Abstract:-

The equilibrium set up between the different forms of four related acids, benzylmalonanilic acid I, benzylmalon-c-toluidic acid II, N-ethyl-benzylmalonanilic acid III and benzylmalonpiperidinic acid IV, (optically unstable by virtue of a keto-enol group in the molecule) has been investigated by kinetic and other means, in presence of basic reagents of varying strength from weakly basic alkaloids, pyridine, ammonia, piperidine to sodium and potassium hydroxides, in non-hydroxylic and hydroxylic solvents.

The acids I, II and IV, were prepared by a modification of Chattaway's method for malonanilic acid (J., 1910, 27 649). III could not be prepared by this method and with considerable difficulty a successful synthesis was worked out in 3 stages from ethyl cyanacetate as follows:-

\[ \text{CN} \cdot \text{CH}_2 \cdot \text{CO}_2\text{Et} \rightarrow \text{CN} \cdot \text{CH}_2 \cdot \text{CONPhSt} \rightarrow \text{CNCH}_2\text{PhCONPhSt} \rightarrow \text{CO}_2\text{HCH}_2\text{PhCONPhSt} \]

The existence of cyclic in addition to acyclic structures was made evident by the isolation from each acid of a covalent sodium salt, cyclic and acyclic forms from one diastereoisomeride are associated with opposite signs of rotation, the predominance of either form depending on (1) the nature of the solvent and (2) the base forming the salt.

Second order asymmetric transformation was observed for the acids I and II. The absence of demonstrable first order asymmetric transformation is attributed to the existence of stable optically
inactive end intermediates which, in this case, is the determining factor in the establishment of equilibrium.

The acids III and IV containing tertiary nitrogen differ in properties from I and II. No optically activity has yet been detected. It is suggested that this fact, together with the observed difficulty of salt formation and ease of solubility in chloroform indicates an increased tendency of these acids to exist in the cyclic form.
STUDIES IN ASYMMETRIC TRANSFORMATION.

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(New compounds have been underlined throughout).

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I. INTRODUCTION, INCLUDING PREVIOUS WORK.

The definition of and inter-relation between first- and second-order asymmetric transformation has been given by Jamison and Turner (J., 1942, 437) as follows:

"A configuratively unstable substance in solution (or in the liquid state) consists of equal quantities of the $\delta$- and the $l$- form. On addition of a second (but optically stable) $\delta$ (or) $l$- compound which combines with the first substance to form a pair of diastereoisomerides, an equilibrium is set up in which one diastereoisomeride predominates to a greater or less extent. The setting up of this equilibrium we have called a first-order asymmetric transformation, and our definition agrees with Kuhn's (Ber., 1932, 65, 49) in so far as it recognises the necessity of the second, optically stable, substance for the retention of optical activity in the configuratively unstable compound. Only in very rare instances will first-order asymmetric transformation approach complete change into one or other diastereoisomeride, because of the small energy differences controlling these processes in general.

"On the other hand, second-order asymmetric transformation, in any case in which interconversion of diastereoisomerides is possible (first-order transformation) and crystallisation can be induced, may be expected to be almost
quantitatively realisable, and to give one diastereoisomeride in the optically pure, crystalline condition. That the optical activity of the configuratively unstable compound when this is removed from combination with the optically stable substance, should be detectable by a physical measurement, is immaterial for the purpose of definition of terms, although it was mainly on this arbitrary point that Kuhn based his distinction between the two types of transformation."

The first record of a first order asymmetric transformation, although it was not then recognised as such, was provided by the observation of Read and McMath (J., 1925, 127, 1572) that after equilibrium had been established between 1-hydroxyhydrindamine and chlorobromomethane sulphonic acid in acetone solution the equilibrium mixture contained 81% of base-1-acid and 19% of base-d-acid.

Mills and Elliot (J., 1928, 1291) observed a mutarotation when one equivalent of brucine was added to a chloroform solution of dl-N-benzenesulphonyl-8-nitro-1-naphthylglycine and further that a small excess of acid increased the amount of change. They also obtained with this acid an asymmetric transformation of the second-order. Out of acetone solution almost complete separation of the sparingly soluble brucine-1-acid salt occurred, and from a solution of this salt in methyl alcohol, the brucine-d-acid
salt separated after a few minutes, being sparingly soluble in the second solvent.

Other examples of first order asymmetric transformations have been given by Jamison and Turner (J., 1938, 1646; 1940, 264) in carboxylic acids of suitably substituted N-benzoyl-diphenylamines: compounds owing their optical activity to restricted rotation within the molecule.

Many examples of second order asymmetric transformations have been recorded in the literature since Pope and Peachey (Proc. Chem. Soc., 1900, 16, 12, 42, 46) found that methylethylpropyltin camphor- and bromocamphorsulphonates separated as the d-d salts only, even on evaporation of the mother liquor. This is an example of optical instability due to the ease of racemisation of the metal complex.

Mills and Bain (J., 1910, 97, 1866) obtained from cyclohexanone oxime-4-carboxylic acid the morphine-d-salt only from ethyl alcohol, and the quinine-l-salt only from the same solvent. A similar result was published by the same authors (J., 1914, 105, 64) for the benzoylphenylhydrazone of cyclohexanone-4-carboxylic acid.

Werner (Ber., 1912, 46, 3061) found that only one form of the salt $\text{Cr} (\text{C}_2\text{O}_4)_3 K$ (Base H)$_2$ separated from dilute alcohol on addition of strychnine to potassium dihydrogenchromoaxalate $\text{K} H_2\text{Cr} (\text{C}_2\text{O}_4)_3$, and from water
only one form of the salt $\text{Cr} \left( \text{C}_2\text{O}_4 \right)_3 \cdot 7 \text{ (Base H)}_3$. A similar result was recorded by Thomas (J., 1921, 119, 1140) for $\alpha$-phenylethylamine and $\text{H}_3\text{Fe} \left( \text{C}_2\text{O}_4 \right)_3 \cdot 7$.

Two acids in which the mechanism for the interconversion of the diastereoisomeric salts was dependent on a keto-enol change were examined by Leuchs (Ber., 1913, 46, 2420; 1921, 54, 830). 2-α-Carboxybenzylhydridone

\[
\begin{align*}
\text{CH}_2 \text{CH}_2 \text{CO} \quad \text{CH}_2 \text{CH}_2 \text{COH}
\end{align*}
\]

crystallised as a brucine salt from acetone in 94% yield of base-α-acid. Leuchs obtained the free acid by decomposing the brucine salt in chloroform solution with dilute sulphuric acid, and showed that the free acid racemised very slowly in chloroform and very rapidly, as would be expected, in neutral or alkaline aqueous solution. He also prepared the bromo-compound,

\[
\begin{align*}
\text{CH}_2 \text{CH}_2 \text{CBr} \quad \text{CH}_2 \text{CH}_2 \text{COH}
\end{align*}
\]

in which there is no mechanism for the interconversion of the salts, and showed that this compound was optically stable.

The asymmetric transformation of 2-α-carboxybenzyl-
hydrindone proceeds through the optically inactive enolic form. The equilibrium may be represented.

The rate of the transformation must be dependent on the rate of the keto-enol change.

The second acid examined by Leuchs, 2-keto-1;2;3;4-tetrahydroquinoline-3-carboxylic acid,

and first prepared by Reissert (Ber., 1896, 29, 665) was found to separate from methyl alcohol as the quinidine-d-acid salt only. The free d-acid was obtained and its racemisation observed in acetic acid solution. Here again the mechanism for the interconversion of the diastereoisomerides is the formation of an intermediate optically inactive enolic form.
Leuchs also drew attention to the fact that a second enolic form was possible owing to the mobility of the hydrogen atom attached to the nitrogen giving the lactim.

\[
\text{\begin{align*}
\text{\includegraphics[width=0.2\textwidth]{leuchs.png}}
\end{align*}}
\]

Since the asymmetry of the carbon atom was preserved Leuchs dismissed this change as unimportant and not contributing to the transformation of \( \alpha \) acid into \( \delta \) acid. Nevertheless although it does not influence the amount of the change, quite clearly it may influence the rate of the change. Preventing the formation of the lactim by methylation might increase the rate of racemisation of the acid.

Examples of second order asymmetric transformations of substances owing their asymmetry to restricted rotation within the molecule are now fairly numerous.

Meisenheimer and Beisswenger (Ber., 1932, 65, 32) obtained the brucine-\( \alpha \)-acid salt only from ethyl hydrogen 1:1'-dinaphthyl-8:8'-dicarboxylate from ethylacetate solution.

\[
\text{\begin{align*}
\text{\includegraphics[width=0.2\textwidth]{meisenheimer.png}}
\end{align*}}
\]

Yuan and Adams (J. Amer. Chem. Soc. 1932, 54, 2960, 4430) found that both brucine and cinchonidine in ethyl
alcohol gave the base-l-acid salt with 2,5-dimethoxy-2' -nitrodiphenyl-6'-carboxylic acid.

Similarly with

\[
\begin{align*}
R &= \text{Me, Cl, Br or NH}_2 \\
\end{align*}
\]

only one brucine salt was obtained.

Meisenheimer, Theilacker and Beisswenger (Annalen, 1932, 495, 249) from the β-oxime of 2-hydroxy-1-acetyl-naphthalene-3-carboxylic acid obtained the base-l-acid salt only with brucine in methyl alcohol. With conine in general the base-l-acid salt was obtained but on one occasion the base-d-acid salt separated. The normal relationship being superseded by the chance crystallisation of this form.

Mills and Kelham (J., 1937, 274) obtained only one brucine salt from N-acetyl-N-methyl-p-toluidine-3-sulphonic acid.
They observed that the mutarotation of the brucine salt in chloroform solution obeyed the first order law.

Jamison and Turner (loc. cit.) obtained N-benzoyl-4:6:4'-tribromodiphenylamine-2-carboxylic acid as the cinchonidine-\(d\)-salt from warm acetone.

Substantial evidence of a qualitative nature has therefore accumulated concerning the phenomenon of asymmetric transformation, but the first quantitative study was undertaken by Jamison and Turner (loc. cit.) in an attempt to define the conditions under which it takes place and to obtain an insight into the mechanism. These authors examined kinetically the attainment of equilibrium between base-\(l\)-acid and base-\(d\)-acid cinchonidine salts of N-benzoyl-4:6:4'-tribromodiphenylamine-2-carboxylic acid in chloroform solution, and the effect on the attainment of equilibrium of an excess of the racemic acid.

It was confirmed that the velocity constants for approach to equilibrium for the diastereoisomerides in chloroform solution were slightly different.

\[
\text{base } \text{d acid} \xrightleftharpoons{k_1 \quad k_2} \text{ base } \text{l acid}
\]

\[k_1 + k_2 = 0.0206 \text{ (Min}^{-1}; \log_{10}. \text{ These units are used throughout). Measured for the cinchonidine-}d\text{-salt at } 18^\circ.\]

From the difference in specific rotation due to optical activation between the value for the partial racemate
and that for the equilibrium mixture the equilibrium constant \( K \) was found to be 1.035 at 18\(^{\circ}\). Whence, since \( K = \frac{k_1}{k_2} \), \( k_1 = 0.0105 \) and \( k_2 = 0.0101 \).

The effect of an excess of \( \text{dl} \) acid has been shown to increase the rate of transformation, and either to accentuate or reverse the amount of the change occurring when the acid:base ratio is 1:1. This led to the development of a new method for the detection, by means of addition curves, of potential optical activity even of a highly unstable kind.

Thus the mobility of the system or the rate at which asymmetric transformation occurs depends on the sum of \( k_1 \) and \( k_2 \) while the extent to which it occurs depends on the difference between \( k_1 \) and \( k_2 \).

Attention was also drawn to the importance of the solvent, since the diastereoisomerides formed by an optically stable base \( R_3N \) and an optically unstable acid \( HA \) probably exist as individuals in non-ionic forms \( R_3N \ldots H \ldots A \) in non-hydroxylic solvents, but chiefly as the ions \( R_3NH \ldots O^+ \) \( dA \) and \( lA \) in hydroxylic solvents. Therefore first-order asymmetric transformation should occur more extensively in non-hydroxylic solvents, although second-order asymmetric transformation may take place in either. This was found to be the case.
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The present work was undertaken with a view to obtaining kinetic measurements in asymmetric transformations dependent on a mechanism different from restricted rotation, since the position of equilibrium of a system depends only on the relative free energies of the components and is independent of the mechanism of interconversion between them.

It was first planned to examine 2-keto-1:2:3:4-tetrahydroquinoline-3-carboxylic acid obtained by Leuchs (loc. cit.) since an asymmetric transformation of the second order had already been observed by him in this case. The mechanism of interconversion in this case is a keto-enol change within the molecule. But owing to the difficulty of obtaining the starting material, o-nitrobenzylchloride, combined with the low yields and insolubility of the acid, this project was abandoned. Comparison of the formulae

\[
\begin{align*}
\text{H} & \quad \text{C}^2_2 \text{CH}-\text{CO}_2\text{H} \\
\text{N} & \quad \text{H} \\
\text{C}^2_2 & \text{CH}-\text{CO}_2\text{H} \\
\text{R} & \quad \text{N} \\
\end{align*}
\]

suggests that the anilides of benzylmalonic acid might provide suitable material for investigation.

Review of the literature has shown that very little is known about the benzylmalonanilic series, and no malonanilic acids containing tertiary nitrogen have so far
been prepared.

The four related acids, benzylmalonanilic acid I, benzylmalon-0-toluidic acid II, N-ethyl-benzylmalonanilic acid III and benzylmalonpiperidinic acid IV, were prepared and examined. Details of their preparation will be given in a later section.

All four acids are potentially optically active, since each contains an asymmetric carbon atom, and are optically unstable by virtue of the possibility of tautomerism between the keto and enol forms of the acid.
In addition I and II can exhibit amido-imidol tautomerism (cf. Leuchs lactim form, loc. cit, page 6) in which the asymmetric configuration is retained.

Examples of this type of tautomerism are numerous since Baeyer (Ber., 1882, 15, 2097) isolated from isatin two isomeric methylethers corresponding to the formulae but only one form of the parent substance to which he assigned the formula. Now more probably

Pope and Whitworth (Proc. Roy. Soc., A., 1931, 134, 357) prepared spiro-5:5'-dihydantoin, which they showed was present in the ketonic form in alcohol, water and even in pyridine solutions, but in the presence of one or two
equivalents of alkali respectively, the mono- and di-enolic forms predominated.

\[ \text{HN} - \text{CO} \quad \text{NH} - \text{CO} \quad \text{CO} - \text{NH} \quad \text{CO} - \text{NH} \]

\[ \text{NH} - \text{CO} \quad \text{NH} - \text{CO} \quad \text{CO} - \text{NH} \quad \text{CO} - \text{NH} \]

The mono- and di-enolic forms had specific rotations different from that of the original keto-form. Since there is no mechanism for racemisation within the molecule, apart from ring opening and hydrolysis, which according to Pope and Whitworth does not occur in the cold, except with more concentrated caustic soda solutions, acidification should have given the keto form without loss of activity. Pope and Whitworth however did not examine this to see if it were true.

Further examples are found in $\alpha$-pyridone and $\alpha$-hydroxy pyridine,

\[ \text{NH} - \text{CO} \quad \text{NH} - \text{CO} \]

in dioxindole where again both keto-enol and amido-imidol tautomerism are possible,

\[ \text{H} \quad \text{C} \quad \text{O} \quad \text{H} \quad \text{C} \quad \text{O} \quad \text{H} \quad \text{C} \quad \text{O} \quad \text{H} \quad \text{C} \quad \text{O} \]

in uric acid and many other purine derivatives.
It is interesting to note that although amido-imidol tautomerism apparently does not occur except in the presence of strongly alkaline reagents, (pyridine in general is not sufficiently basic to induce the change, e.g. McKenzie (J., 1935, 104) observed none of the lactim form of dioxindole in presence of pyridine and see also Pope and Whitworth loc. cit. page 12) both diketopiperazine (Corey, J. Am. Chem. Soc., 1938, 60. 1598) and cyanuric acid (Wiebenga and Moerman. Z. Krist., 1938, 99, 217) have been shown to be planar, suggesting the Kekulé type of structure.

Furthermore in the benzylmalonanilic acid series ring
formation is clearly possible, but was first made evident during the present investigation by the isolation from each acid of an insoluble sodium salt which must have the structure

\[ \text{from I and II} \]

\[ \text{from III} \]

\[ \text{from IV} \]

From qualitative observation it appeared that the rate of formation of the sodium salts is roughly in the order \( IV > III > II > I \). This order corresponds with the greater basicity of the nitrogen atom in \( IV \), and hence its increased tendency to donate electrons as compared with \( I \). In each case a stable six-membered ring is formed and the structure includes a conjugated double-bond system.

The salt is written in the enolic form since on adding 1 equivalent of sodium hydroxide to an alcoholic solution of the optically active benzylmalon-o-toluidic acid, the activity of the solution immediately disappeared; on adding less than 1 equivalent the activity immediately
decreased proportionately to the amount added, and further racemisation proceeded very slowly.

Examples of other covalent sodium compounds have been given by Sidgwick, Brady and Hunter, and others.

Sidgwick (J., 1925, 127. 2381) obtained the 4-covalent sodium compounds of benzoyl- and acetyl-acetone. These compounds were easily soluble in toluene:

\[
\begin{align*}
\text{CH}_3 & \quad \text{PhCH}_2 \\
\text{HC} & \quad \text{C} \quad \text{Na} \quad \text{OH}_2 \\
\end{align*}
\]

Brady (J., 1934, 840) isolated a covalent sodium compound of 4-isonitroso-1-phenyl-3-methyl-5-pyrazolone practically insoluble in water but soluble in boiling alcohol and slightly soluble in chloroform and benzene.
Hunter (J., 1939, 484), by treating the condensation product of methylaniline and ethyl acetoacetate with caustic soda, obtained the covalent sodium compound of acetoacetmethylenilide, and similarly, using ethyl aniline, the sodium compound of acetoacetethylanilide.

\[
\begin{align*}
\text{CH}_3\text{C} & \equiv \text{C} \text{N} \text{CH}_3 \\
\text{O} & \sim \text{N} \text{Na} \text{CH}_3
\end{align*}
\]

From a consideration of the equilibrium existing in a non-hydroxylic solvent i.e. under conditions suitable for first-order asymmetric transformation, it appears that the stability of the enol intermediate is an important factor.

The equilibrium which is set up in a non-hydroxylic solvent for diastereoisomerides of the type examined by Jamison and Turner (loc. cit) can be expressed directly as below:

\[
\begin{align*}
\text{R}_3\text{N} + \text{d HA} & \rightleftharpoons K^+ \text{R}_3\text{N. d HA} \\
\text{k}^+ & \text{A} \rightleftharpoons \text{k}^- \text{A} \text{ k}^+ \text{A} \rightleftharpoons \text{k}^- \text{A} \\
\text{R}_3\text{N} + \text{l HA} & \rightleftharpoons K^- \text{R}_3\text{N. l HA}
\end{align*}
\]

\(K^+, K^-\) are the equilibrium constants as shown. It may
be assumed that the equilibrium represented by $K^+$ and $K^-$ are rapidly attained and their rate constants may be ignored.

The rate of disappearance of $R_3N$ $\perp$ HA can be expressed

$$-\frac{d[A]}{dt} = k^+_A[A] - k^+_A[A] + k^-_S[S] - k^-_S[S] \ldots \ldots (1)$$

where $A, A^+, S, S^-$ represent concentrations of the free acid and salt respectively and $k^+_a, k^-_a, k^+_s, k^-_s$ are the rate constants as shown.

The equilibrium which is set up for an acid owing its optical instability to the presence within the molecule of a keto-enol system is necessarily somewhat more complex, since interconversion between the $d$ and $l$ isomerides takes place through the intermediate enol form.

The rate of disappearance of $R_3N$ $\perp$ HA may be expressed
Two cases may be distinguished. If the difference of stability between the keto- and enol-forms is such that the enol is markedly more unstable than the keto-form, the rate determining step will be the formation of enol and its rate of decomposition may be neglected. Equation (2) reduces to

\[- \frac{d\[\hat{S}\]}{dt} = k_2^e[A] - k_4^e[E] + k_5^e[E] - k_2^a[A] + k_4^a[A] + k_5\hat{S}^e \]

\[-k^e_f[S] + k^e_g[S] - k^e_{fS}\] ............................(2)

which is identical with equation (1), so that the same results of asymmetric transformation should be realisable, the proportion of enol-form present at any stage during the establishment of equilibrium, and at its attainment, being vanishingly small.

If the enol-form has approximately the same, or greater, stability than the keto-form, the optical activity of the system will be diminished owing to the presence of a considerable proportion of the reactants in the enol-form. Since asymmetric transformation depends on the difference between \(k^e_s + k^a_{gS}\) and \(k^g_{sS} + k^a_{gS}\), it should still be observable except in the limiting case when the difference of stability is such that the acid exists almost completely
in the enol-form and the optical activity of the system as a whole at equilibrium is almost zero.

Nevertheless since the less stable keto-form will also be less soluble than the enol intermediate, in accordance with the van't Hoff-Dimroth rule, second-order asymmetric transformation is still possible provided that the solubility of one of the diastereoisomerides is sufficiently low for it to begin to crystallise.
II. DISCUSSION OF THE STEREOREMICAL PROPERTIES OF THE ACIDS OF THE BENZYLMAIONALIC ACID SERIES.

Examination of the alkaloidal salts of benzylmalonanilic acid I showed that brucine benzylmalonanilate crystallised from ethyl alcohol and from acetone in long silky needles in over 80% yield, showing either that an asymmetric transformation had occurred, or that the salt had separated as a partial racemate. A chloroform solution of the salt mutarotated in a negative direction to an equilibrium value according to the first-order law, indicating that an asymmetric transformation had taken place (Fig. I.)

![Mutarotation of Brucine β-Benzylmalonanilate in Chloroform](Fig.I)
The optically active acid was obtained by decomposing a chloroform solution of the brucine salt with hydrochloric acid at 0°, and completing the precipitation of the acid by adding light petroleum (b.p. 40-60°). The active acid was dissolved in alcohol and re-precipitated by addition of water to free it from traces of brucine. The acid so obtained was laevorotatory in ethyl alcohol and showed no tendency to mutarotate. In aqueous ammonia the rotation fell to zero in twelve hours according to the first order law. Thus although the brucine salt in chloroform solution mutarotated in a negative direction, the optically active acid isolated from it, in alcohol solution, had a negative rotation. Owing to the low solubility of the acid in chloroform it was impossible to examine it in this solvent.

Cinchonidine benzylmalonanilate separated from acetone in 90% yield. A chloroform solution of the salt mutarotated in a positive direction (Fig. II) and the optically active acid, obtained by decomposing the salt at 0° in chloroform solution, had a positive rotation in ethyl alcohol. Thus a second-order asymmetric transformation has occurred with benzylmalonanilic acid and the alkaloids brucine and cinchonidine in opposed senses, so that \(1\)-benzylmalonanilic acid was obtained from the
brucine salt and \( \delta \)-benzylmalonanilic acid from the cinchonidine salt.

![Mutarotation of Cinchonidine \( \delta \)-Benzylmalonanilate in Chloroform at 17°](image)

**Fig. II**

No first order asymmetric transformation could be observed with brucine or strychnine in acetone or dioxan solutions. Since benzylmalonanilic acid was not freely soluble in non-hydroxylic solvents, the more soluble benzylmalon-\( o \)-toluidic acid was prepared and subjected to a more detailed stereochemical investigation, in order to confirm and extend these results.
Second-order asymmetric transformation was observed with benzylmalon-o-toluidic acid and cinchonidine in acetone solution, but after allowing the salt isolated to mutarotate to equilibrium in alcohol or chloroform solutions, in each case an acid was isolated from the equilibrated salt which was optically inactive; i.e. the activity of the acid at equilibrium is indistinguishable from zero. "Activation" experiments with cinchonine, cinchonidine, quinine, quinidine and brucine in chloroform and dioxan gave negative results, i.e. no first-order asymmetric transformation was observable.

The results obtained from the racemisation experiments on the salts of benzylmalon-o-toluidic acid can only be satisfactorily explained on the assumption that the acid does actually exist in open chain or ring forms according to the nature a) of the solvent and b) of the base forming the salt. It has been observed that benzoic acid exists in the dimeric form in non-polar solvents and in the monomeric form in polar solvents such as water, ethylalcohol and formic acid, in which association with the solvent takes place (Pauling, Nature of the Chemical Bond, 307; also Lassetre Jour. Amer. Chem. Soc. 1939. 61 54 & Lassetre, Chem. Reviews 1937.)
The factors tending to overcome dimerisation in benzoic acid would also tend to prevent ring formation in benzylmalon-o-toluidic acid.

