THESIS

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W. D. McKenzie.

STUDIES RELATING

TO THE

HYDROLYSIS OF ALIPHATIC AMIDES.

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INTRODUCTION

The work described in this thesis is concerned with problems connected with the hydrolysis of the amide group but, although the whole investigation thus has a common theme, it falls conveniently into three divisions, dealing with γ amino butyramide, malonic acid amides and oxalic acid amides respectively.

A study of the hydrolysis of γ amino butyramide was desirable in order to obtain more evidence on the mechanism of hydrolysis of glutamine, the molecule of which bears a strong structural resemblance to that of the butyric acid derivative. A satisfactory method for the preparation of this compound was not arrived at in the present work and the relevant portion of this thesis deals with attempts to prepare the compound. The hydrolysis in acid solution of malonic acid amides was initiated by results obtained in this Department on the effect of substituents on the rate of hydrolysis of C- substituted malonamides. Such results indicated the need for data on the kinetics of hydrolysis of the mono-amide of malonic acid and the correlation of such data with that obtained for the corresponding diamide. The studies on oxalic acid amides arose directly from this work, the interest lying in the fact that in these derivatives the carbonyl groups are directly bonded.

In connection with the kinetic studies it should be pointed out that the hydrolysis was believed to occur by an essentially bimolecular reaction involving, initially, the addition of a proton to the carbonyl group. The amides studied were found to hydrolyse at measureable rates at 97°C to 98°C in a range of hydrochloric acid from 0 to .5 molar. First order kinetics for the hydrolyses were obtained in this range when the concentration of acid molecules was kept very

much greater than that of amide molecules (greater than 100/1). The amide was then present in semi-micro quantities which could be determined conveniently by the methods developed for similar systems by Penfold[1] and Sanders[37] from methods used by Taylor[5] and Krieble and Holst[4]. As the kinetics of first order reactions have received simple and adequate treatment the possibility of consecutive reactions in the hydrolysis of the diamides could also be considered.

It has been convenient to treat, under the following headings, each amide investigated:-

(i) Preparation, in which the preparation of the amide used in the hydrolysis is discussed.

(ii) Method of analysis, in which (a) the reasons for the choice of the method used and (b) any difficulties experienced, are discussed.

(iii) Kinetics of Hydrolysis, in which the results obtained, as described in the section on "The Expression of Results", are given.

The complete hydrolysis of each diamide is discussed in a section immediately following those containing full information from the hydrolysis of the mono-and di-amide. General conclusions on the hydrolysis of amides are discussed in the final main section.

II   GENERAL PROCEDURE

   (i) Methods of analysis

The kinetics of the hydrolyses were followed by quant-
itative estimation of the ammonia produced by the hydrolysis,
with standard sodium hypobromite solution

$$RCONH_2 + H_2O \longrightarrow RCOOH + NH_3$$

$$2NH_3 + 3NaBrO \longrightarrow 3NaBr + 3H_2O + N_2$$
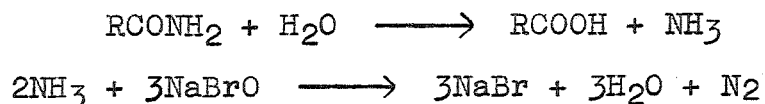
This method, which has been used for similar work by
Sanders[37], Stone[2], and Taylor[4], was suitable for use on the
semi-micro scale of the present investigation. In the
estimation, two slightly different techniques have been used
as required by the nature of the amide concerned.

In the "direct" method a known volume of standard
hypobromite was allowed to react with an aliquot of the
hydrolysate containing unhydrolysed amide and the products
of hydrolysis. This method could only be used if no
appreciable reaction was observed between the hypobromite
and the amide and/or products of hydrolysis, other than
ammonia.

When such reaction occurred it was frequently possible
to distil the ammonia from the hydrolysate, under reduced
pressure, without appreciable hydrolysis of the amide. The
ammonia was collected in dilute acid and estimated, as in
the direct method.

Nessler's reagent was used to give a qualitative test
for the presence of ammonia in the hydrolysate and, in all
the cases investigated, positive evidence was obtained. Some
unhydrolysed amide solutions produced a faint milkiness of the
solution; any attempt to adapt the Nessler reaction to the
study of the kinetics of hydrolysis would thus have to take
into account possible interference indicated by this observa-
tion.

To determine which of the two "hypobromite" methods was suitable a solution of amide of the concentration used in the hydrolysis was prepared and aliquots tested for reaction with the standard hypobromite under the experimental conditions. When no significant interference was observed the direct method was used because it is much less tedious than the distillation method. If such interference had occurred the solution of amide was tested in the distillation apparatus for hydrolysis in the alkaline buffer solution used for the distillation. This was of course, an essential preliminary to any use of the distillation method, in order to determine whether the results of the latter procedure would be amenable to simple interpretation.

It has previously been shown that under the conditions of the direct method the hypobromite will not react appreciably with the amide groups of most fatty acids and the method has been used successfully by Taylor[5], Krieble and Holst[4], Sanders[37], and Stone[2], in similar investigations. Together with the supplementary distillation technique a wide range of amides may be investigated and these two methods have been used throughout the present investigation.

The sodium hypobromite solution was standardised by titrating, with standard sodium thiosulphate solution, the iodine released by the oxidation of potassium iodide.

$$NaBrO + 2KI + H_2O \longrightarrow NaBr + 2KOH + I_2$$

$$I_2 + 2Na_2S_2O_3 \longrightarrow Na_2S_4O_6 + 2NaI$$

When ammonia was present in the hydrolysate and reacted with some of the hypobromite there was a decrease in the volume of thiosulphate required to react with the iodine. This decrease gave a direct measure of the quantity of ammonia in the hydrolysate and the extent of hydrolysis could thus be determined. Trials using ammonium sulphate indicated that

these methods were capable of estimating the ammonia present
to within ±2% under the experimental conditions.

Calibrations.

A set of weights, from 50g. to .01g. was calibrated
against the laboratory 50g. standard.   All volumetric
apparatus used was calibrated with the aid of these weights.
However, the individual ammonia determinations were accurate
only to within ±2%.   Thus the use of "B" grade apparatus
made the use of the calibrations necessary only in the
preparation of the primary standard solutions of sodium
thiosulphate and of hydrochloric acid

(ii) Reagents

Except where indicated, all chemicals used were of
A.R. quality.

Borax - Sodium Hydroxide Solution.

20g. of sodium hydroxide and 50g. of borax were
dissolved in about 800 ml. of water and the solution boiled
for 30 minutes to expel ammonia.   After cooling the solution
was made up to 1 litre.

Potassium Iodide Solution

25g. of potassium iodide were dissolved in 500 ml. of
distilled water and the solution stored in a brown bottle.

4N Sulphuric Acid.

56 ml. of concentrated "puriss" sulphuric acid was made up
to 500 cc. with distilled water.

.02N Sulphuric Acid.

1.4 ml. of concentrated sulphuric acid was made up to
500 ml. with water.

Starch Solution.

1.25g. of soluble starch and 1g. of salicylic acid were
dissolved in water and the solution made up to 500 ml.

Hydrochloric acid Solutions.

An approximately 1N solution was prepared from concentrated hydrochloric acid and the solution standardised with anhydrous sodium carbonate using bromo thymol blue indicator[6]. Acid of the normality required for the hydrolyses was then prepared by dilution of this acid.

Sodium Thiosulphate Solution.

An approximately .1N solution was prepared and a small amount of sodium carbonate added as a preservative. This solution was standardised against potassium iodate at intervals of about two weeks throughout the investigation as some reduction in strength was found to occur. The .01N solution was prepared each day by ten-fold dilution with distilled water[7].

Borate Buffer

47g. of boric acid and 8.6g. of sodium hydroxide were dissolved in about 800 ml. of distilled water, the solution boiled for 30 minutes, cooled, and made up to 1 litre.

Bromine Solution.

20g. of potassium bromide were dissolved in a little water, 2 ml. of bromine added, the solution shaken until the bromine had completely dissolved,and made up to 1 litre with water.

Hypobromite solution.

Each day 30 ml. of bromine solution was made up to 300 ml. with borate buffer and the solution stored in a dark bottle covered with black tape. The solution, however, showed appreciable decomposition over intervals of more than one hour. To overcome this a plot of "thiosulphate" against "time" was made and used to determine the strength of the hypobromite standard at the time of estimation.

(iii) <u>Procedure for Hydrolysis Runs.</u>

A concentration of amide represented by .2 mg. of available N_2 per 15 cc. of hydrolysate (.000476 mols per litre) was convenient for the hydrolysis. The ratio of hydrochloric acid to amide groups of 131:1 in .125M hydrochloric acid was suitable to obtain the desired pseudo-unimolecularity of the hydrolysis and the concentration of ammonia produced could be conveniently handled by the semi-micro technique.

The hydrolyses were carried out in a reaction flask consisting of round flask of 800 ml. capacity to which was attached a water-cooled reflux condenser. A ground glass stoppered neck was placed at a suitable angle for the extraction of samples. The flask, containing the hydrolytic solution, was placed in a boiling water bath and the hydrolysis carried out at the equilibrium temperature attained. Temperature equilibrium varied between 97°C and 98°C, dependent upon atmospheric pressure, and all hydrolysis runs were carried out within this range.

A standard solution of the amide, of suitable concentration was prepared by direct weighing of the pure amide on a "Seko" semi-micro balance. A quantity of acid of such a volume and normality that the addition of a small pipetted aliquot of the standard amide solution gave the desired concentrations of acid and amide, was placed in the reaction flask and allowed to come to temperature equilibrium. The requisite volume of amide solution was then pipetted in and the flask shaken to ensure thorough mixing.

At suitable intervals samples were extracted, cooled in ice to 20°C, an aliquot of the hydrolytic solution withdrawn with a pipette and analysed as soon as possible. Cooling in ice to 20°C arrested the reaction sufficiently rapidly to make

the analyses at definite intervals accurate to within the experimental error.

At least two runs were carried out at each of five concentrations in the range O to .5M HCl although for a completely reliable mean it was fully realised that a greater number of runs should be carried out.   However, apart from the fact that available time was limited it was consider-ed that the good agreement obtained for duplicate runs provided a reliable basis for the broad understanding of reaction mechanisms.

(iv) Procedure for analysis.

In the direct method the aliquot was neutralised with sodium hydroxide, 10 ml. of hypobromite added by means of a pipette and allowed to react with the hydrolysate for 3 minutes.   This time of contact ensured complete reaction with the available ammonia but had to be kept rigidly constant because some decomposition of the hypobromite occurred in the presence of light and air.   5 ml. of 4N sulphuric acid and 2 ml. of potassium iodide solution were then added and the liberated iodine titrated with .01N sodium thiosulphate from a micro burette of 10 ml. capacity.

Details of the distillation apparatus used are given in Diagram I.   The receiving flask was charged with 25 ml. of .02N sulphuric acid and immersed in ice-water.   The aliquot of the hydrolysate was placed in the distilling flask, suffic-ient borax-sodium hydroxide added to make the solution distinct-ly alkaline and the apparatus immediately assembled.   The pressure in the apparatus was lowered to 20 mm. and a slow current of air passed through the system.   The distilling flask was then immersed in a beaker of water maintained at 40°C and distillation carried out for 15 minutes.   These
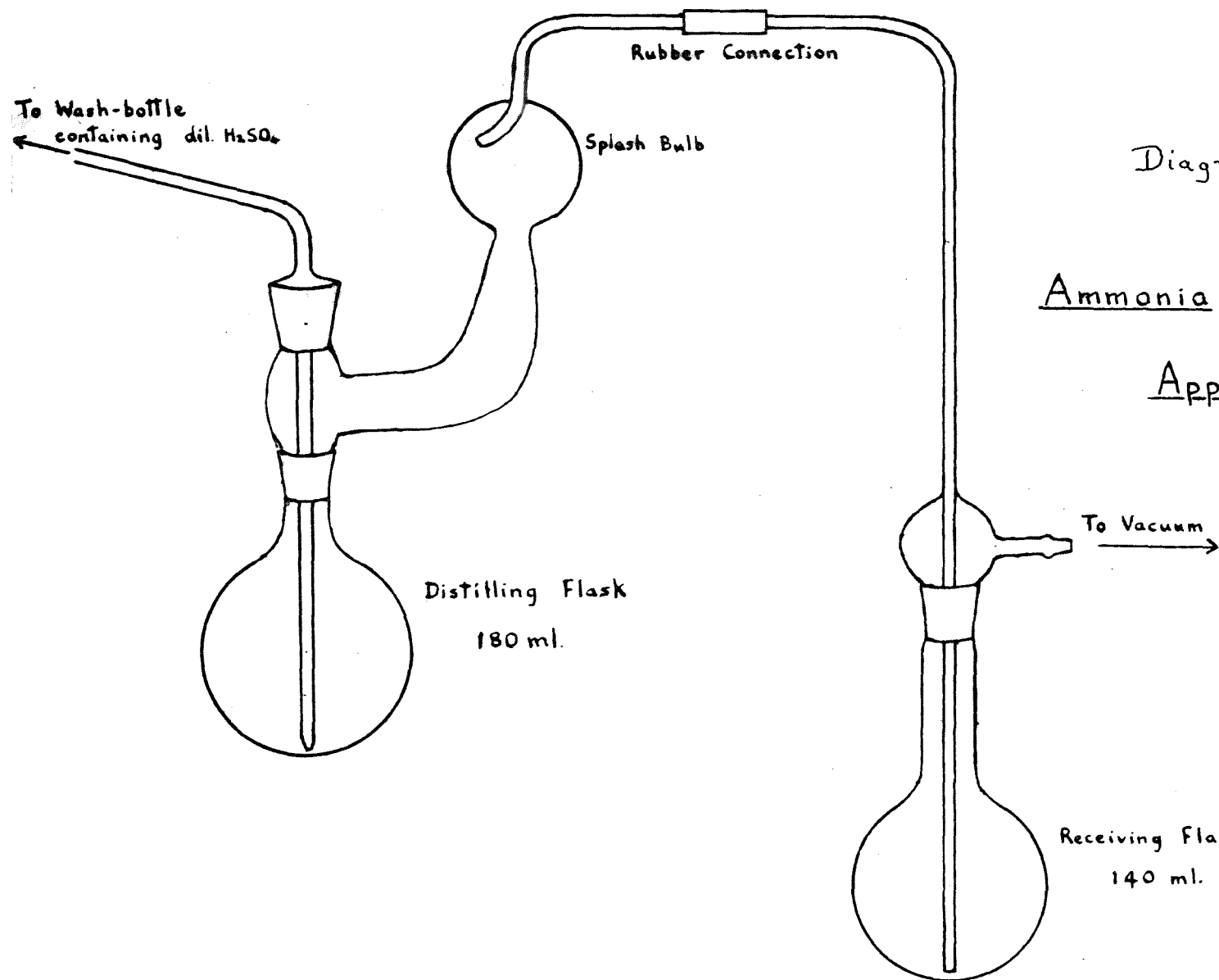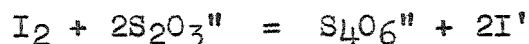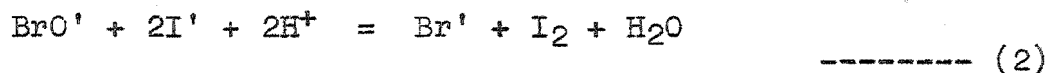
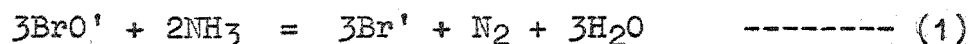To Wash-bottle
containing dil. H_2SO_4

Rubber Connection

Splash Bulb

Diagram I

Ammonia   Distillation

Apparatus.

To Vacuum

Distilling Flask

180 ml.

