The Role of Neighboring Groups in Replacement Reactions. II. The Effects of Small Amounts of Water on the Reaction of Silver Acetate in Acetic Acid with Some Butene and Cyclohexene Derivatives[1]

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

In a previous[3] publication on the effects of neighboring groups in replacement reactions we reported that the reaction of silver acetate in dry acetic acid with *trans*-1-acetoxy-2-bromocyclohexane, *threo*- and *erythro*-2-acetoxy-3-bromobutane, *trans*-1,2-dibromocyclohexane and *dl*- and *meso*-2,3-dibromobutane proceeded with what appears to be quite complete retention of configuration. This and other evidence pointed to the participation of the neighboring —Br and —OAc groups in the replacement process, intermediates I and II being involved.

In the course of this investigation, we noticed a pronounced and interesting effect of the presence of water in the acetic acid on the nature of the product and the steric result. The presence of water causes the appearance of roughly 65–75% of the equivalent amount of monoacetate in the product and shifts the steric result to as much as 95–98% of inversion of configuration. This is shown in Table I.

That monoacetate of the glycol is the direct product of the reaction in the presence of water is shown by the behavior of some of the monoacetates and diacetates toward the reaction conditions (Table II). The monoacetates are converted to diacetates to a considerable extent, while the diacetates are converted to monoacetates to only a negligible extent.

Since monoacetate is the direct product of reaction, the presence of water is able to cause the introduction of an hydroxyl group instead of an acetate group by the action of silver acetate on the bromoacetates. However, it appears unlikely

(1) A large 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) Winstein and Buckles, THIS JOURNAL, **64**, 2780 (1942).

TABLE I

THE EFFECT OF WATER ON THE REACTION OF SOME HALIDES WITH SILVER ACETATE IN ACETIC ACID

Compound	Moles H_2O	N^a	Diacetate[b] m. p., °C.	Corrected steric result % inversion
threo-2-Acetoxy-3-	0	0	41	2
bromobutane	0.25	0.10	34.8	19
	.50	.39	15.7	55
	.75	.58	−4.5	82
	1.0	.70	0.5	94
	1.0[c]	.72	2.1	95
erythro-2-Acetoxy-3-bromobutane	1.0		41.3	96
dl-2,3-Dibromobutane	0.5	.39	14.2	57
	1.0	.65	2.0	96
meso-2,3-Dibromobutane	1.0	.67	40.5	96
dl-trans-1-Acetoxy-2-bromocyclohexane	0.00[c]	0		7
	0.51	.37		67
	1.0	.65		92
	1.0[d]	.64		94
	1.0[c]	.52		92
	2.0	.65		98
dl-trans-1,2-Dibromocyclohexane	1.0	.64		90
	2.0			98

[a] Mole fraction of monoacetate in reaction product. [b] *dl*-2,3-Diacetoxybutane melts at 42.9°, the *meso*-isomer at 3.0°. [c] 1 mole of potassium acetate per mole of halide was used in the reaction mixture. [d] Volume of reaction mixture was twice as large as usual so that the initial concentration of water was half as large.

TABLE II

THE BEHAVIOR OF MONO- AND DIACETATES TOWARD THE CONDITIONS FOR REACTION OF HALIDES WITH SILVER ACETATE

Compound	Moles H_2O	Hours of heating	N	% retention
meso-2,3-Diacetoxybutane	1.0[b]	11	0.02	100
erythro-3-Acetoxy-2-butanol	0.3	7.5	.76	100
cis-1,2-Diacetoxycyclohexane	1.0	11	.03	...
cis-2-Acetoxycyclohexanol[a]	0.51	11	.51	...
trans-1,2-Diacetoxycyclohexane	2.0	11	..	99

