21. *Isotopic Exchange Reactions of Organic Compounds. Part III. Kinetics of the Isomerisation and Isotope Exchange of Vinylacetic Acid.*

By D. J. G. Ives.

The present paper is concerned with an extension of previous work (Ives and Rydon, J., 1935, 1735) on the isomerisation of vinylacetic acid to crotonic acid, with deuterium as an indicator. It has been found that the exchange reaction of vinylacetic acid proceeds faster than the isomerisation, the respective velocity constants being 0·009 and 0·0058 min.$^{-1}$, indicating that the isomerisation proceeds by a bimolecular mechanism. A kinetic proof is given that the deuterium : hydrogen ratio of the hydrogen in the α-position of the βγ-isomeride in equilibrium with the solvent is unchanged during the formation of the intermediate ions postulated by the prototropic theory of three-carbon tautomerism, a result previously deduced by other means.

On the basis of this constancy of the D/H ratio in the α-position, it has been possible to calculate the relative rates of removal from, and addition to, the vinylacetic acid molecules of protons and deuterons, the values obtained being 3·15 and 3·55 respectively, giving a value for the exchange equilibrium constant of 0·89.

In Part I (Ives and Rydon, J., 1935, 1735) it was shown that the isomerisation of vinylacetic acid in presence of aqueous alkali was accompanied by a hydrogen-exchange reaction. Although this qualitative result was of interest in so far as it excluded any intramolecular mechanism for three-carbon tautomerism, it left open the more important questions of the number of hydrogen atoms taking part in the exchange reaction, the exchange equilibrium constant, and the rate of the reaction relative to that of isomerisation. These questions are now discussed.

For a determination, *ab initio*, of the equilibrium constant of, and the number of atoms involved in, a given exchange reaction, experiments must be carried out with " heavy " solvents covering substantially the complete range of deuterium concentrations; calculation indicates that any less variation in the deuterium content of the solvent will not provide results of any certainty. The difficulty of the problem in the present case is further increased by the isomerisation of the system during the exchange reaction; at any given time after the commencement of the reaction, the system is a mixture of a substance which does exchange with one that does not (the exchange reaction of crotonic acid is extremely slow, see Part I, *loc. cit.*). An experimental investigation of this point has not, therefore, been undertaken, but there can be no real doubt that in vinylacetic acid only the α-hydrogen atoms are involved in the exchange reaction, both on general grounds, and by comparison with the results described in the previous paper : with the possible exception of phenylacetic acid, none of the acids there studied shows more than a negligible rate of exchange in comparison with vinylacetic acid, of which the α-hydrogens only are unique.

The present work is therefore confined to the rate comparison of the two reactions and the evaluation of the isotopic discrimination factor of the exchange reaction, which also involves a knowledge of the relative rates of addition to, or removal from, the molecule of protons and deuterons.

The experimental conditions were the same as those used in Part I (*loc. cit.*), *viz.*, treatment with 1·05 mols. of N-sodium hydroxide at 100°. The results are shown in Table I, where E is the exchange number (= apparent number of hydrogen atoms exchanged, on the assumption of no isotopic discrimination) and k is the velocity constant of the isomerisation in minutes^{-1}, calculated on the assumption of 100% αβ at equilibrium.

TABLE I.

Time, mins.	15	30	45	60	90	120	180	240	360	480
E	0·265	0·376	0·563	0·649	0·814	0·877	0·934	0·921	0·900	0·847
αβ, %	10·5	16·0	19·0	26·0	41·0	52·0	—	—	—	—
10^4k, mins.$^{-1}$	73·7	58·0	46·9	50·1	58·6	61·2		Mean = 58		

It is clear that the exchange reaction is faster than, and cannot, therefore, be entirely dependent on, the isomerisation : the intermediate ions postulated by Ingold, Shoppee, and Thorpe's theory of prototropic change (J., 1926, 1477) must therefore be kinetically free in this case, and the isomerisation must proceed by the bimolecular mechanism (cf. Hsü, Ingold, and Wilson, J., 1935, 1778). It is interesting to compare the present results with those of Ingold, de Salas, and Wilson (J., 1936, 1328) on the isomerisation and deuterium exchange of *cyclo*hexylideneacetonitrile : the present case differs in that the exchange reaction of the βγ-isomeride is not instantaneous, but is similar in that the deuterium content of the solute first rises to a maximum and then decreases. The explanation for this decrease which has been advanced by these authors applies equally well to the system now considered, but requires some further elucidation.

