THE CYCLISATION OF ANILS.

by

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-:SUMMARY:-

Previous work on cyclisation reactions in acidic media, is reviewed, particular attention being paid to those reactions which take place in concentrated sulphuric acid, especially the synthesis of quinoline compounds from anils of β-diketones by the Combes method.

A method of analysis of dilute aqueous sulphuric acid solutions containing acetylacetone and full experimental details for the measurement of the rate-constant of the cyclisation of the anil, β-p-toluidinopropenylmethyl ketone in concentrated sulphuric acid to 2:4:6-trimethyl-quinoline are given. The analysis of the aliquots taken from the reaction mixture depends on the hydrolysis of the anil into p-toluidine and acetylacetone and the subsequent estimation of the acetylacetone.

The cyclisation reaction is found to be first order with respect to the anil and the rate-constant is found to increase with increasing strength of sulphuric acid. Unlike most nitration reactions, which have a maximum rate at about 90% sulphuric acid, the rate of this cyclisation reaction increases with increasing acidity and does so very rapidly as absolute sulphuric acid is approached.

The tautomerism of anils and the nature of β-p-toluidinoprop-enylmethyl ketone in sulphuric acid is discussed. The rate-constant k_1 is found to be related to Hammett's acidity function H_o and the anil is therefore assumed to take up a single proton in concentrated sulphuric acid.

A mechanism of cyclisation is suggested involving the uptake of a proton, ring-closure and subsequent loss of molecule of water.

A note is made of the failures of certain anils to cyclise and a reason for this failure is suggested.

Acknowledgment.

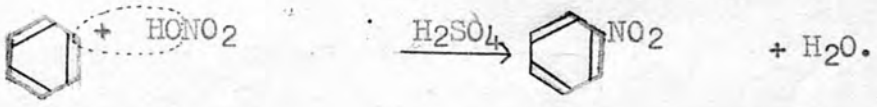
I would like to thank Dr. T. G. Bonner for suggesting the subject of this work and for his unfailing help and encouragement throughout the investigation. I also wish to thank Professor Gwyn Williams for his interest and support.

Contents.

I. Introduction.

1. Sulphuric acid and electrophilic substitutions.

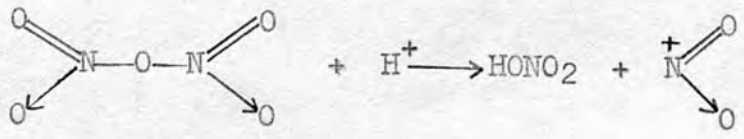
Concentrated sulphuric acid is a particularly useful medium for carrying out many organic reactions, in particular, electrophilic substitutions such as the nitration of aromatic compounds, certain acylation and alkylation reactions of the Friedel-crafts type and cyclisation or cyclodehydration reactions. It is only recently that the actual function of the sulphuric acid in electrophilic substitutions has been appreciated. For example, the nitration of benzene was formerly represented by the equation.



and it was assumed that, in this reaction, and indeed in all such reactions where a molecule of water is eliminated, the function of the sulphuric acid was to remove the elements of water from the reactants.

More recent work, however, has shown that the mechanism of this reaction is not the elimination of a molecule of water between the aromatic hydrocarbon and the nitrating reagent, but the formation of a cation from the nitric acid, which attacks the benzene nucleus. The mechanism proposed for nitration reactions is the formation of the nitronium ion NO_2^+ from the nitric acid.

This active intermediate may also be formed by the interaction of a proton with the acid anhydride, dintrogen pentoxide.



A comprehensive review of the evidence for the existence of the nitronium ion NO_2^+ was published by Bennett, Brand and Williams in 1946.[1] They put forward evidence to show

(a) that in sulphuric acid, nitric acid exists as a new form

(b) that the new form is cationic

(c) that the cation is NO_2^+

(d) that NO_2^+ is the active nitrating entity.

Since 1946 Westheimer and Kharasch[2], Cox and Jeffery[3] and Ingold and his coworkers[4] have put forward evidence establishing the existence of the nitronium ion in nitric: sulphuric acid mixtures.

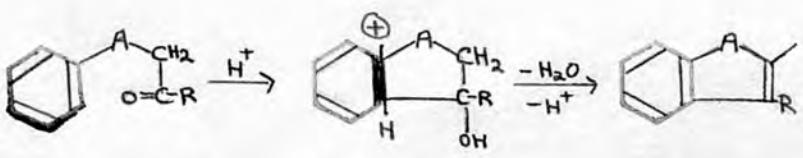
Further information from studies of the kinetics of nitration reactions in sulphuric acid show that the rate of nitration reactions reaches a maximum in about 90% sulphuric acid, and there is some indication that the rise to a maximum is a property of the medium, and not of the aromatic compound, providing the latter is present in sufficiently low concentrations to have a negligible effect on the solvent. It appears that the two effects of the sulphuric acid media are to (1) ionise the nitric acid and (2) solvate the aromatic substance. On the aqueous side of the maximum (1) has a greater effect than (2) and the effect of (1) and hence the rate of nitration, increases with increasing con-

centration of sulphuric acid; but, when the acid concentration has reached about 90%, the effect of (2) is such that it overcomes that of (1) and, although the extent of ionisation of the nitric acid continues to increase, the rate of nitration falls. As the concentration of sulphuric acid increases to 100%, its solvating action increases so that the rate of nitration falls steadily.

It was with a view to studying further the action of sulphuric acid as a medium in electrophilic substitution reactions that various cyclisation reactions were reviewed with a view to kinetic study.

2. Cyclisation reactions and cyclising media.

In 1946 Bradsher[5] reviewed and correlated the known examples of aromatic cyclisations of the type in which a ketone or an aldehyde usually the latter, in the presence of acid - catalysts condenses with an aromatic nucleus to form a cyclic carbinol, which then undergoes dehydration to form another ring. This type of cyclisation has been designated as aromatic cyclodehydration and is almost unique in its ability to afford a new, full aromatic ring without resort to dehydrogenation. This type of reaction can conveniently be represented by the following equations:-



(R=alkyl or aryl or H; A= - C = C -; -O-; -S-; -NH-;-NH-;-N=C-;-C=N-.)

Bradsher divided the cyclisations, which he was considering, into two main classes, namely bicyclic and tricyclic, depending on the nature of the final product.

