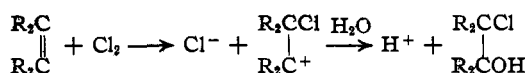


[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

## The Mechanism of Addition Reactions. Chloro- and Bromo-Beta-Lactones from Dimethylmaleic and Dimethylfumaric Acids

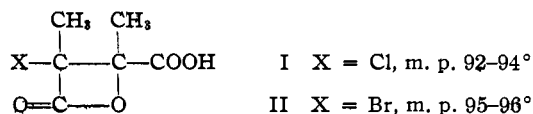
BY D. STANLEY TARBELL AND PAUL D. BARTLETT

Recent kinetic evidence on the bromination of stilbene in methyl alcoholic solution<sup>1</sup> has by analogy strengthened the view that the following steps are involved in the formation of chlorohydrins in aqueous solution

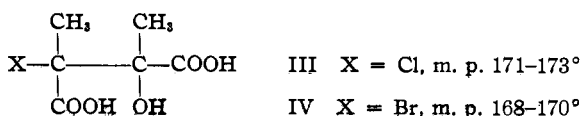


where the first and second steps may or may not occur synchronously. We have investigated the aqueous chlorination and bromination of dimethylmaleic and dimethylfumaric acids in the search for more detailed information about this process.

When the sodium salt of dimethylmaleic acid is treated with chlorine water or bromine water, there can be isolated in poor yield from the resulting oil a halogenated beta-lactone (I or II),



whose structure is established by analysis, neutralization equivalent and molecular weight determinations. Several hours of standing in 5% sulfuric acid at room temperature opens the lactone ring irreversibly to the halohydrin acid (III or IV). This accounts for the small amounts of



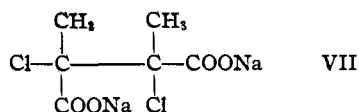
halohydrin acid which appear occasionally along with the lactones when these have been allowed to stand in solution before isolation.

The reaction of sodium dimethylfumarate with chlorine water or bromine water takes an exactly similar course, leading to a pair of beta-lactones (V, m. p. 141-142°, and VI, m. p. 148-150°) which are stereoisomeric with I and II. Acid hydrolysis opens these lactones to the same chlorohydrin and bromohydrin, respectively, (III and IV) as are obtained from the lactones of the maleic series. Since these halohydrin acids melt with decomposition, a check on the stereochemical purity and identity of the chlorohydrins was ob-

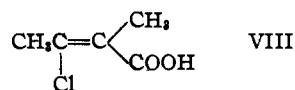
(1) Bartlett and Tarbell, *THIS JOURNAL*, **58**, 466 (1936).

tained by measuring the rate of their reaction with aqueous sodium hydroxide, a type of process whose rate in the unmethylated series<sup>2</sup> is very dependent upon configuration. Both I and V yielded samples of III which reacted as a single substance with sodium hydroxide, and both at the same rate, within the experimental accuracy. This test was not applied to the bromohydrin acids.

The beta-lactones cannot be made from the halohydrins; therefore if any *one-step addition* (of chlorine or hypochlorous acid) preceded the formation of the chlorolactone in solution, it must have been the addition of chlorine to give a symmetrical sodium dichlorodimethylsuccinate (VII) which might then eliminate sodium chloride to form the lactone. Only one of the two possible



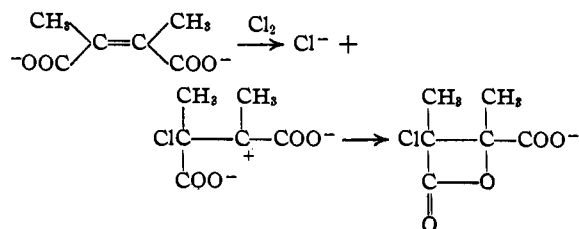
acids of this structure is known,<sup>3</sup> but since both lactones have been prepared, the known acid should give one of them if a dichloro acid is intermediate at all in this process. It was found, as expected from previous work,<sup>4</sup> that when this acid was neutralized with sodium bicarbonate and allowed to stand at room temperature for two days, there was produced chlorotiglic acid (VIII),



m. p. 66-68°, some of the starting material still remaining unchanged, and no beta-lactone appearing. A quantitative run on the elimination of sodium chloride from VII showed that this reaction requires about twenty-four hours at 25°, while both lactones have been isolated in less than half an hour from the reaction mixture. Therefore the dichloro acid is not intermediate in the formation of the lactone, which is instead the product of a two-step addition process.