Receiving Flask

140 ml.

conditions were found to be satisfactory by performing
trial runs on ammonium sulphate at similar concentrations.
The ammonia collected in the receiving flasks was then
estimated with hypobromite as previously described.

In both methods the hypobromite was standardised by
complete duplication of the processes involved, using,
instead of the hydrolysate, an aliquot of acid of the same
normality as used for the hydrolysis.

(v) Calculation and Expression of Results.

The following equations describe the reactions of the
analysis.

$$3BrO' + 2NH_3 = 3Br' + N_2 + 3H_2O \qquad \text{-------- (1)}$$
$$BrO' + 2I' + 2H^+ = Br' + I_2 + H_2O$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad \text{-------- (2)}$$
$$I_2 + 2S_2O_3'' = S_4O_6'' + 2I'$$

In (1) $\frac{3}{2}$ mol. of BrO' react with 1 mol of NH_3

In (2) $\frac{1}{2}$ mol of BrO' is equivalent to 1 equiv. of S_2O_3''

i.e. 3 equivs. of S_2O_3'' are equivalent to 1 mol of NH_3

Hence the reduction in the thiosulphate titration value is
directly proportional to the amount of NH_3 present.

i.e. 1 ml. of .01N $Na_2S_2O_3$ is equivalent to .0467 mg. of N_2

Let w_{mg} be the weight of available N_2 per aliquot

x_{ml} be the decrease in titre at time t

N be the normality of the $Na_2S_2O_3$

Then weight of hydrolysed N_2 present per aliquot

$$= .0467 \times \frac{N}{.01} \times x$$

$$= y_{mg}$$

and weight of unhydrolysed N_2 per aliquot $= w - y_{mg}$

Since the conditions of the hydrolysis were designed to
make the reaction first order the kinetics should be described
by the equation

$$- \frac{dc}{dt} = kc \quad \text{----------}$$

(where c is the concentration of amide at time t and k is the
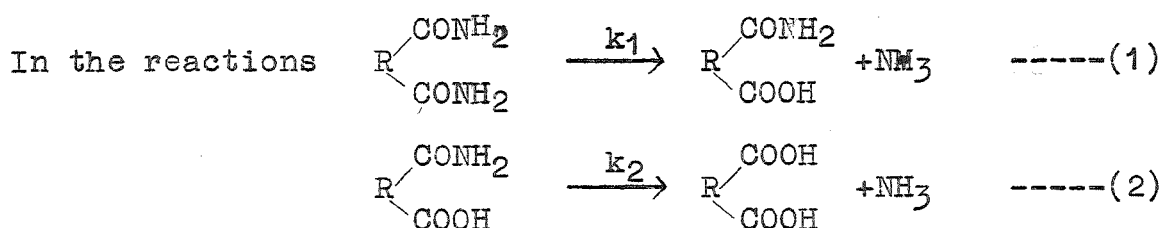rate constant of the hydrolysis)

or $\quad - \frac{d(\ln c)}{dt} = k.$

Hence a plot of "ln c" against "time" should be linear and of slope $-k$. As the value of k so obtained will be independent of the units of concentration it has been convenient to plot "log (mg of unhydrolysed N_2 per aliquot)" against "time" to obtain k. The percentage hydrolysis of each aliquot was also determined and "(percentage hydrolysis)" against "time" graphs plotted.

(vi) <u>Interpretation of the experimental results</u>.

In the case of a monoamide the rate constant obtained in the "ln(w - y)"/"time" plot is the rate of hydrolysis per amide group, as well as the rate of hydrolysis per molecule since the two are identical. In the case of a diamide simultaneous hydrolysis of both groups must be regarded as improbable and it is therefore important to clarify the relationship between the rates of the two consecutive hydrolyses and the overall rate of hydrolysis measured in the "ln(w - y)"/"time" plots.

Swain[8] has given a rigid mathematical analysis of the kinetics of two consecutive first order reactions and concludes that the initial slope of the graph of "ln(w - y)" against "time" is $\frac{k_1}{2}$, where k_1 is the rate constant of the first reaction, and that the final slope is k_2 where k_2 is the rate of the second reaction. A simpler proof has been developed and is given below

In the reactions $R\diagup^{CONH_2}_{\diagdown CONH_2} \xrightarrow{k_1} R\diagup^{CONH_2}_{\diagdown COOH} + NH_3$ -----(1)

$R\diagup^{CONH_2}_{\diagdown COOH} \xrightarrow{k_2} R\diagup^{COOH}_{\diagdown COOH} + NH_3$ -----(2)

k_1 applies to the rate constant of the hydrolysis of diamide to monoamide (1) and k_2 to the rate constant of the hydrolysis of monoamide to dicarboxylic acid (2)

Then using the same symbols as p.12

$\frac{w}{2mg}$ is the total weight of amide N_2 per aliquot available for reaction (1)

At the beginning of the reaction t and y are small.

$$-k_1 = \frac{d}{dt} \ln(\frac{w}{2} - y)$$

$$= \frac{d}{dt} \ln(1 - \frac{y}{\frac{w}{2}}) + \frac{d}{dt} (\ln\frac{w}{2})$$

$$= \frac{d}{dt} (-\frac{y}{\frac{w}{2}}) \quad \text{since } \ln(1 - x) = -x \text{ when x is small.}$$

k applies to the overall reaction rate as determined experimentally

$$-k = \frac{d}{dt} \ln(w - y)$$

$$= \frac{d}{dt}(-\frac{y}{w}) \quad \text{--------- as above}$$

Whence $k = \frac{k_1}{2}$ as $t \longrightarrow 0$.

As $t \longrightarrow \infty$, w and y are almost equal and reaction (1) is almost complete.

Then for reaction (2)

$$-k_2 = \frac{d}{dt} \ln\left[\frac{w}{2} - (y - \frac{w}{2})\right]$$

But as $t \longrightarrow \infty$ $(y - \frac{w}{2}) \longrightarrow \frac{y}{2}$

whence $-k_2 = \frac{d}{dt} \ln(\frac{w}{2} - \frac{y}{2})$

$$= \frac{d}{dt} \ln(w - y)$$

Whence as $t \longrightarrow \infty$ $k_2 = k$

Thus we have $k_1 = 2k$ as $t \longrightarrow 0$

$$k_2 = k \text{ as } t \longrightarrow \infty$$

In general it is not possible to obtain k_1 and k_2 very accurately from the graphs at $t = 0$ and $t = \infty$. Swain, by the solution of a general equation, has developed a simple graphical method to obtain k_1 and k_2 to within an accuracy of 1% This method has been used in the present discussion of the hydrolysis of malonamide and oxamide.

It is important to realise that k_1 is equal to $2k$ as
$t \longrightarrow 0$ because the presence of two amide groups has doubled
the probability of the occurrence of hydrolysis. It may
therefore be said that k measures the rate of hydrolysis per
amide group and that over the whole "$\ln(w - y)/t$" plot k
measures the average rate of hydrolysis per amide group at
any instant.

When the rates of hydrolysis of the amide groups in the
mono-and diamide are the same the value of k will be constant
and the "$\ln(w - y)/t$" plot for the whole hydrolysis will imply
a single continuous first order reaction. When the rate of
hydrolysis of the two amide groups are not equal the average
rate of hydrolysis per amide group will vary with time and
the "$\ln(w - y)/t$" plot will not be mono-linear. Examples of
these two types are given in Stone's[2] work on the hydrolysis
of malonamide and amino malonamide respectively.

The emphasis which has been placed (p.15) on the fact
that the "$\ln(w - y)/t$" plot gives (as its slope at any instant),
the average rate of hydrolysis per amide group recalls a
similar problem encountered by Meyer[40] in the hydrolysis of
esters. He observed that hydrolysis, in acid and alkali,
of glycol diacetate and of glycerol triacetate took place in
2 and 3 steps respectively and that the ratio of the rate
constants for the steps were 2:1 and 3:2:1 respectively. In
these instances there exists a similar relationship in the
rate of hydrolysis of the ester groups to that of the amide
groups of malonamide. With the hydrolysis of the esters of
dibasic acids in acid he obtained rate constants in the ratio
of 2:1 but in alkali no such relationship existed. It seems
clear that in the alkaline solution the negatively charged
carboxylate ion present after the first stage influenced the
rate of the second stage by producing a marked change in the

electronic environment of the second hydrolysable group.

A similar arrangement of rate constants was obtained by Stone[2] with amino malonamide. In this case the plot of "$\ln(w - y)$" against "time" was not linear and it was suggested that partial "zwitterion" formation occurred after hydrolysis of one amide group and that its formation affected the rate of hydrolysis of the second amide group.

The main points of this discussion may be summarised as follows:-

(1) The slope of the "$\ln(w - y)$" against "time" plots measure, with both mono and diamides, the average rate of hydrolysis per amide group at any instant.

(2) In a consecutive reaction

$$2k = k_1 \text{ as } t \longrightarrow 0$$

$$k = k_2 \text{ at } t \longrightarrow \infty$$

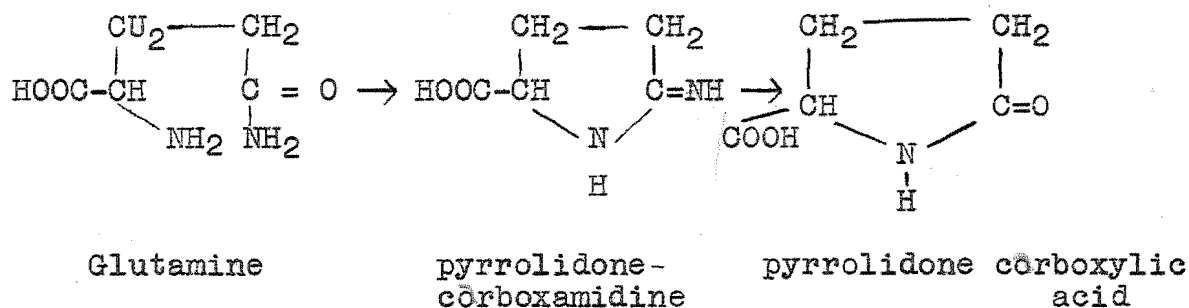where k is the slope of the graph at time t

and k_1 and k_2 the rate constants of the first and second reactions respectively.

(3) In the case where the rate of hydrolysis per amide group is constant the hydrolysis will appear as a single, continuous, pseudo-unimolecular reaction.

III   γ AMINO BUTYRAMIDE

Penfold[1] and Hogg[3], from their work on the hydrolysis

of glutamine, have proposed a mechanism involving an intermed-

iate, pyrrolidonecorboxamidine, and have obtained the rate

constants of the two steps:

$$\underset{\text{Glutamine}}{\begin{matrix} CU_2\!-\!-\!CH_2 \\ | \qquad | \\ HOOC\!-\!CH \quad C=O \\ \diagdown NH_2 \; NH_2 \end{matrix}} \rightarrow \underset{\substack{\text{pyrrolidone-}\\\text{corboxamidine}}}{\begin{matrix} CH_2\!-\!CH_2 \\ | \qquad | \\ HOOC\!-\!CH \quad C=NH \\ \diagdown N \diagup \\ H \end{matrix}} \rightarrow \underset{\substack{\text{pyrrolidone corboxylic}\\\text{acid}}}{\begin{matrix} CH_2\!-\!-\!CH_2 \\ | \qquad | \\ CH \qquad C=O \\ COOH \diagdown N \diagup \\ H \end{matrix}}$$

Some evidence for such a course of reaction was obtained

by each of the two workers but further investigation was

desirable.   If the suggested sequence of reactions is correct

it is conceivable that a similar intermediate might be formed

in the hydrolysis of any γ amide, the simplest being γ amino

butyramide.   Observations on the rate and manner of hydrolysis

of the butyric acid derivative might throw further light on the

mechanism of glutamine hydrolysis, and any evidence of inter-

mediate ring formation would be of considerable general interest.

As will be seen, however, attempts to prepare the amide in

these laboratories have proved unsuccessful and the objective

of this part of the research work has not been achieved.

Attempted preparation of γ amino butyramide.

No reference to this amide could be found in the litera-

ture although Kanewskaja[9] has described the amide of

benzolated γ amino butyric acid which he prepared from the methyl

ester of γ benzomino butyric acid and alcoholic NH_3.   It was

therefore decided to attempt the preparation of γ amino

butyramide from the ethyl ester, the preparation of which has

been described by Tafel and Stern[11].

γ amino butyric acid itself has been prepared by a number

of investigators.   Gabriel[12,13] obtained it from potassium

phthalimide and ɤchloro butyronitrile and full details of a
modification of this method are given in Organic Syntheses[14].
Schotton[15], Gabriel[13] and Abderbalden and Kautzch[16] have
described the preparation of the acid by the oxidation of
pipenylurethone with fuming nitric acid.   Arhusov and
Poshil'tsova[17] have obtained the acid by hydrolysis with
hydrochloric acid of ɤamino butyronitrile prepared by the
catalytic reduction of succinonitrile over Raney Nickel.   The
nitrile has also been prepared by Kiel[18] from ɤchloro
butyronitrile and alcoholic ammonia.   The possibility of
direct hydrolysis of the nitrile to the amide under the in-
fluence of alkaline hydrogen peroxide added to the desirability
of preparation of the acid via the nitrile.   An attempt at
this direct hydrolysis of an intermediate might have proved
fruitful as the successful ammonolysis of the ester has not
been described.

The method of Arhusov and Poshil'tsova which appeared to
give a readily available quantity of the acid in good yield was
first attempted.   This method required the partial hydrogen-
ation of succinonitrile at 75 - 80°C and .5 - .8 atm. pressure.

$$
\begin{array}{ccccc}
CH_2 - CN & & CH_2 - CH_2NH_2 & & CH_2 - CH_2 - NH_2 \\
| & \xrightarrow[Raney\ Ni]{(H_2)} & | & \xrightarrow[HCl]{Hydrolyse} & | \\
CH_2 - CN & & CH_2 - CN & & CH_2 - COOH \\
\end{array}
$$

Succinon-
itrile   ɤamino butyric
                                                                   acid
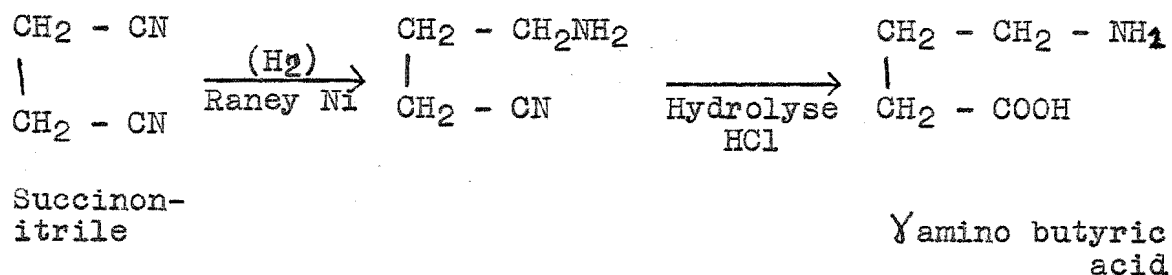
An apparatus consisting of 2 gas burettes controlled by
mercury, a monometer and a reaction flask, to contain the
succinonitrile and the catalyst in butyl alcohol, was assembled.
The volume of hydrogen added was measured by the gas burette,
and the required pressure obtained by adjustment of their mercury
levels.   The reaction flask was heated by the passage of a
current of water through a coil set in the flask and the flask
contents agitated by means of a shaking device.

Succinonitrile was prepared by the action of concentrated aqueous potassium cyanide on a boiling solution of ethylene dibromide in alcohol as described by Fauconnier[21]. It was obtained as a waxy hygroscopic solid (solidification point 52°C) on fractional distillation of the resulting solution when it distilled over at 146° - 148°C at 10 mm. in 30% yield (Fauconnier cit. 75-80%). The catalyst was prepared as described by Mozingo[22] and the hydrogen obtained from a cylinder and used after oxygen had been removed by passage through Fieser's reagent[23].