We consider first vinylacetic acid in deuterium equilibrium with the solvent, neglecting the isomerisation for the time being. α-Hydrogen and α-deuterium atoms are removed as protons and deuterons, respectively, by the basic hydroxyl ions present in the solvent, and are returned by the acid water molecules. The relative rates of removal and addition of protons and deuterons are, however, different, and the equilibrium ratio of deuterium to hydrogen, D/H, in the exchangeable position in the vinylacetic acid will be given by the quotient f_2x/f_1, where f_2 is the ratio of the rate of removal of protons to that of deuterons, f_1 is the ratio of the rates of addition of protons and deuterons, and x is the ratio of deuterium to hydrogen in the solvent; f_1 and f_2 are both considerably greater than unity and f_1 is greater than f_2.

We now consider the process of isomerisation. Ingold, de Salas, and Wilson (*loc. cit.*) state that the D/H ratio for the hydrogen in the α-position of the intermediate ion (and therefore for the hydrogen in the α-position in the αβ-isomeride) must be the same as in the βγ-isomeride, where it is governed by an equilibrium. On isomerisation, a proton or a deuteron is added *irreversibly* in the γ-position of the ion, and consequently, the D/H ratio of the hydrogen in the γ-position of the $\alpha\beta$-isomeride is governed by an irreversible process and not by an equilibrium, and will therefore be poorer in deuterium by an amount commensurate with the difference between $1/f_1$ and f_2/f_1. The decrease in the deuterium content of the solute which occurs during isomerisation is therefore explained.

This explanation depends on the identity of the D/H ratio of the hydrogen in the α-position of the ions with that in the α-position of the parent molecules, which follows from the fact that exchange equilibria are determined by the vibration frequencies of the links involved, which are only slightly constitutive. The ions themselves are not, of course, in direct equilibrium with the solvent (this would involve the formation of a doubly charged anion, the original charge on the carboxyl group being neglected), but it is clear thermodynamically that this is immaterial: the D/H ratio of the ions must be the same, whether their equilibrium with the solvent is direct or indirect. It has been found, however, that the exchange equilibrium constant of vinylacetic acid is 0·89, whereas the corresponding constant for *cyclo*hexylideneacetonitrile found by Ingold, de Salas, and Wilson (*loc. cit.*) is 0·67. This raises some doubt as to how far exchange equilibria involving C–H and O–H links are independent of constitution, and therefore within what limit the D/H ratios of the hydrogen in the α-positions of the ions and molecules are identical. In order to obtain more insight into the mechanism by which this identity might be established, it was thought worth while to examine this point on a kinetic basis, and at first sight it appeared difficult to confirm this identity: for example, if protons are removed from the molecules faster than deuterons, it would appear that the resulting ions must contain relatively more deuterium than the parent molecules. The reversal of this ionisation is also governed by a discrimination factor which appears to operate in the same sense. It would also seem to be erroneous to postulate an irreversible addition (governed by the partition factor $1/f_1$ without a previous irreversible removal (governed by the factor f_2), unless the molecule is to accumulate a hydrogen atom extra to the number usually allowed by the rules of valency. The net effect on the total deuterium content of the solute of these *two* irreversible processes might be supposed to be the same as that of the original equilibrium. These arguments, however, are fallacious because they overlook the statistical factors involved, which are now considered.

For simplicity, we take a case in which the solvent (in infinite excess) is alcohol, containing only one exchangeable hydrogen atom per molecule. The possible equilibria between the $\beta\gamma$-molecules and ions of varying degrees of deuteration may be decomposed into the following reactions, each of which must be given equal statistical weight, and to which velocity constants may be ascribed. We again ignore the complication of isomerisation, which is permissible, since we are considering the equilibrium between ions and $\beta\gamma$-molecules only.

