"CYCLISATION OF SOME BZ-SUBSTITUTED ANILS OF ACETYLACETONE IN SULPHURIC ACID"

By

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SUMMARY

Previous work on cyclodehydration reactions leading to the formation of an aromatic ring is reviewed. Further investigations are reported on the cylodehydration of anils of acetylacetone in aqueous sulphuric acid and perchloric acid to give 2:4-dimethylquinolines.

It has now been shown that in the range of media where cyclisation occurs, the anils are probably completely monoprotonated and stable. From the relationship found between rate coefficient and the acidity function H_0 it is concluded that cyclisation is an internal electrophilic substitution reaction which proceeds through a diprotonated anil formed in relatively small amount and not through the monoprotonated form as previously assumed.

In more aqueous acids, where the acid is not strong enough to bring about cyclisation, hydrolysis of the anil to acetylacetone and the aromatic amine occurs. A correlation has been found between the rate coefficient of hydrolysis, the acidity function H_0 and the activity of the water present, and a satisfactory mechanism has been put forward to interpret this result.

The rates of cyclisation of anils with both one and two substituents in the benzene nucleus have been measured and the results examined by means of the Hammett equation $\log k/k_o = \rho\sigma$. The additivity of substituent effects which is observed in the pK_a values of the parent anilines is only found to be operative in a limited number of the cyclisation reactions.

The m-halogeno anils are all found to cyclise faster than the unsubstituted anil, i.e., a halogen atom is activating in this electrophilic substitution of the benzene ring. There is a definite parallelism between these rates and the partial rate factors for p-nitration and p-halogenation of the corresponding halogenobenzenes, indicating that the same electronic effects occur in all three reactions.

The constants of the Arrhenius equation have been evaluated for the cyclodehydration of aniline anil and p-toluidine anil in different media and the results are discussed.

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Acknowledgement

I wish to thank Dr. T.G. Bonner for his unfailing help and encouragement throughout the course of this investigation.

I also wish to thank Royal Holloway College and the Ministry of Education for financial assistance enabling me to carry out this work.

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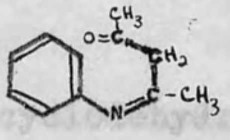
Discussion of Results:

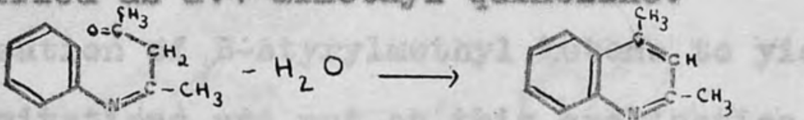
INTRODUCTION

1. Combes' Synthesis:[1,2.]

In 1888 Combes studied the action of amines with acetylacetone and showed that aniline reacted with this diketone eliminating water to give the anil β-ANILINOPROPENYL-METHYL KETONE.



He then dissolved the anil in a small quantity of concentrated Sulphuric acid, warmed the mixture on a water bath for a few minutes and poured it into a large excess of cold water. On saturating with ammonium hydroxide, an oil separated which he identified as 2:4-dimethyl quinoline.



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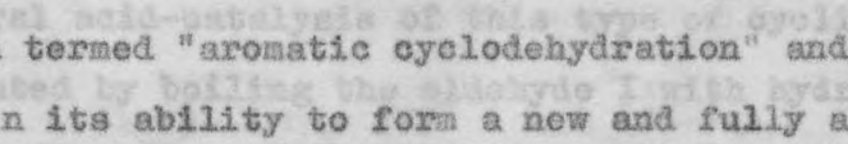
2. Aromatic Cyclodehydration:

Reaction (1) consists of an intramolecular condensation in the presence of an acid catalyst in which the new ring formed is aromatic in character. This type of cyclisation has been termed "aromatic cyclodehydration" and is almost unique in its ability to form a new and fully aromatic ring without resort to dehydrogenation.

Bradsher[3] represents this type of intramolecular condensation by the following general equation:-



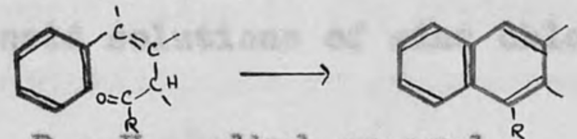
R = alkyl, aryl or H.

A = – C = C – ; – O – ; – S – ; – NH – ; – N = C – ; C = N –

The aromatic characters of the new ring arises when the component A is capable of stabilising the newly created double bond e.g. A = – CH = CH – making the compound resistant to further attack.

Known examples of cyclodehydration have been classified as follows:-

1. Naphthalene series:



R = H, alkyl or aryl.

Cyclisation of β-styrylmethyl ketone to yield naphthalanes. Severe limitations are put on this cyclisation by the presence of a double bond as well as a reactive methylene group, both of which may be affected under conditions employed in the cyclisation.

General acid-catalysis of this type of cyclisation was demonstrated by boiling the aldehyde I with hydrobromic and acetic acids, when a 25% yield of naphthalene was obtined.

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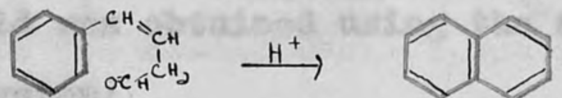
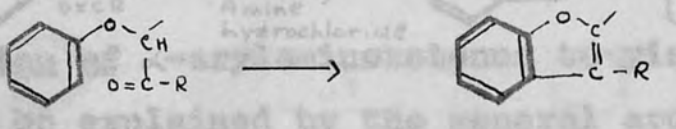


2. Benzofuran series:

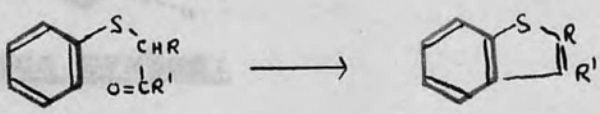


R = H, alkyl or aryl.

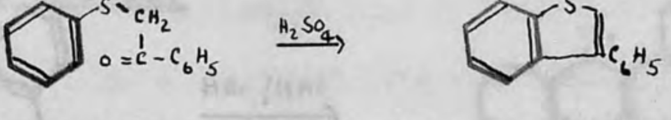
The absence of a double bond in the aldehyde or ketone, renders it more stable than its counter part in the naphthalene series and there is no problem arising from geometric isomerism. The presence of a strong ortho - para - directing ether link results in a markedly greater ease of cyclisation, an important factor because the stability of the benzofuran nucleus in acidic media is considerably less than shown by naphthalene derivatives.

Media used in the cyclisation were concentrated sulphuric acid, acetic acid solutions of zinc chloride and anhydrous oxalic acid.

3. Thianaphthene system:

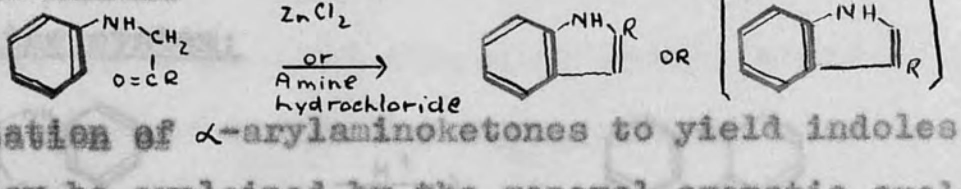


Many attempts to synthesise thianaphthene derivatives by this method failed. K. Fries and his co-workers showed that concentrated sulphuric acid converted phenacyl-3-hydroxy-sulphide to 3-phenyl-6-hydroxythianaphthene in 45% yield.



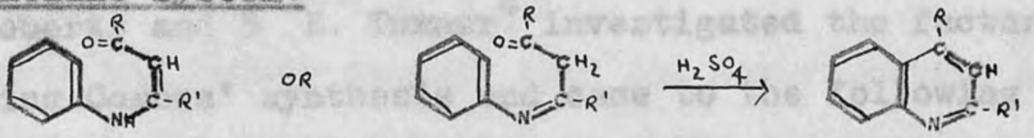
A better yield was obtained using the methyl ether.

4. Indole system:



Cyclisation of α-arylaminoketones to yield indoles. This reaction may be explained by the general aromatic cyclodehydration reaction, but in many instances the reaction must be more complicated as it involves a rearrangement.

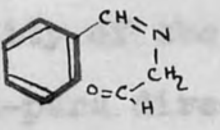
5. Quinoline system:



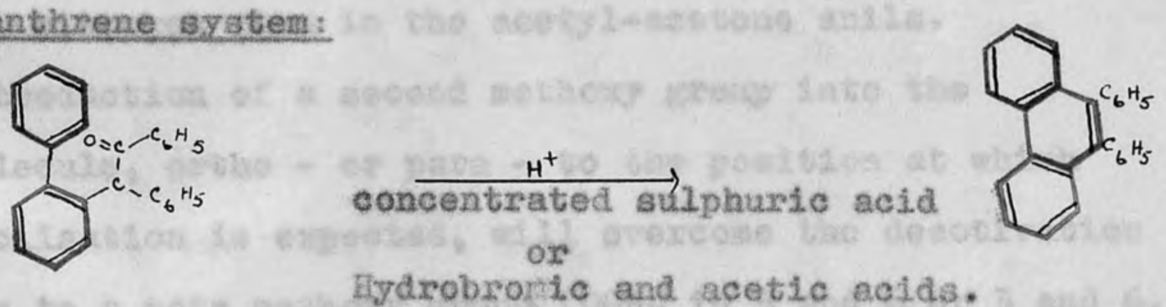
Quinolines may be prepared by the acid-catalysed cyclodehydration of β-diketone anils,. Concentrated sulphuric acid is the medium usually employed.

6. Isoquinoline system:

Limited application to the cyclisation of derivatives of benzaldimino-acetaldehyde in concentrated sulphuric acid.



7. Phenanthrene system:

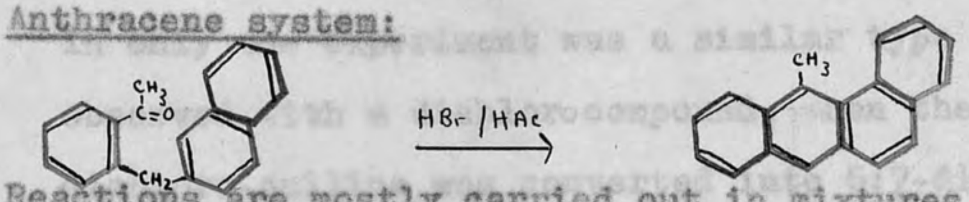


concentrated sulphuric acid

or

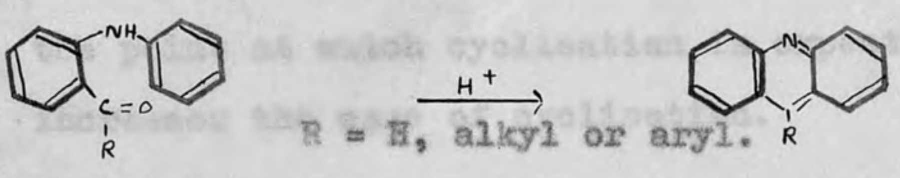
Hydrobromic and acetic acids.

8. Anthracene system:



Reactions are mostly carried out in mixtures of hydrobromic and acetic acids.

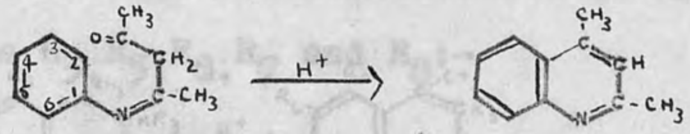
9. Acridine system:



R = H, alkyl or aryl.

Cyclisation may be brought about in sulphuric acid, either concentrated or diluted with acetic acid.

3. Effect of substituents on Quinoline synthesis:



E. Roberts and E. E. Turner[4] investigated the factors influencing Combes' synthesis and came to the following conclusions:-

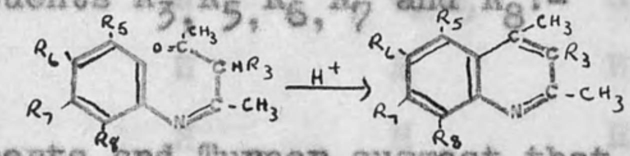
i) Methoxy group in position 4 or 6 i.e. meta - to point of ring closure completely inhibits cyclisation .

ii) Chlorine group in position 4 or 6 likewise prevents cyclisation. Their explanation was that replacement of hydrogen by chlorine, but not by methyl, diminishes the basicity of the aniline molecule, so it diminishes the ortho-para directive influence, already small, of the nitrogen atom in the acetyl-acetone anils.

iii) Introduction of a second methoxy group into the molecule, ortho - or para - to the position at which cyclisation is expected, will overcome the deactivation due to a meta methoxy group (OCH_3 in 5 and 6 or 3 and 6.) In only one experiment was a similar type of action observed with a dichlorocompound, when the anil of 4:5 dichloro-aniline was converted into 6:7-dichloroquinoline.

iv) A single ortho-para directing group, ortho or para to the point at which cyclisation is expected to occur, increases the ease of cyclisation.

Table I sets out the results obtained on varying the substituents R_3, R_5, R_6, R_7 and R_8:-



Roberts and Turner suggest that the non-formation of quinolines in the cases referred to above can hardly be due to an initial condensation to the extent of a few units %, the water formed then hydrolysing the unchanged anil of a weak base, for if this were so, condensation would have been observed where absolute or slightly fuming acid was used.

TABLE I

Summary of substituent effects.

Failed to cyclise:

R_3	R_5	R_6	R_7	R_8	Ref
H	H	OCH_3	H	H	5
H	H	H	H	OCH_3	4
H	H	H	H	Cl	4
H	H	Cl	H	H	4
H	H	Cl	H	Cl	4
H	Cl	H	H	Cl	4
H	Cl	H	Cl	H	4

Cyclised:

R_3	R_5	R_6	R_7	R_8	Ref
H	H	H	H	H	1, 2, 6.
CH_3	H	H	H	H	1, 2.

					Refs.
H	H	CH_3	H	H	1, 2.
H	H	C_2H_5	H	H	7.
H	H	H	H	CH_3	1, 2.
H	H	H	H	C_2H_5	8.
H	H	H	H	n-C_3H_7	9
H	CH_3	H	H	CH_3	10.
CH_3	H	H	H	CH_3	11.
CH_3	H	H	H	C_2H_5	12.
CH_3	H	H	H	n-C_3H_7	13.
H	H	H	$-(CH_2)_4-$		9.
H	H	H	OCH_3	OCH_3	14.
H	OCH_3	H	H	OCH_3	14.
H	H	OCH_3	OCH_3	OCH_3	15.
H	OCH_3	OCH_3	OCH_3	H	15.
H	OCH_3	OCH_3	H	Br	14.
H	H	H	Cl	H	4.
H	H	Cl	Cl	H	4.

Anils of benzoyl acetone behave in a manner very similar to thoseof acetylacetone.

It has been observed[5] that the presence of a methoxy group meta to the point at which cyclisation is expected ($R_6 = OCH_3$) causes a complete inhibition of cyclisation.

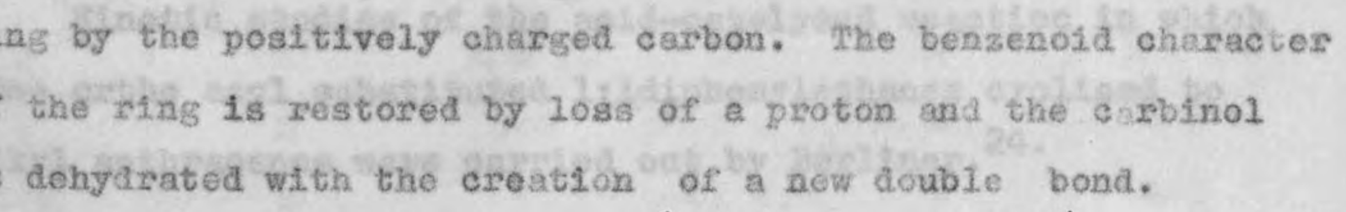
Cyclised:

Ar	R_6	R_7	Refs.
C_6H_5	H	H	6, 16.
C_6H_5	CH_3	H	6.
o $-CH_3OC_6H_4$	H	H	17, 18.
m $-CH_3OC_6H_4$	H	H	17, 18.
p $-CH_3OC_6H_4$	H	H	17, 18.
o $-C_2H_5OC_6H_4$	H	H	17.
C_6H_5	H	OH	19.

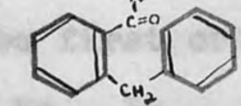
C. Beyer[16] in his original paper on the cyclisation of the anil of dibenzoylmethane to 2:4-diphenylquinoline by the action of concentrated sulphuric acid, found that it took place with great difficulty. A methoxy -group para to the position of expected ring closure, facilitates the reaction which is accomplished in very good yield under very mild conditions.[20]

4. Electrophilic substitution:

Bradsher[3] proposed that the general mechanism for cyclisation probably involved the uptake of a proton on the carbonyl oxygen, followed by an electrophilic attack upon the benzenoid ring by the positively charged carbon. The benzenoid character of the ring is restored by loss of a proton and the carbinol is dehydrated with the creation of a new double bond.



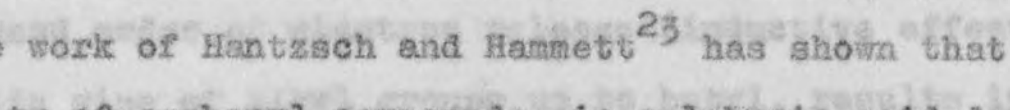
In 1942 Berliner[21] proposed a general mechanism for cyclisation of the type developed by C. K. Bradsher[22] in which 9-substituted anthracenes were prepared from the corresponding ketones.



R = alkyl or phenyl

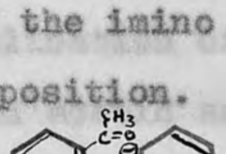
He proposed that addition of a proton to the carbonyloxygen was followed by an electrophilic substitution reaction.

The work of Hantzsch and Hammett[23] has shown that the solubility of carbonyl compounds in sulphuric acid depends on salt formation as illustrated by acetophenone:-

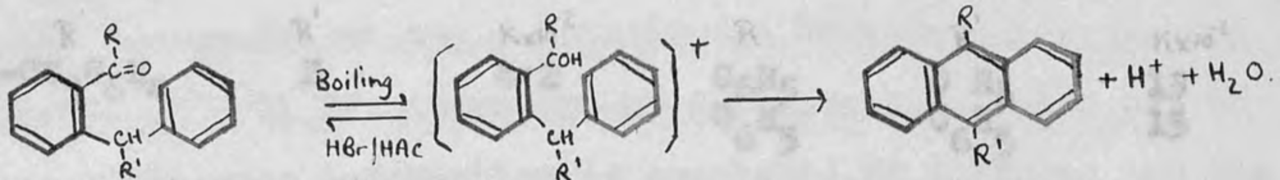


The positively charged conjugate acid of the ketone is formed and is a hybrid of two resonance forms where the positive charge is distributed between the carbon and oxygen atoms.

Cyclisation is found to proceed more readily in the acridine series because the imino group is more strongly ortho directing than the methylene group; one of the resonance structures of the imino compound has a full negative charge in the ortho position.



Kinetic studies of the acid-catalysed reaction in which some ortho acyl substituted 1:ldiphenylethanes cyclised to alkyl anthracenes were carried out by Berliner.[24].



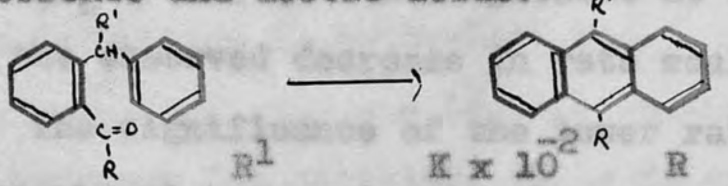
In this series $R' = H$.

The rate of reaction was found to depend on acid concentration and to be first order with respect to the cyclising compound.

R	Me.	Et.	n-Pr.	n-But.	n-pent.	n-hexyl.	phenyl.	benzyl.
$k\ min^{-1}$	4·6	1·8	0·99	0·35	0·36	0·36	0·16	0·91

An increased order of electron release (inductive effect) with increase in size of alkyl groups up to butyl, results in an increase in electron density on the positive central carbon atom, thus making the substitution reaction more difficult. Equally plausible explanations are possible from purely stereochemical considerations. The slow reaction of the phenyl ketone is ascribed to steric effects as well as to an increase in the resonance conjugation of the conjugate acid with the benzene ring, which distributes the charge over two nuclei making it less available for the attack on the point of ring closure.

C. K. Bradsher and F. A. Vingiello[25] investigated kinetically the cyclisation of o - benzylphenones in a mixture of hydrobromic and acetic acids.



R	R^1	$K \times 10^{-2}$	R	R^1	$K \times 10^{-2}$
H	H	540	p-Br C_6H_4	H	4·2
CH_3	H	70	p-Cl C_6H_4	H	4·1
C_2H_5	H	30	p-F C_6H_4	H	2·8
$C_6H_5CH_2$	H	23	C_6H_5	H	14·4

R	R'	$K \times 10^{-2}$	R	R'	$K \times 10^{-2}$
p-$CH_3C_6H_4$	H	4·2	C_6H_5	CH_3	13
			C_6H_5	C_6H_5	13

Factors which determine the rate of cyclisation are:-

1. Steric nature of groups R and R^1.
2. Effective positive character of central carbonatom of conjugate acid.
3. Electron density at ortho position of the benzene ring into which cyclisation will take place.
4. Number of such positions available.

An important factor will be the position of equilibrium between the base and its conjugate acid. An increase in electron density at the carbonyl groups of the ketone would increase the proportion of conjugate acid present and so hasten the overall reaction; this conclusion is in opposition to that drawn by Berliner.

The hyperconjugation effect of alkyl groups, R, would also tend to increase the electron density at the carbonyl group but as the size of the alkyl group increases up to butyl, the hyperconjugation effect decreases and so the proportion of conjugate acid present at equilibrium would decrease and the observed decrease in rate would be expected.

The significance of the lower rate of cyclisation of fluoro-phenyl ketone is not clear for the decreasing order of electron release of the various substituents groups as indicated by the ionisation of the p-substituted benzoic acids appears to be $CH_3 > H > F > Cl > Br$. However, no definate conclusion can be drawn until more information is available to indicate how the proportion of conjugate acid varies at equilibrium with the alkyl groups as to the relative importance of the hyperconjugative and inductive effects.

5. Acid Catalysis:

Aromatic cyclodehydration was represented by Bradsher[3] as an acid catalysed ring closure followed by dehydration. Hammett and Deyrup[26] developed an acidity scale H_o to obtain an estimate of the relative strengths of strong acids. The H_o scale is defined in terms of ionisation equilibria of a particular class of indicators which function as uncharged bases:-

$$B + H^+ \rightleftharpoons BH^+$$

The acidity function H_o is defined by the equation:-

$$H_o = -\log C_{BH^+}/C_B + pK_{BH^+}$$

where C_{BH^+} / C_B is the ratio of the concentrations of the conjugate acid and base of the indicator, and is directly measurable spectrophotometrically or colorimetrically; and K_{BH^+} is the thermodynamic ionisation constant of the conjugate acid BH^+. This definition is equivalent to:-

$H_o = -\log a_{H^+} f_B/f_{BH^+}$ where a_{H^+} represents the hydrogen ion activity, while f_B and f_{BH^+} are molar concentration activity coefficients which become unity in ideal dilute aqueous solution. In this extreme case $H_o = -\log a_{H^+}$ which is identical with the conventional hydrogen - ion concentration or pH of the solution.

The fundamental assumtion of Hammett's work is that the relative strength of two bases of the same charge type is independent of the medium. Available data seemed to justify this assumption. Hammett and Deyrup[26] compiled the H_o acidity scale by means of stepwise colorimetric measurements of the ionisation ratios of many basic indicators. For two indicators, Band C, ionising to a measurable extent in the same solution:-

$$pK_a^B - pK_a^C = -\log a_{H^+} a_B/a_{BH^+} + \log a_{H^+} a_C/a_{CH^+}$$

Since the indicators are present in sufficiently low concentration as not to appreciably effect the oxonium ion concentration of the medium, the hydrogen ion activity will be the same in solutions containing indicator B as in similar solutions containing indicator C. $\therefore pK_a^B - pK_a^C = -\log a_B/a_{BH^+} + \log a_C/a_{CH^+}$

$$= \log \frac{C_c\, C_{BH^+}}{C_B\, C_{CH^+}} + \log \frac{f_c\, f_{BH^+}}{f_B\, f_{CH^+}}$$

If the fundamental assumption that f_B/f_{BH^+} is the same for all bases is correct, then $\log f_C\, f_{BH^+}/ f_B\, f_{CH^+} = 0$

$$\text{and } pK_a^B - pK_a^C = \log C_c\, C_{BH^+}/C_B C_{BH^+}$$

Experimentally Hammett chose a series of indicators ionising over the range of 0-100% sulphuric acid and for each indicator $\log C_B/C_{BH^+}$ was plotted against % sulphuric acid. If the assumtion that f_B/f_{BH^+} is the same for all indicators, then for two indicators, B and C, two exactly parallel straight lines should be obtained when log C_B/C_{BH^+} (for each indicator) is plotted against % H_2SO_4. Within the limits of experimental error Hammett's data confirmed this assumption, although all his data was not entirely consistent. Studies of H_o have been extended to 107 % H_2SO_4[27] and in other media of high dielectric constant. Brand, James and Rutherford[28] obtained a value of 110 for the dielectric constant of anhydrous sulphuric acid at 20°C. In a solution of high dielectric constant interionic forces in dilute solution of substances soluble in pure sulphuric acid, even for ionised solutes, are expected to be very small and such dilute solutions are considered to be ideal.[29,30] In media of low dielectric constant there is evidence of greater specifity on the part of the indicators[31,32] and the interpretation of such indicator measurements is complicated by ion - pair formation.[33]

Water behaves in sulphuric acid as strong 1:1 electrolyte

$$H_2O + H_2SO_4 = H_3O^+ + HSO_4^-$$

Deno and Taft[34] estimated that this reaction had an equilibrium constant of 50 at 25°C, so that in sulphuric acid containing less than 10% water, the reaction is more than 97% complete. As in dilute aqueous solutions, the acidity of the solution is determined by the self ionisation of the solvent:-

$$a_{H^+}a_{HSO_4^-}/a_{H_2SO_4} = K$$

where K is a thermodynamic equilibrium constant. Brand[27] showed that for concentrations between 87 and 99.8 % H_2SO_4, H_o satisfied an ideal solution of form H_0 = const. + log $C_{HSO_4^-}/C_{H_2SO_4}$ where $C_{HSO_4^-}$ and $C_{H_2SO_4}$ were computed on the simple assumption that the water ionisation reaction goes to completion and that the activity coefficients of the ionic and molecular species present stay constant over this range.

Hammett and Paul[35] showed that the rate of hydrolysis of sucrose increased more rapidly than the pH of the solution, and it was observed that the log of the first order rate constant k_1, i.e. log k_1 varied linearly with $-H_0$ to give a line of unit slope.

$\therefore \log k_1 + H_0 = \text{constant}.$

Hammett[36] expected this correlation if the hydrolysis mechanism involved a first-order rate determining reaction of the conjugate acid of the sucrose.

$$\left.\begin{array}{lll} S + H^+ & \rightleftharpoons SH^+ & \text{Equilibrium} \\ SH^+ & \rightarrow X^+ & \text{rate determining} \\ X^+ + H_2O & \rightarrow \text{products} + H^+ & \text{Fast.} \end{array}\right\} \text{A 1.}$$

Applying Bronsteds equation for the effects of changes in the medium to the rate determining step:-

$$\text{Rate} = -dC_S/dt = k' C_{SH^+} f_{SH^+}/f_{\neq} = k' C_S a_{H^+} f_S/K_{SH^+} f_{\neq}$$

k'-rate coefficient for the rate determining step.

$f_{\neq}$ -activity coefficient for the transition state.

K_{SH^+} - acid ionisation constant of SH^+.

Hammett assumed that C_S^{total} is small in comparison with the total catalysing acid present. S is such a weak base that it is almost entirely in the uncharged basic form over the range of media considered so that C_S is practically the same as the overall concentration C_S^{total}, then the first order rate constant k, satisfies the equation:-

$$k_1 C_S = dC_S/dt = k' a_H + fs/K_{SH^+} f_{\neq}.$$

Substituting for a_{H^+}

$$k_1 = k' h_0 \, f_{BH^+} \, fs/K_{SH^+} \, f_B \, f_{\neq} \quad \text{if } C_{SH^+} \ll C_S.$$

$$H_0 = -\log h_0 .$$

$$\therefore \log k_1 = -H_0 + \log f_{BH^+} fs/f_B f_{\neq} + \text{constant}.$$

The observed linear correlation between log k_1 and H_0 follows if the activity coefficient ratio in the equation stays constant with changing meium i.e. if $f_S/f_{\neq} = f_{BH^+}/f_B$. The assumption would be plausible if it could be assumed that $f_{\neq}$ varied in the same way as f_{SH^+}, the activity coefficient of the conjugate acidof S. Since the transition state will only differ from the conjugate acid in displacement along the reaction co-ordinate this assumption is reasonable.