[a] This material was 84 mole % monoacetate, 16 mole % diacetate. [b] In all these experiments an equimolar mixture of silver acetate and silver bromide was added.
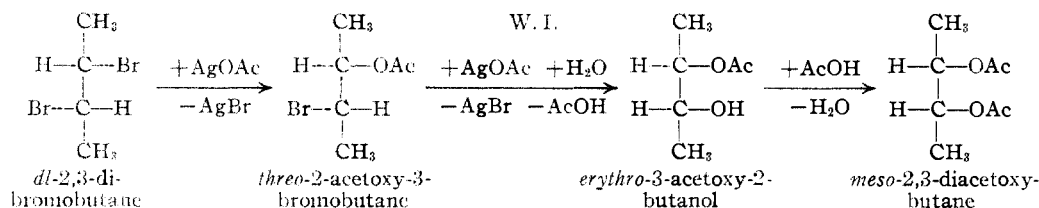
Fig. 1.— erythro-3-Acetoxy-2-butanol and meso-2,3-diacetoxybutane from dl-2,3-dibromobutane or threo-2-acetoxy-3-bromobutane.

that water causes the introduction of an hydroxyl group instead of an acetate group when silver acetate reacts to replace the first bromine atom of the dibromides. This is evident from the behavior of the bromohydrins which would thus be formed (Table III).

TABLE III

THE BEHAVIOR OF BUTENE AND CYCLOHEXENE BROMO-HYDRINS TOWARD SILVER ACETATE IN ACETIC ACID

Compound	Moles H$_2$O	N	% retention
threo-3-Bromo-2-butanol	1.0	..	75[a]
trans-2-Bromocyclohexanol	1.0	78	92
trans-2-Bromocyclohexanol	0.64[b]	71	93

[a] The yield of diacetate on acetylating the crude ester product of the reaction was only 26%.   [b] One mole of silver bromide was added also.

Firstly, threo-3-bromo-2-butanol gives only a poor yield[4] of expected product with silver acetate in acetic acid. Secondly, with the butene bromohydrin, the steric result is 75% retention,[5] while with the cyclohexene bromohydrin it is at least 93% retention. All our experience[3,6] would lead us to expect bromohydrin to be formed from dibromide with retention of configuration, so retention of configuration should be the steric result for the conversion of dibromide to monoacetate by way of bromohydrin. Actually inversion is the major steric result in the presence of enough water.

Figure 1 illustrates the reaction course for the preparation of a mixture of monoacetate and diacetate from one of the dibromides or bromoacetates with silver acetate in wet acetic acid containing moderate amounts of water.[7] If dibromide is the starting material, bromoacetate is produced with retention of configuration just as

(4) With the cyclohexene bromohydrin the yield of expected product was not much inferior to that obtained from dibromide.

(5) The reason for this steric result in the case of the butene bromohydrin is not yet clear. In view of the poor yield, the amount of inversion observed could be due to reaction of a small amount (ca. 7%) of bromoacetate produced from bromohydrin.

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

(7) Mr. Robert Henderson has found that very much larger amounts of water in the reaction mixture for the treatment of the dibromobutanes have some marked effects such as depressing the yield of product greatly.

in the absence of water.[3] Then bromoacetate gives rise to monoacetate with inversion of configuration, the monoacetate then slowly being acetylated. The inversion of configuration is denoted by W. I.

In the presence of small amounts of water the scheme shown in Fig. 1 apparently proceeds until the water is largely consumed and then the scheme for dry acetic acid (with retention of configuration) operates. Since water is slowly produced from the monoacetate, it becomes clear why there is a tendency for the amount of inversion of configuration to run somewhat higher than equivalent to the amount of water in the original reaction mixture.