Illustration of the equilibrium possible between the different forms of the acid indicates the complexity of the system, but at the same time it shows clearly that all the possible optically inactive intermediate enol forms contain a conjugated double-bond system, and all except the first are in the form of a six-membered ring.
EQUILIBRIUM POSSIBLE BETWEEN DIFFERENT FORMS OF BENZYLMALON-O-TOLUIDIC ACID
Watson (J., 1933, 221) has pointed out that all stable enols appear to contain a system of single and double bonds, and that the system is usually terminated with the groups \( \times C = O \); \( - C = N \) or \( - C_6H_5 \), this group being separated from the hydroxyl by a conjugated system. Lowry (J., 1923, 123, 2114), from a consideration of \( \alpha \)-benzoylcamphor and \( \beta \)-bromo nitrocamphor concluded that coordination in addition to conjugation increases the stability, and Sidgwick (J., 1925, 127, 907), by considering the angles between the double and single bonds in the enols of acetoacetic ester, acetylacetone, benzoylacetone, dibenzoylmethane etc. has concluded that the six-membered ring which includes two double bonds is strainless and moreover that it has a very wide distribution. For example, it is found in the majority of mordant dyes, in the derivatives of \( \beta \)-hydroxyacetophenone,

\[
\begin{align*}
\text{CH}_3 & \quad \text{C} \\
& \quad \text{O} \\
& \quad \text{H}
\end{align*}
\]

in the mono and dioximes of \( \beta \)-diketones.

\[
\begin{align*}
R-C & \quad C \quad R' \\
& \quad \text{N} \quad \text{OH} \\
& \quad \text{H}
\end{align*}
\]

and

\[
\begin{align*}
R-C & \quad C \quad R' \\
& \quad \text{N} \quad \text{OH} \\
& \quad \text{H}
\end{align*}
\]

, in methyl salicylate.
in salicylaldehyde and many others. It will be seen that all these examples of stable six-membered rings are also examples of strong internal hydrogen bonding.

Conditions for a stable enol form can therefore be satisfied in benzylmalon-o-toluidic-acid, and since the conjugated double bond system is absent from all the optically active keto forms of the acid, it would appear that this form is less stable than the corresponding enol. This, taken in conjunction with the absence of demonstrable first-order asymmetric transformation, indicates that benzylmalonanilic acid and benzylmalon-o-toluidic acid fall into the special limiting case, and exist almost entirely in the enol form at equilibrium.

The experimental evidence that benzylmalon-o-toluidic acid and its salts exist in open chain or ring forms in different solvents is provided by the observations that the acid and its pyridine salt have a positive rotation in hydroxylic and polar solvents and racemise slowly, while the pyridine salt has a negative rotation in

\* It is being continually borne in mind, of course, that mere change in sign of rotation with change of solvent occurs for what are yet unexplained reasons.
chloroform and racemises much more quickly. The cinchonidine salt mutarotates in different directions in alcohol and in chloroform, and the addition of piperidine to the optically active acid changes the sign of rotation on the formation of a piperidine salt in alcohol.

Optically active benzylmalon-o-toluidic acid is obtained by decomposing the cinchonidine salt with formic acid and completing the precipitation by addition of water. From the equilibrium diagram (page 26) it can be seen that the optically active benzylmalon-o-toluidic acid can be formulated in six ways. The imidol forms are improbable in the absence of alkaline reagents and, although in any solvent the remaining four must all be present to some extent, the contribution of (iv) will be negligible except when the acid is ionised or present in the form of an ionised salt. Of the ring forms (ii) and (iii), (iii) is more probable than (ii) since the tendency of oxygen to donate electrons is somewhat greater than that of nitrogen, and a model of the ring (ii) containing no double bonds shows that it must be buckled unless the length of the hydrogen bond $\text{O} - \text{H}$ $\ldots \ldots \ldots \text{N}$ is not greater than 1.35 Å. Measurements of hydrogen bond lengths so far obtained are greatly in excess of this,
e.g. in the dimeride of formic acid the hydrogen bond length \( \overset{\text{O}}{\text{O}} \cdots \overset{\text{H}}{\text{O}} \) is 2.67 Å (Pauling and Brockway, Proc. Nat. Acad. Sci. 1934, 20, 336), and the rather weaker hydrogen bonds \( \overset{\text{O}}{\text{O}} \cdots \overset{\text{H}}{\text{N}} \) in urea, diketopiperazine and glycine are even longer, varying from 2.76 - 2.98 Å. The shortest hydrogen bond length so far measured is 2.54 ± 0.05 Å in potassium dihydrogen phosphate (Hendricks, Am. J. Sci. 1927, 14, 269; West, Z. Krist. 1930, 74, 306). The values so far given are all for intermolecular hydrogen bonding; the only internal hydrogen bond which has been measured is that which occurs in the phthalocyanine molecule.

Robertson and Woodward (J., 1936, 1195) found the distance \( a \) to be 2.76 Å, and the distance \( b \) involving the hydrogen
bond to be 2.65 Å. This is considerably shorter (0.73 Å) than the \( \text{N} \cdots \text{H} \cdots \text{N} \) intermolecular bond in ammonia 3.38 Å (Badger & Bauer, J. Chem. Phys. 1937, 5, 839) but the diminution is some 18-20%, not 50% as would be required for the \( \text{O} \cdots \text{H} \cdots \text{O} \) distance in ring (ii) benzylmalon-\( o \)-toluidic acid.

In formic acid solution (i) is most probable, solvation with formic acid preventing ring formation. The solid which separates from the solution may be the ring form, satisfying the van't Hoff-Dimroth rule that the less stable form separates, but unless both forms can separate as inoculable solids, in the absence of the crystalline form of the more sparingly soluble, apparent reversal of this rule may occur, especially if the solubilities are approximately the same: a false conclusion could obviously be arrived at in some cases, cf. the case stated above for the conine salt of the \( \beta \)-oxime of 2-hydroxy-1-acetynaphthalene-3-carboxylic acid (Meisenheimer, Annalen, 1932, 495, 249). On several occasions benzylmalon-\( o \)-toluidic acid separated as the inactive form, suggesting that in these experiments the solution had been inoculated with the stable enolic form, the six-ring with conjugated double bonds. It is therefore difficult to say with certainty what is the structure
of the solid separating from formic acid, although the nature of the acid in solution is fairly clear.

According to the above explanation the acid exists mainly as the open chain in formic acid solution and also in ethyl alcohol. In both these solvents the acid has a positive rotation $\alpha = 80.3^\circ$ at $18.3^\circ$ in formic acid and $[\alpha] = 56.4^\circ$ in ethyl alcohol. The acid racemised very slowly in formic acid $k$ of the order 0.00083 at $18^\circ$. (Fig. III).

In alcohol the acid is optically stable in the absence of catalysts. There is no evidence concerning the state
of the acid or its relative stability in chloroform solution in the absence of pyridine, owing to its low solubility. Although this low solubility is in fact evidence in favour of form (i) rather than (ii) for the free acid.

The pyridine salt of benzylmalon-o-toluidic acid has been examined in ethylalcohol, acetonitrile, ethyl acetate and chloroform solutions. It was insoluble in carbon tetrachloride, benzene and cyclohexane.

Additions of successive amounts of pyridine, up to one equivalent, to an alcoholic solution of the acid caused no immediate change of rotation. It is therefore reasonable to assume that no change of structure occurs on the formation of the pyridine salt. Both the undissociated salt and the acid and base ions may be present in the solution, the ionic form probably predominating, and the racemisation may be represented:-
The salt racemises very slowly \( k = 0.00043 \) at \( 25^\circ \). (Fig. IV).
In chloroform solution the pyridine salt is much more difficultly soluble and has a small negative rotation. \([\alpha] = 11.7^\circ\). There can be no association of the salt with the solvent, and the environment favours dimerisation or ring formation. A pyridine salt being formed, the acid cannot exist as a dimeride, as the carboxyl group is involved in salt formation. The association with pyridine increases the negative charge on the carboxyl oxygen and therefore increases its ability to donate electrons. The negative rotation is therefore associated with the cyclic structure and the racemisation of the salt is represented:

\[
\begin{array}{c}
\text{PhCH}_2\text{C} = \text{O} \quad \text{H} \quad \text{N} \\
\text{H} \quad \text{C} \quad \text{N} \quad \text{CH}_3 \\
\text{PhCH}_2
\end{array}
\]
The observed rate of racemisation was much greater than in alcohol. $k = 0.015$ at $25^\circ$ (Fig. V). This is attributed to the possibility of strain in the six-membered ring containing one double bond only, since this ring is found in far fewer compounds than the six-membered ring conjugated system, which we have shown earlier (pg. 27) to be almost strainless and of wide distribution. This difference of stability is demonstrated by Baker (J., 1934, 1684) in the degree of chelation of
2:4 - and 4:6-diacetylresorcinols. Chelation is much more complete in the 2:4-compound than in the 4:6-compound, where one ring contains one double bond only.

2:4-diacetylresorcinol  

4:6-diacetylresorcinol.

In acetonitrile and ethyl acetate the pyridine salt again had a positive rotation. It is therefore assumed that the open chain form is present. But since neither acetonitrile nor ethyl acetate can act as proton donors, association with the solvent is impossible and the ring form is no doubt also present to some extent. The rate constants for racemisation of the pyridine salt in acetonitrile and ethyl acetate are $k = 0.0051$ and $k = 0.0016$ at $25^\circ$ respectively. That is intermediate
between the rate constants for racemisation of the pyridine salt in alcohol and in chloroform. This would be expected if both acyclic and cyclic structures were present during the transformation (Figs. VI and VII).
RACEMISATION OF PYRIDINE SALT OF BENZYL MALON-O-TOLUIDIN ACID IN ETHYL ACETATE AT 25°C.

Fig. VII.
The piperidine salt of benzylmalon-o-toluidic acid also gave some interesting results. The salt was examined in ethyl alcohol and in aqueous solution. It could not be examined in chloroform since piperidine reacts with chloroform. From dioxan the piperidine salt crystallised, this rendering polarimetric observations impossible.

Piperidine is a much stronger base than pyridine and its salts are probably much more ionised; the tendency to ring formation which is always greater in the ionised state (Watson, Modern Theories of Organic Chemistry, 234, Baker, Nature 1936, 137, 236) will have more effect than in the pyridine salt.

Addition of successive amounts of piperidine to an alcoholic solution of the optically active acid caused an immediate linear change of the angle of rotation with each addition and finally a change of the sign of rotation from positive to negative as one equivalent of piperidine had been added. Addition of further piperidine caused no further change but the salt racemised slowly, finally becoming inactive. (Fig. VIII).
TITRATION EXPERIMENT: 4-BENZYMALON-8-TOULUIDIC ACID WITH PIPERIDINE.

Fig. VIII.
The linear change of rotation is attributed to the formation of the ring (iv) from the open chain, and the racemisation may therefore be represented

The lower rate of racemisation \( k = 0.0035 \) at 18.3 °C as compared with the pyridine salt in chloroform \( k = 0.015 \)° at 25°C may be accounted for by the increased stability of ring (iv) compared with (iii) by the contribution of the resonance energy of the system \( \text{C} = \text{O} \) to the resonance energy of the system \( \text{O} \) which is present in both, it may be due almost entirely to the difference in temperature at which the two reactions were carried out.

The rate constant for the racemisation of the piperidine salt was found to be the same for \( \frac{1}{2} \) equivalent of piperidine, 1 equivalent and just greater than 1 equivalent. (Figs. IX, X and XI).
Figure IX

Racemisation of Piperidine Salt of D-Benzylmalon-δ-toluidic Acid in Alcohol at 18.3°C

Figure IX

Racemisation of Pimidine Salt of D-Benzylmalon-δ-toluidic Acid in Alcohol at 18.3°C
The piperidine salt was also examined in an aqueous solution containing 2 equivalents of piperidine in excess. This solution is still more polar than alcohol and favours increased ionisation, but the increased tendency of water to solvate will compete with the tendency for ring formation, and the presence of the common piperidinium ion will tend to decrease dissociation. The observed rotation was positive but very small, indicating as anticipated that ring formation was incomplete. Racemisation proceeded more quickly than in the preceding experiment, with which however, it is, of course, not strictly comparable owing to the presence of 2 equivalents of piperidine in excess.

The ammonium salt was examined in aqueous solution containing 2 equivalents of ammonia in excess. The rotation of the solution was small and positive, and racemisation took place more slowly than with the piperidine salt. The ammonium salt should be less ionised and therefore there will be less of the cyclic form. In aqueous alcohol in presence of 1 equivalent of ammonia the rotation of the solution was zero. Probably the rotation was in fact very small with the open chain positive and cyclic negative rotations counteracting.

The addition of 1 equivalent of potassium or sodium.
hydroxide to an alcoholic solution of the acid caused an immediate disappearance of activity, which may be attributed to the immediate formation of the very stable ring.

Addition of \( \frac{1}{2} \) equivalent of sodium hydroxide to an alcoholic solution of the acid caused the rotation to fall in amount corresponding to the conversion of half the acid into the stable inactive ring form. The remainder of the acid must still have been present in the straight chain, and in accordance with this supposition it racemised very slowly but completely giving \( k \) of the order 0.00097 at 18°C.

For the pyridine salt in chloroform and in alcohol there was a marked induction period which was observed to a lesser extent for the pyridine salt in ethylacetate and the piperidine salt in alcohol. This may represent the rate of cyclisation or in solutions where cyclisation is less probable, the attainment of equilibrium between the amido-imidol forms which is not accompanied by loss of activity. (Fig. XIII).
INDUCTION PERIODS FOR PYRIDINE SALT OF d-BENZYLMALON-O-TOLUIDIC ACID
IN VARIOUS SOLVENTS.

Fig. XII
The mutarotation of the cinchonidine salt in different directions in alcohol and chloroform has already been mentioned. The salt mutarotated in a negative direction in alcohol corresponding to an original positive rotation of the acid, and in a positive direction in chloroform corresponding with a negative rotation of the acid, which agrees with the results already discussed. The rate of mutarotation was slightly faster in chloroform, $k = 0.0064$ at 18.3° (Fig. XIII) for alcohol $k = 0.0044$ at 18.3° (Fig. XIV).
The mutarotation of a solution of the cinchonidine salt in formic acid was also examined. This solution mutarotated extremely slowly in a negative direction of the order 0.00095 at 18°. (Fig. XV) This is a further indication that in formic acid solution the acid exists in the open chain structure.
During the course of the experiments on the cinchonidine salt it was observed that concentration had a marked effect on the specific rotation in chloroform solution. The specific rotation of the salt decreased linearly with increasing concentration over the range considered.

A complete investigation of the effect of concentration was not carried out, although it is possible that the effect of concentration on the specific rotation is due to the varying amounts of the cyclic and acyclic forms present at different concentrations. At the same time it was observed that the concentration did not affect the specific rotation of the cinchonidine salt in ethyl alcohol solution. This difference is what might be expected.
An attempt was also made to resolve benzylmalon-\(\alpha\)-toluidic acid by means of cinchonidine. The \(\text{dl}\)-acid (1 mol.) was warmed with cinchonidine (1 mol.) in acetone solution until all had dissolved and then rapidly filtered and cooled to \(-15^\circ\), and inoculated with cinchonidine \(\text{d-benzylmalon-}\alpha\text{-toluidate}\). The \(\text{d}\)-salt separated. This was rapidly filtered off through a previously cooled funnel into a flask immersed in a freezing mixture, and the filtrate evaporated in vacuo, but the salt residue was inactive. Had it been possible to carry out the whole reaction at \(-15^\circ\) without the initial warming which in this case was necessary for solution, it should have been possible to effect a resolution in this way. But the initial warming in presence of cinchonidine permits the tautomeric change to the stable enol form, and the separation of the dextro salt at \(-15^\circ\) represents an asymmetric transformation of the second-order still going on at this temperature with the salt in solution present in the inactive enol form.
Diagrammatic representation of the racemisation of salts of J-benzylmalonic-9-toluic acid in various solvents.
N-Ethyl-benzylmalonanilic acid III and benzylmalon-piperidinic acid IV, which were also prepared, differ from benzylmalonanilic acid and benzyl\textit{N}-o-toluidic acid in that both the former are extremely soluble in chloroform and other non-hydroxylic solvents, while the latter are much more difficultly soluble in chloroform and practically insoluble in carbon tetrachloride, benzene and cyclohexane.

The ease of solubility of these two acids in chloroform suggests that they are present already in the ring form. The absence of a proton attached to the nitrogen atom would, as previously suggested, page 15, increase the tendency for ring formation, by increasing the tendency of the nitrogen atom to donate electrons. In each case the optically active ring molecule contains no double bonds in the ring, it would not therefore be expected to be very stable (Sidgwick loc. cit., page 27) and the more probable ring form occurring should be the inactive enol, containing a double bond in the ring and including a conjugated system of double bonds.
Attempts have been made to prepare the brucine, strychnine, morphine, cinchonine, cinchonidine, quinine and quinidine salts of N-ethyl-benzylmalonanilic acid using as solvents in each case methyl alcohol, ethyl alcohol and acetone, and in the case of quinine and quinidine dioxan also. The brucine salt separated from acetone or alcohol only when almost all the solvent had evaporated and addition of a few drops of solvent caused it to redissolve. Quinine salts began to crystallise in fine needles from ethylalcohol and dioxan again only when practically all the solvent had evaporated. The quinine salt which had separated from alcohol was taken up in chloroform, in which it dissolved instantaneously, and examined polarimetrically. No mutarotation was observed. No mutarotation was observed on mixing equivalent proportions of the acid and cinchonidine in
chloroform solution, or on mixing the base with excess of acid.

Salt formation was found to be difficult also with benzylmalonpiperidinic acid. Attempts were made to prepare cinchonine, cinchonidine, quinine, quinidine brucine and strychnine salts of this acid, using methyl alcohol, ethyl alcohol and acetone as solvents. A cinchonidine salt m.p. 158° (decomp.) separated from acetone in small glistening needles and practically 100% yield after a few minutes, quinine and quinidine salts separated only on evaporation of the solvent and redissolved immediately on adding a few drops of solvent, and a brucine salt separated from aqueous alcohol after several weeks. Strychnine and benzylmalonpiperidinic acid crystallised separately from an alcoholic solution of both. In each case on polarimetric examination of the salts in chloroform solution, no mutarotation was observable, and again no first-order asymmetric transformation was observed with alkaloids in chloroform solution.

If in any solution most of the acid is present in the ring form this would account for the difficulty of salt formation which could occur only by the opening of the ring, or on the enolic - OH group after the keto-enol change had been catalysed by the base. Since in each
case the salts isolated showed no tendency to muta-rotate, the base apparently being combined with inactive acid, the latter explanation is the more probable. That the acids do not exist in the enolic form in the absence of a base is shown by the fact that XXX bromine is not absorbed by a chloroform solution of either acid except on prolonged standing.

From the results of the experiments on these four related acids it is concluded that, after the introduction of a substance which will permit the keto-enol change to take place within the molecule, since the stability of the inactive enol is such that at equilibrium most of the acid exists in this form, first-order asymmetric transformation takes place to such a limited extent that it cannot be detected by physical measurement, but is made a logically necessary intermediate step, by the occurrence under suitable conditions of second-order asymmetric transformation.
III. PREPARATION OF BENZYLMALONANILIC AND RELATED ACIDS.

Benzylmalonanilic acid was obtained by Dieckmann (Ber., 1904, 37, 4633) by hydrolysing the product of the condensation between benzylacetoacetic ester and phenyl-carbimide. He described the acid as a substance crystallising from alcohol and decomposing on heating to give -phenylpropionanilide m.p. 97°. This result was confirmed in the present work.

It was found that benzylmalonanilic acid could be prepared easily and in a workable yield by adapting the method employed by Chattaway (J., 1910, 27, 940) for malonanilic acid, i.e. by heating ethyl benzylmalonate (1½ mol.) with aniline (1 mol.), separating the mono- and di-anilides so formed by making use of their different solubilities in alcohol, and saponifying the monoanilide ester with sodium carbonate.

\[
\begin{align*}
\text{PhCH}_2\text{C} & \text{CO}_2\text{Et} + \text{PhNH}_2 \rightarrow \text{PhCH}_2\text{C} & \text{CO}_2\text{Et} + \text{PhCH}_2\text{C} & \text{CONHPh} \\
\text{CO}_2\text{Et} & \text{CONNHPh} & \text{CONHPh} & \text{CONHPh}
\end{align*}
\]

40% of the aniline was converted into the mono-anilide and 60% into the dianilide.

On addition of caustic soda to the acid, an
insoluble covalent sodium salt was precipitated, which crystallised from water in long beautiful needles and melted with decomposition on heating to 220°. It is given the structure previously described (page 15)

Benzylmalon-o-toluidic acid was prepared in a similar way by heating ethyl benzylmalonate (1 1/2 mol.) with o-toluidine (1 mol.) Both benzylmalon-o-toluidic acid and benzylmalondi-o-toluidide were formed.

Benzylmalon-o-toluidic acid crystallised from alcohol in colourless needles m.p. 154° (decomp.) (uncorr.) It is considerably more soluble in alcohol than
benzylmalonanilic acid and dissolves easily also in acetone, dioxan and ethyl acetate solutions.

With caustic soda benzylmalon-0-toluidic acid also formed a covalent sodium salt, which crystallised from water in flattened needles melting with decomposition on heating to 238°.

It was with considerable difficulty that a successful synthesis was worked out for N-ethyl benzylmalonanilic acid. It was found that the acid could not be made by Chattaway's method. The only product isolated on heating ethyl|benzylmalonate with methyl aniline or ethyl aniline was 2:4-diketo-3-benzyl-1-methyl-1:2:3:4-tetrahydroquinoline and the corresponding ethyl compound respectively, ring closure having taken place with elimination of a second molecule of alcohol.
Although the reaction should take place in two stages, it was not found possible to isolate any of the intermediate compound. On lowering the temperature no reaction at all took place even on prolonged heating.

Reissert (Ber., 1892, 25, 1193) obtained 2:4-diketo-1-methyl-1:2:3:4-tetrahydroquinoline by heating ethylmalonate with methylaniline for seven hours and distilling off the alcohol formed during the reaction.

The presence of the benzyl group no doubt facilitates ring formation which occurred much more easily in the former than in the latter case. In fact in this latter case it was found possible to isolate small amounts of the intermediate compound by heating ethylmalonate in very large excess with methylaniline for 12 hours at a temperature not exceeding 120°. The unchanged ester and methylaniline were removed by distillation in vacuum and a fraction b.p. 165° was obtained. Considerable decomposition occurred during the distillation. The ester was hydrolysed with 10% aqueous caustic soda, and on acidifying
the product with hydrochloric acid, an acid slowly separated, which crystallised from alcohol in colourless needles m.p. 120° (decomp. uncorr.) The decomposition product solidified and was identified as acetophenyl-
methylamide, m.p. 101-102°.

\[
\begin{align*}
\text{CH}_2\text{CO}_2\text{H} & \quad \longrightarrow \quad \text{CH}_3\text{CONPHMe} + \text{CO}_2 \\
\text{CONPHMe} &
\end{align*}
\]

Direct methylation of benzylmalonanilic ester immediately gave rise to the difficulty that the product of the reaction might be benzylmethylmalonanilic acid.

\[
\begin{align*}
\text{PhCH}_2\text{COCl} & \\
\text{PhCH}_3\text{CONNHPh} &
\end{align*}
\]

Since the preparation of di-substituted malonic esters occurs most readily in absolute alcohol, (no methylation of ethyl benzylmalonate takes place in diluted alcoholic solution to which one part by volume of water has been added to ten parts by volume of ethylalcohol) methylation on the nitrogen atom was attempted in this strength of alcohol, using metallic sodium and methyl iodide. No methylation occurred, the unchanged benzyl-
malonanilic ester being identified by saponification to benzylmalonanilic acid.

Benzylmalonic ester-chloride \[
\begin{align*}
\text{PhCH}_2\text{COCl} & \\
\text{H} & \quad \text{CO}_2\text{Et}
\end{align*}
\] was
considered as an intermediate product which with methyl-
laniline should give the required acid. Marguery
(Bull. Soc. chim. 1905, 33. 551) obtained from ethyl
hydrogen benzylmalonate
by thionyl chloride only
sufficient ester-chloride to permit of its identifica-
tion as the amide

The very low rate of reaction of thionyl chloride with
malonic acid itself was noted by Staudinger and Beretza
(Ber., 1908, 41, 2209). The ester-chloride did not
therefore seem to be a very satisfactory or practical
route to the substituted benzylmalonanilic acid, and none
of the acid could be isolated after addition of methyl-
aniline to the product from thionyl chloride and the
ester-acid.

Ethyl β-phenylpropionate and methylethylphenyl-
carbamate were mixed in absolute ether in presence of
powdered sodium in the cold, i.e. under conditions which
favour Claisen condensation between two esters.
The reaction gave an indeterminate result: no N-ethylbenzylmalonanilic ester was obtained, and the remainder of the materials formed a jelly from which no chemical individual could be isolated.

Under similar conditions, ethyl carbonate and \( \beta \)-phenylpropionophenylethylamide were mixed in presence of powdered sodium.

\[
\begin{array}{c}
\text{PhCH}_2\text{CHCONPhEl} \\
\text{CHCONPHEl}
\end{array}
\quad \rightarrow \quad
\begin{array}{c}
\text{PhCH}_2\text{CHCONPhEl} \\
\text{COOEt}
\end{array}
\]

\( \beta \)-Phenylpropionophenylethylamide was prepared by the action of ethyl aniline on \( \beta \)-phenylpropionylchloride. No condensation occurred between the two esters and the starting materials were recovered unchanged.

Interaction between phenylethylcarbamyl chloride and ethylsodiomalonate also gave an undesired result, for although sodium chloride was formed the products isolated were ethyl malonate and ethyl aniline. The extension of this synthesis to the benzyl series was therefore not attempted.