About 1g. of succinonitrile in butyl alcohol solution and a quantity of the activated catalyst were placed in the flask and the H_2 added from the gas burettes as required. Circulation of water and violent shaking were maintained until sufficient hydrogen had been adsorbed or absorption had ceased without addition of sufficient hydrogen.

The 2:1 ratio of nitrile to catalyst by weight used by these authors failed to produce complete hydrogenation in the 19 hour interval quoted. However, higher ratios of 1:1 and 2:1 gave complete hydrogenation in 8-10 and 4-6 hours respectively. In all cases the odour of ammonia was conspicuous immediately after opening the hydrogenation flask; this suggested that side reactions had occurred.

The product of the hydrogenation was a black odiferous liquid which, after the nickel had been filtered off and the butyl alcohol removed, left a black semi-solid oil. Attempts to benzoylate this residue as described by the authors were unsuccessful as any deposit of oil was lost in a voluminous precipitate of nickel hydroxide produced in the alkaline solution. It appeared possible that the nickel was attached to the amine by some type of chemical bonding.

The black residue obtained after the removal of the

of the butyl alcohol was dissolved in chloroform and after
passage of dry HCl a black precipitate, which should have
been the amine salt, was obtained. After separation from
the chloroform the solid was dissolved in water and the
flocculent white precipitate obtained on addition of alkali
filtered off. The filtrate was extracted with chloroform
and a small quantity of a light brown oil obtained from the
extract. On hydrolysis with hydrochloric acid this oil
yielded a trace of a substance with the characteristic foul
odour of the hydrochloride of ɣ amino butyric acid some of
which had been obtained by the oxidation of piperylurethane
(vide infra). Although the knowledge of this reaction was
incomplete it was abandonded when such small yields were ob-
tained from repeated trials as it appeared unsatisfactory for
the ready production of ɣ amino butyric acid.

An attempt was made to produce ɣ amino butyric acid by
the oxidation of piperylurethane with fuming nitric acid as
described by Schotten[15]
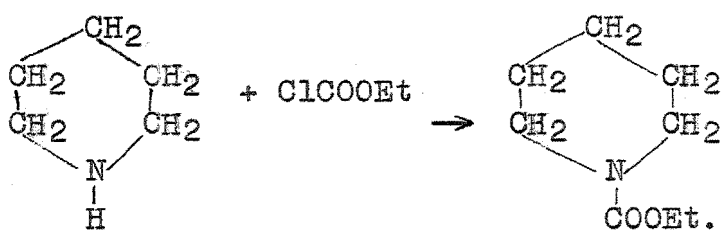
Piperidine   Piperylurethane
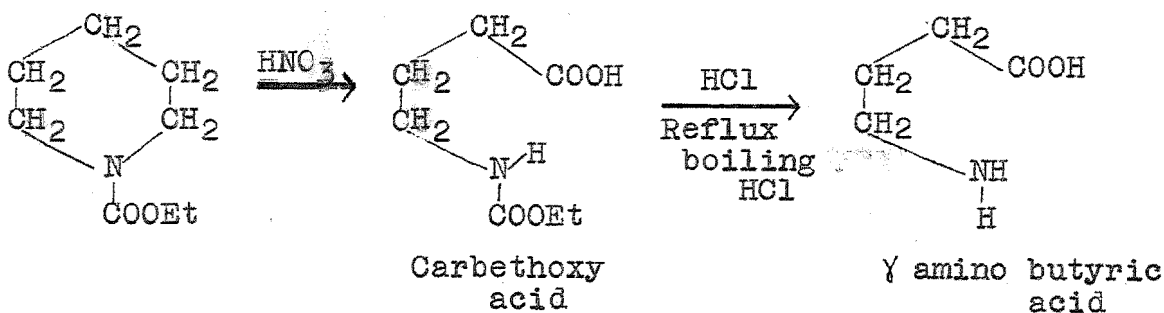
Carbethoxy   ɣ amino butyric
acid   acid

Piperylurethane was prepared by addition of ethyl chloro-
formate to piperidine in aqueous solution as described by
Schotten[24]. Being insoluble and slightly heavier than water
the piperylurethane was easily separated and purified by

distillation when a 60% yield distilling at 114°C was obtained.

The oxidation of piperylurethane was then carried out as described by Gabriel[13]

10 cc. of piperylurethane were dropped gradually into 20 cc. of fuming nitric acid and, after pouring into water, the carbethoxy acid extracted with benzene. The extracted acid was heated with concentrated hydrochloric acid under reflux for 2 hours when the solution became very dark. After concentration on a water bath the acid was boiled with silver carbonate, filtered to remove silver chloride, treated with hydrogen sulphide, filtered to remove silver sulphide and the solution of the free acid concentrated to a smaller volume. Several times this volume of methanol was then added, followed by just sufficient ether to make the solution milky and then a few drops of methanol until it became clear again. The resulting solution was very reluctant to crystallise but after keeping in a refrigerator for a week a few crystals m.p. 190°C (dec.) were obtained. The melting point obtained by Gabriel[13] was 184°C but Tafel and Stern[11] reported a melting point of 202°C. This variation of the melting point is compatible with the decomposition observed here.

Repeated attempts to obtain a larger yield of these crystals gave only a heavy brown oil which would not crystallise. For this reason attempts were made to produce the ester directly from the crude hydrochloride by esterification by the Fisher-Spier method as described by Tafel and Stern[11]. The crude hydrochloride of the acid was dried over concentrated sulphuric acid and treated with dry hydrogen chloride for 2 hours in alcoholic solution. After boiling with activated carbon the alcohol was removed to leave a brown oil which on standing separated to a pasty mass. Attempts to purify this by solution in alcohol and precipitation with ether returned

it once more to an oily condition.

Kanewskaja obtained, on benzoylation of the crude hydro-
chloride, a good yield of an oil which crystallised on cooling
but when this was attempted the oil obtained failed to crystall-
ise.   It does seem that in the hydrolysis of the carbethoxy
acid a breakdown had occurred to give an impurity not obtained
by other workers and which prevented crystallisation of the
products obtained.   Since the preparation appeared to be at a
standstill, due, at least in part, to the operator's inability
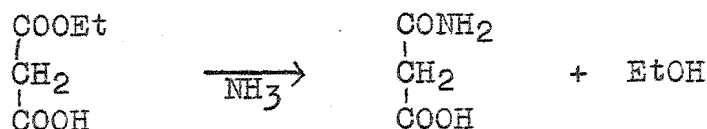to handle such oils, it was abandoned at this stage.

IV <u>AMIDES OF MALONIC ACID.</u>

In the investigation, in this Department, of the effects of substituents on the rate of hydrolysis of ₵-substituted malonamides Stone[2] found that the hydrolysis of malonamide was represented in the "ln(w - y)" against "time" plots by a simple monolinear graph.   This meant that the hydrolysis of malonamide could be a single continuous first order reaction, or a consecutive reaction in which the rate of hydrolysis of the two groups is the same. (c.f. Page 13 et seq.).   To distinguish between these two possibilities a study of the rate of hydrolysis of the half amide, malonamic acid, was desirable. This was undertaken and is described, together with the correlation of the data so obtained with that obtained by Stone[2] for malonamide, in this section of the present investigation.

A   <u>Malonamic Acid</u>

(i) Malonamic acid was prepared by the reaction of ethyl hydrogen malonate with .880 ammonia at $0^{o}C$ as described by Jeffrey and Vogel[25]

$$
\begin{array}{ccc}
\begin{array}{l} COOEt \\ | \\ CH_2 \\ | \\ COOH \end{array} & \xrightarrow{NH_3} & \begin{array}{l} CONH_2 \\ | \\ CH_2 \\ | \\ COOH \end{array} \quad + \quad EtOH
\end{array}
$$

<u>Ethyl hydrogen malonate</u>

This was obtained by Walker's[26] method of half saponification of diethyl malonate with alcoholic potassium hydroxide. 40g. of malonic ester were dissolved in 150 ml. of alcohol and a solution of 14g. of potassium hydroxide in alcohol added gradually from a dropping funnel.   After digesting for $1\frac{1}{2}$ hours on a water bath the alcohol was removed, the mixed mono- and dipotassium salts dissolved in water and any unsaponified diester removed by extraction with ether.   After dehydration the dry potassium salts were separated by extraction of the

ethyl potassium malonate with boiling alcohol in a soxhlet apparatus. The salt so obtained was dissolved in a little water, acidified with an equivalent quantity of sulphuric acid to liberate the free acid and extracted with ether. The ethereal solution was washed with a little water, dried over sodium sulphate and the ethyl hydrogen malonate obtained by distillation at 140 - 141°C (20 mm.) in an overall yield of 40%. Jeffrey and Vogel reported a boiling point of 145 - 146°C at 18 mm. but do not give a yield.

Malonamic Acid

21g. of ethyl hydrogen malonate was reacted with 35 ml. of .880 ammonia at 0°C for 48 hours and, after acidification with excess ice cold dilute sulphuric acid, extracted with methyl ethyl ketone. The extract was dried and the methyl ethyl ketone removed, leaving a light brown oil. This oil yielded crystals of malonamic acid on addition of ether and stirring, the yield being about 3g. or 14%. The product melted at 110 - 114°C and after three recrystallisations melted at 118°C. It should be pointed out that Jeffery and Vogel[25] recommended the use of diethyl ketone for extraction but this was not available. In this way they obtained a yield of 53% which, after five recrystallisations, melted at 121°C. In this connection also, Galat[27] claimed a yield of 61% by the use of isopropanol to extract the malonamic acid and quoted a melting point of 110 - 115°C (dec)

In a further experiment excess ammonia was removed from the reaction mixture by drawing a current of air, at reduced pressure, through the solution cooled to 0°C. Much less acid was then needed for acidification and the subsequent extraction with methyl ethyl ketone was correspondingly more efficient. The yield of malonamic acid was thus raised by

'more than one third to ca. 20%.

(ii) Method of Analysis

A trial showed that there was no appreciable reaction between malonamic acid and hypobromite at the concentrations used in the experiment. The direct method of analysis of the ammonia present was therefore used.

(iii) Kinetics of the hydrolyses

The "$\ln(w - y)$" against "time" plots obtained as described on page 12 were all linear throughout their entire length.   Table II, giving the results for .125 M hydrochloric acid, and Graphs IIB and IIA giving the corresponding "$\ln(w - y)$" against "time" and "percentage hydrolysis" against "time" graphs respectively, have been included as typical samples of the results obtained.   In Graph IIB the "$\ln(w - y)$" axis has been displaced as shown to allow the separate graphs to be plotted on the same page.

The rate constants obtained from the slopes of the "$\ln(w - y)$/time" graphs are given in the following table:

Table I

M_{HCl}	k obtained		Mean Value of k
.0625	.0071	.0072	.0072
.125	.0148	.0144	.0147
	.0151	.0145	
.20	.0230	.0230	.0230
.25	.0262	.0269	.0265
.35	.0335	.0343	.0339
.5	.0496	.0505	.0504
	.0504	.0511	

A plot of k/M_{HCl} (Graph I) was linear giving a value of k equal to .0015 at t = 0, and the catalytic coeficient obtained from the slope of this graph was .098

Thus the rate of hydrolysis may be described by

$$k = .0015 + .098 \; M_{HCl}$$

Table II

Malonamic Acid in .125 M HCl

Key:- t   =   time mins.

       V   =   Volume of the thiosulphate titre

       ΔV   =   Decrease in the volume of thiosulphate titre

       y   =   mg. of nitrogen hydrolysed per aliquot

       w - y   =   mg. of nitrogen not hydrolysed per aliquot

       ln(w - y) = $\log_e$(w - y)

       %   =   percentage hydrolysis of the amide

       w   =   total mg. of hydrolysable nitrogen present
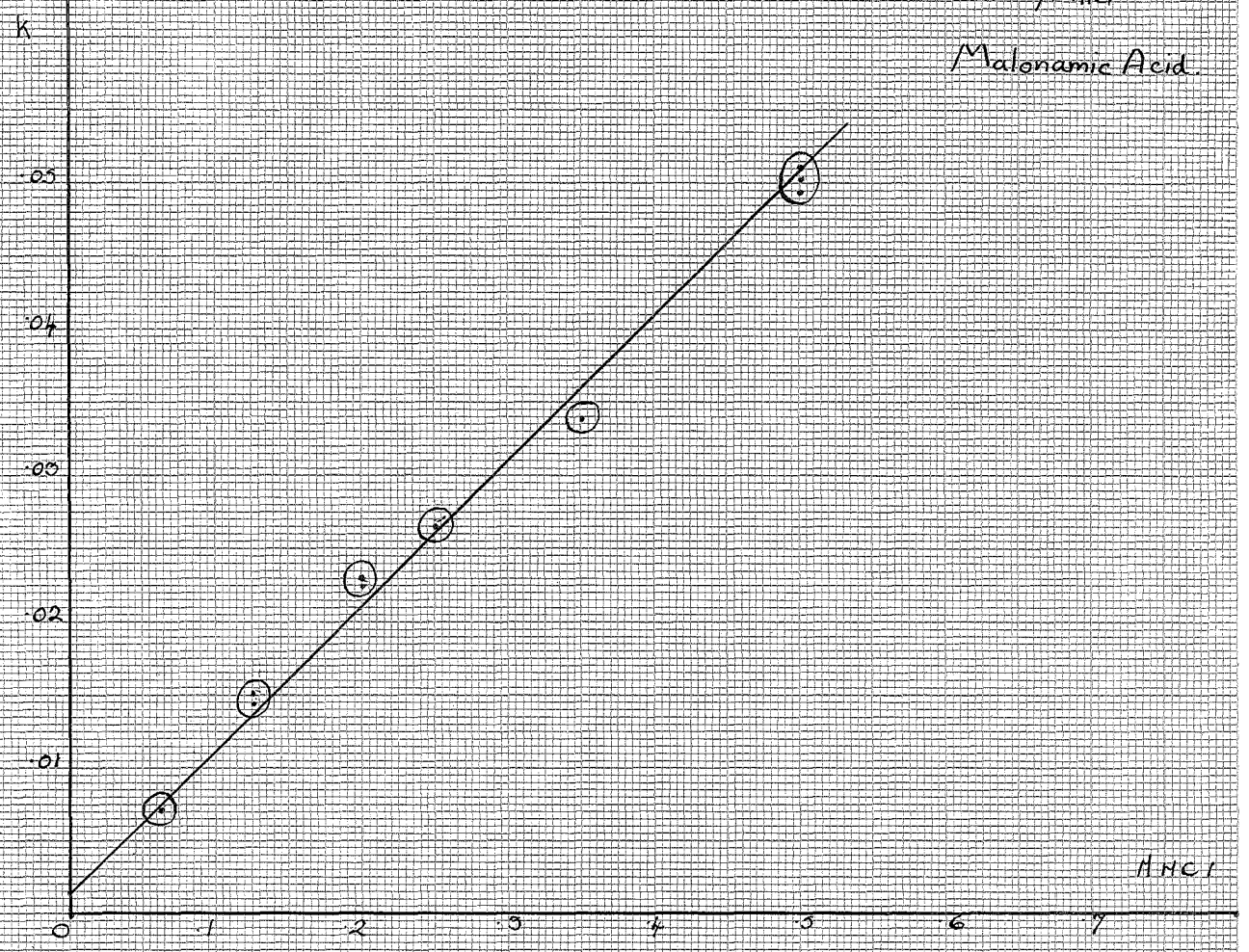   per aliquot.

