A sample of α-formamino-α-hydroxypropionic acid was tightly stoppered in a sample bottle and allowed to stand two months. The material liquefied after several days and developed considerable pressure which was released occasionally. On dissolving the material in hot ethyl acetate and cooling, *dl*-N-acetylalanine, which was identified by mixed melting point determination, was obtained.

Heating 0.4 cc. (0.05 g.) of pyruvic acid with 0.1 cc. (0.11 g.) of formamide for two hours at 100° under atmospheric pressure, warming the reaction mixture with ethyl acetate, cooling and filtering gave 0.156 g. (49%) of *dl*-N-acetylalanine.

Rate of Formation of *dl*-N-Acetylalanine.—Heating 0.4 cc. of pyruvic acid with 0.1 cc. of formamide at 100° and measuring the volume of gas evolved gave the values in Table I under the listed conditions.

TABLE I

Vol. gas evolved at 30° (760 mm.), cc.	Time, min., with no added material		Time, min., 0.05 cc. of dioxane added	Time, min., 0.05 cc. of water added
	Run 1	Run 2		
10	7:15	7:45	7:30	2:45
20	16:15	16:45	17:20	6:15
30	26:15	27:05	27:45	9:15
40	41:45	42:30	40:30	17:40

Heating 118.0 mg. of α-formiminopropionic acid with 88 mg. of pyruvic acid under the same conditions gave no appreciable gas evolution, whereas addition of 18 mg. of water followed by heating at 100° gave 10 cc. of gas in 4:15 minutes and 20 cc. in 11:10 minutes.

Attempted Isolation of Intermediates.—Addition of four volumes of pyruvic acid to one volume of formamide resulted in the slow formation of crystals. This mixture was warmed to 50° for several minutes and allowed to stand overnight. After warming one portion of this material slowly until the temperature at which gas evolution just began (80–90°), and then cooling, crystallization from chloroform gave a small amount of material melting at 173–174°. A mixed melting point with α-formiminopropionic acid showed no depression. A small portion of the original mixture was dissolved in chloroform and cooled to obtain a sample of material melting at 50–52°. A mixed melting point with α-formamino-α-hydroxypropionic acid showed no depression.

Summary

1. Condensation of pyruvic acid with formamide has been found to form α-hydroxy-α-formaminopropionic acid at low temperatures.

2. α-Hydroxy-α-formaminopropionic acid has been shown to be unstable, slowly decomposing at room temperature under an anhydrous atmosphere to form α-formiminopropionic acid or its tautomer; however, it has also been found that if the hydroxy compound is allowed to stand in a closed container or is heated, *dl*-N-acetylalanine is formed.

3. Some physical and chemical properties of these compounds have been reported; and a few proposals concerning the mechanisms of their formation have been made.

NEW ORLEANS, LA. RECEIVED SEPTEMBER 10, 1945

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF CALIFORNIA, LOS ANGELES]

The Role of Neighboring Groups in Replacement Reactions. VIII. The Reaction of Stilbene Dichlorides with Silver Acetate

BY S. WINSTEIN AND DEXTER SEYMOUR

We are prompted by the work of Reulos[1] on the steric result of some reactions of stilbene halohydrins to report at this time the results of some related work which has remained interrupted by the war since 1942.

In connection with one phase of our work on the participation of neighboring groups in replacement reactions,[2] we treated the stilbene dichlorides I and II with silver acetate in acetic acid and scrutinized the products as to configuration. The necessary assignment of configurations to the stilbene dichlorides is certain from the synthesis of both optically active stilbene dichlorides by Weissberger and Bach.[3] Also, the configurations of hydrobenzoin (*meso*) and isohydrobenzoin (*dl*) VII, the esters of which are the products derived from the stilbene dichlorides, are clear from similar work by Read, Campbell and Barker.[4]

We found the *meso*-dichloride I in dry acetic acid gave rise to nearly pure *meso*-diacetate IV, while in moist acetic acid containing more than the stoichiometric amount of water it yielded nearly pure *dl*-glycol VII after saponification of the ester product, a process which we know does not affect configuration. We estimated that the products were 93% *meso* and 92% *dl*, respectively. The *dl*-dichloride II gave rise to quite similar products, which, however, appeared to be less pure stereochemically. We estimated the diacetate produced in dry acetic acid was 77% *meso* and the glycol obtained from saponification of the product from the treatment in moist acetic acid was 86% *dl*.

