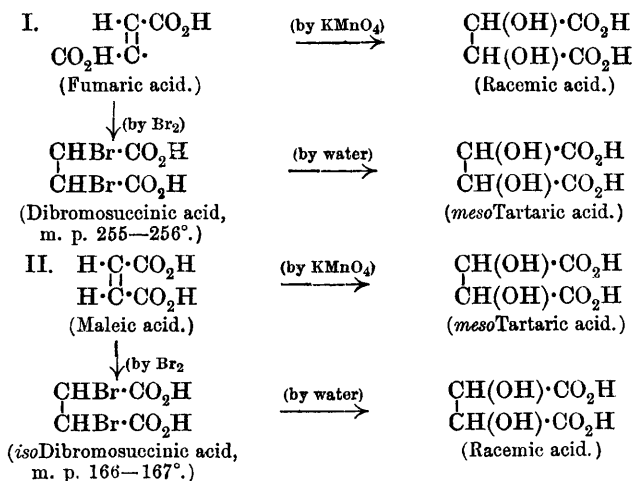


CXXVIII.—*Configuration of the Stereoisomeric Dibromosuccinic Acids.*

By ALEX. MCKENZIE.

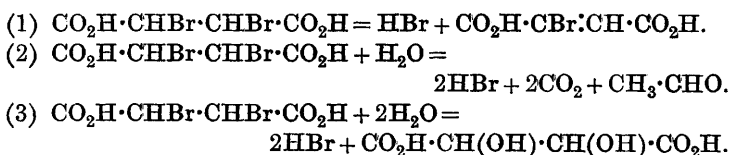
THE attention of the author was directed to the question of the configuration of the stereoisomeric dibromosuccinic acids in consequence of the following remarkable changes which are recorded in the literature:



Fumaric acid behaves on oxidation in accordance with the conception of *cis*-addition so ably advocated by J. Wislicenus, the double linking being severed, and the hydroxy-groups taking up a position on the same side of the new molecule. Both Pasteur and Jungfleisch had, however, shown that a mixture of racemic and *meso*tartaric acids could be obtained when the silver salt of dibromosuccinic acid was acted on by water. Again, Kekulé boiled dibromosuccinic acid with water, and isolated calcium *meso*tartrate

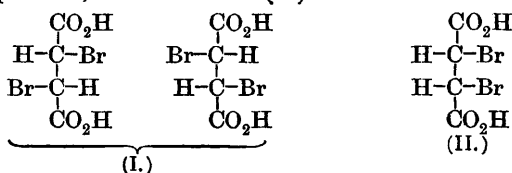
from the product of the reaction, a result which was also arrived at by Anschütz. On the other hand, whilst maleic acid underwent oxidation in accordance with the views of Wislicenus, racemic acid was obtained by Demuth and Victor Meyer from *isodibromosuccinic* acid, and Kekulé remarked that the behaviour of the silver salt of this bromo-acid towards water was similar to that of the silver salt of the isomeric acid, inasmuch as a mixture of racemate and *mesotartrate* was formed. The conversions of dibromosuccinic acid into *mesotartaric* acid and of *isodibromosuccinic* acid into racemic acid were inexplicable on the current views of addition to unsaturated compounds. As a consequence of the investigations, more particularly of Lossen and of Michael, these views have not stood the test of experiment; on the contrary, as pointed out by Frankland in his Presidential Address (this vol., p. 654), *trans*-addition to acetylenic or ethylenic compounds is the rule rather than the exception.

The action of water and of bases on the dibromo-acids under consideration was studied in detail by Lossen. When salts of the *iso*-acid were acted on by two equivalent amounts of base in aqueous solution, acetylenedicarboxylic acid was formed, both at the ordinary temperature and on boiling. The following three reactions took place when aqueous solutions of the acids were heated with water:



A mixture of dihydroxy-acids was formed in each case, and consisted of about 75 per cent. of *mesotartaric* acid, when dibromosuccinic acid was decomposed, and of about 81 per cent. of racemic acid from *isodibromosuccinic* acid.

In spite of the large amount of research devoted to the dibromosuccinic acids,\* the question of their configuration had not been settled. Obviously one of them (I) must be resolvable into optically active components, and the other (II) must be of the *meso*-type:



\* For references to the literature, Meyer and Jacobson, *Lehrbuch der organischen Chemie*, 1910, Erster Band, Zweiter Teil, 524, may be consulted.

