XXXVIII.—*The Constitution of Camphoric Acid.*

By JAMES WALKER.

IN 1893 (Trans., 63, 495), I showed that the campholytic acid derived from sodium ortho-ethyl camphorate by electrolysis was an $\alpha\beta$ -unsaturated acid, this conclusion being based on the fact that its dibromide decomposed on neutralisation according to the following equation :

a behaviour which Fittig had proved to be characteristic of the dibromides of such acids. Now, as appears from the researches of

Kolbe and of Crum Brown and myself, when an unsaturated compound is formed on the electrolysis of a salt of a carboxylic acid, the acid loses the groups CO_2H and H from neighbouring carbon atoms, the double bond in the unsaturated compound being thus between the α - and β -carbon atoms, as reckoned from the carboxyl group which has disappeared. The double bond of campholytic acid then is in the $\alpha\beta$ -position with regard to the carboxyl group of the camphoric acid which has disappeared on electrolysis; but it is also in the $\alpha\beta$ -position with regard to the carboxyl group, which remains after electrolysis. This gives us only two possibilities for the relative position of the carboxyl groups in the camphoric acid molecule. Either the molecule contains the group

or the group

These groupings, and no others, fulfil the required conditions, but the first is inadmissible, since it represents camphoric acid as a malonic acid derivative, which is altogether at variance with the known facts. There remains therefore only the conclusion (*loc. cit.*, 509) that the camphoric acid molecule contains the complex

This conclusion, although it received immediate confirmation from the work of Noyes in 1894, was not generally accepted at the time, chiefly, no doubt, on account of the apparent difficulty in explaining the formation of camphanic acid from camphoric acid (compare *Trans.*, 1895, 67, 345).

If exception is taken to the reasoning given above, it can only be on the ground that campholytic acid is not an $\alpha\beta$ -unsaturated acid, that it is not a direct product of the electrolysis, or that the carboxyl group and hydrogen atom which are removed on electrolysis do not leave the molecule from neighbouring carbon atoms. The second and third of these points will be discussed later in connection with Perkin's formula for isolaunonic acid. With regard to the first, reference need only be made to the decomposition of the hydrobromide of campholytic acid on neutralisation (this vol., p. 380), and to the nature of the isomerism with isolaunonic acid (p. 382), which is universally admitted to be an $\alpha\beta$ -unsaturated acid. The reasoning is further

strengthened by the proof that isolauronic acid itself is, along with campholytic acid, a direct product of the electrolysis (this vol., p. 376).

An investigation as to the products of electrolysis of potassium alloethyl camphorate (Trans., 1895, 67, 337; 1896, 69, 248), permitted a further conclusion to be drawn, namely, that camphoric acid contained the complex

Now Perkin and Thorpe (Trans., 1897, 71, 1169), by their synthesis of camphoronic acid, a product of the oxidation of camphoric acid, proved conclusively that this acid has the constitution which had been suggested by Bretz, namely:

Camphoric acid therefore must contain the complex

which, when combined with the complex derived from the behaviour of the electrolytic products, yields the Perkin-Bouveault formula,

for the acid itself.

This formula was first suggested by Perkin, and afterwards, apparently independently, by Bouveault. Perkin, however, was led by his own experiments (Trans., 1898, 73, 796) to favour another formula which was proposed by him at the same time, namely,

The behaviour of dihydro-isolauronic acid chiefly weighed with Perkin in preferring this to the Perkin-Bouveault formula, but, as Blanc has shown (*Bull. Soc. Chim.*, 1899, [iii], 21, 830), Perkin's observations are open to a totally different interpretation from that put upon them by the author, and on the whole tell in favour of the Perkin-Bouveault formula.