t	V	ΔV	y	w - y	-ln(w - y)	%
0	6.59	0	0	.1667	1.79	0
1. 2	6.51	.08	.0036	.1631	1.81	2.2
10	6.13	.46	.0205	.1462	1.92	12.3
30	5.35	1.23	.0548	.1119	2.19	32.9
					k = .0144	
50	4.71	1.86	.0829	.0838	2.48	49.8
70	4.17	2.39	.1066	.0601	2.78	63.9
90	3.84	2.71	.1208	.0459	3.08	72.5
110	3.62	2.93	.1307	.0360	3.33	78.4
130	3.38	3.16	.1408	.0259	3.65	84.5
150	3.22	3.31	.1476	.0191	3.95	88.6
2. 0	6.60	0	0	.1667	1.79	0
2	6.49	.11	.0049	.1618	1.82	2.9
15	5.81	.79	.0352	.1315	2.03	21.2
25	5.55	1.05	.0468	.1199	2.12	28.1
					k = .0148	
40	5.02	1.58	.0705	.0962	2.34	42.3
55	4.52	2.08	.0929	.0738	2.60	55.8
70	4.19	2.41	.1075	.0592	2.82	64.5
90	3.84	2.76	.1231	.0436	3.13	78.8

Table II (contd.)

	t	V	ΔV	y	w − y	−ln(w − y)	%
3.	0	6.38	0	0	.1667	1.79	0
	2	6.25	.13	.0058	.1609	1.83	3.5
	13	5.79	.59	.0263	.1304	2.04	15.8
	28	5.12	1.26	.0562	.1105	2.20	33.7
						k = .0151	
	40	4.72	1.66	.0741	.0926	2.38	44.4
	51	4.43	1.95	.0871	.0796	2.53	52.3
	70	4.00	2.38	.1062	.0605	2.80	63.7
	90	3.60	2.78	.1239	.0428	3.15	74.3
4.	0	6.38	0	.0060	.1667	1.79	0
	2	6.21	.17	.0076	.1591	1.84	4.6
	15	5.66	.72	.0321	.1346	2.01	19.3
						k = .0145	
	30	5.05	1.33	.0593	.1074	2.23	35.6
	45	4.60	1.78	.0794	.0873	2.44	47.6
	60	4.20	2.18	.0972	.0695	2.66	58.4
	75	3.92	2.46	.1096	.0571	2.85	65.7

Graph I

Plot k/M_{HCl}

Malonamic Acid

k

·05

·04

·03

·02

·01

M_{HCl}

0   ·1   ·2   ·3   ·4   ·5   ·6   ·7

Graph III

Plot k/M_{HCl}

Malonamide

k

·05

·04

·03

·02

·01

M_{HCl}

0   ·1   ·2   ·3   ·4   ·5   ·6   ·7
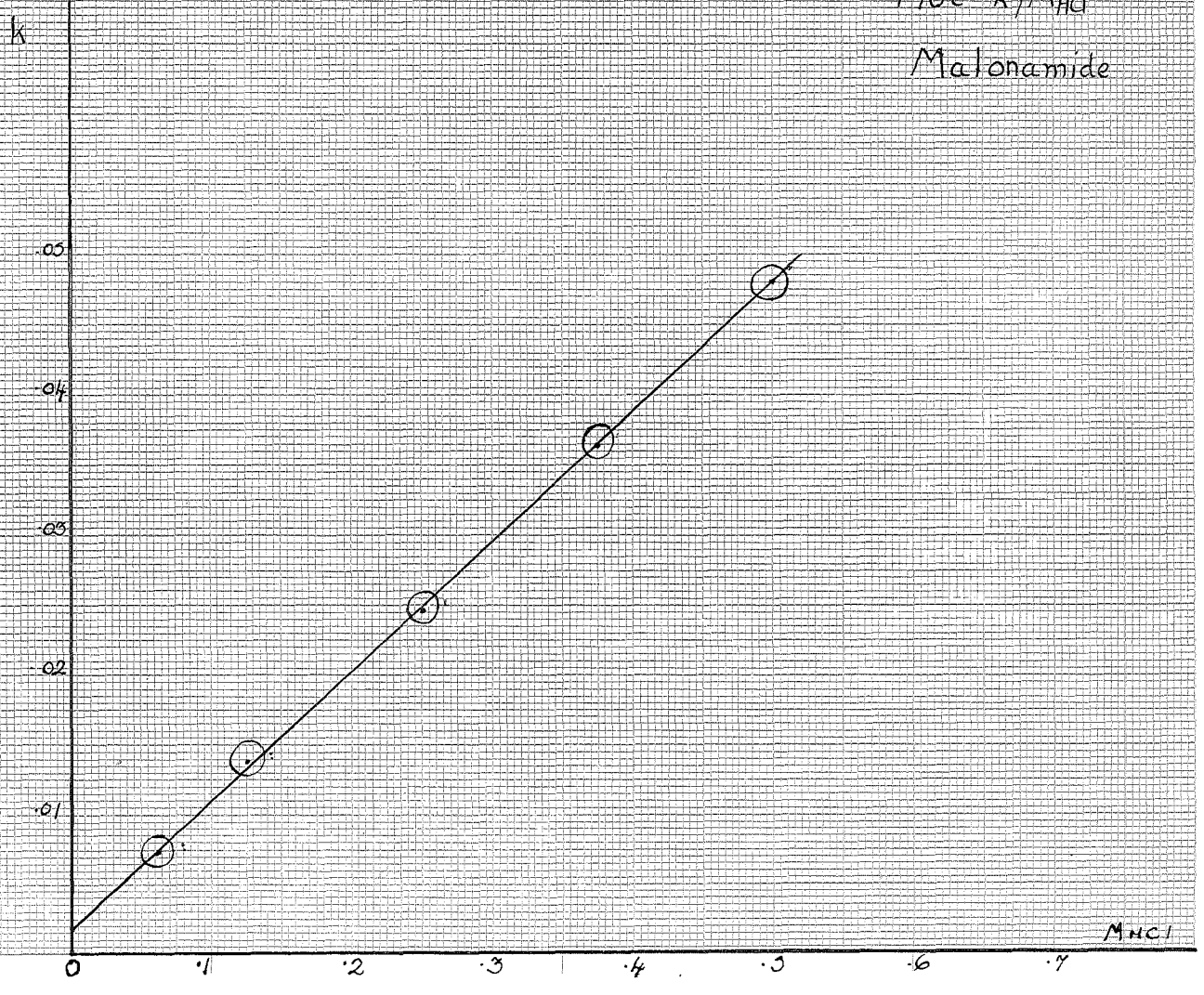
Graph II

Malonamic Acid in ·0625 M HCl

(A) % Hydrolysis / time

Percentage
Hydrolysis

Time mins

(B) ln (w−y) / time

−ln (w−y)

Time mins
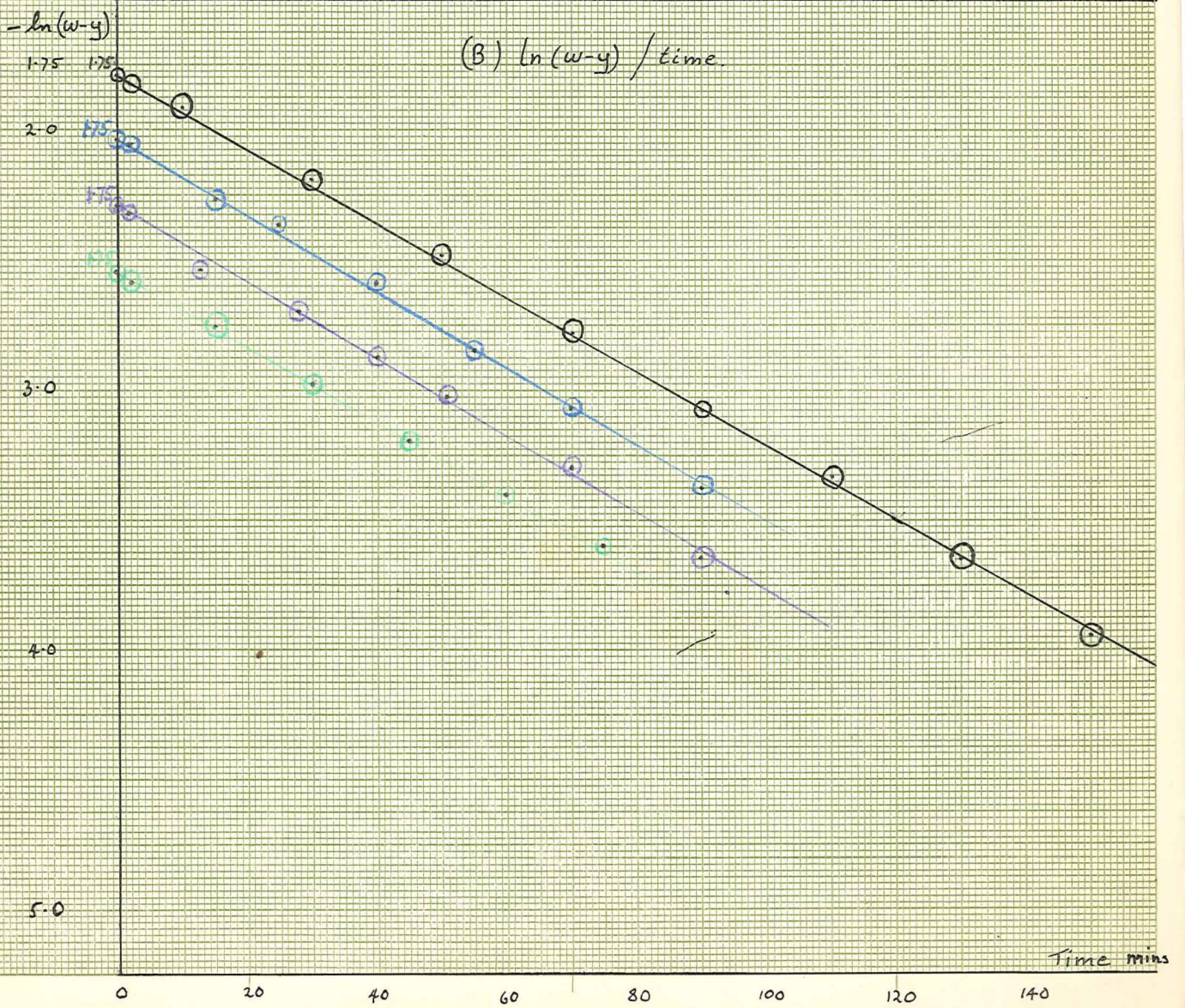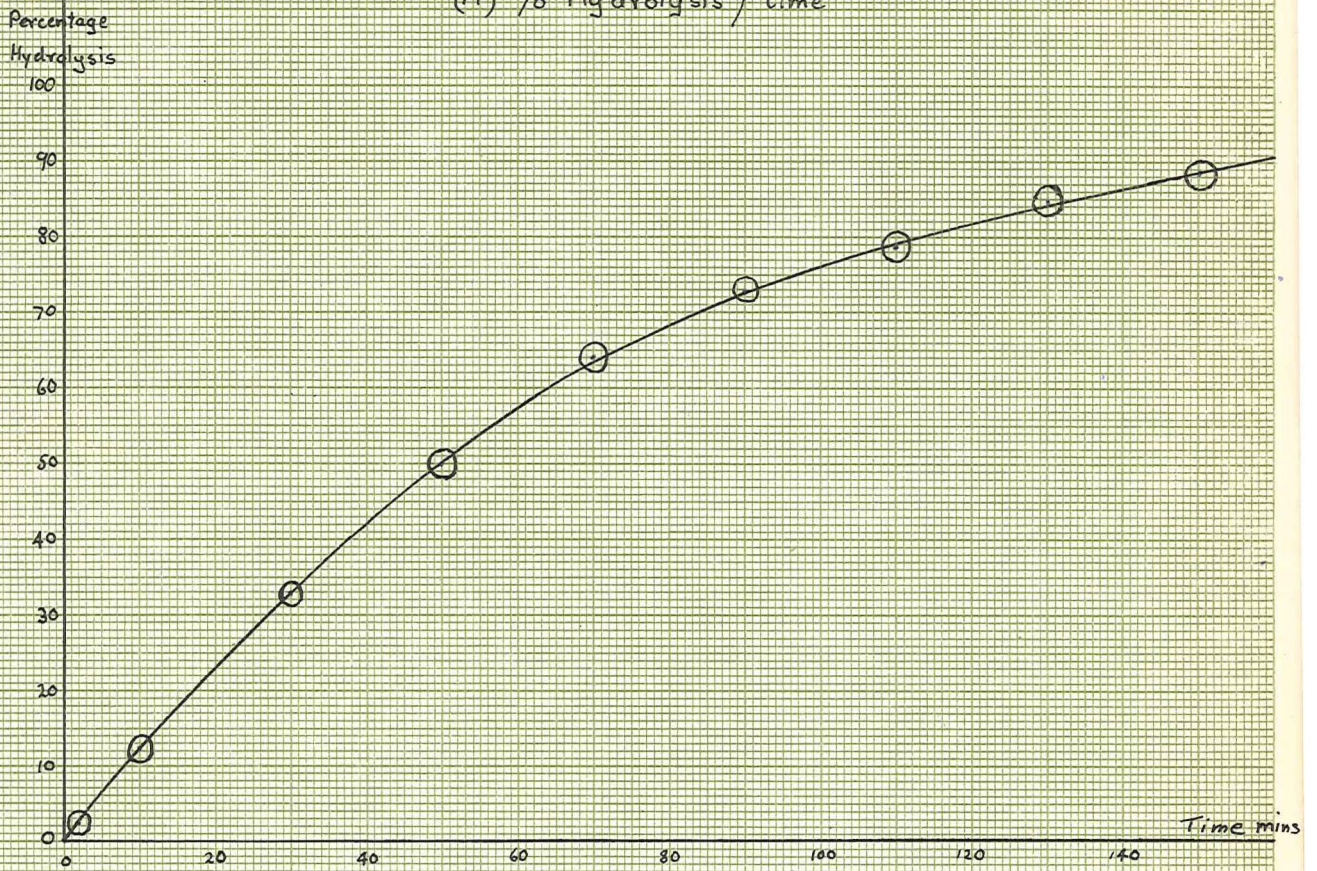
B   Malonamide

The kinetics of the hydrolysis of malonamide were studied by Stone[2]. A few runs with malonamide were carried out in the present work and the results obtained agreed with those quoted by Stone. The results gave linear "$\ln(w - y)/t$" plots and the rate constants obtained by Stone from the slopes are tabulated below

Table III

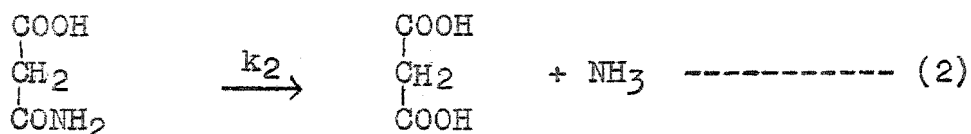| M_{HCl}	k
.0625	.0074
.125	.0139
.250	.0247
.375	.0364
.500	.0480

The plot k/M_{HCl} (Graph III) was again linear and the catalytic coeficient and the k_0 value were obtained as previously

Catalytic coef.   =   .093

k_0 =   .002

C   Discussion of the Kinetics of Hydrolysis of Malonamide

From the results given in Tables I and III it may be seen that the rates of hydrolysis of malonamic acid and malonamide at each acid concentration are almost identical throughout the range. Malonamide gives linear "$\ln(w - y)/time$" plots throughout the entire hydrolysis and is therefore a one stage reaction involving the simultaneous hydrolysis of both groups or the pseudo one stage reaction mentioned on page 15 . Since it is much more probable that it is a two stage process this latter case will be considered first.