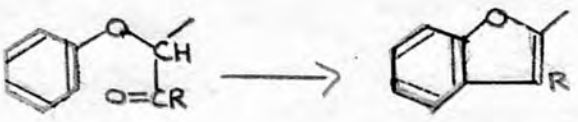
In the former class came:-

(a) The Naphthalene Syntheses, in which compounds of the β-styrylmethyl ketone type cyclise to give naphthalene derivatives.

(R=H, alkyl or aryl).

For these cyclisations the medium usually employed was boiling 50% sulphuric acid, but in some cases, cyclisation was effected by merely heating the ketone to 120°, or heating with a methyl alcohol solution of hydrogen chloride, or a mixture of hydrobromic and acetic acids.

(b) The Benzofuran series, in which a phenoxyacetaldehyde or phenoxymethyl ketone yields a benzofuran nucleus.



(R=H, alkyl or aryl).

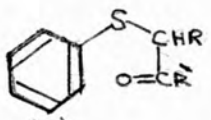
In these compounds, the aldehyde or ketone, having no double bond, is more stable towards acid than its counterpart in the naphthalene series, there is also no possibility of

Geometric isomerism. The presence of a strong O-p- directing ether linkage results in a markedly greater case of cyclisation.

The media employed for these reactions are concentrated sulphuric acid, and acetic acid solutions of zinc chloride.

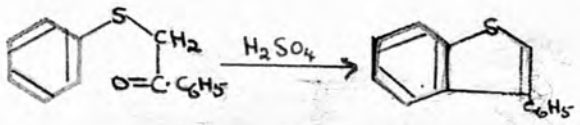
(c)The Thianaphthene series:-

Many attempts were made to cyclise compounds of the type (1), but most of them failed.

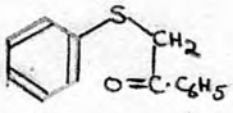


(I)

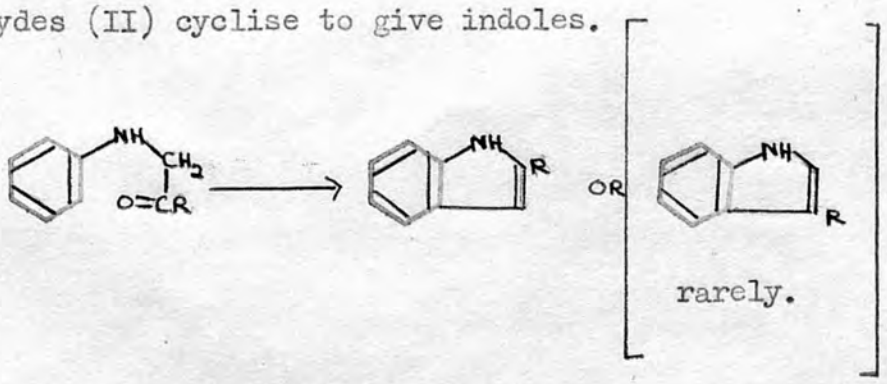
Work by Fries et al[7] has shown, however, that in concentrated sulphuric acid phenacyl-3-hydroxy sulphide could be cyclised to yield 3-phenyl-6-hydroxy thianaphthene in 45% yield.



A better yield has been obtained by using the methyl-ether,



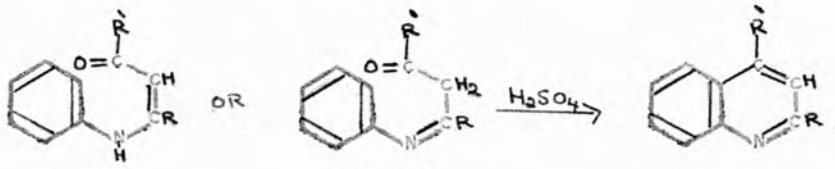
(d)The Indole system, in which α-anilino ketones or aldehydes (II) cyclise to give indoles.



Many instances of cyclisation of compounds of the type (II) to give indoles have been reported. The reactions have been carried out by heating the ketone with an amine, or heating its hydrochloride, or heating it with zinc chloride in the presence of aniline hydrochloride.

(e) The Quinoline series:-

Quinolines may be prepared by the acid-catalysed dehydration of diketone anils of the type (III)



(IIIa) (IIIb)

Hydrolysis of the carbon to nitrogen bond tends to take place under the conditions used for cyclisation, but the ring closure of diketone anils, in particular those of acetylacetone, constitutes one of the two most important and extensive applications of aromatic cyclodehydrations.

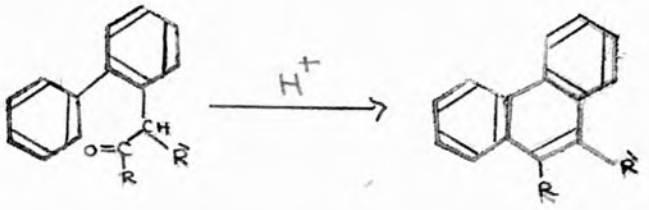
The medium employed for these types of cyclisations is concentrated sulphuric acid.

(f) The Isoquinoline system:-

A limited number of cyclisations to form isoquinolines have been carried out in sulphuric acid media.

In the Tricyclic systems Brādsher listed:-

(a) The Phenanthrene derivatives, where the type of reaction that occurs is:-



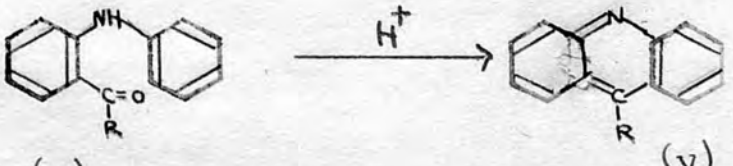
(R=H, alkyl or aryl)

These types of reactions can be carried out in concentrated sulphuric acid, and hydrobromic and acetic acid mixtures.

(b) The Anthracene system, where the general reaction is:-

The reactions have mostly been carried out in mixtures of hydrobromic and acetic acids.

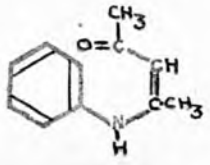
(c) The Acridine system, where compounds of type (IV) undergo cyclisation in acetic acid solutions of concentrated or dilute sulphuric acid to give acridine compounds (V).



(IV) (V)

These reactions are carried out in solutions of sulphuric acid (either concentrated or dilute) in acetic acid.