$$\left.\begin{array}{l}
:\mathrm{CH_2} + \mathrm{Et\bar{O}} \longrightarrow :\mathrm{\bar{C}H} + \mathrm{EtOH} \\
:\mathrm{CH_2} + \mathrm{Et\bar{O}} \longrightarrow :\mathrm{\bar{C}H} + \mathrm{EtOH} \\
:\mathrm{CHD} + \mathrm{Et\bar{O}} \longrightarrow :\mathrm{\bar{C}D} + \mathrm{EtOH}
\end{array}\right\}\ \text{Removal of H : velocity const., } k_{i\mathrm{H}}.$$

$$\left.\begin{array}{l}
:\mathrm{CHD} + \mathrm{Et\bar{O}} \longrightarrow :\mathrm{\bar{C}H} + \mathrm{EtOD} \\
:\mathrm{CD_2} + \mathrm{Et\bar{O}} \longrightarrow :\mathrm{\bar{C}D} + \mathrm{EtOD} \\
:\mathrm{CD_2} + \mathrm{Et\bar{O}} \longrightarrow :\mathrm{\bar{C}D} + \mathrm{EtOD}
\end{array}\right\}\ \text{Removal of D : velocity const., } k_{i\mathrm{D}}.$$

$$\left.\begin{array}{l}
:\mathrm{\bar{C}H} + \mathrm{EtOH} \longrightarrow :\mathrm{CH_2} + \mathrm{Et\bar{O}} \\
:\mathrm{\bar{C}D} + \mathrm{EtOH} \longrightarrow :\mathrm{CHD} + \mathrm{Et\bar{O}}
\end{array}\right\}\ \text{Addition of H : velocity const., } k_{a\mathrm{H}}.$$

$$\left.\begin{array}{l}
:\mathrm{\bar{C}H} + \mathrm{EtOD} \longrightarrow :\mathrm{CHD} + \mathrm{Et\bar{O}} \\
:\mathrm{\bar{C}D} + \mathrm{EtOD} \longrightarrow :\mathrm{CD_2} + \mathrm{Et\bar{O}}
\end{array}\right\}\ \text{Addition of D : velocity const., } k_{a\mathrm{D}}.$$

The reactions of removal of H or D from the molecules $:CH_2$ and $:CD_2$ respectively have been duplicated to emphasise that a statistical factor of 2 applies to these reactions. It is clear, for example, that the probability that a $:\bar{C}H$ ion will be produced from $:CH_2$ at the moment of attack by the base is double the probability that a $:\bar{C}H$ ion will be produced from $:CHD$ in similar circumstances, quite apart from any consideration of the relative ease of removal of H or D.

When the system is in equilibrium, the rate of formation of each of the species present, molecules or ions, must be equal to the rate of its disappearance. We can therefore set up the following equations, which must be true at equilibrium.

$$k_{aH}[:\bar{C}H][EtOH] = 2k_{iH}[:CH_2][Et\bar{O}] \quad . \ . \ . \ . \ . \ . \quad (1)$$

$$k_{aH}[:\bar{C}D][EtOH] + k_{aD}[:\bar{C}H][EtOD] = k_{iH}[:CHD][Et\bar{O}] + k_{iD}[:CHD][Et\bar{O}] \ . \quad (2)$$

$$k_{aD}[:\bar{C}D][EtOD] = 2k_{iD}[:CD_2][Et\bar{O}] \quad . \ . \ . \ . \ . \ . \quad (3)$$

$$2k_{iH}[:CH_2][Et\bar{O}] + k_{iD}[:CHD][Et\bar{O}] = k_{aH}[:\bar{C}H][EtOH] + k_{aD}[:\bar{C}H][EtOD] \ . \quad (4)$$

$$k_{iH}[:CHD][Et\bar{O}] + 2k_{iD}[:CD_2][Et\bar{O}] = k_{aH}[:\bar{C}D][EtOH] + k_{aD}[:\bar{C}D][EtOD] \ . \quad (5)$$

From equations (3) and (5) we obtain

$$k_{iH}[:CHD][Et\bar{O}] = k_{aH}[:\bar{C}D][EtOH] \quad . \ . \ . \ . \ . \ . \quad (6)$$

and from equations (1) and (4),

$$k_{iD}[:CHD][Et\bar{O}] = k_{aD}[:\bar{C}H][EtOD] \quad . \ . \ . \ . \ . \ . \quad (7)$$