The most probable explanation of the effect of the water involves the formation of intermediate II even when some water is present. Then intermediate II reacts with water at carbon atom C-3 to give the conjugate acid of the orthomonoacetate of the glycol III which by loss of a proton
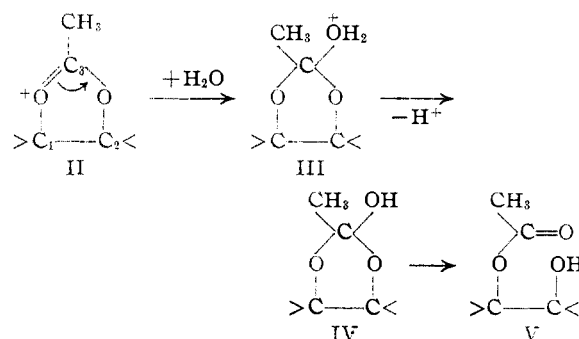
gives rise to the orthomonoacetate of the glycol IV.[8] The orthomonoacetate IV and the ordinary

(8) At least part of the orthomonoacetate formation in the presence of water may arise from reaction of molecules of acetoxybromide, to which water has already added, according to the scheme shown.
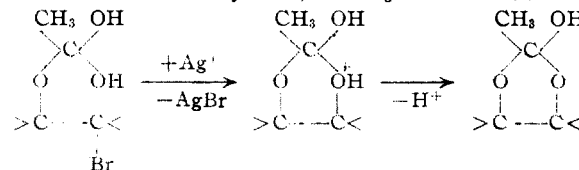
This scheme involves the participation of a neighboring orthoacetate group in the process of replacement of the bromine atom.

monoacetate V are presumed to be readily inter-convertible without any configurational changes under the conditions of the replacement reaction.[9] Thus, the preparation of monoacetate is attended by one Walden inversion which occurs in the formation of intermediate II.

There are several favorable aspects to this explanation. First, intermediates of type II must be reactive at carbon atom C-3, for aceto-halogen sugars in which the neighboring ace-toxy group is *trans* to the halogen atom often give rise to orthoacetate derivatives in reactions similar in nature to the one discussed in this paper.[10,11] Secondly, the ability of water to affect the reaction only when the acetoxy group is the neighboring group becomes understandable. Thirdly, the very high percentage of inversion of configuration that occurs when enough water is present is to be expected from a process involving the production of an intermediate such as II.

Other Halides with Silver Acetate in Wet Acetic Acid.—Rothstein[12] obtained *cis*-ester from cyclohexene dibromide and Brunel[13] obtained what is now known to be *cis*-ester from 1-acetoxy-2-iodocyclohexane,[14] 1-bromo-2-iodocyclohexane,[14] and 1-chloro-2-iodocyclohexane.[14] These results demand the presence of water in the acetic acid used as solvent, by analogy with the results we have reported.

A case which comes to mind of the introduction of an hydroxyl group on treatment of an acyloxy-halide with silver acetate in acetic acid is the conversion[15] of such compounds as 1-iodo-2,3-di-*p*-nitrobenzoxypropane VI to 1,3-di-*p*-nitrobenz-oxypropanol-2 IX.

This work is interesting here not only because an hydroxyl group is introduced instead of an acetoxy group but because an acyl group has migrated[3] in the process. If our mechanism for the effect of water in acetic acid on the course of

the reaction of acyloxyhalide with silver acetate is correct, the transformation VI → IX proceeds according to the scheme[16] VI → VII → VIII → IX.
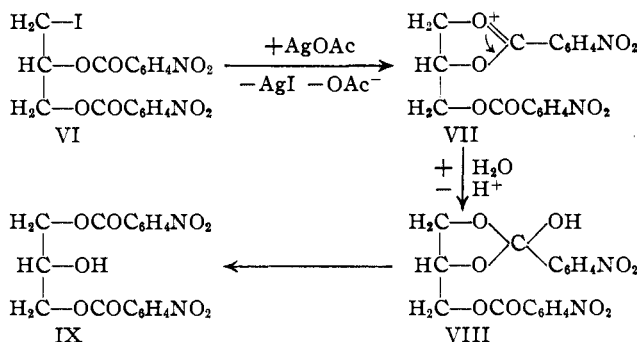
Form VIII was suggested by E. Fischer[15] as an intermediate for the migration of acyl groups in partially acylated polyhydroxy compounds.