That Perkin's second formula is irreconcilable with the results of electrolysis is plain from the fact that it does not contain a complex with the carboxyl groups in the ortho-position relatively to each other. If the electrolysis of the sodium ethyl salt of an acid having Perkin's formula (II) occurred in the ordinary way, the ethyl ester of the unsaturated acid thereby produced should have formula I. Now this acid is a $\beta\gamma$ -unsaturated acid, and Perkin himself attributes the formula marked III to isolaunonic acid,

which, along with its stereoisomeride, campholytic acid, is the substance actually produced. That an ester having formula III should be formed directly from a substance having formula II is in the highest degree improbable, and that it should be formed by the isomeric transformation of the acid having formula I is almost equally unlikely, for not only is the electrolysis conducted at the ordinary temperature and in a solution which is, at most, feebly alkaline with sodium hydrogen carbonate, but the ester produced immediately separates from the aqueous liquid, and is thus exposed to the action of no chemical agents whatever. The improbability of an isomeric transformation of a primary $\beta\gamma$ -product into an $\alpha\beta$ -acid is still further increased by the fact that the $\beta\gamma$ -acids obtained from the electrolysis of potassium allo-ethyl camphorate show no tendency whatever, under the experimental conditions, to pass into $\alpha\beta$ -acids.

The formula for isolaunonic acid (and campholytic acid) derived from the Bouveault-Perkin formula for camphoric acid is

As Blanc has pointed out, this formula has no asymmetric carbon atom, and the acid corresponding to it must therefore be inactive. The isolaunonic acid formula of Perkin, on the other hand, has one asymmetric carbon atom, so that the corresponding acid should exhibit optical activity, unless it be a racemic mixture. Now, the isolaunonic acid prepared from camphoric anhydride and aluminium chloride by Blanc's method is optically inactive, and so are its salts and esters. The acid prepared by electrolysis is also inactive, and this inactivity is likewise characteristic of isolaunonic acid prepared

from the campholytic acid of electrolysis, as well as of the campholytic acid prepared from isolaunonic acid (this vol., pp. 378, 380). The hydrocarbon isolaunolene, C_8H_{14} , derived from the hydrobromides of campholytic and isolaunonic acids (this vol., p. 380), is also inactive, which is in accordance with formula IV derived from the Perkin-Bouveault formula of camphoric acid, and in disagreement with formula V, derived from Perkin's later formula for this substance, which still contains an asymmetric carbon atom.

There is absolutely no reason to suppose that racemisation of active compounds takes place during electrolysis, for the allo-campholytic acid produced by the electrolysis of potassium orthoethyl camphorate is strongly active, in accordance with the formulæ deduced from either the Perkin-Bouveault or the Perkin formula for camphoric acid. An attempt, too, to resolve isolaunonic acid into active constituents by means of cinchonine was made by Blanc, and failed. It must be conceded, therefore, that the inactivity of isolaunonic acid, from whatever source derived, as well as of the related substances, campholytic acid and isolaunolene, affords very strong evidence in favour of the Perkin-Bouveault formula for camphoric acid. It is impossible, either from Perkin's second formula or from Bredt's formula, to derive a formula for isolaunonic acid which shows this substance to be at once an $\alpha\beta$ -unsaturated acid, and inherently inactive.

The Perkin-Bouveault formula for camphoric acid has recently received synthetic confirmation from Noyes (*Ber.*, 1900, **33**, 54), who, by heating calcium $\alpha\beta\beta$ -trimethyladipate, prepared the corresponding ketone, thus:

Now, just as diethyl ketone can be produced from diethylhydroxyacetic acid,

so $\alpha\beta$ -trimethyladipone can be derived from α -hydroxydihydro-isolauronic acid by oxidation, proving that the latter has the formula given below,

Chemists are agreed, however, that one of the carboxyl groups of camphoric acid is attached to the carbon atom which is united with the solitary methyl group, and the above reactions show that the second carboxyl group is attached to the neighbouring carbon atom. Camphoric acid is therefore a derivative of succinic acid, in accordance with Perkin's first formula, and not a glutaric acid derivative, as Perkin's second formula and Bredt's formula would represent it.