3. The quinoline Synthesis.

The method of synthesising quinoline compounds by cyclisation of the anils of primary aromatic amines and acetylacetone (or β-diketones) was developed by Combes[8]. He used the fact, previously reported by Beyer, that the condensation product of acetylacetone and aniline will lose a molecule of water to form 2:4-dimethylquinoline. Combes extended this synthesis to form substituted 2:4-dimethylquinolines by using, as starting materials, acetylacetone or substituted acetylacetones and various primary aromatic amines, these he condensed to form anils, e.g. β-anilino-propenylmethyl ketone,  which were then

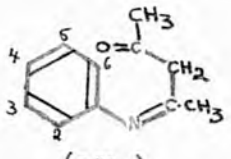
able to lose a molecule of water to form quinolines. Combes heated the anils in concentrated sulphuric acid, poured the mixture into water, and precipitated the quinoline compound with ammonium hydroxide. He was successful in forming cyclic compounds from acetylacetone and aniline, substituted acetylacetones and aniline, and acetylacetone and o-or-p-toluidine.

4. The effect of substituents on the ease of cyclisation.

Roberts and Turner[9] used the Combes synthesis to synthesise many substituted quinoline compounds. They reported that the

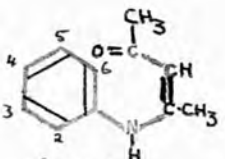
ease of cyclisation of the anils of acetylacetone and primary aromatic amines was considerably affected by the nature of the substituent groups. From their observations of which anils cyclised easily, which did so only with difficulty and which did not cyclise at all, Roberts and Turner were able to draw certain conclusions. They propounded that:-

(a) If a strongly o-p directing group is present in a meta position to the nitrogen atom (3,5 in VI) condensation proceeds readily even if a similar group is present in an 'unfavourable' position as in 2:5,-3:4, and 2:3 dimethoxyquinoline.



(VIa)

OR



(VIb)

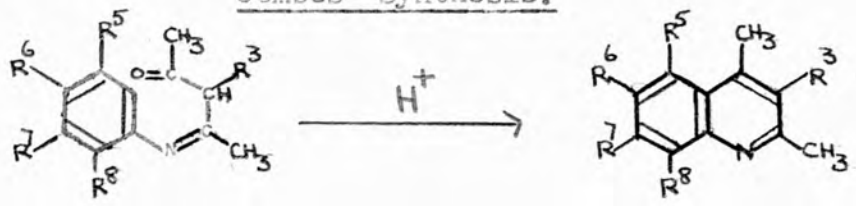
(b) If a strongly o-p directing group is in position 4, in absence of other substituents in 'favourable' positions, formation of a quinoline appears to be prevented. (O, P,-anisidine).

(e) The effect of chlorine is what would be anticipated, i.e. one chlorine atom in a 'favourable' position (meta to the nitrogen atom) is associated with exceptional ease of quinoline formation, a chlorine atom in another position prevents condensation. They found that the presence of a methoxyl group meta to the position at which cyclisation is expected to occur (i.e. o-p- to the nitrogen atom) completely inhibits cyclisation. An inhibition of this type has been observed in other cyclisations (10,11,12,13,14) and is likewise characteristic of aromatic cyclodehydration (15,16,17,18).

The Combes Synthesis has found many applications, as reference to the following table will show.

Table 1.

Combes Synthesis.



Cyclised.

R^3	R^5	R^6	R^7	R^8	References.
H	H	H	H	H	(19) (20) (21)
CH_3	H	H	H	H	(19) (20)
H	H	CH_3	H	H	(19) (20)
H	H	C_2H_5	H	H	(22)
H	H	H	H	CH_3	(19) (20)
H	H	H	H	C_2H_5	(23)
H	H	H	H	n-C_3H_7	(24)
H	CH_3	H	H	CH_3	(25)
CH_3	H	H	H	CH_3	(26)
CH_3	H	H	H	C_3H_7	(27)
CH_3	H	H	H	n-C_3H_7	(28)
H	H	H	—$(CH_2)_4$—		(25)
H	H	H	OCH_3	OCH_3	(29)
H	OCH_3	H	H	OCH_3	(30)
H	H	OCH_3	OCH_3	OCH_3	(30)
H	OCH_3	OCH_3	OCH_3	H	(30)
H	OCH_3	OCH_3	H	Br	(29)
H	H	H	Cl	H	(9)
H	H	Cl	Cl	H	(9)

Failed to cyclise.

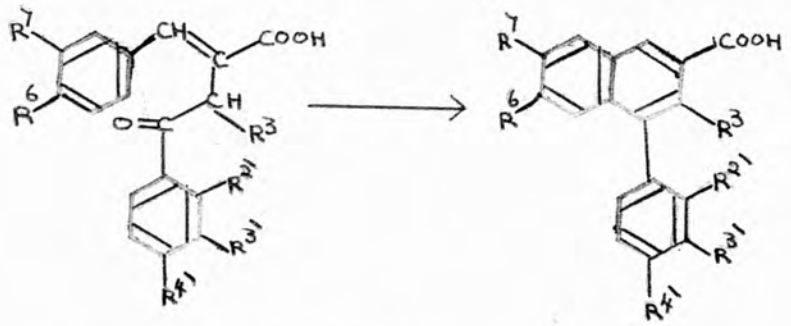
R^3	R^5	R^6	R^7	R^8	References.
H	H	OCH_3	H	H	(17)
H	H	H	H	OCH_3	(9)
H	H	H	H	Cl	(9)
H	H	Cl	H	H	(9)
H	H	Cl	H	Cl	(9)
H	Cl	H	H	Cl	(9)
H	Cl	H	Cl	H	(9)

Roberts and Turner deduced that the failures to obtain a cyclic compound, which they had listed, could not be due to condensation to the extent of a few units per cent of water and the water formed, with the sulphuric acid, hydrolysing the unchanged anil of a weak base, for, if this were so, condensation should have been observed where absolute or slightly fuming sulphuric acid was used.

Similar work on the naphthalene type of cyclisation, using hydrobromic and acetic acid mixtures as media, has been published by Ohmaki[31], in which he reported that ease of cyclisation of compounds of the α-benzal-β-benzoylpropionic acid type was influenced by the nature of the substituents in R^7 (see table 2), but not at all by ($R^{2'}$, $R^{3'}$, $R^{4'}$). He concluded that R^7 must be a hydroxyl, alkoxyl or a terminus of a methylenedioxy group for cyclisation to take place.

Table 2.

Cyclisation experiments with α- benzol-β-benzoylpropionic acid.



Cyclised.

