibrium constant, salt effects, temperature coefficient and heat of activation.

CORVALLIS, OREGON RECEIVED AUGUST 6, 1942

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF HARVARD UNIVERSITY, THE ILLINOIS INSTITUTE OF TECHNOLOGY, AND THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

The Role of Neighboring Groups in Replacement Reactions. I. Retention of Configuration in the Reaction of Some Dihalides and Acetoxyhalides with Silver Acetate[1]

BY S. WINSTEIN[2] AND R. E. BUCKLES

Three mechanisms for nucleophilic replacement reactions at a saturated carbon atom are currently recognized.[3,4] One is the now familiar[5] bimolecular (S_N2) substitution with complete Walden inversion. A second mechanism (S_Ni) involves the rearrangement of an intermediate product[3,6] in such a way that retention of configuration is the steric result.

The third mechanism has been termed unimolecular[3] (S_N1) or polymolecular.[3,4,7] It seems to consist of at least two steps, the most probable rate-determining step being an ionization. There are several indications that the carbonium ion intermediate is, in some respects, quite unfree.[4] For example, the steric result of reaction by this mechanism generally is predominant inversion. Quite analogous to the S_N1 mechanism is a process involving the electrophilic attack of a reagent such as silver ion on a halogen atom.[3,4]

Ionization to an ion-pair, solvated in a way characteristic of ions, may be thought to be the rate-determining step in the S_N1 mechanism. Solvation of the ions makes this step feasible; therefore, the rate varies with the arrangement of solvent molecules around what is to be the ion-pair. Solvent molecules must be included in the transition state, without, however, drawing bonds between the solvent molecules and the carbonium ion.[3,9,10] If the carbonium ion is very reactive it will react preferentially with a molecule in the solvation cluster to give inversion as the major steric result.[3] There may thus be some connection between rates and final product compositions in mixed solvents.[3,8] If reaction of the carbonium ion takes place after dissociation of the ion-pair, complete racemization is the steric result.[7]

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(1) A portion of the material reported in this paper was presented before the Organic Division at the St. Louis meeting of the American Chemical Society, April, **1941**.

(2) National Research Fellow in Chemistry, Harvard University, 1939–1940.

(3) (a) Cowdrey, Hughes, Ingold, Masterman and Scott, *J. Chem. Soc.*, 1252 (1937); (b) Bateman, Church, Hughes, Ingold and Taher, *ibid.*, 979 (1940).

(4) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapters V and VI.

(5) (a) Olson, *J. Chem. Phys.*, **1**, 418 (1933); (b) Bergmann, Polanyi and Szabo, *Z. physik. Chem.*, **20**, 161 (1933).

(6) Hughes, Ingold and Whitfield, *Nature*, **147**, 206 (1941).

(7) (a) Steigman and Hammett, THIS JOURNAL, **59**, 2536 (1937); (b) Farinacci and Hammett, *ibid.*, **59**, 2542 (1937); (c) Beste and Hammett, *ibid.*, **62**, 2481 (1940).

(8) Winstein, *ibid.*, **61**, 1635 (1939).

(9) Balfe and Kenyon, *ibid.*, **62**, 445 (1940).

(10) It is possible that the failure of a tertiary halide with the halogen atom on a bridge-head to undergo solvolytic reaction, as demonstrated by Bartlett and co-workers, [THIS JOURNAL, **61**, 3184 (1939); **62**, 1183 (1940)] should be ascribed partly to the fact that the solvation energy of the cationic end of the ion-pair to be formed is apt to be much smaller than usual. Solvent is kept away from the cationic carbon atom by the hydrocarbon cage more effectively than is possible with the most highly hindered open-chain compounds in which the cationic carbon atom can flatten out.

To understand the rates and steric results of nucleophilic replacement reactions of the most complex compounds (perhaps with several functional groups) it is necessary to demonstrate and understand the effects of substituent groups other than their supply or withdrawal of electrons to the seat of substitution by induction and resonance.[3] One of the most interesting effects is that of participation of a group on a neighboring or more distant carbon atom in a replacement process at a carbon atom. Thus, a replacement reaction might really consist of two steps, the first one an intramolecular S_N2 reaction, the second the opening of a ring. Two inversions or apparent retention will be the steric result.