Eliminating $[:\bar{C}H]$ from equations (1) and (7), and $[:\bar{C}D]$ from equations (3) and (6), we obtain

$$2k_{aD}k_{iH}[EtOD][Et\bar{O}][:CH_2] = k_{aH}k_{iD}[EtOH][Et\bar{O}][:CHD] \quad . \ . \ . \quad (8)$$

and

$$k_{aD}k_{iH}[EtOD][Et\bar{O}][:CHD] = 2k_{aH}k_{iD}[EtOH][Et\bar{O}][:CD_2] \quad . \ . \ . \quad (9)$$

Adding equations (8) and (9), and cancelling $[Et\bar{O}]$ throughout, we have

$$2k_{aD}k_{iH}[EtOD][:CH_2] + k_{aD}k_{iH}[EtOD][:CHD] = k_{aH}k_{iD}[EtOH][:CHD] + 2k_{aH}k_{iD}[EtOH][:CD_2] \quad (10)$$

Rearranging,

$$k_{aD}k_{iH}[EtOD](2[:CH_2] + [:CHD]) = k_{aH}k_{iD}[EtOH]([:CHD] + 2[:CD_2])$$

Hence,

$$([:CHD] + 2[:CD_2])/(2[:CH_2] + [:CHD]) = k_{aD}k_{iH}[EtOD]/k_{aH}k_{iD}[EtOH] \ . \quad (11)$$

which gives the D/H ratio of the α-hydrogen in the βγ-molecules.

The D/H ratio of the α-hydrogen in the ions is given directly by equations (6) and (7):

$$\frac{[:\bar{C}D]}{[:\bar{C}H]} = \frac{k_{iH}[Et\bar{O}][:CHD]}{k_{aH}[EtOH]} \times \frac{k_{aD}[EtOD]}{k_{iD}[Et\bar{O}][:CHD]} = \frac{k_{aD}k_{iH}[EtOD]}{k_{aH}k_{iD}[EtOH]} \quad . \ . \quad (12)$$

which is identical with equation (11).

Substituting $k_{iH}/k_{iD} = f_2$, $k_{aH}/k_{aD} = f_1$, and $[EtOD]/[EtOH] = x$, we obtain the relationship previously stated, that the D/H ratio of the α-hydrogen in the βγ-molecules (and therefore in the ions) is f_2x/f_1. Equation (2) has not been used in this proof, but it is obviously satisfied by the results. It can also be shown that the equivalence between the deuterium contents of the ions and molecules holds, even when the system has not reached equilibrium.

In the case of water as solvent, a general treatment on these lines would be more complex, but it is clear that the same proof will approximately apply in the case of dilute deuterium water.

We now analyse the vinylacetic acid results. The processes which occur in the system may be symbolised by means of the following scheme :

$$\begin{aligned}&\mathrm{A} \longrightarrow \mathrm{B}, \text{ with velocity const. } k_1\\ &\mathrm{A} \longrightarrow \mathrm{C}, \text{ with velocity const. } k_2\\ &\mathrm{B} \longrightarrow \mathrm{D}, \text{ with velocity const. } k_3\end{aligned}$$

where A is " light " vinylacetic acid, B is vinylacetic acid in deuterium equilibrium with the solvent, C is crotonic acid produced by isomerisation of A (and therefore deuterated in the γ-position only), D is crotonic acid produced by isomerisation of B, and k_1, k_2, and k_3 are the respective pseudo-unimolecular velocity constants of these reactions.

It can be shown as follows that k_2 and k_3 are identical. Hydrogen, or deuterium, will add on to the ion $\mathrm{CH_2{=}CH{-}\bar{C}H{-}CO_2H}$ at exactly the same rate as it adds on to the ion $\mathrm{CH_2{=}CH{-}\bar{C}D{-}CO_2H}$; there is no reason to suppose that the initial presence of deuterium in an ion, instead of hydrogen, in any way affects the subsequent addition of hydrogen or deuterium. The rate of disappearance of " heavy " vinylacetic acid is therefore identical with the rate of disappearance of " light " vinylacetic acid, *i.e.*, $k_2 = k_3$, and the remaining system of vinylacetic acid remains unaltered in its " deuterium specification " whilst decreasing in size. Further, in the scheme

$$\beta\gamma\text{-molecules} \rightleftharpoons \text{ions} \longrightarrow \alpha\beta\text{-molecules}$$

the second stage is to all intents and purposes irreversible (see preceding paper) and is the rate-controlling step of the isomerisation; k_2 may therefore be equated to the experimentally determined rate of isomerisation.