Zincke[5] had previously studied the reaction of the stilbene dichlorides with silver acetate in glacial acetic acid and with silver benzoate in xylene and obtained what, in his time, were very puzzling results. The two dihalides gave rise to substantially similar products, which were, however, largely *dl* from the first reaction and largely *meso* from the second. We know now from our pre-

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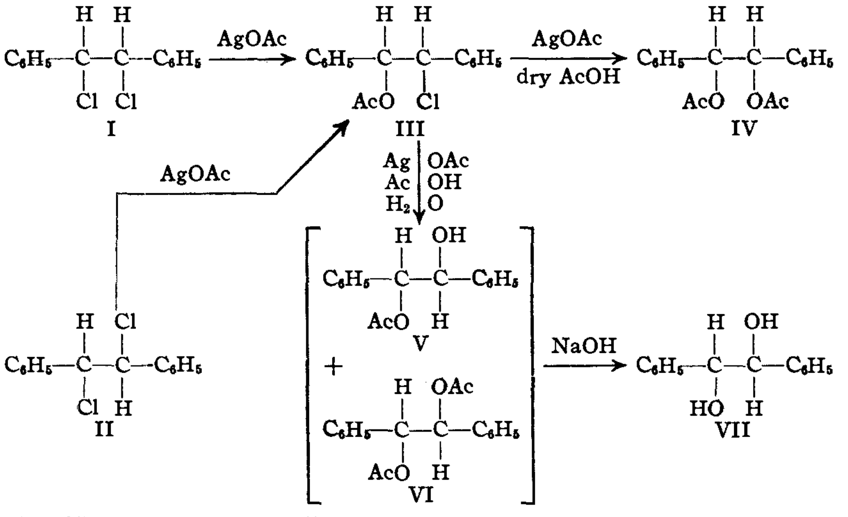
[1] (a) Reulos, *Compt. rend.*, **216**, 774 (1943); (b) Reulos and Le Tellier, *ibid.*, **217**, 698 (1943) (Reprint received February 2, 1945); *C. A.*, **39**, 926 (1945).

[2] For preceding paper in this series, Winstein and Henderson, THIS JOURNAL, **65**, 2196 (1943).

[3] Weissberger and Bach, *Ber.*, **64B**, 1095 (1931).

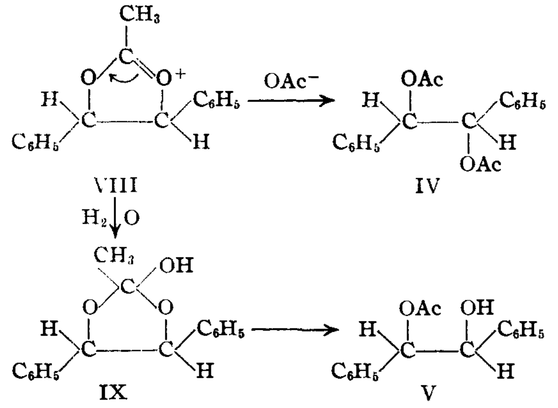
[4] Read, Campbell and Barker, *J. Chem. Soc.*, 2305 (1929).

[5] Zincke, *Ann.*, **198**, 115 (1879).



vious[6,7] and present work that the steric results of reactions involving a neighboring acetoxy group may be reversed by small amounts of water in a glacial acetic acid solvent. As it happens, silver acetate in dry acetic acid and silver benzoate in xylene give rise to substantially similar steric results. Zincke knew no reason to avoid small amounts of water in his acetic acid solvent and these were sufficient to control his steric results.