Even more interesting is the involvement of a neighboring group in a replacement reaction which appears to be of the S_N1 type. In this connection, several reactions have been found to proceed with retention of configuration because of an extra functional group.[3,11,12,13]

In this article we present and discuss several additional examples of reactions which similarly involve participation of a neighboring group and we include a discussion of general expectations as to the scope and results of such participation.

We have now studied the steric result of the reaction of silver acetate in dry acetic acid with the *threo-* and *erythro*-2-acetoxy-3-bromobutanes, the *dl-* and *meso*-2,3-dibromobutanes, *trans*-1-acetoxy-2-bromocyclohexane and *trans*-1,2-dibromocyclohexane. Table I gives a summary of the results of the conversions. The steric results are based on configurations of the starting materials and products which are either proved or highly probable.[12,14,15,16,17]

It is seen that the acetoxybromobutanes and the butene dihalides react with silver acetate to give diacetates with quite high retention of configuration. Thus, retention of configuration is the steric result in the replacement of both the first and second bromine atom of the dibromide by the acetoxy group. Similarly the cyclohexene derivatives react with retention of configuration to give *trans*-diacetate under conditions which cause no configurational change of *cis*-diacetate.

TABLE I

SUMMARY OF STERIC RESULTS OF REACTION OF SILVER ACETATE WITH SOME HALIDES IN ACETIC ACID

Starting halide	Diacetate[a] M. p., °C.	Diacetate[a] Config.	Corrected[b] steric result
trans-1-Acetoxy-2-bromocyclohexane	102[c]	97% *trans*	97% Retention
threo-2-Acetoxy-3-bromobutane	41	95.5% *dl*	98% Retention
erythro-2-Acetoxy-3-bromobutane	0.5	91% *meso*	91% Retention
trans-1,2-Dibromocyclohexane	103[c]	98% *trans*	98% Retention
dl-2,3-Dibromobutane	39	91% *dl*	94% Retention
meso-2,3-Dibromobutane	−1.5	87% *meso*	>87% Retention[d]

[a] Melting point of *dl*-2,3-diacetoxybutane, 42.9°; *meso* isomer 3.0°. [b] There is included a correction for slight configurational impurity of two starting materials. [c] Melting point of glycol from saponification of the diacetate. Melting point of *trans*-1,2-cyclohexanediol, 104°. [d] This result is a lower limit since it was obtained early in the course of the work and the acetic acid solvent was not freed from water as thoroughly as in later work; see ref. 18.

The retentions of configuration are almost complete and would appear even better were one able to eliminate small configurational impurity of starting materials; also, if one were able completely to eliminate another reaction to be discussed elsewhere,[18] which gives rise to inverted products and which can be made predominant under other conditions. Also, there is the possibility that the halides are to a very small degree isomerized to diastereomers by silver halide in the course of the conversions. This would give rise to a small amount of apparent inversion in the steric result.

Besides acetic acid as a solvent medium for the reaction of the cyclohexene derivatives with silver acetate, acetic anhydride was also employed. The results obtained were entirely similar in steric result to those in acetic acid but the yields of diacetate were much inferior and it was difficult to fractionate out pure material.

The retentions of configuration observed are best accounted for by the participation in the replacement process of the —Br atom or —OAc group on the carbon atom neighboring the seat of substitution. This participation involves bond formation to the carbon atom being substituted either simultaneously with or very shortly after the removal of halide ion by silver ion in some form with the production of intermediate I or II with quite complete inversion. The reaction of these intermediates with acetate ion[19] with a

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(11) Cowdrey, Hughes and Ingold, *J. Chem. Soc.*, 1208 (1937).

(12) (a) Winstein and Lucas, THIS JOURNAL, **61**, 1576 (1939); (b) Winstein and Lucas, *ibid.*, **61**, 2845 (1939).

(13) Lucas and Gould, *ibid.*, **63**, 2541 (1941).

(14) Bartlett, *ibid.*, **57**, 224 (1935).

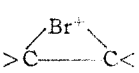
(15) Lucas and Gould, *ibid.*, **64**, 601 (1942).

(16) Winstein, *ibid.*, **64**, 2792 (1942).

(17) Rothstein, *Ann. Chim.*, **14**, 461 (1930).

(18) Winstein and Buckles, *ibid.*, **64**, 2787 (1942).

(19) Although the reaction is formulated in this way, it is not entirely clear whether acetate ion or acetic acid[12b] is the reagent in this case. This point will be settled later.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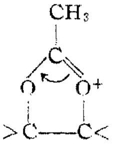
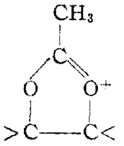

II

second inversion gives a net apparent retention of configuration as the steric result.