Finally N-ethyl-benzylmalonanilic acid was successfully synthesised in three stages from ethylcyanoacetate:

(1) Ethyl cyanoacetate was converted into cyanoacetophenylethylamide by heating ethylcyanoacetate with
ethylanilide (Guareschi, *Atti R. Accad. Scienze Torino*, XXVII),

\[
\text{CNCH}_2\text{CO}_2\text{Et} + \text{PhEtNH} \rightarrow \begin{array}{c}
\text{CH}_2 \\ \text{CN} \\
\text{CONPhEt}
\end{array}
\]

(2) Cyanoacetphenylethylamide was converted into benzylcyanoacetphenylethylamide by the action of benzyl chloride on the sodium derivative of cyanoacetphenylethylamide in absolute alcohol.

\[
\begin{array}{c}
\text{CH}_2 \ \ \text{CN} \\
\text{CONPhEt}
\end{array} \xrightarrow{\text{NaOEt}} \begin{array}{c}
\text{PhCH}_2 \ \ \text{CN} \\
\text{CONPhEt}
\end{array}
\]

Benzylcyanoacetphenylethylamide was obtained highly crystalline in 93% yield, and separate from ethylalcohol in white needles m.p. 112° (uncorr.)

(3) *N*-Ethyl-benzylmalonanilic acid was obtained by partial hydrolysis of benzylcyanoacetphenylethylamide with alcoholic caustic potash.

There are six possible products of the hydrolysis:
Benzylmalonic acid (5) can be removed easily as it is very soluble in water. The unchanged starting material (6) was insoluble in alkali and so removed by extracting the product in alkaline solution with ether (2) (3) and (4) did not appear to be present in any appreciable amount from the amount of ammonia evolved during the hydrolysis, and N-ethyl-benzylmalonanilic acid was obtained from the aqueous layer after removing traces of ether — by acidifying with HCl.

N-Ethyl-benzylmalonanilic acid was found to be extremely easily soluble in most organic solvents other than light petroleum. It crystallised with difficulty as rhombohedra m.p. 106-107 (decomp.) (uncor.) from a mixture of CCl₄ and light petroleum (b.p. 60-80°C).

On addition of sodium hydroxide N-ethyl-benzylmalonanilic acid forms a sodium salt sparingly soluble in cold water, and crystallising in glistening plates on cooling a solution in hot water. It is immediately melts soluble in benzene, and with decomposition on heating to 180°C. As for the other covalent sodium salts formed in this series the structure suggested is

```
PhCH₂ — C — O
\   \  \  \  \  \\
|  N—Et | OH₂
\  \  \  \\
|  OH   | Ph
```

The determined sodium content indicated the presence of 10 molecules of water. A specimen of the salt was weighed immediately after re-crystallisation from water, and left in a vacuum desiccator over magnesium perchlorate for 2 days. The loss in weight corresponded to $8\text{H}_2\text{O}$, the last 2 molecules were apparently held in different combination from the other 8. This confirmed the constitution suggested. (0.5579 g. of salt lost 0.1650 g. $\text{H}_2\text{O}$ i.e. 148 g. of $\text{H}_2\text{O}$. $\text{C}_{18}\text{H}_{18}\text{O}_3\text{Na. }10\text{H}_2\text{O}$ requires a loss of 144 g. for 8 $\text{H}_2\text{O}$).

It may be noted that in addition to the potentially asymmetric carbon atom, the asymmetry of which is destroyed by the keto-enol change, this sodium salt contains an asymmetric nitrogen atom, possessing the same type of asymmetry as in the amine oxides.

![Diagram of the compound](image)
Attempts were also made to prepare N-methyl-benzylmalonanilic acid. Cyanoacetphenylmethylamide was prepared by the method of Guareschi (loc. cit. p. 64). But on treating this compound with benzylchloride in the presence of sodium ethoxide, a mixture of unchanged cyanoacetphenylmethylamide and mono- and dibenzylcyanoacetphenylmethylamide resulted, from which the dibenzyl-derivative could be separated by crystallisation from benzene, but the unchanged cyanoacetphenylmethylamide and benzylcyanoacetphenylmethylamide formed a 1:1- mixture which melted sharply at 98°, and could not be separated by fractional crystallisation from alcohol, benzene or glacial acetic acid.

An alternative method was then attempted according to the following scheme:-

\[
\text{PhCHO} + \text{CH}_2\text{CN} \rightarrow \text{PhCH} = \text{C} \text{CN} \rightarrow \text{PhCH} = \text{C} \text{CONPhMe} \rightarrow \text{PhCH} \text{CH}_2 \text{CO}_2\text{H}
\]

**Benzylidene cyanooacetphenylmethylamide** was prepared by a Knoevenagel condensation between benzaldehyde and cyanoacetphenylmethylamide in presence of a trace of piperidine. When the condensation was carried out using equivalent quantities of benzaldehyde and cyanoacetphenylmethylamide. The product was \(\beta\)-phenyl-\(\alpha\)-
dicyanoglutaridiphenylmethyamide, one molecule of benzaldehyde condensing with two molecules of the nitrile.

\[
\text{PhCHO} + \text{HCN} \rightarrow \text{PhCH} = \text{CN}
\]

On hydrolysing with 70% sulphuric acid \(\beta\)-phenylglutaric acid \(\text{CO}_2\text{H} \cdot \text{CH}_2 \cdot \text{CHPh} \cdot \text{CH}_2 \cdot \text{CO}_2\text{H}\) m.p. 138° (Knoevenagel Ber., 1902, 35, 393) was obtained. The condensation was therefore carried out in presence of excess benzaldehyde. The excess subsequently being removed by vacuum distillation and benzylidenecyanoacetphenylmethyamide resulted in 93% yield.

On attempting to hydrolyse benzylidenecyanoacetphenylmethyamide with alcoholic potassium hydroxide, an acid was obtained which has not yet been identified, but which was not the required N-methyl-benzylidene-malonanilic acid. The acid was crystallised from glacial acetic acid in yellow prisms m.p. 180° (decomp.) (uncorr.) The decomposition product solidified and re-melted at 145°.
N-Methyl-β-phenylethylmalonanilic acid was obtained in very small yield by condensing β-phenylethyl bromide with cyanoacetphenylmethylanilide in absolute alcoholic solution in presence of sodium ethoxide, followed by partial hydrolysis of the product.

\[
\text{PhCH}_2\text{CH}_2\text{Br} + \text{CH}_2\text{CN} \underset{\text{PhCH}_2\text{CH}_2\text{CN} \rightarrow \text{PhCH}_2\text{CH}_2\text{CO}_2\text{H}}{\text{abs. alcoholic soln.}} \text{CONPhMe} 
\]

But the β-phenylethylcyanoacetphenylmethylamide was not obtained pure. It could not be crystallised even on cooling to \(-15^\circ\), probably owing to the presence of considerable amounts of unchanged material. It was therefore impossible to calculate the exact amount of potassium hydroxide necessary to hydrolyse the nitrile group only, and in fact it proved impossible to control the hydrolysis. Several products in addition to the required acid were isolated, showing that the anilide group as well as the nitrile underwent hydrolysis.

An acid obtained m.p. 130° (decomp.) was identified with β-phenylethylmalonic acid \(\text{PhCH}_2\text{CH}_2\text{CO}_2\text{H}\) (Fischer, \textit{Ber.}, 1906, \textit{39}, 2211).

The decomposition product γ-phenylbutyric acid \(\text{PhCH}_2\text{CH}._2\text{CO}_2\text{H}\) re-melted at 51° (Semmler \textit{Ber.}, 1906, \textit{39}, 726).

Also β-phenylethylmalonamic acid \(\text{PhCH}_2\text{CH}_2\text{CONH}_2\) m.p. 144° (decomp.) (uncorr.) was isolated,
the decomposition product re-melting at 83° was identified with \( \gamma \)-phenylbutyramide \( \text{PhCHCH}_2\cdot\text{CONH}_2 \) (Willqrodt, \textit{J. Pr. Chem.} 2, 801 (19)).

\textit{N}-Methyl-\( \beta \)-phenylethylmalonanilic acid was isolated from the mixture by means of the insoluble sodium salt which it forms with sodium hydroxide. In comparison with the covalent sodium salts previously described this is formulated

\[ \text{PhCHCH}_2\cdot\text{CONH}_2 \]

The acid obtained by decomposing the sodium salt with dilute hydrochloric acid was crystallised from benzene in shining plates. m.p. 119° (decomp.) (uncorr.)

The method of preparation of the acid was not satisfactory, and as the acid gave no alkaloidal salts with brucine or cinchonidine in alcohol or acetone, the investigation was not pursued.

\textit{Benzylmalonpiperidinic acid} was prepared by the method of Chattaway (\textit{J. 1910} 27, 940), by heating ethyl benzyImalonate with piperidine. In this case no benzylmalondipiperidide separated on cooling the reaction mixture. The whole was therefore steam distilled in
presence of excess of sodium carbonate until no further oily drops of ester appeared. Benzylmalonpiperidinic acid separated on acidifying with hydrochloric acid

\[
\text{PhCH}_2\text{CO}_2\text{Et} + \text{HN} \rightarrow \text{PhCH}_2\text{CO}_2\text{Et} \rightarrow \text{PhCH}_2\text{CO}_2\text{Et} \rightarrow \text{PhCH}_2\text{CO}_2\text{Et}
\]

The acid was highly crystalline and separated from ethyl alcohol, in which it easily soluble, in colourless prisms, m.p. 135° (decomp.) (uncorr.) the acid is very freely soluble in chloroform.

With sodium hydroxide a sodium salt separated immediately, crystallising on cooling a solution in hot water in masses of fine needles, melting with decomposition at about 260°.
EXPERIMENTAL.

Except where otherwise stated, all polarimetric measurements were carried out using $\lambda = 5461$ in a 2 dm. tube, and $k$ is expressed in Briggsian logarithms and min. Temperature controlled experiments were carried out in a jacketed tube through which water was pumped from an electrically heated and mechanically stirred thermostat.

Preparation of Reissert's acid 2-keto-1:2:3:4-tetra-hydroquinoline-3-carboxylic acid.

ref. Reissert Ber., 1896, 29, 656
Leuchs Ber., 1921, 54, 830.

Preparation of Ethyl-o-nitrobenzylmalonate
Prepared according to Reissert.

4.6 G. of sodium (2 atoms) were dissolved in 100 c.c. of absolute alcohol and 32 g. of ethyl malonate (2 molecules) were added. 17.1 G. (1 molecule) of o-nitrobenzyl chloride dissolved in 170 c.c. of alcohol were allowed to run in slowly with shaking. After 45 minutes the mixture was poured into 2 litres of water, extracted with ether and distilled in vacuo. Ethyl o-nitrobenzylmalonate distilled in the region of 170°/2 m.m. The yield was 14 g. (48% of theory).

The experiment was repeated using a greater excess
of ethyl malonate (4 molecules to 1 molecule of o-nitrobenzylchloride) and absolute methyl alcohol as solvent. The methyl alcohol was refluxed over aluminium amalgam immediately before use.

9.2 G. of sodium were dissolved in 200 c.c. of absolute methyl alcohol and 64 g. of ethyl malonate added. 17.1 G. of o-nitrobenzylchloride in 170 c.c. of methyl alcohol were run in slowly. On vacuum distillation the product distilled with a much more constant boiling point of \(170^\circ/2\) m.m. than in the previous experiment. The distillate was practically colourless, and on cooling solidified. The yield was lower, 12 g. The product crystallised from methyl alcohol in prisms, m.p. 41-42\(^\circ\) (uncorr.)

Reduction of Ethyl o-nitrobenzylmalonate.

The reduction was carried out exactly as described by Reissert (loc. cit.) using zinc dust in presence of dry hydrochloric acid.

5 G. of ethyl o-nitrobenzylmalonate gave 3.7 g. of ethyl 2-keto-1:2:3:4 tetrahydroquinoline-3-carboxylate, i.e. in theoretical yield.


The hydrolysis was carried out as described by
Reissert.

2 G. of caustic potash were dissolved in 2 c.c. of water and 70 c.c. of alcohol and 3.7 g. of ester were added and the mixture heated under reflux for 20 minutes. On evaporation of the alcohol the potassium salt of the acid separated. The free acid was obtained by adding hydrochloric acid to an aqueous solution of the potassium salt. The acid separated slowly in yellow needles. It crystallised from alcohol, m.p. 146°, (decomp.)

Synthesis of Benzylmalonanilic acid.

ref. Chattaway (J. 1910, 27, 940).
Preparation of Ethyl benzylmalonate.
ref. Leuchs (Ber., 1911, 44, 1507)

Ethyl benzylmalonate was made according to the method of Leuchs. 2 Atoms of sodium were dissolved in 12 parts by weight of absolute alcohol, 2 molecules of ethyl malonate were added and 1 molecule of benzyl chloride. The reaction was carried out in the cold but completed by heating on a boiling waterbath for one hour. The mixture was then poured into a large volume of water extracted with ether, the ether distilled off and the residue distilled in vacuo b.p. 148°/2 m.m. The yields varied from 80-85% of the theoretical.

Preparation of Benzylmalonanilic Acid.
ref. Chattaway (J. 1910, 27, 940)
Dieckmann (Ber., 1904, 37, 4633)
37 G. of ethyl benzylmalonate (1.5 molecules) were heated with 9 g. of aniline (1 molecule) to gentle boiling for 30 minutes. On cooling, the contents of the flask solidified. The solid was extracted with four times its bulk of alcohol and filtered. The residue, 8.5 g., consisted of crude benzylmalondianilide. \[
\text{PhCH}_2\text{C}^\text{CONHPH}_3
\]
which crystallised from ethyl alcohol in colourless needles m.p. 218°.
The filtrate from the alcohol extraction was treated with a solution of 8 g. of sodium carbonate in 100 c.c. of water and steam was blown through for one hour. The residue was filtered and the filtrate acidified with hydrochloric acid. Benzylmalonanilic acid was precipitated. The yield was 12 g. of crude acid, 11 g. after crystallisation from ethyl alcohol, from which it separated in colourless needles, m.p. 180° decomp. The melting point varies according to the rate of heating and the highest recorded melting point is 185° decomp. The decomposition product melted at 97° and was $\beta$-phenylpropionanilide, c.f. Dieckmann (Ber., 1904, 37. 4633).

The acid was not very soluble in alcohol, and in order to recrystallise it, it required prolonged refluxing with alcohol. It is almost completely insoluble in chloroform even at the boiling point, and it is soluble with some difficulty in acetone.

Preparation of Sodium Benzylmalonanilate.

Benzylmalonanilic acid was dissolved in sodium hydroxide and on adding excess sodium hydroxide, sodium benzylmalonanilate separated. The salt was crystallised from water in clusters of long needles, melting with decomposition on heating to 220°. It is soluble in
alcohol. (Found: M.W. 329. Na. 7.0% \( \text{C}_{16} \text{H}_{14} \text{O}_5 \text{N}_2 \text{H}_2 \text{O} \) requires m.w. 327 Na. 7.0%).

Alkaloidal Salts of Benzylmalonanilic Acid.

Preparation of Brucine 1-Benzylmalonanilate -

(i) 2.69 G. of the dl-acid and 3.94 g. of brucine were dissolved together with gentle warming in 150 c.c. of ethyl alcohol. The solution was filtered and the filtrate on standing or more quickly on warming, deposited 5.50 g. (83% of theory) of brucine 1-benzylmalonanilate in fine silky colourless needles. m.p. 128° (decomp.) (Found: C, 68.7; H, 6.7; N, 6.1.
\( \text{C}_{39} \text{H}_{42} \text{N}_3 \text{O}_7 \text{H}_2 \text{O} \) requires C, 68.7; H, 6.4; N, 6.2%).

(ii) 0.2 G. of the dl-acid and 0.3 g. of brucine were dissolved together in 6-10 c.c. of acetone. A brucine salt began to crystallise after two hours. The salt was not examined.

Attempt to Prepare Strychnine Benzylmalonanilate.

(i) 0.2 G. of the dl-acid and 0.3 g. of strychnine were dissolved together in 6.10 c.c. of ethyl alcohol. Strychnine separated.
(ii) 0.2 G. of the 
 was dissolved together in 6-10 c.c. of acetone. Again 

**Attempt to prepare Quinidine Benzylmalonanilate.**

(i) 0.27 G. of the 
 were dissolved together in 6-10 c.c. of alcohol. No 

(ii) 0.27 G. of the 
 were dissolved together in 6-10 c.c. of acetone. No 

**Preparation of cinchonidine d-Benzylmalonanilate.**

1.34 G. of the 
 were dissolved together in 30 c.c. of acetone with gentle 

\[ \text{Found: C, 71.9; H, 6.4; } \text{requires } \text{C, 72.0; H, 7.0%.} \]

**Mutarotation of Cinchonidine-d-Benzylmalonanilate. Solvent; Chloroform.**

Temp., 18°. \[ \text{C = } -7920. \] Readings were begun 2.5 mins.
after wetting the salt. The total change is very small, 0.16°... unsuitable for calculating the reaction constant. The readings are plotted in Fig. II, p. 23

<table>
<thead>
<tr>
<th>Time after 2.5 mins.</th>
<th>α</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2.14</td>
</tr>
<tr>
<td>7.5</td>
<td>2.12</td>
</tr>
<tr>
<td>28.5</td>
<td>2.07</td>
</tr>
<tr>
<td>42.5</td>
<td>2.05</td>
</tr>
<tr>
<td>57.5</td>
<td>2.039</td>
</tr>
<tr>
<td>87.5</td>
<td>2.017</td>
</tr>
<tr>
<td>117.5</td>
<td>2.008</td>
</tr>
<tr>
<td>∞</td>
<td>1.98</td>
</tr>
</tbody>
</table>

Mutarotation of Brucine 1-Benzylmalonanilate.

Solvent chloroform.

Preliminary experiments. (i) Temp., 11° C ± 2.0. Change of rotation observed during 20 mins. The solution was then shaken with hydrochloric acid, benzylmalonanilic acid separated. The chloroform layer was run off and filtered through sodium sulphate directly into the polarimeter tube. The observed rotation was very small and showed no tendency to change further and was probably due to traces of brucine. Readings were begun within 4.0 mins. of wetting the salt.
at 29.0 the solution was shaken with HCl. The chloroform/
solution was read at 34.0 mins. $\alpha = -0.05^\circ$. No further change.

(ii) Temp., $12^\circ$. $C = 2.0$ Readings were begun 6.5
mins. after wetting the salt. Mutarotation was virtually
complete in 77 mins.

<table>
<thead>
<tr>
<th>Time after 6.5 mins.</th>
<th>$\alpha$</th>
<th>$k$</th>
<th>Time after 6.5 mins.</th>
<th>$\alpha$</th>
<th>$k$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>-0.25</td>
<td>-</td>
<td>12.50</td>
<td>-0.44</td>
<td>0.023</td>
</tr>
<tr>
<td>1.45</td>
<td>-0.27</td>
<td>0.015</td>
<td>15.50</td>
<td>-0.46</td>
<td>0.022</td>
</tr>
<tr>
<td>3.15</td>
<td>-0.29</td>
<td>0.018</td>
<td>27.50</td>
<td>-0.54</td>
<td>0.022</td>
</tr>
<tr>
<td>4.45</td>
<td>-0.32</td>
<td>0.016</td>
<td>33.50</td>
<td>-0.56</td>
<td>0.019</td>
</tr>
<tr>
<td>5.45</td>
<td>-0.33</td>
<td>0.023</td>
<td>51.50</td>
<td>-0.61</td>
<td>0.022</td>
</tr>
<tr>
<td>7.00</td>
<td>-0.37</td>
<td>0.023</td>
<td>70.50</td>
<td>-0.64</td>
<td>-</td>
</tr>
<tr>
<td>9.50</td>
<td>-0.38</td>
<td>0.020</td>
<td>83.50</td>
<td>-0.64</td>
<td>-</td>
</tr>
<tr>
<td>10.90</td>
<td>-0.40</td>
<td>0.023</td>
<td>$\infty$</td>
<td>-0.64</td>
<td>-</td>
</tr>
</tbody>
</table>

Whence $k = 0.021$ (limits 0.015 and 0.023)
Mutarotation of Brucine-1-Benzylmalonanilate in Chloroform at 12°.

Fig. XVI.

Mutarotation of Brucine-1-Benzylmalonanilate.

I. Temp. 25.15° C = 2.0055. Readings were begun 3.27 mins. after wetting the salt. The readings are plotted in Fig. I pg. 21.
<table>
<thead>
<tr>
<th>Time in mins. after 3.27</th>
<th>( \alpha )</th>
<th>k</th>
<th>Time in mins. after 3.27 ctd.</th>
<th>( \alpha )</th>
<th>k</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>-0.40</td>
<td>-</td>
<td>5.71</td>
<td>-0.64</td>
<td>0.0796</td>
</tr>
<tr>
<td>0.47</td>
<td>-0.44</td>
<td>-</td>
<td>6.28</td>
<td>-0.67</td>
<td>0.0905</td>
</tr>
<tr>
<td>1.08</td>
<td>-0.48</td>
<td>-</td>
<td>6.85</td>
<td>-0.68</td>
<td>0.0896</td>
</tr>
<tr>
<td>1.59</td>
<td>-0.51</td>
<td>-</td>
<td>7.78</td>
<td>-0.69</td>
<td>0.0855</td>
</tr>
<tr>
<td>1.84</td>
<td>-0.52</td>
<td>0.0925</td>
<td>9.26</td>
<td>-0.71</td>
<td>0.0853</td>
</tr>
<tr>
<td>2.17</td>
<td>-0.53</td>
<td>0.0864</td>
<td>10.00</td>
<td>-0.72</td>
<td>-</td>
</tr>
<tr>
<td>2.52</td>
<td>-0.55</td>
<td>0.0897</td>
<td>10.45</td>
<td>-0.73</td>
<td>-</td>
</tr>
<tr>
<td>2.95</td>
<td>-0.55</td>
<td>0.0766</td>
<td>10.89</td>
<td>-0.72</td>
<td>-</td>
</tr>
<tr>
<td>3.43</td>
<td>-0.58</td>
<td>0.0844</td>
<td>11.42</td>
<td>-0.73</td>
<td>-</td>
</tr>
<tr>
<td>3.75</td>
<td>-0.58</td>
<td>0.0772</td>
<td>11.79</td>
<td>-0.74</td>
<td>-</td>
</tr>
<tr>
<td>4.11</td>
<td>-0.60</td>
<td>0.0822</td>
<td>12.10</td>
<td>-0.75</td>
<td>-</td>
</tr>
<tr>
<td>4.53</td>
<td>-0.62</td>
<td>0.0866</td>
<td>12.47</td>
<td>-0.74</td>
<td>-</td>
</tr>
<tr>
<td>4.86</td>
<td>-0.62</td>
<td>0.0807</td>
<td>12.77</td>
<td>-0.74</td>
<td>-</td>
</tr>
<tr>
<td>5.20</td>
<td>-0.64</td>
<td>0.0874</td>
<td>( \infty )</td>
<td>-0.77</td>
<td>-</td>
</tr>
</tbody>
</table>

Whence \( k = 0.0848 \) (limits 0.0807, 0.0925)

\( \square \) Temp., 25.15\(^\circ\). \( C = 1.9885 \). Readings were begun 3.15 mins. after wetting the salt with solvent.
<table>
<thead>
<tr>
<th>Time after 3.15 mins.</th>
<th>$\alpha$</th>
<th>$k$</th>
<th>Time after 3.15 mins. ctd.</th>
<th>$\alpha$</th>
<th>$k$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>-0.39</td>
<td>-</td>
<td>5.85</td>
<td>-0.63</td>
<td>0.0680</td>
</tr>
<tr>
<td>0.90</td>
<td>-0.45</td>
<td>0.0784</td>
<td>7.30</td>
<td>-0.66</td>
<td>0.0669</td>
</tr>
<tr>
<td>1.75</td>
<td>-0.50</td>
<td>0.0799</td>
<td>9.05</td>
<td>-0.69</td>
<td>0.0666</td>
</tr>
<tr>
<td>2.65</td>
<td>-0.54</td>
<td>0.0771</td>
<td>14.45</td>
<td>-0.75</td>
<td>0.0693</td>
</tr>
<tr>
<td>3.55</td>
<td>-0.57</td>
<td>0.0732</td>
<td>19.70</td>
<td>-0.755</td>
<td>-</td>
</tr>
<tr>
<td>4.25</td>
<td>-0.59</td>
<td>0.0708</td>
<td>00</td>
<td>-0.79</td>
<td>-</td>
</tr>
<tr>
<td>5.05</td>
<td>-0.61</td>
<td>0.0688</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

whence $k = 0.0708$ (limits 0.0601 and 0.0799)

Mutarotation of 4-Benzyloxymalononate in Chloroform at 25.16°C

Fig. XVII.
Preparation of 1-Benzy1malonanilic Acid.

1-Benzy1malonanilic acid was obtained by decomposing the brucine salt in chloroform solution at 0° with hydrochloric acid, and completing the precipitation of the acid by adding light petroleum (b.p. 40-60°). The acid was freed from traces of brucine by dissolving in ethylalcohol and precipitating with water. 0.067 G. of the acid dissolved to 20 c.c. in ethyl alcohol gave \( \alpha = -0.92° \) at 14° i.e. \([\alpha] = -13.73°\) and showed no tendency to racemisation.