The Neighboring Hydroxyl Group.—The quite high retention of configuration observed in the treatment of cyclohexene bromohydrin with silver acetate in acetic acid and the predominating retention of configuration in the similar treatment of the butene bromohydrin suggest that the ester product XI is produced chiefly by way of the conjugate acid of the oxide X, the opening of
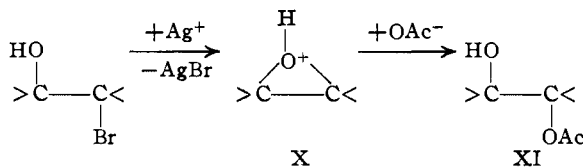
the oxide ring occurring with inversion.[17] Thus, it would appear that a neighboring hydroxyl group can be similar in action to a bromine or acetoxy group.[3]

Experimental

trans-2-**Bromocyclohexanol,** *threo*-3-**Bromo-2-butanol,** *trans*-1-**Acetoxy-2-bromocyclohexane,** *trans*-1,2-**Dibromo-cyclohexane,** *erythro*- **and** *threo*-2-**Acetoxy-3-bromobutane and** *dl*-2,3-**Dibromobutane.**—These substances were either the same as or prepared similarly to the ones used in the previous work.[3]

meso-2,3-**Dibromobutane.**—This material, b. p. (50 mm.) 73.3–73.5°, was prepared by the action of fuming hydrobromic acid[17,18] on the *dl*-2,3-diacetoxybutane which was obtained in the course of this and the previous[3] work and which was purified by recrystallization from petroleum ether.

cis-1,2-**Cyclohexanediol.**—This substance, m. p. 98°, was prepared by saponification of esters obtained in the

(9) The ready interconversion of IV to V would be expected from the available work on compounds such as these (Meerwein and Sönke, *J. prakt. Chem.*, **137**, 295 (1933); Hibbert and Greig, *Can. J. Research*, **4**, 254 (1931)).

(10) (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).

(11) Generalizations are still lacking as to the factors which determine relative reactivity at carbons C-1 and C-2 as compared to C-3. In the present work it seems necessary to say that acetate ion reacts at C-1 and C-2, while water reacts very rapidly at C-3.

(12) Rothstein, *Ann. chim.*, **14**, 461 (1930).

(13) Brunel, *ibid.*, [8] **6**, 200 (1905).

(14) These compounds are all presumably *trans*.

(15) E. Fischer, *Ber.*, **53**, 1621 (1920).

(16) One desirable support for this scheme would be to show that the α,β-diglyceride does not proceed rapidly enough to the α,α'-glyceride by way of the ortho form VIII.

(17) Winstein and Lucas, THIS JOURNAL, **61**, 1581 (1939).

(18) Wilson and Lucas, *ibid.*, **58**, 2396 (1936).

present work. It was purified by recrystallization from carbon tetrachloride. When prepared in large batches by saponification of the ester from the reaction of 1 mole of dibromide with silver acetate in wet acetic acid, the glycol was sometimes not as pure as from the 0.1-mole runs. It was helpful to dissolve the glycol in acetone, filter off an acetone-insoluble impurity, evaporate the acetone from the filtrate and then recrystallize the residue from carbon tetrachloride.

cis- and *trans-*1,2-Diacetoxycyclohexanes.—These substances were the same ones used before.[3]

Monoacetate of *meso-*2,3-Butanediol.—This material was the one previously[17] prepared. Most of it, b. p. 79.2° (10 mm.), $n^{25}D$ 1.4215 was from butene oxide and a little, b. p. 74.5–75.5° (8 mm.),[19] was from *meso-*glycol.

Monoacetate of *cis-*1,2-Cyclohexanediol.—A mixture of 29 g. (0.25 mole) of *cis-*glycol, 25.5 g. (0.25 mole) of acetic anhydride, and 25 ml. of acetic acid was treated with several drops of concd. sulfuric acid. After the heat evolution had ceased and the solution had returned to room temperature, the mixture was diluted with 300 ml. of water and extracted with three 100-ml. portions of ether. The ether extracts were washed with carbonate solution and dried over potassium carbonate. Distillation at 12 mm. through the Weston-type[20] column yielded 27.5 g., 67%, of product boiling at 114–115°, $n^{25}D$ 1.4607. This product had a saponification equivalent weight of 142, indicating a composition of 84 mole per cent. monoacetate and 16 mole per cent. diacetate.