The bromonium ion I has been considered an intermediate in the reaction of the 3-bromo-2-butanols with hydrobromic acid[12] and in one ionic mechanism of addition of bromine to the ethylenic linkage.[12,20] Lucas and Gould have recently presented evidence for an analogous chloronium ion.[13]

For two reasons, the ion II is chosen as the intermediate when a neighboring acetoxy group participates in the replacement process. First, II should be energetically preferable over other possible forms because of freedom from strain and because of resonance between equivalent forms III and IV. The arrow in formula II indicates the symmetrical nature of II. Secondly, in reactions similar to the one being dealt with, orthoacetate derivatives are often isolated.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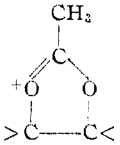

IV

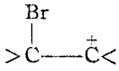
The argument in favor of the mechanism involving intermediates I and II for the retentions of configuration is strengthened by the results with some optically active materials (Table II). 2-Bromoöctane with α_D (1 dcm.) 5.39° was converted by silver acetate in acetic acid to an acetate with α_D (1 dcm.) − 0.61°. On the basis of densities and specific rotations in the literature[3a,21] for 2-bromoöctane and 2-acetoxyoctane, it appears that 72% of the optical activity survives in the process and that the results correspond to 86% inversion and 14% retention. Thus, in the absence of a neighboring group the reaction conditions lead to a typical[3,4] S_N1 steric result. 2,3-Dibromobutane with α_D (1 dcm.) − 2.43° yielded a diacetate which was completely inactive in spite of the fact that active diacetate did not lose its activity under the conditions of the experiment. Also, *trans*-1-acetoxy-2-bromocyclohexane with α_D (1 dcm.) −0.19° yielded a completely inactive diacetate. These results are in perfect accord with the prediction[12] of complete loss of activity for a mechanism involving an inactive internally compensated intermediate (I or II).

TABLE II

SUMMARY OF THE RESULTS OF THE TREATMENT OF ACTIVE COMPOUNDS WITH SILVER ACETATE IN DRY ACETIC ACID

Starting compound Name	α_D (1 dcm.)°	Final product α_D (1 dcm.)°
2-Bromoöctane	5.39	−0.61
2,3-Dibromobutane	−2.43	.00±0.01
trans-1-Acetoxy-2-bromocyclohexane	−0.19	.00 ± .01
2,3-Diacetoxybutane	− .48	− .45

We are still inquiring into the question whether the closings of the rings in intermediates I and II are one-stage[12] or two-stage[3] processes. The two-stage processes would involve the bromine-substituted carbonium ion V and the acetoxy-substituted carbonium ion VI. In this connection some relative reactivities are pertinent. There is a tremendous difference in reactivity of the 2-butene chlorohydrins and bromohydrins toward fuming hydrobromic acid. This has been mentioned by Lucas and Gould[13] and we have independently noticed it. A similar difference in reactivity appears in the cyclohexene series.[22] It does not appear reasonable that inductive effects can account for such a large difference. Bromine and chlorine atoms generally have effects of comparable magnitude[23] and thus would hinder about equally well the formation of conjugate acid from halohydrin and the departure of a water molecule with the shared pair of electrons from the halohydrin-conjugate acid. Thus, the bromine atom is able to meet much better than the chlorine atom a demand of the carbon atom being substituted. This effectiveness of the bromine atom must rest in its larger size and larger polarizability.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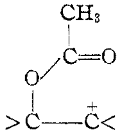
VI

Also, there is a tremendous difference in the reactivity of the *cis*- and *trans*-1-acetoxy-2-chlorocyclohexanes toward silver acetate.[24] Under conditions more drastic than those needed to

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[20] Roberts and Kimball, THIS JOURNAL, **59**, 947 (1937).

[21] (a) Hughes, Ingold and Masterman, *J. Chem. Soc.*, 1196 (1937); (b) Pickard and Kenyon, *ibid.*, 45 (1911); (c) Pickard and Kenyon, *ibid.*, 830 (1914).

[22] Winstein, unpublished work.

[23] See, for example, Branch and Calvin, "The Theory of Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1941, p. 204.