In the present paper it is shown that dibromosuccinic acid may now be designated as *mesodibromosuccinic acid* and *isodibromosuccinic acid* as *r-dibromosuccinic acid*. The alkaloid employed for effecting the resolution of the latter acid was morphine, but special precautions had to be taken owing to the ease with which bromine was eliminated. *l*-Dibromosuccinic acid melts at 157–158°, and has  $[\alpha]_D^{25} - 148^\circ$  in ethyl acetate solution.

The conclusion that *isodibromosuccinic acid* is resolvable into optically active components was arrived at independently by Holmberg (*Svensk Kem. Tidskr.*, No. 5, 1911), who was not aware of the author's preliminary note on this subject (*Proc.*, 1911, **27**, 150). Holmberg's publication, which is also of a preliminary nature, appeared several months later than the author's, and describes the partial resolution of the acid by means of cinchonine, the difficulties encountered being similar to those of the author. The most active product obtained by Holmberg had  $[\alpha]_D - 137.6^\circ$  in ethyl acetate solution, but he does not claim to have obtained the optically pure acid.

The transformations referred to at the beginning of this paper bear a close analogy to those involving a Walden inversion. In the displacement of halogen by the hydroxy-groups, it was conceivable that one had to deal with a change of configuration, or, in other words, with a process which was closely analogous to a Walden inversion.\* The other alternative was that the direct hydroxylation of fumaric and maleic acids with permanganate followed a stereochemical course of a different order from that followed by the direct addition of bromine. The experiments of the author are in favour of the latter view. Further, since the oxidation of fumaric and maleic acids by permanganate does not apparently lead to the formation of a mixture of racemic and *mesotartaric acids*, it appears likely that the configurational change takes place during the addition of bromine. The problem encountered here is similar to that in a Walden inversion, for the proof of the occurrence of which phenomenon two different substitution processes are necessary, and it is difficult to say at which one of these the configuration is altered.

It was not found possible to prove that *l*-tartaric acid can be obtained from *l*-dibromosuccinic acid or its salts by the action of

\* I am in favour of restricting the term "Walden inversion" to changes undergone by optically active substances only. E. Fischer (*Annalen*, 1911, **386**, 374) attributes to me the extension of the term to configurational changes with optically inactive compounds, a view with which he does not agree. Perhaps the statement "a process which was equivalent to a Walden inversion with optically inactive material" in the preliminary note (*loc. cit.*) is liable to misconception.

A. McK.

water, since, in addition to the formation of bromofumaric acid, profound racemisation took place. This is another example of the case where the halogen in direct attachment to an asymmetric carbon atom in an optically active acid is very readily removed by the action of water, the resulting hydroxy-acid being highly racemised [compare the action of water on *l*-phenylchloroacetic acid (McKenzie and Clough, *Trans.*, 1908, **93**, 811; 1909, **95**, 777) and on *l*- $\alpha$ -chloro- $\alpha$ -phenylpropionic acid (*Trans.*, 1910, **97**, 1016)].

### EXPERIMENTAL.

#### *Bromination of Maleic Acid.*

A mixture of dibromosuccinic acid (m. p. 255—256°) and *isodibromosuccinic acid* (m. p. 166—167°) was obtained by Kekulé (*Annalen*, 1861, **117**, 123; *Annalen, Suppl.*, 1861, **1**, 131, 352, and 1862, **2**, 88) by the bromination of maleic acid in the presence of water, and the separation of these acids was effected by taking advantage of the readiness with which the *iso*-acid dissolves in water. Kekulé held the view that the *iso*-acid is derived from maleic acid, and that the concomitant formation of the isomeride is to be ascribed to secondary actions, namely, the transformation of maleic acid into fumaric acid by means of the hydrogen bromide evolved, and the subsequent bromination of the fumaric acid produced in this manner.