Racemisation of the Ammonium salt of 1-Benzy1malonanilic Acid.

0.0400 G. of the acid were dissolved in 0.1 N ammonia solution to 20 c.c. Readings were begun after 1 min. There is an immediate decrease in rotation, simultaneous with the formation of the ammonium salt and thereafter the salt racemises slowly to zero. The observable change is extremely small.
<table>
<thead>
<tr>
<th>Time after 1 min.</th>
<th>α</th>
<th>k</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.16</td>
<td>-</td>
</tr>
<tr>
<td>0.5</td>
<td>0.14</td>
<td>-</td>
</tr>
<tr>
<td>2.3</td>
<td>0.13</td>
<td>0.00392</td>
</tr>
<tr>
<td>4.1</td>
<td>0.12</td>
<td>0.00312</td>
</tr>
<tr>
<td>4.6</td>
<td>0.10</td>
<td>0.00444</td>
</tr>
<tr>
<td>62</td>
<td>0.09</td>
<td>0.00403</td>
</tr>
<tr>
<td>120</td>
<td>0.06</td>
<td>0.00355</td>
</tr>
<tr>
<td>12 hrs.</td>
<td>0.00</td>
<td>-</td>
</tr>
</tbody>
</table>

Whence $k$ is of the order $0.0038$.

**Preparation of d-Benzylmalonanilic Acid.**

d-Benzylmalonanilic acid was obtained by decomposing the cinchonidine salt in chloroform solution at $0\degree$ with hydrochloric acid and completing the precipitation by addition of light petroleum (b.p. $40-60\degree$) $0.1449$ G. dissolved to 20 c.c. gave $\alpha = +1.38\degree$ at $18\degree$ whence $[\alpha] = 9.52\degree$.

**Attempted Activation Experiments of Benzylmalonanilic acid with Alkaloids.**

Anhydrous brucine was prepared by dissolving the dihydrate in chloroform and evaporating to dryness on a waterbath. The anhydrous brucine was kept in a vacuum desiccator over magnesium perchlorate.

Dry chloroform free from alcohol was prepared by
extracting repeatedly with several times its own volume of water, drying over calcium chloride and finally over sodium sulphate. It was kept over sodium sulphate until required.

(i) 0.1970 G. of brucine were dissolved in chloroform and the solution made up to 20 c.c. and the rotation determined. 0.1340 G. of inactive benzylmalonanilic acid were added but even after 20 minutes shaking it had failed to dissolve. It was therefore impossible to observe any activation of the acid by brucine in chloroform.

Acid + brucine activation in acetone.

0.098 G. of brucine were dissolved in A.R. acetone and the solution was made up to 20 c.c., 0.067 g. of acid were added. The acid dissolved on shaking vigorously and the readings were begun 3.60 minutes after mixing.

<table>
<thead>
<tr>
<th>Time after 3.60 mins.</th>
<th>11.5° 5461</th>
<th>Time after 3.60 mins. ctd.</th>
<th>11.5° 5461 ctd.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>-0.45</td>
<td>9.30</td>
<td>-0.45</td>
</tr>
<tr>
<td>0.30</td>
<td>-0.43</td>
<td>9.74</td>
<td>-0.47</td>
</tr>
<tr>
<td>1.05</td>
<td>-0.44</td>
<td>10.04</td>
<td>-0.47</td>
</tr>
<tr>
<td>1.40</td>
<td>-0.43</td>
<td>10.42</td>
<td>-0.46</td>
</tr>
<tr>
<td>1.75</td>
<td>-0.44</td>
<td>3 hours</td>
<td>-0.45</td>
</tr>
</tbody>
</table>

Therefore there was no activation of the acid by brucine in acetone solution during 3 hours.
Acid + Brucine activation in Dioxan.

0.20 G. of benzylmalonanilic acid were dissolved in dioxan by gentle warming. After it had completely dissolved, the solution was cooled and made up to 20 c.c. The acid showed no tendency to crystallise out. 0.29 G. of brucine were added, but this dissolved slowly and the first reading was obtained 4.10 minutes after addition of the brucine.

<table>
<thead>
<tr>
<th>Time after 4.10 mins.</th>
<th>( \alpha ) 11.5°</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>- 1.10</td>
</tr>
<tr>
<td>0.50</td>
<td>- 1.08</td>
</tr>
<tr>
<td>1.15</td>
<td>- 1.10</td>
</tr>
<tr>
<td>35.90</td>
<td>- 1.10</td>
</tr>
<tr>
<td>3 hours</td>
<td>- 1.10</td>
</tr>
</tbody>
</table>

Therefore there was no activation during 3 hours.

Acid + Strychnine in Acetone.

0.10 G. of acid were dissolved in acetone and the solution made up to 20 c.c. 0.12 G. of strychnine were added, this dissolved very slowly and required five minutes for complete solution. Readings were begun 6.10 minutes after addition of the strychnine.
Therefore there was no activation of benzylmalonanilic acid by strychnine in acetone solution.

Preparation of dl-Benzylmalon-o-toluidic and Benzylmalondi-o-toluidide.

37 g. of ethyl benzylmalonate (1.5 mol.) were heated to gentle boiling with 10.7 g. of o-toluidine (1 mol.) for 1.5 hrs. On cooling and extracting with 4 times its own volume of alcohol, the mixture gave 10.5 g. of benzylmalondi-o-toluidide. The alcoholic extract was steam distilled in presence of excess of sodium carbonate (16 g.) and the residue on acidifying with hydrochloric acid gave 8 g. of dl-benzylmalon-o-toluidic acid, which crystallised from ethyl alcohol in clusters of glistening needles, m.p. 154° (decomp. uncorr.) (Found: C, 72.0; H, 6.2; N, 4.9. C₁₇H₁₇O₃N requires C, 72.1; H, 6.0; N, 4.9%).

Benzylmalondi-o-toluidide crystallised from ethyl alcohol, in which it is only sparingly soluble, in small colourless needles. m.p. 190° (uncorr.) (Found: C, 77.8; H, 6.3;
Preparation of Sodium Benzyllumalon-\text{-}o\text{-}toluidate.

\textit{dl-Benzyllumalon-o-toluidic acid} was dissolved in caustic soda and on adding excess of sodium hydroxide, sodium benzyllumalonanilate separated. The salt crystallised on cooling a solution in hot water in long flattened needles, which lose water of crystallisation at 100\(^{\circ}\) and melt with decomposition on heating to 238\(^{\circ}\). (Found Na, 6.6; \(C_{17}H_{17}O_3N\) Na.2 H\(_2\)O requires Na, 6.8%).

Alkaloidal Salts of Benzyllumalon-o-toluidic Acid.

Preparation of Cinchonidine-\text{-}d-Benzyllumalon-o-toluidate.

(i) 4.25 g. of the \textit{dl}-acid and 4.41 g. of cinchonidine were dissolved together with gentle warming in 100 c.c. of acetone. The solution was filtered and then heated under reflux at 70\(^{\circ}\) for 4 hrs. The d-salt separated slowly during this time in colourless needles. 1st Crop 4.68 g. (54\% theoretical) and on evaporating the filtrate to half bulk and heating at 70\(^{\circ}\) for a further 4 hrs., 2.47 g. d-salt separated. Total separation 83\% of theory. m.p. 155-156\(^{\circ}\) (decomp.) (uncorr.)

1st crop 0.2189 G. dissolved to 20 c.c. in chloroform \(\alpha = -1.65^{\circ}\) whence \(\left[\alpha\right] = -75.4^{\circ}\)
2nd crop 0.2007 G. dissolved to 20 c.c. in chloroform
\[ \alpha = 1.52 \text{ whence } [\alpha] = -75.7^\circ \]

In each case was read 5.0 mins. after wetting the salt.
(Found: C, 74.8; H, 6.7; N, 7.4. \( C_{36}H_{39}O_5N_3 \) requires C, 74.8; H, 6.8; N, 7.3%).
(ii) Repeated using 34 g. dl-acid and 35.3 g. Cinchonidine in 450 c.c. acetone. The salt isolated was inactive inoculation with the stable form reversing the van't Hoff-Dimroth rule.
(iii) Repeated as (ii) to give the d-salt.

Attempt to Prepare Brucine Benzylmalon-o-toluidate.
(i) 0.3 G. of the dl-acid and 0.4 g. of brucine were dissolved together in 5 c.c. of ethyl alcohol. No brucine salt crystallised.
(ii) 0.3 G. of the dl-acid and 0.4 g. of brucine were dissolved together in 5 c.c. of methyl alcohol. No brucine salt crystallised.
(iii) 0.3 G. of the dl-acid and 0.4 g. of brucine were dissolved together in 5 c.c. of acetone. No brucine salt crystallised.

Mutarotation of cinchonidine d-Benzylmalonatetoluidate.
Solvent Chloroform. Temp. 15\(^\circ\)
(i) Preliminary experiments. \( c = 1.1460 \). Readings were begun 3.0 mins. after wetting the salt.
(ii) Temp., $18^\circ$. $c = 1.1855$. Readings were begun 4.0 mins. after wetting the salt.
### Table

<table>
<thead>
<tr>
<th>Time after 4 mins.</th>
<th>( \alpha )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-1.76</td>
</tr>
<tr>
<td>18.5</td>
<td>-1.71</td>
</tr>
<tr>
<td>37.5</td>
<td>-1.67</td>
</tr>
<tr>
<td>57.5</td>
<td>-1.64</td>
</tr>
<tr>
<td>174</td>
<td>-1.59</td>
</tr>
</tbody>
</table>

### Diagram

**Mutarotation of Cinchonidine \( \beta \)-Benzy1malon-\( \beta \)-Toluate in Chloroform at 18°**

**Fig. XIX.**

### Controlled Experiments

(1) Temp., 18.3°. \( c = 1.510 \). Readings were begun 6.0 mins. after wetting the salt. The readings are plotted **Fig. XIII** page 48.
<table>
<thead>
<tr>
<th>Time after 6 mins.</th>
<th>( \alpha )</th>
<th>( k )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-2.160</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>-2.145</td>
<td>0.00516</td>
</tr>
<tr>
<td>10</td>
<td>-2.128</td>
<td>0.00571</td>
</tr>
<tr>
<td>15</td>
<td>-2.113</td>
<td>0.00577</td>
</tr>
<tr>
<td>20</td>
<td>-2.095</td>
<td>0.00625</td>
</tr>
<tr>
<td>25</td>
<td>-2.082</td>
<td>0.00619</td>
</tr>
<tr>
<td>30</td>
<td>-2.068</td>
<td>0.00632</td>
</tr>
<tr>
<td>35</td>
<td>-2.059</td>
<td>0.00613</td>
</tr>
<tr>
<td>40</td>
<td>-2.037</td>
<td>0.00696</td>
</tr>
<tr>
<td>45</td>
<td>-2.023</td>
<td>0.00722</td>
</tr>
<tr>
<td>50</td>
<td>-2.017</td>
<td>0.00694</td>
</tr>
<tr>
<td>55</td>
<td>-2.010</td>
<td>0.00679</td>
</tr>
<tr>
<td>65</td>
<td>-1.985</td>
<td>0.00747</td>
</tr>
<tr>
<td>75</td>
<td>-1.972</td>
<td>0.00744</td>
</tr>
<tr>
<td>85</td>
<td>-1.960</td>
<td>0.00743</td>
</tr>
<tr>
<td>95</td>
<td>-1.949</td>
<td>0.00753</td>
</tr>
<tr>
<td>( \infty )</td>
<td>-1.900</td>
<td>-</td>
</tr>
</tbody>
</table>

whence \( k = 0.0066 \) (limits, \( 0.0052 \) and \( 0.0075 \)).
(ii) Temp., 18.3° C = 1.6426. Readings were begun 5.0 mins. after wetting the salt.

<table>
<thead>
<tr>
<th>Time after 5 mins.</th>
<th>α</th>
<th>k</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-2.350</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>-2.331</td>
<td>0.00576</td>
</tr>
<tr>
<td>10</td>
<td>-2.314</td>
<td>0.00562</td>
</tr>
<tr>
<td>20</td>
<td>-2.281</td>
<td>0.00575</td>
</tr>
<tr>
<td>30</td>
<td>-2.263</td>
<td>0.00502</td>
</tr>
<tr>
<td>35</td>
<td>-2.249</td>
<td>0.00516</td>
</tr>
<tr>
<td>40</td>
<td>-2.235</td>
<td>0.00532</td>
</tr>
<tr>
<td>45</td>
<td>-2.209</td>
<td>0.00623</td>
</tr>
<tr>
<td>55</td>
<td>-2.198</td>
<td>0.00567</td>
</tr>
<tr>
<td>65</td>
<td>-2.178</td>
<td>0.00578</td>
</tr>
<tr>
<td>75</td>
<td>-2.140</td>
<td>0.00711</td>
</tr>
<tr>
<td>85</td>
<td>-2.124</td>
<td>0.00730</td>
</tr>
<tr>
<td>95</td>
<td>-2.116</td>
<td>0.00709</td>
</tr>
<tr>
<td>105</td>
<td>-2.110</td>
<td>0.00683</td>
</tr>
<tr>
<td>115</td>
<td>-2.101</td>
<td>0.00688</td>
</tr>
<tr>
<td>∞</td>
<td>-2.053</td>
<td>-</td>
</tr>
</tbody>
</table>

Whence \( k = 0.0061 \) (limits, 0.0050 and 0.0075)
Mean $k$ from (i) and (ii) = 0.0064.
Solvent: Ethyl Alcohol.

Preliminary Experiment. Temp., 15°. c = 1.0210. After
10 mins. \( \alpha = -1.54^\circ \) whence \([\alpha] = -75.05^\circ\), after
18 hrs. \( \alpha = 1.75^\circ \) whence \([\alpha] = -85.7^\circ\).

CONTROLLED EXPERIMENTS.

(i) Temp., 18.30°. c = 1.4780. Readings were begun
6.0 mins. after wetting the salt. The readings are
plotted in Fig. XIV page 49.

<table>
<thead>
<tr>
<th>Time after 6.0 mins.</th>
<th>( \alpha )</th>
<th>( k )</th>
<th>Time after 6 mins. ctd.</th>
<th>( \alpha ) ctd.</th>
<th>( k ) ctd.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-2.234</td>
<td>-</td>
<td>60</td>
<td>-2.340</td>
<td>0.00387</td>
</tr>
<tr>
<td>5</td>
<td>-2.244</td>
<td>-</td>
<td>90</td>
<td>-2.380</td>
<td>0.00408</td>
</tr>
<tr>
<td>10</td>
<td>-2.260</td>
<td>0.00465</td>
<td>100</td>
<td>-2.391</td>
<td>0.00413</td>
</tr>
<tr>
<td>15</td>
<td>-2.271</td>
<td>0.00452</td>
<td>110</td>
<td>-2.399</td>
<td>0.00408</td>
</tr>
<tr>
<td>20</td>
<td>-2.281</td>
<td>0.00441</td>
<td>120</td>
<td>-2.410</td>
<td>0.00421</td>
</tr>
<tr>
<td>25</td>
<td>-2.299</td>
<td>0.00509</td>
<td>190</td>
<td>-2.459</td>
<td>0.00429</td>
</tr>
<tr>
<td>30</td>
<td>-2.304</td>
<td>0.00459</td>
<td>220</td>
<td>-2.463</td>
<td>0.00444</td>
</tr>
<tr>
<td>35</td>
<td>-2.316</td>
<td>0.00479</td>
<td>399</td>
<td>-2.480</td>
<td>0.00352</td>
</tr>
<tr>
<td>40</td>
<td>-2.318</td>
<td>0.00432</td>
<td>00</td>
<td>-2.490</td>
<td>-</td>
</tr>
<tr>
<td>50</td>
<td>-2.332</td>
<td>0.00419</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

whence \( k = 0.0043 \) (limits, 0.0051 and 0.0035)
(ii) Temp., 18.30°. c = 1.6033. Readings were begun 10.0 mins. after wetting the salt.

<table>
<thead>
<tr>
<th>Time after 10 mins.</th>
<th>α</th>
<th>k</th>
<th>Time after 10 mins. ctd.</th>
<th>α ctd.</th>
<th>k ctd.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-2.456</td>
<td>-</td>
<td>50</td>
<td>-2.556</td>
<td>0.00424</td>
</tr>
<tr>
<td>5</td>
<td>-2.467</td>
<td>0.00376</td>
<td>55</td>
<td>-2.564</td>
<td>0.00426</td>
</tr>
<tr>
<td>10</td>
<td>-2.481</td>
<td>0.00441</td>
<td>60</td>
<td>-2.568</td>
<td>0.00427</td>
</tr>
<tr>
<td>15</td>
<td>-2.490</td>
<td>0.00407</td>
<td>70</td>
<td>-2.593</td>
<td>0.00467</td>
</tr>
<tr>
<td>20</td>
<td>-2.508</td>
<td>0.00321</td>
<td>80</td>
<td>-2.610</td>
<td>0.00490</td>
</tr>
<tr>
<td>25</td>
<td>-2.516</td>
<td>0.00442</td>
<td>140</td>
<td>-2.666</td>
<td>0.00516</td>
</tr>
<tr>
<td>30</td>
<td>-2.523</td>
<td>0.00433</td>
<td>150</td>
<td>-2.670</td>
<td>0.00507</td>
</tr>
<tr>
<td>35</td>
<td>-2.533</td>
<td>0.00438</td>
<td>160</td>
<td>-2.672</td>
<td>0.00487</td>
</tr>
<tr>
<td>40</td>
<td>-2.541</td>
<td>0.00432</td>
<td>170</td>
<td>-2.677</td>
<td>0.00490</td>
</tr>
<tr>
<td>45</td>
<td>-2.548</td>
<td>0.00424</td>
<td>200</td>
<td>-2.689</td>
<td>0.00499</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>-2.715</td>
<td>-</td>
</tr>
</tbody>
</table>

whence \( k = 0.0045 \) (limits, 0.0038 and 0.0051)
MUTARotation of Cinchonidine \(\varphi\)-Benzylmalon-\(\varphi\)-Toluate in Alcohol at 18.3°

![Graph showing mutarotation](image)

mean \(k\) form (i) and (ii) = 0.0044.

**Solvent:** Formic Acid.

Temporal, 18°. \(c = 0.8605\). Readings were begun 3.0 mins. after wetting the salt. The readings are plotted in Fig. XV page 50.
<table>
<thead>
<tr>
<th>Time in hours</th>
<th>$\alpha$</th>
<th>$k$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-0.88</td>
<td>-</td>
</tr>
<tr>
<td>$2\frac{1}{2}$</td>
<td>-1.03</td>
<td>0.00096</td>
</tr>
<tr>
<td>5</td>
<td>-1.17</td>
<td>0.00087</td>
</tr>
<tr>
<td>6</td>
<td>-1.22</td>
<td>0.00092</td>
</tr>
<tr>
<td>$21\frac{1}{2}$</td>
<td>-1.49</td>
<td>0.00103</td>
</tr>
<tr>
<td>$26\frac{1}{2}$</td>
<td>-1.53</td>
<td>-</td>
</tr>
<tr>
<td>$\infty$</td>
<td>-1.52</td>
<td>-</td>
</tr>
</tbody>
</table>

whence $k$ is of the order 0.00095. The change was too small and too slow for accurate determination of the rate constant.

**Examination of the Equilibrated Cinchonidine salt in chloroform solution.**

After equilibration the solvent was rapidly evaporated in vacuo.

(i) The salt residue was crystallised from ethyl alcohol, from which it separated in tiny needles. 0.3010 G. were dissolved to 20 c.c. in chloroform $\alpha = -1.88^\circ$. whence $[\alpha] = -62.45^\circ$. No mutarotation was observed.

(ii) The salt residue was decomposed with formic acid. Benzylmalon-o-toluidic acid was precipitated, and the precipitation was completed by pouring the formic acid mixture into water. 0.0416 G. of the acid dissolved to 20 c.c. in ethyl alcohol gave $\alpha = 0.00^\circ$ i.e.
the acid isolated from the equilibrated salt is optically inactive.

Preparation of d-Benzylmalon-o-toluidic Acid.

7 g. of cinchonidine d-benzylmalon-o-toluidate were ground up in a mortar with 30 c.c. of formic acid in the cold. d-Benzylmalon-o-toluidic acid separated, water was added at first drop by drop and then more quickly to 250 c.c. The mixture was filtered and ground up with a further 200 c.c. of water, again filtered, washed once with water and dried on a waterbath. Yield 2.98 g. (88% of Theory) m.p. 155-156° (decomp.) (uncorr.)

0.1622 g. dissolved to 15 c.c. in ethyl alcohol

\[ \alpha = +0.61 \quad \text{whence } [\alpha] = 56.4° \] at 18°.

No racemisation observable within 24 hrs.

**Solubility of d-Benzylmalon-o-toluidic Acid and the Pyridine Salt in various solvents.**

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Acid</th>
<th>Acid + 1 Equiv. of Pyridine</th>
</tr>
</thead>
<tbody>
<tr>
<td>C₂H₅OH</td>
<td>Soluble</td>
<td>Soluble</td>
</tr>
<tr>
<td>C₃H₆CO₂CH₃</td>
<td>Soluble</td>
<td>Soluble</td>
</tr>
<tr>
<td>CH₃CO₂C₂H₅</td>
<td>Slightly soluble</td>
<td>Soluble</td>
</tr>
<tr>
<td>CH₃CN</td>
<td>Soluble</td>
<td>Soluble</td>
</tr>
<tr>
<td>Dioxan</td>
<td>Soluble</td>
<td>Soluble</td>
</tr>
<tr>
<td>H₃CO₂H</td>
<td>Soluble</td>
<td>Soluble</td>
</tr>
<tr>
<td>CHCl₃</td>
<td>Very slightly soluble</td>
<td>Soluble</td>
</tr>
<tr>
<td>CCl₄</td>
<td>insoluble</td>
<td>insoluble</td>
</tr>
<tr>
<td>C₆H₆</td>
<td>insoluble</td>
<td>insoluble</td>
</tr>
<tr>
<td>C₆H₁₂</td>
<td>insoluble</td>
<td>insoluble</td>
</tr>
</tbody>
</table>
Racemisation of d-Benzylmalon-o-toluidic Acid in Formic Acid Solution.

(i) Temp., 18°. \( c = 0.4173 \). Readings were begun within 6.0 mins. of wetting the acid. The readings are plotted in Fig. III page 32.

<table>
<thead>
<tr>
<th>Time in Hours</th>
<th>( \alpha )</th>
<th>( k )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>+ 0.55</td>
<td>-</td>
</tr>
<tr>
<td>2.0</td>
<td>0.38</td>
<td>0.0013</td>
</tr>
<tr>
<td>3.0</td>
<td>0.33</td>
<td>0.0012</td>
</tr>
<tr>
<td>18.5</td>
<td>0.07</td>
<td>0.00081</td>
</tr>
<tr>
<td>23.5</td>
<td>0.04</td>
<td>0.00081</td>
</tr>
<tr>
<td>00</td>
<td>0.00</td>
<td>-</td>
</tr>
</tbody>
</table>

(ii) Temp. 18.3° solvent Formic acid containing 1.0 c.c. of water in 15 c.c. acid solution \( c = 1.3320 \).

<table>
<thead>
<tr>
<th>Time in hours</th>
<th>( \alpha )</th>
<th>( k )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>+ 0.41</td>
<td>-</td>
</tr>
<tr>
<td>1.33</td>
<td>0.355</td>
<td>0.00078</td>
</tr>
<tr>
<td>3.0</td>
<td>0.300</td>
<td>0.00078</td>
</tr>
<tr>
<td>4.0</td>
<td>0.265</td>
<td>0.00079</td>
</tr>
<tr>
<td>5.0</td>
<td>0.240</td>
<td>0.00078</td>
</tr>
<tr>
<td>6.0</td>
<td>0.210</td>
<td>0.00081</td>
</tr>
<tr>
<td>7.0</td>
<td>0.190</td>
<td>0.00080</td>
</tr>
<tr>
<td>22.0</td>
<td>0.070</td>
<td>-</td>
</tr>
</tbody>
</table>

whence \( k = 0.00079 \) (limits 0.00078 and 0.00081).
Racemisation of the Pyridine Salt of Benzylmalon-o-toluidic Acid.

Solvent: Chloroform.

Temp., 25.00°. A solution of pyridine in chloroform was prepared containing 2.1155 g. of pyridine in 20 c.c. chloroform solution. In each experiment 1 equivalent of this solution was added to the acid. C is given as the concentration of the acid if the solvent were pure chloroform (i.e. neglecting the effect of pyridine on the solvent.)

(i) $c_{acid} = 1.2233$ and 15 c.c. of this solution require 0.48 c.c. pyridine solution. Readings were begun 4.7 mins. after adding the pyridine solution. There was an induction period lasting for 12 mins. The readings
for the induction period are plotted in Fig. XII page 47. Thereafter the salt racemised according to the first order law.