Although our work is incomplete, it gives some information regarding the mechanism of replacement of the individual chlorine atoms. We can be fairly definite regarding the replacement of only the second chlorine atom. We know that small amounts of water in the acetic acid solvent substantially reverse the steric result from either halide. In this situation, this is a strong indication that a neighboring acetoxy group[6,7] is participating in the replacement process for both halides. This, however, demands substantially similar steric results at the replacement of the second halogen atom of either dihalide, the acetoxychloride III, being largely the *erythro*-isomer whether one starts with *meso*- or *dl*-stilbene dichloride. So, for the replacement of the second halogen atom, acetoxychloride III is converted to the intermediate VIII, which gives rise to diacetate IV on reaction with acetate ion in dry acetic acid or to orthomonoacetate IX on reaction with water.[6,7] The orthomonoacetate gives rise to ordinary monoacetate V. Forst and Zincke[8] were able to isolate crystalline monoacetate of *dl*-glycol from the treatment of α-stilbene dibromide with silver acetate in acetic acid.



The present observations extend our information regarding the variations possible in the nature of the carbon atom being substituted, which still permit a neighboring acetoxy group to participate in the replacement process. In the present study, even when a phenyl group, which strongly stabilizes a carbonium ion, is a substituent on the carbon atom being substituted, a neighboring acetoxy group, at least in the *erythro*-acetoxychloride III, participates in the replacement reaction.

The formation of largely the same acetoxychloride from either stilbene dichloride is in contrast to the results obtained with the simpler butene derivatives in previous work. In the previous work with reactions analogous to the one used here, a neighboring bromine atom participated in the replacement process for either diastereomer to give rise to a bromonium ion and eventual over-all apparent retention of configuration.[6,9] We considered the possibility that the stilbene dichlorides or intermediate acetoxychlorides were isomerizing to largely the same material in the reaction mixture before undergoing transformation. In fact, the stilbene dichlorides are known[5,10] to isomerize to a mixture largely *meso* when held above the melting point for a time. However, we found that *dl*-dichloride was isomerized to only a minor extent by heating in acetic acid in the presence of silver chloride. This caused us to dismiss stereoisomerization of this sort as an important factor.

A possible explanation (which awaits experimental test) of the results is that normal participation of the neighboring chlorine atom occurs only with the *meso*-isomer. The stilbene dihalides are interesting among open-chain 1,2-dihalides with respect to preferred configuration[11] about the central carbon–carbon bond, this being one reason for their inclusion in our experimental program. The *meso*-isomer has the two halogen atoms quite *trans*, the *dl*-isomer more nearly *cis*. Conditions are favorable for participation of the neighboring

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(6) Winstein and Buckles, This Journal, **64**, 2780, 2787 (1942).

(7) Winstein, Hess and Buckles, *ibid.*, **64**, 2796 (1942).

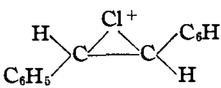
(8) Forst and Zincke, *Ann.*, **182**, 246 (1876).

(9) Winstein and Lucas, *ibid.*, **61**, 1576, 2845 (1939).

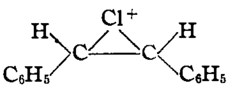
(10) Zincke, *Ber.*, **10**, 999 (1877).

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

chlorine atom in the case of the *meso*-dihalide, for the neighboring chlorine atom is situated quite *trans* and closes a ring X which has the phenyl groups situated *trans*. On the other hand, conditions are less favorable for participation of the neighboring chlorine atom in the case of the *dl*-dichloride to produce the *cis*-chloronium ion XI, which, if formed, may isomerize to X before undergoing further reaction.