The quantities k_1, f_1, and f_2 can now be calculated as follows. Let a = initial concentration of A, y = concentration of A at time t, and x = concentration of B at time t. Then the rate of loss of A is given by

$$dy/dt = k_1y + k_2y \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (13)$$

$$\therefore\ y = a\mathrm{e}^{-(k_1+k_2)t} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (14)$$

and the rate of formation of B by

$$dx/dt = k_1y - k_2x = k_1a\mathrm{e}^{-(k_1+k_2)t} - k_2x \quad . \quad . \quad . \quad . \quad . \quad . \quad (15)$$

$$\therefore\ dx/dt + k_2x = ak_1\mathrm{e}^{-(k_1+k_2)t} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (16)$$

Multiplying both sides by e^{k_2t}, we obtain,

$$(dx/dt)\mathrm{e}^{k_2t} + k_2x\,.\,\mathrm{e}^{k_2t} = ak_1\mathrm{e}^{-k_1t} \quad . \quad . \quad . \quad . \quad . \quad . \quad (17)$$

or

$$(dx/dt)\mathrm{e}^{k_2t} + x[d(\mathrm{e}^{k_2t})/dt] = ak_1\mathrm{e}^{-k_1t}$$

The left-hand side of this equation is now a perfect differential: integrating, we obtain $x\,.\,\mathrm{e}^{k_2t} = -a\mathrm{e}^{-k_1t} + I$, where I is an integration constant which can be evaluated, since when $t = 0$, $x = 0$; therefore

$$x = a\mathrm{e}^{-k_2t}(1 - \mathrm{e}^{-k_1t}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (18)$$

The further quantities required are the concentrations of C and D. Let these have the values m and n respectively at time t. Then the rate of formation of C is given by

$$dm/dt = k_2y = k_2a\mathrm{e}^{-(k_1+k_2)t} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (19)$$

and on integration we obtain

$$m = ak_2[1 - \mathrm{e}^{-(k_1+k_2)t}]/(k_1 + k_2) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (20)$$

The concentration of (C + D) at time t is clearly given by

$$m + n = a(1 - e^{-k_2 t}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (21)$$

and hence,

$$n = a(1 - e^{-k_2 t}) - ak_2[1 - e^{-(k_1 + k_2)t}]/(k_1 + k_2) \quad . \quad . \quad . \quad . \quad (22)$$

Equations (18), (20), and (22) provide a means of calculating the concentrations of B, C, and D at time t in terms of k_1 and k_2; k_1, the velocity constant of the exchange reaction of vinylacetic acid, is unknown, but may be estimated in the following way. At any time, the deuterium in the mixed solute (expressed in terms of exchange numbers) will be arranged thus:

$$\begin{cases} 2xf_2/f_1 \text{ atoms in } x \text{ mols of B} \\ m/f_1 \text{ atoms in } m \text{ mols of C (in the } \gamma\text{-position)} \\ nf_2/f_1 + n/f_1 \text{ atoms in } n \text{ mols of D (in the } \alpha\text{- and } \gamma\text{-positions, respectively)} \end{cases}$$

The sum of these quantities may be equated to the total exchange number, determined experimentally:

$$2xf_2/f_1 + m/f_1 + nf_2/f_1 + n/f_1 = E \quad . \quad . \quad . \quad . \quad . \quad (23)$$

and hence

$$(m + n)/E = f_1 - f_2(2x + n)/E \quad . \quad . \quad . \quad . \quad . \quad . \quad (24)$$

Since f_1 and f_2 are constants (cf. Ingold, de Salas, and Wilson, *loc. cit.*), this expression must be linear, and we therefore choose the value of k_1 which satisfies this condition.

FIG. 1.