The experimental results of Kekule were confirmed by Fittig and Petri (*Annalen*, 1879, **195**, 57), who further obtained no evidence for the formation of the *iso*-acid when fumaric acid was brominated. In the light of the observation of Fittig and Dorn (*Annalen*, 1877, **188**, 91) that maleic acid was readily converted into fumaric acid by fuming hydrogen bromide at the ordinary temperature, it accordingly appeared that maleic acid could be transformed into fumaric acid, both by bromine and by hydrogen bromide. Fittig and Petri did not, however, stop the bromination of maleic acid at the stage at which fumaric acid separated, but they prolonged the addition of bromine, since *isodibromosuccinic acid* is separated more easily from its mixture with dibromosuccinic acid than from its mixture with fumaric acid.

The formation of fumaric acid by the bromination of maleic acid in the presence of water was also noted by Wislicenus (*Annalen*, 1888, **246**, 64), who recovered, as fumaric acid, no less than 27 per cent. of the original quantity of maleic acid.

The most practical method for preparing *isodibromosuccinic acid* hitherto recorded is that of Michael (*J. pr. Chem.*, 1895, [ii], **52**, 293), who brominated a chloroform solution of maleic anhydride

in the presence of sunlight, and decomposed the resulting *isodi*-bromosuccinic anhydride with water.

The acid employed in the present research was prepared in the following manner: Bromine (19 c.c.) was gradually added within an interval of five minutes to 400 c.c. of ethyl ether (Kahlbaum's, dried over sodium). A slight elevation of temperature occurred. After ten minutes the clear liquid began to become turbid, and at this stage the addition of maleic acid (40 grams) was started, about 2 grams being added each time with constant shaking. The temperature of the ether was not allowed to rise above 25°. Towards the end of the action there was, as a rule, a very slight evolution of hydrogen bromide, but only the merest trace of fumaric acid was deposited. It is important that the preparation is conducted in dull daylight, and not in sunlight or in light rich in ultra-violet rays. The addition of maleic acid lasted about thirty minutes. The orange-coloured solution after being washed once with water, then with sulphurous acid, and finally twice with water, was dried over anhydrous magnesium sulphate. In order to minimise the risk of decomposition of the bromo-acid, the ether was allowed to evaporate spontaneously at the ordinary temperature, and the residual oily solid was dried in a vacuum over sulphuric acid for about a week until it became entirely solid. The yield varied from 75 to 91 grams. The *isodibromosuccinic* acid obtained in this manner was free from fumaric and dibromosuccinic acids. It dissolved very readily in cold water, and melted and decomposed at 166—167°. (Found, Br=57.8. Calc., Br=57.9 per cent.; equivalent=138.1. Calc., 137.9.)

Bromine combines with ethyl ether with great facility. This is shown clearly by Tschelinzeff and Konowaloff (*Ber.*, 1909, **42**, 1531), who ascribe the formula  $\begin{matrix} \text{C}_2\text{H}_5 \\ \text{C}_2\text{H}_5 \end{matrix} \text{O} \begin{matrix} \text{Br} \\ \text{Br} \end{matrix}$  to the additive compound produced by the interaction. This oxonium compound gradually separates as an oil when dry ether and bromine are mixed, and it doubtless acts in the foregoing preparation as a carrier of bromine. I find that whilst no obvious elimination of hydrogen bromide occurs during the separation of the oil, the latter decomposes very readily at the ordinary temperature with the evolution of hydrogen bromide and the formation of a compound (probably a brominated ether), which then undergoes further decomposition in the presence of water to give a mixture of ethyl bromide and an aldehyde.

Since the additive compound of bromine and ethyl ether separates much more readily in sunlight than in the dark, the maleic acid should accordingly be added in the preparation of *isodibromosuc*-

cinic acid before the separation of the oil commences, since the liberation of hydrogen bromide which so readily occurs from the oil is, of course, to be avoided.

In order to illustrate the effect of altering the conditions of the bromination of maleic acid in the presence of ether, the following experiments are perhaps worth recording. Maleic acid (100 grams) was added to 1 litre of commercial ether provided by a British firm. Bromine (44 c.c.) was then gradually added within an interval of thirty minutes in bright sunlight. The liquid quickly became turbid and warm, the maleic acid was gradually dissolved, hydrogen bromide was evolved, and a powdery solid separated in quantity. The mixture was cooled from time to time. The solid was separated and washed with ether; it amounted to 59 grams, and was identified as fumaric acid. (Found, equivalent=58.0, the calculated value.) The ethereal solution contained the two isomeric dibromosuccinic acids with a large preponderance of the *iso*-acid.