(2) Kuhn and Ebel, *Ber.*, **58**, 919 (1925).(3) Michael, *J. prakt. Chem.*, [2] **46**, 382 (1892).(4) Otto and Beckurts, *Ber.*, **18**, 847 (1885); Otto and Holst, *J. prakt. Chem.*, **149**, 467 (1890).

The most likely such process, in view of the evidence in the case of analogous reactions, is

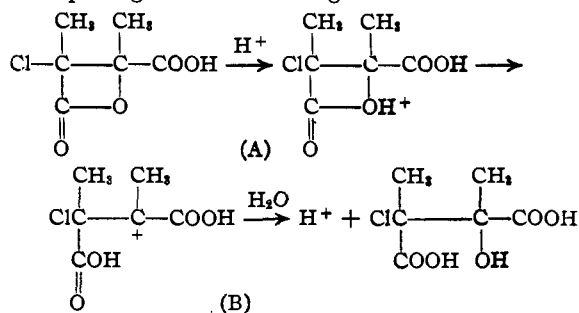


These steps may be pictured as occurring in succession, or synchronously. Against the idea of successive reaction steps stands the unlikelihood that the intermediate zwitterion could long survive without a stereochemical equilibration which would lead to identical products from both dimethylmaleic and dimethylfumaric acids. On the other hand, the idea of a simultaneous attack of halogen and carboxylate oxygen upon the ends of the double bond places us immediately in stereochemical difficulties; for a model of the molecule in question shows that either a methyl or a carboxylate group directly confronts the attacking oxygen in the fumarate or maleate ion, and very large torsion of the rigid double bond structure would be necessary if this attack occurred *before* the complete opening of the double bond by the halogen. These difficulties are best avoided by the hypothesis that the reaction steps occur in the quickest possible succession.

Two other well-known puzzling facts of organic chemistry are reëmphasized in this series. One is the total inertness of the completely substituted ethylene, dimethylmaleic anhydride, toward bromine, described below. The other is the great effect of methyl substitution in favoring ring-closure. Free dimethylmaleic acid is completely unknown, the spontaneous formation of its anhydride being very rapid under all experimental conditions; the appearance of beta-lactones on halogenation of its salts is another manifestation of the enhancement of ring closure by methyl groups. Probably a satisfactory explanation of these effects of methyl substitution, and of the course of the halogenlactone formation, can be found only at the same source.

The formation of a common chlorohydrin acid from the two isomeric chlorolactones makes it clear that the ring-opening of these lactones by 5% sulfuric acid is not an ordinary ester hydrolysis, a process which occurs without stereochemical inversion at the alcoholic hydroxyl group. Mod-

els show so little difference in the apparent availability of the lactonic carbonyl groups of the two isomers to attack, that we propose that *neither* ring-opening is a normal ester hydrolysis, but that the opening occurs according to the mechanism



Here the exchange reaction between the positive ion (B) and water is assumed to be slow enough to permit the positive ion (B) to take up its preferred configuration before reaction. Thus in the lactone *formation* the presence of an active negative ion near the positive carbonium center makes reaction faster than steric equilibration; under the acid conditions of hydrolysis the intermediate must react with a neutral molecule (water), and the reverse is true.

The hydrolysis of the lactones under alkaline conditions would have been interesting from this point of view, but it was attended by replacement of the halogen and led to no isolable compounds. From treatment of the chlorohydrin with barium hydroxide at 0° a small amount of material was obtained, m. p. 158–160° with decomposition, which gave analytical figures for the oxidic acid, 2,3-epoxybutane-2,3-dicarboxylic acid. That no hydroxylactone was formed in this reaction was shown by a rate run in which the amount of chloride ion produced was always equal to that of hydroxyl ion consumed. When the sodium salt of the chlorolactone (I) was heated in aqueous solution on the steam-bath, chlorotiglic acid was produced; similar treatment of the isomeric chlorolactone salt yielded a solid mixture melting at 180–240°, which was not studied further.