X



XI

On the other hand, it is just as possible, from all the indications we have, that the neighboring chlorine atom, with a phenyl group on the carbon atom being substituted, does not participate seriously in the replacement process in the case of either dihalide. On this basis, the *erythro*-acetoxychloride could be the major product from both dihalides.[12]

Reulos[1] obtained retention of configuration in the conversion of both the *erythro*- and *threo*-stilbene chlorohydrins to dichlorides with phosphorus pentachloride. These results alone do not yield information concerning participation of the neighboring chlorine atom since reagents of the type of phosphorus pentachloride (especially thionyl chloride) are apt to react with retention of configuration with alcohols of the α-phenylalkyl type by another mechanism.[13] We postpone any more extended discussion of replacement reactions of compounds related to stilbene until our own work has proceeded further.

Experimental[14]

Stilbene Dichlorides.—The *meso*-dichloride, m. p. 193–194°, and the *dl*-dichloride, m. p. 92–94°, were prepared from stilbene by the method of Kharasch and Brown.[15]

Some *dl*-dichloride was prepared by a method similar to Pfeiffer's.[16] Twenty grams of stilbene was added in portions to a cold 200-ml. portion of anhydrous ether in a 3 liter beaker after the ether was saturated with chlorine gas in the dark. A vigorous reaction ensued on exposure to sunlight. When the reaction seemed complete, the ether was evaporated and 200 ml. of fresh ether was added. Slow evaporation gave several fractions of solid. The end fractions after several crystallizations from ligroin yielded 7.5 g. (27%) of *dl*-stilbene dichloride, m. p. 91–94°.

Melting Point-Composition Data.—For estimating the composition of diacetate mixtures, a melting point–composition diagram, Fig. 1, was constructed for mixtures of the diacetates of hydrobenzoin and isohydrobenzoin. The hydrobenzoin diacetate, m. p. 133–134°, was obtained from *meso*-stilbene dichloride. The isohydrobenzoin diacetate, m. p. 114–116°, was some obtained by acetylation of isohydrobenzoin obtained in this work. We obtained purer materials later in the work, but the melting point data were not redetermined, Fig. 1 serving our purpose satisfactorily. Capillary melting points were taken on mixtures weighed out on an analytical balance and ground on a watch glass. For the glycol mixtures we used the melting point–composition diagram of Böeseken and Elsen.[17]

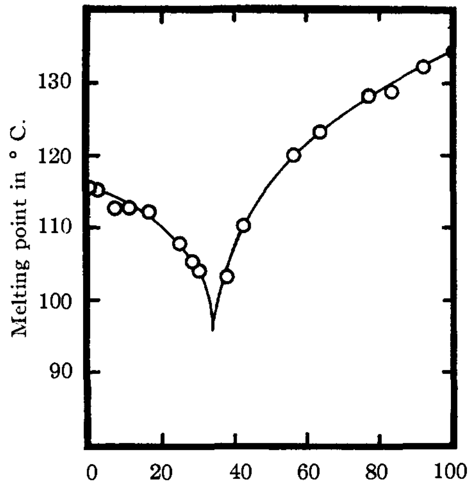


Fig. 1.—Melting point–composition diagram for hydrobenzoin diacetate–isohydrobenzoin diacetate mixtures.

Reaction of Stilbene Dichlorides with Silver Acetate in Acetic Acid.—The stilbene dichlorides were treated with silver acetate as in our previous work[8] with other halides. A 25% excess of silver acetate was used. Twenty ml. of solvent was used for 0.01 mole of dichloride, a reaction time of nine hours with an oil-bath at 100–110° being allowed. The reactions in moist acetic acid were carried out with 1.5 moles of water per mole of dichloride. Yields were approximately 80%.