Conversion of Dibromides and Acetoxybromides to Mixtures of Mono- and Diacetates.—The halogen compounds were allowed to react with silver acetate in acetic acid as described previously.[3] The amount of water in the reaction mixture before addition of the halogen compound was estimated as before. Enough additional water was added to make up the desired quantity and the halogen compound was added after the mixture was stirred for a few minutes. Sometimes potassium acetate was added along with the water. The product was isolated as before except when potassium acetate was used in the experiment. Then, the reaction mixture was filtered as before and concentrated at reduced pressure. Ether was added to enable separation from solid potassium acetate. Then the ether was distilled off and the product isolated at reduced pressure.

The mixtures of mono- and diacetates distilled over a small range of temperatures but the mono- and diacetates boil sufficiently near the same temperature to enable sharp separation from acetic acid and high-boiling residue. The yields in the presence of water were about the same as in its absence.

Analysis of Ester Mixtures.—Usually a small portion of the mono- and diacetate mixture obtained by distillation was used for a determination of the saponification equivalent of the sample by the method of Redemann and Lucas.[21] Then the mole fraction of monoacetate in the sample could be calculated.

To obtain a configurational analysis of the ester product, the procedure was similar to the one used before.[3] The cyclohexene derivatives were saponified to glycol. The

(19) Previously incorrectly reported as b. p. 74.5–75.5° (10 mm.) [THIS JOURNAL, 61, 1583 (1939)].

(20) Weston, *Ind. Eng. Chem., Anal. Ed.,* 5, 179 (1933).

(21) Redemann and Lucas, *ibid.,* 9, 521 (1937).

butene derivatives were acetylated, distilled and the diacetates analyzed as before.

Behavior of Mono- and Diacetates.—The behavior of mono- and diacetates toward the reaction conditions was studied by using a mixture of silver acetate and bromide to best simulate the actual reaction conditions and isolating and analyzing the products as for the conversion reactions.

With *trans-*1,2-diacetoxycyclohexane only a very small amount of ester was treated. It was not distilled but separated with ether after diluting the filtered acetic acid solution with water. The ether solution was neutralized and dried, the ether was evaporated and the residue was subjected to the saponification procedure.

The diacetates on treatment with silver salts in wet acetic acid, gave rise to products with refractive indices and saponification equivalents slightly high. The values of N, the mole fraction of monoacetate in the product, are given in Table II. There seems to be a very slight change to monoacetate, but it is not possible to estimate such small changes very accurately with the methods we used.

Behavior of Butene and Cyclohexene Bromohydrins.—The bromohydrins were treated with silver acetate and silver bromide in wet acetic acid in the same way as for an acetoxybromide. The *threo-*3-bromo-2-butanol yielded only a small amount of ester product which was at once acetylated. The cyclohexene bromohydrin gave products which, in spite of the approximate character of the temperature control of the bath, etc., seemed definitely higher in monoacetate content than the *cis-*products obtained from dibromide and acetoxybromide.

Summary

The presence of small amounts of water in the acetic acid used as a medium for the action of silver acetate on 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, gives rise to a steric result shifted toward inversion and a product containing monoacetate. The percentage of inversion is usually slightly greater than equivalent to the water present in the acetic acid solvent and approaches 100 quite closely.

There is evidence that monoacetate is directly produced when water is involved in the replacement process and that the monoacetate is slowly esterified. Also, water seems to be involved in the replacement process for only the second bromine atom of the dibromides.

All the facts are best accounted for by the idea that the water exerts its effect through formation of the orthoester intermediate,

CH₃ OH
\>C/
O   O
| |
\>C——C<