Configuration of the Camphoric Acids.

It has been shown (this vol., p. 390) that *d*-camphoric acid and *l*-isocamphoric acid have the same configuration of the allo-asymmetric carbon atom. This circumstance, when taken in conjunction with other well-known facts, enables us to write the configurations of all the camphoric acids on the basis of the Perkin-Bouveault formula.

In the first place, we have to determine which of the carboxyl groups in the formula is to be called the ortho-carboxyl group and which the allo-carboxyl group. This may be readily done by considering the ease with which the respective groups are esterified, and with which the corresponding esters are hydrolysed. One of the carboxyl groups in the formula is attached to a tertiary, and the other to a secondary carbon atom. Now, it is well known that the esters of tertiary acids are much less readily produced and hydrolysed than those of secondary acids. According to the experience of all observers (for example, Friedel, Brühl, and myself) it is a comparatively difficult matter to produce allo-alkyl derivatives and to hydrolyse them after they are obtained (compare this vol., p. 389), whilst the production and hydrolysis of the ortho-camphoric esters can be readily effected. We must therefore give the designation ortho to the secondary asymmetric carbon atom and to the carboxyl group with which it is united, reserving the term allo for the tertiary asymmetric carbon atom and the corresponding carboxyl group, thus :

This mode of designation is in entire agreement with the results of electrolysis, the allo-ethyl salts yielding $\beta\gamma$ -unsaturated acids, and the ortho-ethyl salts yielding $\alpha\beta$ -unsaturated acids, as would be directly deduced from the formula.

Since camphoric acid and its optical antipode easily yield anhydrides, whilst anhydrides of the isocamphoric acids have never been prepared, we must assume that in the first instance the carboxyl groups are on the same side, and in the second instance on different sides of the ring. If, then, we write the configuration formula of *d*-camphoric acid as follows:

that of *l*-camphoric acid becomes

But since *d*-camphoric acid has the same configuration of the allo asymmetric carbon atom as *l*-isocamphoric acid, we have for the remaining acids the following formulæ:

Dissociation Constants of Camphoric Acid and its Derivatives.

Ostwald (*Zeit. physikal. Chem.*, 1889, 3, 402) found for camphoric acid the constant $K = 0.00225$. On comparing this value with the dissociation constants of the following normal saturated dicarboxylic acids,

Acid.		K.
Malonic	$\text{CO}_2\text{H}\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$	0.158
Succinic	$\text{CO}_2\text{H}\cdot(\text{CH}_2)_2\cdot\text{CO}_2\text{H}$...	0.0066
Glutaric.....	$\text{CO}_2\text{H}\cdot(\text{CH}_2)_3\cdot\text{CO}_2\text{H}$...	0.0047
Adipic	$\text{CO}_2\text{H}\cdot(\text{CH}_2)_4\cdot\text{CO}_2\text{H}$...	0.0037
Sebacic	$\text{CO}_2\text{H}\cdot(\text{CH}_2)_8\cdot\text{CO}_2\text{H}$...	0.0023

we find it to be comparatively small, and Ostwald drew the conclusion that the carboxyl groups in the camphoric acid molecule were probably far apart from each other, seeing that in this series the value of the dissociation constant falls off as the number of carbon atoms between the carboxyl groups increases.

Now, the Perkin-Bouveault formula represents camphoric acid as a succinic acid derivative, whilst according to the formula of Bredt and the second formula of Perkin, it is a derivative of glutaric acid. In either case, the dissociation constant is much less than that of the parent substance.