The reaction mixtures from the runs in dry acetic acid were allowed to cool and were filtered. The silver salts were washed twice with boiling alcohol. From the filtrate and the alcohol solution by crystallization and recrystallization from alcohol were isolated systematically fractions of pure *meso*-diacetate and mixed diacetates. Sublimation at 1–3 mm. (bath at 125–150°) could be carried out quantitatively and was useful for purifying some of the fractions. Small fractions were obtained which contained some high-melting impurity, and these were best handled by a saponification and then a sublimation of the glycol. The small fractions of mixed diacetates or glycols were submitted to a carbon–hydrogen analysis for verification of identity. With the aid of melting points and mixed melting points with pure materials, the compositions were obtained from Fig. 1 and Böeseken and Elsen's diagram.[17] To illustrate, from 0.01 mole of *meso*-stilbene dichloride in dry acetic acid was obtained 2.198 g. of *meso*-diacetate (a little in the form of glycol, m. p. 136–138°) m. p. 135–137° and 0.247 g. of mixed fractions. The estimated weight of *dl*-diacetate was 0.172 g., 7% of the total product.

In working up the runs from 0.01 mole of dichloride in moist acetic acid, the silver salts were filtered off and washed several times with ether. The filtrate and ether washings were neutralized with sodium carbonate solution and the mixture was extracted with ether. The ether extract was dried over potassium carbonate and the ether was removed on a steam-bath. The residue was refluxed two hours with 10 ml. of 10% aqueous sodium hydroxide in 50 ml. of alcohol. Then water was added to cloudiness and crystals appeared on cooling. A systematic procedure as with the diacetates gave pure *dl*-glycol, m. p. 119.8–120.3°, and some impure fractions.

Stability of *dl*-Dichloride.—Freshly precipitated silver chloride (1.14 g.) was washed well with water, then three times with glacial acetic acid. It was then transferred to

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[12] Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, pp. 178–181.

[13] Cowdrey, Hughes, Ingold, Masterman and Scott, *J. Chem. Soc.*, 1252 (1937).

[14] Melting points corrected.

[15] Kharasch and Brown, This Journal, **61**, 3432 (1939).

[16] Pfeiffer, *Ber.*, **45**, 1816 (1912).

[17] Böeseken and Elsen, *Rec. trav. chem.*, **47**, 694 (1928).

a solution of 1.00 g. *dl*-stilbene dichloride in 10 ml. glacial acetic acid in the same apparatus used for the conversions with silver acetate. The mixture was heated with stirring for four and one-half hours with a bath at 100–110°. The mixture was cooled and filtered, the silver chloride being washed with acetic acid. Dilution of the filtrate and washings with water yielded an oily material which soon crystallized. This was washed with water and dried over potassium hydroxide.

The dry product weighed 0.98 g. (98% recovery) and the m. p. was 86.5–91.0°; mixed m. p. with *dl*-dichloride was 89.5–92.5°. A 0.93-g. portion of this material was crystallized from hexane, yielding crops: 0.50 g., 53%, m. p. 92–94°; 0.24 g., 25%, m. p. 91–93°; 0.13 g., 13%, m. p. 89–92°; total recovery, 91%.

Summary

The diastereomeric stilbene dichlorides are transformed by silver acetate in acetic acid to the ester of a glycol predominantly *meso* when a dry solvent is used and predominantly *dl* when the solvent contains more than the stoichiometric amount of water. It seems likely that the stilbene dichlorides are first converted mainly to *erythro*-acetoxychloride. In the course of replacement of the second halogen atom, there is participation by a neighboring acetoxy group.

Los Angeles, California Received September 17, 1945

[Contribution from the Chemical Laboratory of The Ohio State University]

Sugar Interconversion under Reducing Conditions. I[1]

By M. L. Wolfrom, M. Konigsberg,[2] F. B. Moody[2] and R. Max Goepp, Jr.[3]

The reducing sugars undergo very extensive transformations when subjected to the vigorous action of strong alkali.[4] The initial or incipient reaction, demonstrable under conditions of mild alkalinity, was discovered by Lobry de Bruyn and Alberda van Ekenstein[5] and consists in the reciprocal interconversion of epimeric aldoses and their corresponding ketose. The nature of this reaction has been explained[6] by the assumption of an enediol common to the three sugars.