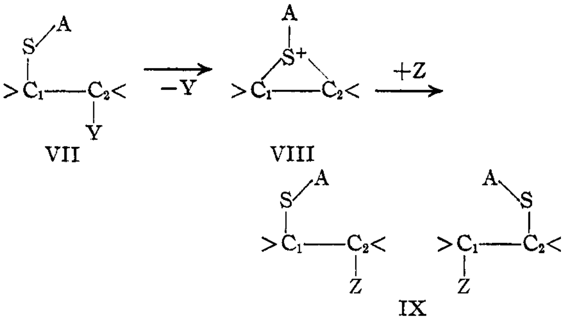
[24] Winstein and Buckles, unpublished work.

bring about reaction of the *trans*-compound, the *cis*-compound is completely unreactive. The *trans*-acetoxy group seems to be able to supply some driving force for the reaction and the *cis*-acetoxy group is essentially unable to do this. These relative reactivities are more easily understood on the basis of a one-stage closing of the ring in intermediates like I or II than on another basis. This holds also for the rather complete inversion accompanying the formation of I or II together with the rather complete lack of competition of outside reagents (solvent, AcO^-, etc.) with the neighboring group for attachment to the carbon atom being substituted.

We are also attempting to decide whether the opening of the ring in intermediates like I or II occurs in one or two stages.[25]

Participation of Neighboring Groups.—The observed retentions of configuration due to the participation of a neighboring group in an S_N1-like replacement process involve the effect of a carboxylate ion group[11] in solvolytic and analogous reactions of salts of α-halogen acids; the effect of a neighboring bromine atom in the reaction of a bromohydrin with hydrogen bromide[12] and in the reaction of a dibromide with silver acetate; the effect of a neighboring chlorine atom in the reaction of a chlorohydrin with thionyl chloride[13]; and the effect of a neighboring acetoxy group in the reaction of acetoxybromides with silver acetate. One would expect this effect to be very general, likely neighboring groups for such participation, including those already mentioned, being $—O^-$ of a carboxylate ion group, halogen, —OCOR, $—NH_2$ or $—NR_2$, —SR, —OR, —OH and of course $—O^-$.

It is worth pointing out briefly some expected results of the participation of neighboring groups in replacement processes of the S_N1 type. We will symbolize VII as the starting compound with Y the group to be replaced and AS the neighboring group, Z being the entering group.



First, if VII is the derivative of an unsymmetrical olefin, it becomes possible for some or most of the product IX to have Z on a different carbon atom than the one left by Y.

A second expectation involves the results when VII is either the *cis*- or *trans*-derivative of a cyclic olefin. If the new ring in the intermediate VIII is a small one, it is possible for the neighboring group to participate in the replacement process only when one starts with *trans*-VII and not when one starts with *cis*-VII. Thus, retention of configuration will be the steric result when one starts with *trans*-VII and the usual predominating inversion will be the steric result when one starts with *cis*-VII. There will then be a tendency for both isomeric VII's to give, in reactions of the S_N1 type, a product with the groups Z and SA *trans* to each other.[26]

A situation which appears to illustrate this point arises in the reaction of silver acetate with acetohalogen sugars to form normal polyacetates. Tipson[27] has made the generalization that acetate groups 1 and 2 in the product are *trans* to each other and Isbell[28] has pointed out that this result arises because of the ability of acetate group 2 to enter into the replacement process if it is *trans* to the original halogen and not if it is *cis* to the original halogen.

Somewhat the same differences which are foreseen for *cis*- and *trans*-derivatives of cyclic olefins may be looked for in the case of pairs of open-chain diastereomers where rotation is seriously restricted about the bond between carbon atoms C-1 and C-2. The configurations about this bond might be so preferred[29] that it is easy for a neighboring group to participate in a replacement process of one diastereomer and difficult in the case of the other.

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(25) If generalizations such as rate sequences, *t*-Bu > *i*-Pr > Et > Me for S_N1 reactions and *t*-Bu < *i*-Pr < Et < Me for S_N2 reactions hold[18] for intermediates like I or II it would be possible to learn the nature of a reaction from the direction of the opening of the ring of an unsymmetrical intermediate. Considerable success[22] can be attained in this way in understanding the direction of opening of oxide rings but even with oxides one generalization, at least, does not hold. For S_N2 reactions, hydroxide ion should be a reagent superior to a water molecule. However, in kinetic work on reactions of oxides which appear to be S_N2, hydroxide ion has proved to be an ineffective reagent while water is an effective one [Brönsted, Kilpatrick and Kilpatrick, THIS JOURNAL, **51**, 428 (1929)].