**INDUCTION PERIOD.**

<table>
<thead>
<tr>
<th>Time in mins.</th>
<th>4.7</th>
<th>5.05</th>
<th>5.4</th>
<th>5.75</th>
<th>6.05</th>
<th>6.5</th>
<th>7.75</th>
<th>8.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \alpha )</td>
<td>-0.28</td>
<td>-0.29</td>
<td>-0.28</td>
<td>-0.28</td>
<td>-0.29</td>
<td>-0.29</td>
<td>-0.30</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time in mins.</th>
<th>8.4</th>
<th>9.75</th>
<th>10.0</th>
<th>10.3</th>
<th>11.7</th>
<th>11.95</th>
<th>12.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \alpha )</td>
<td>-0.28</td>
<td>-0.29</td>
<td>-0.29</td>
<td>-0.27</td>
<td>-0.26</td>
<td>-0.26</td>
<td>-0.25</td>
</tr>
</tbody>
</table>

The readings for the racemisation of the salt are plotted in Fig. \( \bar{\text{V}} \) page 36.
Time in mins. after 12 mins | $\alpha$ | $k$
---|---|---
0 | -0.257 | -
2 | -0.237 | -0.0176
4 | -0.223 | 0.0154
6 | -0.210 | 0.0146
8 | -0.203 | 0.0128
11 | -0.177 | 0.0147
14 | -0.170 | 0.0128
17 | -0.153 | 0.0132
20 | -0.137 | 0.0137
23 | -0.120 | 0.0144
25 | -0.110 | 0.0147
28 | -0.100 | 0.0147
31 | -0.097 | 0.0136
35 | -0.090 | 0.0130
$\infty$ | 0.00 | 

Whence $k = 0.014$ (limits, 0.0128 and 0.0176)

(ii) Temp., 25.00°.

cacid = 1.2793 and 15 c.c. of this solution require 0.51 c.c. of pyridine solution. Readings were begun 4.8 mins. after adding the pyridine solution. Induction period not observed.
<table>
<thead>
<tr>
<th>Time in mins. after 4.8 mins.</th>
<th>$\alpha$</th>
<th>$k$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-0.300</td>
<td>-</td>
</tr>
<tr>
<td>2.8</td>
<td>-0.270</td>
<td>0.0163</td>
</tr>
<tr>
<td>3.9</td>
<td>-0.253</td>
<td>0.0190</td>
</tr>
<tr>
<td>5.1</td>
<td>-0.243</td>
<td>0.0179</td>
</tr>
<tr>
<td>5.7</td>
<td>-0.240</td>
<td>0.0170</td>
</tr>
<tr>
<td>6.5</td>
<td>-0.230</td>
<td>0.0178</td>
</tr>
<tr>
<td>7.5</td>
<td>-0.220</td>
<td>0.0180</td>
</tr>
<tr>
<td>9.4</td>
<td>-0.203</td>
<td>0.0180</td>
</tr>
<tr>
<td>12.2</td>
<td>-0.190</td>
<td>0.0163</td>
</tr>
<tr>
<td>14.7</td>
<td>-0.172</td>
<td>0.0164</td>
</tr>
<tr>
<td>17.95</td>
<td>-0.167</td>
<td>0.0142</td>
</tr>
<tr>
<td>21.6</td>
<td>-0.147</td>
<td>0.0143</td>
</tr>
<tr>
<td>24.7</td>
<td>-0.130</td>
<td>0.0185</td>
</tr>
<tr>
<td>27.6</td>
<td>-0.120</td>
<td>0.0144</td>
</tr>
<tr>
<td>30.6</td>
<td>-0.113</td>
<td>0.0139</td>
</tr>
<tr>
<td>35.8</td>
<td>-0.083</td>
<td>0.0156</td>
</tr>
<tr>
<td>42.5</td>
<td>-0.060</td>
<td>0.0164</td>
</tr>
<tr>
<td>00</td>
<td>0.00</td>
<td>-</td>
</tr>
</tbody>
</table>

Whence $k = 0.016$ (limits, 0.014 and 0.019)
Mean $k$ from (i) and (ii) is 0.015.

Solvent: Ethyl Alcohol.

(i) Temp., 25.00°C. A solution of pyridine in ethyl alcohol was prepared containing 2.2412 g. of pyridine in 20 c.c. of ethyl alcohol solution.

As before $c_{\text{acid}} = 1.2487$ and 15 c.c. of this solution require 0.47 c.c. of pyridine solution.
Readings were begun 4.7 mins. after adding the pyridine solution. There was an induction period lasting 75 mins. The readings for the induction period are plotting in Fig. XII page

**Induction Period.**

<table>
<thead>
<tr>
<th>Time</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>25</th>
<th>30</th>
<th>35</th>
<th>40</th>
<th>45</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.305</td>
<td>1.295</td>
<td>1.275</td>
<td>1.245</td>
<td>1.255</td>
<td>1.258</td>
<td>1.263</td>
<td>1.245</td>
<td>1.263</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time</th>
<th>50</th>
<th>55</th>
<th>60</th>
<th>65</th>
<th>70</th>
<th>75</th>
<th>80</th>
<th>85</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.254</td>
<td>1.253</td>
<td>1.252</td>
<td>1.242</td>
<td>1.235</td>
<td>1.238</td>
<td>1.230</td>
<td>1.222</td>
</tr>
</tbody>
</table>

The readings for the racemisation of the salt are plotted in Fig. IV page 34.
<table>
<thead>
<tr>
<th>Time in mins. after 75 mins.</th>
<th>( \alpha )</th>
<th>( k )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>+1.236</td>
<td>-</td>
</tr>
<tr>
<td>55</td>
<td>+1.162</td>
<td>0.000485</td>
</tr>
<tr>
<td>85</td>
<td>+1.127</td>
<td>0.000461</td>
</tr>
<tr>
<td>165</td>
<td>1.055</td>
<td>0.000410</td>
</tr>
<tr>
<td>195</td>
<td>1.023</td>
<td>0.000421</td>
</tr>
<tr>
<td>225</td>
<td>0.992</td>
<td>0.000424</td>
</tr>
<tr>
<td>255</td>
<td>0.968</td>
<td>0.000416</td>
</tr>
<tr>
<td>285</td>
<td>0.937</td>
<td>0.000426</td>
</tr>
<tr>
<td>315</td>
<td>0.909</td>
<td>0.000423</td>
</tr>
<tr>
<td>345</td>
<td>0.881</td>
<td>0.000426</td>
</tr>
<tr>
<td>375</td>
<td>0.867</td>
<td>0.000411</td>
</tr>
<tr>
<td>405</td>
<td>0.846</td>
<td>0.000406</td>
</tr>
<tr>
<td>435</td>
<td>0.825</td>
<td>0.000403</td>
</tr>
<tr>
<td>555</td>
<td>0.739</td>
<td>0.000406</td>
</tr>
<tr>
<td>585</td>
<td>0.709</td>
<td>0.000413</td>
</tr>
<tr>
<td>615</td>
<td>0.698</td>
<td>0.000403</td>
</tr>
<tr>
<td>645</td>
<td>0.675</td>
<td>0.000423</td>
</tr>
<tr>
<td>1335</td>
<td>0.366</td>
<td>0.000396</td>
</tr>
<tr>
<td>00</td>
<td>0.00</td>
<td>-</td>
</tr>
</tbody>
</table>

whence \( k = 0.00043 \) (limits, 0.000396 and 0.000485)

(iii) Temp., 25.00\(^0\) \(\text{C} \), \(c_{\text{acid}} = 1.0700\) and 15 c.c. of this solution require 0.40 c.c. of pyridine solution. Readings were begun 8.3 mins. after adding the pyridine solution. The induction period lasted for 70 mins.
### Induction Period

<table>
<thead>
<tr>
<th>Time</th>
<th>8.3</th>
<th>9.0</th>
<th>10.5</th>
<th>10.8</th>
<th>11.2</th>
<th>11.8</th>
<th>12.4</th>
<th>12.8</th>
<th>13.5</th>
<th>17.2</th>
<th>17.7</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \alpha )</td>
<td>1.08</td>
<td>1.08</td>
<td>1.08</td>
<td>1.11</td>
<td>1.11</td>
<td>1.09</td>
<td>1.08</td>
<td>1.09</td>
<td>1.08</td>
<td>1.10</td>
<td>1.07</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time</th>
<th>18.3</th>
<th>18.7</th>
<th>19.2</th>
<th>19.7</th>
<th>21.0</th>
<th>21.5</th>
<th>22.0</th>
<th>30</th>
<th>40</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \alpha )</td>
<td>1.07</td>
<td>1.075</td>
<td>1.08</td>
<td>1.075</td>
<td>1.075</td>
<td>1.075</td>
<td>1.075</td>
<td>1.075</td>
<td>1.075</td>
<td>1.065</td>
</tr>
</tbody>
</table>

### Racemisation of the salt.

<table>
<thead>
<tr>
<th>Time in mins. after 70 mins.</th>
<th>( \alpha )</th>
<th>( k )</th>
<th>Time ctd.</th>
<th>( \alpha ) ctd.</th>
<th>( k ) ctd.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>+1.056</td>
<td>-</td>
<td>320</td>
<td>0.813</td>
<td>0.00036</td>
</tr>
<tr>
<td>10</td>
<td>1.045</td>
<td>0.00046</td>
<td>350</td>
<td>0.799</td>
<td>0.00035</td>
</tr>
<tr>
<td>20</td>
<td>1.039</td>
<td>0.00031</td>
<td>380</td>
<td>0.778</td>
<td>0.00035</td>
</tr>
<tr>
<td>30</td>
<td>1.024</td>
<td>0.00045</td>
<td>410</td>
<td>0.760</td>
<td>0.00035</td>
</tr>
<tr>
<td>40</td>
<td>1.017</td>
<td>0.00041</td>
<td>430</td>
<td>0.747</td>
<td>0.00035</td>
</tr>
<tr>
<td>50</td>
<td>1.009</td>
<td>0.00040</td>
<td>530</td>
<td>0.684</td>
<td>0.00035</td>
</tr>
<tr>
<td>60</td>
<td>0.999</td>
<td>0.00040</td>
<td>560</td>
<td>0.676</td>
<td>0.00035</td>
</tr>
<tr>
<td>80</td>
<td>0.972</td>
<td>0.00045</td>
<td>590</td>
<td>0.666</td>
<td>0.00034</td>
</tr>
<tr>
<td>150</td>
<td>0.919</td>
<td>0.00040</td>
<td>620</td>
<td>0.645</td>
<td>0.00035</td>
</tr>
<tr>
<td>170</td>
<td>0.910</td>
<td>0.00044</td>
<td>650</td>
<td>0.632</td>
<td>0.00034</td>
</tr>
<tr>
<td>180</td>
<td>0.904</td>
<td>0.00038</td>
<td>1310</td>
<td>0.377</td>
<td>0.00034</td>
</tr>
<tr>
<td>190</td>
<td>0.898</td>
<td>0.00037</td>
<td>1370</td>
<td>0.359</td>
<td>0.00035</td>
</tr>
<tr>
<td>200</td>
<td>0.892</td>
<td>0.00037</td>
<td>1430</td>
<td>0.341</td>
<td>0.00034</td>
</tr>
<tr>
<td>230</td>
<td>0.878</td>
<td>0.00035</td>
<td>1550</td>
<td>0.323</td>
<td>0.00033</td>
</tr>
<tr>
<td>260</td>
<td>0.860</td>
<td>0.00034</td>
<td>1680</td>
<td>0.293</td>
<td>0.00033</td>
</tr>
<tr>
<td>290</td>
<td>0.839</td>
<td>0.00034</td>
<td>00</td>
<td>0.00</td>
<td>-</td>
</tr>
</tbody>
</table>

whence \( k = 0.00036 \) (limits 0.00031 and 0.00046)

Mean \( k \) from (i) & (ii) = 0.00040.
Racemisation of Pyridine Salt of \( \delta \)-Benzyloformic-\( \delta \)-Toluic Acid in Alcohol at 25°C.

Fig. XXV.
Solvent: Acetonitrile.

(i) Temp., 25.00°. A solution of Pyridine in acetonitrile was prepared containing 2.4800 g. of pyridine in 20 c.c. acetonitrile solution.

As before $c_{\text{acid}} = 0.7740$ and 15 c.c. of this solution require 0.26 c.c. of pyridine solution. Readings were begun 5.0 mins. after adding the pyridine solution. The Readings are plotted in Fig. VI page 38.

<table>
<thead>
<tr>
<th>Time after 5.0 mins.</th>
<th>$\alpha$</th>
<th>$k$</th>
<th>Time std.</th>
<th>$\alpha$ std.</th>
<th>$k$ std.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>+0.555</td>
<td>-</td>
<td>70</td>
<td>+0.244</td>
<td>0.00510</td>
</tr>
<tr>
<td>5</td>
<td>0.521</td>
<td>0.00550</td>
<td>75</td>
<td>0.230</td>
<td>0.00510</td>
</tr>
<tr>
<td>10</td>
<td>0.497</td>
<td>0.00479</td>
<td>80</td>
<td>0.218</td>
<td>0.00507</td>
</tr>
<tr>
<td>15</td>
<td>0.474</td>
<td>0.00457</td>
<td>100</td>
<td>0.170</td>
<td>0.00514</td>
</tr>
<tr>
<td>20</td>
<td>0.446</td>
<td>0.00475</td>
<td>110</td>
<td>0.133</td>
<td>0.00564</td>
</tr>
<tr>
<td>25</td>
<td>0.422</td>
<td>0.00476</td>
<td>120</td>
<td>0.122</td>
<td>0.00548</td>
</tr>
<tr>
<td>35</td>
<td>0.372</td>
<td>0.00497</td>
<td>130</td>
<td>0.105</td>
<td>0.00555</td>
</tr>
<tr>
<td>40</td>
<td>0.346</td>
<td>0.00513</td>
<td>140</td>
<td>0.100</td>
<td>0.00532</td>
</tr>
<tr>
<td>45</td>
<td>0.322</td>
<td>0.00525</td>
<td>150</td>
<td>0.096</td>
<td>0.00508</td>
</tr>
<tr>
<td>50</td>
<td>0.307</td>
<td>0.00514</td>
<td>160</td>
<td>0.092</td>
<td>0.00488</td>
</tr>
<tr>
<td>55</td>
<td>0.292</td>
<td>0.00507</td>
<td>170</td>
<td>0.079</td>
<td>0.00498</td>
</tr>
<tr>
<td>60</td>
<td>0.275</td>
<td>0.00508</td>
<td>00</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>65</td>
<td>0.258</td>
<td>0.00512</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

whence $k = 0.0051$ (limits, 0.0046 and 0.0056)
(ii) Temp., 25.00°. \( c_{\text{acid}} = 0.8233 \) and 15 c.c. of this solution require 0.28 c.c. of pyridine solution. Readings were begun 6.0 mins. after adding the pyridine solution.

<table>
<thead>
<tr>
<th>Time after 10 mins.</th>
<th>( \alpha )</th>
<th>( k )</th>
<th>Time ctd.</th>
<th>( \alpha_{\text{ctd.}} )</th>
<th>( k_{\text{ctd.}} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>+0.565</td>
<td>-</td>
<td>60</td>
<td>+0.270</td>
<td>0.00534</td>
</tr>
<tr>
<td>2</td>
<td>0.555</td>
<td>-</td>
<td>65</td>
<td>0.256</td>
<td>0.00503</td>
</tr>
<tr>
<td>4</td>
<td>0.543</td>
<td>0.00430</td>
<td>70</td>
<td>0.242</td>
<td>0.00526</td>
</tr>
<tr>
<td>6</td>
<td>0.529</td>
<td>0.00475</td>
<td>75</td>
<td>0.237</td>
<td>0.00500</td>
</tr>
<tr>
<td>14</td>
<td>0.475</td>
<td>0.00539</td>
<td>80</td>
<td>0.218</td>
<td>0.00517</td>
</tr>
<tr>
<td>20</td>
<td>0.465</td>
<td>0.00423</td>
<td>85</td>
<td>0.210</td>
<td>0.00506</td>
</tr>
<tr>
<td>30</td>
<td>0.408</td>
<td>0.00471</td>
<td>95</td>
<td>0.183</td>
<td>0.00515</td>
</tr>
<tr>
<td>35</td>
<td>0.378</td>
<td>0.00499</td>
<td>105</td>
<td>0.158</td>
<td>0.00527</td>
</tr>
<tr>
<td>40</td>
<td>0.348</td>
<td>0.00526</td>
<td>115</td>
<td>0.141</td>
<td>0.00524</td>
</tr>
<tr>
<td>45</td>
<td>0.321</td>
<td>0.00546</td>
<td>125</td>
<td>0.127</td>
<td>0.00518</td>
</tr>
<tr>
<td>50</td>
<td>0.300</td>
<td>0.00550</td>
<td>140</td>
<td>0.103</td>
<td>0.00528</td>
</tr>
<tr>
<td>55</td>
<td>0.283</td>
<td>0.00546</td>
<td>00</td>
<td>0.00</td>
<td>-</td>
</tr>
</tbody>
</table>

Whence \( k = 0.0052 \) (limits, 0.00499 and 0.00550)
Mean $k$ from (i) & (ii) = 0.0052

Solvent: Ethyl Acetate.

(i) Temp., 25.00°. A solution in pyridine was prepared containing 1.9762 g. of pyridine in 20 c.c. of ethyl acetate solution.

As before $c_{\text{acid}} = 1.2947$ and 15 c.c. of this solution require 0.55 c.c. of pyridine solution. Readings were
begun 4.4 mins. after adding the pyridine solution.

There was an induction period lasting for 25 mins. The readings for the induction period are plotted in Fig. XIII page 47.

**Induction Period.**

<table>
<thead>
<tr>
<th>Time</th>
<th>4.4</th>
<th>4.9</th>
<th>5.25</th>
<th>5.6</th>
<th>5.85</th>
<th>6.25</th>
<th>7.2</th>
<th>7.5</th>
<th>7.8</th>
<th>10.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \alpha )</td>
<td>+0.72</td>
<td>0.71</td>
<td>0.73</td>
<td>0.70</td>
<td>0.72</td>
<td>0.72</td>
<td>0.71</td>
<td>0.72</td>
<td>0.72</td>
<td>0.71</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>10.4</th>
<th>10.75</th>
<th>15.0</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \alpha )</td>
<td>0.71</td>
<td>0.70</td>
<td>0.698</td>
<td>0.693</td>
</tr>
</tbody>
</table>

The readings for the racemisation of the salt are plotted in Fig. VII page 39.

<table>
<thead>
<tr>
<th>Time in mins. after 25 mins.</th>
<th>( \alpha )</th>
<th>( k )</th>
<th>Time std.</th>
<th>( \alpha ) std.</th>
<th>( k ) std.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>+0.668</td>
<td>-</td>
<td>165</td>
<td>+0.348</td>
<td>0.00172</td>
</tr>
<tr>
<td>10</td>
<td>.650</td>
<td>0.00119</td>
<td>180</td>
<td>.323</td>
<td>0.00175</td>
</tr>
<tr>
<td>20</td>
<td>.628</td>
<td>0.00134</td>
<td>195</td>
<td>.306</td>
<td>0.00173</td>
</tr>
<tr>
<td>30</td>
<td>.605</td>
<td>0.00143</td>
<td>245</td>
<td>.258</td>
<td>0.00169</td>
</tr>
<tr>
<td>60</td>
<td>.516</td>
<td>0.00187</td>
<td>255</td>
<td>.245</td>
<td>0.00171</td>
</tr>
<tr>
<td>70</td>
<td>.505</td>
<td>0.00174</td>
<td>270</td>
<td>.238</td>
<td>0.00166</td>
</tr>
<tr>
<td>80</td>
<td>.492</td>
<td>0.00166</td>
<td>285</td>
<td>.227</td>
<td>0.00164</td>
</tr>
<tr>
<td>90</td>
<td>.477</td>
<td>0.00180</td>
<td>300</td>
<td>.214</td>
<td>0.00165</td>
</tr>
<tr>
<td>105</td>
<td>.450</td>
<td>0.00163</td>
<td>315</td>
<td>.210</td>
<td>0.00160</td>
</tr>
<tr>
<td>120</td>
<td>.432</td>
<td>0.00158</td>
<td>330</td>
<td>.205</td>
<td>0.00155</td>
</tr>
<tr>
<td>135</td>
<td>.402</td>
<td>0.00163</td>
<td>00</td>
<td>0.00</td>
<td>-</td>
</tr>
<tr>
<td>150</td>
<td>.375</td>
<td>0.00167</td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

whence \( k = 0.0016 \) (limits, 0.00187 and 0.00119)
(ii) Temp., 25.00\(^\circ\). \(c = 1.4533\) and 15 c.c. of this solution require 0.59 c.c. of pyridine solution. Readings were begun 5.8 mins. after adding the pyridine solution.

**Induction Period 25 mins.**

<table>
<thead>
<tr>
<th>Time</th>
<th>5.8</th>
<th>6.5</th>
<th>7.0</th>
<th>7.5</th>
<th>8.0</th>
<th>8.4</th>
<th>8.9</th>
<th>9.8</th>
<th>10.5</th>
<th>11.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\alpha)</td>
<td>0.81</td>
<td>0.81</td>
<td>0.79</td>
<td>0.77</td>
<td>0.78</td>
<td>0.76</td>
<td>0.76</td>
<td>0.76</td>
<td>0.76</td>
<td>0.76</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time</th>
<th>12.5</th>
<th>14.0</th>
<th>15.0</th>
<th>16.0</th>
<th>17.0</th>
<th>18.0</th>
<th>21.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\alpha)</td>
<td>0.76</td>
<td>0.76</td>
<td>0.75</td>
<td>0.73</td>
<td>0.73</td>
<td>0.73</td>
<td>0.72</td>
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</table>

<table>
<thead>
<tr>
<th>Time in mins. after 26 mins.</th>
<th>(\alpha)</th>
<th>(k)</th>
<th>Time ctd.</th>
<th>(\alpha)</th>
<th>(k)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>+0.715</td>
<td>-</td>
<td>190</td>
<td>.312</td>
<td>0.00190</td>
</tr>
<tr>
<td>10</td>
<td>.690</td>
<td>0.00155</td>
<td>200</td>
<td>.308</td>
<td>0.00183</td>
</tr>
<tr>
<td>15</td>
<td>.677</td>
<td>0.00158</td>
<td>210</td>
<td>.285</td>
<td>0.00190</td>
</tr>
<tr>
<td>20</td>
<td>.670</td>
<td>0.00141</td>
<td>220</td>
<td>.278</td>
<td>0.00186</td>
</tr>
<tr>
<td>30</td>
<td>.652</td>
<td>0.00134</td>
<td>230</td>
<td>.274</td>
<td>0.00181</td>
</tr>
<tr>
<td>40</td>
<td>.628</td>
<td>0.00141</td>
<td>250</td>
<td>.260</td>
<td>0.00178</td>
</tr>
<tr>
<td>50</td>
<td>.595</td>
<td>0.00160</td>
<td>270</td>
<td>.240</td>
<td>0.00176</td>
</tr>
<tr>
<td>60</td>
<td>.550</td>
<td>0.00190</td>
<td>290</td>
<td>.220</td>
<td>0.00177</td>
</tr>
<tr>
<td>70</td>
<td>.530</td>
<td>0.00186</td>
<td>320</td>
<td>.202</td>
<td>0.00172</td>
</tr>
<tr>
<td>80</td>
<td>.510</td>
<td>0.00184</td>
<td>335</td>
<td>.195</td>
<td>0.00169</td>
</tr>
<tr>
<td>90</td>
<td>.492</td>
<td>0.00180</td>
<td>00</td>
<td>0.00</td>
<td>-</td>
</tr>
<tr>
<td>185</td>
<td>.320</td>
<td>0.00189</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Whence \(k = 0.0017\) (limits, 0.0013 and 0.0019).
RACEMISATION OF PYRIMINE SALT OF BENZYLMALON-0-TOLUIDIC ACID IN ETHYL ACETATE AT 25-0° II

Mean k from (i) & (ii) = 0.0017.
Solvent: Dioxan.

Temp., 18.3°. A solution of pyridine in dioxan was prepared containing 0.2876 g. of pyridine in 20 c.c. of dioxan solution. \( c_{acid} = 1.3807 \) and 15 c.c. of this solution require 0.55 c.c. of pyridine solution. Readings were begun 10 mins. after adding the pyridine solution.

<table>
<thead>
<tr>
<th>Time in mins. after 10 mins</th>
<th>( \alpha )</th>
<th>( k )</th>
<th>Time ctd.</th>
<th>( \alpha_{ctd.} )</th>
<th>( k_{ctd.} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>+1.205</td>
<td>-</td>
<td>180</td>
<td>0.597</td>
<td>0.00169</td>
</tr>
<tr>
<td>10</td>
<td>1.159</td>
<td>0.00168</td>
<td>200</td>
<td>0.564</td>
<td>0.00164</td>
</tr>
<tr>
<td>30</td>
<td>1.075</td>
<td>0.00165</td>
<td>220</td>
<td>0.509</td>
<td>0.00170</td>
</tr>
<tr>
<td>40</td>
<td>1.040</td>
<td>0.00160</td>
<td>240</td>
<td>0.497</td>
<td>0.00167</td>
</tr>
<tr>
<td>50</td>
<td>0.995</td>
<td>0.00166</td>
<td>260</td>
<td>0.449</td>
<td>0.00164</td>
</tr>
<tr>
<td>60</td>
<td>0.958</td>
<td>0.00166</td>
<td>280</td>
<td>0.402</td>
<td>0.00170</td>
</tr>
<tr>
<td>70</td>
<td>0.914</td>
<td>0.00171</td>
<td>300</td>
<td>0.375</td>
<td>0.00169</td>
</tr>
<tr>
<td>80</td>
<td>0.883</td>
<td>0.00169</td>
<td>320</td>
<td>0.337</td>
<td>0.00173</td>
</tr>
<tr>
<td>90</td>
<td>0.862</td>
<td>0.00162</td>
<td>360</td>
<td>0.285</td>
<td>0.00174</td>
</tr>
<tr>
<td>100</td>
<td>0.837</td>
<td>0.00158</td>
<td>420</td>
<td>0.241</td>
<td>0.00166</td>
</tr>
<tr>
<td>110</td>
<td>0.801</td>
<td>0.00161</td>
<td>( \infty )</td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>160</td>
<td>0.660</td>
<td>0.00163</td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

whence \( k = 0.00166 \) (limits, 0.00158 and 0.00174).
Experiment to Demonstrate the Formation of Pyridine Salt of 
d-Benzylmalon-ε-toluidic Acid in Ethyl Alcohol occurs 
without Change of Rotation in the Solution.