R^3	R^6	R^7	$R^{2'}$	$R^{3'}$	$R^{4'}$	References.
H	OCH_3	OCH_3	H	H	H	(32) (33)
H	- O - CH_2 - O -		H	H	H	(31)
H	OH	OCH_3	H	H	OCH_3	(31)
H	- O - CH_2 - O -		H	H	OCH_3	(31)
H	H	OH	H	H	OCH_3	(31)
H	OH	OCH_3	H	OCH_3	OCH_3	(31)
H	OCH_3	OCH_3	H	OCH_3	OCH_3	(33) (31)
CH_3	OCH_3	OCH_3	H	OCH_3	OCH_3	(34)
H	OC_2H_5	OCH_3	H	OCH_3	OCH_3	(31)
H	- O - CH_2 - O -		H	OCH_3	OCH_3	(31)
H	OH	OCH_3	OCH_3	H	OCH_3	(31)
H	- O - CH_2 - O -		OCH_3	H	OCH_3	(31)

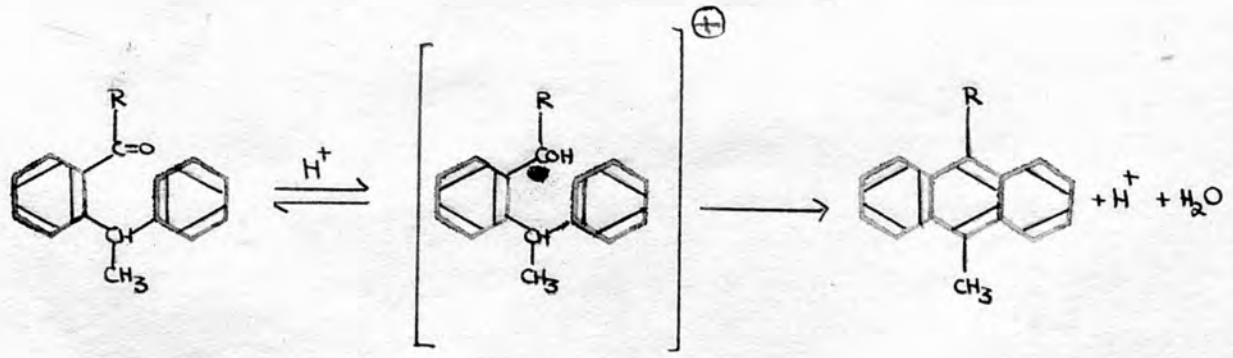
Failed to Cyclise.

(R^3 and $R^{2'}$ = H).

R^6	R^7	$R^{3'}$	$R^{4'}$	References.
H	H	H	H	(31)
H	H	H	CH_3O	(32) (31)
CH_3O	H	H	CH_3O	(31)
H	H	CH_3O	CH_3O	(31)
CH_3O	H	CH_3O	CH_3O	(31)
CH_3O	H	CH_3O	CH_3O	(31)
H	CH_3	CH_3O	CH_3O	(31)

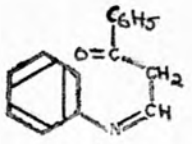
As already stated the ease of formation of benzofuran derivatives is affected by the substituents.

Berliner[35] reported that the rate of cyclisation of 9,10 disubstituted anthracenes in mixtures of boiling acetic and hydrobromic acids was influenced by the nature of the substituent R.



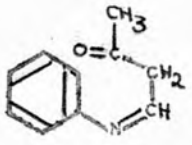
5. Anils which fail to cyclise.

Besides those cases of the failure of certain anils to cyclise, which have already been mentioned, other instances have been reported. Thus Claisen and Fischer[36] reported that the anil of formylacetophenone (VII) gave no quinoline compound with concentrated sulphuric acid.



(VII)

Thielepape[18] has reported that the anil of formylacetone (VIII) and the p-aniside of acetone-oxalic ester (IX) both fail to cyclise.



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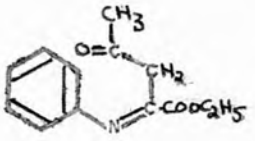
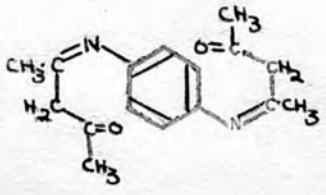


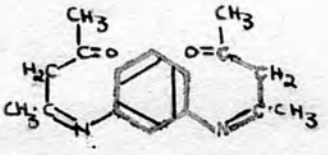
(IX)

Marckwald and Schmidt[37] first studied the reaction of dianils from p- and m- phenylenediamines.



(X)

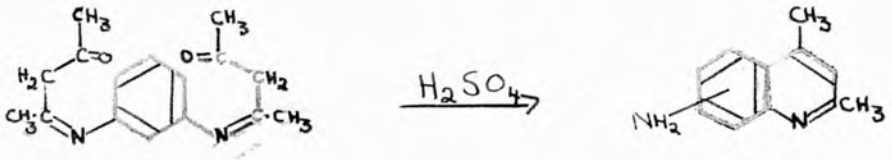
p-



(XI)

m—

The para derivative (X) merely underwent fission, but the meta isomer (XI) gave, by cyclisation and fission, what is believed to be[9] the 7-amino-2:4-dimethylquinoline rather than the 5-isomer.

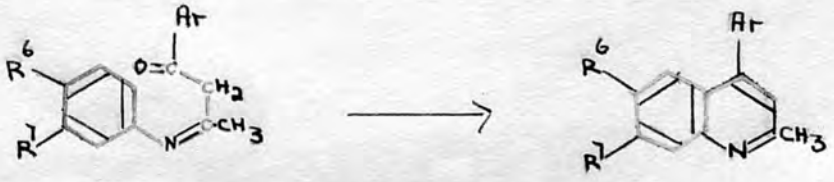


Murray and Turner[38] used the combes synthesis to prepare diquinolinyl ethers.

(R = 2 methyl - 4 - quinolinoxy or 4 - methyl - 2 - quinolinoxy)

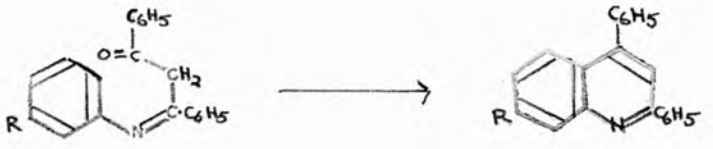
They found that the anils in which R = CH_3, OCH_3 or CH_2H_5 would not cyclise. They did not establish whether the product from those which did cyclise was the 7- or the 5- isomer.