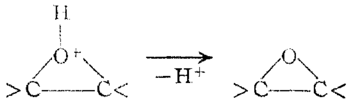
(26) The effect of the neighboring group might contribute toward the existence of a large difference in reactivity of *cis*- and *trans*-VII in S_N1 type reactions.

(27) Tipson, *J. Biol. Chem.*, **130**, 55 (1939).

(28) (a) Isbell, "Annual Review of Biochemistry," Annual Reviews, Inc., Stanford Univ. Press, Stanford Univ. P. O., Calif., 1940, page 65; (b) Frush and Isbell, *J. Research Natl. Bur. of Standards*, **27**, 413 (1941).

(29) Weissberger, *J. Org. Chem.*, **2**, 245 (1937).

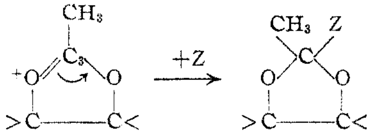
Finally, reactions involving the intermediate VIII might yield products other than IX in view of the ability of VIII to undergo other reactions. Thus, if VIII were to become X, we might expect to get oxide XI by the loss of a proton. Indeed



X XI

oxides are often isolated from S_N1 or analogous reactions of halohydrins, monotosylates of glycols, etc.

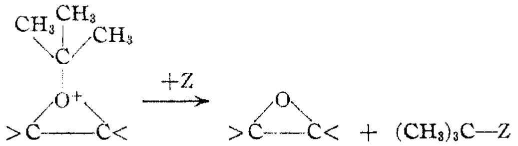
If II is the intermediate, then reaction at carbon C-3 should give an orthoacetate deriva-



II XII

tive XII. Isbell[28] has pointed out that acetohalogen sugars often give rise to orthoacetate derivatives, and that these orthoacetate derivatives are obtained only when the neighboring acetate group is *trans* to the halogen and not when it is *cis*. This is because an intermediate like II is easily possible only for the *trans*-compound.

It seems possible that other intermediates might discard, instead of a proton, some other group. Thus, it seems possible that an intermediate such as XIII might give rise to oxide XI and a tertiary butyl derivative XIV.



XIII XI XIV

Experimental

***trans*-2-Bromocyclohexanol.**—This material was prepared from cyclohexene and acetbromamide.[30] 1.56 moles of cyclohexene and an equivalent amount of acetbromamide were stirred under reflux with 1200 ml. of water for one and one-half hours. The reaction was controlled by addition of concd. sulfuric acid, 2 ml. at the start, 2 ml. after one half hour and 1 ml. at the end of an hour. The temperature of the reaction mixture was kept below 50° with an ice-bath. At the end of the one and one-half-hour period the mixture had returned to room temperature. The bromohydrin layer was separated and the aqueous layer was extracted with 150 ml. of ether. The extract and bromohydrin were combined and washed with 250 ml. of water to remove acetamide. The ether was distilled off and the bromohydrin was distilled rapidly through a Weston-type[31] column at reduced pressure. The yield was 219 g. (79%), b. p. 86.6–88.4° (10 mm.), $n^{25}\text{D}$ 1.5184.

***trans*-1-Acetoxy-2-bromocyclohexane.**—Acetylation of the bromohydrin was carried out with a 20% excess of acetic anhydride. To 45 g. of bromohydrin, acetic anhydride and 2 drops of concd. sulfuric acid were added. The mixture warmed up and soon returned to room temperature. The mixture was shaken with a little calcium carbonate to neutralize the catalyst, filtered and distilled at reduced pressure through a short column. 48 g. (87%) of the acetate was obtained; b. p. 109–110° (12 mm.), $n^{25}\text{D}$ 1.4857.

***trans*-1,2-Dibromocyclohexane.**—Bromine was added to cyclohexene by the method of Greengard.[32] Material, b. p. 99.6–99.9° (13 mm.), $n^{25}\text{D}$ 1.5506, was used in this work.

***trans*-1,2-Cyclohexanediol.**—This material was some prepared from cyclohexene oxide in connection with other work[18] and some prepared by saponification of the diacetate obtained from the action of silver acetate on dibromocyclohexane in dry acetic acid. Recrystallization from carbon tetrachloride yields a product, m. p. 104°.