In agreement with Michael,<sup>3</sup> we were unable to obtain a bromine addition product from dimethylmaleic anhydride in carbon tetrachloride solution. Illumination with a 400-watt projection lamp discharged the bromine color in a few minutes, but hydrogen bromide was evolved copiously, and the starting material was the only solid obtainable from the solution. Only the bromohydrin acid resulted from treatment of the bromolactone II

with 40% hydrobromic acid. Equivalent quantities of dimethylmaleic anhydride and bromine stood for three weeks in glacial acetic acid 1 *N* in hydrogen bromide (catalytic conditions, in the experience of Williams and James<sup>5</sup>) without visible reaction.

### Experimental

**Preparation of Dimethylmaleic Anhydride.**—Acetoacetic ester was methylated with methyl bromide, the bisulfite derivative of the methylated ester treated with sodium cyanide, the nitrile hydrolyzed and the resulting dimethylmaleic acid dehydrated, according to the procedure of Ott,<sup>6</sup> with an over-all yield of 19.5%.

**Bromination of Dimethylmaleic Acid.**—Twenty-five grams of dimethylmaleic anhydride was neutralized with 16 g. of sodium hydroxide in 200 cc. of water, and added to a solution of 32 g. of bromine in 2 liters of water. Reaction was complete in a few minutes. The solution was extracted three times with ether, then acidified with 0.2 equivalent of sulfuric acid and extracted three times more. The ether was evaporated, yielding 38.3 g. of mixed oil and crystals. After four crystallizations from benzene-petroleum ether, there resulted 5.3 g. (11%) of bromohydrin acid, m. p. 155–160°, and 14.8 g. of pure lactone (33%), m. p. 95–96°, crystallizing in clumps of thick needles. The presence of ether interferes with crystallization of the lactone. It is very soluble in the common solvents, except petroleum ether.

*Anal.*<sup>7</sup> Calcd. for C<sub>8</sub>H<sub>7</sub>O<sub>4</sub>Br: C, 32.3; H, 3.2; Br, 35.83. Found: C, 32.3; H, 3.4; Br, 36.37, 35.10. Molecular weight calculated, 223; found in benzene, 422; in acetic acid, 197, 192. Equivalent weight by titration with alkali in the cold, 205; in hot water, 85.4, indicating that the ring has been opened and the bromine removed.

In the presence of much bromide ion no dibromo acid was isolated, but only the lactone. Five grams of anhydride, 3.2 g. of sodium hydroxide, and 6.4 g. of bromine reacted in 25 cc. of water containing 10 g. of sodium bromide; 2.7 g. (30%) of lactone, m. p. 80–90°, was obtained, and the only other product in evidence was a soluble lachrymator.

**Action of Acids on the Bromolactone.**—One gram of bromolactone was dissolved in 50 cc. of 10% sulfuric acid and let stand overnight at room temperature; a white solid, melting with decomposition at 168–170°, was obtained, which was recrystallized from chloroform. It is soluble in water, ether, acetone, ethyl acetate, slightly soluble in chloroform, and almost insoluble in benzene. It is best recrystallized from ethyl acetate–chloroform, or ethyl acetate–benzene.

*Anal.* Calcd. for C<sub>8</sub>H<sub>9</sub>O<sub>5</sub>Br: C, 29.9; H, 4.1. Found: C, 29.8, 29.9; H, 4.2, 4.1.

To find out whether the bromohydrin acid isolated in the bromination of dimethylmaleic acid was formed from the lactone, a rough rate run was carried out by dissolving 1.0 g. of lactone in 50 cc. of 5% sulfuric acid, and determining the melting points of samples extracted at intervals.

(5) Williams and James, *J. Chem. Soc.*, 343 (1928).

(6) Ott, *Ber.*, 61, 2131 (1928).

(7) These three analyses were carried out by Mrs. G. M. Wellwood.

Time	M. p., °C.
15 min.	60–80
71 min.	80–100
220 min.	130–145
20 hrs.	166–169

It appears that the reaction is fairly complete at four hours, and hence the bromohydrin and chlorohydrin acids are considered secondary products.