A pyridine solution was prepared containing 0.9078 g. pyridine in 13.78 c.c. of ethyl alcohol.

c = 0.5940 gave $\alpha = +0.62$. 16.5 c.c. of this acid solution was used and it requires 0.41 c.c. of pyridine solution to contain 1 equivalent of acid and 1 equivalent of pyridine.
<table>
<thead>
<tr>
<th>Time in mins. after 1st addn. of pyridine.</th>
<th>Amt. of Pyridine added in c.c.</th>
<th>Total amount of Pyridine in c.c.</th>
<th>$\alpha$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+0.62</td>
</tr>
<tr>
<td>0.5 - 5.7</td>
<td>0.05</td>
<td>0.05</td>
<td>0.616</td>
</tr>
<tr>
<td>7.7 - 12.7</td>
<td>0.1</td>
<td>0.15</td>
<td>0.612</td>
</tr>
<tr>
<td>15.9 - 25.7</td>
<td>0.3</td>
<td>0.45</td>
<td>0.610*</td>
</tr>
<tr>
<td>27.3 - 49.6</td>
<td>0.1</td>
<td>0.55</td>
<td>0.600</td>
</tr>
<tr>
<td>50.4 - 52.1</td>
<td>0.25</td>
<td>0.80</td>
<td>0.601</td>
</tr>
</tbody>
</table>

*slight excess Pyridine present at this point

Experiment to Demonstrate the Formation of the Piperidine Salt of d-Benzylmalon-o-toluidic Acid in Ethyl Alcohol Occurs with Change of Rotation in Magnitude and in sign in the solution.

A piperidine solution was prepared containing 0.6761 g. piperidine in 5.7 c.c. of ethyl alcohol solution. $c_{\text{acid}} = 1.1965$ gave $\alpha = +1.34^\circ$, 16.5 c.c. of this solution was used and it requires 0.5 c.c. piperidine solution to contain 1 equivalent of acid and 1 equivalent of piperidine.

The readings are plotted in Fig. VIII, page 41.
the solution became negative in sign as one equivalent of piperidine was added and thereafter the further addition of a second equivalent of piperidine produced no immediate change of rotation, but the solution slowly racemised to zero.

Racemisation of the Piperidine Salt of d-Benzylmalon-o-toluidic Acid.

Solvent: Ethyl Alcohol.

Temp., 18.3°. A piperidine solution was prepared containing 2.8393 g. of piperidine in 20 c.c. of ethyl alcohol solution.
(i) Piperidine in slight excess (1.26 equivalents.)
\[ c_{\text{acid}} = 1.3707 \] and 15 c.c. of this solution require 0.5416 for 1.26 equivalents of piperidine. Readings were begun 12.0 mins. after addition of the piperidine solution. The readings are plotted in Fig. IX, page 43.

<table>
<thead>
<tr>
<th>Time in mins. after 12 mins.</th>
<th>( \alpha )</th>
<th>( k )</th>
<th>Time ctd.</th>
<th>( \alpha ) ctd.</th>
<th>( k ) ctd.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>-0.350</td>
<td>-</td>
<td>90</td>
<td>-0.178</td>
<td>0.00326</td>
</tr>
<tr>
<td>4</td>
<td>-0.332</td>
<td>-</td>
<td>110</td>
<td>-0.164</td>
<td>0.00299</td>
</tr>
<tr>
<td>10</td>
<td>-0.324</td>
<td>0.00336</td>
<td>120</td>
<td>-0.153</td>
<td>0.00299</td>
</tr>
<tr>
<td>20</td>
<td>-0.311</td>
<td>0.00257</td>
<td>130</td>
<td>-0.143</td>
<td>0.00291</td>
</tr>
<tr>
<td>30</td>
<td>-0.295</td>
<td>0.00248</td>
<td>140</td>
<td>-0.132</td>
<td>0.00292</td>
</tr>
<tr>
<td>40</td>
<td>-0.276</td>
<td>0.00258</td>
<td>150</td>
<td>-0.127</td>
<td>0.00295</td>
</tr>
<tr>
<td>50</td>
<td>-0.253</td>
<td>0.00282</td>
<td>180</td>
<td>-0.111</td>
<td>0.00297</td>
</tr>
<tr>
<td>60</td>
<td>-0.231</td>
<td>0.00301</td>
<td>214</td>
<td>-0.098</td>
<td>0.00258</td>
</tr>
<tr>
<td>70</td>
<td>-0.213</td>
<td>0.00308</td>
<td>( \infty )</td>
<td>0.00</td>
<td>-</td>
</tr>
<tr>
<td>80</td>
<td>-0.192</td>
<td>0.00326</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Whence \( k = 0.0029 \) (limits, 0.0025 and 0.0034)

(ii) One Equivalent of Piperidine.

\[ c_{\text{acid}} = 1.4180 \] and 15 c.c. of this solution require 0.45 c.c. of piperidine solution. Readings were begun 10 mins. after the addition of the piperidine solution. The readings are plotted in Fig. IX, page 43.
Whence $k = 0.0030$ (limits, 0.0027 and 0.0033)

(iii) Half an Equivalent of Piperidine.

$C_{\text{acid}} = 1.4673$ and 15 c.c. of this solution require 0.23 c.c. of piperidine solution for $\frac{1}{2}$ equivalent of piperidine. Readings were begun 10 mins. after addition of the piperidine solution. The readings are plotted in Fig. XI page 44.
<table>
<thead>
<tr>
<th>Time in mins. after 10 mins.</th>
<th>$\alpha$</th>
<th>$k$</th>
<th>Time ctd.</th>
<th>$\alpha$ ctd.</th>
<th>$k$ ctd.</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>+ 0.678</td>
<td>-</td>
<td>70</td>
<td>0.398</td>
<td>0.0035</td>
</tr>
<tr>
<td>5</td>
<td>0.665</td>
<td>-</td>
<td>75</td>
<td>0.374</td>
<td>0.0036</td>
</tr>
<tr>
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<td>0.633</td>
<td>0.0030</td>
<td>80</td>
<td>0.360</td>
<td>0.0034</td>
</tr>
<tr>
<td>15</td>
<td>0.594</td>
<td>0.0038</td>
<td>90</td>
<td>0.330</td>
<td>0.0035</td>
</tr>
<tr>
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<td>0.563</td>
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<td>0.0035</td>
</tr>
<tr>
<td>25</td>
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<td>0.0039</td>
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<td>0.281</td>
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<td>0.233</td>
<td>0.0034</td>
</tr>
<tr>
<td>40</td>
<td>0.493</td>
<td>0.0037</td>
<td>150</td>
<td>0.202</td>
<td>0.0035</td>
</tr>
<tr>
<td>45</td>
<td>0.479</td>
<td>0.0034</td>
<td>170</td>
<td>0.160</td>
<td>0.0035</td>
</tr>
<tr>
<td>50</td>
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<td>0.0034</td>
<td>190</td>
<td>0.131</td>
<td>-</td>
</tr>
<tr>
<td>55</td>
<td>0.440</td>
<td>0.0034</td>
<td>210</td>
<td>0.100</td>
<td>-</td>
</tr>
<tr>
<td>60</td>
<td>0.429</td>
<td>0.0033</td>
<td>230</td>
<td>0.083</td>
<td>-</td>
</tr>
<tr>
<td>65</td>
<td>0.410</td>
<td>0.0034</td>
<td>$\infty$</td>
<td>0.00</td>
<td>-</td>
</tr>
</tbody>
</table>

Whence $k = 0.0035$ (limits, 0.0030 and 0.0040).

(iv) **Half an Equivalent of Piperidine.**

$c_{\text{acid}} = 1.4107$ and 15 c.c. of this solution requires
0.22 c.c. of piperidine solution for $\frac{1}{2}$ equivalent of
piperidine. Readings were begun 5 mins. after addition
of piperidine solution.
<table>
<thead>
<tr>
<th>Time in mins. after 5 mins.</th>
<th>$\alpha$</th>
<th>$k$</th>
<th>Time ctd.</th>
<th>$\alpha_{\text{ctd.}}$</th>
<th>$k_{\text{ctd.}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>+0.682</td>
<td>-</td>
<td>65</td>
<td>0.433</td>
<td>0.0030</td>
</tr>
<tr>
<td>5</td>
<td>0.659</td>
<td>0.0030</td>
<td>70</td>
<td>0.415</td>
<td>0.0031</td>
</tr>
<tr>
<td>10</td>
<td>0.640</td>
<td>0.0028</td>
<td>75</td>
<td>0.407</td>
<td>0.0030</td>
</tr>
<tr>
<td>15</td>
<td>0.619</td>
<td>0.0029</td>
<td>80</td>
<td>0.383</td>
<td>0.0031</td>
</tr>
<tr>
<td>20</td>
<td>0.591</td>
<td>0.0031</td>
<td>85</td>
<td>0.370</td>
<td>0.0032</td>
</tr>
<tr>
<td>25</td>
<td>0.560</td>
<td>0.0034</td>
<td>90</td>
<td>0.357</td>
<td>0.0031</td>
</tr>
<tr>
<td>30</td>
<td>0.544</td>
<td>0.0033</td>
<td>95</td>
<td>0.337</td>
<td>0.0032</td>
</tr>
<tr>
<td>35</td>
<td>0.528</td>
<td>0.0032</td>
<td>100</td>
<td>0.324</td>
<td>0.0032</td>
</tr>
<tr>
<td>40</td>
<td>0.508</td>
<td>0.0032</td>
<td>110</td>
<td>0.303</td>
<td>0.0033</td>
</tr>
<tr>
<td>45</td>
<td>0.490</td>
<td>0.0032</td>
<td>120</td>
<td>0.281</td>
<td>0.0033</td>
</tr>
<tr>
<td>50</td>
<td>0.479</td>
<td>0.0031</td>
<td>130</td>
<td>0.259</td>
<td>0.0033</td>
</tr>
<tr>
<td>55</td>
<td>0.469</td>
<td>0.0030</td>
<td>140</td>
<td>0.240</td>
<td>0.0034</td>
</tr>
<tr>
<td>60</td>
<td>0.455</td>
<td>0.0029</td>
<td>00</td>
<td>0.00</td>
<td>-</td>
</tr>
</tbody>
</table>

whence $k = 0.0032$ (limits, 0.0028 and 0.0034)
Mean \( k \) from (i) (ii) (iii) & (iv) = 0.0032.
Solvent: Dioxan.

Temp., 18.3°. A solution of piperidine in dioxan was prepared containing 2.2339 g. of piperidine in 20 c.c. of dioxan solution. \( c_{\text{acid}} = 1.2927 \) and 15 c.c. of this solution requires 0.52 c.c. of piperidine solution. On addition of the piperidine solution crystals appeared which proved to be the piperidine salt. m.p. 159° (decomp. uncorr.) (Found: N, 7.6. \( \text{C}_{22}\text{H}_{28}\text{O}_{3}\text{N}_{2} \) requires N, 7.6%).

Solvent: Water.

(i) Temp., 18°. 3 Equivalents of piperidine were present. A solution of piperidine in water was prepared containing 2.9420 g. of piperidine in 20 c.c. of aqueous solution. \( c_{\text{acid}} = 2.2360 \) requires 2.05 c.c. of piperidine solution for 3 equivalents of piperidine. Initial rotation of the piperidine salt is very small and positive. Readings were begun 5.0 mins. after adding the piperidine.
Whence \( k \) is of the order \( 0.023 \).

(ii) Temp., \( 19^\circ \). Solvent: \( "50\%" \) Aqueous Piperidine: A piperidine solution was prepared by mixing equal volumes of piperidine and water, the mixture became hot and was allowed to cool. \( c_{\text{acid}} = 0.9907 \). Readings were begun 7.0 mins. after wetting the acid. \( \alpha = 0.00^\circ \).
Experiments showing the Immediate Loss of Activity on the Formation of the Potassium and Sodium Ring Salts of $d$-Benzylmalon-$o$-toluidic Acid.

(i) Titration Experiment with Alcoholic Potassium hydroxide. 14.3 c.c. of an ethyl alcohol solution of $d$-benzylmalon-$o$-toluidic acid, $c_{\text{acid}} = 1.0235$, require 1.89 c.c. of 0.2743 N. alcoholic KOH for neutralisation. The alcoholic KOH was added in successive amounts of about 0.35 c.c., the rotation of the solution decreased linearly becoming zero just before 1 equivalent had been added, showing that slight racemisation of acid present as such, accompanies salt formation.

<table>
<thead>
<tr>
<th>Time in mins. after 1st addition of KOH</th>
<th>Amount of KOH solution added in c.c.</th>
<th>Total amount of KOH solution.</th>
<th>$\alpha$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+ 1.12</td>
</tr>
<tr>
<td>3 - 11.7</td>
<td>0.37</td>
<td>0.37</td>
<td>0.801</td>
</tr>
<tr>
<td>13 - 20.1</td>
<td>0.36</td>
<td>0.73</td>
<td>0.636</td>
</tr>
<tr>
<td>23 - 30.4</td>
<td>0.33</td>
<td>1.06</td>
<td>0.345</td>
</tr>
<tr>
<td>33 - 30.8</td>
<td>0.38</td>
<td>1.44</td>
<td>0.122</td>
</tr>
<tr>
<td>43 - 51.5</td>
<td>0.36</td>
<td>1.80</td>
<td>0.00</td>
</tr>
<tr>
<td>53 - 60</td>
<td>0.09</td>
<td>1.89</td>
<td>0.00</td>
</tr>
</tbody>
</table>
(ii) To 20 c.c. of an ethyl alcoholic solution

c_{acid} = 1.5110, 3.893 c.c. of 0.2743 N alcoholic KOH
(1 equiv.) were added. Readings were taken 4.0 mins. after wetting the acid. \( \alpha = 0.00^\circ \). i.e. the solution becomes immediately inactive on formation of the potassium salt.

(iii) Titration Experiment with Alcoholic sodium Hydroxide.

14.3 c.c. of an ethyl alcoholic solution of \( d \)-benzyl-
malon-o-toluidic acid, \( c_{\text{acid}} = 1.2050 \), require 1.47 c.c. of 0.4159 N alcoholic NaOH for neutralisation. Alcoholic NaOH added in successive amounts. A linear decrease of rotation of the solution was observed with accompanying slight racemisation of the acid remaining as such, resulting in the reading reaching zero before 1 equivalent of base had been added.

<table>
<thead>
<tr>
<th>Time in mins. after 1st addition of NaOH</th>
<th>Amt. of NaOH solution added in c.c.</th>
<th>Total amt. of NaOH soln. added in c.c.</th>
<th>( \alpha )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+ 0.437</td>
</tr>
<tr>
<td>0.5 - 8.0</td>
<td>0.29</td>
<td>0.29</td>
<td>0.346-0.325</td>
</tr>
<tr>
<td>10 - 18.8</td>
<td>0.29</td>
<td>0.58</td>
<td>0.246-0.226</td>
</tr>
<tr>
<td>20 - 29.5</td>
<td>0.29</td>
<td>0.87</td>
<td>0.138-0.127</td>
</tr>
<tr>
<td>30 - 39.0</td>
<td>0.29</td>
<td>1.16</td>
<td>0.32</td>
</tr>
<tr>
<td>40 - 43.7</td>
<td>0.31</td>
<td>1.47</td>
<td>0.00</td>
</tr>
</tbody>
</table>
(iv) To 20 c.c. of an ethyl alcohol solution $c_{\text{acid}} = 1.4260$ 2.423 c.c. of 0.4159 N. alcoholic NaOH solution were added. Readings were taken 3.7 mins. after wetting the acid. $\alpha = 0.00^\circ$. i.e. the solution becomes immediately inactive on formation of the sodium salt.
Racemisation of d-Benzylmalon-o-toluic Acid in presence of the sodium salt.

Solvent: Ethyl Alcohol.

Temp., 18°. To 15 c.c. of an ethyl alcohol solution of the acid, \( C_{\text{acid}} = 1.440 \), 0.92 c.c. of 0.4159 N. alcoholic NaOH solution (\( \frac{1}{2} \) equiv.) were added. The rotation of the solution was small and the acid racemised very slowly. Readings were begun 7.0 mins. after wetting the NaOH solution.

<table>
<thead>
<tr>
<th>Time in mins. after 7 mins.</th>
<th>( \alpha )</th>
<th>( k )</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>+0.223</td>
<td>-</td>
</tr>
<tr>
<td>30</td>
<td>0.208</td>
<td>0.00101</td>
</tr>
<tr>
<td>120</td>
<td>0.176</td>
<td>0.00086</td>
</tr>
<tr>
<td>300</td>
<td>0.113</td>
<td>0.00098</td>
</tr>
<tr>
<td>450</td>
<td>0.100</td>
<td>0.00091</td>
</tr>
<tr>
<td>00</td>
<td>0.00</td>
<td>-</td>
</tr>
</tbody>
</table>

whence \( k = 0.00095 \pm 0.00005 \)

Racemisation of the Ammonium Salt of d-Benzylmalon-o-toluic Acid.

Solvent: Ethyl Alcohol.

Temp., 18°. To 20 c.c. of an ethyl alcohol solution of the acid, \( C_{\text{acid}} = 1.0690 \), 1.785 c.c. of 0.4234 N aqueous
ammonia (1 equiv.) were added. Readings were begun 5.5 mins. after adding the ammonia solution. = 0.00°.

**Solvent: Water.**

Temp., 18°. 2 Equivalents of ammonia in excess were present. 0.2553 G. of d-benzylmalon-o-toluidic acid and 6.39 c.c. of 0.4234 N. ammonia solution (4 equivs.) were made up to 20 c.c. with water. Readings were begun 4.0 mins. after adding the ammonia solution. The ammonium salt racemised extremely slowly and the initial rotation was very small.

<table>
<thead>
<tr>
<th>Time in hours after addition of ammonia</th>
<th>$\Delta$</th>
<th>$k_{\text{hours}^{-1}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>+0.213</td>
<td>-</td>
</tr>
<tr>
<td>1</td>
<td>0.209</td>
<td>0.0083</td>
</tr>
<tr>
<td>16</td>
<td>0.146</td>
<td>0.0103</td>
</tr>
<tr>
<td>64</td>
<td>0.061</td>
<td>0.0085</td>
</tr>
<tr>
<td>00</td>
<td>0.00</td>
<td>-</td>
</tr>
</tbody>
</table>

Whence $k$ is of the order 0.00015 mins$^{-1}$

**Effect of a Neutral Salt on d-Benzylmalon-o-toluidic Acid.**

Solvent: Ethyl Alcohol. Temp., 18.3°. 0.2372 G. of d-benzylmalon-o-toluidic acid and 0.1263 g. (1 equiv.) of
tetraethylammonium chloride were dissolved to 15 c.c. in ethyl alcohol. Readings were begun within 4.0 mins. of wetting. $\alpha = 1.45^\circ$ whence $[\alpha] = 45.84^\circ$. No racemisation was observed within 24 hours. Thus the catalytic effect of a neutral salt on the keto-end change is negligible.

**Effect of Concentration on Specific Rotation of Cinchondine d-Benzylmalon-o-toluidate in Chloroform solution.**

<table>
<thead>
<tr>
<th>Concentration in grm. per 100 c.c. solution</th>
<th>$[\alpha]$ &quot;Initial&quot;</th>
<th>$[\alpha]$ Final</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3375</td>
<td>-86.07°</td>
<td>-77.03°</td>
</tr>
<tr>
<td>1.0035</td>
<td>-75.7°</td>
<td>-67.2°</td>
</tr>
<tr>
<td>1.0945</td>
<td>-75.4°</td>
<td>-66.7°</td>
</tr>
<tr>
<td>1.1460</td>
<td>-73.73°</td>
<td>-65.4°</td>
</tr>
<tr>
<td>1.1755</td>
<td>-74.23°</td>
<td>-67.07°</td>
</tr>
<tr>
<td>1.5050</td>
<td>-</td>
<td>-62.45°</td>
</tr>
<tr>
<td>1.5495</td>
<td>-68.73°</td>
<td>-61.95°</td>
</tr>
</tbody>
</table>
"Initial" is the actual specific rotation value obtained within 3-5 mins. of the beginning of the reaction and is not the true initial specific rotation obtained by extrapolation.

Optical Activation Experiments of Benzylmalon-o-toluidic Acid with Alkaloids.

Solvent: Chloroform. Temp., $16^\circ$.

(i) 0.147 G. (1 mol.) of cinchonidine was dissolved to 20 c.c. in chloroform, and 0.1415 g. (1 mol.) of $\text{dl}$-benzylmalon-o-toluidic acid was added. Readings were begun 5 mins. after addition of the acid. $\alpha = -1.81^\circ$.

No mutarotation was observed within 24 hours.
(ii) 0.1470 G. (1 mol.) of cinchonidine was dissolved to 20 c.c. in chloroform and 0.283 g. (2 mol.) of dl-benzylmalon-o-toluidic acid was added. Readings were begun 10 mins. after addition of the acid $\alpha = - 2.03^\circ$. No mutarotation was observable within 24 hours.

Solvent: Alcohol. Temp., 16°.

0.147 G. (1 mol.) of cinchonidine was dissolved to 20 c.c. in ethyl alcohol, and 0.1415 g. (1 mol.) of dl-benzylmalon-o-toluidic acid was added. Readings were begun 6 mins. after addition of the acid. $\alpha = - 2.34$. No mutarotation was observed within 24 hours.

Solvent: Dioxan. Temp., 18.3°.

(i) 0.147 G. (1 mol.) of cinchonine was dissolved to 20 c.c. in dioxan, and 0.1415 g. (1 mol.) of dl-benzylmalon-o-toluidic acid was added. Readings were begun 10 mins. after addition of the acid. $\alpha = + 3.375^\circ$. No mutarotation was observed within 24 hours.

(ii) 0.1620 G. (1 mol.) of quinine was dissolved to 20 c.c. in dioxan, and 0.1415 g. (1 mol.) of dl-benzylmalon-o-toluidic acid was added. Readings were begun 10 mins. after addition of the acid. $\alpha = - 2.90^\circ$. No mutarotation was observed within 24 hrs.

(iii) 0.1620 G. (1 mol.) of quinidine was dissolved to 20 c.c. in dioxan, and 0.1415 g. (1 mol.) of dl-benzylmalon-o-toluidic acid was added. Readings were begun 10 mins. after addition of the acid. $\alpha = + 3.97^\circ$. No mutarotation was observed within 24 hrs.

(iv) 0.1970 G. (1 mol.) of brucine was dissolved to 20 c.c. in dioxan, and 0.1415 g. (1 mol.) of dl-benzyl-
malon-o-toluidic acid was added. Readings were begun 7 mins. after addition of the acid. $\alpha = -0.72^\circ$.

No mutarotation was observed within 24 hrs.

**Attempted Resolution of Benzylmalon-o-toluidic Acid.**

2.83 G. of dl-acid and 2.94 g. of cinchonidine were dissolved together with gentle warming in 100 c.c. of acetone and rapidly filtered into a beaker cooled to $-15^\circ$ in a freezing mixture of ice and salt. The solution was inoculated with cinchonidine d-benzylmalon-o-toluidate and allowed to stand for 45 mins. The salt which had separated during this time was then filtered off rapidly through a previously cooled buchner funnel and the filtrate collected in a cooled receiver. The filtrate was evaporated in vacuo to give a salt residue. Yield of 1st crop 2.53 g. (44% of theory).

**Examination of the First Salt Crop separating after inoculation.**

Solvent : Chloroform.

Temp., 18. $c = 1.10$. Readings were begun 2.5 mins. after wetting the salt. At 4.0 mins. $\alpha = -1.64^\circ$ $[\alpha] = -75.05^\circ$ and after 24 hrs. $\alpha = 1.51^\circ$ $[\alpha] = -69.09^\circ$. 
Examination of the Residue from the evaporation of Filtrate.

Solvent: Chloroform.

Temp., 18.3 °C. \( d = 1.4453 \). Readings were begun 5 mins. after wetting the salt. \( \alpha = -1.603 \). No mutarotation was observed.

\[ [\alpha] = -55.5^\circ \]. If this were the corresponding diastereoisomer, mutarotation would have been observed. The specific rotation is lower than that observed for the equilibrated base-d-acid salt, but this must be due to the presence of impurities in the total evaporate.

Synthesis of N-Ethyl-benzylmalonanilic Acid.