***cis*-1,2-Cyclohexanediol.**—This material was some prepared in another study.[18]

***cis*- and *trans*-1,2-Diacetoxycyclohexanes.**—These substances were prepared by acetylation of the glycols by the procedure used with the bromocyclohexanol. The diacetates were obtained in 90 to 95% yield, the *cis*, b. p. 117.8–118.0° (12 mm.), $n^{25}\text{D}$ 1.4475, the *trans*, b. p. 120° (12 mm.), $n^{25}\text{D}$ 1.4457.

***threo*-3-Bromo-2-butanol.**—This substance was prepared from the reaction of acetbromamide and *cis*-2-butene[12] obtained from *meso*-2,3-butanediol by way of the diacetate and dibromide.[33] The general procedure has been described previously.[12] The reaction was controllable when 0.4 mole of butene was added to the acetbromamide in 250 ml. of water to which 4 ml. of 6 *N* sulfuric acid had been added. Under these conditions the reaction mixture was worked up after one and one-quarter to two hours and the yield, 82%, (107 g. bromohydrin from a total of 0.855 mole of butene used in two runs) was superior to that formerly obtained.[12]

***erythro*-3-Bromo-2-butanol.**—This material was prepared from pure oxide.[12]

***threo*- and *erythro*-2-Acetoxy-3-bromobutanes.**—These substances were prepared by acetylation of the corresponding bromohydrins as previously described.[34] In the acetylation of bromohydrins from the reaction of olefin with acetbromamide, a drop or two of concd. sulfuric acid was needed as a catalyst, and the reaction mixture was shaken with a little calcium carbonate before distillation.

***dl*-2,3-Dibromobutane.**—This material was prepared from *meso*-diacetate.[33,34]

***meso*-2,3-Dibromobutane.**—This dibromide was some prepared by the action of fuming hydrobromic acid on pure oxide or the bromohydrin or the acetoxybromobutane derived from it.[12,34]

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[30] Schmidt, Knilling and Ascherl, *Ber.*, **59B**, 1280 (1926).

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

[32] Greengard, Org. Syntheses, **XII**, 26 (1932).

[33] Wilson and Lucas, This Journal, **58**, 2396 (1936).

[34] Winstein and Lucas, *ibid.*, **61**, 1581 (1939).

Reaction of the Dibromides and Acetoxy-bromides with Silver Acetate.—The reaction of the halides with silver acetate in acetic acid at 100–110° with automatic stirring yielded results superior to some[35] reported for other conditions. Silver acetate (approximately 25% excess) was precipitated by adding excess aqueous sodium or potassium acetate to aqueous silver nitrate. It was filtered and washed carefully three times with glacial acetic acid on a Büchner funnel. The moist mass was then transferred to the reaction flask equipped with a mercury-sealed stirrer and reflux condenser protected by a drying tube. 100 ml. of reagent grade glacial acetic acid for each 0.1 mole of halide was added and the mixture was stirred for fifteen minutes. Then a sample of the acetic acid solvent was pipetted through cotton and the water content of the acid estimated from the melting point. An amount of acetic anhydride, in excess by 2 or 3 ml. of the amount necessary to react with the water in the solvent, was then added and the mixture was kept warm for about two hours[36] with stirring with an oil-bath at 100–110°. Then the halide was added and to insure complete reaction the mixture was stirred for eight hours in the case of the butene derivatives and eleven hours for the cyclohexene derivatives, the oil-bath being maintained at 100–110°. Sometimes the reaction was vigorous at the start and it was necessary to interrupt the heating for a short while. At the end of the proper time, the reaction mixture was allowed to cool and it was filtered. The filtrate was distilled at reduced pressure through the Weston-type column to isolate the diacetates. Starting with 0.1-mole quantities of the halides the yields averaged 70%, and they were better on larger runs. The products agreed within experimental error in boiling point, refractive index and saponification equivalent with authentic samples.

When acetic anhydride was used as a reaction medium in the case of the cyclohexene derivatives the procedure was the same in preparing and washing the silver acetate. Then acetic anhydride was added instead of acetic acid, the mixture was heated for a time to remove water, and the reaction was then carried on as usual and the product was isolated as usual. A good deal of high-boiling residue was formed in these reactions and only a 30–40% yield of somewhat impure diacetate could be distilled out with difficulty.