An alternate mechanism to A - 1 is the following:-

$$\left.\begin{array}{lr} S + H^+ \rightleftharpoons SH^+ & \text{Equilibrium} \\ SH^+ + Y \rightleftharpoons \text{Products} + H^+ & \text{Rate Determining} \end{array}\right\} A - 2.$$

where Y is substrate

The rate determining step is essentially bimolecular. A similar argument to that given above leads to the general rate equation:-

$$\log k_1 = \log C_{H^+} + \log f_S f_{H^+} a_{H_2O}/f_{\neq} + \text{constant}$$ e.g. Iodination of acetophenone in aqueous perchloric acids exhibits a linear relationship between log k_1 and log C_{H^+}.[37]

These results have been summararised by Zucker and Hammott

1.All A-1 reactions for uncharged reactants will follow H_0.

i.e. log k,vS H_0 will be linear with unit slope.

2.All A-2 solvolytic reactions for uncharged reactants will show linearity between log k, and log C_{H^+} with unit slope.

Each mechanism presupposes a rapid initial equilibrium between the reactant, S, and its conjugate acid, SH^+.

In their original paper[26] Hammett and Dryrup discussed several correlations of rate with H_0 e.g. decomposition of formic and malic acids in 95 - 100% H_2SO_4. For citric and oxalic acids plots of log k, against $-H_0$ gave slopes of 2 for the region 98 - 100% H_2SO_4. The formation of a diprotonated species was proposed to account for this value. The rate of decomposition of citric acid was found to reach a maximum value and then drop for higher acidities, a phenomenon supposed to be due to the reactant being converted into an unreactive form.

Triphenylacetic acid [38] in sulphuric acid decomposes to carbon monoxide, and the slope of the logk, VS H_0 plot was found to be 2·6. This result was thought to indicate that the reacting species was the diacidium ion. A slope of 2·1 was obtained when logk, was plotted against H_0 for the decarboxylation. of benzoylformic acid[39] in 94 - 98% sulphuric acid. The investigators conclude that the reactant is the diacidium ion $C_6H_5CO\ CO_2H_3^{++}$. If two protons were added in the preliminary equilibrium the appropriate acidity function is H_+. Indicator measurements in sulphuric acid by Bonner and Lockhart[40] have demonstrated the parellelism of the H_o and H_+ acidity scales[41]. The acidity function C_o governs the ionisation of indicators ionising in the following manner:- $ROH + H^+ \rightleftharpoons R + H_2O$ and since C_o is approximately equal to $2H_o$, the above data seems to indicate that dehydration precedes the decarboxylation.

Hammett[26,36] reported an approximate correlation of rate and H_o for the condensation of o-benzoyl benzoic acid to anthraquinone[42]. Deane and Huffman[43-45] extended the kinetic studies into fuming sulphuric acid but found poor correlation with H_o. At the highest acidities the rate becomes almost independent of acidity, possibly due to the fact that the reactant is extensively converted into the conjugate acid when the linear relationship will no longer hold.

Although first order rate - constants were obtained by Schubert and Zahler[46] in the acid catalysed decarbonylation reaction of aromatic aldehydes and by Schubert, Donohue and Gardner[47] in the decarboxylation of aromatic acids, the authors conclude that the Hammett unimolecular mechanism did not apply to these reactions. In both reactions studied, extensive conversion of the aromatic compound B to its conjugate acid BH^+ occurs in relatively aqueous acids (60-80% H_2SO_4) and a modified form of Hammett equation was used:-

$$\log k + H_o = \log B/B \text{ stoich} = \text{constant}$$

where B is concentration of the unionised base

B stoich is total concentration of the base.

The results obtained did not fit this equation and alternative bimolecular and termolecular mechanisms were suggested. In the decarboxylation reaction, evidence was obtained for a bimolecular reaction between the aromatic compound and the molecular sulphuric acid. A similar bimolecular reaction was proposed by Sommer, Barie and Gould[48] for the formation of methane from β-trimethylsilyl-propionic acid in sulphuric acid solution; the ratio of the first order rate constant for the evolution of methane to the concentration of molecular sulphuric acid was shown to be constant over the range 89 - 97% sulphuric acid and Deno and Taft[34] later established that the constancy of this ratio was maintained down to 85% sulphuric acid.

Bonner, Thorne and Wilkins[49] studied the rate of cyclisation of the acetyl acetone anils of aniline and p-toluidine to the corresponding 2:4-dimethylquinolines over the range 84 - 98% sulphuric acid. Constant values of $\log k_1 + H_o$ were obtained for each compound. The authors proposed that the first order cyclisation reaction proceeded by the reacting species taking up a proton from the medium without further modification of the resulting cation, then, provided only a relatively small fraction of the compound is present in the cationic form, the rate constant k_1 and the acidity function H_o would be related by the equation $\log k_1 + H_o$ = constant which was found experimentally.

6. Effect of Structure or Reactivity:

The work of Turner and Roberts[4] indicated the importance of substituents in the benzene ring on the ease of cyclisation of acetylacetone anils but no quantitative survey had been made by these workers.

One of the most useful means of obtaining a quantitative analysis of sustituent effects is to use Hammett's[50] empirocal relationship

$$\log {}^{k}/k_o = \rho\sigma \; . \qquad ....(1)$$

where k is the rate or equilibrium constant of the substituted compound

k_o is the rate or equilibrium constant of the unsubstituted compound.

ρ is a reaction constant characteristic of the reaction or equilibrium considered, the medium and temperature being constant. It is put equal to unity for ionisation of benzoic acids in aqueous solution at 25°C.

σ is the substituent constant characteristic of the substituent considered.

Hammett found that a linear relationship existed between the rate constants for the hydrolysis of meta - and para - substituted benzoic esters with the ionisation constants of similarly substituted benzoic acids. Similar relationships were found to hold for other side chain reactions to rate and equilibrium constants. Therefore, two series of constants that are linearly related to a third, are related in the same way to each other. It is possible to relate the various series to one standard of reference which was chosen as the ionisation of benzoic acids. A large amount of accurate data on ionisation constants of benzoic acids was available from the work of Dippy and Co-Workers.

Referring to equation (1) Hammett defined the reaction constant equal to Unity for the ionisation of benzoic acids. Hence the substituent constant σ was defined as $\log K_i / K_i^0$

where K_i is the ionisation constant of the substituted benzoic acid

K_i^0 is the ionisation constant of benzoic acid

and is independent of the reaction studied.

The above equation does not hold for o - substituents in benzene derivatives or aliphatic compounds. Meta-and para- substituents affect the electrostatic energy, while the main effect of ortho - substituents is to alter the non-electrostatic energy of the reacting molecule.

The Hammett equation relates the change in free energy of a molecule on substitution to the ionisation constant or rate constant for the compound considered. The free energy changes summarises changes in:-

(i) Entropy.

(ii) Potential Energy.

(iii) Kinetic Energy.

Entropy changes are assumed constant for the Hammett equation to be obeyed. Entropy is not usually affected by meta - or para - substituents, since presumably the seat of reaction is sufficiently far removed from the substituent. Constancy of entropy terms implies constancy of kinetic energy which means that free energy changes are controlled solely by changes in potential energy.

Data on activation energies in aromatic substitution reactions are limited and substitution effects are usually discussed in terms of changes in electron density at the point of reaction.

7. Reaction constants of the Hammett equation:

The effect of substituents meta - or para - in the benzene ring on the rate or equilibrium of a reaction in which the reacting group or side-chain is attached to the ring has been represented by Hammett with a simple formula:-[51,52.]

$$\log K/K_0 = \rho\sigma = -A(B_1/D + B_2)/RTd^2$$

where d is the distance from substituent to the reacting group

D is the dielectric constant of the medium

A_1 is a constant which depends only on the substituent and its postion in the ring relative to the reacting group

B_1 is a constant which is determined by the electrostatic interaction between the reacting benzene derivative and the medium

B_2 describes the susceptibility of the reaction to changes in the electron density at the reaction site.

A_1, B_1, B_2 are constants independent of the temperature and solvent. The $1/d^2$ term was introduced to relate the effectiveness of transfer of electrical effects induced by the substituent to the seat of reaction

Jaffe[53] has calculated relative rate constants by molecular orbital theory from atom -atom polarisabilities. Calculations were carried out on the effect of introducing a group Z between the side chain Y and the substituted ring Ar. The reaction constant should be greatly reduced and may change sign if the group Z is conjugated with Ar and Y and involves an odd number of atoms between Ar and Y. This was confirmed for the acid dissociation constants in water for benzylidene pyvuric acids.

The reaction constant ρ indicates the susceptibility of the reation to changes in electron density at the site of reaction i.e. a positive value for ρ indicates a reaction facilitated by low electron density at the reaction site, and a negative value for ρ indicates a reaction facilitated by high electron density at the site of reaction.

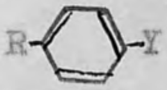
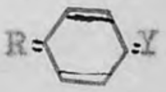
Hammett[51,52] predicted that ρ would vary inversely with temperature. This relationship has been tested for several reactions, and in some cases this has been found to be correct.[54]

8. Substitent constants of the Hammett equation:

A substituent produces different changes in electron density on the different carbon atoms of the ring through internal electron displacements i.e. inductive effects which depend on electrostatic forces and electromeric shifts which can be visualised in terms of the resonance concept. Positive values of σ indicate a decrease in electron density at the point of reaction and negative value of σ indicates an increase in electron density at the site of reaction. Electromeric shifts are relayed directly to the ortho- and para - positions, and affect the meta - position indirectly and must be much smaller in that position. Similarly the inductive forces influence the ortho -

and para-positions more strongly than the meta-position. The sign of the σ value assesses the resultant of the changes in electron density where inductive and electromeric shifts are operating.

Hammett's original σ values were based on data on the ionisation constants of meta - and para-substituted benzoic acids. It has been found necessary to introduce modified values designated σ^* which are used when considering the substituent effects of para-groups in the reactions of anilines, phenols, phenolic esters, dimethylanilines and anilides. σ^* values also have to be used for reactions in which the polarizability effects of electron attracting substituents in the para-position are greatly reduced by the presence of other competing groups in the molecule.

Some groups e.g. NO_2 which are electron attracting are assigned more than one σ value. Several resonant structures e.g.  and ⊖  ⊕ I. can be written for the substituted compound. Different σ values arise depending on the importance of structures of type I.

Polarizability effects are believed to arise if they favour a reaction. They were invoked to account for the fact that results i.e. $\log k/k_0$ for the rate reaction of benzylchlorides with trimethylamine in benzene when plotted against σ fell on two curves, one for p-substituents and the other for the meta-substituents[63]; electromeric shifts can only operate with the para-substituents. Hammett suggested an equation of the form $\log k/k_0 = [\sigma + \sigma' f(\rho)]\rho$ where σ' expressing the polarizability effects should be used.

Jaffe[55-57] has correlated σ values with electron densities in mono-substituted benzenes in the molecular- orbital method. Absolute σ values were impossible to calculate as they are very sensitive to Coulombic and resonance integral values. The calculations considered resonance and inductive effects, neither effect alone lead to satisfactory results and were substantiated by the fact that these parameters allowed for the calculation of the absorption frequencies, mesomeric moments and directing power of the substituents which were consistent with the experimental data.

In order to derive numerical values for ρ for various reactions the experimental data was interpreted by the method of least squares. Jaffe[54] has made a comprehensive review of the data on substituent and reaction constants.

Price[58] and Gallup[59] etal have calculated σ values from electrostatic considerations only it is not surprising that when electromeric forces are of considerable importance, that deviations from the Hammett equation do occur.

Hydrolysis of Anils:

Bonner, Thorne and Wilkins[49] found that the hydrolysis of the anils proceeds very rapidly in ca. 3M sulphuric acid, but the hydrolysis was not investigated kinetically. All kinetic studies on the hydrolysis of similar compounds reported in the literature appear to have been made in aqueous alcohol solutions. Willi and Robertson[60] studied the hydrolysis of a series of 4:4'-substituted benzalanilines $R-C_6H_4-CH=N-C_6H_4-R'$ in 50/50w/w water-methanol acetate buffered solutions of constant ionic strength the reaction was first order with respect to the benzalaniline. They showed that addition of 10^{-3} M sodium hydroxide gave a rate constant less than 10^{-4} at room temperature and concluded that catalysis by bases or water is negligible. At constant pH they found that the rate of hydrolysis varied with the concentration of buffer at constant ionic strength. With acetate buffers their kinetic data fitted the rate equation

$$k = k'_{H^+}[H^+] + k'_{HAC}[HAC].$$

indicating a typical result for benzylideneaniline at 20°C:-

C_{KCl}	C_{NaAc}	C_{HAC}	k	k'_{H^+}	k'_{HAC}
0·100	0·010	$2{\cdot}53\times10^{3}$	0·388	$2{\cdot}29\times10^{5}$	45·9

where C'S represent initial concentrations.

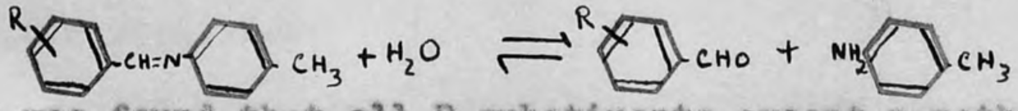
In appreciably acid solutions $[H^+] = 10^{-3}-10^{-2}M$, the rate of hydrolysis becomes immeasurably fast; an exception to this is p-dimethylaminobenzalaniline but the relatively slow rate of hydrolysis here is readily interpreted as taking place through its less reactive conjugate acid. While a large proportion of their results obeyed the equation above, the equation was not valid for all of them and in unbuffered solutions the corresponding equation $k = k_{H^+}[H^+]$ was not obeyed at all. No correlation of magnitude of substituent effects on the reaction with the Hammett substituent constants was observed.

Kastening, Holleck and Melkonian[61] in a study of the rate of hydrolysis of benzalaniline over the range pH 6-13, concluded that below pH 11 catalysis by $OH^{\ominus}$ was negligible and used the kinetic equation

$$k = k_o + k_{H^+} [H_3O^+]$$

They postulate the formation of an intermediate N- (α-oxybenzyl) aniline $C_6H_5CH(OH)NHC_6H_5$ for which they claim there is evidence from ultra-violet and infra-red absorption spectra.

Mme Odile Bloch-Claudé[62] followed kinetically both the hydrolysis and the formation of the condensation product from p-toluidine and aromatic substituents were investigated on the hydrolysis reaction



and it was found that all R substiuents except m-methoxy reduced the rate of hydrolysis relative to benzal-p-toluidine.

The investigation of hydrolysis of compounds containing the $C_6H_5N = C{<}$ group in strongly acid aqueous media does not appear to have been undertaken.

Object of present research:

An investigation of the kinetics of cyclisation of BZ - substituted anils of acetylacetone in acid media, with the possibility of the ring closure occurring through a diprotonated species.

The kinetics of hydrolysis of anils in strongly acid media were studied to establish the mechanism of hydrolysis under these conditions.

A review of substituent effects on the rates of cyclisation and hydrolysis of the anils was made and the effects compared with data available on the pK_a 'S of the corresponding amines.

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Experimental Section.

Preparation and Storage of materials and media.

1. Inorganic Salts:

All inorganic solids used were either of analar or other appropriate purity. Where necessary, solids were dried for 2 - 3 hours at 110°C before use.

2. Solutions:

Sulphuric acid. Analar 98% w/w

N. Sulphuric acid. B.D.H. Volumetric standard.

N/10. Sulphuric acid. A.R. concentrated acid was diluted with distilled water.

N. Hydrochloric acid. B.D.H. Volumetric standard.

N/10 Hydrochloric acid. Accurate dilution of B.D.H. Volumetric standard.

2N. Sodium hydroxide. Analar sodium hydroxide was used.

N Sodium hydroxide. B.D.H. Volumetric standard.

0·1N sodium hydroxide. Volumetric standard was diluted.

Perchloric acid. Analar 72% w/w.

Acetic acid. Analar glacial acetic acid.

3. Organic Compounds:

i) Acetylacetone. B.D.H. acetylacetone was dried over potassium carbonate and distilled in an all glass apparatus. The first runnings were rejected and the bulk of the distillate was collected as a colourless liquid Bpt 139°C.

ii) Aniline. B.D.H. aniline was dried over sodium hydroxide and distilled two or three times in an all glass apparatus, when it was collected as a colourless liquid Bpt 183°C.

iii) O-toluidine. B.D.H. O-toluidine was dried over sodium hydroxide and distilled in an all glass apparatus at reduced pressure, when it was collected as a colourless liquid Bpt 121°/80mm.

iv) m-toluidine. B.D.H. m-toluidine was dried over sodium hydroxide and distilled in an all glass apparatus at reduced pressure, when it was collected as a colourless liquid Bpt 123°/80 mm.

v) p-toluidine analar B.D.H. p-toluidine was crushed and recrystallised from aqueous alcohol (50/50 v/v). The crystals were dried in a vacuum desiccator over P_2O_5. Mpt. after 3 crystallisations 42°C.

vi) m-Chloroaniline. B.D.H. m-chloroaniline was distilled in an all glass apparatus under reduced pressure, when it was collected as a colourless liquid Bpt 119°/22mm.

vii) p-Chloroaniline. B.D.H. p-chloroaniline was recrystallised from aqueous alcohol. The crystals were dried in a vacuum desiccator over P_2O_6. Mpt 70-71°C.

viii) m-fluoro-aniline Light & Co. m-fluro aniline was redistilled in an all glass apparatus at reduced pressure, when it was collected as a colourless liquid Bpt 84°/20mm.

ix) p-fluro-aniline Light & Co. p-fluoro aniline was redistilled in an all glass apparatus, at reduced pressure, when it was collected as a colourless liquid Bpt 86°/20mm.

x) <u>m-Bromoaniline</u>. m-Bromoaniline (Light & Co.) was distilled in an all glass apparatus under reduced pressure, when it was collected as a colourless liquid Bpt 140°/20mm.

xi) <u>p-xylidine</u>. B.D.H. p-xylidine was distilled in an all glass apparatus and collected as a colourless liquid. Bpt 212°C.

xii) <u>1:2-dimethyl-3-amine benzene</u>. (Light & Co.) was distilled in an all glass apparatus, at reduced pressure and collected as a colourless liquid Bpt 130°/20mm.

xiii) <u>1:2-dimethyl-4-amine benzene.</u> (Light & Co.) was distilled in an all glass apparatus at reduced pressure, when it was collected as a colourless liquid Bpt 150°/20mm.

xiv) <u>1:3-dimethyl-4-amine benzene.</u> (B.D.H.) was recrystallised from ligroin. Crystals were dried in a vacuum desiccator over P_2O_5. Mpt 50-51°C.

xv) <u>4-Chloro-2-aminotoluene.</u> (Light & Co.) was distilled in an all glass apparatus at reduced pressure, when it was collected as a colourless liquid Bpt 140°/40mm.

xvi) <u>5-Chloro-2-amino toluene.</u> (Light & Co.) was recrystallised from ethyl alcohol. The crystals were dried in a vacuum desiccator over P_2O_5. Mpt 30-1°C.

xvii) <u>6-Chloro-2-amino toluene.</u> (Light & Co.) was distilled in an all glass apparatus at reduced pressure, when it was collected as a colourless liquid Bpt 160°/30mm.

xviii) <u>m-iodo-aniline.</u> 40 gms meta-nitro-aniline were dissolved on warming in a solution of 350 mls water and 140 gms concentrated sulphuric acid and then the solution was quickly cooled to 5°C, when the amine sulphate crystallised out. 40 gms of sodium nitrate were dissolved in a small volume of water and the solution cooled to 5°C., and then added slowly to the amine solution to diazotise the amine. After the diazotisation was complete a solution of 80gms potassium iodide in 80gms water was added slowly to the diazonium solution. When the effervescence ceased, the solution was warmed on a waterbath for some time to drive off any remaining nitrogen. The excess iodine was removed by adding sodium bisulphate to the solution. After cooling the solution the crystals of m-iodonitrobenzene which had formed were filtered off. These crystals were added slowly to a mixture of 150gms stannous chloride in a solution of 175gms alcohol and 175 gms concentrated hydrochloric acid and the temperature of the mixture was not allowed to rise above 35°C. The solution was left to stand overnight to allow for complete separation of the salt which was then filtered off. The alcohol was removed by distillation under reduced pressure. Sodium hydroxide was added to the remaining solution until it was alkaline and the crude meta-iodo-aniline was extracted from this alkaline solution by steam distillation. The aqueous distillate was extracted several times with ether and the ethereal solution was dried over sodium sulphate, filtered and ether distilled off under reduced pressure. The crude product was distilled under reduced pressure and the fraction Bpt 151°/20mm was collected as a pale yellow oil. Approximately 40% yield of pure m-iodoaniline was obtained.

xix) 2-Chloro-4-amino-toluene[64] - was prepared from 2-amine - 4-nitrotoluene.

Preparation of cuprous chloride. - 105gms copper sulphate and 30·5gms sodium chloride were dissolved in 400 ml/warm water. An alkaline solution of sodium sulphite (26·5g. NahSO_3 and 17·5g in 200ml water) was added to the resulting hot solution during 5 minutes with constant shaking. The solution was then cooled to room temperature and the nearly colourless supernatent liquid was decanted from the precipitate which was then filtered and washed with water containing a little sulphurous acid to prevent oxidation.

The cuprous chloride was dissolved in 170ml concentrated hydrochloric acid, the flask was loosely stoppered and cooled in ice. 51 gms of 2-amine-4-nitro-toluene were dissolved in 85ml concentrated hydrochloric acid and 85 ml water. The mixture was cooled in an ice salt freezing mixture, when the hydrochloride separated out. 25gms sodium nitrite were dissolved in 50 ml water and added to the cooled solution during 15-20 minutes with stirring. The hydrochloride dissolved as the very soluble diazonium salt was formed. The cold diazonium solution was poured into the cold cuprous chloride solution with shaking. A thick precipitate formed of the addition product of the diazonium.salt and the cuprous chloride. The solution was allowed to attain room temperature and then heated on a water bath for 1 hour to complete the breakdown of the addition complex. The mixture was steam distilled and the crude 2-Cl-4-nitro-toluene was filtered off from the distillate. 49gms i.e. 84% yield of product Mpt 63-4° were obtained. 49gms of the nitro compound and 75gms of granualted tin were treated under reflux with 170 ml concentrated hydrochloric acid added in small portions and then heated for 2 hours on a water bath. The mixture was cooled and then made alkaline with 125gms sodium hydroxide in 200 mls water, and the mixture was steam distilled. The distillate was saturated with 100gms sodium chloride and ether extracted. The ether was distilled off and the residual liquid was distilled under reduced pressure the fraction Bpt 146-7°C/40mm was collected. 28gms were obtained i.e. 63% yield of 2-chloro-4 amine toluene.

xx) 2Chloro-5-amino-toluene[65]. Freshly distilled m-toluidine was treated with a mixture of equal volumes of glacial acetic acid and acetic anhydride. Much heat was evolved and after the solution had cooled it was poured into water when aceto-m-toluidine crystallised out. The acetyl derivative was recrystallised from an acetic acid water mixture (1:3 by volume). Mpt 66°C.

18gms of aceto-m-toluidide were dissolved in 60ml glacial acetic acid. 17ml concentrated hydrochloric acid were then added to this cold solution followed by a solution of 5.2gms sodium chlorate in 20mls water. The reddish mixture was kept at room temperature for a day and then poured into 150ml water when a brown oil separated out and was removed. The aqueous solution was extracted several times with ether and the ether was distilled off. 40ml concentrated hydrochloric acid were added to the brown solution and the mixture as refluxed on a water bath for an hour, when a solid appeared in the flask. The solution was made alkaline and the free base was liberated as a brown oil which was removed by steam distillation. The amine was filtered off from the distillate and obtained as a white crystalline solid Mpt 59°C. After recrystallisation from ligroin Mpt 80-1°C. Yield of pure amine was approx. 38% theoretical.

xxi) Preparation of Amine Hydrochlorides. The hydrochlorides were prepared by the action of cold concentrated hydrochloric acid on the free base. The hydrochlorides were recrystallised 2 or 3 times from ethylalcohol and dried in a vacuum desiccator over P_2O_5.

Hydrochloride	Mpt
Aniline	197-8°C
O-toluidine	214-5°C
m-toluidine	227-8°C
p-toluidine	242-3°C
m-chloro aniline	220-2°C
p-chloro aniline	Decomposed
p-xylidine	227-8°C
1:2dimethyl-3aminobenzene	253-4°C
1:3dimethyl-4aminobenzene	235-6°C
1:2dimethyl-4aminobenzene	255-6°C
2-Cl-4aminotoluene	230-1°C
4-Cl-2aminotoluene	Decomposed
5-Cl-2aminotoluene	"

xxii) <u>Preparation of anils.</u> Anils were prepared by the method described by Turner and Roberts.[4] The amine and acetyl acetone were taken in the ratio 1gm-mol amine to 1·1gm-mol acetylacetone and boiled gently under reflux for 1-2 hours. The cooled product was thoroughly shaken with water, benzene added and the two layers separated. The benzene layer was washed two or three times with water, dried over anhydrous sodium sulphate and the benzene was distilled off. The anils occasionally solidified on cooling and were then recrystallised. Crude liquid anils were distilled under reduced pressure and the resulting solid anils were recrystallised. Most anils were obtained in 60-70% yield by this method.

Amine	Solvent	Mpt	Ref.
Aniline	Ligroin	50-2°C	(1,2,6.)
O-toluidine	40-60° Petroleum Ether	33-4°C	(1,2.)
m-toluidine			173°/22mm
p-toluidine	40-60° Petroleum Ether	65-6°C	(1,2.)
m-chloroaniline	40-60° Petroleum Ether	37-8°C	(4.)
p-chloroaniline	40-60° Petroleum Ether	60-1°C	(4)
m-Fluoro aniline	40-60° Petroleum Ether	35-6°C	
p-Fluoro aniline		44°C	
m-Bromoaniline	40-60° Petroleum Ether	37-8°C	196°/16mm
m-Iodo-aniline	60-80° Petroleum Ether	56-7°C	
p-xylidine	40-60° Petroleum Ether	45-6°C	188°/37mm (10)
1:2dimethyl-3-aminobenzene	60-80° Petroleum Ether	83-4°C	
1:3dimethyl-3-aminobenzene	40-60° Petroleum Ether	38-40°C	
1:2dimethyl-4-aminobenzene			190 C/20mm
2-Chloro-4-amino-toluene	40-60° Petroleum Ether	67-68·5°C	
4-Chloro-2-amino-toluene	40-60° Petroleum Ether	67-8°C	
6-Chloro-3-aminotoluene	40-60° Petroleum Ether	46-7°C	
6-Chloro-2-amino-toluene	60-80° Petroleum Ether	81-2°C	

Analyses. Anils

2-Chloro-4-aminotoluene.	Calc. %	C64·42	H14·11	N6·262	Cl 15·85
	Found %			N6·526	Cl 16·11
6-Chloro-3-aminotoluene	Calc. %	C64·42	H14·11	N6·262	Cl 15·85
	Found %			N6·506	Cl 15·55
m-Chloro-aniline	Calc. %	C62·99	H 5·703	N6·668	Cl 16·90
	Found %			N6·945	Cl 17·00

Media and Solutions.

Sulphuric Acid

Media were prepared by diluting Analar sulphuric acid with distilled water.

Media were standardised using potassium iodate as primary standard, and N hydrochloric acid as intermediate standard. Approximately N/10 potassium iodate solutions were made up accurately and used to standardise approximately N/10 sodium thiosulphate solutions using starch solutions as indicator. Approximately N/10 hydrochloric acid was then standardised against the sodium thiosulphate, and kept as a subsidiary standard.

Values for a typical standardisation of hydrochloric acid are given below:-

Wt. of potassium iodate = 3·5542gms.

Volume of solution = 1000 mls.

Normality of KIO_3 solution = 0·09963N.

Standardisation of sodium thiosulphate:

Volume of standard (0·09963N) KIO_3 solution taken = 20ml. 20ml 10% solution of iodate free potassium iodide and approximately 10ml 2N sulphuric acid were added. The mixture was titrated with the sodium thiosulphate solution, using starch solution near the end point. Four titrations were carried out, the values obtained being 20·00, 20·00, 20·00ml.

∴ Normality of the $Na_2S_2O_3$ solution = 0·09963N

Standardisation of hydrochloric acid:

25·00ml B.D.H. N hydrochloric acid were diluted to 250ml with distilled water.

Volume of this approximately N/10 hydrochloric acid taken = 20ml.