Attempt to prepare N-Ethyl-benzylmalonanilic acid by the Method of Chattaway. (J., 1910, 97, 940)

Preparation of 2:4-Diketo-3-benzyl-1-methyl-1:2:3:4 tetrahydroquinoline. 37 G. of ethyl benzylmalonate (1\(\frac{1}{2} \) mol.) and 10.7 g. of methylaniline (1 mol.) were heated together to gentle boiling for 30 minutes, but after this time no reaction had taken place, heating was therefore continued for another hour and on cooling the mixture solidified. The solid was extracted with a little alcohol and filtered. The residue was crystallised from alcohol and gave a product 12 g. m.p. 218°. To the filtrate a solution of 10 g. of sodium carbonate in 100 c.c.
of water was added and steam blown through for one hour. The residue was filtered and acidified with hydrochloric acid, 2 g. of solid separated. On crystallisation from alcohol this product also melted at 218°, and was identical with the first solid separating. The experiment was repeated with the same result. Analysis showed that the product was not benzylmalondimethylanilide but 2:4-diketo-3-benzyl-1-methyl-1:2:3:4-tetrahydroquinoline. (Found: C, 76.7; H, 5.7; N, 5.3. C_{17}H_{19}O_{2}N requires C, 76.8; H, 6.1; N, 5.3%).

(ii) 10 g. of methyl aniline were heated with a large excess of ethyl benzylmalonate (50 g.) for 12 hours at a temperature not exceeding 120°. No reaction occurred and on vacuum distillation methylaniline and ethyl benzylmalonate were recovered unchanged.

Preparation of 2:4-Diketo-3-benzyl-1-ethyl-1:2:3:4-tetrahydroquinoline.

This was prepared to confirm that the same ring closure took place with ethyl aniline.

5 G. of ethyl benzylmalonate (1 mol.) and 5 g. of ethylaniline (2 mols.) gave a product m.p. 228-230° which crystallised from alcohol in shining plates.

Found: N 5.0 C_{18}H_{17}O_{2}N requires N 5.0%)
Preparation of 2:4-Diketo-1-methyl-1:2:3:4-tetrahydroquinoline.

Made according to Reissert (Ber., 1892, 25, 1193) by heating ethyl malonate with methylaniline. The product crystallised from ethyl alcohol in orange yellow prisms. m.p. 259 - 260°.

Preparation of N-Methyl-Malonanilic acid.

40 G. of ethyl malonate (2.5 molecules) were heated with 10.7 g. of methyl aniline (1 molecule) in a metal-bath at 120-130° for 12 hours. The resulting liquid was vacuum distilled. A first fraction of 42 g. contained unchanged ethyl malonate and methylaniline, but a small fraction boiling above 165° (at 7 mms.) was collected. The yield was 6 g. Considerable decomposition occurred while collecting this fraction. The product was hydrolysed by boiling for a few minutes with 10% caustic soda solution. On cooling and acidifying with hydrochloric acid white needles separated after standing for about 1 hour, m.p. 116 - 120° (decomp.), on rapid heating. Crystallisation from a very small amount of alcohol in which it is very easily soluble gave needles m.p. 116-120° (decomp.)

The product of the decomposition solidified on cooling and re-melted at 101-102° which is the melting point required for acetphenylmethylamide.
Two attempts to repeat the experiment resulted in almost complete decomposition on distilling the anilic ester. It was not therefore considered as a suitable intermediate for the preparation of N-methyl-benzylmalonanilic acid.

**Method II.**

**Attempted methylation of Ethyl benzylmalonanilate.**

\[
\begin{align*}
\text{PhCH}_2\text{C} & \overset{\text{CONHPh}}{\longrightarrow} & \text{PhCH}_2\text{C} & \overset{\text{CONPhMe}}{\longrightarrow} \\
\text{H} \text{CO}_2\text{Et} & & \text{H} \text{CO}_2\text{Et}
\end{align*}
\]

22 G. of benzylmalonanilic ester were prepared by extracting the mixture of mono- and di-anilides with alcohol and evaporating the alcoholic solution. On cooling, the ester was obtained as a semi-solid residue. This was dissolved in 230 c.c. of absolute alcohol and 20 c.c. of water were added. 1.69 G. of sodium and 12 g. of methyl iodide were added and the mixture boiled under reflux for 4 hours. No apparent reaction took place. A further 1.69 g. of sodium and 12 g. of methyl iodide were added and the mixture heated for another 4 hours. Most of the alcohol was evaporated and the residue poured into water. The ester separated as a thick oil. It was saponified and acidified. The acid recovered melted at 180° with decomposition, and is therefore
identical with benzylmalonanilic acid, no methylation having taken place.

Method III.

Scheme:

\[
\begin{align*}
\text{PhCH}_2\text{CO}_2\text{Et} & \rightarrow \text{PhCH}_2\text{CO}_2\text{K} & \rightarrow \text{PhCH}_2\text{CO}_2\text{H} & \rightarrow \text{PhCH}_2\text{CONPhMe}_2 \\
\text{PhCH}_2\text{CO}_2\text{Et} & \rightarrow \text{PhCH}_2\text{CO}_2\text{H} & \rightarrow \text{PhCH}_2\text{CONPhMe}_2 & \rightarrow \text{PhCH}_2\text{CONPhMe}_2
\end{align*}
\]

Method due to Marquery (Bull. Soc. chim., 1905, 33, 351.)

To 60 g. of ethyl benzylmalonate (1 molecule) dissolved in 30 c.c. of absolute alcohol, 13.8 g. of caustic potash (1 molecule) dissolved in 250 c.c. of absolute alcohol were added, and the solution allowed to stand overnight. Next day the alcohol was distilled off and the last traces removed in a vacuum. The potassium salt solidified in glistening plates. The solid was dissolved in water and the solution extracted with ether to remove any unchanged ester. The water layer was acidified with hydrochloric acid and a yellow oil was
precipitated. N.B. Marquery, while stating that the insolubility of the malonic ester-acids increases as their molecular weights increase, describes benzylmalonic ester-acid as very soluble in water. The oil was extracted with ether, the solution dried, and the ether removed by distillation. The yield of acid was 40 g., i.e. 75% of the theoretical. The oil was identified as ethyl hydrogen benzylmalonate by the action of heat. 10 G. of the oil were heated in a small distilling flask in a metal-bath. Decomposition began at 200°, carbon dioxide was evolved. The contents of the flask first set to a jelly but as the temperature rose this quickly liquified and distilled at 242-245°. Hydrolysis of the distillate with alcoholic caustic potash and precipitation with hydrochloric acid gave \( \beta \)-phenylpropionic acid m.p. 45°. This was confirmed by converting it into the chloride by means of thionyl chloride in benzene solution, evaporating off the excess thionyl chloride and benzene and adding aqueous ammonia. \( \beta \)-phenylpropionamide crystallised in colourless needles m.p. 82°.

50 g. of ethyl benzylmalonate and 11.8 g. of potassium hydroxide gave 37 g. of ethyl hydrogen benzylmalonate, i.e. an 85% yield over the two processes.
Action of Thionyl chloride on Ethyl hydrogen benzylmalonate.

15 G. of ethyl hydrogen benzylmalonate were dissolved in 50 c.c. of benzene and 8 g. of Thionyl chloride were allowed to drop in slowly. There was no apparent reaction. The flask was warmed gently but still no reaction appeared to take place. The mixture was then heated under reflux for 2 hours. The unchanged thionyl chloride was removed by evaporation and methyl aniline, calculated on the theoretical yield of ester-chloride, was allowed to drop slowly into the benzene solution and refluxed for one hour. The benzene was distilled off and the residue treated with Na CO and steam blown through. No precipitation of the anilic acid occurred on acidifying with hydrochloric acid.

Method IV.

Scheme: -

\[
\text{PhCH=CHCOH} \rightarrow \text{PhCHCHCOH} \rightarrow \text{PhCHCHCOEt} \rightarrow \text{PhCHCHCOEt} \rightarrow \text{PhCHCHCOEt}
\]
Preparation of $\beta$-Phenylpropionic acid.

Cinnamic acid was reduced to $\beta$-phenylpropionic acid using 3% sodium amalgam. The cinnamic acid was dissolved in dilute ammonia as the ammonium salt is considerably more soluble than the sodium salt. 100 g. of cinnamic acid required 2 kilog. of sodium amalgam and gave 91 g. of $\beta$-phenylpropionic acid, i.e. 91% of the theoretical yield.

Preparation of Ethyl $\beta$-phenylpropionate.

Esterification of $\beta$-phenylpropionic acid was carried out using excess of absolute alcohol in presence of sulphuric acid.

65 g. of acid gave 60 g. of ester. b.p. 247°, i.e. 81% of the theoretical yield.

Methyl phenylethylcarbamate.

Methyl phenylethylcarbamate, Ph Et N. CO₂Me, was prepared from phenylethylcarbamyl chloride by the action of sodium methoxide. 3.3 G. of sodium (1 atom) were dissolved in 36 g. of methylalcohol and 27 g. of phenylethylcarbamyl chloride were added in small portions. Salt separated and the reaction mixture became hot. It was heated under reflux for 30 minutes and then poured into $\frac{1}{2}$ litres of water, extracted with chloroform, dried, and
the chloroform removed by distillation. The residual liquid was vacuum distilled. Two fractions were collected, one boiling below 130° and the other above 160° at 15 m.m. This second fraction solidified and on crystallisation from methyl alcohol gave white needles m.p. 70°.

The condensation was repeated using 2 atoms of sodium to one atom of carbamyl chloride carrying out the reaction in the cold.

6.7 G. of sodium were dissolved in 72 g. of methyl alcohol and 27 g. of phenylethylcarbamyl chloride were added. The extraction was carried out as before and on vacuum distillation the first fraction collected gave 12 g. and the second fraction a solid of 5-6 g.

A third exactly similar experiment gave a first fraction of 14 g. and a solid fraction of 4 g.

The first fractions of these three experiments were distilled collecting between 115-120° at 15 m.m.

A fourth experiment was carried out using 12 g. of sodium, 144 g. of methyl alcohol and 40 g. of phenylethylcarbamyl chloride. The reaction mixture was kept cool in ice water. After chloroform extraction and removal of the chloroform by distillation, about 5 g. of the residual liquid was distilled from a small flask at ordinary pressure and gave a liquid boiling at 240° with very little
decomposition. The rest was then distilled at ordinary pressure (b.p. 240°). The yield was 32 g., 80% of the theoretical. None of the solid product was isolated.

A fifth experiment was carried out exactly as the fourth again yielding a product in 80% of the theoretical amount.

The solid compound of the first three experiments was identified as diphenyldiethylurea Ph Et N.CO.NEtPh. A specimen of diphenyldiethylurea was prepared by condensing phenylethylcarbamyl chloride with ethylaniline in presence of sodium carbonate and a trace of water. The product was crystallised from methyl alcohol and melted at 70°. A mixed melting point of this substance and the solid compound isolated, showed no depression but melted at 70°. The melting point given by Michler (Ber., 1876, 2, 712) for diphenyldiethylurea was 78°.

Ethyl/3-phenylpropionate and methyl phenylethylcarbamate were mixed in presence of powdered sodium under conditions which favour Claisen condensation between esters. 6.3 G. of sodium (1 atom) were powdered under toluene, washed with absolute ether and then covered with 150 c.c. of absolute ether. A mixture of 50 g. of ethyl /3-phenylpropionate (1 molecule) and 52 g. of methyl phenylethylcarbamate (1 molecule) was run in slowly by
means of a dropping funnel, and the flask immersed in a mixture of ice and salt.

The reaction mixture became warm, and an apparent reaction took place almost immediately. The mixture finally set to an orange-yellow gelatinous mass. It was left overnight, then decomposed with ice-water and the two layers separated. The product was expected to be present as a sodium derivative in the aqueous layer. On acidifying with acetic acid no precipitation occurred. The acidified solution was extracted with ether and the ether distilled off. Only a very small trace of oily residue remained and this residue could not be hydrolysed with alkali but left a resinous product. The ether layer was then examined. A jelly remained after the ether had been removed. This was vacuum distilled and 26 g. of methyl phenylethylcarbamate were recovered. The remainder could not be distilled but remained as a jelly even above 200° (bath temperature).

Method V.

Scheme:— Claisen Condensation between Ethyl Carbonate and \( \beta \)-Phenylpropionphenylethylamide.

\[
\text{PhCH}_2\text{CH}_2\text{CO}_2\text{H} \rightarrow \text{PhCH}_2\text{CH}_2\text{COCl} \rightarrow \text{PhCH}_2\text{CH}_2\text{CONPHEL}^\beta
\]

\[
\rightarrow \text{PhCH}_2\text{CH}_2\text{CONPHEL}^\beta \rightarrow \text{PhCH}_2\text{CH}_2\text{CO}_2\text{Et} \rightarrow \text{PhCH}_2\text{CH}_2\text{CONPHEL}^\beta
\]
Preparation of Ethyl carbonate.

Ethyl carbonate was prepared by dropping sodium into ethyl oxalate heated in a distilling flask in an oil-bath kept at 140-150°. Carbon monoxide was eliminated and ethyl carbonate distilled between 120-140°. The rate of distillation of the ethyl carbonate fell off rapidly after the first half-hour, and the yields were very low. A large amount of a tarry product remained in the distilling flask. The distillate was fractionated using a Dufton column and the constant boiling fraction 125-127° was collected. The yield was 38 g. from 300 g. of ethyl oxalate.

Preparation of β-Phenylpropionphenylethylamide.

β-Phenylpropionyl chloride was prepared by the action of thionyl chloride on β-phenylpropionic acid. 50 G. of acid were dissolved in 100 c.c. of benzene and 42 g. of thionyl chloride added and the mixture boiled under reflux for two hours after reaction had occurred, to remove all the thionyl chloride remaining. 80 G. of freshly distilled ethylaniline were slowly added to the boiling solution. Ethylaniline hydrochloride separated. The solution was filtered hot, a little more hydrochloride separated from the filtrate on cooling. The benzene solution was therefore washed with water and then extracted
three times with very dilute hydrochloric acid, three times with dilute sodium carbonate and finally with dilute ammonium chloride and evaporated on a water bath. The residue failed to solidify so the evaporate was vacuum distilled. All the liquid distilled over between 200-205° at 7 mm., the main fraction distilling at 201°. The distillate was redistilled and the fraction collected b.p. 201°/7 mm.

The \(\beta\)-phenylpropionphenylethylamide was an oily liquid, stable towards alkalis and hydrochloric acid, but hydrolysed by 70% sulphuric acid, ethylaniline was detected on basifying.

3.8 G. of sodium were powdered under toluene, washed with a little absolute ether and then covered with 150 c.c. of absolute ether. 20 G. of ethyl carbonate and 49 g. of \(\beta\)-phenylpropionphenylethylamide were mixed together and run in slowly from a dropping funnel. No reaction occurred in the cold, the sodium remained undissolved. The flask was then heated on a waterbath for one hour but a large amount of sodium still remained. The mixture was decomposed carefully with ice-water and the two layers separated. The aqueous layer was acidified with acetic acid but no precipitation occurred. The ether layer was dried over sodium sulphate and the ether
removed by distillation. The residue was distilled in vacuum. Some ethyl carbonate was recovered and 44 g. of \( \beta \)-phenylpropionphenylethylamide b.p. 201°/7 mm. There was no third fraction.

Method VI.

Scheme:

\[
\begin{align*}
\text{PhEtNCOCl} & \quad + \quad \text{CH}_2\text{CO}_2\text{Et} \quad \longrightarrow \quad \text{PhEtNCOCH}_2\text{CO}_2\text{Et} \\
\text{PhCH}_2\text{C} & \quad \text{CONPhEt} \quad \longrightarrow \quad \text{PhCH}_2\text{C} \quad \text{CONPhEt}
\end{align*}
\]

4.6 g. of sodium (2 atoms) were dissolved in 100 c.c. of absolute alcohol and 32 g. of ethylmalonate (2 molecules) and 18 g. of phenylethylcarbemyl chloride (1 molecule) were added. Sodium chloride separated in the cold. After 45 minutes the mixture was poured into water and ether extracted, washed with very dilute hydrochloric acid, dried and the ether distilled off. The residue was distilled under reduced pressure. Ethyl malonate distilled and with it a product which crystallised on cooling and was identified as ethylaniline hydrochloride. m.p. 178°.
Method VII.

Scheme:

\[
\begin{align*}
\text{PhCH}_2\text{CO}_2\text{Et} & \to \text{PhCH}_2\text{CONa} \to \text{PhCH}_2\text{CONPhEt} \\
\text{H} & \text{H} \quad \text{H} & \text{CONa} \quad \text{CONPhEt}
\end{align*}
\]

Benzylmalonyl chloride.

17 g. of benzylmalonic acid were treated with 41.5 g. of phosphorus pentachloride. The benzylmalonyl chloride formed was distilled under reduced pressure collecting the fraction boiling between 125-130° at 15 m.m. The yield was 13 g. i.e. 65% of the theoretical.

13 g. of benzylmalonyl chloride were dissolved in 50 c.c. of benzene and 13 g. of ethylaniline, dissolved in 25 c.c. of benzene, were run in slowly drop by drop with constant shaking. Ethylaniline hydrochloride separated. The mixture was allowed to stand for 15 minutes and then shaken with 50 c.c. of a 10% sodium carbonate solution and the two layers separated. The aqueous layer was acidified with hydrochloric acid, no immediate precipitation occurred but on standing a substance slowly crystallised out in colourless needles m.p. 55° to the extent of 1 g. This substance is not yet characterised but was evidently not the required N-ethyl-benzylmalonanic acid. The benzene layer was washed with caustic soda, separated, dried and the benzene
evaporated. The residue very slowly solidified. It was crystallised from methyl alcohol from which it separated with alcohol of crystallisation which was lost at 116-118°, and the resulting compound melted at 148°.

From the reaction it was thought that this compound would be the dianilide but analysis showed that it was not so. The compound was heated to 150° in a metal bath for 1 hr. to remove solvent of crystallisation and then crystallised in fine needles from light petroleum b.p. 60-80°, in which it is sparingly soluble. (Found C, 78.0; H, 5.8; N, 5.0. Diethylanilide C_{26}H_{28}O_{2}N_{2} requires C, 78.0; H, 7.0; N, 7.0%).

A very small amount of benzylmalonyl chloride was shaken with aqueous ammonia (d 0.88). A white solid separated which dissolved on adding water and then crystallised out in white needles m.p. 138°. Therefore this was not the expected diamide of benzylmalonic acid which melts at 225°.

**Method VIII.**

**Synthesis of N-ethyl-benzylmalonanilic acid.**

Scheme:-

\[ \text{CNCHCOEt} \rightarrow \text{CNCHCONPhEt} \rightarrow \text{PhCHCHCONPhEt} \rightarrow \text{PhCH}_2\text{C}^\text{CONPhEt} \]
Preparation of Ethyl Cyanoacetate.

Ethyl cyanoacetate was prepared from ethyl chloroacetate by the method of Noyes (J. Amer. Chem. Soc., 1904, 26, 1545.)

A mixture of 75 G. of potassium cyanide 70 c.c. of methyl alcohol and 136 g. of ethyl chloroacetate was boiled under reflux for 4 hours. The reaction mixture was then cooled, filtered and the methyl alcohol distilled off and used to wash the salt which had separated. The washings were added to the first filtrate, and the methyl alcohol distilled off again and the process repeated. Finally, a little ether was added to the residue from the distillation, precipitating some more insoluble material which was filtered, and the filtrate distilled under reduced pressure. The ethyl cyanoacetate was twice fractionated collecting the liquid finally boiling between 101-110° at 15 m.m. 136 G. of ethyl chloroacetate gave 59 g. ethyl cyanoacetate, i.e. 48% of the theoretical yield.

A preparation using excess of potassium cyanide (1.5 molecules) decreased the yield to 39% of the theoretical.
Preparation of Cyanoacetphenylethylamide.


5.6 G. of ethyl cyanoacetate (1 molecule) were heated with 6 g. of ethyl aniline (1 molecule) in an oil bath. A reaction began at 190° and ethyl alcohol started to reflux. In one experiment this was distilled off and collected in a small measuring cylinder. 1.2 C.c. were obtained, i.e. approximately 50% of the theoretical. After 3 hours the product was vacuum distilled. Unchanged ethyl aniline and ethyl cyanoacetate distilled over in the first fraction, boiling between 90-110° at 13 mm. Cyanoacetphenylethylamide distilled at 200-201° at 13 mm., solidified on cooling and was crystallised from ethyl alcohol m.p. 51°. The yield was 4 gm. i.e. 43% of the theoretical.

The experiment was repeated using 22 g. of ethyl cyanoacetate and 24 g. of ethylaniline which gave 19 g. of cyanoacetphenylethylamide, i.e. 50% of the theoretical.

Raising the bath temperature to 220-230° and prolonging the time of heating to 6 hours did not increase the yield which remained at 50%.
Preparation of Benzylcyanoacetphenylethylamide.

2.3 g. of sodium (1 atom) were dissolved in 50 c.c. of alcohol and 18.8 g. of cyanoacetphenylethylamide (1 molecule) were added. The sodium derivative began to separate and so, without cooling, 12.6 g. of benzyl chloride (1 molecule) were run in so that all had been added within 5 minutes. The flask was shaken continuously, the mixture became hot and sodium chloride separated. The reaction was completed by heating under reflux on a water-bath for 30 minutes, after which time the mixture reacted neutral to litmus. A little water was added to dissolve the sodium chloride and some of the alcohol allowed to evaporate off from the water-bath, (ten minutes). The remainder was poured into 1 litre of water when the benzylcyanoacetphenylethylamide separated out as a solid. It crystallised in colourless needles from ethyl alcohol m.p. 110-112° (uncorr.) The yield was 26 g. i.e. 93% of the theoretical.

The experiment was repeated. 24 g. of cyanoacet-phenylethylamide gave 31 g. benzylcyanoacetphenylethylamide, i.e. 89% of the theoretical.

N-Ethyl-benzylmalonanilic acid.

1.3 g. of caustic potash were dissolved in 3 c.c. of water and 11 c.c. of alcohol were added. The solution
was warmed and 5.5 g. of benzylcyanoacetphenylethylamide were added and the mixture heated on a water-bath under reflux for 1 hour. Large quantities of ammonia were evolved, and a small amount of ethylaniline could be detected by its smell. The alcohol was evaporated off leaving a solid residue.

There were six products which could be formed:—

(5) If present would easily be removed because of the ease of solubility of benzylmalonic acid in water. From the amount of ammonia evolved in the reaction it was thought that (2), (3) and (4) if present would be there only in small quantities. (6) The unchanged starting material was known to be insoluble in alkali, and so to remove it, the solid residue was taken up in water, the solution reacting alkaline to litmus, and extracted with
ether three times. 0.53 G. of benzylcyanoacetphenylethyl-
alamide were recovered from the ethereal solution. The
aqueous layer was heated on a water-bath for a few minutes
to drive off traces of ether, and acidified carefully
with dilute hydrochloric acid, an oily liquid was thrown
out which hardened to a gum but did not solidify even on
cooling to 0°.

On addition of caustic soda to the gum an insoluble
sodium salt of the acid was precipitated. This salt
was examined later. It was filtered and treated with
hydrochloric acid, again the acid separated as a gum
which would not solidify. It was extracted with chloro-
form and the chloroform solution dried over sodium
sulphate, and the chloroform removed by evaporation,
the last traces in a vacuum desiccator. The residual
glass was left for 12 hours. No crystallisation occurred.
The glass was quite unaffected by petroleum ether, but
dissolved very quickly in methyl alcohol. The methyl
alcohol solution was left to evaporate spontaneously.
After 2 days crystallisation began, and 2.8 g. of a solid
was obtained melting from 90-100° and decomposing about
110°. It was crystallised from carbon tetrachloride and
light petroleum (b.p. 60-80°) and melted at 101-102° with
decomposition. Recrystallisation raised the melting
point to 106-107° (decomp.) (uncorr.) The crystals separated as rhombohedra and the yield was 48% of the theoretical. (Found: C, 73.0; H, 6.9. C_{10}H_{19}O_{3}N requires C, 72.7; H, 6.5%).

The hydrolysis was repeated. 5.5 g. of the nitrile gave 2 g. of acid, i.e. 34%, and an experiment leaving the nitrile (15 g.) with caustic potash in the cold for 12 hours before refluxing gave a still lower yield of acid, 4 g. i.e. 25%.

30 g. of nitrile on hydrolysis and precipitation of the sodium salt gave 22 g. of the salt after drying in a vacuum. This salt was crystallised from water in shining plates and melted with decomposition on heating to 180°. It was sparingly soluble in cold water but readily soluble in benzene. (Found: Na, 4.6. C_{18}H_{18}O_{3}Na 10 H_{2}O requires Na, 4.6%).

0.5579 g. of sodium compound immediately after crystallisation from water were left in a vacuum desiccator over magnesium perchlorate for 2 days. The loss in weight was 0.1650 g. corresponding to 8 H_{2}O. There was no further loss in weight on leaving for a further 2 days.

Thus the sodium compound contains 2 molecules of water covalently bound to the sodium, and 8 molecules of
water of crystallisation.