It appears that the anils of benzoylacetone behave in a manner similar to the acetylacetone anils, with regard to those which will undergo cyclisation and those which will not, with the additional feature that a methoxy group para to the nitrogen atom completely inhibits cyclisation.



(R^6 = OCH_3, no cyclisation).

Beyer[39], in his original paper stated that the anil of dibenzoylmethane (R = H in XII) cyclised to 2:4-diphenylquinoline only with great difficulty.

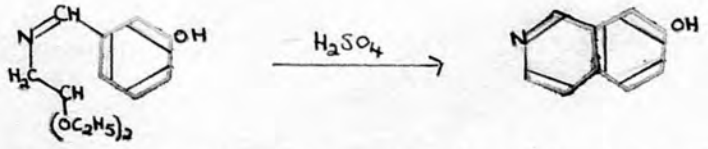


(XII)

So great is the activation produced, however, by the introduction of a methoxyl group para to the point of expected cyclisations, that under these circumstances cyclisation is accomplished in very good yield and under very mild conditions.[40]

6. The effect of strength of media on cyclisation.

While in most cyclisations, which have been studied, the strength of the medium has not been specified, Woodward and Doering[41] reported that, in trying to cyclise the condensation product of m-hydroxybenzaldehyde with aminoacetal to give 7-hydroxyisoquinole in sulphuric acid,



the success of the cyclisation was dependant on the concentration of the acid, 76% sulphuric acid being the strength which gave the best yield.

II Object of Present Research.

A study of the kinetics of cyclisation of β-p-(toluidino)-propenylmethyl ketone to 2:4:6 trimethyl quinoline in concentrated sulphuric acid in order to obtain further information concerning the mechanism of the reaction and the part played by the sulphuric acid in the reaction.

The investigation involved the devising of a method by which the sulphuric acid solutions containing 2:4:6 trimethyl-quinoline and unchanged β-p-(toluidino)-propenylmethyl ketone could be analaysed, and the measurement of the rate constant for the reaction in various percentage concentrations of sulphuric acid.

III Experimental Section.

1. Preparation and storage of materials and media.

(a) Materials.

Acetylacetone.

Before use the liquid was redistilled in a glass apparatus. The first runnings were rejected and the bulk of the distillate collected as a colourless liquid b.p. 139°c.

p-Toluidine.

B.D.H. Analar crystalline p-toluidine was crushed and recrystallised from aqueous alcohol containing 50% water, by volume. The crystals were dried in a vacuum desiccator over P_2O_5 and paraffin wax. It was usually necessary to recrystallise two or three times before pure crystals m.p. 42°c, were obtained.

β-(p-Toluidino) propenylmethyl Ketone.

This anil was prepared by the method described by Roberts and Turner[9].

p-Toluidine and acetylacetone (prepared as above) were taken in the ratio of 1 g. molecule p-toluidine to 1.1g. molecules acetylacetone and boiled gently under reflux for two 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 sodium sulphate and heated to 100°C until all the benzene was removed. The anil then solidified on cooling and was recrystallised twice from petroleum ether (b.p. 40-60°C). The final product melted at 65-66°C.

(b) Media and Solutions.

Sulphuric Acid.

B.D.H. analar sulphuric acid was used, it was approximately 98% W/W.

The acid was standardised and then diluted with the amount of water calculated to give the required % sulphuric acid. If the acid required was stronger than the stock solution the requisite amount of sulphur trioxide was added. The acids were stored in one litre bottes with ground glass stoppers.

N/10 Sulphuric Acid was prepared by diluting Analar concentrated sulphuric acid with water.

1N Sulphuric Acid. B.D.H. 1N sulphuric acid was used.

Hydrochloric Acid. N hydrochloric acid was made up from the concentrated acid by dilution with water.

Sodium Hydroxide. Hopkins and Williams N/10 NaOH was used. 1N and 2N NaOH solutions were made up from Analar, pellet, sodium hydroxide. The 1N solution was always standardised before use. Slight variations in the strength of the other two sodium hydroxide solutions did not matter as they were not used for quantitative estimations.

Ferric Ammonium Sulphate.

Analar $FeNH_4(SO_4)_2.12H_2O$ was used. 5% and 6.5% solutions were prepared by weighing out 50 and 65 g. and dissolving in N/10 H_2SO_4 in 1000 ml flasks and making up to the mark with N/10 H_2SO_4. The solutions were filtered before use.

N/10 Sodium Borate.

9.536g. borax were dissolved in water by warming the mixture in a beaker. The solution was then transferred to a 500 ml. standard flask and made up to the mark with water.

Acetylacetone Solutions.

Solutions containing amounts of acetylacetone of the order of 0.2 - 0.3 g. were prepared. The acetylacetone was weighed out into a 50 ml. standard flask from a dropping tube and dissolved in the required solvent. The solution was then transferred to the standard flask and made up to the mark.

2. Standardisation of Media.

Sulphuric acid was titrated against 1N sodium hydroxide which was standardised against 1N HCl. The hydrochloric acid was diluted to N/10 and standardised against an N/10 solution of sodium borate, methyl red being used as the indicator. The 1N HCl was then used to standardise the 1N NaOH using screened methyl orange as indicator.

The standardised 1N NaOH was used to estimate the % sulphuric acid in the media. About 1g. of the medium was weighed out from a weight pipette and dissolved in about 25 mls. water and titrated against the 1N NaOH using screened methyl orange as indicator. Hence the % sulphuric acid in the medium was calculated. Figures of the % sulphuric acid are given to the nearest 0.1%.

Standardisation of N/10 H_2SO_4

N/10 H_2SO_4 was standardised by titration with N/10 Borax using methyl red as indicator.

3. Calibration of pipettes.

The 5ml. pipette used was calibrated by weighing the amount of water delivered by draining for a given time and, from this, calculating the corresponding volume. In 30 seconds at room temperature the pipette delivered 5.0mls. water.

A grade B 2ml. pipette with the tip cut off to provide for more rapid delivery of the liquid was used for concentrated sulphuric acid. The pipette was calibrated for concentrated sulphuric acid, instead of water, in the same way, as the 5ml. pipette.

The pipette delivered the following weights of 97% sulphuric acid in 30 seconds.

3.49g. 3.49g. 3.49g. 3.48g. 3.49g.

Volume H_2SO_4 delivered = 1.90 mls.