The two reactions may be written

$$
\begin{array}{c}
CONH_2 \\
| \\
CH_2 \\
| \\
CONH_2
\end{array}
\xrightarrow{k_1}
\begin{array}{c}
COOH \\
| \\
CH_2 \\
| \\
CONH_2
\end{array}
+ NH_3 \quad \text{----------} \quad (1)
$$

$$
\begin{array}{c}
COOH \\
| \\
CH_2 \\
| \\
CONH_2
\end{array}
\xrightarrow{k_2}
\begin{array}{c}
COOH \\
| \\
CH_2 \\
| \\
COOH
\end{array}
+ NH_3 \quad \text{----------} \quad (2)
$$
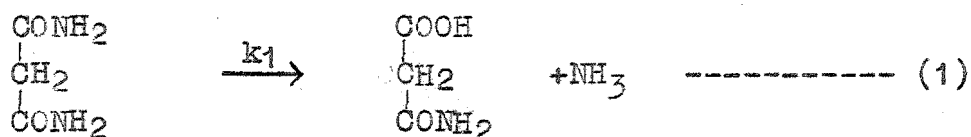
If k_1 is the rate constant of the first reaction, k_2 that of
the second reaction, and k the overall rate constant as
measured in the "ln(w - y)/time" plots, k_1 and k_2 may be
interpreted on the basis of the work of Swain[8] and of the
simpler treatment of consecutive reactions described on page
13 et seq. k_1 will be equal to 2k and k_2 equal to k
i.e. twice the slope, and equal to the slope, of the
"ln(w - y)/time" plots respectively. Since the k_2 obtained
from malonamic acid hydrolyses agrees with k_2 obtained from
malonamide the hypothesis that the hydrolysis of malonamide
is a two stage process is confirmed.

The fact that k_1 is equal to $2k_2$ may be explained by the
rate of hydrolysis per amide group (as measured graphically)
being constant and equal to k, the presence of two groups in
malonamide doubling the probability of the occurrence of
hydrolysis. This means that the proximity of the carboxyl
and amide groups have the same effect upon the rate of
hydrolysis of the amide group in acid solution. This aspect
of the hydrolysis of malonamide has been further discussed in
Section VI.

It must be mentioned here that in a recent paper[42] Hall
has described a reaction of malonamic acid which, if it occurs
as described by that author, renders meaningless our results
on malonamide and malonamic acid. In an earlier paper[41]
Hall described the kinetics of decomposition of malonic acid
in hydrochloric acid solution at $80^\circ C$ and $90^\circ C$ and found it to

written

$$HOOCCH_2COOH \longrightarrow CH_3COOH + CO_2$$

In a continuation of this work[42] he studied the rate of decomposition of malonamic acid in a range of hydrochloric acid solutions from .2M to .006M at 80°C and 90°C to extend the knowledge of the decarboxylation reaction.   Under these conditions Hall claimed that the reaction was the decarboxylation of malonamic acid to acetamide.

$$NH_2\ CO\ CH_2\ COOH \longrightarrow NH_2CO\ CH_3 + CO_2$$
Malonamic acid   Acetamide
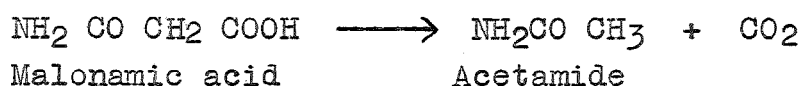
He also stated that no ammonia was recognised in qualitative tests on the reacting solutions.

In connection with the present work, on the hydrolysis of malonamic acid, tests on the hydrolysate with Nessler's reagent gave the brown coloration characteristic of the presence of ammonia and the rates of hydrolysis were followed by quantitative estimation of ammonia with hypobromite. Sanders[37] followed the rates of hydrolysis of acetamide by distillation of the ammonia from the hydrolysate into acid, which prevented the hypobromite reacting with anything but ammonia.   He also found that any acetamide present in the hydrolysate was not appreciably decomposed to give ammonia during the distillation process and obtained rate constants about four times as great as those of malonamide and malonamic acid.   The rate constants were also larger than those obtained by Hall for the decarboxylation reaction which indicates that, even if decarboxylation were the initial step in the hydrolysis, ammonia must have been present in the hydrolysate.

In .2M HCl Hall's first order rate constants were 1.78×10^{-6} and 6.81×10^{-6} hrs^{-1} at 80°C and 90°C respectively. These may be expressed as .000107 and .000407 mins^{-1}

respectively and by use of the Arrhenius equation the value
of the rate constant at 100°C was obtained by the present
author as .00146 min^{-1}.   In .2 M HCl the rate constant for
the hydrolysis of malonamic acid is .021 mins^{-1}, fifteen times
as large as that for the decarboxylation.   Hall also stated
that the rate constants for malonamic acid decarboxylation
were significantly lower than those for malonic acid.   These
points suggest that hydrolysis of the amide, followed by
decarboxylation, may have been the reaction followed by Hall.

It therefore appears that ammonia must have been present
in the reacting solution from the hydrolysis of acetamide
even if not from malonamic acid directly.   For this reason
decarboxylation has not been considered to be a preliminary
stage in the hydrolysis of malonamic acid and the validity of
Hall's work must be questioned.

V AMIDES OF OXALIC ACID

Following on from the observations on the hydrolysis of malonamide it would be of considerable interest to compare the hydrolysis with that of oxamide. By analogy with malonamide we would expect the groups to hydrolyse in two successive reactions. However, as the two carbonyl groups are directly linked in this case somewhat irregular results might be expected and it may be possible to obtain some idea of the electronic effects of the proximity of the two groups. The study of the hydrolysis of oxamide and oxamic acid was therefore undertaken under similar conditions to facilitate comparison with the hydrolysis of malonamide

A Oxamic Acid

i. Preparation.

Oxamic acid was prepared by Oelker's[43] method of hydrolysis of oxalic acid ethyl ester amide (oxamethane) with aqueous ammonia

$$\begin{array}{ccc} CONH_2 & & CONH_2 \\ | & \longrightarrow & | \\ COOC_2H_5 & & COOH \end{array}$$
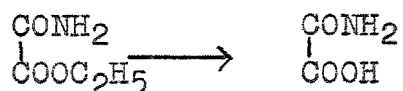
Oxamethane was obtained by the reaction of equivalent quantities of diethyl oxalate and alcoholic ammonia at $0^\circ C$ as described Weddige[28].

Oxamethane

Half a gram-mol of ethyl oxalate (73g.) was dissolved in 2 to 3 times its volume of alcohol and a volume of standard alcoholic ammonia solution containing an equivalent quantity of ammonia added. An almost quantitative yield (over 90%) of white crystals of oxamethane was obtained after shaking and leaving for a few hours. After recrystallisation from alcohol a melting point of $114^\circ C$ was obtained (cit.[28] 114-$115^\circ C$)

Oxamic Acid

aqueous ammonia was added until the solution remained alkaline to prolonged boiling. The solution was concentrated, cooled and filtered to remove insoluble oxamide. On acidification with an equivalent quantity of hydrochloric acid oxamic acid was deposited as a white powder in 60% yield. Purification was effected by recrystallisation from water to give a final product of melting point 209°C (dec). Oelkers[43] reported a melting point of 210°C but has not recorded the yield obtained.

ii. Analysis

The hydrolysis was followed by the distillation technique as oxamic acid and hypobromite reacted extensively under the experimental conditions. This reaction, however, is worthy of further consideration.

One mole of hypobromite reacted with one mole of oxamide in approximately six minutes but further reaction ensued over longer periods. Graph IV illustrates the course of the reaction in a plot of "Moles of hypobromite used per mole of oxamide" against "time". This shows the comparatively fast reaction of equimolar portions of oxamic acid and hypobromite followed by slower reaction with further hypobromite.

Graph IV was compiled from Table IV which details the extent of the reaction at various times for as long as it has been followed.

Table IV

Time of Reaction (mins)	Apparent percentage of hydrolysis of oxamide.	No. of mols of hypobromite added per mole of oxamic acid.
3	58.0	.87
6	65.9	.99
9	66.7	1.00
10	67.2	1.01
15	70.2	1.05
25	75.9	1.14
30	79.3	1.19
40	82.3	1.23
60	89.8	1.35
90	100	1.50

Miliotis[29] has recorded that ethyl oxamate under the influence of hypobromite rearranged to give, as an intermediate, ethyl carbamate which in the presence of the warm alkali gave ethyl alcohol

$$\begin{array}{c} COOEt \\ | \\ CONH_2 \end{array} \xrightarrow{\underset{NaOH}{Br_2}} \begin{array}{c} O \\ || \\ C - OEt \\ | \\ NH_2 \end{array} \xrightarrow{OH} EtOH + CO_2 + NH_3$$
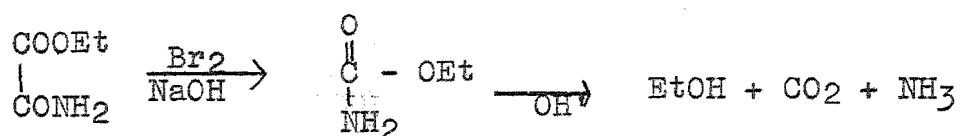
The first step of the Hofmann rearrangement is believed to be N bromination and it is here suggested that the comparatively rapid reaction of 1 mol of hypobromite in 6 mins. corresponds to this and that the much slower reaction corresponds either to further bromination or to reaction with the NH_3 produced on breakdown of the carbamic acid. Since the concen- of amide was too small to allow the isolation of intermediate products this reaction course must remain purely speculative at present.

Distillation of ammonia from the alkaline buffer solution was possible without any appreciable hydrolysis of oxamic acid.

Graph IV

Reaction of Hypobromite & Oxamic Acid

Plot of extent of reaction/time

Apparent per-
centage hydrolysis
of oxamic acid
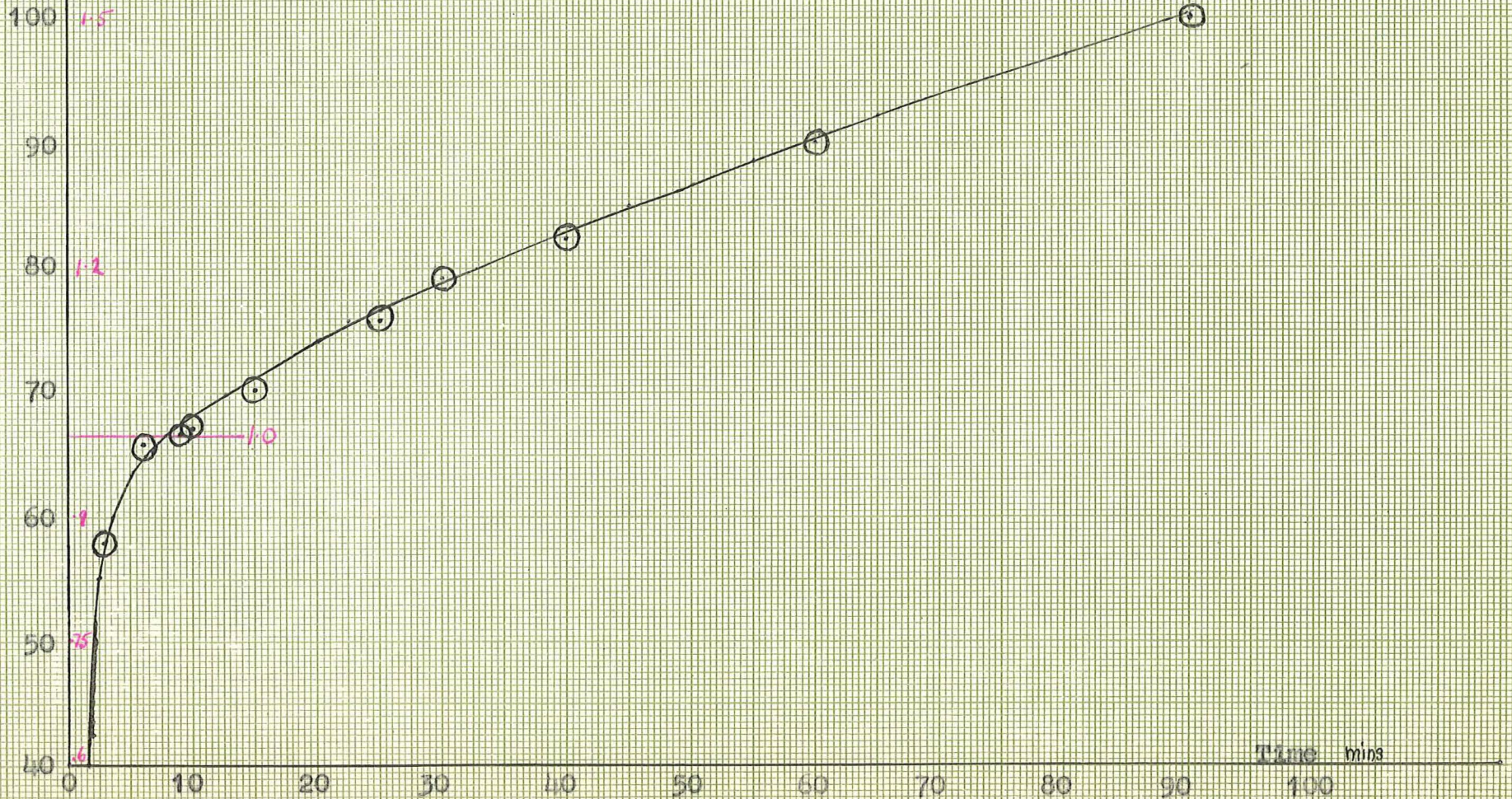
Mols of hypobromite reacted
per mol of oxamic acid

Time mins

A hydrolysis run on oxamic acid in .0625 M hydrochloric acid
was also carried out using the direct method of analysis and a
time of reaction with hypobromite of 9 minutes, resulted in a
linear plot and a rate constant of .0178 although the whole
graph was displaced on the "ln" axis by an amount corresponding
to 68% hydrolysis. The extent of the reaction between
hypobromite and oxamic acid for 9 minutes was such as to
suggest 68% hydrolysis of the amide. The production of a
straight line when the extent of reaction with the amide has
been kept constant will be discussed on page 37 where it has
been used, in the case of oxamide, to obtain the rate constants.
The value obtained for oxamic acid in .0625 M HCl by the dis-
tillation technique was .0175 mins^{-1} which agrees closely with
that obtained by the direct method and justifies the use of the
displaced graphs in the case of oxamide.

iii Kinetics of the Hydrolyses

The "ln(w - y)/t" plots were all linear and the values of
the rate constants obtained from their slopes are given in the
following table:-

Table V

M_{HCl}	k obtained		Mean Value of k
.0625	.0178	.0178	.0178
.125	.0304	.0306	.0305
.25	.054	.053	.054
.35	.070	.070	.070
.5	.096	.099	.098

A plot of k/M_{HCl} was linear and gave a value of k of .007
at M = 0 (k_o). The catalytic coeficient obtained from the
slope of the graph was .184. The rate of hydrolysis may thus
be described by the equation

$$k = .007 + .184 \ M_{HCl}$$

Graph V shows the plot of k/M_{HCl}

B Oxamide

(i) Preparation

Oxamide was prepared by the reaction, originally describ-
ed by Liebig[30] and Henry[31], between .880 ammonia and
diethyl oxalate following instructions given by Middleton[33].

Ethyl oxalate

This was obtained directly by refluxing oxalic acid
with ethyl alcohol as described by Kenyon[32]. One gram
mole (90g.) of oxalic acid and 500 ml. of alcohol were placed
in a suitable apparatus and refluxed for five hours. The
alcohol vapour distilled off was dried by passing it through
a trap containing potassium carbonate before it was returned
to the refluxing system. On fractional distillation of the
resulting solution an 85% yield of diethyl oxalate boiling
at 97 - 103°C at 21 mm. was obtained. Kenyon[32] reported an
80 - 90% yield of a fraction boiling at 98 - 101°C/21 mm.