20ml 10% solution of iodate free potassium iodide, and 30ml N/10 potassium iodate solution were added. The mixture was standardised against the standard sodium thiosulphate solution, using starch indicator as before. Four titrations were carried out, the volumes taken being 19·92, 19·92, 19·90, 19·91ml.

Normality of the hydrochloric acid solution = 0·09919N.

∴ B.D.H.N Hydrochloric acid was 0·0992N.

Standardisations of sulphuric acid media:

Sulphuric acid media were then standardised against the hydrochloric acid subsidiary standard through sodium hydroxide solutions.

Standardisations of sodium hydroxide:

Sodium hydroxide solutions were standardised against standard hydrochloric acid by the usual acid base titrations, screened methyl orange was used as the indicator.

Typical titration readings for 20ml samples of N hydrochloric acid are 19·82, 19·82, 19·81, 19·82ml. NaOH.

Standardisations of sulphuric acid:

Approximately 1gm samples of the medium to be standardised were accurately weighed out by means of a weight pipette, diluted with 25mls water and titrated with the recently standardised sodium hydroxide solution, using screened methyl orange as the indicator. A typical analysis is given below:

1·001 N sodium hydroxide was used. 1ml NaOH $\equiv$ 0·04904gms H_2SO_4

W+ H_2SO_4medium	mls NaOH	%H_2SO_4.	
1·2880	19·63	74·82	
1·2302	18·75	74·84	Mean % H_2SO_4 = 74·8
1·1071	16·87	74·84	
1·2079	18·41	74·82	

The second column in the above table gives results which can only be correct to 1 in 2000, therefore, the percentage sulphuric acid can only be given to the nearest 0·05%.

Bearing in mind the cumulative errors in standardisation and manipulation it is probably most reasonable to quote % strength of sulphuric acid to nearest 0·1%.

Perchloric acid:

Media were prepared by diluting analar Perchloric acid with distilled water.

Media were standardised using potassium iodate as primary standard and N hydrochloric acid as intermediate standard. The method of analysis was identical with that used to estimate sulphuric acid. A typical analysis is given below:

1.001 N sodium hydroxide was used. 1ml NaOH solution ≡ 0·1006gms $HClO_4$.

Wt $HClO_4$	mls NaOH	% $HClO_4$
2·0030	14·22	71·42
2·0544	14·58	71·41
1·9645	13·95	71·41

Mean % $HClO_4$ = 71·4

Again % acid is given to the nearest 0·1% for the same reason asthat given for sulphuric acid.

N/10 Sulphuric Acid:

The N/10 sulphuric acid was standardised by titration against standard N/10 sodium hydroxide (prepared by dilution of the standard N sodium hydroxide solution) using screened methyl orange as indicator.

Ferric Ammonium sulphate:

A 6·5% solution was prepared by dissolving 65g. ferric ammonium sulphate in decinormal sulphuric acid, filtering into a 1000ml volumetric flask and making up to the mark with decinormal sulphuric acid.

Acetylacetone:

The solutions used contained 0·1 – 0·15g. acetylacetone in 500ml N/10 sulphuric acid. The acetylacetone was weighed out from a dropping tube into a 50ml flask and dissolved in N/10 sulphuric acid. This solution was then transferred to a 500ml standard flask. The 50ml flask was well washed with N/10 sulphuric acid and the washings added to the solution in the 500 ml flask. Finally the volume was made up to 500ml with N/10 sulphuric acid.

Calibration of apparatus:

The tip was cut off the grade B 2ml pipette used for the delivery of concentrated sulphuric acid to allow for more rapid delivery of the liquid. It was calibrated by weighing the amount of sulphuric acid delivered after draining for a given time. The following amounts of 91·2% sulphuric acid at 0°C were delivered by draining for 30 sec:-

3·51g, 3·52g, 3·52g, 3·50g, 3·50g, 3·50g.

Density of sulphuric acid = 1·843. ∴ Volume of sulphuric acid delivered = 1·90ml to an error of 0·01ml.

Estimation of acetylacetone:

In order to follow the rate of cyclisation of the Schiff's bases, to BZ-substituted 2:4-dimethyl-quinolines in concentrated sulphuric acid, the method developed by T. G. Bonner and M. P. Thorne[61] was used. This colorimetric determination of acetylacetone in aqueous solution, in which the acetylacetone is converted to its soluble red ferric salt as Schiff's bases are hydrolysed quantitatively to acetyl acetone and amine in dilute sulphuric acid, the reaction mixture can be analysed by determining the acetyl acetone liberated when an aliquot portion is run into water.

Absorption Spectrum of the ferric- acetylacetone compound:

This was studied with a Uvispek spectrophotometer. To 5ml of the 6·5%w/v solution of ferric ammonium sulphate was added 10ml acetylacetone solution ($2{\cdot}404 \times 10^{-3}$M) and 5ml N/10 sulphuric acid. A blank solution was prepared by substituting an equal volume of N/10 sulphuric acid solution for the acetylacetone solution.

The final solution contained the equivalent of $1{\cdot}202 \times 10^{-3}$M acetylacetone. The maximum absorption occured at 486 mμ with an extinction coefficient 648. 5.

Preparation of Standard Curves. (See figs:- 1 and 2).

As the acidity of the acid solutions of acetylacetone obtained in the kinetic run had to be adjusted by the addition of sodium hydroxide, the final solutions to be analysed colorimetrically contained considerable amount of sodium sulphate (about 0·5g sodium sulphate per 5ml aliquot of acetylacetone solution). The standard curve was prepared using solutions containing comparable amounts of sodium sulphate.

To 10ml of the ferric reagent was added a measured volume (2 - 6·5ml) of the acetylacetone solution in N/10 sulphuric acid (0·1219g acetylacetone solution in 500ml N/10 sulphuric acid). A known volume of a solution of sodium sulphate in N/10 sulphuric acid was added and the total volume made up to 40ml with N/10 sulphuric acid from a burette. These solutions were left to stand for 15 mins for the red colour to develop its full intensity. A blank solution was prepared by substituting an equal volume of decinormal sulphuric acid for the acetylacetone solution and the optical density of the solutions was compared against this blank solution using 4 Cm cells in a "Spekker" photoelectric absorptio~~n~~meter using a filament lamp and a (No.603) filter i.e. wavelength band 4,700 - 5,000λ. The instrument records directly the value of the logarithen of the quotient of the optical densities of the two dolutions (I_o/I).

Acetyl acetone solution:0·1219gms acetyl acetone in 500 ml N/10 Sulphuric acid. 4 Cm cells used.

Volume Acetylacetone Solution in ml	Mgms acetyl-acetone	Volume N/10 Sulphuric Acid	Volume Ferric Reagent	log I_o/I
2·5	0·610	27·5	10	·319; ·319
3·0	0·731	27·0	10	·392; ·391
3·5	0·853	26·5	10	·466; ·466
4·0	0·975	26·0	10	·538; ·538
4·5	0·097	25·5	10	·608; ·608
5·0	1·219	25·0	10	·684; ·684

1·62g Sodium Sulphate/40ml.

Acetylacetone					
Soln in ml. Volume	mgms	Volume Na_2SO_4 soln	Volume N/10 Sulphuric Acid	Volume Ferric Reagent	Log I_o/I
2·0	0·487	20	8·0	10	·296; ·296
2·5	0·610	20	7·5	10	·373; ·373
3·0	0·731	20	7·0	10	·444; ·443
3·5	0·853	20	6·5	10	·513; ·513
4·0	0·975	20	6·0	10	·587; ·587
4·5	1·097	20	5·5	10	·653; ·653
5·0	1·219	20	5·0	10	·724; ·724

4·05g Na_2SO_4 per 50ml solution.

Volume Acetly-Acetone Solution	Mgms Acetyl-Acetone	Wt. Na_2SO_4	Volume Ferric Reagent	Volume N/10 Sulphuric Acid	log $^{I_0}/_{I}$
2·0	0·389	4·05	12·5	35·5	·232; ·231
2·5	0·488	4·05	12·5	35·0	·292; ·292
3·0	0·584	4·05	12·5	34·5	·349; ·349
3·5	0·682	4·05	12·5	34·0	·404; ·404
4·0	0·799	4·05	12·5	33·5	·464; ·464
4·5	0·877	4·05	12·5	33·0	·524; ·524
5·0	0·974	4·05	12·5	32·5	·582; ·582
5·5	1·080	4·05	12·5	32·0	·658; ·659
6·0	1·178	4·05	12·5	31·5	·718; ·718
6·5	1·276	4·05	12·5	31·0	·770; ·769

0·40g sodium sulphate /40ml solution. 0·1227g acetyl acetone /50ml N/10 H_2SO_4

2·50	0·6134	5ml	10	22·5	·372; ·372
3·0	0·7360	5ml	10	22·0	·443; ·442
3·5	0·859	5ml	10	21·5	·515; ·515
4·0	0·980	5ml	10	21·0	·598; ·598
4·5	1·103	5 ml	10	20·5	·660; ·660
5·0	1·225	5ml	10	20·0	·732; ·732
5·5	1·347	5ml	10	19·5	·812; ·812

Kinetic runs were also carried out in concentrated perchloric acid. The final solutions to be estimated colorimetrically would contain sodium perchlorate. A standard graph was prepared using solutions containing comparable amounts of sodium perchlorate.

Acetylacetone solution:- 0·0936g acetylacetone in 500mls N/10 H_2SO_4

Sodium perchlorate solution:- 16·6g $NaClO_4$ in 200mls N/10 H_2SO_4

Volume Ferric Reagent	Volume $NaClO_4$ Solution	Volume Acetyl acetone Solution	Volume N/10 Sulphuric Acid	$\log I_o/I$
10	0	0	30	
10	0	5	25	.581;.581
10	10	0	20	
10	5	5	20	.591;.592 .591;.590
10	10	5	15	.596;.597 .597;.597
10	15	5	10	.602;.602 .602;.601
10	20	5	5	.608;.606 .608;.607
10	25	5	0	.607;.607 .610;.610

Within experimental error, the amount of sodium perchlorate present in the solution for analysis does not affect the determination of acetyl acetone content.

Preparation of standard graph.

Volume Ferric Reagent	Volume $NaClO_4$ Solution	Volume Acetyl acetone Solution	Vol. N/10 Sulphuric Acid	Mgms Acetyl acetone	$\log I_o/I$
10	5	0	25	0	
10	5	3	22	0.5616	.345 .351 .351
10	5	4	21	0.7488	.469 .469
10	5	5	20	0.9360	.580 .579 .579
10	5	6	19	1.1232	.699 .699
10	10	0	20	0	
10	10	2.5	17.5	0.4680	.298 .298
10	10	3.5	16.5	0.6552	.456 .456
10	10	4.5	15.5	0.8424	.530 .530
10	10	5.5	14.5	1.0276	.647 .646 .646

Addition of amines and quinolines:

When the anils are hydrolysed by dilute sulphuric acid, equimolar amounts of acetylacetone and amine are formed. It was necessary to investigate the effect of the amines on the coloured ferric complex. No interference occurs with aniline, p-toluidine, or the corresponding quinolines.[48]

Typical examples of the investigation of the effect of other amines and quinolines on the method of determination of acetyl acetone content are given.

m-toluidine:

Final volumes made up to 40ml with N/10 sulphuric acid.

Amine solution: 0.0781g - amine/500ml N/10 sulphuric acid.

Acetylacetone solution: 0.1203g/500ml N/10 sulphuric acid.

Vol.Fe^{+++} reagent	Vol. Acetyl(1) Acetone solution	Vol.of amine solution(11)	Vol. amine solution(111)	$\log {}^{I_o}/_{I(1)}$	$\log {}^{I_o}/_{I(11)}$	$\log {}^{I_o}/_{I(111)}$
10	3	5	10	.412 .412	.418 .418	.418 .418
10	4	5	10	.558 .558	.558 .558	.560 .560
10	5	5	10	.686 .686	.693 .693	.695 .695
10	6	5	10	.818 .818	.818 .818	.819 .819

2:4-dimethyl-7-chloroquinoline:

Quinoline solution:-0.1789gms quinoline in 100ml N/10 H_2SO_4.

Vol.Fe^{+++} reagent	Vol.Acetyl(1) acetone solution	Vol. Quinoline(11) solution	$\log {}^{I_o}/_{I(1)}$	$\log {}^{I_o}/_{I(11)}$
10	3	10	.412 .412	.413 .414
10	4	10	.558 .558	.552 .552
10	5	5	.686 .686	.676 .676
10	6	5	.818 .818	.808 .808

It was established by similar tests for all the amines and quinolines studied, that they did not interfere in the method of estimating acetylacetone.

Experimental method used for obtining kinetic data on the cyclisation of anils:

General procedure.

The cyclisations were carried out in a thermostat controlled to 0.02°C, the temperature being read with an N.P.L.calibrated thermometer.

The reaction vessel was a 250 ml round bottom flask fitted with a mercury seal stirrer and a side arm to allow for the introduction of the medium and the withdrawal of aliquots from the reaction mixture. The anil was ground into a fine powder and sufficient to give an initial concentration of 0.05 moles/litre was ~~was~~ weighed into the reaction flask.

A 50 ml standard flask was filled to within 1 ml of the mark with the medium, placed in the thermostat for the flask and contents to reach the temperature of the thermostat and then made up to the mark with acid which had been maintained at the temperature of the thermostat. The flask and contents were then weighed and replaced in the thermostat to regain the temperature of the thermostat. At the zero time the acid was poured into the reaction vessel and allowed to drain for 30 seconds and then reweighed. Throughout the time of reaction the reaction mixture was kept stirred.

Eight 2 ml aliquots were removed from the reaction vessel during the course of a run. Each 2 ml aliquot was run into 20ml ice-cold water, contained in a 100 ml conical flask. This dilution stopped the reaction and provided a 2N Sulphuric acid solution for the hydrolysis of the anil. After the mixture had been kept for 2 hours at room temperature to ensure complete hydrolysis of unconverted anil, 2.5g pellet sodium hydroxide were added to the ice-cold solution to neutralise the bulk of the acid present. The solution was finally adjusted to neuttrality by successive titration with N-sodium hydroxide,N-sulphuric acid and 0.1N sodium hydroxide (B.D.H. Universal Indicator paper); the proximity of the end point is indicated by separation of the quinoline. 5 ml of N-sulphuric acid were added and the solution was filtered into a 50 ml volumetric flask and made up to the mark with washings. The solution, now 0.1N with respect to sulphuric acid, was analysed by adding 5-,10-,15-or 20-ml aliquot portions to 10 ml of the ferric ammonium sulphate reagent and dilution to a final volume of 40 ml with 0.1N sulphuric acid. The optical density was measured against a blank solution prepared in the same way from 2 ml of the pure medium. Reactions were followed to 75 - 85% change.

To ensure that the reaction did go to completion, for each compound studied one experiment was carried out until the presence of aceylacetone was barely detectable.

Calculation of results:

The velocity constant k was calculated by means of the unimolecular equation

$$kt = - 2.303 \left[\log(a-x) - \log a\right]$$

where a is the initial concentration of anil and x is the amount of quinoline compound at time t.

All concentrations were expressed in moles litre^{-1} and k was expressed in minutes^{-1}.

k was obtained graphically by plotting log W against time, W=weight of acetylacetone equivalent to the 2 ml aliquot removed from the reaction mixture.(log W differs from log (a-x) by a constant amount).

Experiments were done in duplicate and agreement to within 1% was generally obtained.

e.g. Typical duplicate results for the cyclisation of anils are:-

Typical Duplicate runs. (See Figs: - 3 and 4.)

0.05M p-toluidine anil in 91.2% sulphuric acid at 0°C.

Time Expt no 43. 0.051M solution.

Time in mins	Aliquot Remov/ 50ml.	Final Soln	Spekker Reading	mgms AcAc	mgms AcAc /50ml.W	$\log_{10}W$	%conv
0					9.819	0.9921	
21	5	40	0.499 0.500	0.817	8.17	.9122	16.8
45	5	40	0.466 0.466	0.762	7.62	.8820	22.4
96	10	40	0.794 0.794	1.315	6.775	.8309	31.0
160	10	40	0.712 0.712	1.175	5.875	.7690	40.1
241	10	40	0.623 0.623	1.025	5.125	.7097	47.8
325	15	40	0.741 0.741	1.225	4.083	.6110	58.5
413	20	40	0.812 0.812	1.347	3.368	.5273	65.5
548	20	40	0.610 0.610	1.004	2.510	.3997	74.4

k = 0.0022min.$^{-1}$

Expt no 44.   0.052M solution.

Time in mins	Aliquot remov/ 50ml	Final soln	Spekker Reading	mgms AcAc	mgms AcAc /50mlW	$\log_{10}W$	%conv
0					9.745	0.9888	
25	5	40	0.512 0.512	0.840	8.40	.9243	13.9
63	5	40	0.485 0.485	0.795	7.95	.9004	18.5
151	10	40	0.782 0.782	1.295	6.475	.8112	33.5
256	10	40	0.634 0.634	1.043	5.215	.7172	46.5
372	15	40	0.738 0.738	1.220	4.067	.6095	58.2
464	15	40	0.579 0.579	0.951	3.170	.5011	67.5
570	20	40	0.652 0.652	1.075	2.688	.4294	72.4
650	20	40	0.557 0.557	0.915	2.188	.3401	77.6

$k = 0.00221 \text{min}^{-1}$

0.05M 1:2-dimethyl - 3-amino-benzene anil in 80.8% $HClO_4$ at 25°

Expt no.119.   0.0505M.

Time in mins	Aliquot remov/ 50ml.	Final Soln	Spekker Reading	mgms AcAc	mgms AcAc /50mlW	$\log_{10}W$	%con
					9.902	.9957	
4	5	40	.439 .439	0.728	7.28	.8621	26.
7	5	40	.366 .366	0.604	6.04	.7810	39.
11	10	40	.544 .544	0.899	4.495	.6527	54.
15	10	40	.408 .408	0.675	3.375	.5282	65.
19	15	40	.476 .476	0.795	2.65	.4232	73.
23	15	40	.350 .350	0.575	1.917	.2826	81
27	20	40	.372 .371	0.611	1.518	.1812	84
32	20	40	.257 .257	0.417	1.043	.0182	89

k = 0.0697 min^{-1}

Expt no.120. 0.0500M.

Time in mins	Aliquot remov/ 50ml.	Final Soln	Spekker Reading	mgms AcAc	mgms AcAc /50ml W	$\log_{10}W$	%conv
					9.792	.9909	
8	5	40	.342 .342	.562	5.62	.7497	42.6
11	10	40	.570 .571	.951	4.755	.6772	51.4
15	10	40	.437 .437	.725	3.625	.5593	62.9
19	10	40	.309 .309	.507	2.535	.4040	74.1
24	15	40	.340 .340	.560	1.867	.2711	80.8
30	15	40	.226 .226	.365	1.217	.0832	87.5

k = 0.0697 min^{-1}

Hydrolysis of anils:

Experiments were carried out to establish that the anils were completely hydrolysed in dilute sulphuric acid.

2 samples (approx.0.1gm) of each anil were dissolved in 50 ml 2N sulphuric acid and left to stand for a short time. 4g solid sodium hydroxide were then added to each solution which were then accurately neutralised, 50 ml N-sulphuric acid added and the volume made up to 500 ml. A 10 ml aliquot of these solutions was anlaysed colorimetrically as previously described.

Anil	Wt of sample analysed	% Acetylacetone recovery
O-toluidine	0.1513	99.3
m-toluidine	0.1030 0.1172	100.3 99.1
m-chloroaniline	0.0948 0.0970	99.4 99.8
m-fluoroaniline	0.1098 0.1009	100.7 104.6

Anil	Wt of samples for analysis	% Acetylacetone recovery
m-Bromoaniline	0.1012	99.2
	0.0989	98.8
m-Iodo aniline	0.0663	100.6
	0.0649	100.3
p-xylidine	0.1005	100.4
	0.0911	99.7
1:2-dimethyl-3-amino-benzene	0.987	99.3
1:2-dimethyl-4-amino-benzene	0.1076	100.8
	0.1083	101.6
2-chloro-4-aminotoluene	0.1067	98.2
	0.0968	99.6
4-chloro-2-aminotoluene	0.1011	100.1
	0.0990	100.0
6-chloro-3-aminotoluene	0.0868	98.3
	0.0873	99.5
6-chloro-3-aminotoluene	0.0957	99.3
	0.1007	99.8
1:2-dimethyl-4-amino-benzene	0.1033	98.2
	0.1060	100.0
Perchloric Acid.		
1:2-dimethyl-3-amino-benzene	0.0970	99.2
	0.0982	99.9

Products obtained on cyclisation:

As the kinetics of the conversion of the anils into the quinoline compounds were being studied by measuring the rate of disappearance of the anil, it was necessary tp make certain that the product of the reaction, throughout its whole course, was a 2:4-dimethyl quinoline.

To establish this fact, approx. 1g. samples of the anils were dissolved in 10mls of 98% sulphuric acid (this corresponds to 10 times the concentration of organic reactant used in kinetic experiments) and kept at room temperature for several hours. The solution was poured into ice-cold water (100ml) and left for 2 hours to ensure complete hydrolysis. The solution at 5° was treated with an ice-cold sulution of sodium nitrite (0.05g) in water (5ml) to diazotise any amine resulting from the hydrolysis, and then warmed to convert the diazonium salt into phenol. After cooling, soium hydroxide (15g.) was added to make the solution alkaline. The 2:4-dimethyl-quinoline was extracted with ether, and the ether extracts washed with water and dried over sodium sulphate. After filtration and evaporation the crude quinoline was obtained.

Quinoline	% Yield	Mpt.	Solvent used for recrystallisation
2:4:8-trimethyl-quinoline	94.7	41°C	Et-OH/Water
2:4:7-trimethyl-quinoline	98.9		
2:4-dimethyl-7-chloro quinoline	93.1	44.5-45.5°C	40-60° Petroleum ether
7-fluoro-2:4-dimethyl quinoline	91.4	45-6 °C	- do -
7-bromo-2:4-dimethyl quinoline	95.2	46-7 °C	- do -
7-iodo-2:4-dimethyl quinoline	99.2	54-5 °C	- do -
2:4:5:8-tetramethyl quinoline	94.7	44-5 °C	- do -
2:4:7:8-tetramethyl quinoline	88.5	30-1 °C	- do -
2:4:6:8-tetramethyl quinoline	94.0	86 °C	- do -

Quinoline	% Yield	Mpt.	Solvent used for recrystallisation
2:4:6:7-tetramethyl quinoline	97.3	79-80°C	40-60 Petroleum ether
7-Chloro-2:4:6-trimethyl quinoline	93.1	81-2°C	80-100 - do -
5-Chloro 2:4:8-trimethyl quinoline	91.3	54-5°C	40-60 - do -
6-Chloro-2:4:7-trimethyl quinoline	98.0	89-90°C	80-100 - do -
7-Chloro-2:4:8-trimethyl quinoline	96.0	68-9 °C	60-80 - do -
Perchloric acids			
2:4:7:8-tetramethyl quinoline	98.7	28-30°C	40-60 - do -

Analyses:

7-Chloro-2:4:6-trimethylquinoline	Calc.	C70.04	H5.403	N6.810	Cl 17.24 %
	Found			N7.058	Cl 17.29 %
2:4:7:8-tetramethylquinoline	Calc.	C84:31	H7.923	N7.584	%
	Found	C84.26	H8.288	N7.633	%
2:4:6:7-tetramethylquinoline	Calc	C84.31	H7.923	N7.584	%
	Found	C84.39	H8.084	N7.674	%
7-Chloro-2:4:8-trimethyl quinoline	Calc.	C70.04	H5.403	N6.810	Cl 17.24 %
	Found			N6.814	Cl 17.93 %

Effect of variation of the initial concentration of anil.

In general, cyclisation reactions were carried out with an initial concentration of 0.05 moles litre^{-1}.

It was necessary to make up the solution to a final volume ~~of~~ of 100 ml decinormal with respect to sulphuric acid when the initial anil concentration was 0.2M.

2-p-toluidine-pent-2-en-4-one was used for these studies 0.2 - 0.02M at 25°C in 93.7% sulphuric acid and it was found that as the initial concentration of anil increased, so the rate of cyclisation decreased. A similar result was obtained by Bonner, Thorne and Wilkins[48] who studied the variation of the rate of cyclisation with initial concentration of the β-anilino-pent-2-en-4-one in 95.7% sulphuric acid at 25°C.

Effect of variation of temperature on rate of cyclisation:

The cyclisation of 2-p-toluidine-pent-2-en-4-one and β-anilino-pent-2-en-4-one was carried out at different temperatures with the initial concentration of anil 0.05M.

Hydrolysis of anils in concentrated sulphuric acid media:

The stability of the anils was investigated in concentrated sulphuric acid in the range where cyclisation, if it was occuring, was known to be too slow to measure. The anil of 1:2dimethyl-3-amino-Benzene was known to cyclise at a measurable rate down to 70% Sulphuric acid. If the anil was stable in a lower acid concentration, by adding a stronger Sulphuric acid it should have been possible to produce a medium suitable to follow the kinetics of cyclisation of the anil by the procedure already described. The stability of the anil was investigated as follows:

0.2g of anil were dissolved in 5ml 60% sulphuric acid and maintained at 25°C overnight when 15ml 100% sulphuric acid were added, at zero time, and the mixture shaken. 2ml aliquots were removed at known time intervals. The acetyl-acetone content of the samples was estimated as before. A constant value was obtained for the acetylacetone content indicating 71% hydrolysis of the anil. The experiment was repeated, but the 60% solution was maintained at 25°C for only 1½hours before 15 ml 100% sulphuric acid were added 2 ml aliquots were removed and analysed as before. A slight decrease in acetylacetone content was observed with increasing time. The acetylacetone analysis indicated only 22% hydrolysis of the anil. These results were interpreted as indication that in the 60% sulphuric acid medium the anil was hydrolysing and the addition of the 100% sulphuric acid caused any remaining anil to cyclise. The heat evolved on addition of the 100% sulphuric acid would facilitate the cyclisation reaction. It was found possible to follow kinetically the cyclisation of this unchanged anil, if the 60% acid solution was ice-cold before the ice-cold 100% sulphuric acid was added to it. This hydrolysis of the anil could then be followed kinetically by withdrawing samples and running them into 100% sulphuric acid where any unhydrolysed anil would be converted into quinoline.

Acetyl acetone recovery under the conditions for hydrolysis:

It was essential to establish that acetylacetone could be recovered quantitatively when subjected to the procedure suggested for obtaining kinetic data.

A known weight of acetylacetone was dissolved in 25ml 60% sulphuric acid and kept at 25°C overnight. A 2ml aliquot of this solution was removed and run into 20ml ice-cold water, neutralised, 5ml N sulphuric acid added and made up to 50ml. a 10ml aliquot of this solution was removed for acetylacetone analysis. Typical results are shown:-

Wt acetylacetone taken	% recovery acetylacetone
0.3224	99.4
0.4302	99.6

The effect of adding amine to the acetylacetone solution in 60% sulphuric acid was examined by the same technique:-

Wt acetylacetone taken g.	Wt of amine added g.	% recovery acetylacetone
0.3224	1.0168	74.2
0.4302	0.5759	74.0

These results indicate that an equilibrium is established when the amine and acetylacetone are present together in 60% sulphuric acid i.e. they combine to give some anil.

Recovery of amine under conditions of hydrolysis.

A solution containing .3gms anil of 1:2dimethyl 3-amino benzene in 15ml 60.1% sulphuric acid was kept at 25°C for 2days. It was then poured into 100ml ice-cold water and the solution made alkaline with sodium hydroxide. The alkaline solution was shaken with ether several times and the ether extract washed with water and dried over sodium sulphate. After filtration the ether was distilled off and the product weighed. An attempt was made to prepare the acetyl derivative on the assumption that the amine had been recovered. The above residue was refluxed with 2ml glacial acetic acid for ½ hour and then poured into the ice-cold water and the solution was made alkaline. A white crystalline product was formed which was filtered off, dried and weighed. A melting point determination was carried out on this sample, which was then recrystallised from water.

Equivalent of 0.3117 gms amine originally present in acid. 0.3110gm amine recovered from acid, proving that the amine could be recovered unchanged from the medium and did not sulphate under the conditions used for hydrolysis.

M.pt of crude acetyl derivative = 133-134°C.

M.pt of recrystallised acetyl derivative = 134-5°C.
(Beilstein - 135°C.)

% yield crude product = 77%

Investigation of formation of anils in strongly acid media:

It was necessary to establish that no anil was reformed when the 2 ml aliquots from the hydrolysis were run into the 100% sulphuric acid.