**Chlorination of Dimethylmaleic Acid.**—Five grams of the anhydride was neutralized with 3.2 g. of sodium hydroxide in 100 cc. of water, and chlorine passed in until the presence of an excess was shown by a test with potassium iodide paper. Isolation and fractional crystallization of the product in the same manner as for the bromolactone gave 0.55 g. of chlorohydrin acid (7%), m. p. 150–168°, and 2.9 g. (41%) of chlorolactone, m. p. 80–90°. The best sample of this lactone obtained melted at 92–94°. The chlorolactone has the same solubility properties and general crystalline form as the bromolactone.

*Anal.* Calcd. for C<sub>8</sub>H<sub>7</sub>O<sub>4</sub>Cl: C, 40.3; H, 4.0; mol. wt., 178.5. Found: C, 39.9, 40.0, 40.0; H, 4.7, 4.5, 4.8; mol. wt. in glacial acetic acid, 158.

**Hydrolysis of the Chlorolactone I.**—One gram of the chlorolactone was dissolved in 50 cc. of 10% sulfuric acid and let stand overnight at room temperature. Extraction and crystallization of the product from ethyl acetate–benzene gave a substance which decomposed at 173–174° when heated from 150° at 5° per minute. The solubility properties are similar to those of the bromohydrin.

*Anal.* Calcd. for C<sub>8</sub>H<sub>9</sub>O<sub>5</sub>Cl: C, 36.6; H, 4.6. Found: C, 36.6; H, 4.9.

The chlorohydrin acid was also prepared in 62% yield from dimethylmaleic anhydride by conducting the hydrolysis without isolation of the chlorolactone.

**Formation of the Oxidic Acid.**—Two grams of the chlorohydrin acid was dissolved in 50 cc. of water, treated with 4.7 g. of barium hydroxide, and kept overnight at 0°. The solution was neutral in the morning. It was evaporated under diminished pressure over a period of several days and 1.4 g. of barium salt filtered off. This was suspended in water and acidified with 10 cc. of 1 *N* hydrochloric acid. From the ether extract a small amount of white compound crystallized, which gave no Beilstein test. Recrystallized from ethyl acetate–benzene, it melted at 158–160° with decomposition.

*Anal.* Calcd. for C<sub>8</sub>H<sub>8</sub>O<sub>5</sub>: C, 45.0; H, 5.0. Found: C, 44.7; H, 5.3.

**Reaction Rate of Chlorohydrin Acid with Sodium Hydroxide.**—1.010 g. of chlorohydrin acid was dissolved in water and made up to 100 cc. Fifty cubic centimeters of this solution, cooled to 0°, was added to a solution of 300 cc. of water and 85.94 cc. of 0.0973 *N* sodium hydroxide at the same temperature. This was 25% excess alkali over that required to produce the sodium salt of the oxidic acid. Parallel 25-cc. samples were pipetted out at intervals and titrated for hydroxyl ion and chloride ion, respectively. The Cl<sup>-</sup> ion produced was equal, within a few per cent., to the OH<sup>-</sup> ion consumed, throughout the reaction. The relationship between time and log (OH<sup>-</sup>)/(chlorohydrin) is linear, and from it we obtain the rate constant for the bi-

molecular reaction 0.163 (time in minutes, concentration in moles per liter).

Time	OH <sup>-</sup> consumed	Cl <sup>-</sup> produced
250	0.00126	0.00134
885	.00299	.00310
1095	.00331	.00347
1480	.00392	.00398
2365	.00457	.00468
2725	.00466	.00489

**Preparation of Dimethylfumaric Acid.**—This was accomplished by the method of Ott<sup>8</sup> a high pressure hydrogenation bomb served as the reaction vessel. Sodium dimethylmaleate is heated in aqueous solution for two days at 185–190°. Acidification and extraction yields a mixture of dimethylmaleic anhydride, dimethylfumaric acid and methylitaconic acid, which can be separated by crystallization from chloroform, in which only the dimethylfumaric acid is insoluble. This is recrystallized from water, and melts at 245°. It was obtained in 37% yield, 7.5% of methylitaconic acid being obtained and 41% of dimethylmaleic anhydride recovered from the same run.