The low value of the dissociation constant of camphoric acid might be accounted for in two ways. In the first place, the formation of a ring might lower the value of the constant. This explanation, however, is invalid, as I have shown (*Trans.*, 1892, 61, 705) that ring formation has little effect on the dissociation constants of acids. In the second place, the replacement of hydrogen atoms of succinic or glutaric acid by hydrocarbon radicles might be the cause of the diminution. At first sight, this explanation appears equally invalid with the first, for the dissociation constants of the alkyl-succinic and alkyl-glutaric acids are, almost without exception, considerably greater than those of the parent acids. For example, for the methyl succinic acids we have

Acid.		K.
Succinic	$\text{CO}_2\text{H}\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$	0.0066
Methylsuccinic	$\text{CO}_2\text{H}\cdot\text{CH}_2\cdot\text{CHMe}\cdot\text{CO}_2\text{H}$...	0.0086
Dimethylsuccinic ...	$\text{CO}_2\text{H}\cdot\text{CH}_2\cdot\text{CMe}_2\cdot\text{CO}_2\text{H}$...	0.0081
Trimethylsuccinic...	$\text{CO}_2\text{H}\cdot\text{CHMe}\cdot\text{CMe}_2\cdot\text{CO}_2\text{H}$.	0.031
Tetramethylsuccinic	$\text{CO}_2\text{H}\cdot\text{CMe}_2\cdot\text{CMe}_2\cdot\text{CO}_2\text{H}$...	0.031

In dealing with a case of this nature, it must be borne in mind, however, that the relatively large values of the dicarboxylic acids are chiefly due to the mutual reinforcement of the carboxyl groups, so that the replacement of hydrogen by an alkyl group may act on the constant in two distinct ways: (1) through the influence of the substitution pure and simple, (2) through the influence due to a change effected in the relative position of the carboxyl groups. The nature of these two influences may easily be investigated separately.

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If we consider monocarboxylic acids, the second mode of action is obviously excluded, and we can roughly estimate the effect of a pure substitution. For this purpose, we may take acetic acid and some of its simpler derivatives:

Acid.		K.
Acetic	$\text{CH}_3\cdot\text{CO}_2\text{H}$	0.00180
Propionic	$\text{CH}_2\text{Me}\cdot\text{CO}_2\text{H}$	0.00134
Isobutyric.....	$\text{CHMe}_2\cdot\text{CO}_2\text{H}$	0.00162
Trimethylacetic ...	$\text{CMe}_3\cdot\text{CO}_2\text{H}$	0.00098
Dimethylethylacetic	$\text{CMe}_2\text{Et}\cdot\text{CO}_2\text{H}$	0.00096

For each alkyl derivative, the constant is less than that of acetic acid, the influence being especially marked in the trialkyl derivatives. The same effect may be observed with unsaturated acids, thus:

Acid.		K.
Acrylic	$\text{CH}_2\cdot\text{CH}\cdot\text{CO}_2\text{H}$	0.0056
Crotonic	$\text{CHMe}\cdot\text{CH}\cdot\text{CO}_2\text{H}$	0.0020
Isocrotonic		0.0036
Angelie	$\text{CHMe}\cdot\text{CMe}\cdot\text{CO}_2\text{H}$...	0.0050
Tiglic.....		0.00096
Methylethylacrylic..	$\text{CHEt}\cdot\text{CMe}\cdot\text{CO}_2\text{H}$	0.00111

When disturbing influences are absent, therefore, it may be said that the substitution of alkyl for hydrogen frequently lowers the constant to one-half, and in some cases to one-fifth the value for the parent acid.

It is thus practically certain that the rise in the dissociation constant, when hydrogen is replaced by alkyl in succinic or glutaric acid, is due to the approximation of the carboxyl groups, and not to the direct influence of the displacement.