A known weight of acetyl acetone was dissolved in 10ml 60% sulphuric acid. A 2ml aliquot of this solution was made up to 10ml with 100% sulphuric acid and the acetyl acetone content determined as before(1.). 0.5gms 1:2-dimethyl-3amino-benzene was then added to the 60% solution and as soon as the amine dissolved a 2ml aliquot was removed and made up to 10ml with

100% sulphuric acid and the acetylacetone content determined after 24 hours (2). After 24 hours another 2ml aliquot was removed from the 60% sulphuric acid solution and made up to 10ml with 100% sulphuric acid, and the acetyl acetone content determined(3).

Results:

Solution No.	$\log {}^{I_o}/_{I}$	Equivalent Acetylacetone Content	% Acetylacetone remaining
(1)	.830 .830	1.395	
(2)	.831 .831	1.396	100%
(3)	.564 .564	0.940	67.3%

These results demonstrated that no anil formation occurs in 100% acid but does occur in 60% acid.

General Procedure for measuring rate of hydrolysis of anils:

Kinetic measurements were carried out at 25°C in a thermostat controlled to ± 0.02°C. The reaction vessel was a 50ml quickfit conical flask. The anil was weighed into a B24 socket cap, the amount taken providing a 0.1.M. solution when dissolved in 25ml of the medium. The reaction flask was weighed and 25ml medium were placed in the flask and the flask was weighed to enable one to calculate the exact volume of medium used. The flask was placed in the thermostat for the medium to attain the temperature of the thermostat. To start the reaction, the reaction flask was removed from the thermostat and the filled socket cap inserted. The medium and reactant were brought together at zero time by vigorous shaking and after complete -

dissolution the flask was returned to the thermostat. Six to eight 2ml aliquots were removed from the reaction mixture and run into 100% sulphuric acid and made up to 10ml/in 10ml graduated flask. This stopped the hydrolysis and converted any unhydrolysed anil to quinoline compound. After 2 hours, two 2ml aliquots of each solution were run into 20ml ice-cold water and then neutralised as described for the cyclisation and made up to 50ml. The acetylacetone content of these solutions was determined colorimetrically.

Calculation of results:

The velocity constant k_1 was calculated from the equation

$$k_1 = \frac{2.303x_e}{t(2a-x_e)} \quad \log \frac{ax_e + x(a-x_e)}{a(x_e - x)}$$

for a first order reaction opposed by one of the second order.

a = initial concentration of anil.

x = concentration of anil at time t.

$x = x_e$ at equilibrium when $dx/_{dt} = 0$.

If the hydrolysis of the anil is first order with respect to the anil, a plot of $\log \frac{ax_e + x\ (a-x_e)}{a(x_e-x)}$ against t should be a straight line, and from the slope of the line k_1 (minutes^{-1}) could be calculated. Experiments were carried out in duplicat and agreement to within 2% was usually obtained.

Typical duplicate results for the hydrolysis of the anil of 1:2-dimethyl-3amino-benzene in 52.8% sulphuric acid at 25°C are shown:- 0.10M initial concentration.

Typical duplicate runs - See Fig:- 5.

0.10M 1:2dimethyl-3-amino-benzene anil in 52.8% sulphuric acid at 25°C.

Expt. no.129. 0.10M solution:

Time t	Aliquot remov/ 50 ml.	Final Solution	Spekker Reading	mgms AcAc.	mgms AcAc/50 ml.
7	30	40	.300 .300	.490	.817
17	20	40	.442 .443	.735	1.833
24	20	40	.596 .597	.995	2.488
34	15	40	.552 .551	.920	3.067
46	10	40	.423 .423	.700	3.500
59	10	40	.505 .505	.840	4.200
94	10	40	.581 .581	.970	4.850
Infin	5	40	.315 .315	.516	5.160

$$k = \frac{2.303x_e.}{t(2a-x_e)} \log_{10} \frac{ax_e + x\,(a-x_e)}{a(x_e-x)}$$

$a = 5.853$ $a - x_e = 0.693$ $ax_e = 30.20$

$x_e = 5.160$ $2a - x_e = 6.546$

t.	x.	$x(a-x_e)$.	$ax_e+x(a-x_e)$.	x_e-x.	$\log a(x_e-x)$	log- ax_e+x $(a-x_e)$.	log - $\frac{ax_e+x(a-x_e)}{a(x_e-x)}$
7	.817	.5661	30.7661	4.353	1.4062	1.4881	.0819
17	1.833	1.271	31.471	3.327	1.2894	1.4979	.2085
24	2.488	1.724	31.924	2.672	1.1942	1.5041	.3099
34	3.067	2.125	32.325	2.093	1.0881	1.5095	.4214
46	3.500	2.425	32.625	1.660	0.9875	1.5136	.5261

t.	x.	$x(a-x_e)$.	$ax_e+x(a-x_e)$.	x_e-x.	$\log a(x_e-x)$	$\log \frac{ax_e+x}{(a-x_e)}$.	$\log \frac{ax_e+x(a-x_e)}{a(x_e-x)}$
59	4.200	2.910	33.110	0.960	0.7497	1.5199	.7702
94	4.850	3.360	33.560	0.310	0.2588	1.5258	1.2670

$$k = \frac{1.04 \times 2.303 \times 5.15}{78.5 \times 6.548} = 0.0241 \text{ min.}^{-1}$$

Expt.no.130. 0.099M solution:

Time	Aliquot remov/50/ml	Final Solution	Spekker Reading	mgms AcAc.	mgms AcAc./50ml
10	30	40	.464 .465	.770	1.283
16	25	40	.559 .559	.932	1.864
22	20	40	.557 .557	.930	2.325
28	15	40	.508 .508	.848	2.827
39	15	40	.633 .632	1.057	3.523
51	10	40	.483 .483	.804	4.020
74	10	40	.570 .570	.951	4.755
Infin.	5	40	.308 .308	.515	5.150

$$k = \frac{2.303\, x_e}{t(2a-x_e)} \quad \log_{10} \frac{ax_e + x(a-x_e)}{a(x_e - x)}$$

$a = 5.849$ $a - x_e = .699$ $ax_e = 30.11$

$x_e = 5.150$ $2a - x_e = 6.548$

t.	x.	$x(a-xe)$.	$ax_e+x)a-x_e)$.	x_e-x.	$\log a(x_e-x)$.	$\log \frac{ax_e+x}{(a-x_e)}$.	$\log \frac{ax_e+x(a-x_e)}{a(x_e-x)}$
10	1.283	1.129	31.339	3.867	1.3545	1.4961	.1416
16	1.864	1.303	31.413	3.286	1.2838	1.4970	.2132
22	2.325	1.625	31.735	2.825	1.2181	1.5017	.2836
28	2.827	1.976	32.086	2.323	1.1332	1.5060	.3728

t.	x.	x(a-xe).	$ax_e+x(a-x_e)$.	x_e-x.	$\log a(x_e-x)$.	log $\frac{ax_e+x}{(a-x_e)}$.	log $\frac{ax_e+(a-x_e)}{a(x_e-x)}$
39	3.523.	2.462	32.572	1.627	.9785	1.5128	.5344
51	4.020	2.809	32.919	1.130	.8202	1.5175	.6973
74	4.755	3.324	33.434	0.395	.3637	1.5241	1.1604

$$k = \frac{1.04 \times 2.303 \times 5.15}{78.5 \times 6.548} = 0.0241 \text{ min}^{-1}$$

Effect of ammonium sulphate on rate of hydrolysis:

Ammonium sulphate was added to the 60.1% sulphuric acid. The effect of 1.0M ammonium sulphate on the rate of hydrolysis of the anil of 1:2dimethyl-3amino-benzene was investigated. The medium was prepared by weighing out sufficient ammonium sulphate into a weighed 100ml volumetric flask to give a 1M solution when dissolved in 100ml 60.1% sulphuric acid.. 60.1% sulphuric acid was added and the flask was well shaken to dissolve the ammonium sulphate. The volume was made up to 100ml at 25°C and the flask was reweighed. Addition of ammonium sulphate facilitated the hydrolysis of the anil.

0.1M anil concentration, 1M$(NH_4)_2SO_4$, 60.1% sulphuric acid 25°C

Expt.No. 134 k_1 = .00533

135 k_1 = .00538

Hydrolysis of anils in 50% acetic acid/benzene mixtures:

An investigation of the stability of the anils in acetic acid was carried out. A spectrophotometric investigation of solutions of anils in acetic acid showed that in glacial acetic acid rapid decomposition of the anils occured. In order to make a kinetic investigation of the decomposition of the anils a 50%

mixture of acetic acid and benzene was chosen. It was confirmed that in acetic acid/benzene solutions,at the wavelength of maximum absorption of the anil, acetylacetone and the amines had negligible absorption. It was possible to measure the rate of hydrolysis of the anils by measuring the absorption at the wavelength of maximum absorption of the anil.

First order rate constants were obtained for the hydrolysis of substituted anils in 50% v/v acetic acid/benzene at 25°C.

Hydrolysis of anils in 50% v/v acetic acid/benzene at 25°C. See fig:- 6 for typical dup.runs

Compound	Expt.No.	k_1
Aniline	160	0.00157
	161	0.00159
p-toluidine	162	0.00184
	163	0.00183
O-toluidine	164	0.00126
	165	0.00126
m-toluidine	148	0.00184
	150	0.00185
1:3dimethyl-4-aminobenzene:-	166	0.00144
	167	0.00145

Determination of the pKa's of amines:

The pK_a was determined by a potentiometric titration.

The cell employed was a glass electrode-calomel electrode system, the pH-was measured on a Cambridge pH-meter. The glass electrode was first standardised against solutions of known pH. The amine hydrochlorides were dissolved in water and titrated against 0.IN sodium hydroxide.

General procedure:

25ml 0.02M solution of hydrochloride were brought to 25°C in a thermostat controlled to ±0.02°C. The pH-meter was calibrated with buffer solutions e.g. Phosphate buffer pH=6.81 or phthalate buffer = 4.00. The electrodes were immersed in the hydrochloride solution and the pH of the solution determined. 0.IN sodium hydroxide was added from a microburette, the solution was kept stirred. The pH was determined for each addition of the sodium hydroxide. The titration was continued well past the equivalent point.

Evaluation of pKa: See fig:- 9

By measuring the hydrogen ion activity of a known concentration of an acid and its salt, the dissociation constant, K_a, can be calculated from the equation:-

$$K_a = \frac{[H_3O+][A^-]}{[HA]} \quad \frac{fH_3O^+ fA^-}{fHA}$$

$$pK_a = pH + \log \frac{[HA]}{[A^-]} + \log fHA - \log fA^-$$

The concentration of the anion A^- can be calculated from the concentration of hydronium ion, whereas the concentration of the unionised acid, HA, is given by the initial value of the acid introduced less the concentration of hydronium ion. The activity coefficient of the acid may be taken as unity and that of the anion may be calculated from Dekye-Hückel theory.

At the half-netralisation point, the ration of $[HA]/[A^-]$ is approximately unity for a weak acid and its highly ionised salt e.g. $C_6H_5NH_2$ and $C_6H_5NH_3^+ + Cl^-$, so that the pK_a is equal to the pH value plus a correction for the activity coefficient of the anion, $pK_a = pH - \log f_{A^-}$. The activity coefficient term was considered negligible in this investigation.

pK_a of amines at 25°C in aqueous solution:

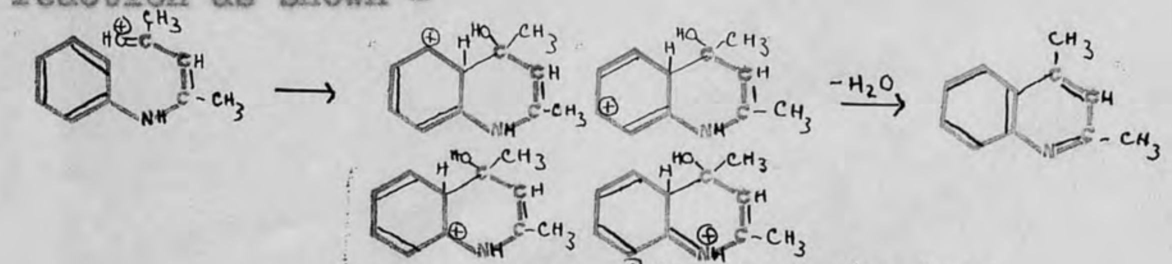
Amine	pKa
aniline	4.70
o-toluidine	4.48
m-toluidine	4.81
p-toluidine	5.01
m-chloroaniline	3.59
p-chloroaniline	3.99
p-xylidene	4.50
1:2-dimethyl-3-aminobenzene	4.68
1:3-dimethyl-4-aminobenzene	4.97
1:2-dimethyl-4-aminobenzene	5.22
2-chloro-4-aminotoluene	4.05
4-chloro-2-aminotoluene	3.38
5-chloro-2-aminotoluene	3.82

-ooOoo-

Discussion of results.

1. Mechanism of cyclisation

Bonner, Thorne and Wilkins[49] investigated the cyclisation of the anils of acetylacetone with aniline and p-toluidine in a range of acid media from 84.5 - 97.3% sulphuric acid. The use of strongly acidic media indicated reaction through a protonated form with the alternative possibilities of a rate determining ring closure proceeding either before or after dehydration, which it is possible to decide upon by correlation of rate constant and the appropriate acidity function. The rate of cyclisation was found to be first order with respect to the cyclising compound. The rate constants increased with increasing acidity of the medium, the rate of cyclisation becoming immeasurably fast in absolute sulphuric acid. The authors established that the first order rate constants k_1 for a fixed initial concentration of condensation product were related to the acidity function H_o by the Hammett relationship $\log k_1 + H_o = \text{constant}$ over the range of media considered. It was concluded that the cyclisation proceeded through a monoprotonated species, formed in fractionally small amount, undergoing a rate determining ring closure followed by rapid dehydration to form the 2 : 4 - dimethyl-quinoline, and represented the reaction as shown -



Resonance structures of intermediates.

Later consideration and dicsussion has suggested that the anil could be completely monoprotonated in the strong acids used in the cyclisation reaction, forming a stable monovalent cation which does not itself undergo cyclodehydration; the reaction might then proceed through a diprotonated anil formed in fractionally small amount.

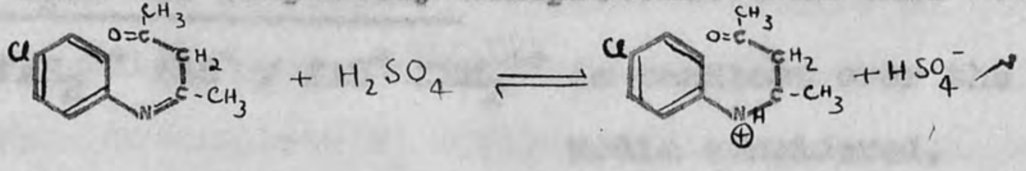
To investigate this possibility, an anil which was known to fail to cyclise in concentrated sulphuric acid was selected as the solute for the determination of lowering of freezing point data in pure sulphuric acid. The anil used was the acetylacetone anil of p-chloroaniline, which Roberts and Turner had failed to cyclise[4]. A spectroscopic investigation of the stability of the anil in 100% sulphuric acid showed that the hydrolysis of the anil was slow, and would be virtually negligible during the time taken to determine the freezing point of a solution.

The ratio of the actual freezing point depression per mole to that produced by a non-electrolyte the van't Hoff factor i_1 is a relatively accurate measure of the number of ions produced by the solution of one molecule of solute e.g. Benzoic acid is known to be fully protonated in 100% sulphuric acid[66]: -

$$C_6H_5COOH + H_2SO_4 \rightleftharpoons C_6H_5COOH_2^+ + HSO_4^-$$

An i factor of 2 has been found for this reaction indicating complete monoprotonation of the benzoic acid. A satisfactory value of 2.07 for the i factor for this compound, in the rather approximate determination made in the present work, was obtained.

A similar determination of lowering of freezing point with the acetylacetone anil of p-chloroaniline in 100% sulphuric acid gave an i- factor of 2.05, indicating that the anil was completely monoprotonated in this medium.



If the first step in the cyclodehydration reaction is the formation of a reactive diprotonated species, derivation of the appropriate equation relating k\ and the acidity function H_+ is similar to that outlined in the earlier treatment of Bonner, Thorne and Wilkins[49].

Let $[AH^+]_I$ - total concentration of anil completely monoprotonated in media used for cyclisation.

$[AH_2^{++}]$ - concentration of diprotonated species.

$[AH^+]$ - concentration of monoprotonated anil.

k_1 - experimental velocity constant for a given medium.

k_o - theoretical velocity constant, assumed constant over the range of media considered.

In any medium if ring closure precedes dehydration:-

$A + H^+ \rightarrow AH^+$ complete.

$AH^+ + H^+ \rightleftharpoons AH_2^{++}$

$AH_2^{++} \rightarrow$ products

Then $k_1 \ [AH^+]_I = k_o \ [AH_2^{++}]$

where k_1 is the experimental rate constant

k_o is the theoretical rate constant

$k_1 = k_o [AH_2^{++}] / [AH^+]_I = k_o [AH_2^{++}] / [AH^+]$ if $[AH_2^{++}] << [AH^+]_I$

$\log k_1 = \log k_o + \log [AH_2^{++}] / [AH^+]$

$H_+ = -\log K - \log [AH_2^{++}] / [AH^+]$ assuming that the anil can be considered as a Hammett type base.

$\underline{\log k_1 + H_+ = \text{constant}}$

if $fAH_2^{++} \, fBH^+ / fAH^+ \, fBH_2^{++}$ is constant over the range of media considered.

A proton transfer to a univalent cation base, AH^+, to form the conjugate acid, AH_2^{++}, corresponds to an acidity function H_+ defined by

$H_+ = -\log a_{H^+} fAH^+ / fAH_2^{++} = pK_a^{AH_2^{++}} + \log [AH^+]/[AH_2^{++}]$

Hammett's acidity function H_o, which measures the tendency of a solution to transfer a proton to a neutral indicator base, B, to form the conjugate acid, BH^+, is defined as:-

$H_o = -\log a_{H^+} fB / fBH^+ = pK_a^{BH^+} + \log [B] / [BH^+]$

The difference between H_+ and H_o

$H_+ - H_o = \log fB \, fAH_2^{++} / fBH^+ \, fAH^+$ .... (1)

which was calculated by Brand [67] and has the value 0.28 in 100% sulphuric acid; H_o in this medium is -10.60, and since the value of the acidity function changes rapidly with medium composition in this region, the difference may not be significant.

Coryell and Fix[68] state that all Hammett acidity functions are parallel functions of medium composition and refer to the constant difference of 0.8 log unit between

H_o and H_- found in the range 4 - 6 M sulphuric acid. Any two acidity functions will be parallel functions of medium composition if the activity co-efficient ratio corresponding to equation (1) is unity or constant over the range of media studied.

Bonner and Lockhart [69] have demonstrated the parallelism of H_o and H_+ over the ranges 30 - 55% and 75 - 95% sulphuric acid. No complete H_+ acidity scale has been measured, thus it is necessary to use values of H_o in all correlations of rates with acidity functions.

Bonner, Thorne and Wilkins[49] demonstrated the constancy of Log k_1 + H_o for aniline and p-toluidine anil. Log k_1 + H_o was also found to be constant for 1 : 2 -dimethyl-3-aminobenzene anil in sulphuric and perchloric acids.

Variation of rate of cyclisation of anil of 1:2 -dimethyl-3-aminobenzene with % H_2SO_4 at 25°C.

Expt. No.	% H_2SO_4	Initial conc. of anil	k_1 min^{-1}	log k_1	H_o [26]	log k_1 + H_o
119	80.8	0.0500	0.0692	-1.16	-7.15	-8.31
120	80.8	0.0505	0.0697			
117	78.6	0.0498	0.0226	-1.65	-6.66	-8.31
118	78.6	0.0506	0.0223			
95	74.8	0.493	0.00592	-2.23	-6.13	-8.36
96	74.8	0.502	0.00586			
126	70.5	0.508	0.00135	-2.86	-5.53	-8.39
127	70.5	0.509	0.00140			

Variation of rate of cyclisation of anil of 1 :2-dimethyl -3-aminobenzene with % $HClO_4$ at 25°C.

Expt. No.	% $HClO_4$	Initial conc. of anil	k_1 min^{-1}	log k_1	log k_1 + H_o
110	71.4	0.0507	0.111	-0.95	-9.02
111	71.4	0.0509	0.115		
112	69.4	0.0503	0.0652	-1.18	-9.03
113	69.4	0.0509	0.0652		
114	66.7	0.0500	0.0109	-1.97	-8.92
115	66.7	0.0503	0.0107		
125	63.6	0.0506	0.00164	-2.79	-8.91
128	63.6	0.0510	0.00164		

H_o values were obtained from the work of Bonner and Lockhart.

In the cyclisation reaction the correlation of log k_1 with H_o i.e. log k_1 VS H_o gives a straight line of unit slope, must indicate that the cyclisation reaction, when it occurs, proceeds through a diprotonated species formed in fractionally small amount.

A similar treatment based on the alternative mechanism of dehydration preceding ring closure leads to a similar relationship as that derived by Bonner, Thorne and Wilkins[49] e.g.

$$AOH^+ + H^+ \rightleftharpoons AOH_2^{++}$$

$$AOH_2^{++} \rightarrow A^{++} + H_2O$$

$$A^{++} \rightarrow \text{products}$$

which yields the relationship log k_1 + C_o = constant.

The acidity function C_o defines the ionisation of indicators which ionise according to the equation $ROH + H^+ \rightleftharpoons R^+ + H_2O$ Deno and Co-Workers [70] have studied a series of indicators ionising over a range 10-98% sulphuric acid, and in a manner analogous to that used by Hammett when defining his H_o scale, they have constructed the C_o acidity scale for this type of ionisation. A linear plot of log k_1 VS C_o is not obtained (see fig. 10) and values of log k_1 + C_o for three compounds studied are not constant over the range of media considered. This mechanism can be rejected.

Variation of log k_1 + C_o with medium composition (see fig.10)

Compound	% H_2SO_4	log k_1	C_o	log k_1 + C_o
Aniline anil	97.3	-1.68	-19.15	-20.83
	95.5	-1.92	-18.25	-20.17
	91.2	-2.47	-17.05	-19.52
	88.6	-2.78	-16.40	-19.18
p-toluidine anil				
	95.5	-1.07	-18.25	-19.32
	91.1	-1.67	-17.05	-18.72
	87.6	-2.13	-16.11	-18.24
	84.5	-2.62	-15.30	-17.92
1 : 2 -dimethyl-3-aminobenzeneanil				
	80.8	-1.16	-14.38	-15.54
	78.6	-1.65	-13.77	-15.42
	74.8	-2.23	-12.80	-15.03
	70.5	-2.86	-11.68	-14.54

The results on aniline anil and p-toluidine anil were taken from the work of Bonner, Thorne and Wilkins [49]. Co values were obtained from the work of Denoetal [70].

In all cases so far studied log k_1 VS H_o gives straight line plots with slopes approximately unity:- (see fig. 11)

Compound	Acid	Range	Slope log k_1 VS H_o
Aniline anil	H_2SO_4	88.6 - 97.3%	0.99
p-toluidine anil	H_2SO_4	84.5 - 95.5%	1.17
1 : 2-dimethyl-3-amino benzene anil	H_2SO_4	70.5 - 80.8%	1.05
1 : 2-dimethyl-3-amino benzene anil	$HClO_4$	63.6 - 71.4%	0.92

In the derivation of the expression log k_1 + H_o = constant, it is assumed that over the range of media considered an activity coefficient term of type fAH^+ / fAH_2^{++} varies in exactly the same way as the ratio fBH^+ / fBH_2^{++} of the Hammett indicator ionising over the range of acid considered. A precise parallelism of log k_1 with H_o will only exist if this assumption is correct.

McIntyre and Long [71] have studied the acid catalysed hydrolysis of methylal and have shown that for the strong acids hydrochloric, sulphuric and perchloric, that the first order rate constants k_h increase very rapidly with increasing acid concentration and a plot of log k_h VS H_o gave slopes of approximately unity for each acid.

e.g. Acid Catalysed hydrolysis of methylal

Acid	Slope log k_h VS H_o
Hydrochloric	1.25
Sulphuric	1.15
perchloric	1.08

Long attributes these differences to variations of the activity coefficient ratios of the type fAH^+ / fAH_2^{++} and fBH^+ / fBH_2^{++}. Salt effects are known to be specific for these three acids and changes in activity coefficient ratios would depend on the specific acid used. Hence exact parallelism between rate and H_o is not generally to be expected, even if the activated complex does in fact behave like the conjugate acid of the reacting neutral molecule.

Similar divergences from unit slope of the plot of log k and H_o have been observed in the hydrogen isotope exchange reaction of p-cresol and p-chlorophenol in strong acids [72].

e.g.

Compound	Acid	Slope log k VS H_o
p - cresol	HCl	1.42
p -cresol	H_2SO_4	1.08
p -chlorophenol	H_3PO_4	1.00
p -chlorophenol	H_2SO_4	0.90

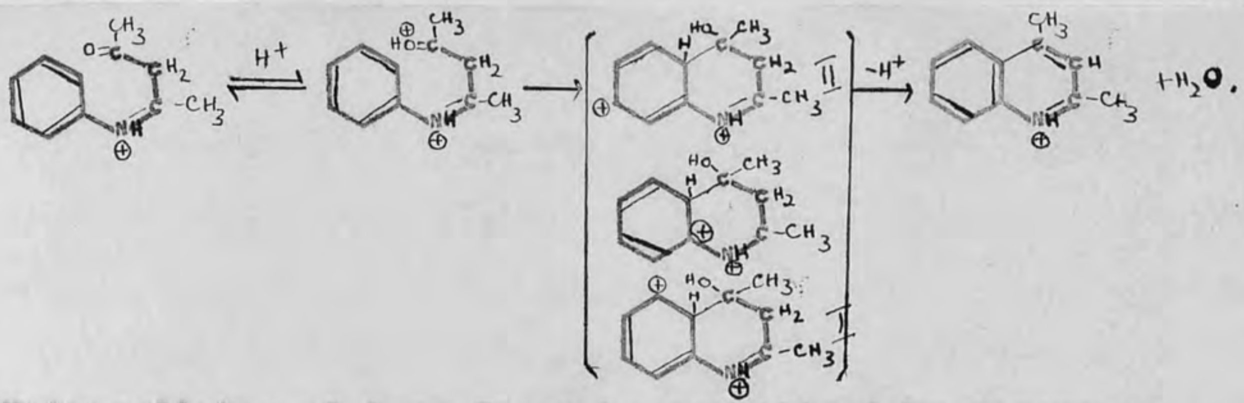
The results on the cyclisation of the anil of 1 : 2-dimethyl-3-aminobenzene in sulphuric and perchloric acids are seen to be in agreement with the results of previous workers who found differences in the slopes of the plots of log k VS H_o in different acids. Divergences from exactly unit slope must be due to specific salt effects.

It might be advantageous to use an indicator similar in size and constitution to the entity undergoing the acid catalysed reaction, since then one might expect the salt effects to be very similar i.e. that the activity coefficients would change in the same way with the change of medium. Data is available which seems to indicate the importance of size of the indicator molecule from the kinetic data on the O-nitration of iso-amylalcohol by nitric acid in acid solution. In sulphuric acid it had been established that C-nitration was brought about by the nitronium ion NO_2^+, and rates of nitration had been correlated with C_o. Rates of O-nitration of iso-amylalcohol were obtained in perchloric acid, and log k VS % perchloric acid was found to have exactly the same slope as log $(NO^+) / (HNO_2)$ NS % perchloic acid. Data on the ionisation of nitrous acid in perchloric acid had been obtained by Singer and Vamplew[73].

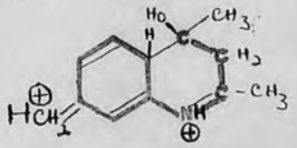
$$HNO_2 + H^+ \rightleftharpoons H_2NO_2^+$$
$$H_2NO_2 \rightarrow H_2O + NO^+$$

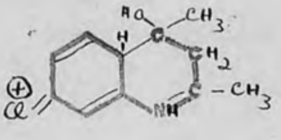
This ionisation is of identical type with that of the conversion of the nitric acid to nitronium ion. The above correlations indicate that O-nitration is brought about by the nitronium ion. In sulphuric acid there is a difference of ca. 10% between the slopes of log k VS % H_2SO_4 and C_o VS % H_2SO_4. Hence the size of the species chosen for comparison may be of importance in correlations of rate with acidity of medium.

If the rate-determining step in the cyclodehydration reaction is ring-closure of the diprotonated anil, followed by rapid dehydration the reaction can be represented as follows



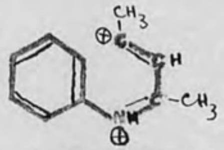
Intermediates of type I can be stabilised by resonance structures in which the + ve charge resides in the position para-to the point of ring closure as in structure II. Substitution of hydrogen at this para- position by halogen or methyl would enhance the effect of the contribution of structure II.