Oxamide

20 ml. of diethyl oxalate, 100 ml. of water and 100 ml.
of .880 ammonia were placed in a stoppered flask and shaken
vigorously for fifteen minutes. The oxamide deposited was
filtered off under suction, washed with water and dried.
Purification was effected by recrystallisation from water.
A melting point could not be obtained as oxamide undergoes
partial decomposition and sublimation on heating.

(ii) Analysis

As with oxamic acid considerable reaction between oxamide
and hypobromite was observed. In blank determinations on
oxamide in pure water a decrease in the thiosulphate titre,
equivalent to 33% hydrolysis of the oxamide, was obtained after
three minutes reaction and no measureable change was noted on
reaction for longer periods.

In the determination of the extent of hydrolysis by the
reaction of hypobromite with the liberated ammonia the

following overall equations are applicable:-

$$\begin{matrix} CONH_2 \\ | \\ CONH_2 \end{matrix} \xrightarrow[\substack{\text{lysis} \\ \text{in acid}}]{\text{Hydro-}} \begin{matrix} COOH \\ | \\ COOH \end{matrix} + 2NH_3$$

$$2NH_3 + 3NaBrO \longrightarrow 3NaBr + 3H_2O + N_2$$
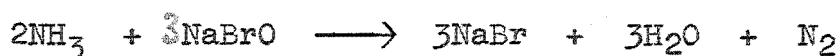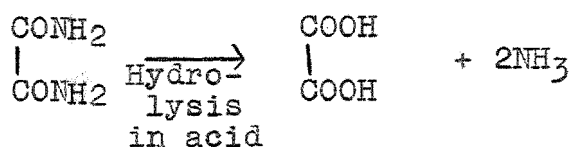
i.e. complete hydrolysis of 1 mole of oxamide will cause reaction with three moles of hypobromite. Hence the apparent 33% hydrolysis was equivalent to the reaction of 1 mol of hypobromite per mole of oxamide.

Foster[34,35] described the reaction of hypobromite and oxamide to liberate 70% of the total nitrogen and identified cyanate ion in the reacting solution. This suggests that some rearrangement had occurred and on analogy with oxamic acid we may postulate that the reaction with one mole of hypobromite was mono bromination of one $-NH_2$ group but no further evidence for this can be given.

Distillation of ammonia from the alkaline solution of the hydrolysate was useless since appreciable hydrolysis of oxamide occurred. The fact that alkaline distillation is suitable for oxamic acid and not for oxamide is in agreement with the observation of Westheimer and Sookoff[36] that the relative rates of hydrolysis in alkali were in the ratio of 1 to 100.

In a trial run by the direct method a plot of "$\ln(w - y)$" against "time" gave a good straight line which projected back to a point on the "$\ln$" axis corresponding to 33% hydrolysis. Such graphs have been used to determine the rate constant and the justification of their use will be explained below.

It is necessary to assume that the concentration of oxamic acid was, at all times, unimportant compared with the concentration of oxamide. The linearity of the "$\ln(w - y)$/time"

plot may then be explained by allowing for the reaction of one mole of hypobromite with each unhydrolysed mole of oxamide. It may be seen from the discussion of the analytical method that the titration differences were always proportional to the concentration of ammonia in the hydrolysate and for simplicity the proportionality constant has been taken as unity.

Let the hypobromite standardising titre be $\quad$ b

Let the titre using unhydrolysed oxamide solution be b'

Let the titre for complete hydrolysis be $\quad$ f

Because oxamide and hypobromite react in equimolar quantities, for an unhydrolysed oxamide sample

$$\frac{\text{Apparent hydrolysis of oxamide}}{\text{Actual concentration of oxamide}} = \frac{b - b'}{b - f}$$

$$= K \quad \text{------------(A)}$$

This ratio was found experimentally to be constant over a range of concentrations and all the graphs of "$\ln(w - y)$/time" projected back to the same point at "t" = 0.

If at time "t" minutes the titration value is "a" the estimated extent of hydrolysis is "$b - a$".

Let $\overline{\overline{b - a}}$ be the actual extent of hydrolysis

Actual extent of hydrolysis $(\overline{\overline{b - a}})$

= (Total apparent extent of hydrolysis) - (the apparent hydrolysis due to the interaction of oxamide with hypobromite)

= $(b-a)$ - K(Actual concentration of oxamide) ------ from (A)

= $(b-a)$ - K(Orig. conc. of oxamide - Extent of hydrolysis)

= $(b-a)$ - K$\left[(b - f) - (\overline{\overline{b - a}})\right]$

whence

$$\overline{\overline{b - a}} = \frac{b - a - K(b - f)}{1 - K}$$

Actual concentration of amide

$$= b - f - \overline{\overline{b - a}}$$

$$= b - f - \frac{b - a - K(b - f)}{1 - K}$$

$$= \frac{a - f}{1 - K}$$

$\therefore$ (The actual conc. of amide) $= \dfrac{1}{1 - K}$ (Estimate conc. of amide)

$\therefore$ A plot of "ln(Apparent conc. of oxamide)/t" should give the same slope as the plot "ln(Actual conc. of oxamide)/t" with a displacement on the "ln" axis equal to $\ln \dfrac{1}{1 - K}$. The graphs obtained from the oxamide plots were straight lines and had this displacement of the "ln" axis at "t" = 0.

This interpretation is strengthened by the fact that oxamic acid gives, by both the distillation and direct techniques, the same rate constant although in the direct method the line is displaced by an amount corresponding to the interaction of the oxamic acid and hypobromite. Although independent determinations of the rate constants of oxamide were not possible, and the above interpretation involves the assumption that the concentration of oxamic acid was negligible at all times, it has been used to determine the rate constants.

The plots of "ln(w - y)/time" so obtained were all linear throughout their entire length and showed no evidence of any irregularities although the accuracy of the titrations was limited somewhat by the narrowing of the titration range (ΔV).

Graphs VIIA and VIIB show the "ln(w - y)/time" and the "percentage-time" plots before and after allowance for the reaction between hypobromite and oxamide had been made. The results from which the graphs were drawn are set out in Table VII.

The difficulty with the experimental hydrolysis lay in the solubility of oxamide being too small to permit the preparation of a standard solution. To overcome this the exact quantity required for the volume of acid was weighed out and washed into the reaction flask with a quantity of acid which had been extracted from the flask after temperature equilibrium had been reached. This method proved satisfactory since at 97°C the oxamide dissolved quite rapidly in the larger volume of acid and no serious temperature drop was introduced.

(iii) Kinetics of the Hydrolyses

The rate constants obtained from the plots of "log(w - y)/time" are given in the following table.

Table VI

M_{HCl}	k obtained		Mean Value of k
.0156	.0011		.0011
.0625	.0062	.0067	.0065
.0125	.0130	.0130	.0130
.25	.0234	.0241	.0238
.35	.0338	.0336	.0337
.5	.0483	.0493	.0488

A plot of k/M_{HCl} was linear and passed through the origin. The catalytic coeficient obtained as the slope of the graph was .0972.   The rate of hydrolysis may be described by the equation

$$k = .0972 \; M_{HCl}$$

Graph VI shows the plot of k/M_{HCl}

Table VII

.35 M_{HCl} Oxamide

t	ΔV	y	w - y	ln(w-y)	$\%_1$	(w-y)*	ln(w-y)*	$\%_2$
0	0	0	.1964	1.62	0	.1964	1.62	0
5	2.13	.0923	.1041	2.26	46.9	.1562	1.86	20.5
10	2.50	.1082	.0882	2.43	55.2	.1322	2.02	32.8
15	2.86	.1238	.0726	2.62	63.1	.1087	2.22	44.7
20	3.11	.1347	.0617	2.78	68.5	.0925	2.38	52.9
25	3.27	.1418	.0546	2.91	72.2	.0818	2.49	58.4
30	3.51	.1521	.0443	3.12	77.3	.0664	2.71	66.2
35	3.68	.1593	.0371	3.29	81.2	.0557	2.88	71.7
40	3.80	.1647	.0317	3.45	83.7	.0476	3.05	75.8
45	3.91	.1692	.0272	3.61	86.2	.0408	3.19	79.3
				2.02	33.3			

t   = time

ΔV   = titre difference

Graph V

Plot k/M_{HCl}

Oxanic Acid

k

.10
.09
.08
.07
.06
.05
.04
.03
.02
.01
0

M_{HCl}

0   .1   .2   .3   .4   .5   .6   .7
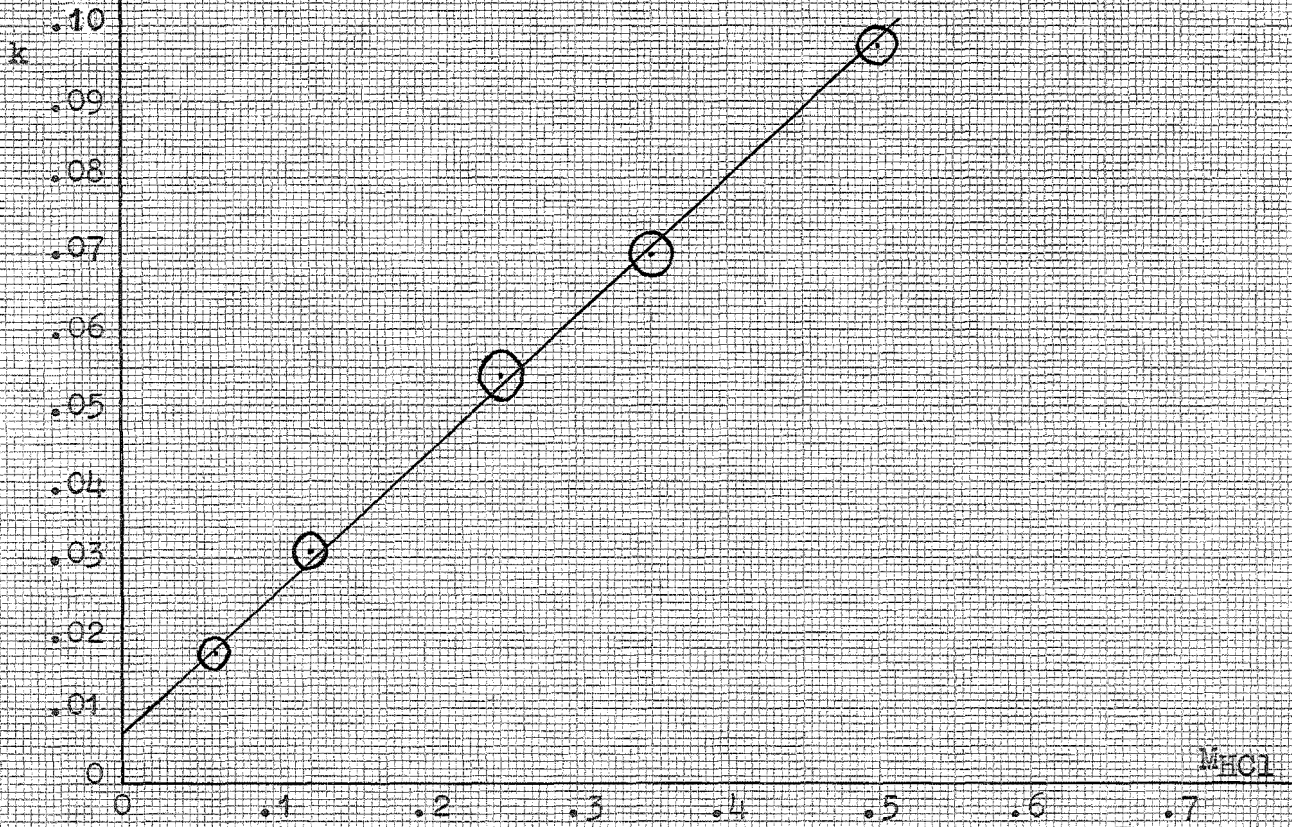
Graph VI

Plot k/M_{HCl}

Oxamide

k

.05
.04
.03
.02
.01

M_{HCl}

0   .1   .2   .3   .4   .5   .6   .7
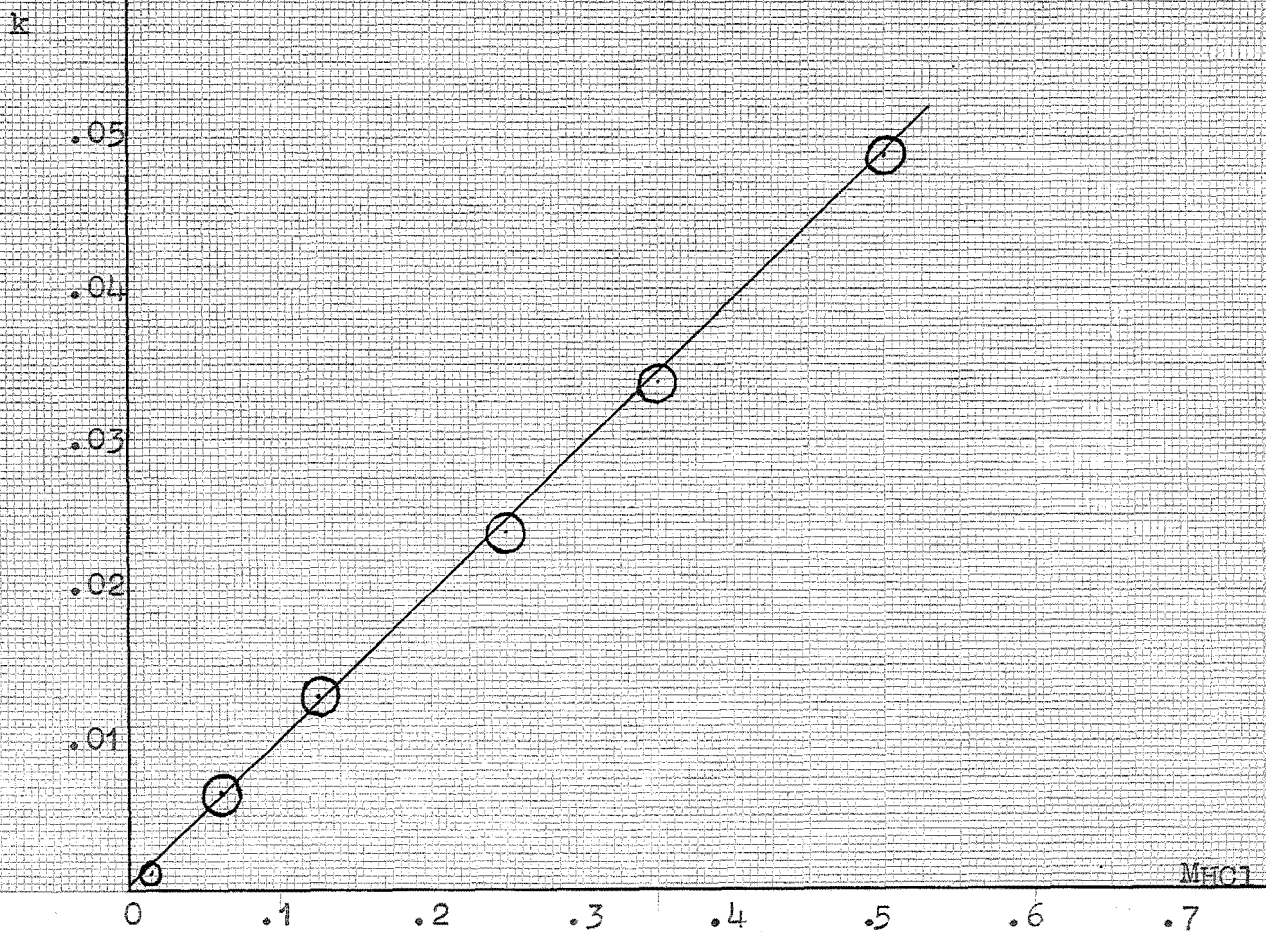
Graph VIIA