From the point of view of stereochemistry, the carbon atoms in open chain saturated compounds must be conceived as possessing a considerable degree of freedom of movement, a freedom with which they, in great measure, part when they form links in a closed chain, or are joined by a double or triple linking. The substitution of alkyl for hydrogen in an unsaturated dicarboxylic acid, or a saturated cyclic dicarboxylic acid, might therefore be expected to show the customary diminution of the dissociation constant, undisturbed by any marked increase due to the secondary effect of approximation of the carboxyl groups. Data for unsaturated dicarboxylic acids are somewhat scanty, but, such as they are, they bear out the preceding deduction. Thus we have (Walden, *Zeit. physikal. Chem.*, 1891, 8, 494):

	Acid.	K.		Acid.	K.
Maleic	$\begin{array}{c} \text{H} \text{---} \text{CO}_2\text{H} \\ \parallel \\ \text{H} \text{---} \text{CO}_2\text{H} \end{array}$	1.17	Fumaric	$\begin{array}{c} \text{H} \text{---} \text{CO}_2\text{H} \\ \parallel \\ \text{CO}_2\text{H} \text{---} \text{H} \end{array}$	0.093
Citr- aconic	$\begin{array}{c} \text{Me} \text{---} \text{CO}_2\text{H} \\ \parallel \\ \text{H} \text{---} \text{CO}_2\text{H} \end{array}$	0.34	Mes- aconic	$\begin{array}{c} \text{Me} \text{---} \text{CO}_2\text{H} \\ \parallel \\ \text{CO}_2\text{H} \text{---} \text{H} \end{array}$	0.079
Ethyl- maleic	$\begin{array}{c} \text{Et} \text{---} \text{CO}_2\text{H} \\ \parallel \\ \text{H} \text{---} \text{CO}_2\text{H} \end{array}$	0.238	Ethyl- fumaric	$\begin{array}{c} \text{Et} \text{---} \text{CO}_2\text{H} \\ \parallel \\ \text{CO}_2\text{H} \text{---} \text{H} \end{array}$	0.094

There is little reduction of the dissociation constant in the case of the alkylfumaric acids, but for the alkylmaleic acids it is reduced to less than a third of its value by the introduction of a methyl group, and to a fifth by the introduction of an ethyl group.

Practically nothing is known of the dissociation constants of saturated cyclic dicarboxylic acids, but in all probability the introduction of alkyl groups instead of hydrogen would exert its primary effect of reducing the constant, as it does in the unsaturated dicarboxylic acids.

These considerations show that, although camphoric acid is regarded as a derivative of glutaric acid, or even of succinic acid, there is in reality nothing abnormal in the small value of its constant, for all chemists agree that in its molecule there remains only one hydrogen atom attached to the carbon atoms with which the carboxyl groups are united.

If the preceding interpretation is correct, monobasic acids derived from camphoric acid should exhibit constants considerably smaller than that of acetic acid, for, in their case, the same influences would be at work to reduce the constant, as in camphoric acid itself. This is, in fact, the case. Thus, for the $\alpha\beta$ -unsaturated tertiary acids, isolaunonic acid and campholytic acid, we have values which are much less than that of acetic acid, and comparable with that of the $\alpha\beta$ -unsaturated tertiary acid, tiglic acid :

Again, the constants of the hydrogen methyl camphorates are as follows:

Once more, the very small values appear, and, as we might expect, the constant of the tertiary or allo-carboxylic acid is less than that of the secondary or ortho-carboxylic acid.

The constants of the isocamphoric acids are still less than those of the camphoric acids proper, in accordance with the fact that the former have the *cis*-configuration, and the latter the *cistrans*-configuration. Thus, for *l*-isocamphoric acid we have the constant 0·00160, and for allo-hydrogen ortho-ethyl camphorate the constant 0·00065.

We conclude then from these measurements that the low value of the constant for camphoric acid need not be due to the carboxyl groups being far apart in the molecule, but to the fact that all but one of the hydrogen atoms of the succinic acid, from which, according to the Perkin-Bouveault formula, camphoric acid is derived, are replaced by hydrocarbon groups, which exert their primary effect in lowering the dissociation constant.

The author desires to express his indebtedness for valuable criticism and suggestions to Professor W. H. Perkin, who kindly revised this paper in manuscript.

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