When 200 c.c. of ethyl ether (Kahlbaum's, dried over sodium), 20 grams of maleic acid, and 9.2 c.c. of bromine were employed under conditions similar to the preceding, the yield of fumaric acid amounted to 3.1 grams, which is much less in proportion than before; the *isodibromosuccinic* acid amounted in this case to 29 grams. The quality of the ether thus has an important influence.

#### *Resolution of isoDibromosuccinic Acid.*

Several alkaloids were tried for the purpose of resolving the acid into its optically active components, and morphine was finally selected as the most suitable. The use of water as the solvent was at first attempted, the morphine being used in the proportion both of 1 mol. and of 2 mols. for 1 mol. of acid and the temperature conditions being varied. Water is, however, an impractical solvent. The *iso*-acid underwent a certain amount of decomposition into bromofumaric acid under the temperature conditions employed, and, owing to the ease with which hydrogen bromide was eliminated, the crystals which separated consisted mainly of morphine hydrobromide. A small proportion of *lævorotatory iso*-acid was actually obtained from these crystals, but the method obviously did not appear likely to be successful.

The solvent selected was methyl alcohol, and it was found advantageous to use equimolecular proportions of morphine and acid. The alkaloidal salt which separated when the *iso*-acid (1 mol.) was added to a solution of morphine (1 mol.) in methyl alcohol could not, however, be submitted to the customary treatment, namely, resolution by crystallisation. It was so very sparingly soluble, not only in methyl alcohol, but also in many other organic solvents,

that crystallisation from such solvents was not a practical operation. It dissolved, however, in warm water, but the salt which separated was morphine hydrobromide. An acid of a high optical activity can, however, be obtained under the following conditions.

Morphine (21 grams, 1 mol.) was dissolved in warm methyl alcohol (290 c.c.), and, when the temperature of the solution was 46°, 19 grams (1 mol.) of the powdered *iso*-acid were added in one instalment, the mixture being shaken vigorously. The solution of the acid was immediately followed by the separation of glassy crystals of a morphine salt. After twenty-four hours at about 15°, the crystals (22 grams) were dissolved in dilute sulphuric acid. The acid obtained by extraction with ether amounted to 6.5 grams, and was strongly lævorotatory in ethyl acetate solution:

$$l=2, c=8.6, \alpha_D -17.32^\circ, [\alpha]_D -100.7^\circ.*$$

The mother liquor, from which the morphine salt had been removed, gave a dextrorotatory acid. 6.5 Grams of the acid with  $[\alpha]_D -100.7^\circ$  were then added to a solution of 7.1 grams of morphine in 100 c.c. of methyl alcohol. The resulting crystals (9.5 grams) gave an acid with the following rotation in ethyl acetate solution:

$$l=2, c=7.4, \alpha_D -16.93^\circ, [\alpha]_D -114.4^\circ.$$

This acid (2.5 grams) was then acted on by a solution of 2.8 grams of morphine in 80 c.c. of methyl alcohol. The yield of salt was 3.5 grams, and the acid from this gave the following rotation in ethyl acetate solution:

$$l=2, c=8.47, \alpha_D -19.98^\circ, [\alpha]_D -118^\circ.$$

The acid was not yet homogeneous, and it was also obvious that the preparation of the optically pure acid could not be effected with readiness by this treatment.

Many unsuccessful attempts were made to obtain the pure *l*-acid by crystallising the strongly lævorotatory acid, which is easily obtained by treating the *iso*-acid once with morphine according to the method just described; for example, 25 grams of an acid with  $[\alpha]_D -116^\circ$  in ethyl acetate solution were crystallised first from benzene (1800 c.c.) and then from a mixture of benzene (200 c.c.) and acetone (6 c.c.), the acid being sparingly soluble in

\* The behaviour of the dibromosuccinic acid (m. p. 255—256°), obtained from fumaric acid, was examined under conditions similar to the above, 10 grams of acid, 12 grams of morphine, and 153 c.c. of methyl alcohol being used. The morphine salt did not separate at once as in the case of the *iso*-acid, but, after five days, 4.5 grams had crystallised. The acid obtained from this salt was optically inactive. Other experiments on the action of various alkaloids on this dibromo-acid were made, and no evidence of the possibility of resolving it was obtained (compare Holmberg, *J. pr. Chem.*, 1911, [ii], 84, 145).



boiling benzene and readily so in cold acetone. The product amounted to 8 grams, and had  $[\alpha]_D -128^\circ$  in ethyl acetate solution, but further attempts to obtain the pure acid by crystallising this product from boiling solvents failed owing partly to the tendency of the acid to decompose under the conditions employed.

