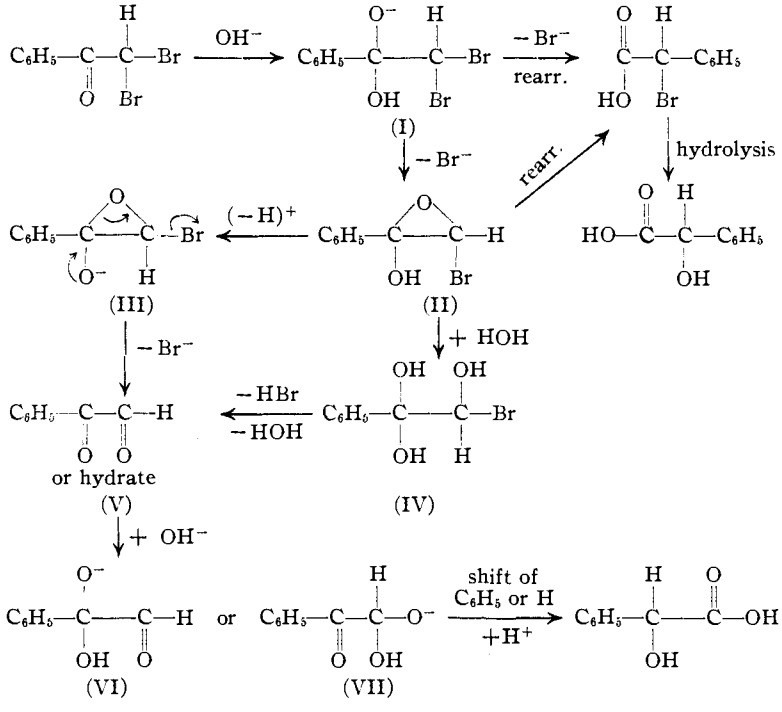
[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, DUKE UNIVERSITY]

The Course of Reaction in the Transformation of α,α-Dibromoacetophenone to Mandelic Acid by Means of Aqueous Alkali[1]

BY ERLE B. AYRES AND CHARLES R. HAUSER

The interesting transformation of α,α-dibromoacetophenone (or α,α-dichloroacetophenone) to mandelic acid in the presence of alkali was assumed by early workers[2] to involve first the direct replacement of the two bromine atoms by hydroxyl groups to form phenylglyoxal or its hydrate, which was then rearranged by the alkali to yield the mandelic acid. It has been shown that phenylglyoxal is rearranged by alkali to yield mandelic acid,[3] but an attempt by Houben and Fischer[4] to isolate phenylglyoxal from the reaction mixture of α,α-dichloroacetophenone and alkali was unsuccessful, although they did obtain a residue which reduced ammoniacal silver nitrate. Recently, Fisher and Walling[5] showed that when α,α-dibromoacetomesitylene, in which the carbonyl group is hindered, is treated with alkali the transformation to the substituted mandelic acid does not take place and the dibromide may be recovered unchanged from the alkaline reaction mixture. From this result it seems clear that alkali does not directly replace the two bromine atoms by hydroxyl groups as the early workers assumed but, instead, the base first attacks the carbonyl group to form presumably anion (I).

In the present investigation the course of reaction from anion (I) to mandelic acid has been considered. It seemed possible that anion (I) might undergo rearrangement to form α-bromophenylacetic acid, or that anion (I) may first form the ethylene oxide (II) which might then undergo rearrangement to the bromoacid; this acid would undoubtedly be readily hydrolyzed by the alkali to form mandelic acid. An anion analogous to (I) has been shown[6] to be the intermediate in the benzilic acid rearrangement, while ethylene oxides analogous to (II) have been indicated to be the intermediates in the Aston and Greenburg rearrangement[7] of certain bromoketones to the esters of tertiary aliphatic acids in the presence of sodium alkoxides. It seemed equally possible, however, that the ethylene oxide (II), which should be formed easily from (I), might be converted into phenylglyoxal (V), which would be rearranged by the alkali to mandelic acid. The conversion of the ethylene oxide (II) to phenylglyoxal (V) might follow two courses; either a proton may be removed by the base from (II) to form (III) which would release bromide ion to give (V), or water may be added to (II) to form (IV) which would eliminate hydrogen bromide and water to give (V). The former course is probably the more likely. The rearrangement of phenylglyoxal to mandelic



(1) Original manuscript received June 15, 1942.
(2) Engler and Wöhrle, *Ber.*, **20**, 2201 (1887).
(3) von Pechmann, *ibid.*, **20**, 2904 (1887).
(4) Houben and Fischer, *ibid.*, **64**, 2636 (1931).
(5) Fisher and Walling, THIS JOURNAL, **57**, 1562 (1935).
(6) Westheimer, *ibid.*, **58**, 2209 (1936); Roberts and Urey, *ibid.*, **60**, 880 (1938).
(7) Aston and Greenburg, *ibid.*, **62**, 2590 (1940).

acid may involve the intermediate formation of anion (VI) or (VII) involving the reaction of the ketone or aldehyde carbonyl group, respectively. In view of the work of Gray and Fuson[8] on mesitylglyoxal, anion (VII) would seem the more likely intermediate. These possible courses of reaction are shown in the accompanying flow sheet.