Oxamide
in .35 M HCl
Plot ln(w-y)/time
(1) As estimated
(2) Allowing hypobromite
oxamide interaction

Graph VIIB

Oxamide
in .35 M HCl
Plot % hydrolysis/time
(1) As estimated
(2) Allowing hypobromite
oxamide interaction

Table VII (contd.)

w-y   =   Mg. of N_2 apparently unhydrolysed

$\%_1$ =   apparent % of hydrolysis

(w-y)*   =   Mg. of N_2 actually unhydrolysed
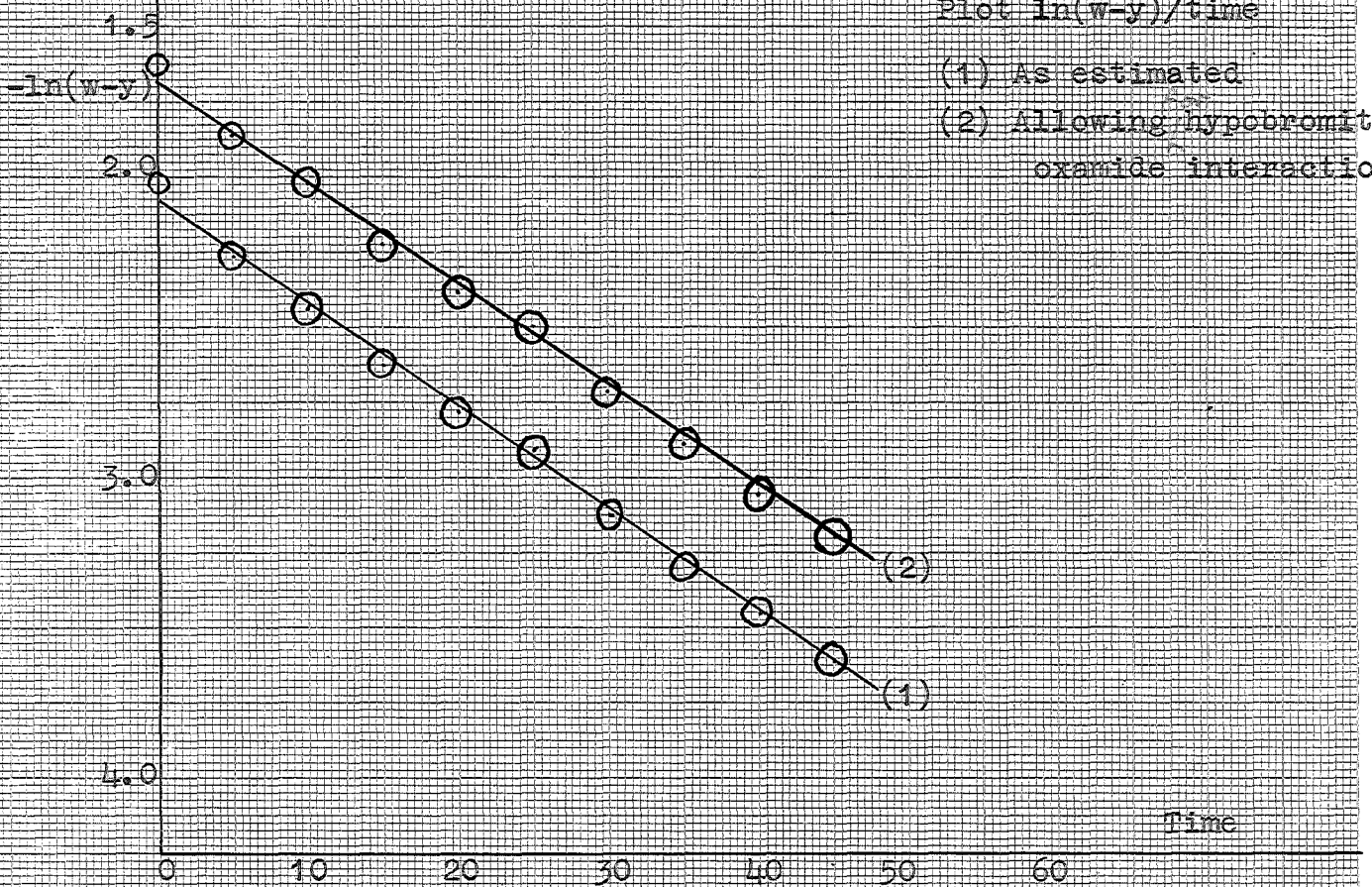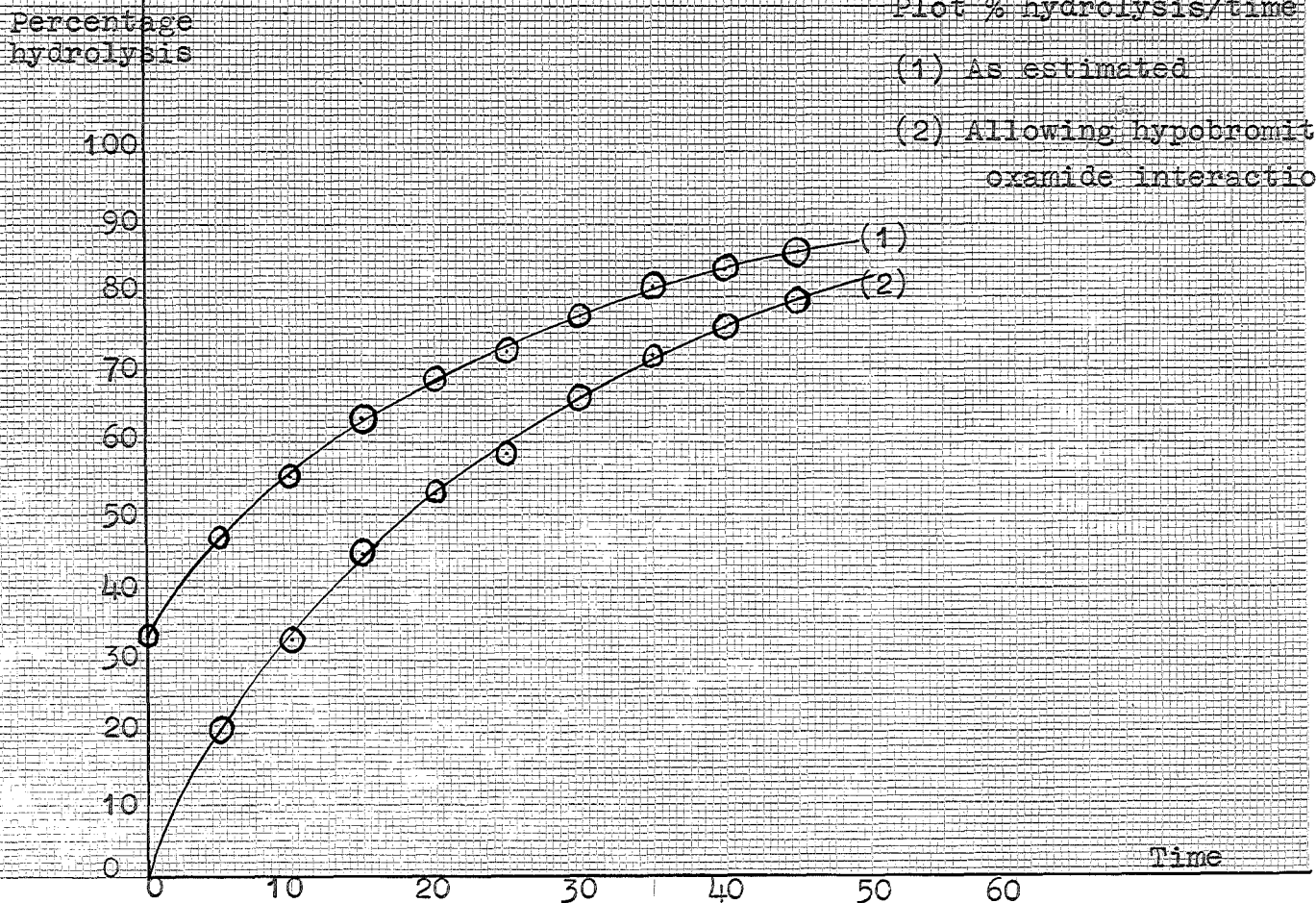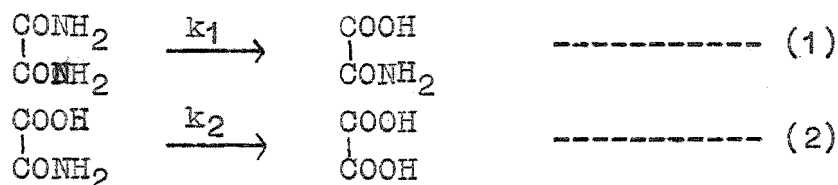
$\%_2$ =   actual % of hydrolysis

C Discussion of the Kinetics of Hydrolysis of Oxamide

The "ln(w - y)/time" plots for oxamide were linear throughout and a close analogy with the kinetics of hydrolysis of malonamide, where the rates of hydrolysis of the amide groups is constant and the hydrolysis takes place in two steps, was suggested.

$$\begin{array}{c} CONH_2 \\ | \\ CONH_2 \end{array} \xrightarrow{k_1} \begin{array}{c} COOH \\ | \\ CONH_2 \end{array} \text{-----------} (1)$$

$$\begin{array}{c} COOH \\ | \\ CONH_2 \end{array} \xrightarrow{k_2} \begin{array}{c} COOH \\ | \\ COOH \end{array} \text{-----------} (2)$$

When k_1 applies to rate of reaction (1) and k_2 to the rate of reaction (2) k_1 would equal $2k_2$ (c.f. malonamide). However, k_2 obtained from the hydrolysis of oxamic acid (page 35) is approximately twice the value of k_2 obtained from the "ln(w - y)/time" plots for oxamide and this anomaly cannot be explained in terms of normal consecutive reactions.

The possibility of the method of analysis used for oxamide and its interpretation (page 36) being at fault cannot be neglected. The method does give consistent results with oxamide and is quite valid in the case of oxamic acid where the conditions of its application were as suitable. However, it did involve the assumption that, if the reaction proceeded through oxamic acid the concentration of oxamic acid was at all times negligible compared with that of oxamide. It will be seen later that it is the kinetics of oxamic acid which appear to be irregular and here the analytical procedures have

been confirmed by two separate methods.

If we assume, for the moment, that the consecutive reactions of equations (1) and (2) of the previous page have occurred, it appears, from the mono-linearity of the "ln(w - y)" against "time" plots that we are dealing with the special case mentioned on page 15 . This then involves the same type of consecutive reactions as found with malonamide and hence $k_1 = 2k_2$.

Swain[8], as mentioned on page 13 , developed a simple graphical technique from the solution of a general equation whereby he was able to obtain values of k_1 and k_2 from the data for the overall hydrolysis of the diamide. To do this all that was required was a knowledge of the time when a definite fraction of the amide was hydrolysed. This was applied to oxamic acid by the use of the times when 15% and 70% of the amide was hydrolysed. Here, values of k_1 and k_2 were obtained, for hydrolysis in .35 M hydrochloric acid, which showed approximately the relationship expected on the basis of the rate of hydrolysis of the amide group being constant (page 15) i.e. $k_1 = 2k_2$

The values obtained were:-

$$k_1 = .0742$$

$$k_2 = .0334$$

Swain[8] has also given the following formula whereby, from k_1 and k_2, t_{max}, the time of maximum concentration of the intermediate oxamic acid may be obtained

$$t_{max} = \frac{\ln k_1 - \ln k_2}{k_1 - k_2} \quad \text{------------} \quad (x)$$

He also gave the formulae:-

$$[A] = ae^{-k_1 t} \quad \text{------------------}(y)$$

$$[B] = \frac{ak_1}{k_1-k_2} \left(-e^{-k_1 t} + e^{-k_2 t}\right) \quad \text{------}(z)$$

(where "a" is the original concentration of oxamide)

whereby $[A]$ the concentration of oxamide and $[B]$ the concentration of oxamic acid at time "t" may be respectively obtained.

Assuming the hydrolysis to be a consecutive reaction, and using the values of k_1 and k_2 obtained previously the following results were obtained.

$$t_{max} = 19.5 \text{ minutes} \text{ ---------------- from (x)}$$

$$[B] = .0171 \text{ mg. of } N_2 \text{ per aliquot as oxamic acid}$$

$$[A] = .023 \text{ mg. of } N_2 \text{ available from hydrolysis of oxamide to oxamic acid ---from (y)}$$

That is at a maximum concentration of oxamic acid

$$\frac{\text{Concentration of oxamic acid}}{\text{Concentration of oxamide}} = \frac{17}{23}$$

and hence, on the basis of a consecutive reaction, we cannot assume the concentration of oxamic acid compared with that of oxamide to be negligible at all times.

However, as the reaction of hypobromite with oxamic acid is quite different in extent from the reaction with oxamide under these conditions considerable deviations from linearity in the "$\ln(w - y)$" against "time" plots would be expected particularly in the region of 19.5 minutes. That this deviation from linearity was not observed, may be regarded as negative evidence in favour of the non-existence of oxamic acid in the hydrolysate.

It is possible to correlate these points if we imagine a fission of the molecule to occur at the C - C bond in both cases and if we assume that the rate of fission is the same for oxamide and oxamic acid.

It has been previously stated that the "$\ln(w - y)$" against "time" plots measured the rate of hydrolysis per amide group as the kinetics were followed by estimation of the ammonia evolved. For oxamide, if the fission occurs at a rate 2k, and if fission results in the quantitative release of ammonia,

ammonia will be produced at a rate of 2k per 2 amide groups; i.e. a rate k per amide group. The plot would thus give the rate of production of ammonia per amide group. For oxamic acid the rate of fission and apparent rate of hydrolysis would be the same and equal to 2k.

This means that the rate constant measured in the "$\ln(w - y)$/time" plots for oxamic acid would be twice that obtained for oxamide as has indeed been observed experimentally. This reaction course also explains the linearity of the graphs for oxamide by the absence of any oxamic acid and vindicates the method of analysis. A check on the rate constants of oxamide by an independent method of analysis would be necessary before this reaction course could be confirmed.

In this discussion it has been postulated that hydrolysis occurs in a manner, essentially the same for oxamide and oxamic acid, involving the fission of the C - C bond. That such a fission could occur is supported by certain observations of Misch[38] who, from X-ray analysis of oxamide crystals, has shown that the C - C distance is 1.65 A° compared with the normal C - C distance of 1.53 A° and that found in oxalic acid of 1.43 A°[39]. This suggests that the C - C bond in oxamide must be considerably weakened and it is not surprising that fission should occur here rather than at the C - N bond. The hydrolysis of oxamide has further been discussed in Section VI.

VI   THE HYDROLYSIS OF AMIDES

The results of the hydrolyses are summarised below.
In all cases the "$\ln(w - y)/t$" plots were linear and the rate
constants so obtained are given in Table VIII.