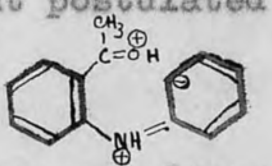
Bonner and Wilkins[74] compared the rates of cyclisation of 2- (2 : 4 : 6 - trideuteroanilino) - pent -2-en-4-one and its protium analogue and found the ratio of the rates to be 2 : 3 in 95.5% and 89.2% sulphuric acid/water. They concluded that fission of the C - H bond could not be the main rate-determining factor, and that the slight isotope effect was a feature of the two step mechanism through an intermediate of type I, in which the formation of this intermediate was the rate determining step.

An alternative mechanism which would give the same correlation of log k with H_+ is one in which there was a rate-determining elimination of water from the diprotonated anil followed by rapid ring closure. There are no theoretical grounds for assuming that the diprotonated anil would eliminate water easily. Consideration of the resonance stabilisation of the transition states favours the mechanism already discussed in which a rate-determining ring-closure is followed by rapid elimination of water. If dehydration preceded ring-closure, the following carbonium ion would result:-



which cannot have any stabilising resonance structures.

A similar cyclisation occurs in the acridine system when o-anilinophenylketones dehydrate to form ketones in acid solution. It is known that p-aminoacetophenone is fully diprotonated in 95% sulphuric acid [69]. In the case of the o-anilinophenylketones, the phenyl group will reduce the basicity of the N-atom, but not sufficiently to prevent complete monoprotonation by strong sulphuric acid. A fractionally small amount of the diprotonated species would be present in media.where cyclisation occurs. This dehydration may proceed through a diprotonated species similar to that postulated for an anil:-



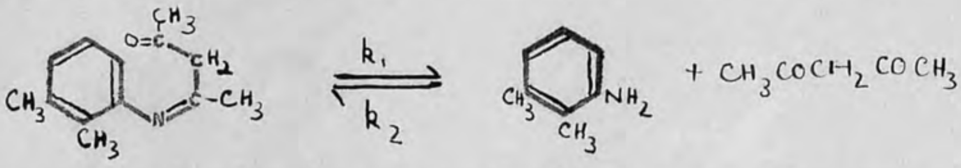
This cyclisation was formerly believed to proceed through a monoprotonated species.

Hydrolysis of anils in acid solution

In the analysis of samples of the reaction solution containing the anil in strong acid, the reaction is stopped by running the sample into water so that the acid content falls to 2 - 3 N sulphuric acid. At this dilution hydrolysis of the unchanged anil to aromatic amine and acetylacetone appears to be instantaneous. Whether hydrolysi or cyclodehydration of an anil occurs in aqueous solution is therefore dependent on the acidity of the solution and therefore on the nature and extent of protonation of the anil.

All previous investigations on the hydrolysis of compounds related to anils appear to have been carried out in dilute aqueous alcoholic solutions at known pH.

The stability of the anil of 1 : 2- dimethyl -3-amino benzene anil was investigated in media where it was established that cyclisation was too slow to measure i.e. acid strength <70% sulphuric acid. If the anil had been stable in these lower strength acids, it should have been possible to increase the acid strength of the medium to a point where the cyclisation of the anil would become measurable kinetically. Results showed that decomposition of the anil was occurring in these more aqueous media and that the decomposition was an equilibrium reaction:-



The kinetics of hydrolysis were studied over the range 62.4 - 52.8% sulphuric acid. Kinetic data were found to fit the kinetic equation based on a reversible reaction in which the forward reaction is a first order hydrolysis opposed by a second order recombination of the products.

Let a = initial concentration of anil

x concentration of amine and acetylacetone at time t.

x_e concentration of amine and acetylacetone at equilibrium.

then $a - x$ concentration of anil at time t.

$a - x_e$ concentration of anil at equilibrium.

The rate of hydrolysis of the anil is given by

$$dx/dt = k_1 (a - x) - k_2 x^2 \ldots\ldots\ldots\ldots\ldots (1)$$

at equilibrium $k_1 (a - x_e) = k_2 x_e^2 \ldots\ldots\ldots\ldots (2)$

substituting for k_2 in equation (1) and integrating

$$k_1 = \frac{x_e}{t\,(2a - x_e)} \log \frac{a x_e + x\,(a - x_e)}{a\,(x_e - x)}$$

First order rate constants for the hydrolysis of the anil were obtained in this manner. The rate of hydrolysis decreased as the acidity of the medium increased; a curve was obtained when log k_1 was plotted against H_o and the sum of log $k_1 + H_o$ was not a constant; it varied from -7.36 in 62.4% sulphuric acid to -5.14 in 52.8% sulphuric acid. Log $k_1 + H_o$ should be a constant if hydrolysis proceeded through a monoprotonated form which was present in fractionally small amount or through a diprotonated species present in fractionally small amount with the remainder being present in the monoprotonated form. The reaction must be in some way dependent on the acidity, because addition of ammonium sulphate, which would decrease the acidity of the medium, increased the rate of hydrolysis of the anil.

Variation of the rate of hydrolysis of anil of 1 : 2-dimethyl-3-aminobenzene with % sulphuric acid at 25° C.

Expt. No.	% H_2SO_4	Initial concn. of anil	k, min^{-1}
132	62.4	0.1007	0.000962
133	62.4	0.1010	0.000973
121	60.1	0.0998	0.00225
122	60.1	0.1000	0.00227
131	57.7	0.0997	0.00534
123	54.9	0.1000	0.0127
124	54.9	0.1010	0.0124
129	52.8	0.0999	0.241
130	52.8	0.994	0.241
134	60.1 IM $(NH_4)_2SO_4$	0.0997	0.00533
135	60.1 IM $(NH_4)_2SO_4$	0.0995	0.00538

It was assumed that the unprotonated species underwent hydrolysis. The assumption seemed reasonable because:-

1. Cryoscopic data on the p-chloroaniline anil showed the stability of monoprotonated anils.

2. Hydrolysis was only found to occur in regions of lower acidity where some uncharged anil would exist.

3. The rapid increase in rate of hydrolysis when media become even less acid, coinciding with the appearance of what must be a rapidly increasing proportion of uncharged anil.

The unprotonated species, present in fractionally small amount, reacted with the free water in the acid to form amine and acetylacetone.

Let A represent the anil which in acid solution is present in the monoprotonated form AH^+.

In the appropriate range of acid solution we have the equilibrium $A + H^+ \rightleftharpoons AH^+$

Let us assume that nearly allthe anil A is present in the monoprotonated form AH^+, only a very small fraction of the anil is present as the free base.

$[AH^+] \sim [A]_T$ where $[A]_T$ - toal anil concentration.

i.e. $[A] << [AH^+]$

$A + H_2O \rightarrow$ products

we can then write a theoretical rate $= kK(A)\ (H_2O)\ /\ f\neq$

$$= kK(A)\ (H_2O) fA\ / f\neq \ .....\ .... (3)$$

k - theoretical rate constant) which should be independent
K - equilibrium constant) of medium over the range considered.

(A) - activity of anil

(H_2O) - activity of water

fA - activity coefficient of anil

$f\neq$ - activity coefficient of transition state.

Experimental rate $= k_{,}\ [A]_T$;.......... (4)

Equating equations (3) and (4)

$$k_1\ [A]_T = kK\ [A]\ (H_2O)\ fA\ /\ f\neq$$

since $[A]_T \approx [AH^+]$

$$\therefore k_1 = kK\ fA\ (H_2O)\ [A]\ /\ f\neq\ [AH^+]$$

$\log k_1 = \log kK\, fA / f_{\neq} + \log [A] / [AH^+] + \log (H_2O)$

$H_o = pK_a^A + \log [A] / [AH^+]$ .... (5)

Substituting for $\log [A] / [AH^+]$ in equation (5)

$\log k_1 = \log kK\, fA / f_{\neq} + H_o - pK_a^A + \log (H_2O)$

$\therefore \underline{\log k_1 - H_o - \log (H_2O) = \log kK\, fA / f_{\neq} - pK_a^A = \text{constant}}$

if the activity coefficient ratio $fA / f_{\neq}$ is constant with change of medium over the range considered.

The value of $\log (H_2O)$ at 25°C was obtained from the data of vapour pressure of water/sulphuric acid at 25°C.

$\log p/p_o = \log (H_2O)$ [75].

where p - vapour pressure of water over sulphuric acid at 25°C

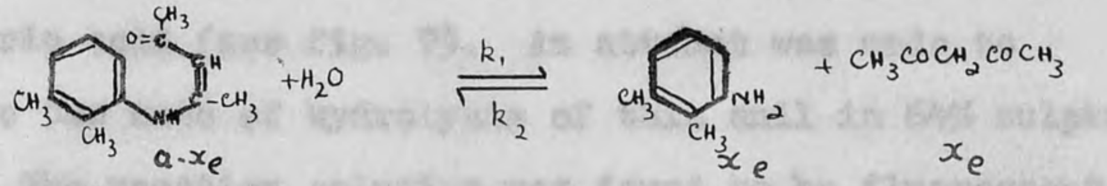
p_o - vapour pressure of water at 25°C

The values of $\log k_1 - H_o - \log p/p_o$ are seen to be constant over the range 62.4 - 52.8% sulphuric acid, verifying the assumption that it is the small fraction of anil which remains unprotonated which reacts with the water of the medium.

<u>Hydrolysis of 0.1 M solutions of 1 : 2-dimethyl -3-amino benzene anilin sulphuric acid at 25°C.</u>

% H_2SO_4	k_1	$\log k_1$	H_o	$\log p/p_o$	$\log k_1 + H_o$	$\log k_1 - H_o$	$\log k_1 - H_o - \log p/p_o$
62.4	0.000976	−3.01	−4.62	−0.88	−7.63	1.61	2.49
60.1	0.00226	−2.65	−4.35	−0.76	−6.96	1.70	2.46
57.7	0.00534	−2.27	−4.07	−0.66	−6.34	1.80	2.46
54.9	0.01255	−1.90	−3.74	−0.58	−5.64	1.84	2.42
52.8	0.0241	−1.62	−3.52	−0.50	−5.14	1.90	2.40

The equilibrium constants and the rates of back reaction were calculated.



$$K = \frac{k_2}{k_1} = \frac{(\text{amine})\ (\text{acetylacetone})}{(\text{anil})}$$

K - equilibrium constant for hydrolysis calculated from experimental results

k_1 - rate of hydrolysis of anil calculated from experimental results.

k_2 - rate of combination of amine and acetylacetone to form anil calculated from K and k_1.

Hydrolysis of 0.1 M solutions of 1 : 2 dimethyl-3-amino benzene anil in sulphuric acid at 25°C

% H_2SO_4	K	$k_2 \times 10^4$ min	$k_1 \times 10^4 \text{min}^{-1}$
62.4	0.420	4.10	9.67
60.1	0.028	0.641	22.6
57.7	0.023	0.012	53.4
54.9	0.016	2.05	126
52.8	0.026	6.31	241

The above results indicate that the equilibrium is well over on the side of hydrolysis of the anil, and so the values of the equilibrium constant K and the rate constant k_2 for the formation of the anil cannot be accurate. The equilibrium constant reaches a minimum in about 55% sulphuric acid, while the minimum value of k_2 occurs about 58% sulphuric acid.

The behaviour of 1:2-dimethyl-3-aminobenzeneanil in sulphuric acid demonstrates the change in reaction as the acidity of the medium decreases over the range 50 - 80% sulphuric acid (see fig. 7). An attempt was made to measure the rate of hydrolysis of this anil in 64% sulphuric acid. The reaction solution was found to be fluorescent after a few hours indicating the formation of some 2 : 4 : 7 : 8 - tetramethylquinoline. Over the range of media 65.7%-70% sulphuric acid, cyclisation and hydrolysis were occurring simultaneously. In this region of acidity, a small proportion of the anil must exist in the neutral form A, because it is this form which reacts with the water and undergoes hydrolysis; also there must be a small fraction of diprotonated anil AH_2^{++} which cyclises. The bulk of the anil in this region undoubtedly exists in the monoprotonated form AH^+.

Substituent effects in mono-substituted anils

Substituent effects for a similarly constituted series of compounds need to be considered in terms of the influence of inductive, electromeric and steric effects of the substituent on the particular reaction or equilibrium concerned . It is usually accepted that since the relative significance of these factors vary with the reaction under consideration a satisfactory quantitative treatment of substituent effects is very difficult. One valuable attempt to achieve this was made by Hammett, although he limited it to consideration of side-chain equilibria and reactions of benzene compounds only i.e. it was not derived for reactions involving direct electrophilic substitution of the benzene nucleus. However, several workers have attempted to apply Hammett's basic equation to electrophilic reactions of benzene compounds. Jaffé [54-7] has made a comprehensive review and analysis of all previous relevant experimental data on side chain and nuclear reactions of benzene compounds.

The empirical equation proposed by Hammett for a series of similarly constituted benzene compounds is the following:-

$$\log k / k_o = \rho\sigma$$

where k is the rate or equilibrium constant of the substituted compound.

k_o is the rate or equilibrium constant of the unsubstituted compound.

ρ is a reaction constant characteristic of the reaction or equilibrium considered, the medium, and temperature being constant. It is put equal to unity for ionisation of benzoic acids in aqueous solution at 25°C.

σ is the substituent constant characteristic of the substituent considered.

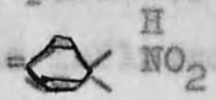
An attempt was made to analyse the kinetic data on cyclisation and hydrolysis of the substituted anils, and the ionisation data of the substituted amines by means of this equation.

De la Mare[76] has compared the standard Hammett σ constants [54] with the data available for electrophilic substitution. He reviewed data established by Ingold, Hughes and co-workers on the partial rate factors for substitution at the para- and meta- positions in nitration, and in the para- position in the halogenation of substituted benzenes compiled by Robertson, de la Mare and Swedlund[77].

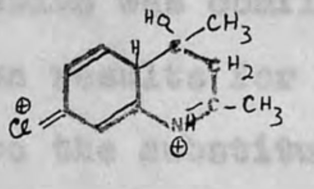
Data from J.C.S. 1954 44 50

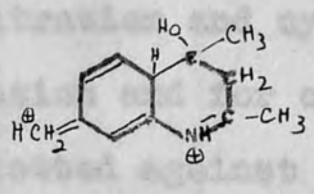
Correlation of Hammett's σ values with partial rate factors for nitration and halogenation

Substituent	σ (p - x)	$\log_{10} f_p$ nitration	$\log_{10} f_p$ halogenation	σ m - x	$\log_{10} f_m$ nitration
NMe_2	-0.600		19.5		
OH	-0.357		11.8		
OMe	-0.268		9.8		
CMe_3	-0.197	1.88	2.8		
CH_3	-0.170	1.76	3.3	-0.069	0.491
OPL	- 0.028		7.9		
NHAc	-0.015		9.1		
PL	0.009		3.4		
F	0.062	-0.10	0.8		
NHB_z	0.078		9.1		
CH_2Cl	0.184	-0.02	0.5		
Cl	0.227	-0.85	-0.4	0.373	-2.975
Br	0.232	-0.96	-0.6	0.391	-2.767
I	0.276	-0.34		0.352	-2.154
$C(CH_3)_3$				-0.12	0.602
$CO_2C_2H_5$				0.334	-2.098

De la Mare[76] plotted the log of partial rate factors for nitration and halogenation against Hammett's σ values. A reasonable linear correlation was obtained for meta nitration i.e. plot of $\log_{10}f_m$ VS σ. A less precise correlation of $\log_{10}f_p$ for nitration and halogenation VS σ was obtained (see fig. 12 and 14). A wider scatter was observed for halogenation, particularly for groups with a high conjugative or hyperconjugative capacity e.g. CH_3. Roberts etal[78] found that the Hammett equation applied rather less accurately to nitration than to other equilibrium and rate data for meta- and para- substituted benezene derivatives, wider discrepancies occurring when nitration was para- to the substituent. Resonance forms of type ⊕ X = 

I will be of considerable importance in the para- substitution of substituted benzenes. No such resonance structures can be envisaged by nitration meta- to the substituent. Resonance structures of type I may be more important than expected from their σ values. Jaffé[55-7], in his calculations of σ by molecular orbital method, demonstrated the importance of considering resonance as well as inductive effects. If the enhanced reactivities are interpreted in terms of the magnitude of the resonance interaction in the transition state in the cyclisation reaction, it is important to consider structures similar to type I in the cyclisation reaction. Structures of the above type are possible as



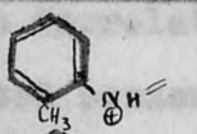
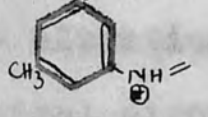
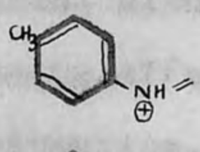
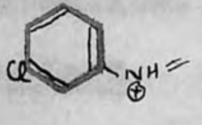
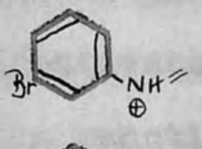
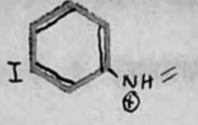
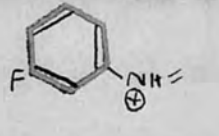


intermediates in the cyclisation reaction when ring closure occurs para- to the substituent. No similar structures are possible when ring closure ocurs meta- to the substituent. It would appear that the Hammett equation is not very useful to assess kinetic data quantitatively in reactions in which the transition state is stabilised by resonance structures of type I. De la Mare prefers to discuss reactions in terms of the separated inductive and mesomeric effects with their time variable analogues because the Hammett σ constants introduce inductive and mesomeric influences combined in amounts which cannot be quantitatively determined and vary with the substituent.

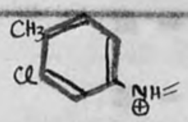
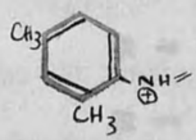
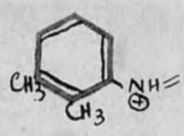
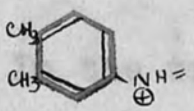
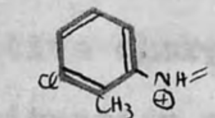
Swain and Langsdorf[79] studied the effects of meta- and para- substituents on the reaction of benzylchlorides with trimethylamine in benzene and benzyl bromides with pyridine in acetone. They plotted $\log k/k_o$ for each reaction against Hammett σ values and in each case they obtained two curves which were concave upwards. They suggested the curvature was probably due to resonance in the transition state; lower rates should then be obtained with substituents which cannot interact effectively by resonance with the reacting centre in the transition state e.g. meta substituents. Their observation was confirmed for nitration and cyclisation. When the results for para- nitration and for cyclisation para- to the substituent were plotted against Hammett σ values, curves were obtained which were concave upwards, while the corresponding plots for meta nitration and cyclisation gave straight lines (see figs. 12 and 13).

An interesting fact arises when one considers the relationship between the rates of cyclisation of substituted anils and the partial rate factors for para- nitration and para- halogenation. A linear relationship exists between the log ratio of the rates of cyclisation of log k / k_o with the log of the partial rate factors for para- halogenation and para- nitration ($\log_{10} f_p$) (see fig. 16)

Correlation of Hammett's σ values with partial rate factors for para- nitration and halogenation, and log ratio of rates of cyclisation

Compound	σ	$\log k/k_o$	$\log_{10} f_p$ nitration	$\log_{10} f_p$ halogenation
	-0.069	0.45		
	-0.170	2.86	1.76	3.3
	-0.069	0.85	0.491	
	0.227	0.35	-0.85	-0.4
	0.232	0.27	-0.96	-0.6
	0.276	0.71	-0.34	
	0.062	1.05	-0.10	0.8

Correlation of Hammett's σ values (cont'd-

Compound	σ	$\log k/k_o$	$\log_{10} f_p$ nitration	$\log_{10} f_p$ halogenation
	0.158	1.16		
	-0.138	1.29		
	-0.239	2.23		
	-0.239	0.20		
	0.158	0.43		

This correlation of rates of cyclisation of mono substituted benzenes para- to the substituent with the rates of para- nitration and halogenation confirms that cyclisation is a typical electrophilic substitution reaction and substituents affect the rate of cyclisation in the same way as for nitration.

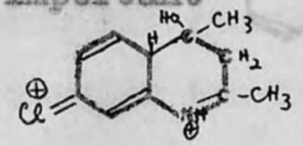
Halogen effect

In electrophilic substitution reactions, halogens usually deactivate the nucleus to substitution. In the cyclisation reaction they are seen to increase the rate of cyclisation (para- to the substituent) relative to aniline anil in the order F > I > Cl > Br.

Rates of cyclisation of halogen substituted anils in 93.8% H_2SO_4 at 25°C

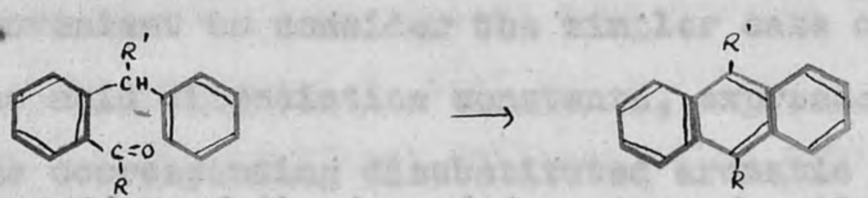
Substituent	$k_1 \times 10^{-2} min^{-1}$
m - F	4.16
m - I	1.90
m - Cl	0.832
m - Br.	0.696
H	0.371

In the transition state the halogens are capable of sharing their electrons with the ring and assuming a positive charge i.e. transition states of type I envisaged in nitration would be important

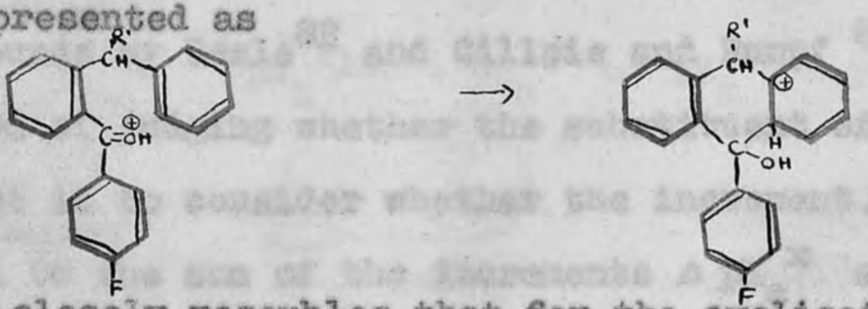


Ingold [80] has suggested that the electromeric polarizability of the halogens would decrease in the order I > Br > Cl > F. Baddeley etal[81] reason that the resonance effect for halogens decreases in the reverse order and that the similarity in the effects ascribed to resonance and mesomerism suggests that these influences have a common origin. Electromeric polarizability should increase in the order I < Br < Cl < F. Simultaneous operation of an inductive effect with the order I > Br > Cl > F was postulated to account for experimental orders in the reverse direction. If one allows that the conjugating effectiveness of halogens is I < Br < Cl < F in interaction symbolised by resonance structures of type I, then the extra rate enhancing influences of the halogens must be ascribed to their electrostatic polarizability under the influence of the strong electrical field in the cyclisation transition state.

Halogen effects were studied by Bradsher and Vingiello[25] in their investigation of the kinetics of cyclisation of O-benzyl-phenones in a mixture of hydrobromic and acetic acids.



The formation of the transition state for the reaction can be represented as



which closely resembles that for the cyclisation reactions of the anils of acetylacetone. It was found possible to correlate the rates of cyclisation of halogen substituents in this series with those of the halogene substituted anils of acetylacetone.

Rates of cyclisation of halogene - substituted compounds.

O-benzylphenones			Anils of acetylacetone	
R	k x 10^2min^{-1}	logk	Substituent	log k_1
p-F-C_6H_4 -	2.8	-1.55	m-F	-1.38
p-Br-C_6H_4 -	4.1	-1.39	m-Br	-2.16
p-Cl-C_6H_4-	4.2	-1.38	m-Cl	-2.08

A linear relationship was found to exist between the log of the rates of cyclisation of the two classes of compounds (see fig. 17)

Additivity of substituent effects

Before analysing the additivity effects of substituents in the cyclodehydration reaction in disubstituted anils, it is convenient to consider the simpler case of the additivities of the acid dissociation constants, expressed as pK_a values, of the corresponding disubstituted aromatic amines. Some accurate and extensive work has been reported on these compounds by Beale[82] and Gillois and Rumpf [83]. One usual method of judging whether the substituent effects are additive or not is to consider whether the increment $\Delta pK_a\ x,y$ is equal to the sum of the increments ΔpK_a^x and ΔpK_a^y where the increments are given by:-

$$\Delta pK_a^{x,y} = pK_a^{x1y} - pK_a^H$$

$$\Delta pK_a^x = pK_a^x - pK_a^H$$

$$\Delta pKa^y = pK_a^y - pK_a^H$$

$pK_a^{x,y}$, pK_a^x, pK_a^y and pK_a^H representing respectively the negative logarithm of the acid dissociation constant of the disubstituted anilinium ion, the two mono-substituted anilinium ions and the anilinium ion itself. Comparison with the Hammett equation

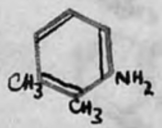
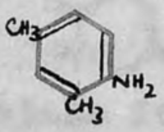
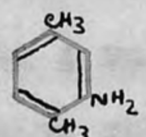
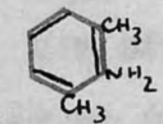
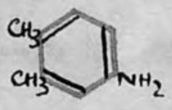
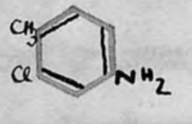
$$-\sigma\rho = pK_a^y - pK_a^H$$

shows that the increment in the latter two equations can be replaced by $-\sigma x\,\rho$ and $-\sigma y\,\rho$ respectively and the test in effect becomes one of seeing whether σ values are additive in disubstituted compounds. Another formal way of testing additivity is to see whether the following equation is obeyed or not

$$pKa^{x1y} + pK_a^{H} = pK_a^{x} + pK_a^{y} \,\ldots\ldots\ldots\ldots\; (1)$$

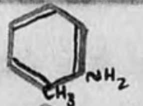
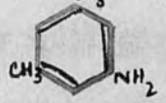
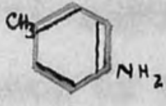
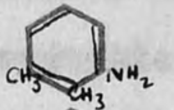
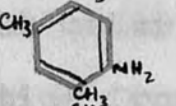
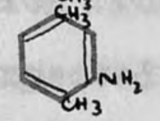
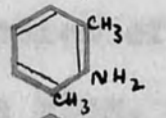
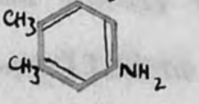
The data of Beale, as well as some results obtained during this work, were used to test the additivity of substituent effects of disubstituted anilines using equation (1).

To test additivity of substituent effects for disubstituted amines

	$pK_a^{x1y} + pK_a^{H}$	=	$pK_a^{x} + pK_a^{y}$	Δ pKa $(pK_a^{xy} + pK_a^{H}) - (pK_a^{x} + pK_a^{y})$
	$\underbrace{4.70 + 4.58}_{9.28}$	=	$\underbrace{4.42 + 4.73}_{9.15}$	+0.13
	$\underbrace{4.89 + 4.58}_{9.47}$		$\underbrace{4.42 + 5.08}_{9.49}$	-0.02
	$\underbrace{4.53 + 4.58}_{9.11}$		$\underbrace{4.42 + 4.73}_{9.15}$	-0.04
	$\underbrace{3.95 + 4.58}_{8.53}$		$\underbrace{4.42 + 4.42}_{8.84}$	-0.31
	$\underbrace{5.17 + 4.58}_{9.75}$		$\underbrace{5.08 + 4.73}_{9.81}$	-0.06
	$\underbrace{4.05 + 4.58}_{8.63}$		$\underbrace{5.08 + 3.59}_{8.67}$	-0.04

A graph of pK_a VS σ was plotted and a value of 2.68 was obtained for ρ (See fig. 18)

Correlation of Hammett's σ values with pK_a of substituted amines

Compound	σ	pK_a
	0.075	4.42
	-0.069	4.73
	-0.170	5.08
	+0.006	4.70
	-0.095	4.89
	+0.006	4.53
	0.150	3.95
	-0.239	5.17

σ values for the disubstituted amines were taken as the sum of the σ values for the corresponding mono substituents assuming substituent effects to be additive.

The effect of substituents in the ring may be considered either as producing changes in the electron density in the lone-pair orbital of the N atom which projects in a direction approximately perpendicular to the plane of the ring but slightly away from it, or in its immediate vicinity, in some cases distorting the symmetry of the orbital. Any effect which moves negative charge towards the nitrogen atom will increase the basicity of the amine, while any effect which distorts the orbital will reduce the strength of the base.