The pure *l*-acid was finally obtained as follows: Morphine (83 grams) was dissolved by heating with methyl alcohol (1150 c.c.), and, when the temperature had sunk to  $46^\circ$ , *isodibromosuccinic* acid (75 grams) was added. On shaking vigorously, the acid dissolved, and, two minutes after its addition, the morphine salt began to crystallise in glassy prisms. After eighteen hours at the laboratory temperature (summer), the crystals (87 grams) were removed.

*Examination of Filtrate.*—The filtrate was allowed to evaporate spontaneously. After a week, gritty crystals (8 grams), differing in appearance from those of the main quantity removed, had separated; they were sparingly soluble in dilute sulphuric acid, and they consisted of morphine hydrobromide. After several weeks the residual oily solid was decomposed by dilute sulphuric acid, and the bromo-acid extracted with ether. Thirty-four grams were obtained with the following rotation in ethyl acetate:

$$l=2, c=5.45, \alpha_D + 5.07^\circ, [\alpha]_D + 46.5^\circ.$$

By adding a large excess of light petroleum to the concentrated solution of this product in ethyl acetate, a solid was obtained with  $[\alpha]_D + 7.7^\circ$ . On allowing the solvent to evaporate at the ordinary temperature, and on repeating the treatment, a further solid with  $[\alpha]_D + 21.3^\circ$  resulted, whilst the filtrate contained an oily dextro-rotatory acid of high rotation. The separation of the pure *d*-acid from the latter product was not attempted.

*Examination of Solid.*—The 87 grams of morphine salt were decomposed by sulphuric acid, and the bromo-acid extracted with ether. The dried ethereal solution was allowed to evaporate spontaneously at the ordinary temperature in order to minimise the risk of decomposition. The resulting acid was at first oily, but ultimately became solid after ten days in a vacuum. Yield, 25 grams. On polarimetric examination in ethyl acetate solution it gave the value:

$$l=2, c=6.99, \alpha_D - 15.57^\circ, [\alpha]_D - 111.4^\circ.$$

This product was very soluble in cold ethyl acetate. On dissolving a portion of it in the minimum amount of this solvent, and then adding a large excess of light petroleum or of carbon tetrachloride, the solid which separated was *laevorotatory* to a less degree than the original, whilst the acid obtained by allowing the filtrate to evaporate spontaneously at the ordinary temperature was more



active; for example, when 5 grams of the acid were treated in this manner with light petroleum, 2.3 grams with  $[\alpha]_D - 82^\circ$  separated, whereas the acid obtained from the filtrate had  $[\alpha]_D - 128.5^\circ$ .

This tedious method was accordingly employed. The acid which separated was neglected, and the acid from the filtrate was examined polarimetrically, its concentrated solution in ethyl acetate then being precipitated afresh. At first light petroleum was used as the precipitant, and afterwards carbon tetrachloride. The acids obtained from the successive filtrates had the values  $[\alpha]_D - 127^\circ$ ,  $-131.6^\circ$ ,  $-140^\circ$ ,  $-144^\circ$  under similar conditions of concentration in ethyl acetate. The acid with  $[\alpha]_D - 144^\circ$  was then crystallised twice from boiling benzene, in which it dissolved with great difficulty, the heating not being unduly prolonged. On cooling, the acid separated quickly in beautiful, glassy needles. After two more crystallisations from benzene, the rotation was practically unchanged. The yield of the pure acid was only about 1 gram.

$$\begin{array}{c} \text{CO}_2\text{H} \\ | \\ \text{Br}-\text{C}-\text{H} \\ | \\ \text{H}-\text{C}-\text{Br} \\ | \\ \text{CO}_2\text{H} \end{array}$$

*l*- $\alpha$ -Dibromosuccinic acid, is very sparingly soluble in

boiling benzene, from which it separates on cooling in glassy needles grouped in rosettes. It is easily soluble in ethyl acetate, acetone, methyl alcohol, or ethyl alcohol, and sparingly so in chloroform, light petroleum, or carbon tetrachloride. Like the *r*-isomeride, it dissolves very readily in cold water. It melts and decomposes fairly sharply at  $157-158^\circ$  with slight preliminary softening:

0.2013 required 28.1 c.c. of *N*/19.18 baryta for neutralisation.