Lewis and co-workers[7] investigated the reciprocal interconversion of 2,3,4,6-tetramethyl-D-glucose and 2,3,4,6-tetramethyl-D-mannose in limewater (0.04 *N*) at 35°. This reaction reached a true equilibrium when the two aldoses were present in approximately equal amount. No ketose was formed since the mobile hydrogen required for ketose formation was herein replaced by a methyl group.

Fredenhagen and Bonhoeffer[8] studied the alkaline interconversion of D-glucose and tetramethyl-D-glucopyranose in a deuterium oxide solvent. The five hydroxyl groups of the former and the one hydroxyl group of the latter exchanged freely with the solvent. If an appreciable amount of enolic intermediate had been formed, a maximum of two atoms of deuterium would have been permanently fixed in the unsubstituted sugar molecule as a carbon to hydrogen bond. Similarly, a maximum of one deuterium atom would have been so bound by the methylated sugar. These predictions were borne out by experiment except that at temperatures below 40° very little bound deuterium was found in the unsubstituted sugar. The authors therefore accepted the enolic mechanism as the only satisfactory explanation of their experiments at temperatures of 40° and above but for temperatures below this, as at 25°, they proposed an entirely different mechanism involving a dimolecular intermediate. This postulated intermediate is untenable in relation to the known structure of the hexose sugars. If the enolic mechanism holds at 40° it is indeed strange that it would not likewise be valid when nothing is altered other than lowering the temperature to 25°.

In the present work we are concerned with interpreting the behavior of mildly alkaline solutions of D-glucose when placed under reducing conditions. To this end we have investigated the composition of a commercial product produced by the electro-reduction of D-glucose under conditions of mild alkalinity (*p*H 7–10) and below 30°.[9] The product was found to consist of sorbitol[10] together with small amounts of D-mannitol (*ca.* 1%) and 2-desoxysorbitol (*syn.* 2-desoxy-D-mannitol) (*ca.* 5%). The D-mannitol could arise from the reduction of D-mannose or D-fructose while the sorbitol could arise from the reduction of D-glucose or D-fructose. It is reasonable to assume that the 2-desoxysorbitol arose from the reduction to hydrocarbon of the carbonyl in the open-chain or *keto*-form of D-fructose. Numerous examples are to be found in the litera-

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(1) Presented before the Division of Sugar Chemistry and Technology at the 107th Meeting of the American Chemical Society, Cleveland, Ohio, April 6, 1944.

(2) Atlas Powder Company Research Associate of The Ohio State University Research Foundation, 1939–1940 (M. K.), 1940–1941 (F. B. M.)

(3) Research Department, Atlas Powder Company, Wilmington, Delaware.

(4) W. L. Evans, *Chem. Revs.*, **31**, 537 (1942).

(5) C. A. Lobry de Bruyn and W. Alberda van Ekenstein, *Rec. trav. chim.*, **14**, 203 (1895).

(6) A. Wohl and C. Neuberg, *Ber.*, **33**, 3099 (1900); J. U. Nef, *Ann.*, **357**, 295 (1907).

(7) M. L. Wolfrom with W. L. Lewis, This Journal, **50**, 837 (1928); R. D. Greene with W. L. Lewis, *ibid.*, 2813.

(8) H. Fredenhagen and K. F. Bonhoeffer, *Z. physik. Chem.*, **A181**, 392 (1938).

(9) H. J. Creighton, *Trans. Electrochem. Soc.*, **75**, 289 (1939); H. J. Creighton, U. S. Patents 1,612,361 (1926); 1,653,004 (1927); 1,712,951 (1929); 1,712,952 (1929); 1,990,582 (1935).

(10) We denote as sorbitol the common form of this hexitol as obtained by the reduction of D-glucose. Carbon one of this sorbitol corresponds to its precursor in D-glucose.