Table VIII

M_{HCl}	Oxamide	Oxamic Acid	Malonamide (Stone[2])	Malonamic Acid
.0625	.0065	.0178	.0074	.0072
.125	.0130	.0305	.0139	.0147
.25	.0238	.053	.0247	.0265
.35	.0337	.070	.034 (From graph)	.0339
.5	.0485	.098	.048	.0504
Cat.Coef.	.0972	.184	.093	.098

For all these cases and for acetamide[37], nitromalonamide
and methyl malonamide[2], the plots of k/M_{HCl} have been linear
and may be described by an equation of the form

$$k = k_0 + k_{H^+} \cdot C_{H^+}$$

where k is the rate constant at any particular acid concentrat-
ion

k_0 is the rate constant at zero conc. of acid

C_{H^+} is the conc. of acid

k_{H^+} is the catalytic coefficient

This means, in all cases that specific hydrogen-ion catalysis
has occurred but does not mean that the addition of a
hydrogen-ion was the rate-determining step.   The following
general mechanism of hydrolysis of the amide group, which makes
the addition of a hydrogen-ion, or the addition of a water
molecule the rate-determining step has been put forward,

The mechanism may be represented:

$$R - \overset{\overset{+}{N}H_2}{\underset{O^-}{c}} \longleftrightarrow R - \overset{NH_2}{\underset{O}{c}} \rightleftharpoons R - \overset{NH}{\underset{OH}{c}} \longleftrightarrow R - \overset{\overset{-}{N}H}{\underset{\underset{+}{OH}}{c}} \qquad (A)$$

amido   imidol

$$\uparrow\downarrow H^+ \qquad (1)$$

$$R - \overset{\overset{+}{N}H_2}{\underset{OH}{c}} \longleftrightarrow R - \overset{NH_2}{\underset{\underset{+}{OH}}{c}} \qquad (B)$$

or

$$R - \overset{\overset{\delta+}{N}H_2}{\underset{OH}{c}} \overset{\delta+}{=} \qquad (C)$$

$$\uparrow\downarrow + \; ^- \overset{}{\underset{H}{O}} - H \qquad (2)$$

$$\left[\begin{array}{c} \overset{NH_2}{\underset{|}{R - c - OH}} \\ H - \overset{|}{O} - \\ \underset{H}{|} \end{array} \right]^{+} \qquad (D)$$

$$R - \overset{}{\underset{OH}{C}} = OH \quad + NH_3 \qquad (E)$$

$$R - \overset{}{\underset{OH}{c}} = O \quad +H^+ \qquad (F)$$

$$\left[R - \overset{}{\underset{O}{c}} = O \right]^{-} \quad +H^+ \qquad (G)$$
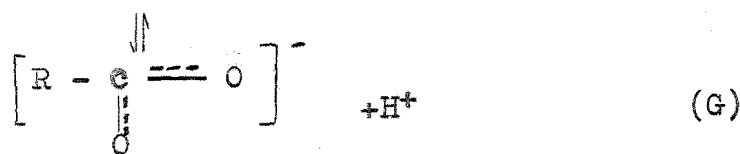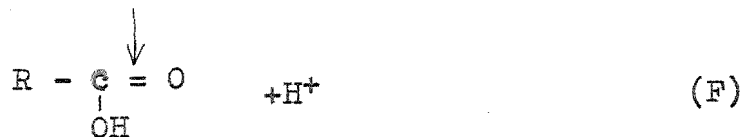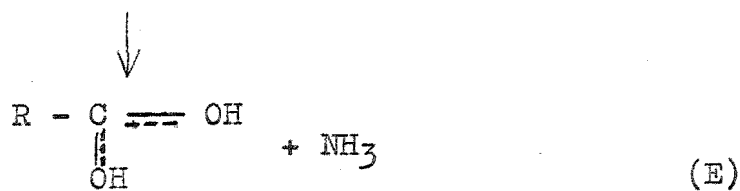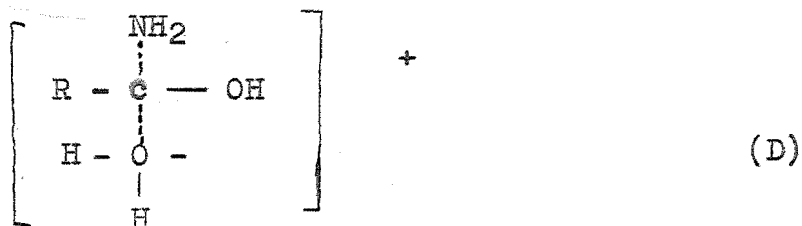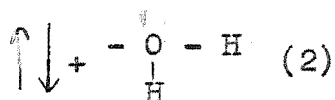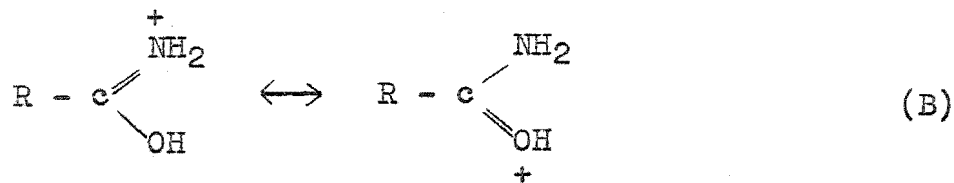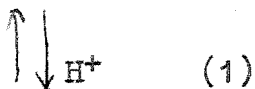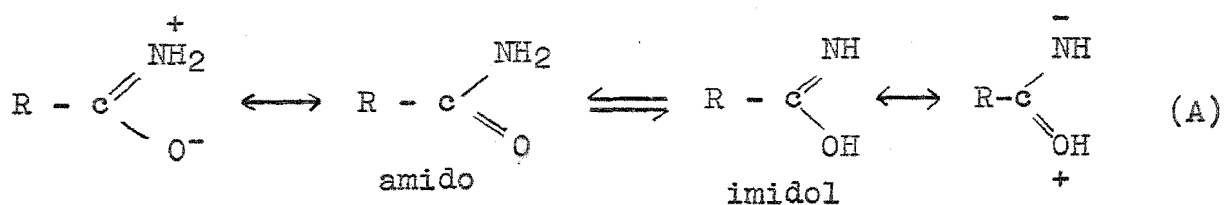
The amide group is believed to exist in solution as the two tautomers of (A)[44] the amido form of which has an appreciable contribution from the mesomer shown.   The mesomer of the imidol form has an unfavourable change distribution and is not considered to exercise a significant contribution.   Since the addition of a proton to the $-NH_2$ group would cause an almost complete loss of resonance the addition of a proton must occur on the oxygen of the carboxyl group.   The intermediate obtained will be the mesomers (B) and may be represented by (C) [45,46,47]

The next step is the addition of a water molecule and the loss of ammonia via the charged mesomeric complex (D) by what is essentially an S_N2 mechanism.   This gives the complex of (E) which still has resonance and by loss of a proton the acid molecule represented by (F) or (G) is obtained.   The mechanism preserves resonance throughout and is therefore, according to Dewar's ideas, a probable mechanism.   However, it does not indicate whether (1) or (2) is rate-determining and it is not possible to decide this from the evidence available.   The linear relationship between the rate constant and the molarity of hydrochloric acid is due to the fact that the hydrolysis is essentially bimolecular but is kinetically pseudo-unimolecular. That is, the rate is dependent upon the concentration of hydrogen-ions but at each definite acid concentration the concentration of hydrogen-ions is constant and first order kinetics are obtained[48].   It is thus possible that the rate of protonation or the rate of addition of the water molecule may be the rate-determining factor.

Malonamide has been shown to hydrolyse in two consecutive reactions in both of which the rate of hydrolysis per amide group is the same.   We may therefore apply this general mechanism to the hydrolysis of malonamide and from the linearity of the k/M_{HCl} plots deduce that the reaction is essentially bimolecular and involves the addition of a hydrogen-ion.

Before considering the hydrolysis of oxamide it is worth-
while to compare the rates of hydrolysis given in Table VIII.
It may be seen that (a) the rates of hydrolysis of malonamide,
malonamic acid, and oxamide at each concentration of acid and
(b) the respective catalytic coeficients are almost identical
whereas the corresponding values for oxamic acid are practically
double. It thus appears that the rate of hydrolysis per amide
group is constant in malonamide, malonamic acid and oxamide
but is double the normal value in oxamic acid. As the rate of
hydrolysis per amide group is constant for the three amides it
would seem that the rate-determining step was identical in these
cases. The fact that there are two amide groups in oxamide
and only one in oxamic acid suggests that there may be a
reaction course, not consecutive hydrolysis of the two groups,
which will account for the rate constant of oxamic acid being
twice that of oxamide although the rate determining step will
be the same in all four cases.

If the rate-determining step is assumed to be the addition
of a proton, which, from previous considerations, may well be
the case, the rate constants may be correlated in terms of the
reaction course suggested in Section VI. If the value k is
assigned to the rate of protonation at a given acid concentrat-
ion, the rate of hydrolysis per amide group, by the general
mechanism proposed, will be k. Malonamide thus hydrolysed in
both steps by this general mechanism such that the average rate
of hydrolysis per amide group was constant throughout and equal
to k.

In the case of oxamide, if fission of the molecule is
hydrogen-ion catalysed, which it should be since the plot of
k/M_{HCl} is linear, the rate of fission could be dependent on the
rate of protonation. Since there are two amide groups in the
oxamide molecule the rate of protonation will be 2k and

therefore the rate of fission will be 2k.   On the assumption that the rate of protonation is again the rate-controlling step the rate of appearance of ammonia will be 2k.   This, however, is expressed as 2k per 2 amide groups, and hence will be recorded graphically as k per amide group.   This means that the rate of hydrolysis per amide group will be the same as that for malonamide and malonamic acid, as has, of course, been observed experimentally.

Stone's[2] results on malonamide indicate that the amide and carboxyl groups have roughly the same electronic effect on the rate of hydrolysis of an adjacent amide grouping.   It appears not unreasonable to assume, from this fact and from normal electronic considerations, that the rates of protonation of the carboxyl group, in the carboxyl and amide radicals are of the same order.   If this assumption is correct the rate of fission of the oxamic acid molecule will be 2k provided it follows the same mechanism as that of oxamide.   The rate of production of ammonia will then be 2k per amide group which is just twice the rate expected from the normal hydrolysis of an amide group.   This result is in accordance with that obtained experimentally.

This mechanism, which postulates that fission of the molecules occurs at the C——C bond, assumes:-

(1)   That there is a similar state of strain in the C - C bond of the two molecules (X-ray examination of oxamic acid crystals does not appear to have been carried out.)

(2)   That protonation of the carboxyl group occurs at the same rate in both the amide and carboxyl radicals and is the rate determining step.

Points in favour of the mechanism are:

(1)   It explains and correlates the experimental data which cannot be done on the basis of consecutive reations.

(2)   There is evidence of strain in the C - C bond of

(3) It explains the apparent absence of oxamic acid in the hydrolysate *from oxamide* and vindicates the analytical method.

(4) It requires the reaction to be hydrogen-ion catalysed. This is known to be correct from the linearity of the "k/M_{HCl}" plots.

With regard to a possible mechanism for the hydrolysis of oxalic acid amides the above discussion leads to a feasible scheme which is given below.
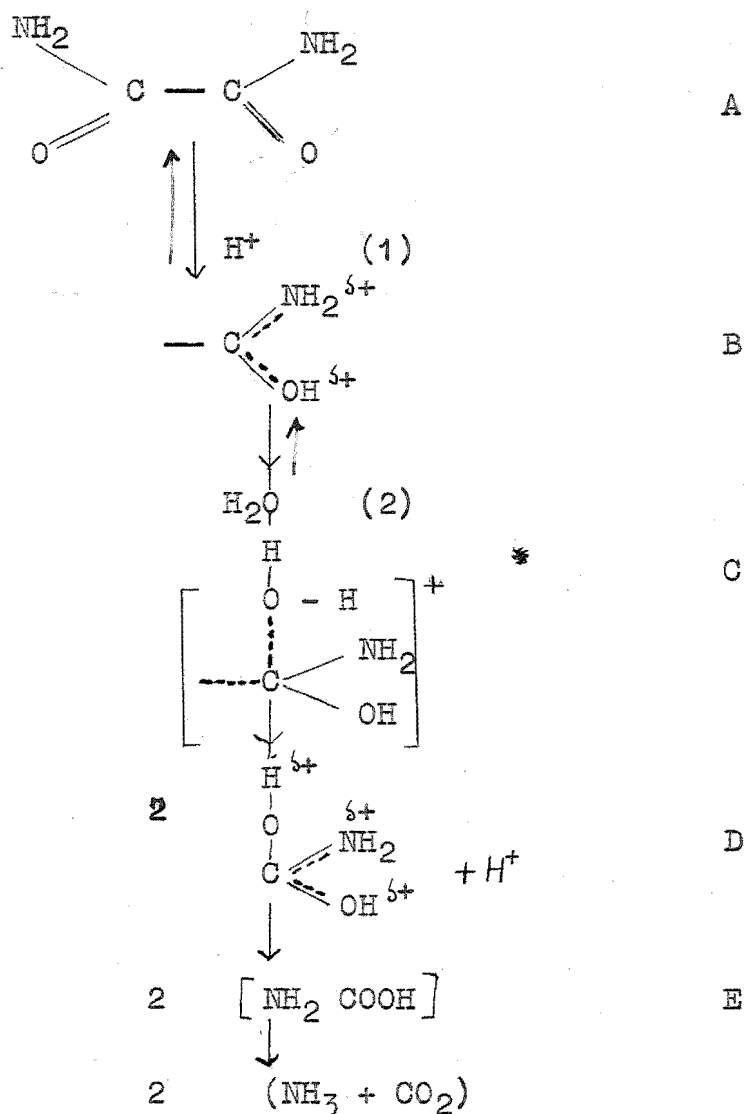
This mechanism is very similar to the one proposed for the general hydrolysis of amides. Oxamide (A) and its protonated form (B) may be written in many mesomeric and tautomeric forms but, for simplicity, only the two above have been included in the mechanism. As in the general mechanism either step (1), protonation, or step (2), the S_N2 addition of a water molecule may be the rate-determining step. In this

case, however, addition of the water molecule involves the simultaneous rupture of the weakened C - C bond whereas the C - N bond generally ruptures. This results in the production of protonated carbamic acid (D) which immediately decomposes to carbon dioxide and ammonia, as carbamic acid has never been isolated in its free state.[49]

With oxamic acid a similar mechanism involving the successive addition of a proton and a water molecule may be proposed for the carboxyl group. In this case the products of fission will be a protonated carbonic acid molecule, as well as an amide radical, of which the former will decompose to carbon dioxide and water and the latter to ammonia and water. In both cases resonance is preserved throughout the intermediate steps and the mechanism may be regarded as a probable one.

In conclusion, it may be said that although the hydrolysis of malonamide shows the typical characteristics of two consecutive reactions the hydrolysis of oxamide cannot be explained in such a manner. A reaction course has been put forward to explain the latter results in terms of a cleavage of the C - C bond which is believed, from results of X-ray analysis[38], to be greatly strained. It is conceivable that this strain results from intermolecular attractions from the carboxyl oxygen and the amino group of the two amide radicals of the oxamide molecule. That the proximity of the two amide groups may also be significant is illustrated by the hydrolysis of malonamide in two consecutive reactions, according to the general mechanism. In this case, when the two amide groups are separated by a further carbon atom, the strain is apparently greatly reduced.

Since the carboxyl and amide groups appear to have identical electronic effects, and the rate of protonation appears to be constant for an amide of a dibasic acid in acid solution of a definite normality, the hydrolysis of succinamide would be

expected to follow the same course of two consecutive reactions in each of which the rate of hydrolysis of the amide group is constant and equal to that of malonamide and oxamide in the same acid. However, the possible formation of succinimide may complicate the issue. Studies of the rates of hydrolysis of the triamides of tricarballylic, and methane tricarboxylic acids should also be of interest.

SUMMARY.

Attempts to prepare γ amino butyramide have been described.

The hydrolysis of malonamic acid has been investigated to extend the knowledge of the hydrolysis of malonamide which had been studied by Stone[2]. Satisfactory correlation with his data was obtained on the basis of a course of reaction involving the successive hydrolysis of the two amides groups at the same rate per amide group.

The hydrolysis of oxamide was found to occur by a first order reaction in which the rate of hydrolysis per amide group is the same as that of malonamide under identical conditions. The hydrolysis of oxamic acid was also a first order reaction but the rate of hydrolysis per amide group was twice that of oxamide and malonamide. A reaction course to correlate these experimental data has been suggested and discussed; a possible mechanism for the reaction has been put forward.

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