Unsuccessful attempts were made to isolate the possible intermediate, α-bromophenylacetic acid, its ammonia derivative (α-aminophenylacetic acid) or its methanol derivative (α-methoxyphenylacetic acid). On the other hand, we have isolated phenylglyoxal hydrate (V) in 15% yield from the reaction mixture. This was effected by allowing the alkali to flow over the dibromide directly into dilute acetic acid. The immediate neutralization of the alkali arrested the rearrangement of the phenylglyoxal and made possible its accumulation and isolation.

These results appear to warrant the conclusion that at least much of the mandelic acid formed on treatment of α,α-dibromoacetophenone with alkali results through the intermediate formation of phenylglyoxal.[9] The probable course of reaction can be followed in the flow sheet. Since phenylglyoxal rearranges rapidly to mandelic acid in the presence of alkali,[4] it seems probable that much more than the 15% yield isolated was produced in the reaction mixture. It should be pointed out that failure to isolate α-bromophenylacetic acid does not conclusively show that none of the mandelic acid resulted through the rearrangement of anion (I) or ethylene oxide (II), since the α-bromo acid would be hydrolyzed readily[10] and might have escaped detection.

Experimental

A 500-ml. filter flask was equipped with a dropping funnel and a Gooch adapter carrying a sintered glass filter crucible of 30 ml. capacity. A small propeller-type glass stirrer driven by air and a small thermometer were adjusted so that the lower end of the stirrer and the bulb of the thermometer almost touched the bottom of the crucible. A buret was arranged so that it would deliver 5% sodium hydroxide solution into the crucible. Approximately one-third of the total amount (11.7 g.) of α,α-dibromoacetophenone[11] used was placed in the crucible with some pieces of cracked ice and a little water. The mixture was stirred and the alkali was added gradually from the buret. The mixture in the crucible was kept at 15 ± 3° by the addition of ice chips, and the solution was drawn into the filter flask by gentle suction at the rate of about 3 ml. per minute. The solution in the flask was kept acidic to phenolphthalein by the addition of 10% acetic acid from the dropping funnel. The rest of the α,α-dibromoacetophenone was added in two portions at fifteen-minute intervals, and the treatment with sodium hydroxide solution was continued for one hour longer. About 1 g. of material remained undissolved in the crucible. The contents of the filter flask were carefully neutralized with 5% sodium hydroxide solution, placed in an ice-bath for one hour, and filtered to remove a slight yellow turbidity. The clear filtrate, approximately 750 ml., was extracted with ether seven times (a total volume of 400 ml. of ether), and the wet ether layer was evaporated under reduced pressure at room temperature. The resulting white crystals, edged with yellow where the last of the ether had evaporated, were dried on a porous plate; yield, 0.8 g., m. p. 67–71°. After recrystallization from warm water, the material melted at 78–80°, and when mixed with an authentic sample of phenylglyoxal hydrate[12] (m. p. 78–80°) the melting point was the same. Both samples of phenylglyoxal had a characteristic odor and caused smarting of the eyes. Addition of aqueous ammonia to water solutions of each gave white precipitates which became curdy upon acidification with hydrochloric acid.[3] A sample (0.2 g.) of each was dissolved in 30 ml. of water, and treated with an excess of phenylhydrazine dissolved in acetic acid. Immediate yellow precipitates formed which became orange-yellow upon warming on the steam-bath for an hour. After two recrystallizations from alcohol, each of the samples of derivative[13] melted at 148–149.5°; a mixed melting point was the same.

An attempt was made to isolate phenylglyoxal in a similar manner from a mixture of alkali and α,α-dichloroacetophenone but this chloro compound melts too low to be handled satisfactorily. Even at 5–10°, the crystals of α,α-dichloroacetophenone softened and were carried through the filter as a fine suspension or emulsion.

Summary

Evidence has been presented that the transformation of α,α-dibromoacetophenone to mandelic acid by means of aqueous alkali occurs with the intermediate formation of phenylglyoxal. Phenylglyoxal has been isolated from the reaction mixture, and the probable courses of reaction have been considered.

DURHAM, NORTH CAROLINA RECEIVED MARCH 8, 1943

(8) Gray and Fuson, THIS JOURNAL, **56**, 739 (1934).

(9) It seems unlikely that the phenylglyoxal obtained in the present investigation resulted from the ethylene oxide (II) being carried into the acetic acid medium and there converted to phenylglyoxal.

(10) Ward, *J. Chem. Soc.*, 1184 (1926).

(11) Evans and Brooks, THIS JOURNAL, **30**, 406 (1908).

(12) Henze, *Z. physiol. Chem.*, **198**, 82 (1931).

(13) Cusmano, *Gazz. chim. ital.*, **68**, 131 (1938), or *C. A.*, **32**, 6234 (1938).