The largest deviation from additivity occurs with 2 : 6-xylidine where the discrepancy is 0.31. A model indicates lack of steric hindrance in this molecule. It must be that, as a result of the symmetry of the electron cloud about the N - C axis each methyl group is able to interact more strongly with the lone-pair orbital because of the presence of the other. This indicates some sort of electrostatic interaction. When the methyl groups are ortho to each other as in 3 : 4 - xylidine there is a slight deviation from additivity. The base is somewhat weaker than expected, indicating that there is some sort of mutual restriction of electron flow from the methyl groups into the benzene ring, an effect which is even more marked in 2 : 3-xylidine where the base is markedly stronger than expected. One would expect the ortho-methyl group in 2 : 3-xylidine to cause a decrease in base strength due to distortion of the electron cloud and by causing steric hindrance to solvation of the anilinium ion; since the base strength is increased, the dominant factor must be the hyperconjugation of the methyl group with the ring. It is not possible to decide whether this is due to a distortion of the Cme - Carbond or to restrictive orientation of the methyl groups or both.

The marked difference in behaviour between 2:5- and 2:3-methyl derivatives of benzene compounds of type PhR has been noted by van Helden et al[84] when $R=NO_2$ and by Dippy et al[85]. when $R=CO_2H$. In both cases an ortho-methyl group to R causes hindrance to mesomerism with the ring, except when $R=NH_2$ and introduction of a 3-methyl group has the apparent effect of increasing the size of the 2-substituent interaction between R and the ring. Van Helden et al also indicate that a further complication may be a hindrance to rotational freedom of the methyl groups.

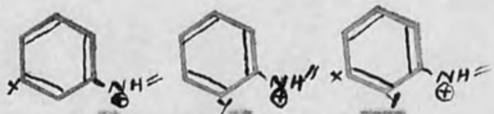
In an analogous manner an attempt was made to analyse the kinetic data on the cyclodehydration of the substituted anils. In order to make a just comparison it was necessary to compare rates of cyclisation at the same temperature and in the same medium so that H_o values were the same for all compounds. The Hammett equation can apply only to the true/rate constant k_o of the reaction which is related to the experimental rate constant k_1 by the equation:

$$\log k_1 + H_o = \log k_o + pK_{AH_2}{}^{++}$$

With all anils completely monoprotonated one can assume that pK_{AH_2}*+ will be much the same for all anils, since $pK_{AH_2}{}^{++}$ is concern~~trat~~ed with a second proton uptake on a side chain already carrying a positive charge, so that $\log k_1$ parallels $\log k_o$ for different anils provided the same media are used i.e. $pK^{x}_{AH_2}{}^{++} \sim pK^{y}_{AH_2}{}^{++} \sim pK^{xy}_{AH_2}{}^{++}$. σ values(see table page (90) for disubstituted anils were the sum of the σ values for the monosubstituted anils.

No exact linear relationship was found between log k/ko and σ for the cyclisation reaction. The results for the meta substituted compounds were seen to lie on a curve, a result very similar to that obtained when the partial rate factors for nitration para to the substituent are plotted against σ (see fig.13). Data for the disubstituted anils show a wide scatter. It was not possible to calculate the reaction constant ρ because of the lack of linearity in the plot of log k vs σ.

The additivity relationship for the cyclisation of individual disubstituted anils can be tested as indicated previously for the pKa values of the corresponding anilines. For the three anils represented below



let the experimental rate constants be $k_{,}^{x}$. $k_{,}^{y}$. $k_{,}^{xy}$.

True Rate constant k_o^{x} . k_o^{y} . k_o^{xy}.

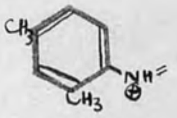
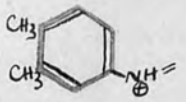
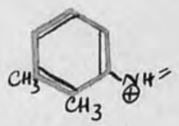
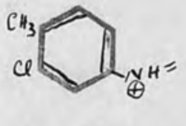
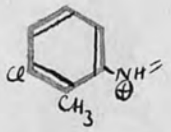
Substituent constant σ_x . σ_y . σ_{xy} .

The Hemmett equations for these compounds are:-

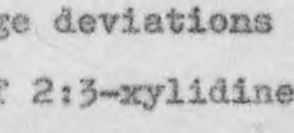
$$\log k_o^{x} - \log k_o = \rho\sigma_x$$
$$\log k_o^{y} - \log k_o = \rho\sigma_y$$
$$\log k_o^{xy} - \log k_o = \rho(\sigma_x + \sigma_y)$$
$$\therefore \log k_o^{xy} + \log k_o = \log k_o^{y} + \log k_o^{x} \text{ if substituent effects are additive.}$$

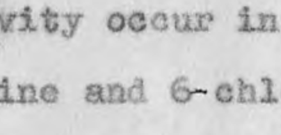
In practice log k, values were used for this comparison. All data used was obtined at 25°C in 93.8% sulphuric acid.

To test additivity effects of disubstituted anils:

	$\log k_1^{xy} + \log k_1^{H}$	$= \log k_1 + \log k_1^{y}$.	$\log \frac{k_1^{xy}k_1^{H}}{k_1^{x}k_1^{y}}$
	-1.14 - 2.43 -3.57	- 1.58 - 1.99 -3.57	0.00
	+ .64 - 2.43 -1.79	- 1.58 + .41 -1.17	0.62
	+ .20 - 2.43 -2.23	- 1.99 + .41 -1.58	0.65
	-1.27 - 2.43 -3.70	-1.58 - 2.08 -3.66	0.04
	-2.00 - 2.43 -4.43	-1.99 - 2.08 -4.07	0.36

Large deviations from additivity occur in the case of the anils of 2:3-xylidine, 3:4-xylidine and 6-chloro -2- toluidine. The discrepancy must arise from restricted flow of electrons into the ring since the rate of cyclisation of the disubstituted compounds in each case is slower than that corresponding to the additivity of substituent effects. This effect will be much more predominant in the case of the anils than for the corresponding amines because of the greater importance of mesomeric effects which give rise to transition states bearing a positive charge in the position para to ring closure, e.g.



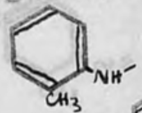
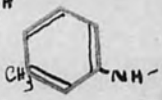
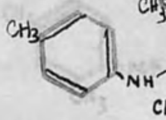
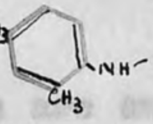
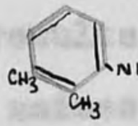
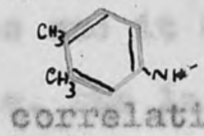


The proximity of large groups e.g. CH_3 ortho to these charge bearing groups may cause steric inhibition to resonance. In order that a methyl group might hyperconjugate with the rest of the molecule it must assume a planar configuration with the ring.

A further test on the additivity of substituent effects was made on the hydrolysis of anils of substituted anil~~s~~s and acetylacetone in 60.1% sulphuric acid at 25°C.

Correlation of Hammett's σ values with log ratio of rates of hydrolysis of anils.

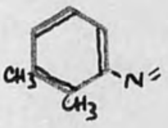
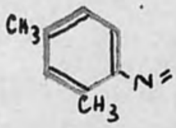
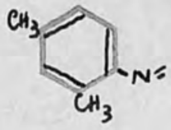
All rates of hydrolysis were in 60.1% H_2SO_4 at 25°C.

Compound		$\log k/k_o$
	-0.392	-0.83
	-0.069	-0.23
	-0.170	-0.40
	-0.562	-1.23
	-0.461	-1.31
	-0.239	-0.56

A linear correlation of log k/ko vs σ was obtained and a value of $\rho = 1.91$ was found for the reaction (see fig.15). A positive value of ρ indicates a reaction facilitated by a low electron density at the reaction site, a factor governing the protonation of the anil in acid solution; a low electron density of the N-atom will decrease the pKa of the anil and so more of the anil will remain unprotonated in the medium considered. Resonance interaction of the substituents with the ring will be unimportant as the important factor~~s~~ in the hydrolysis is the electron density at the N(atom) in the side chain. In this respect the hydrolysis reaction is analogous to the ionisation of the anilinium ions and substituent effects might be expected to be more nearly additive.

Additivity of substituent effects in hydrolysis of disubstituted anils:

A similar treatment to that used in the ionisation of the anilinium ions gives the equation:-

	$\log k^{xy} + \log k_o =$	$\log k^x + \log k^y$	$\Delta \log k$ $\log \frac{k^{xy} k_o}{k^x k^y}$
	$-2.65 - 1.34$ -3.99	$-2.17 - 1.56$ -3.73	$+ 0.26$
	$-1.34 - 2.57$ -3.91	$-2.17 - 1.74$ -3.91	0.00
	$-1.90 - 1.34$ -3.24	$-1.74 - 1.56$ -3.20	0.04

These results are analogous with the additivity effects found in the amines and it can be assumed that the same effects are operating i.e. the large deviation in the case of the anil 1:2-xylidine is due to restrictive orientation of the methyl groups or distortion of the $C_{me} - C_{Ar}$ bond.

Consideration of the cyclisation and hydrolysis of anils and the ionisation of the anilinium ions in aqueous solution i indicates that the Hammett equation $\log k/ko = \rho \sigma$ can be used most usefully in the quantitative analysis of substituent effec in reactions of substituted benzene derivatives when resonance considerations are not very important e.g. pKa of amines and hydrolysis of anils in concentrated sulphuric acid.

Effect of variation of initial concentration on rate of cyclisation:

Wilkins[86] found that the cyclisation reaction was not a true first order reaction, because for aniline anil in 95.7% sulphuric acid, the rate of cyclisation decreased slightly with increased concentration of anil. The rate of cyclisation of p-toluidine anil was studied in 93.7% sulphuric acid at 25°C when the molarity was varied from 0.20M - 0.02M. Over this range of concentration the rate of cyclisation decreased until a constant rate was observed below 0.06M.

Effect of variation of initial concentration of p-toluidine anil on rate of cyclisation in 93.7% sulphuric acid at 25°C.

Expt No.	Initial conc of anil Molarity	k, min^{-1}
9	0.20	0.0462
10	0.20	0.0462
1	0.10	0.0529
13	0.10	0.0525
3	0.08	0.0511
4	0.08	0.0511
5	0.06	0.0537
6	0.06	0.0537
7	0.04	0.0537
8	0.04	0.0537
11	0.02	0.0538
12	0.02	0.0538

A similar effect was observed in nitration reactions in media more aqueous than the optimum (below 90% H_2SO_4) and Williams et al suggest that an increase of initial concentration of the reactant causes an increase of anion concentration due to protonation of the reactant (or decrease in acidity) as does the addition of water, and, therefore, the rate is decreased.

Effects of Temperature:

Rates of cyclisation for aniline and p-toluidine anils were measured over the temperature range 0-50°C in different media and the constants of the Arrhenius equation were calculated.

$$k, = Ae^{-EA/RT}$$

Activation energies and arrhenius parameters:

Compound	% H_2SO_4	$E_A$cals	$\log_{10}$ A.
p-toluidine anil	94.9	15,900	10.35
	91.2	16,500	10.41
	86.8	17,300	10.45
aniline anil	94.9	17,400	10.89
	91.2	15,600	9.06
	86.8	25-35°C 18,400	10.50
		35-50°C 15,300	8.32

The value of the activation energy E_A are based on the experimental rate constant k, and it is necessary to consider the relation of this contant to the true rate constant k_o. The equation connecting the two rate constants is as shown:-

$$\log k, = \log k_o - H_o + pK_{AH_2}{}^{++} \quad .... \quad (1)$$

Variations of H_o and $pK_{AH_2}{}^{++}$ with temperature will be reflecte in the experimental k, on which the E_A values are calculated.

From equation (1) we can differnetiate w.r.t. $^1/_T$.

$$\frac{d(\log k_1)}{d(^1/_T)} = \frac{d(\log k_o)}{d(^1/T)} - \frac{d(H_o)}{d(^1/T)} - \frac{d(\log K_{AH_2^{++}})}{d(1/T)} \quad ..(2)$$

$\frac{d(\log k_1)}{d(1/T)}$ is in fact what is used to calculate E_A.

Equation (2). $$\frac{d(\log k_1)}{d(1/T)} = -E/_R - \frac{d(Ho)}{d(1/T)} + \frac{\Delta H}{R}$$

$$= \frac{\Delta H - E}{R} - \frac{d(Ho)}{d(1/T)}$$

Temkin et al[87] have studied the variation of H_o with temperature over the whole range of sulphuric acid. The variation of H_o was studied over the range 20-80°C. For each medium H_o was plotted against $^1/T$ andthe slope of the line was determined i.e. $d(Ho)/d(1/T)$. Typical results were as follows:-

% H_2SO_4	$d(Ho)/d(1/T)$ cals.
84	550
88	750
92	850
96	930

The activation energy E_A for the cyclisation reaction is the order of 16,000 cals. The variation $d(Ho)/d(1/T)$ is negligible compared with this and falls within the limits of experimental error for the determination of activation energy.

Temkin also states that the pKa's of his indicators did not vary with temperature. In the above equation ΔH will,therefore, be zero.

The activation energy obtained experimentally is, within the limits of experimental error the true activation energy for the reaction. Aniline and p-toluidine anils give E_A values in a range of 2,000 cals.

In the cyclisation reaction it is reasonable to assume that the anil and activated complex will be solvated. If both the reactants and activated complex are solvated, there may be littl change in the activation energy with change of meium, and the influence on the reaction velocity will be small. This seems to be the case for p-toluidine anil which exhibits a small decrease in activation energy as the acidity of the medium increases.

The A factor for the reaction depends on the following consideration:-

$$\begin{aligned} \log_e k_1 &= \log_e k_o - H_o + pK_{AH_2}{}^{++} \\ &= \log_e A - {}^{E}/_{RT} - H_o + pK_{AH_2}{}^{++} \\ &= 2.303 \log_{10} A - ca \cdot 27 - H_o - pK_{AH_2}{}^{++}. \end{aligned}$$

If $H_o \sim pK_{AH_2}{}^{++}$, then the value obtained for A is reasonably correct. Consider relationship $- H_o + pK_{AH_2}{}^{++} = \log \frac{(AH_2^{++})}{(AH^+)}$

if $(AH_2^{++}) = \frac{1}{100} (AH^+)$

then $\log (AH_2^{++}) / (AH^+) = - 2$ which means the A factor will be correct to about ± 1.

The experimental data indicate a constant A factor over the range of media considered. No substantial entropy changes with change in medium occur in the cyclisation of substituted anils in sulphuric acid. This might be expected since the realisation by the side chain of the particular configuration for ring closure is not likely to be affected by medium composition.

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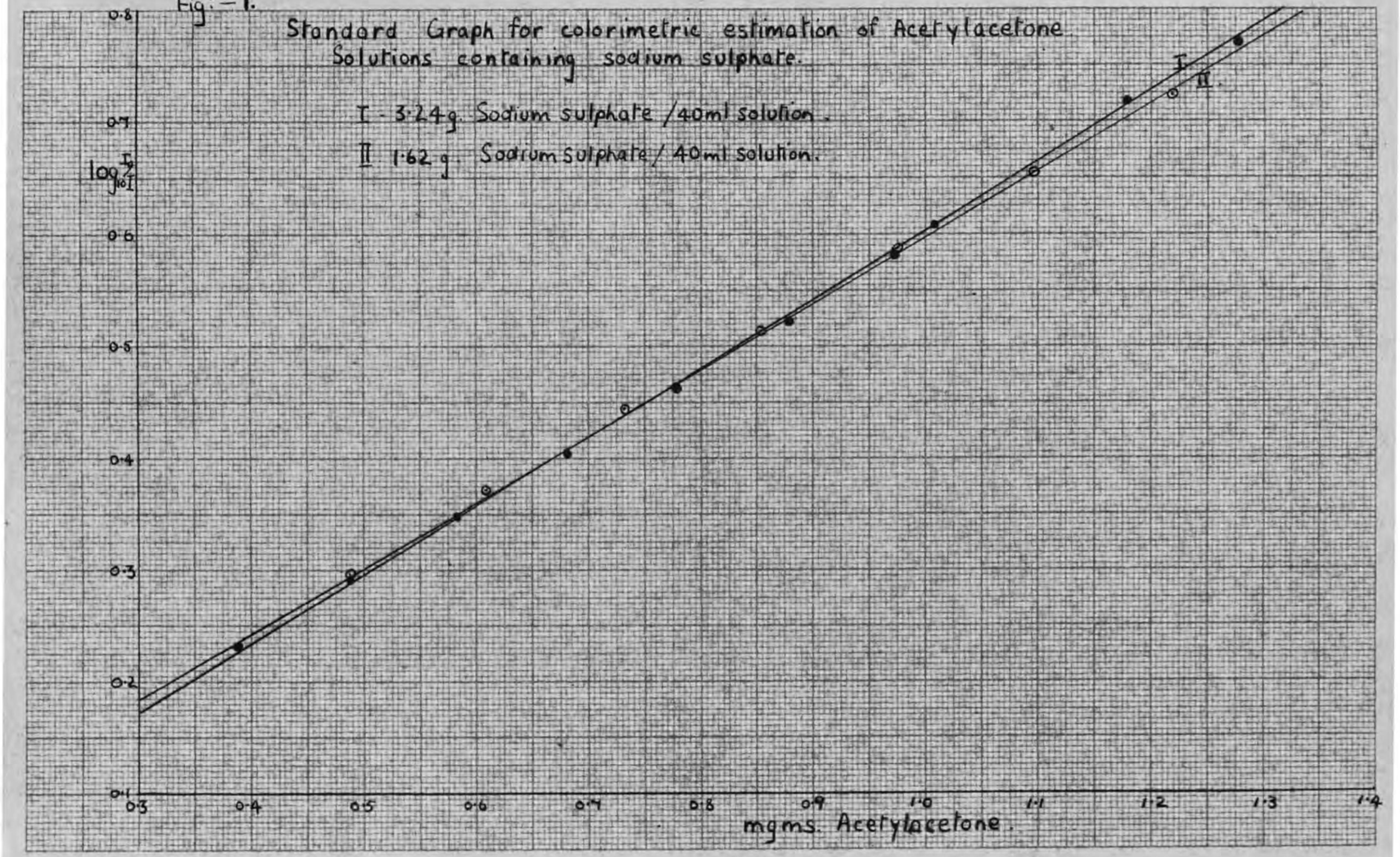
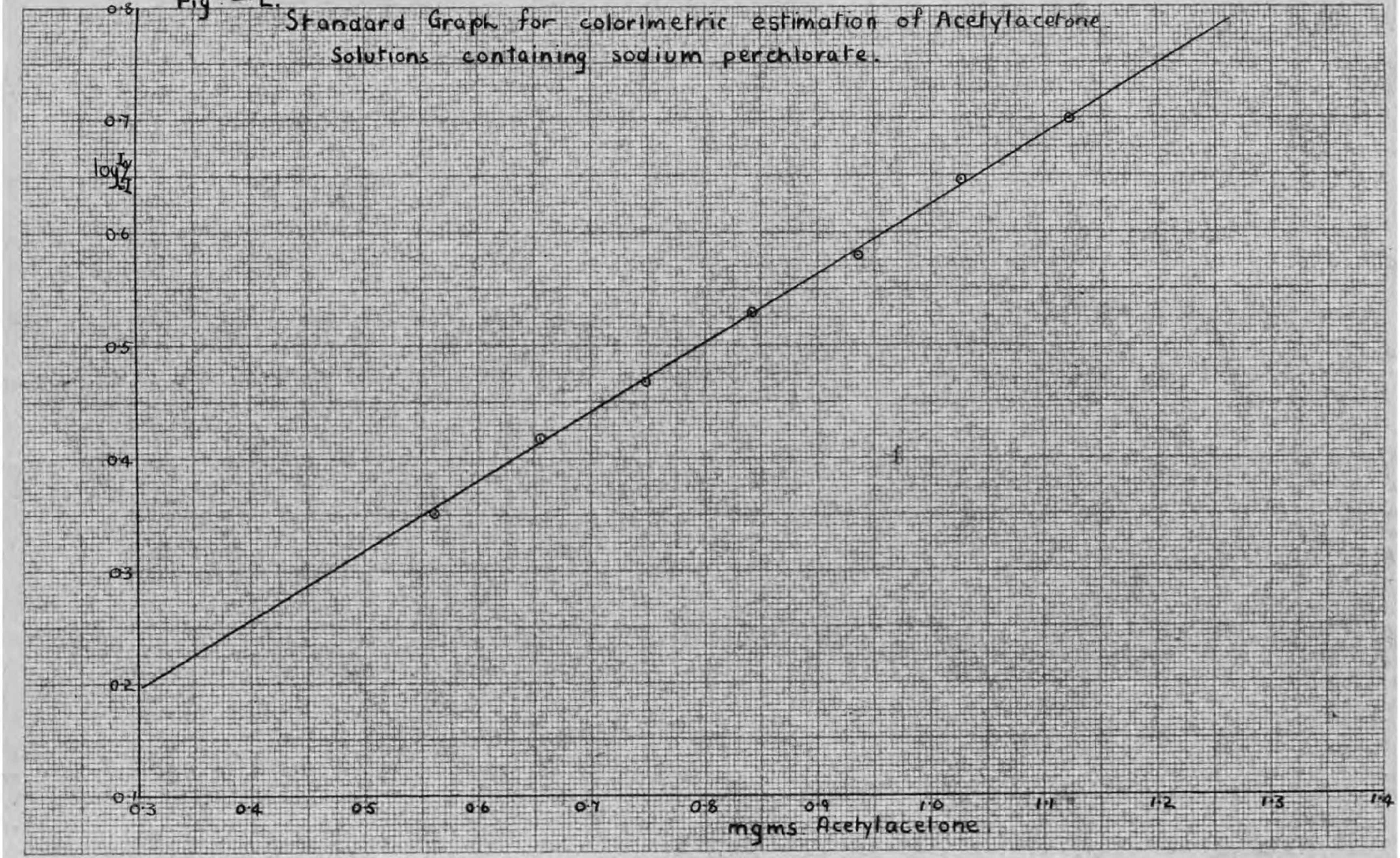
Fig:- 1.



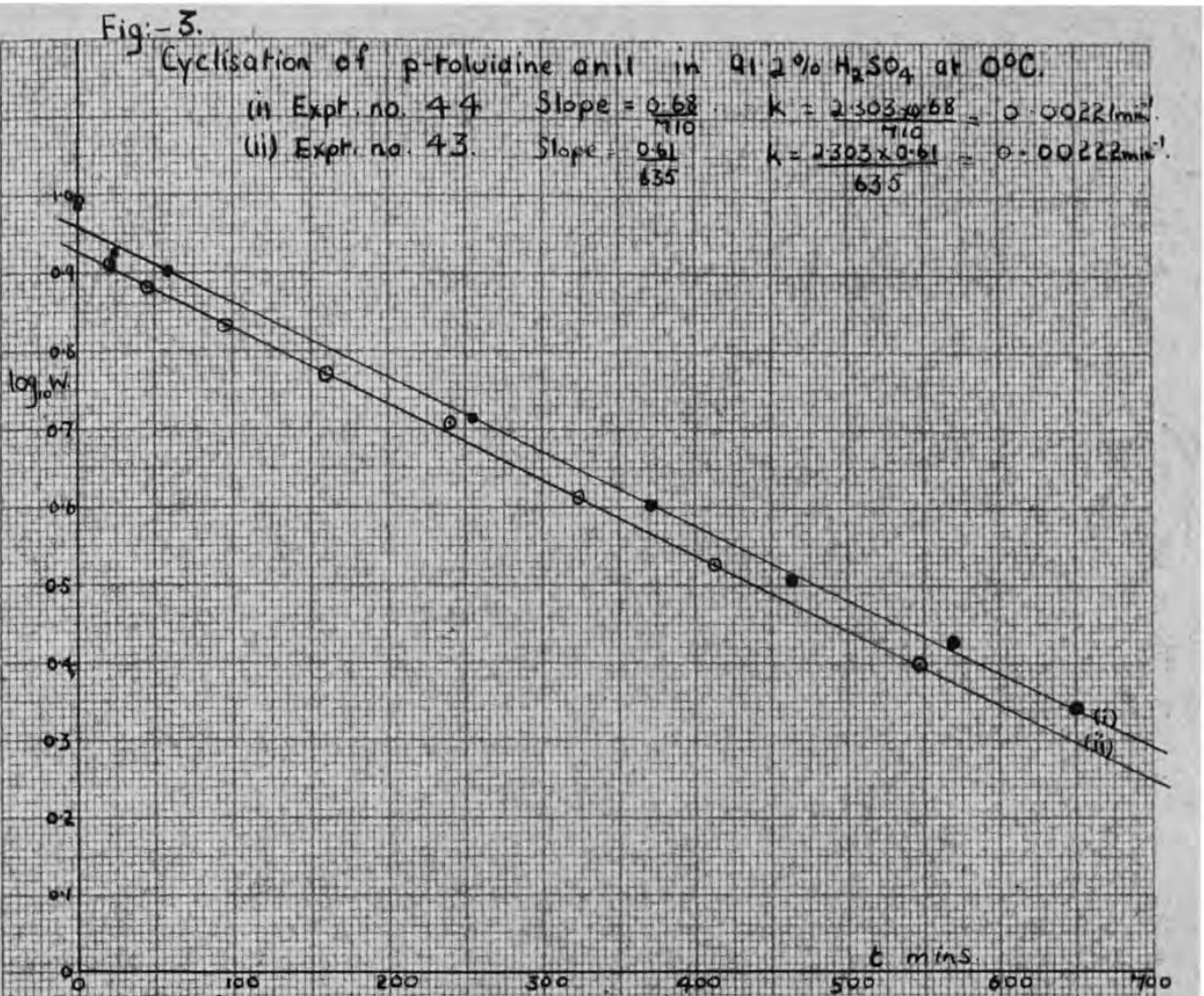
Standard Graph for colorimetric estimation of Acetylacetone
Solutions containing sodium sulphate.

Fig: — 2.



Standard Graph for colorimetric estimation of Acetylacetone
Solutions containing sodium perchlorate.

Fig:- 3.

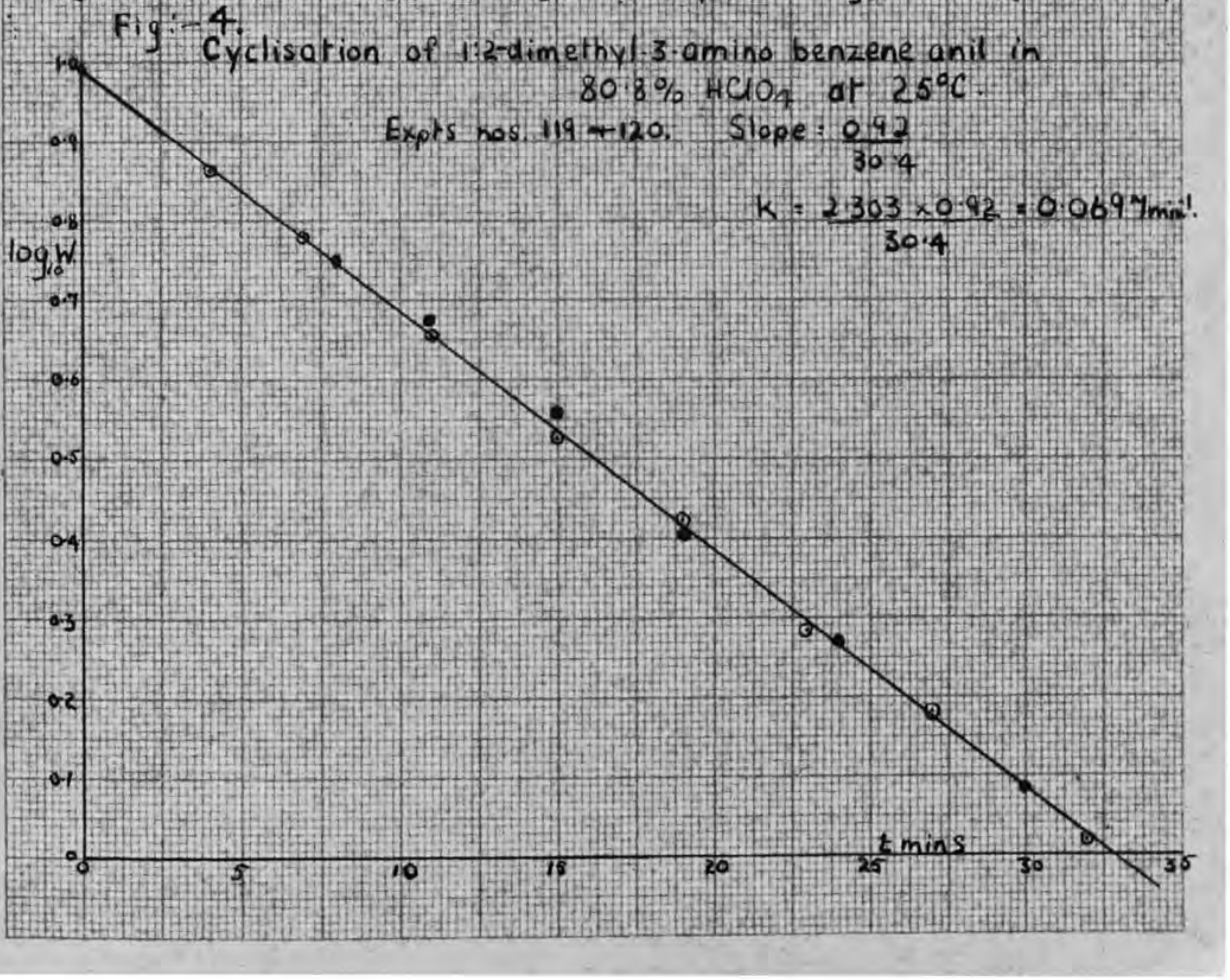


Cyclisation of p-toluidine anil in 91·2% H_2SO_4 at 0°C.