4. Estimation of the anil in the aliquots taken from the kinetic experiments.

In order to carry out kinetic experiments on the conversion of the anil β-(p-toluidino) propenylmethylketone into 2:4:6 trimethylquinoline it was necessary to devise some method by which the percentage of the anil that had undergone cyclisation after any given time could be accurately determined. This could be accomplished by estimating either the amount of quinoline compound present or the amount of anil present in a sample of the reaction mixture at

any given time.

The former method was considered preferable as this would lead to measuring directly the rate of formation of the quinoline compound rather than the rate of disappearance of the anil.

Roberts and Turner[9] had remarked that, when β- (p-toluidino) propenylmethyl ketone is heated in concentrated sulphuric acid to produce 2:4:6 trimethylquinoline, and the reaction mixture poured into water and potassium dichromate solution added, the quinoline compound is precipitated as its dichromate salt. An attempt was made, therefore, to estimate the quinoline compound by precipitating it as the dichromate and weighing the precipitate. The results obtained were unsatisfactory and gave no quantitative estimation of the quinoline compound. A further method of dissolving the precipitate in acid and estimating the amount of dichromate released by titration with ferrousammonium sulphate also proved unsatisfactory.

Other methods of estimating quinoline compounds were not suitable owing to the presence of anil in the samples. As it did not, therefore, seem possible to estimate accurately the amount of quinoline compound present in the samples under the required conditions, it was decided to try to estimate the amount of anil present in the aliquots taken from the reaction mixture and hence find the amount of quinoline that had been formed.

In dilute acid solutions the anil is hydrolysed to

p-toluidine and acetylacetone. It was decided that, if the amount of p-toluidine present, after a sample from the kinetic reaction had been run into water, could be estimated, then the amount of anil present before hydrolysis could be calculated.

It was found that diazotisation of p-toluidine and coupling with β-naphthol gave an orange colour, which varied in intensity with varying concentrations of p-toluidine, and the optical density of the solution could be compared with that of a blank solution using a photoelectric absorptiometer. Further investigation showed that at concentrations of p-toluidine above 0.8 milligrams per 150 cc of solution, a slight red precipitate was formed. This precipitate dissolved in acetic acid and aqueous alcohol solutions. With acetic acid, however, an intense red colour was formed. When alcohol was used to dissolve the precipitate no apparent interference with the formation of the colour took place.

Since the solutions to be analysed for p-toluidine would also contain acetylacetone, the diazotisation and coupling with β-naphthol was carried out in the presence of equi-molecular quantities of p-toluidine and acetylacetone. The colour intensity differed from that of the solution containing no acetylacetone, probably because the diazo compound reacted with the acetylacetone present. This method of estimating the p-toluidine therefore seemed impracticable under the conditions of the experiments.

Other coupling reagents such as α-naphthylamine were tried and proved unsatisfactory.

It was therefore decided to try to estimate the quantity of acetylacetone present in each sample from the kinetic experiments and hence the amount of anil present at the time of withdrawal of the aliquot.

In 1904 Pulsifer[42] published a paper putting forward a new method of estimating ferric iron. He stated that in acetylacetone $CH_3COCH_2COCH_3$ one of the hydrogen atoms attached to the central carbon atom is easily replaced by a metal and he used this reaction to estimate small quantities of ferric iron in solutions, since the salt formed with acetylacetone has a red colour, which can be determined colourimetrically. This method of estimating ferric iron was adapted for the estimation of acetylacetone.

With a solution of ferric ammonium sulphate in N/10 H_2SO_4, acetylacetone solutions give red colours, which became more intense as the concentration of acetylacetone is increased. With ferric chloride a red colour was obtained but the optical density of the solution did not vary quantitatively with the concentration of acetylacetone.

A series of solutions containing concentrations of acetylacetone ranging from 0.00106g. to 0.00742g. in 19 mls. N/10 H_2SO_4 were prepared by taking x mls (x=1,2,3.....) of a standard solution of acetylacetone (containing 0.2637g. in 250 mls. N/10 H_2SO_4) and adding (19-x) mls. N/10 H_2SO_4. To each solution was added 1 ml. of a 5% solution of ferric ammonium sulphate in N/10 H_2SO_4 and, after allowing the solutions to stand for fifteen minutes

so that development of the colour was complete, the optical density of each was compared with that of a blank containing 19 mls. N/10 H_2SO_4 and 1 ml. ferric solution, using a "Spekker" photoelectric obsorptiometer with a sodium filament lamp and a blue-green filter (No: 603).

The absorption spectrum of the ferric-acetylacetonate solution had been previously plotted using a "Uvispek", ultra-violet photoelectric obsorptiometer (Graphl.). The curve shows maximum absorption between the wave-lengths 4700 and 5000A° and hence the blue-green filter was used for the measurements with the "Spekker".

The results of the measurements made with the series of standard solutions are as follows:-

Solution	I	II	III	IV	V	VI	VII
Volume acetylacetone solution in mls.	1	2	3	4	5	6	7
Volume N/10 H_2SO_4 in mls.	18	17	16	15	14	13	12
Volume Fe^{+++} solution in mls.	1	1	1	1	1	1	1
"Spekker" reading.	0.081	0.168	0.251	0.318	0.390	0.466	0.531.

The instrument records directly the value of the logarithm of the quotient of the optical densities of the two solutions (Io/I) and thus the graph of log (Io/I) against concentration of acetylacetone in the solutions was plotted and was found to be a straight line, showing that the solutions obeyed Beer's law over the range of concentrations chosen.

Variation of log (Io/I) with variation of the amounts of ferric solution taken was shown by plotting the value of log (Io/I) for a series of solutions containing 5 mls. acetylacetone solution, (15-x) mls. N/10 H_2SO_4 and x mls. ferric solution (x=1, 2,3.....9). The graph has least slope over the range x=6 to x=7 mls. and therefore it was decided to use 6.5 mls. of 5% ferric solution or 5 mls of 6.5% ferric solution in all future colourimetric estimations.

The graph obtained by plotting $\log(Io/I)$ against the normality of the acid solution for a series of solutions containing 5 mls. acetylacetone solution, 6.5 mls. 5% ferric solution, (8.5-x) mls. N/10 H_2SO_4 and x mls. N H_2SO_4 or H_2O (x=1,2...) showed that for a small change in normality (with respect to the sulphuric acid) the optical density of the ferric-acetylacetone solutions changed quite appreciably. Over the range of normalities 0.001-0.325, $\log(Io/I)$ varied from 0.832 to 0.424. It was therefore necessary to ensure that the pH of the solutions was always constant, i:e: 1. This was in accordance with Pulsifer's results; he stated that in slightly acid solution the addition of even one drop of concentrated acid to the ferric-acetylacetonate reduced the intensity of the colour.