Analysis of Products.—The 1,2-diacetoxycyclohexane samples were identified by saponification to the glycol. 1 ml. of the ester was refluxed two hours with 2 ml. of 35% aqueous sodium hydroxide and 2 ml. of pure alcohol. The solution was washed into a separatory funnel with a minimum of water (1 or 2 ml.). Then the glycol was extracted with five 25-ml. portions of pure chloroform, the extracts were dried over potassium carbonate, distilled to a small volume and the residue was allowed to evaporate to dryness. The solid glycol was thus obtained in nearly quantitative yield. The melting points of the glycol and its mixtures with authentic specimens yielded an estimate of the composition of the glycol. Recrystallization of the crude glycols from carbon tetrachloride yielded pure *trans*-glycol. The saponification procedure was carried out on mixtures of *cis*- and *trans*-diacetates made up by weight, the temperatures of disappearance of solid when the glycol was melted being summarized in Table III.

The diacetoxybutanes were identified by melting point and mixed melting point with the aid of melting point-composition data of Lucas and Mitchell.[37]

TABLE III

MELTING POINTS OF GLYCOLS FROM THE SAPONIFICATION OF MIXTURES OF THE *cis*- AND *trans*-1,2-DIACETOXYCYCLOHEXANES

% *trans*	M. p., °C.	% *trans*	M. p., °C.
0	98	45	72
4	93.5	51	74
5.7	91	66	82
8.7	89	83	92.5
12	88	89	99
23	80.5	93	100.5
35	71.5	100	103.5

The melting points of the solid diacetate were taken by melting the whole sample in a flask or test-tube. In the case of the liquid diacetate, the dependence of composition on melting point is so sensitive that some standardization of the procedure was necessary. About a 10-g. sample of the diacetate was frozen in a test-tube and then with stirring at room temperature allowed to melt, the melting point being taken with a thermometer in the melt. With this technique and the thermometer in use, the very purest diacetate (prepared from glycol, m. p. 34.5°, by acetylation, removal of the sulfuric acid catalyst with calcium carbonate, and careful purification) gave a temperature 0.5° below the value of Lucas and Mitchell. Thus 0.5° was added to the temperature values near the melting point of *meso*-diacetate. To discover on what side of the eutectic a low-melting sample was it was sufficient to add a small amount of *meso*-diacetate and notice whether a decrease or increase in melting point was observed.

The products from the reaction of the cyclohexene derivatives in acetic anhydride gave glycols a little less pure than those obtained from the acetic acid reaction, the acetoxybromocyclohexane product giving a glycol, m. p. 101.5° and the dibromocyclohexane product giving a glycol m. p. 96°. These glycols were again predominantly *trans*.

Corrections for Slight Impurity of Starting Isomers.—In the preparation of *threo*-2-acetoxy-3-bromobutane (from the butene from the dibromide) and the *dl*-2,3-dibromobutane, *meso*-diacetate of slightly low melting point was used. This impurity was partly due to impurity of the glycol used and perhaps partly due to the failure to neutralize the sulfuric acid, used as a catalyst in the acetylation of the glycol, before distillation. This impurity in the starting diacetate is corrected for in Table I.

Preparation of Active 2-Bromoöctane and its Reaction with Silver Acetate.—5.0 ml. of active 2-octanol (kindly supplied by Dr. P. D. Bartlett) α_D (1 dcm.) −7.38°, was mixed with 15.0 ml. of Eastman Kodak Co. *dl*-2-octanol and the mixture was sealed up with hydrobromic acid which was prepared by saturating[12,34] 130 g. of 48% acid with hydrogen bromide gas at 0°. The reaction mixture was left at room temperature with occasional shaking for several days when the reaction vessel was opened and the

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(35) Bainbridge, *J. Chem. Soc.*, **105**, 2291 (1914).

(36) For the reaction of *meso*-2,3-dibromobutane the water was removed by allowing the mixture to stand nearly two days at room temperature before the dibromide was added.

(37) Private communication.

bromide layer separated. The bromide was washed with water, twice with 10 ml. of concd. sulfuric acid, then with water and finally with potassium carbonate solution. The bromide was dried over potassium carbonate and the 21.5 g. of crude material was then distilled through the Weston-type column. 18.5 g., b. p. 74.7–75.3° (14 mm.), αD (1 dcm.) 5.39°, was obtained. The bromide, 18.0 g., was converted to acetate with silver acetate in dry acetic acid as for the butene and cyclohexene derivatives. Distillation through the Weston-type column yielded 9.5 g. (59%) of acetate, b. p. 81.3–82.0° (12.5 mm.), n^{22}D 1.4140, αD (1 dcm.) −0.61°.