The bromination and chlorination of dimethylfumaric acid were carried out in the same manner as for dimethylmaleic acid, but speed in isolation was especially necessary in order to forestall hydrolysis of the halogen lactones to halohydrin acids. These halogen lactones are higher melting than their isomers and are advantageously crystallized from chloroform.

The bromolactone from dimethylfumaric acid was obtained melting at 148–150°, crystallizing in white rods from chloroform. When titrated in the cold with sodium hydroxide to phenolphthalein, it showed an equivalent weight of 185, compared to 223 calculated. The end-point drifted rather rapidly.

*Anal.* Calcd. for C<sub>8</sub>H<sub>7</sub>O<sub>4</sub>Br: C, 32.3; H, 3.2. Found: C, 32.0; H, 3.4.

**The Chlorolactone from Dimethylfumaric Acid.**—Twelve grams of dimethylfumaric acid yielded, after two fractional crystallizations of the product, 0.4 g. of starting material, 3.0 g. of chlorohydrin acid, m. p. 155–160° (18.3%), 4.1 g. of lactone, m. p. 138–140° (27.5%), and 1.6 g. of lower-melting fractions. The best sample obtained melted at 141–142° without decomposition. It is soluble in water and the common organic solvents, and crystallizes from benzene in typical rosetts of needles.

*Anal.* Calcd. for C<sub>8</sub>H<sub>7</sub>O<sub>4</sub>Cl: C, 40.3; H, 4.0; mol. wt., 179. Found: C, 40.0, 40.2; H, 4.3, 4.4; mol. wt. by titration in the cold, 160; in hot water, 65.5.

The identity of the chlorohydrin acid obtained from dimethylfumaric acid with that obtained from dimethylmaleic

acid could not be established by mixed melting points, since this compound melts with decomposition. Therefore a pure sample obtained from dimethylfumaric acid was characterized by the rate of its reaction with sodium hydroxide at 0°, in the same manner as described for the sample from dimethylmaleic acid. The bimolecular rate constant obtained in the present instance was 0.152 compared with 0.163 in the other case. This difference is within the experimental error.

**Experiments with *sym*-Dimethyldichlorosuccinic Acid.**—The acid was prepared by the method of Michael<sup>9</sup> and after recrystallization from benzene–ether melted at 182–184° with decomposition. One gram was neutralized with sodium carbonate in 50 cc. of water and let stand for two days at room temperature. Acidification and extraction, followed by fractional crystallization from benzene, yielded starting material and chlorotiglic acid, m. p. 66–68°.

The rate of elimination of sodium chloride from sodium dimethyldichlorosuccinate was determined by making 100 cc. of an aqueous stock solution containing 0.4805 g. of the free acid. Fifty cubic centimeters of this solution was neutralized by 22.66 cc. of 0.0973 *N* alkali and kept at 25° in a thermostat. Ten cubic centimeter samples were titrated for chloride ion at intervals with silver nitrate.

Time, min.	30	105	1065	2505
Titer	0.48	0.88	4.96	7.91
% reaction	6	12	66	105

Both chlorolactones have been isolated in less than thirty minutes, so the salt of the dichloro acid does not decompose fast enough to account for the formation of either lactone.

### Summary

1. The chlorination or bromination of sodium dimethylmaleate and dimethylfumarate in aqueous solution yields stereoisomeric chloro- or bromo-beta-lactones as the primary products of reaction.

2. The isomeric chlorolactones are readily hydrolyzed irreversibly to a single chlorohydrin acid, and the isomeric bromolactones to a single bromohydrin acid.

3. It is shown that these facts are inconsistent with a mechanism of addition of halogen in a single step, and the probable mechanisms of these reactions are briefly discussed.

4. Conclusions previously reached on the basis of kinetic results are now confirmed by preparative evidence.

CAMBRIDGE, MASS.

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(8) Ott, *Ber.*, **61**, 2131 (1928). Cf. also Fittig, *Ann.*, **304**, 158 (1899), and Lutz and Taylor, *This Journal*, **55**, 1589 (1933).