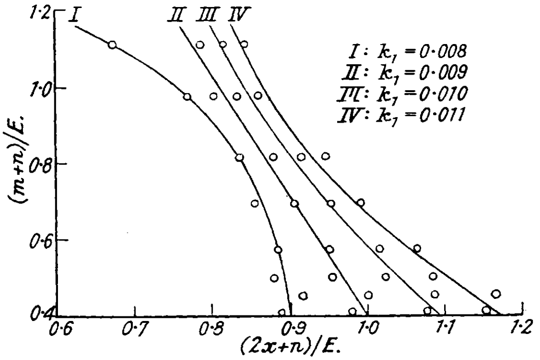
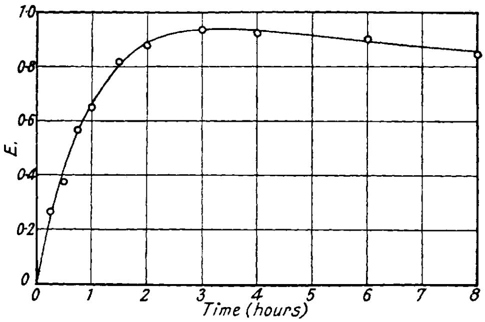


FIG. 2.



Values of $(m + n)/E$ and $(2x + n)/E$ have been calculated for $k_2 = 0{\cdot}0058$ (see Table I) and for various assumed values of k_1 and are plotted in Fig. 1. The first two experimental points have been neglected owing to the greater probable error in the time factor.

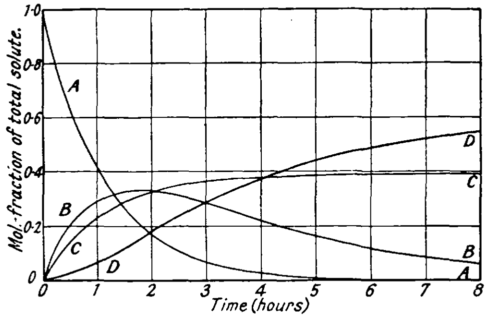
The value $k_1 = 0{\cdot}009$ has been selected as giving the best straight line, although the error in this estimation may be ± 0·001. The method of least squares then gives the values $f_1 = 3{\cdot}55$, $f_2 = 3{\cdot}15$, and hence $f_2/f_1 = 0{\cdot}89$. In order to check these results, theoretical exchange numbers have been calculated and compared with the observed values: this comparison is shown in Table II and graphically in Fig. 2, where the continuous line indicates the theoretical values and the circles the experimental values. The agreement is evidently well within experimental error over the whole range.

TABLE II.

Time, mins.	15	30	45	60	90	120	180	240	360	480
E, calc.	0·234	0·416	0·556	0·664	0·806	0·884	0·937	0·933	0·891	0·859
E, obs.	0·265	0·376	0·563	0·649	0·814	0·877	0·934	0·921	0·900	0·847
Diff. $\times 10^3$	+31	−40	+7	−15	+8	−7	−3	−12	+9	−12

It is of interest to plot the changing amounts of the various species during the course of the isomerisation and exchange reactions, as an aid to visualising the course of events: this has been done in Fig. 3, in terms of mol.-fractions of the total solute.

FIG. 3.



A = " *light* " *vinylacetic acid.*
B = *vinylacetic acid in deuterium equilibrium with solvent.*
C = *crotonic acid from isomerisation of* A (*deuterated in γ-position only*).
D = *crotonic acid from isomerisation of* B.

EXPERIMENTAL.

Preparation of Materials.—Vinylacetic acid was prepared by Linstead, Noble, and Boorman's method (J., **1933**, 560) and redistilled before use, b. p. 79°/20 mm. (Found: equiv., by titration, 86·1. Calc.: 86·05). The other materials were prepared exactly as described in the previous paper.

Equilibration Experiments.—The exchange experiments and isotopic analyses of solvents and solutes were performed as described in the previous paper. For the estimation of isomerides, a separate series of equilibrations in a solvent of normal isotopic composition was carried out under closely similar conditions: it was assumed that the alteration in the rate of isomerisation due to the presence of 2·5% of deuterium oxide in the solvent would be negligible. The mixed acids were isolated in the usual manner and analysed by the bromometric method of Linstead and Noble (J., **1934**, 617), a reference curve being obtained from synthetic mixtures of the pure isomerides.

The author wishes to record his thanks to Prof. S. Sugden, F.R.S., Prof. C. K. Ingold, F.R.S., and Dr. C. L. Wilson for helpful discussions, and to Dr. H. N. Rydon for help and advice in connexion with the experimental work.

BIRKBECK COLLEGE, LONDON, E.C. 4.

[*Received, October* 20*th*, 1937.]