(i) Expt. no. 44 Slope = $\frac{0{\cdot}68}{710}$ $k = \frac{2{\cdot}303 \times 0{\cdot}68}{710} = 0{\cdot}00221\,\text{min}^{-1}$.

(ii) Expt. no. 43. Slope = $\frac{0{\cdot}61}{635}$ $k = \frac{2{\cdot}303 \times 0{\cdot}61}{635} = 0{\cdot}00222\,\text{min}^{-1}$.

Fig:- 4.

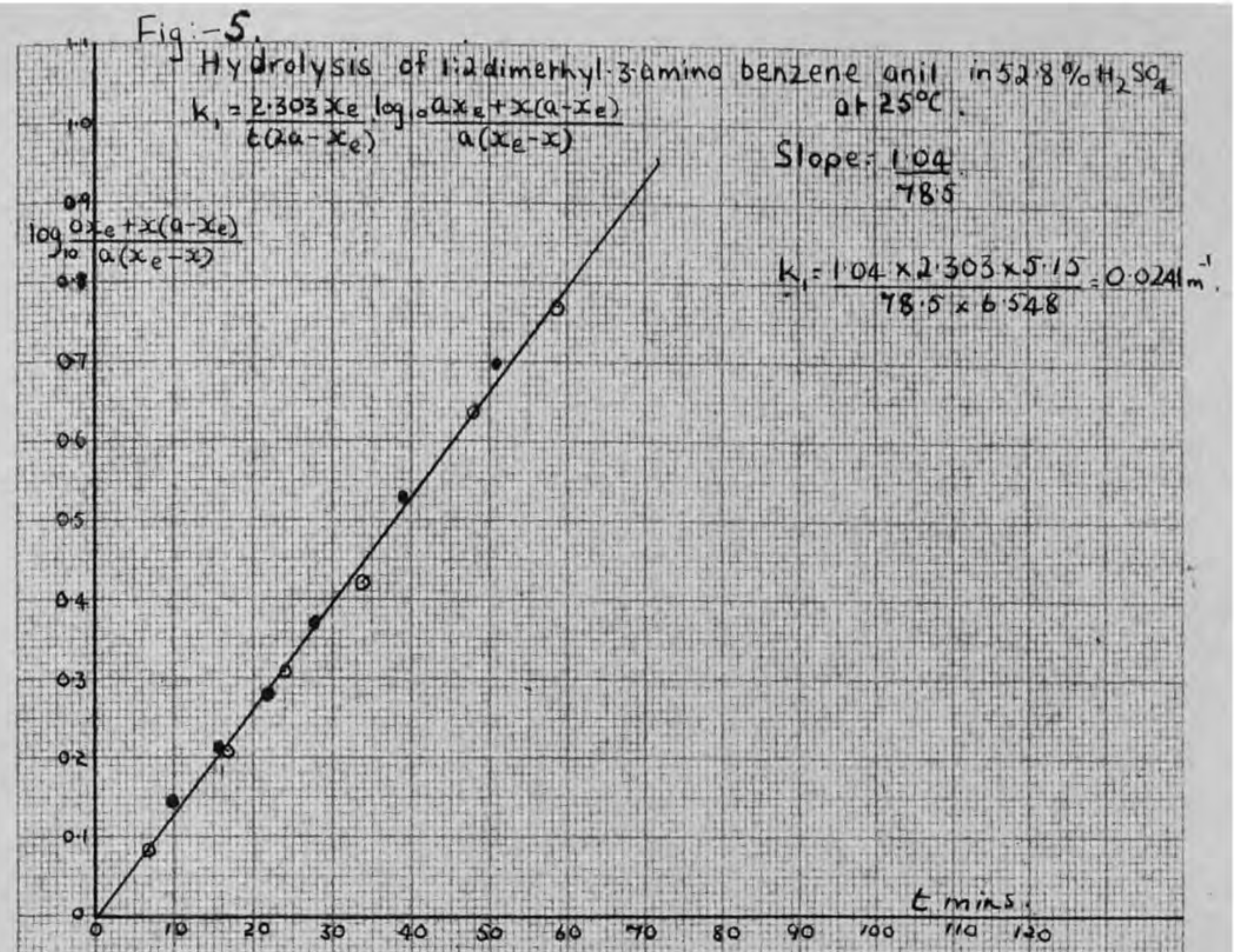


Cyclisation of 1:2-dimethyl-3-amino benzene anil in 80·8% $HClO_4$ at 25°C.

Expts nos. 119 + 120. Slope : $\frac{0{\cdot}92}{30{\cdot}4}$

$k = \frac{2{\cdot}303 \times 0{\cdot}92}{30{\cdot}4} = 0{\cdot}0697\,\text{min}^{-1}$.

Fig:-5.



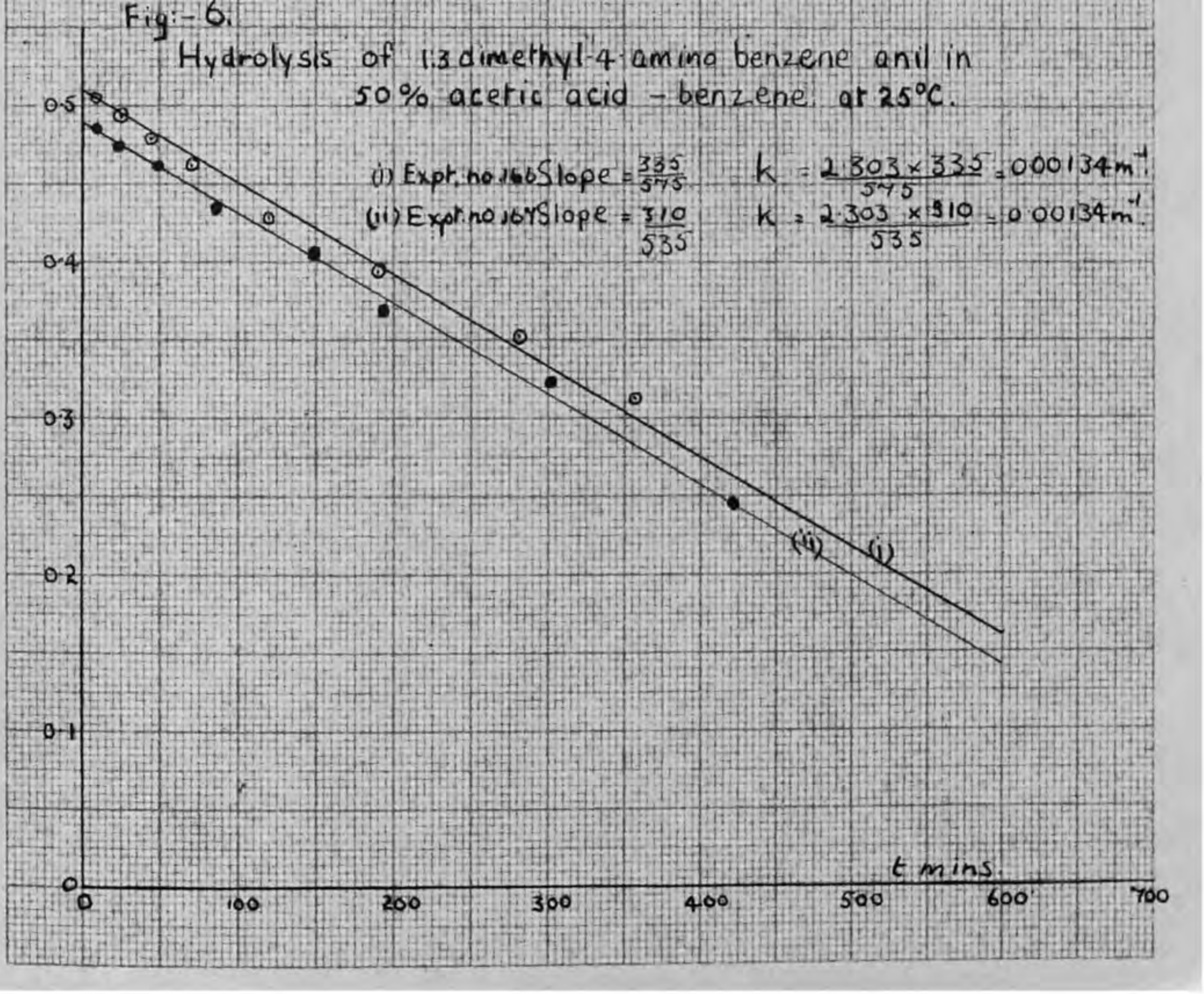
Hydrolysis of 1:2 dimethyl 3 amino benzene anil in 52·8 % H_2SO_4 at 25°C.

$$k_1 = \frac{2{\cdot}303\, x_e}{t(2a - x_e)} \log_{10} \frac{a x_e + x(a-x_e)}{a(x_e - x)}$$

Slope = $\frac{1{\cdot}04}{78{\cdot}5}$

$$k_1 = \frac{1{\cdot}04 \times 2{\cdot}303 \times 5{\cdot}15}{78{\cdot}5 \times 6{\cdot}548} = 0{\cdot}0241\,m^{-1}.$$

Fig:-6.



Hydrolysis of 1:3 dimethyl-4 amino benzene anil in 50 % acetic acid - benzene at 25°C.

(i) Expt. no 166 Slope = $\frac{335}{545}$ $k = \frac{2{\cdot}303 \times 335}{545} = 0{\cdot}00134\,m^{-1}.$

(ii) Expt. no 167 Slope = $\frac{310}{535}$ $k = \frac{2{\cdot}303 \times 310}{535} = 0{\cdot}00134\,m^{-1}.$

Fig:- 7.

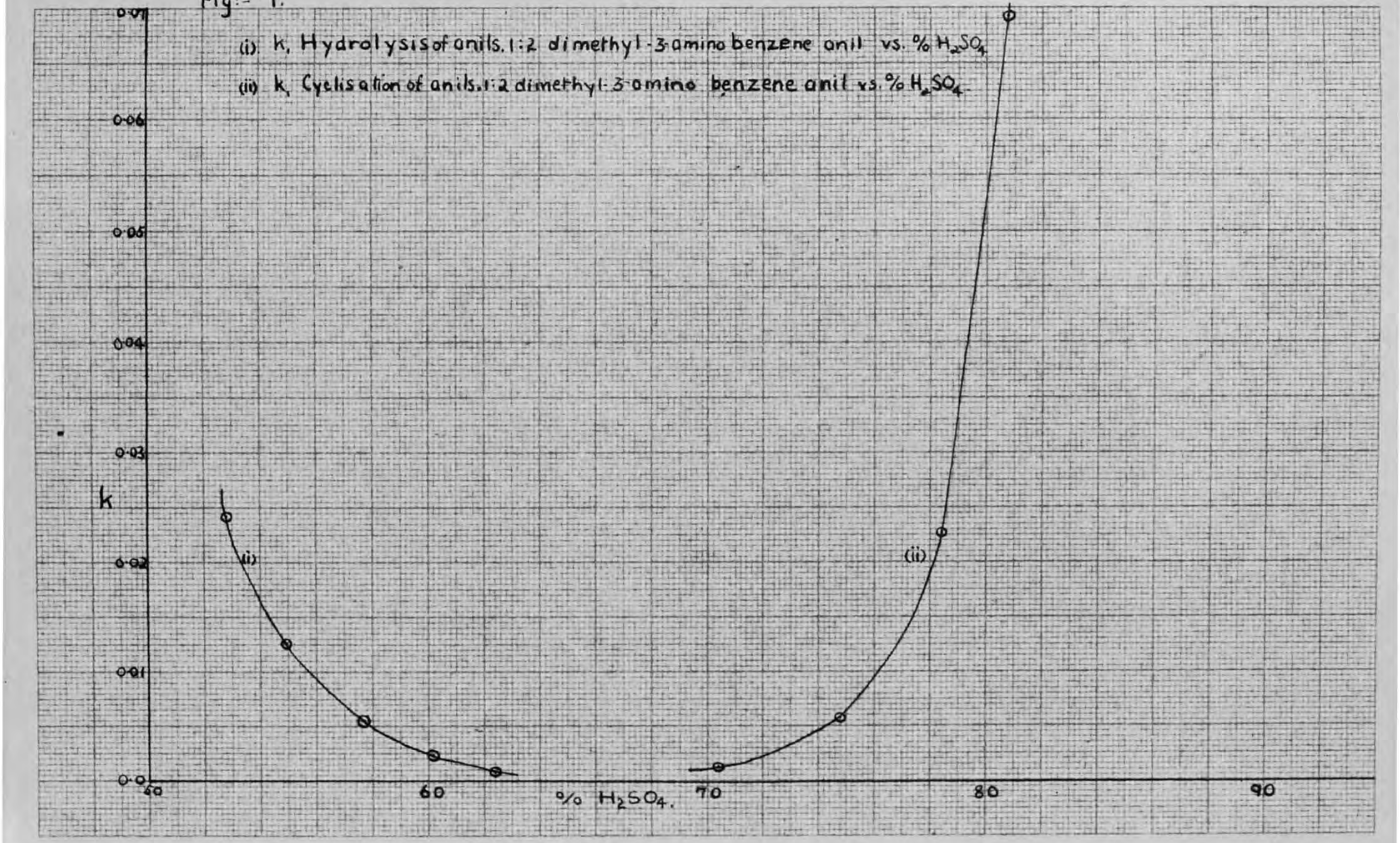

(i) k, Hydrolysis of anils. 1:2 dimethyl-3-amino benzene anil vs. % H_2SO_4
(ii) k, Cyclisation of anils. 1:2 dimethyl-3-amino benzene anil vs. % H_2SO_4
k
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0.0
50
60
70
80
90
% H_2SO_4.
(i)
(ii)

Fig:- 8

Variation of rate of cyclisation of p-toluidine anil (k_1) with initial concentration of reactant in 93·7% H_2SO_4 at 25°C.

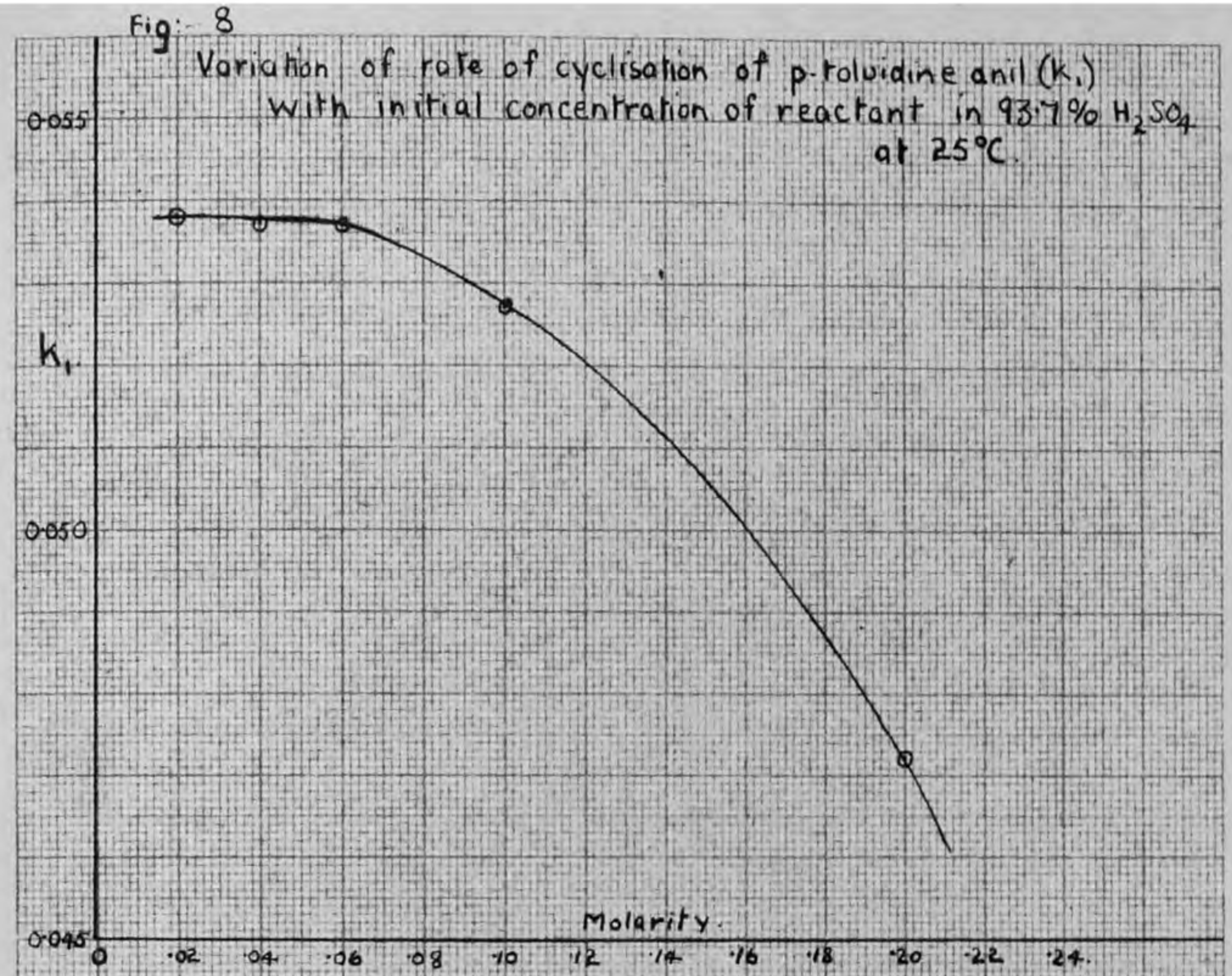


Fig:- 9.

Determination of pK_a of p-toluidine in aqueous solution at 25°C

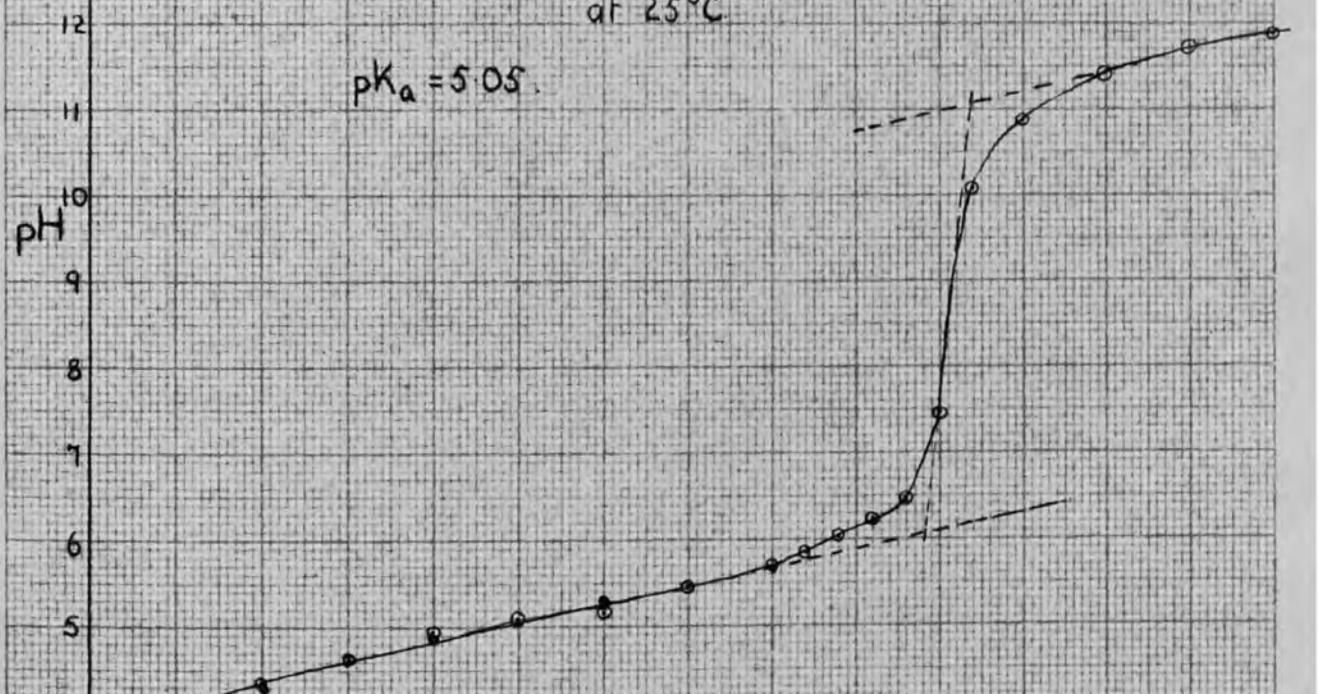
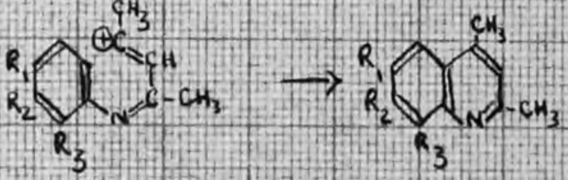


Fig:-10

Correlation of logk_1 and C_0 in the cyclodehydration of Acetylacetone anils to 2:4 dimethyl quinolines.



	R_1	R_2	R_3	Media	Slope
I	H	CH_3	CH_3	H_2SO_4	non-linear
II	CH_3	H	H	H_2SO_4	"
III	H	H	H	H_2SO_4	"

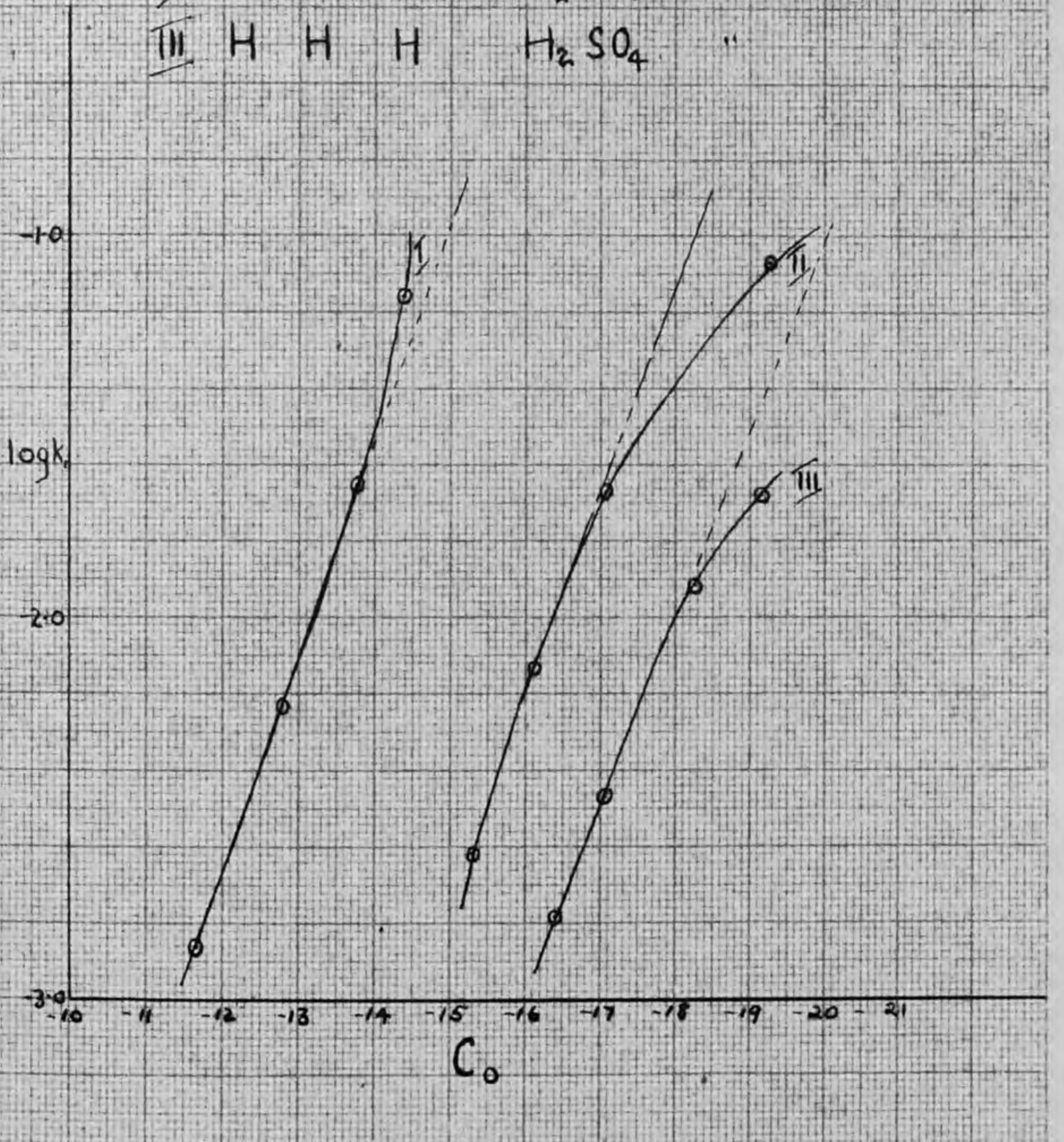
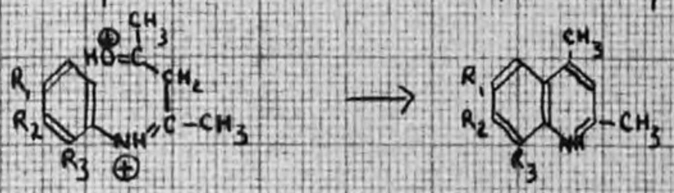


Fig:-11.

Correlation of $\log k_1$ and H_o in the cyclodehydration of Acetylacetone anils to 2:4 dimethyl quinolines.



	R_1	R_2	R_3	Media	Slope
I	H	CH_3	CH_3	H_2SO_4	1·09
II	H	CH_3	CH_3	$HClO_4$	0·92
III	CH_3	H	H	H_2SO_4	1·18
IV	H	H	H	H_2SO_4	1·03

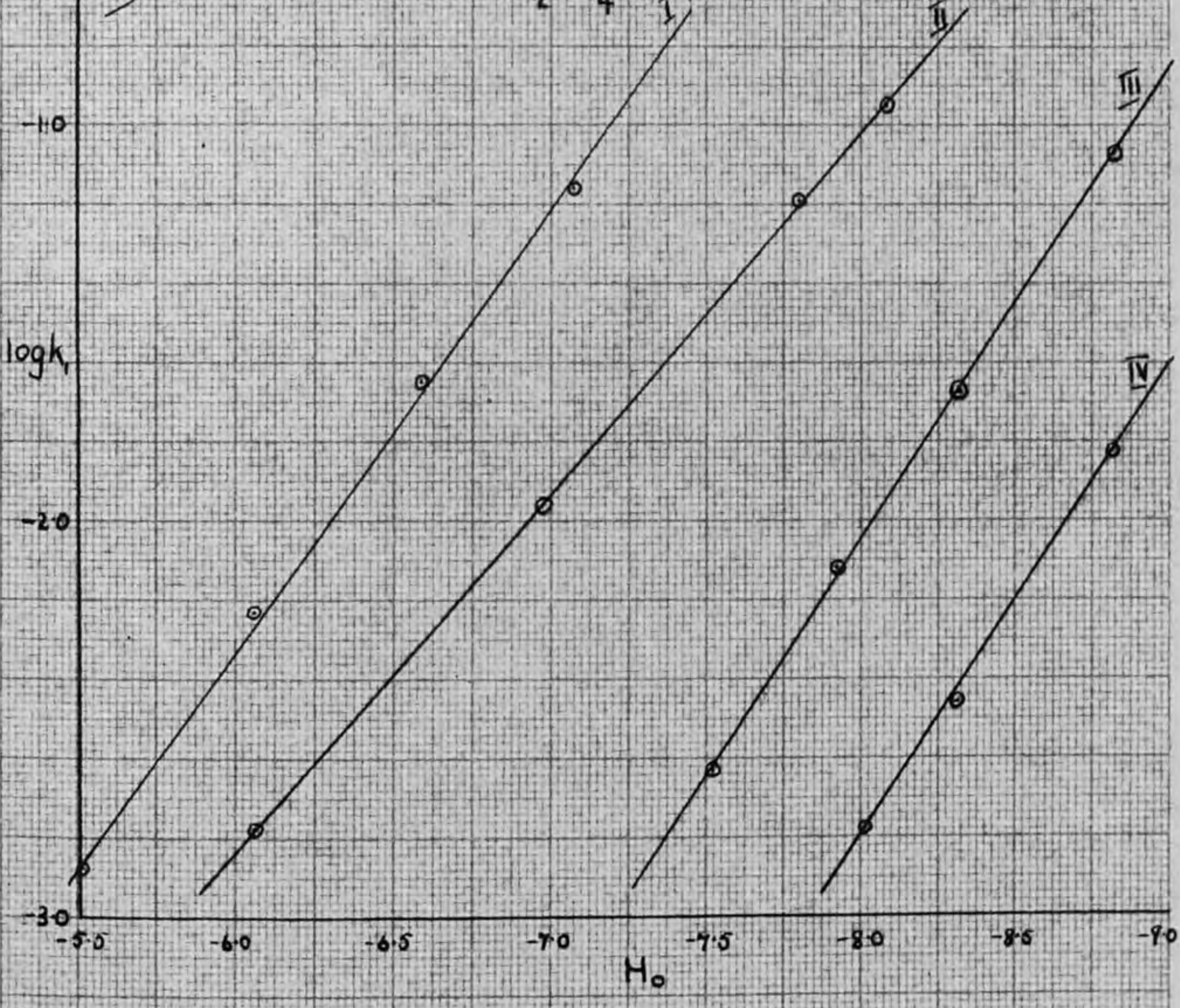


Fig:-12 Data on Nitration. De la Mare. J.C.S. 1954, 4450.
$\log_{10} f_p$ or $\log_{10} f_m$ vs. σ.