As the pH of the final solutions to be estimated in the kinetic experiments had always to be 1, the aliquots had to be neutralised with caustic soda and therefore contained considerable quantities of dissolved sodium sulphate (between 0.52 and 1.56 g.), and it was necessary to ascertain the effect, if any, of the dissolved salt on the optical density of the coloured solutions. Pulsifer

had stated that quantities of inorganic salts to the amount of 0.2g. in 50 cc which furnished certain ions, among them Na^+ and SO_4^{--} had no effect, but he had not made any statements regarding larger concentrations of dissolved salts. Accordingly a solution of 6.5g. Na_2SO_4 in 500 mls N/10 H_2SO_4 was prepared, the following series of solutions made up and the optical densities compared with that of a blank containing N/10 H_2SO_4 instead of acetylacetone solution.

Solutions used:-

1. Acetylacetone solution in N/10 H_2SO_4 containing 0.1g/250 mls solution.
2. 6.5% $FeNH_4(SO_4)_2.12H_2O$ in N/10 H_2SO_4.
3. Na_2SO_4 solution in N/10 H_2SO_4 containing 6.5g. Na_2SO_4/500 mls. solution.

1st. Series:-

Volume acetylacetone solution in mls.	Volume N/10 H_2SO_4 in mls.	Volume Fe solution in mls.	log (Io/I.
6	9	5	.727
5.5	9.5	5	.677
5	10	5	.630
4.5	10.5	5	.570
4	11	5	.503
3.5	11.5	5	.441
3	12	5	.376
2.5	12.5	5	.316

2nd. Series:-

Vol. acetylacetone solution in mls.	Vol. N/10 H_2SO_4 in mls.	Vol. Fe^{+++} solution in mls.	Vol. Na_2SO_4 solution in mls.	log (Io/I)
5.5	5.5	5	4	.658
5	6	5	4	.593
4.5	6.5	5	4	.542
4	7	5	4	.481
3.5	7.5	5	4	.420
3	8	5	4	.366
2.5	8.5	5	4	.308
3rd. Series:-				
5	2	5	8	.593
4	3	5	8	.481
3	4	5	8	.366

These results indicated that some dissolved salt had an effect on the colour, but that the effect did not vary with the amount of dissolved salt present. This was further established by preparing another series of solutions containing acetylacetone, the ferric solution and sodium sulphate solution For these solutions a solution of acetylacetone in N/10 H_2SO_4 containing 0.204gms. in 500 mls. was used, and 5 mls. 6.5% ferric solution in each case.

4th. Series:-

Vol. acetylacetone solution in mls.	Vol. N/10 H_2SO_4 in mls.	Vol. Na_2SO_4 in mls.	log (Io/I)	log (Io/I) after 1 hour.
6	9	-	.768	
5.5	9.5	-	.719	.719
5	10	-	.650	
4.5	10.5	-	.584	.584
4	11	-	.524	
3.5	11.5	-	.461	.460
3	12	-	.395	
2.5	12.5	-	.325	
5th. Series:-				
6	1	8	.748	
5.5	1.5	8	.689	.689
5	2	8	.632	
4.5	2.5	8	.574	.573
4	3	8	.511	
3.5	3.5	8	.452	.452
3	4	8	.388	
2.5	4.5	8	.327	
6th. Series:-				
5	7	3	.632	
4	8	3	.510	
3	9	3	.388	

The final standard graph was prepared from these results. (Graph 2).

Before this method could be used in the kinetic experiments it was necessary to ascertain two facts:-

(1) Whether the anil was completely hydrolysed to acetylacetone and p-toluidine in dilute acid solutions and,

(2) If the other products of the reaction interferred with the formation of the colour.

(1) Known quantities of anil were dissolved in 1N or 2N H_2SO_4 and allowed to stand. The solutions were then exactly neutralised with caustic soda, B.D.H. Universal indicator being used, and sufficient 1N H_2SO_4 added to make the acid strength N/10. The amount of acetylacetone present in a sample of these solutions was estimated colourimetrically, by preparing the ferric acetylacetone complex, as described above, measuring its optical density and thus calculating the amount of acetylacetone present from comparison with a standard curve.

Quantity anil taken.	How hydrolysed.	log(Io/I.)	% hydrolysis.
1. 0.379 g.	In 100 mls 1N H_2SO_4 for 2 hours. Neutralised with NaOH, 50 mls. H_2SO_4 added and made up to 500 mls with H_2O.	5mls. final solution added to 5 mls. 6.5 Fe^{+++} solution, 10 mls. N/10 H_2SO_4. Reading= .610.	Corresponds to . .00979g/100 mls. Theoretical value = .00997g./100 mls. 98.3%
2. 0.1001g.	ditto.	15 mls. final solution added to 5 mls Fe^{+++} solution, Reading=.490	Corresponds to .00785g./100 mls. Theoretical value = .00782g./100. 98.8%
3. 0.1901 g.	ditto.	10 mls final solution added to 5mls. Fe^{+++} solution & 5 mls. N/10 H_2SO_4. Reading = .619.	Corresponds to .0189g./100 mls. Theoretical value = .01901g./100 99.4%

These results indicated, within experimental error that complete hydrolysis of the anil does take place.

(2) Small quantities of p-toluidine and 2:4:6 trimethylquinoline were added to solutions containing known concentrations of acetylacetone and the ferric solution and the optical density compared with those containing the same concentration of acetylacetone and ferric solution but without any of the other two compounds. p-Toluidine and 2:4:6 trimethylquinoline have no effect on the red ferric-acetylacetone colour.

In order to ascertain whether this method for estimating quantitatively the acetylacetone present in the samples gave sufficiently accurate results to warrant its use, known quantities of a standard solution of acetylacetone were taken and the acetylacetone estimated practically by the method described above. In three different cases the practical result was in agreement with the theoretical calculation to within 98.5%-99.0%.

The solution of acetylacetone used was 1g./500 mls.H_2O. 50 mls. this solution were taken and 50 mls. 2N H_2SO_4 added.