Active 2,3-Dibromobutane and its Conversion to Diacetate.—Partial resolution of a 2,3-dibromobutane which was mostly the *dl*-isomer was accomplished by the method of Lucas and Gould.[15] 64.8 g. (0.30 mole) of the dibromide and 39.5 g. of brucine were mixed and allowed to stand for eighteen hours. The brucine was dissolved in excess hydrochloric acid and the dibromide was removed with the aid of 200 ml. of petroleum ether. The extract was washed with water and dried over potassium carbonate. The dibromide was obtained by distillation at reduced pressure; 46 g., b. p. 73.0–73.5° (50 mm.), αD (1 dcm.) −2.43°. When this material was converted to diacetate in the usual way, the product proved to be completely inactive.

A 2,3-diacetoxybutane with αD −0.48° (mostly diacetate of Lucidol glycol) was subjected to the reaction conditions using a mixture of silver acetate and bromide. The recovered diacetate αD − 0.45° showed a change in the rotation no larger than one would expect due to fractionation.

Active 1-Acetoxy-2-bromocyclohexane and its Conversion to Diacetate.—The method of treating the bromohydrin with a deficiency of acetic anhydride in the presence of brucine as described previously[12b] for butene derivatives yielded a slight resolution. A solution of 30 g. of brucine, 54 g. of 2-bromocyclohexanol and 13 ml. of acetic anhydride in 300 ml. of carbon tetrachloride was refluxed for two hours. The reaction mixture was treated as before and fractionation at 12 mm. yielded 23.2 g. of bromohydrin, b. p. 88.5–91.0°, αD (1 dcm.) − 0.20° and 17.8 g. of acetoxybromocyclohexane, b. p. 106.0–107.2°, αD (1 dcm.) − 0.19°. Each fraction was treated with acetic anhydride to convert all the bromohydrin to acetate. The bromohydrin fraction yielded 23.6 g. of acetate, b. p. 109–110° (12 mm.), αD (1 dcm.) − 0.19°. The bromoacetate fraction[38] yielded 14 g., b. p. 109–110° (12 mm.), αD (1 dcm.) − 0.17°.

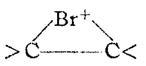
When the acetoxybromocyclohexane, αD (1 dcm.) − 0.19° was converted to diacetate with silver acetate in dry acetic acid in the usual way the diacetate, b. p. 120.0–120.5° (12 mm.) showed no activity at all. The intermediate fraction lower-boiling than the diacetate also showed no activity.

Behavior of *cis*-1,2-Diacetoxycyclohexane under the Reaction Conditions.—A small quantity of *cis*-1,2-diacetoxycyclohexane was heated eleven hours in dry acetic acid with a mixture of silver acetate and silver bromide. The reaction mixture was filtered and diluted with water. The diacetate was then extracted with ether. The ether extract was neutralized with carbonate solution and then dried over potassium carbonate. Evaporation of the ether and saponification of the ester by the procedure in use gave *cis*-glycol, m. p. 97.5° before recrystallization. Thus at least 99% of the glycol maintains its configuration.

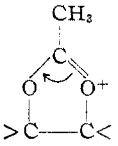
It is a pleasure to thank Professor H. J. Lucas and Messrs. C. W. Gould and F. W. Mitchell, Jr., of the California Institute of Technology for data in advance of publication and Professor P. D. Bartlett of Harvard University for the optically active 2-octanol used. Also, one of us (S. W.) wishes to acknowledge several helpful discussions with Professors P. D. Bartlett and H. J. Lucas.

Summary

The reactions of silver acetate in dry acetic acid with the *erythro-* and *threo*-2-acetoxy-3-bromobutanes, *trans*-1-acetoxy-2-bromocyclohexane, the *meso-* and *dl*-2,3-dibromobutanes, and *trans*-1,2-dibromocyclohexane proceed with predominant retention of configuration. Also, optically active 2,3-dibromobutane and *trans*-1-acetoxy-2-bromocyclohexane give rise to completely inactive diacetates. The steric results are believed due to the participation of a neighboring bromine or acetoxy group in the replacement processes, with production of the intermediates



and



A discussion of the scope of this kind of participation of neighboring groups in replacement processes and the results to be expected from such participation is included.

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[38] The fact that the same sign of rotation is displayed by the acetoxybromocyclohexanes from both fractions shows that the slight resolution obtained by this procedure is not due to a selective acetylation but to some other reaction.