The pure sodium salt was converted into the acid by addition of hydrochloric acid. The semi-solid acid which separated was extracted with carbon tetrachloride and dried over sodium sulphate, and light petroleum (b.p. 60-80°) dried over sodium sulphate was added. The acid did not crystallise but separated as an oily solid. The petroleum ether was evaporated off and the carbon tetrachloride solution re-dried over calcium chloride, and light petroleum dried over calcium chloride added, again the acid did not crystallise but separated as an oily solid. On addition of water followed by evaporation of the petroleum ether and carbon tetrachloride, the acid solidified on cooling and standing. After being filtered and dried it crystallised without difficulty from CCl₄-P.E.
m.p. 103-104° decomposing at 110°.

Other coordination compounds of the acid were not formed so readily as the sodium compound.

On adding a saturated solution of lithium hydroxide to the acid, the acid dissolved on heating but no salt separated on cooling or even on further addition of a saturated lithium hydroxide solution.

An insoluble potassium salt was formed on adding potassium hydroxide to the pure acid but it was a micro-
crystalline powder.

A microcrystalline powder was formed in very small yield on adding a freshly prepared saturated solution of copper acetate to a solution of the pure acid in glacial acetic acid.

**Alkaloidal Salts of N-Ethyl-benzylmalonanilic acid.**

**Attempt to Prepare a Brucine Salt of N-Ethyl-benzylmalonanilic Acid.**

0.10 g. of the acid and 0.13 g. of brucine were dissolved together with gentle warming in 1-2 c.c. of acetone. On cooling to room temperature no crystallisation occurred, and on cooling to 0°C there was still no crystallisation. On standing the acetone evaporated leaving a glass which crystallised on scratching, but re-dissolved on adding a few drops of acetone.

Using methyl alcohol and ethyl alcohol respectively, again a solid separated only on scratching the glass which remained after evaporation of the solvent, and the solid redissolved immediately on addition of a few drops of solvent.

**Attempt to Prepare a Strychnine Salt of N-ethyl-benzylmalonanilic Acid.**

0.10 g. of the acid and 0.11 g. of strychnine were dissolved together in 1-2 c.c. of ethyl alcohol. On
standing at room temperature a slight separation of a powdery solid took place after a short time. This proved to be strychnine.

**Attempt to Prepare A Morphine Salt of N-Ethyl-benzyl-malonanilic Acid.**

0.10 g. of the acid and 0.10 g. of morphine were dissolved together in 1 c.c. of ethyl alcohol, they dissolved extremely easily, and were allowed to stand at room temperature. After 24 hours crystals appeared in the solution and further solid separated on scratching, this proved to be morphine.

0.10 g. of the acid and 0.10 g. of morphine were dissolved in 1 c.c. of methyl alcohol but no crystallisation occurred either at room temperature or at 0°.

**Attempt to Prepare A Cinchonine Salt of N-Ethyl-benzyl-malonanilic Acid.**

0.10 g. of the acid and 0.10 g. of cinchonine were dissolved together in 1-2 c.c. of ethyl alcohol. No crystallisation occurred either at room temperature or on cooling to 0°. A similar result was obtained using methyl alcohol, and using aqueous alcohol the acid separated alone as an oil.
 Attempt to Prepare A Cinchonidine Salt of N-Ethyl-benzylmalonanilic Acid.

0.10 G. of the acid and 0.10 g. of cinchonidine were dissolved together in 1-2 c.c. of ethyl alcohol. No crystallisation occurred either at room temperature or at 0°. Again with methyl alcohol no crystallisation occurred.

 Attempt to Prepare A Quinine Salt of N-Ethyl-benzylmalonanilic Acid.

0.10 G. of the acid and 0.11 g. of quinine were dissolved together in 1-2 c.c. of ethyl alcohol. No crystallisation occurred either at room temperature or at 0° until almost all the solvent had evaporated. Using methyl alcohol as solvent no crystallisation took place. But from dioxan (1-2 c.c.) white needles again crystallised when almost all the solvent had evaporated.

 Attempt to Prepare a Quinidine Salt of N-Ethyl-benzylmalonanilic Acid.

0.10 G. of the acid and 0.11 g. of quinidine were dissolved together in 1-2 c.c. of ethyl alcohol. No crystallisation occurred either at room temperature or at 0°. Using methyl alcohol a similar result was recorded.

The quinine salt which separated from ethyl alcohol was dissolved in chloroform and the solution made up to 20 c.c. The salt dissolved almost instantaneously. The
observed rotation $\alpha = -2.86^\circ$ did not change within five hours.

**Optical Activation Experiment with N-Ethyl-benzylmalonanilic Acid and Cinchonidine.**

Temp., 17$^\circ$. Solvent: Chloroform.

**Acid base ratio 1:1.** 0.20 G. (1 mol.) of cinchonidine was dissolved to 20 c.c. in chloroform and 0.1973 g. (1 mol.) of dl-N-ethyl-benzylmalonanilic acid was added. Readings were begun 5 mins. after addition of the acid. $\alpha = -3.24^\circ$. No mutarotation was observed.

**Acid base ratio 2:1.** 0.20 G. (1 mol.) of cinchonidine was dissolved to 20 c.c. in chloroform and 0.3946 g. (2 mol.) of dl-N-ethyl-benzylmalonanilic acid was added. Readings were begun 5 mins. after addition of the acid. $\alpha = -3.42^\circ$. No mutarotation was observed.

**Acid base ratio 3:1.** 0.20 G. (1 mol.) of cinchonidine was dissolved to 20 c.c. in chloroform and 0.5919 g. of dl-N-ethyl-benzylmalonanilic acid was added. Readings were begun 5 mins. after addition of the acid $\alpha = -3.54^\circ$. No mutarotation was observed.

**Preparation of Benzylmalonpiperidine Acid.**

53 G. of ethyl benzylmalonate ($\frac{1}{2}$ mol.) were heated to gentle boiling with 12 g. of piperidine (1 mol.)
for 1½ hours. No solid separated on cooling. 16 G. of sodium carbonate was added and the mixture steam distilled until all the oily layer of ester disappeared (5 hours). The residue was filtered, cooled and acidified with hydrochloric acid, benzylmalonpiperidinic acid separated 14 g. (37% Theoretical). The acid crystallised from ethyl alcohol in prisms.

m.p. 135° (decomp. uncorr.) (Found: C, 68.7; H, 7.6; N, 5.5. C_{15}H_{19}O_{3}N required C, 68.9; H, 7.3; N, 5.4%).

Preparation of Sodium Benzylmalonpiperidate.

On adding sodium hydroxide to benzylmalonpiperidinic acid the sodium salt was immediately precipitated. It crystallised from warm water in small needles.

m.p. 260° with decomposition. (Found M.W. 319. Na 7.0, C_{15}H_{18}O_{3}N.Na 2.H_{2}O requires M.W. 320 Na 7.0%).

Alkaloidal salts of Benzylmalonpiperidinic Acid.

Preparation of Cinchonidine Benzylmalonpiperidate.

(i) 0.26 G. of the dl-acid were dissolved in 3 c.c. of acetone and poured into 0.29 g. of cinchonidine in 17 c.c. of acetone. On gently warming the solution deposited 0.54 g. (100% theoretical) of cinchonidine benzylmalonpiperidate m.p. 161° (decomp. uncorr.)
(Found: C, 71.6; H, 7.6; H, 7.9 C\textsubscript{34}H\textsubscript{41}O\textsubscript{4}N\textsubscript{3}.H\textsubscript{2}O requires
C, 71.2; H, 7.5; N, 7.4%).

(ii) 0.26 g. of the dl-acid and 0.29 g. of cinchonidine
were dissolved together in 6 c.c. of ethyl alcohol. The
solution was warmed gently for a few minutes and allowed
to stand. Cinchonidine benzylmalonpiperidate separated
in long needles. m.p. 161° (decomp.)

0.0768 G. dissolved in 20 c.c. \(\chi = -0.505^\circ\)
whence \(\left[\alpha\right] = -65.74\). No mutarotation observable within
24 hours.

Attempt to Prepare Cinchonine Benzylmalonpiperidate.

(i) 0.26 G. of the dl-acid and 0.29 g. of cinchonidine
were dissolved together in 20 c.c. of ethyl alcohol and
the solution warmed gently for a few minutes and allowed
to stand. No crystallisation of cinchonine benzyl-
malonpiperidate occurred. Repeated using methyl alcohol
and acetone. Again no crystallisation of salt took place.

Attempt to Prepare Quinidine Benzylmalonpiperidate.

0.26 G. of the dl-acid and 0.32 g. of quinidide were
dissolved together in 10 c.c. of ethyl alcohol. No
crystallisation occurred but on evaporating the solution
the residue solidified. A fresh solution was prepared
and inoculated with this solid but again no crystallisation
took place. Methyl alcohol and acetone gave a similar result.

**Attempt to prepare Quinine Benzylmalonpiperidate.**

0.26 G. of the dl-acid and 0.32 g. of quinine were dissolved together in 5 c.c. of ethyl alcohol. No crystallisation occurred until most of the solution had evaporated, when fine needles of salt separated. m.p. 124.6° (decomp. uncorr.) 0.2231 g. in 20 c.c. Chloroform gave $\alpha = -1.94^\circ$ whence $[\alpha] = -86.95^\circ$. No mutarotation was observed within 24 hours.

**Preparation of Brucine Benzylmalonpiperidate.**

1.04 G. of the dl-acid and 1.72 g. of brucine dihydrate were dissolved together in 15 c.c. of ethyl alcohol. No crystallisation of salt took place on standing. 45 c.c. of water were added and after standing for several weeks fine silky needles separated. m.p. 90° decomposing at 110°. (Found: C, 64.4; H, 7.1; N, 5.9. $C_{38}H_{45}O_N^{3H_2O}/2$ requires C, 64.9; H, 7.0; N 6.2%).

0.1939 G. dissolved in CHCl$_3$ and made up to 15 c.c. $[\alpha] = -0.89$ whence $[\alpha] = -61.22^\circ$. No mutarotation was observed.
Investigation of the Cinchonidine Salt of Benzylmalon-
piperidinic Acid.

(i) 0.1847 G. of cinchonidine salt was dissolved to 20 c.c. in chloroform. Readings were begun 2 mins. after wetting the salt. \( \alpha = -1.12^\circ \) at 17\(^\circ\), whence \( [\alpha] = -60.64^\circ \). No mutarotation was observed within 24 hours. The chloroform solution was shaken with dilute hydrochloric acid and the chloroform layer separated. It was washed with dilute hydrochloric acid and twice with water and then run through anhydrous sodium sulphate directly into the polarimeter tube. \( \alpha = 0.00^\circ \). The acid is optically inactive.

(ii) 0.1846 G. of cinchonidine salt was dissolved to 20 c.c. in chloroform. Readings were begun 3 mins. after wetting the salt. \( \alpha = -1.11^\circ \) at 17\(^\circ\). \( [\alpha] = -60.13^\circ \). No mutarotation was observed within 24 hours.

In Presence of Excess Benzylmalonpiperidinic Acid.

(iii) 0.1260 G. of cinchonidine salt was dissolved to 20 c.c. in chloroform \( \alpha = -0.76^\circ \), \( [\alpha] = -60.3^\circ \). 0.1 G. of benzylmalonpiperidinic acid was added and the rotation read 1.5 mins. after the addition. \( \alpha = -0.76^\circ \) and no change was observable.

(iv) 0.3 G. of Cinchonidine salt in 10 c.c. of acetone
(i.e. insufficient solvent completely to dissolve the salt) were refluxed for 5 hrs. on a water-bath, cooled and the mixture filtered. The filtrate and the residue were both examined.

a) The Residue.

0.1590 G. was dissolved to 20 c.c. in chloroform and read within 3 mins. of wetting the salt. $\alpha = -0.94^\circ$. $[\alpha] = -59.1^\circ$. No mutarotation was observed.

b) The Filtrate.

0.0988 G. was dissolved to 20 c.c. in chloroform.

$\alpha = -0.612^\circ$. $[\alpha] = -61.9^\circ$. No mutarotation was observed.

Attempted Activation of Benzylmalonpiperidinic Acid with Cinchonine.

(i) 0.1305 G. of dl-acid was dissolved in chloroform solution containing 0.36 c.c. of ethyl alcohol and made up to 20 c.c. 0.1470 G. of cinchonine was added.

$\alpha = +3.39^\circ$. No mutarotation was observed.

(ii) The attempted activation was carried out in presence of 1 equivalent of piperidine to 1 equivalent of cinchonine and 2 equivalents of acid. A piperidine ethyl alcohol solution was prepared containing 0.6761 g. of piperidine

$x$ In order to ensure that the true equilibrium had been established and that the results obtained in experiments (i) (ii) & (iii), were representative of the true equilibrium.
in 5.7 c.c. solution so that 0.1425 g. (1 equiv.) was present in 0.36 c.c. solution.

0.2610 G. of dl acid was dissolved in chloroform and 0.36 c.c. of piperidine solution added and the solution made up to 20 c.c. with chloroform. 0.1470 G. of cinchonine was added. \( \alpha = + 3.26^\circ \). No mutarotation was observed.

**Attempted Activation of Benzylmalonpiperidinic Acid with Brucine.**

0.1305 G. of the dl-acid was dissolved in chloroform and the solution made up to 20 c.c. 0.1970 G. of brucine was added. \( \alpha = - 0.65^\circ \). No mutarotation was observed.

**Attempt to Prepare N-Methyl-benzylmalonanilic Acid.**

**Preparation of cyanoacetphenylmethylamidine.**

56 G. of ethyl cyanacacetate and 46 g. of methyl aniline were heated together to gentle boiling for 3 hrs. On cooling cyanoacetphenylmethylamide separated, which crystallised from alcohol in colourless prisms. m.p. 88°. Yield 36 g. (41% theoretical).

**Preparation of Benzylcyanoacetphenylmethylamide.**

(i) 2.3 G. of sodium (1 atom) were dissolved in 50 c.c. of absolute ethyl alcohol and 17.4 g. of cyanacetphenyl-
methylamide (1 mol.) were added with shaking. This dissolved but almost immediately the sodium derivative separated. 12.5 G. of benzyl chloride were run in slowly with shaking, cooling the mixture in ice water. After \( \frac{1}{2} \) hr. the reaction was completed by heating under reflux on a waterbath for 1 hr. The mixture was then poured into water and 22 g. of crude solid separated. On crystallising from alcohol this appeared to be a mixture, which began to melt on heating to 94° and melted completely at 140°.

(ii) Repeated as for (i) to give the same result.

The product from (i) and (ii) was recrystallised from alcohol. A small first fraction (1 g.) was obtained m.p. 160°. This was recrystallised from benzene and melted sharply, 160-162°. The second fraction was recrystallised from benzene, it separated in prisms and melted sharply, 96-98°. Subsequent recrystallisation from alcohol or benzene failed to raise the wetting point.

This product was hydrolysed with alcoholic potassium hydroxide. 1.3 G. of potassium hydroxide were dissolved in 3 c.c. of water and 11 c.c. of ethyl alcohol, to the solution 5 g. of the nitrile was added and the mixture heated under reflux on a water-bath for
Ammonia and considerable quantities of methyl-aniline could be detected. Most of the alcohol was removed by evaporation and then water was added and the evaporation continued almost to dryness. The aqueous solution was extracted with ether, and the aqueous layer acidified after traces of ether had been removed by evaporation. 2.5 g. of a solid separated. This was crystallised from carbon tetrachloride in fine needles m.p. 98°, decomposing at 140°.

(Found: C 68.9; H 5.6; N 7.3. C₁₇H₁₇O₃N requires C, 72.1; H 6.1; N 5.0%) It appears therefore that the acid obtained is a mixture of N-methyl-malonanilic acid and N-methyl-benzylmalonanilic acid which could not be easily separated by fractional crystallisation.

Method II.

Scheme:—
Preparation of Benzylidene cyanacetophenylmethylamide.

(i) 12 G. (1.1 mol.) of freshly distilled acid free benzaldehyde was added to 17.4 G. (1 mol.) of cyanacetophenylmethylamide and the mixture warmed in a tightly corked flask on a water-bath, until all the solid dissolved. The mixture was then cooled to 20° and 0.5 g. of piperidine added. The mixture became cloudy and was left to stand overnight when 15 g. of a solid separated. On crystallisation from alcohol this was separated into two fractions.

Fraction I. Slightly soluble in alcohol crystallising in flat many sided plates. m.p. 180°. Identified as β-phenyl-α,γ-dicyanoglutaridiphenylmethylamide.

\[
\begin{align*}
\text{PhCH} & \text{C} \text{CN} \\
\text{CONPhMe} & \\
\text{PhCH} & \text{C} \text{CN} \\
\text{CONPhMe} & 
\end{align*}
\]

(Found: C, 73.7; H, 5.5; N, 12.1; \( \text{C}_2\text{H}_2\text{ON}_4 \) requires C, 74.3; H, 5.5; N, 12.8%).

Complete hydrolysis with 70% Sulphuric acid gave β-phenylglutaric acid which crystallised from ethyl alcohol m.p. 138° (Knoevenagel Ber., 1902 35. 393).
\(\beta\text{-}\text{phenyl-}\alpha\chi\text{-}\text{dicynoglutardiphenylmethy lamide}\) was recovered unchanged after heating with concentrated hydrochloric acid.

**Fraction II.**

More soluble in alcohol, crystallising in needles m.p. 92\(^0\), and was the required benzylidencyanoacetphenylmethy lamide. (Found: C, 77.6; H, 5.5; N, 10.9. C\(_{17}\)H\(_{14}\)O\(_2\)N requires C, 77.3; H, 5.4; N, 10.7%)

(ii) **Using Benzaldehyde in large Excess.**

20 G. of cyanoacetphenylmethy lamide and 100 g. of benzaldehyde with 3 drops of piperidine were heated for 15 hours on a water-bath. The excess benzaldehyde was distilled off in vacuo and the crude residue crystallised from alcohol. Yield 28 g. (93% theoretical).

Heating \(\beta\text{-}\text{phenyl-}\alpha\chi\text{-}\text{dicynoglutardiphenylmethy lamide}\) with excess benzaldehyde and 3 drops of piperidine on a waterbath for several hours also gave on cooling benzylidenecyanoacetphenylmethy lamide.

**Hydrolysis of Benzylidencyanoacetphenylmethy lamide.**

8 G. of benzylidencyanoacetphenylmethy lamide were heated under reflux on a water-bath with 2 g. of caustic potash in 2 c.c. of water and 20 c.c. of ethyl alcohol.
There was a strong smell of benzaldehyde but no ammonia could be detected, after 5 mins. a solid separated, the mixture was cooled and filtered, and the solid 5.3 g. dried on a water-bath. It was then dissolved in warm water when some resinous product remained undissolved, filtered and acidified with dilute hydrochloric acid. An acid separated which was crystallised from glacial acetic acid in yellow prisms m.p. 180° decomp. Yield 3.7 g. The decomposition product solidified on cooling and re-melted 145°.

The Experiment was repeated using 16 g. of the nitrile to give a similar result.

The acid has not yet been identified.

**Molecular weight determination.**

The molecular weight was determined by means of the silver salt. The acid was dissolved in aqueous ammonia and the excess ammonia boiled off. To the neutral solution of the ammonium salt a saturated solution of silver nitrate was added. A white silver salt was precipitated immediately.

This crystallised from warm water in colourless needles and was anhydrous.
0.1788 g. of Ag. salt gave 0.0679 g. Ag. whence M.w. of the salt = 284 and M.w. of the acid = 187.

Analysis. Found: C, 69.5; H, 4.1; N, 8.0%.

On shaking with aqueous ammonia in the cold a white powdery solid was gradually formed which crystallised from water in colourless needles, decomposing on heating to 228°.

Preparation of N-methyl-β-phenylethylmalonanilic Acid.

Scheme:

\[
\begin{align*}
\text{PhCHCHBr} + \text{CH}_2\text{CONPhMe} & \rightarrow \text{PhCHCHCHCONPhMe} \\
\text{PhCHCHCONPhMe} & \rightarrow \text{PhCHCHCHCO}_2\text{CONPhMe}
\end{align*}
\]

Preparation of β-Phenylethyl bromide.

\(\text{PBr}_3\), 60 g. (2 mol.) was allowed to drop slowly into β-phenylethylalcohol 40 g. (3 mol.) A vigorous reaction took place. When there was no further reaction the mixture was poured slowly into water and the β-phenylethylbromide separated. It was washed with water, dried over calcium chloride and vacuum distilled. b.p. 98° 13 m.m.

Condensation of β-phenylethyl bromide with Cyanacet-phenylethylamide.

(1) 2.3 G. of sodium (1 atom) were dissolved in 150 c.c. of absolute alcohol, and 17.4 g. (1 mol.) of cyanoacet-
phenethylamide (page 155) added. The mixture was heated under reflux on a water bath until all the solid had dissolved. 18.5 G. (1 mol.) of \(\beta\)-phenylethyl bromide was added slowly through the condenser by means of a dropping funnel. Sodium bromide separated slowly. The refluxing was continued until the reaction mixture was neutral (6 hrs.) The mixture was then poured into 300 c.c. of water and an oily liquid separated. This was ether extracted and the ether distilled off. The residue 22 g. did not crystallise even on cooling to \(-10^\circ\).

To hydrolyse the oily residue it was heated under reflux with 5 g. of caustic potash in 5 c.c. of water and 40 c.c. of alcohol. As for the hydrolysis of N-ethylbenzylmalonanilic acid, there is a variety of hydrolysis products possible.

\[
\begin{align*}
1 & \quad \text{PhCHCH}_2\text{C}^\text{\text{-CONPhMe, CO}_2H} \\
2 & \quad \text{PhCHCH}_2\text{C}^\text{\text{-CONPhMe, CONH}_2} \\
3 & \quad \text{PhCHCH}_2\text{C}^\text{\text{-CO}_2H} \\
4 & \quad \text{PhCHCH}_2\text{C}^\text{\text{CN, CO}_2H} \\
5 & \quad \text{PhCHCH}_2\text{C}^\text{\text{CN, CONPhMe, CO}_2H} \\
6 & \quad \text{PhCHCH}_2\text{C}^\text{\text{CN, CONPhMe}}
\end{align*}
\]
The alkaline mixture was extracted with ether to remove unchanged nitrile (vi) and the aqueous layer was acidified with hydrochloric acid. On standing an acid separated slowly. It crystallised in glistening plates from benzene solution. m.p. 119° (decomp. uncorr.) (Found: C, 72.6; H, 6.3; N, 4.8. C₁₉H₁₉O₃N requires C, 72.7; H, 6.4; N, 4.7%).

N-Methyl-β-phenylethylmalonanilic acid gave a sodium salt with caustic soda which crystallised from water in colourless needles. By comparison with the other sodium salts of this series it is formulated

(2) The condensation was repeated using 8.5 g. of cyanacetophenylmethylamide to give 10 g. of oily impure nitrile. Hydrolysis with 3 g. KOH in 3 c.c. of water and 30 c.c. of alcohol gave 3.5 g. of N-methyl-β-phenylethylmalonanilic acid separated through the sodium salt, and in addition 2-3 g. of β-phenylethylmalonamic acid (iii) m.p. 144° (decomp. uncorr.) (Found: C, 63.4; H, 6.5; N, 6.9% requires C, 62.0; H, 5.5; N, 7.0%).

The decomposition product solidified on cooling and
remelted 82-83°. Identified as \( \beta \)-phenylbutyramide m.p. 84°.

\[
\begin{align*}
\text{PhCH}_2\text{CH} & \begin{array}{c}
\text{CO}_2\text{H} \\
\text{CONH}_2
\end{array} \\
\rightarrow 
\text{PhCH}_2\text{CH}_2\text{CONH}_2 + \text{CO}_2
\end{align*}
\]

(3) Repeated as experiment (2), but the main product of the hydrolysis was an acid m.p. 130° (decomp.). The decomposition product solidified on cooling and remelted at 51°. This acid is therefore \( \beta \)-phenylethylmalonic acid (v) m.p. 130° (Fischer Ber., 1906 39, 2211) and the decomposition product \( \gamma \)-phenylbutyric acid m.p. 51°.

\[
\begin{align*}
\text{PhCH}_2\text{CH} & \begin{array}{c}
\text{CO}_2\text{H} \\
\text{CO}_2\text{H}
\end{array} \\
\rightarrow 
\text{PhCH}_2\text{CH}_2\text{CO}_2\text{H} + \text{CO}_2
\end{align*}
\]

In view of the difficulty of controlling this hydrolysis the preparation of N-methyl-\( \beta \)-phenylethylmalonanilic acid was not continued.

Attempts to prepare a Brucine salt of N-methyl-\( \beta \)-phenylethylmalonilic acid.

(i) 0.1 G. of \( \text{dl} \) acid and 0.13 g. of brucine were dissolved together in 2-3 c.c. of alcohol. No brucine salt separated.

(ii) 0.1 G. of \( \text{dl} \) acid and 0.13 g. of brucine were dissolved together in 2-3 c.c. of acetone. No brucine salt separated.
Attempts to Prepare a Cinchonidine Salt of N-Methyl-β-phenylethylmalonanilic acid.

(i) 0.3 g. of dl acid and 0.3 g. of cinchonidine were dissolved together in 6-10 c.c. of ethyl alcohol. No cinchonidine salt separated.

(ii) 0.3 g. of dl acid and 0.3 g. of cinchonidine were dissolved together in 6 c.c. of acetone. No cinchonidine salt separated.