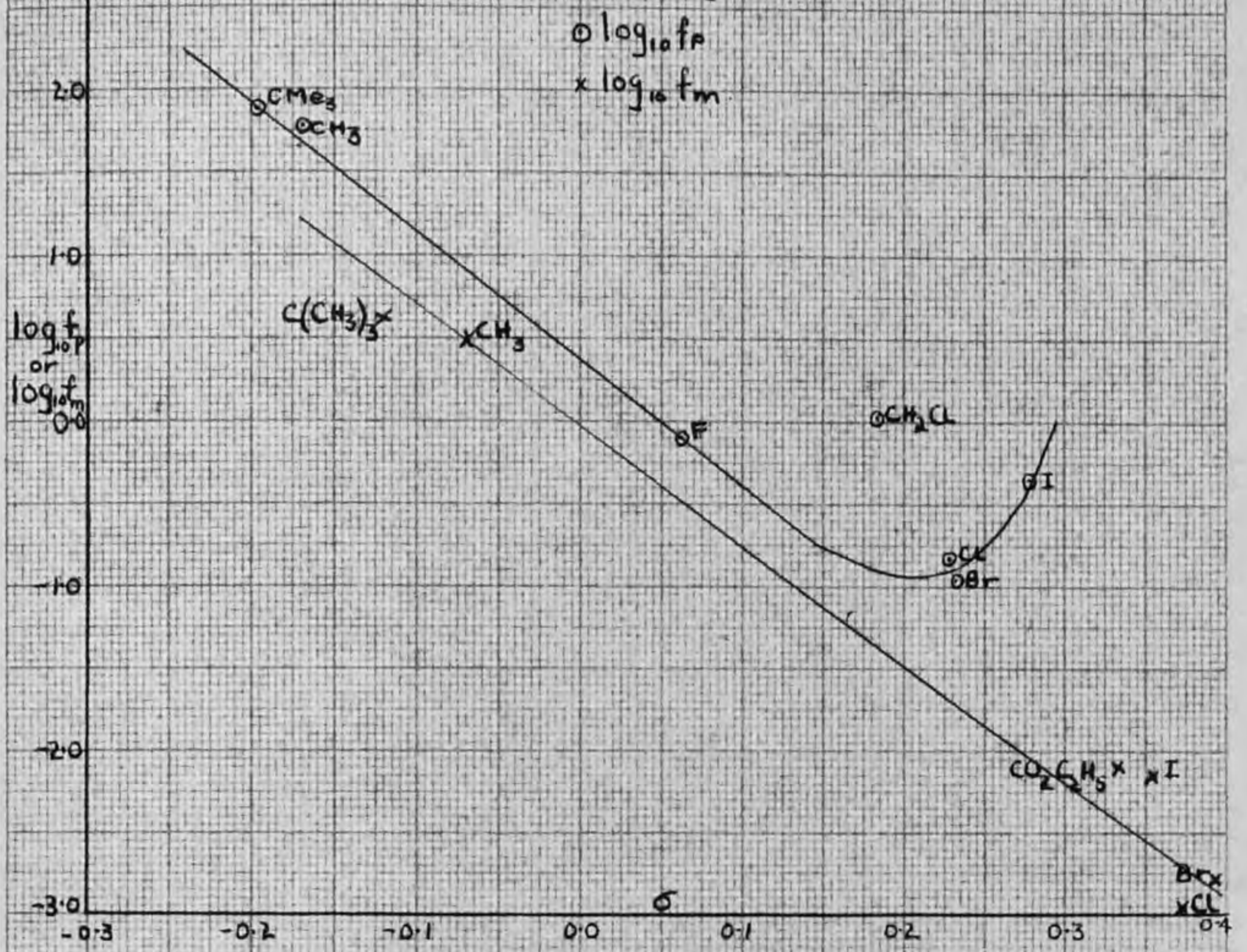
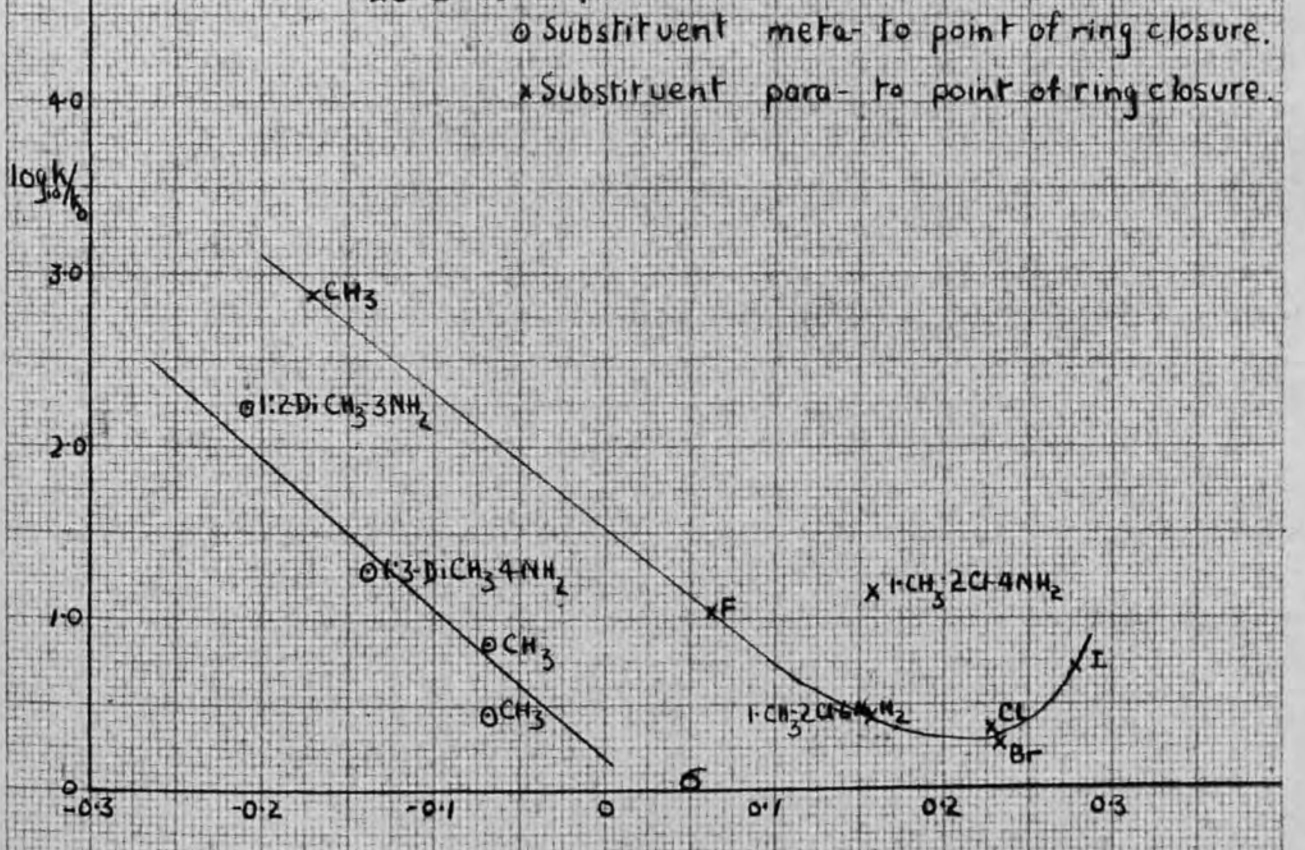


Fig:-13 $\log_{10} k/k_0$ for acetylacetone anils in 93.8% H_2SO_4 at 25°C vs. σ.



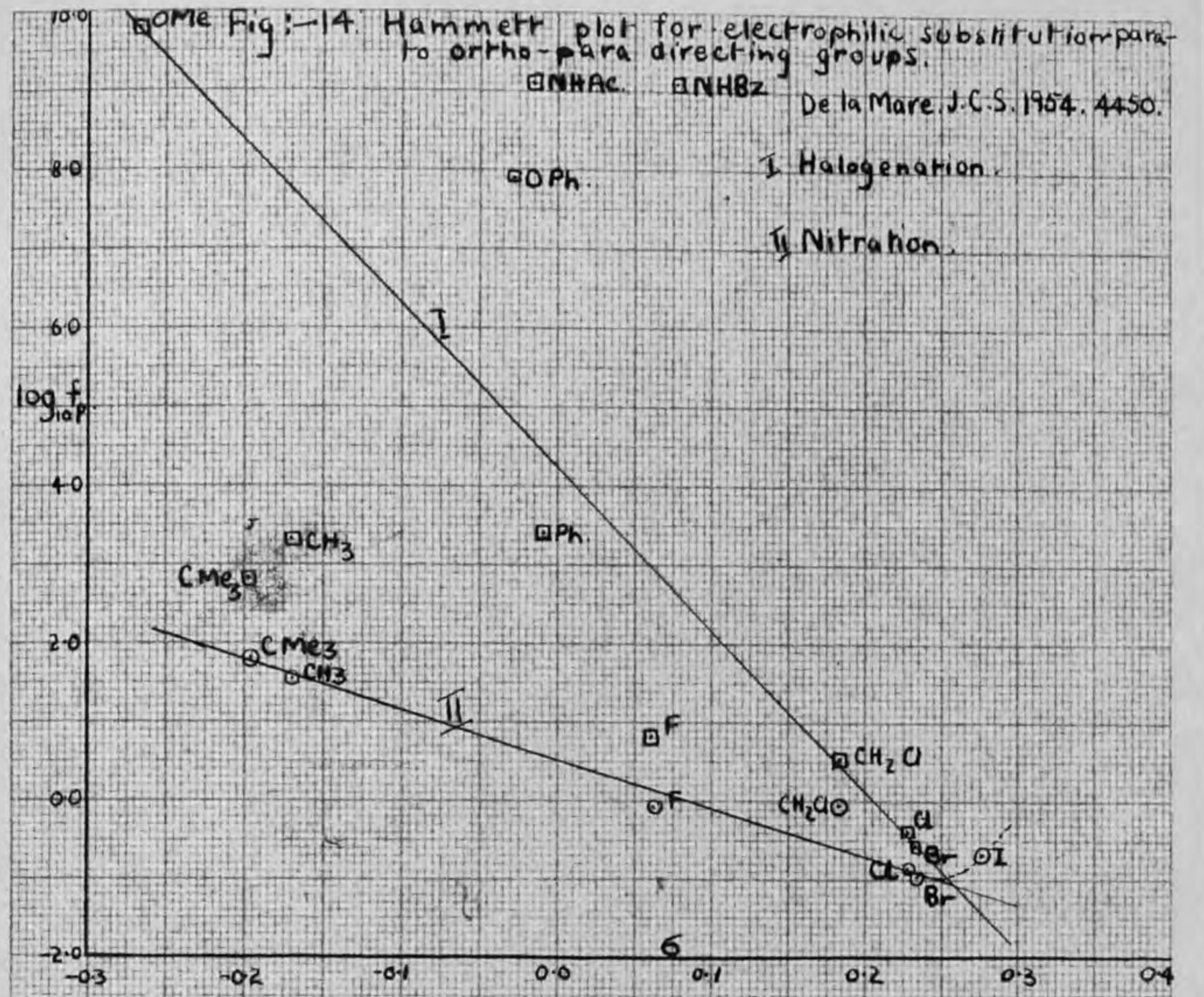


Fig:-14. Hammett plot for electrophilic substitution para to ortho-para directing groups.

De la Mare. J.C.S. 1954. 4450.

I Halogenation.

II Nitration.

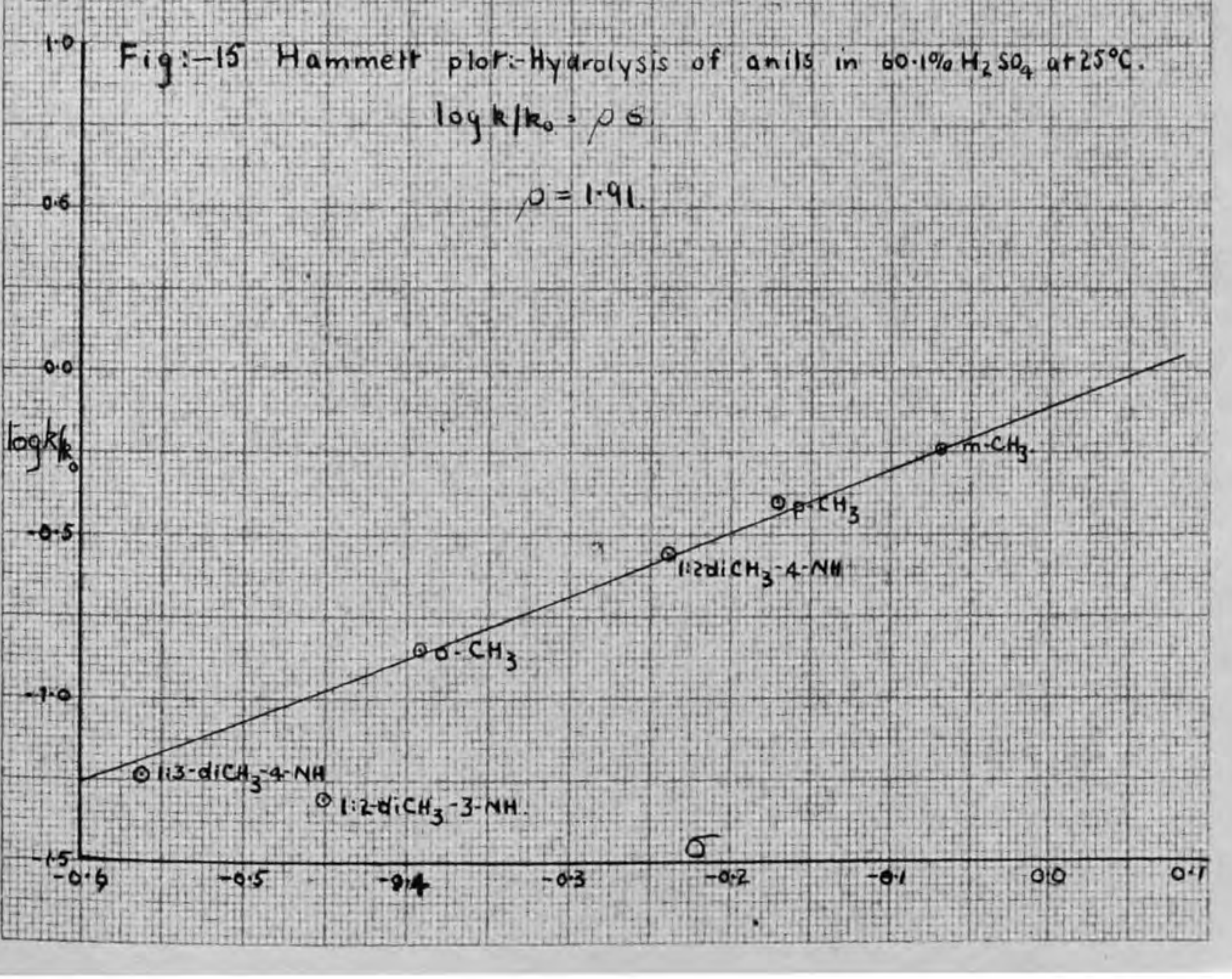


Fig:-15 Hammett plot:- Hydrolysis of anils in 60.1% H_2SO_4 at 25°C.

$\log k/k_0 = \rho\sigma$

$\rho = 1.91.$

Fig.-16 Plot of $\log_{10} f_p$ nitration or halogenation vs. $\log k/k_0$ cyclisation of anils.

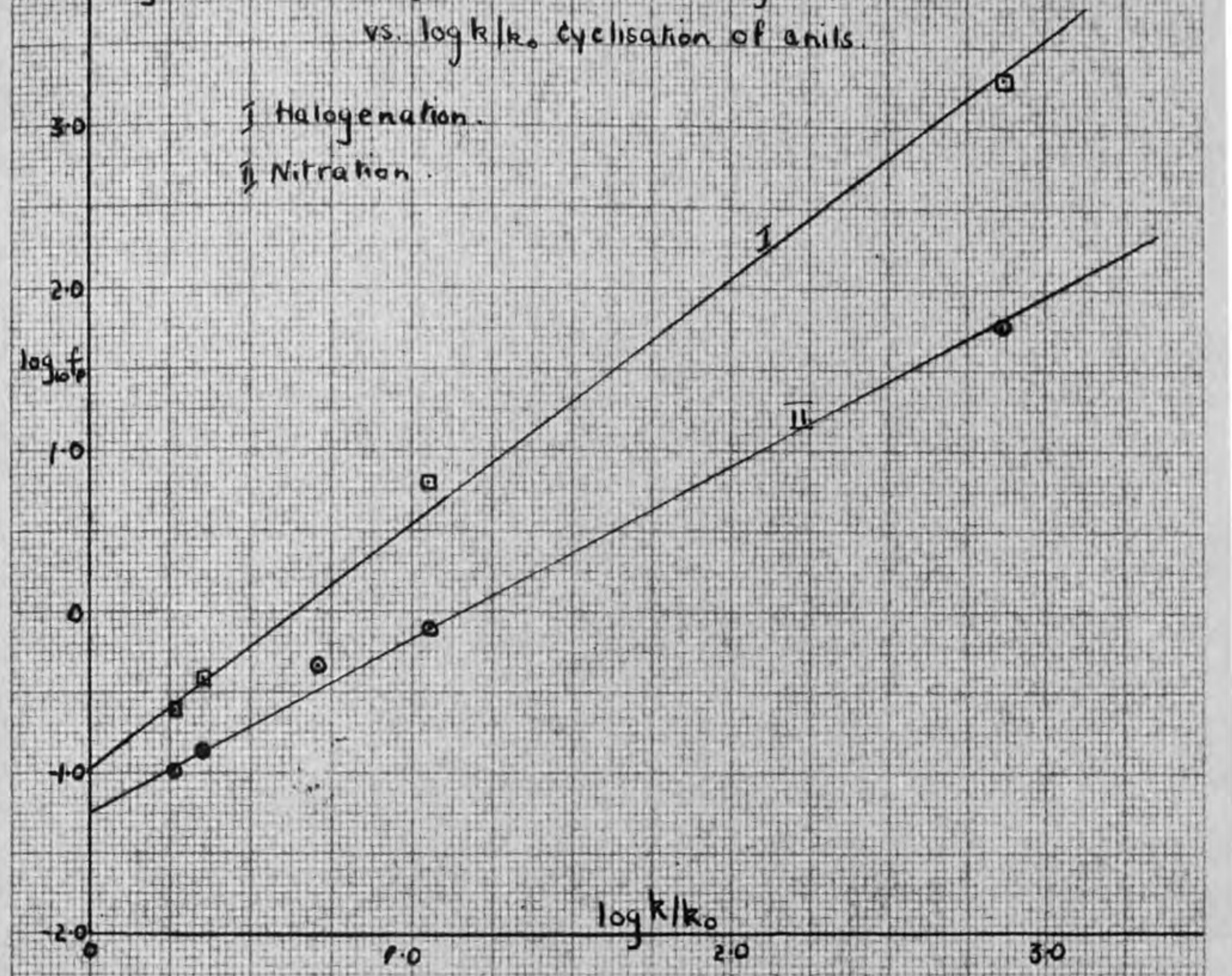
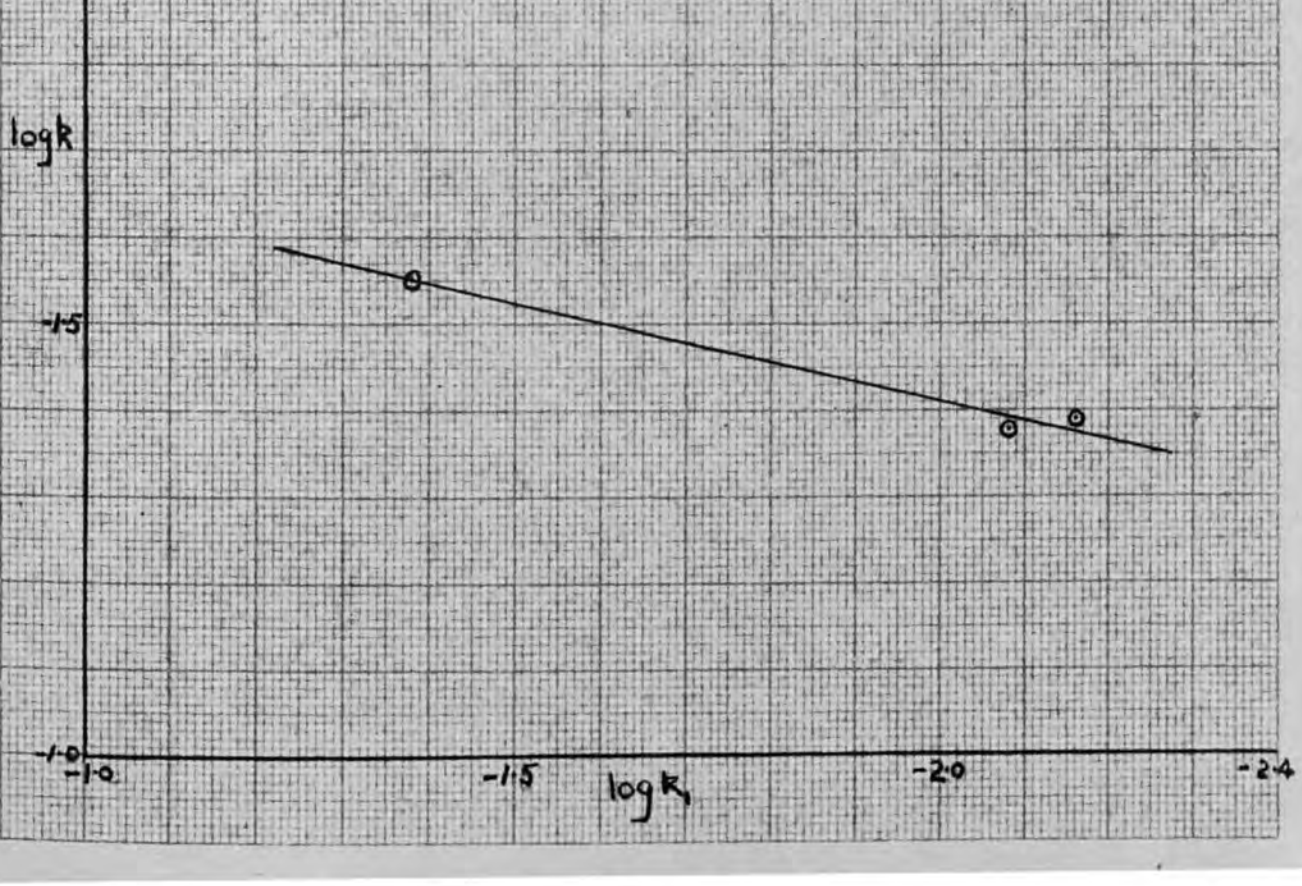


Fig.-17 Plot of log k for cyclisation of o-benzylphenones[1] vs log k_1 cyclisation of anils.

[1] Bradsher and Vingiello. J.C.C. 1949, 1434.



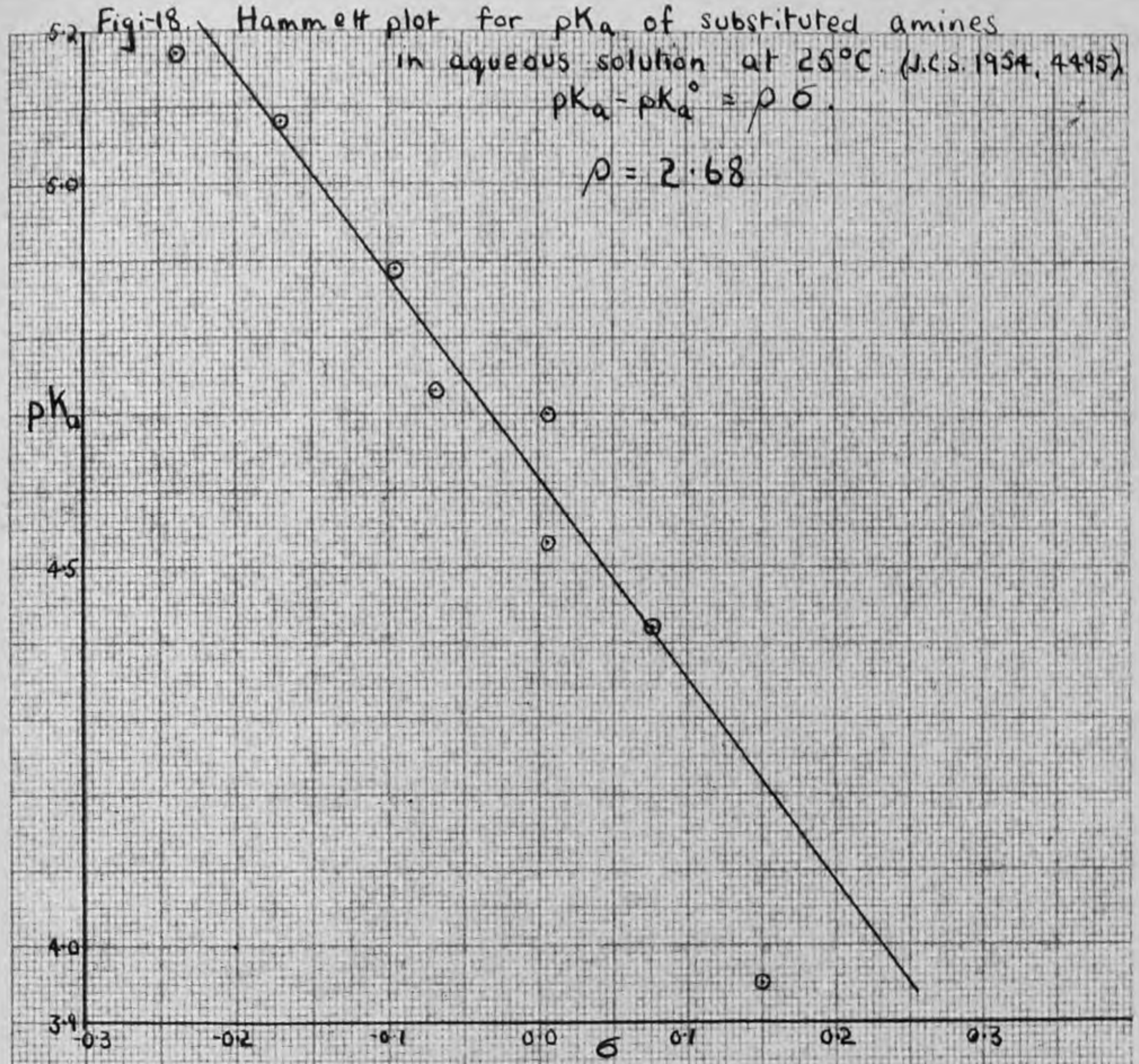


Fig. 18. Hammett plot for pK_a of substituted amines in aqueous solution at 25°C (J.C.S. 1954, 4495)

$pK_a - pK_a^\circ = \rho\sigma$.

$\rho = 2.68$