Equivalent = 137.4 (calc., 137.9).

0.2228 gave 0.3016 AgBr. Br = 57.6.

$\text{C}_4\text{H}_4\text{O}_4\text{Br}_2$  requires Br = 57.9 per cent.

Its specific rotation was determined in ethyl acetate solution:

$l = 2$ ,  $c = 5.788$ ,  $\alpha_D^{25} - 17.13^\circ$ ,  $[\alpha]_D^{25} - 148.0^\circ$ .

The solution used in this determination was allowed to remain in the polarimeter tube for three days at the ordinary temperature; the rotation was then slightly greater than before, namely,  $\alpha_D^{25} - 17.39^\circ$ , whence  $[\alpha]_D - 150.2^\circ$ .

#### *Action of Water on l-Dibromosuccinic Acid and its Salts.*

The *l*-acid (0.2026 gram) was neutralised by *N*/19.18 baryta, and evaporated on the water-bath to 8 c.c., the bulk necessary to fill a 2-dcm. tube. The solution was optically inactive.

The *l*-acid (0.2475 gram) was made up to 10 c.c. with water.

In a 2-dcm. tube fifteen minutes after the solid was dissolved the  $\alpha_D$  was  $-3.08^\circ$  ( $t=12.5^\circ$ ), whence  $[\alpha]_D^{12.5} = -62.2^\circ$ . The solution was slowly evaporated to dryness during one hour, and the solid then dissolved in sufficient water to fill a 2-dcm. tube; the value  $\alpha_D = -0.36^\circ$  was observed, but after heating for five hours at  $100^\circ$  this solution became optically inactive.

The decomposition of the *l*-acid by water takes place slowly at the ordinary temperature. 0.6408 Gram of a mixture of *l*- and *r*-acids with  $[\alpha]_D = -112^\circ$  in ethyl acetate solution was made up to 10 c.c. with water; a portion of this solution was introduced into a 2-dcm. tube, and examined at intervals with the following result:

	$\alpha_D$ .
10th February, 1911 .....	$-6.20^\circ$ (initial value)
11th    "    " .....	6.13
14th    "    " .....	5.65
20th    "    " .....	4.61
28th March   " .....	1.62
1st May    " .....	0.64
30th September   " .....	0.03

An experiment on the action of water on a larger scale was accordingly made with a solution of 13.5 grams of acid (with  $[\alpha]_D = -100.7^\circ$  in ethyl acetate) in 200 c.c. of water. After eight hours at  $100^\circ$  the solution was concentrated by evaporation to a bulk sufficient to fill a 2-dcm. tube, when a slight laevorotation was observed, namely,  $-0.15^\circ$ ; when neutralised by sodium hydroxide and again evaporated, the rotation was now dextrorotatory, namely,  $+0.25^\circ$ . It is accordingly impossible to draw the conclusion that a small amount of *l*-tartaric acid is produced by the action of water on *l*-dibromosuccinic acid.

Silver *l*-dibromosuccinate (1.3 grams) was boiled with 50 c.c. of water for four hours, and the amount of hydrochloric acid requisite to precipitate all the silver in solution was added, the heating being continued for half an hour longer. The filtrate was evaporated to the bulk necessary to fill a 2-dcm. tube, and then gave  $\alpha_D = -0.09^\circ$ .

A slight laevorotation was also observed with the product obtained by boiling 1.4 grams of an acid with  $[\alpha]_D = -129^\circ$ , 4.7 grams of silver oxide, and 340 c.c. of water for ten hours. A little hydrochloric acid was added, and the filtrate when evaporated to small bulk gave  $\alpha_D = -0.08^\circ$  in a 2-dcm. tube.

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