Time left in contact with acid.	Method used to give N/10 solution.	log(Io/I.)	% result.
1. 2 hours.	To 100 mls.in 250mls. flask 65 mls.2NNaOH added. 25 mls. this solution neutralised with 1.4 mls.2NNaOH, 5 mls 1N H_2SO_4 added and made up to 50mls.	10 ml.aliquot taken, 5 mls. Fe^{+++}solution, 5ml.N/10 H_2SO_4 added. Reading=.611.	Corresponds to 0.00198gms/20 mls. Theor: value .002g/20 99.0% accuracy.

Time left in contact with acid.	Method used to give N/10 solution.	log (Io/I.)	% result.
2.Neutralised immediately.	To 100 mls. in 250 flask added. 64mls 2NNaOH. Neutralised 25 mls with 1.1 mls N/10 H_2SO_4 5mls. NH_2SO_4 added and made up to 50 mls.	10 ml. aliquot treated as No.1 Reading=.607.	Corresponds to .00197gr/20 mls. Theor: value .0020g./20 98.5% accuracy.
3.Overnight.	As for example 2.	10 ml. aliquot treated as before. Reading=.610.	Corresponds to .00197 g/20 mls. Theor: value .0220 g/20 mls. 98.6% accuracy.

The optical density of the solutions did not vary over a period of at least two hours, but if left standing overnight the intensity of the colour decreased somewhat.

The value of the optical density did not vary with the order in which the components of the final solutions were added but, in order to ensure complete consistency, the acetylacetone solutions were always added to the solutions containing the ferric ammonium sulphate, sulphuric acid etc.

5. Recovery of 2:4:6-trimethylquinoline.

As it was proposed to study the kinetics of the conversion of anil in the quinoline compound by measuring the rate of disappearance of the anil, it was necessary to make certain that the product of the reaction, throughout its whole course, was the 2:4:6-trimethyl-quinoline. To do this 1g. β-(p-toluidino)-propenylmethylketone was dissolved in 10ml. 90% sulphuric acid and left for 6 hours.

The solution was then poured into 100 ml. of water. After 2 hours it was cooled in ice and an ice-cold solution of 0.05g. sodium nitrite in about 5 ml. of water added to convert any p-toluidine resulting from hydrolysis of unchanged anil in the diazonium salt. The solution was warmed to convert the diazonium salt to p-cresol. After cooling 15g. sodium hydroxide were added to make the solution alkaline and ~~the~~ to precipitate the 2:4:6-trimethylquinoline. After cooling the solution was extracted three times with ether. The ether extracts were combined, washed with water and dried over anhydrous sodium sulphate. The solution was filtered and the ether distilled. The yield of crude product was 84.6% the theoretical yield. M.pt. 39.5-41.5°c. (m.p. pure 2:4:6-trimethylquinoline 43-45°c)

This product was analysed and a specimen recrystalised from petroleum ether (40-60°c).

Analysis - crude product found C, 81.3%; H,7.78%; N, 8.33%.

recrystallised " " C, 84.4%; H,7.77%; N, 8.51%.

calculated, C, 84.2%; H,7.65%; N, 8.18%.

6. Experimental method for obtaining the kinetic data.

The cyclisation was carried out at 25°c in a thermostat controlled to 0.02°c, the temperature being read with an N.P.L. calibrated thermometer.

The reaction vessel was a 100 ml. round bottomed flask having a well-fitting B.24 stopper. The anil was weighed out into a B.24 cap.

A weighed 50 ml. standard flask was used to measure out the medium. The flask was filled to within about 1cc of the mark,

allowed to stand in the thermostat until the sulphuric acid was at 25°c and was then made up to the mark with more H_2SO_4 which had also been warmed in the thermostat.

The H_2SO_4 was then poured into the reaction vessel which had been standing in the thermostat and the flask allowed to drain for about 30 seconds and then reweighed. Thus the weight, and hence the volume, of H_2SO_4 remaining in the 50 ml. flask could be calculated.

To start the reaction the stop-clock was started, the reaction flask removed from the thermostat and unstoppered, and after one minute (zero time) the cap containing the anil was placed in the flask, the flask inverted and shaken vigourously until all the anil had dissolved (1 to 2 minutes). There was no appreciable change in temperature during this time. The flask was replaced in the thermostat, the cap removed and the air in the flask drawn off by means of a cone attached to the flask and the pump. This was done to remove, as quickly as possible, the bubbles of air present in the liquid after shaking.

When the liquid was clear the cone was removed and the stopper replaced until sampling was necessary.

Eight aliquots were removed from the reaction mixture in the course of a run. Before starting the experiment eight 100 ml. conical flasks, each fitted with a rubber bung, and containing about 20 mls. water, were prepared. They were cooled in a trough of ice. The samples were removed by means of a 2 ml. pipette, having a wide delivery hole, which was allowed to drain for 30 seconds. The reaction mixture was drawn into the pipette by means of a long piece

of rubber tubing. The aliquot was then run into the cooled water in the 100 ml. conical flask, the start of the delivery being used as the required time. The conical flask was well shaken and returned to ice until thoroughly cool again. Between samplings the pipette was allowed to drain and before each sampling it was carefully wiped.

The samples were allowed to stand for two hours to ensure complete hydrolysis of the anil and the amount of acetylacetone in each sample determined colourimetrically as described previously, hence the quantity of unchanged anil in the aliquot was found. In order to carry out the colourimetric estimation of acetylacetone the solutions were treated as follows.

Pellet caustic soda (about 2.5 gm) was added to the solutions keeping them cool, until they were nearly neutral and then they were made just alkaline by adding, drop by drop, 2N NaOH from a burette, using B.D.H. Universal indicator paper. (at the neutral point a white precipitate of the quinoline compound begins to appear). The solutions were made just acid again with 1N H_2SO_4 and then brought to the neutral point with N/10 NaOH. 5 mls. of 1N H_2SO_4 were added from a burette so that the final solutions would be N/10 w.r.t. H_2SO_4 and the solutions were filtered through a small fluted filter paper into a 50 ml. standard flask, the filter-paper and the conical flask being thoroughly washed with water, the washings being poured into the 50 ml. standard flask. The solution was made up to the mark with water and was ready for

estimation. 5,10,15 mls of these solutions were taken depending on the amount of acetylacetone present and were run into 5 mls. of 6.5% $FeNH_4(SO_4)_2.12H_2O$ in N/10 H_2SO_4 solution and 10,5,0 mls. N/10 H_2SO_4.

The optical density of each was compared with a blank as described above.

The concentration of acetylacetone in each sample was read off from the standard graph, hence the amount of anil in each aliquot could be calculated.

The reaction was followed over 75%-85% of the reaction.

7. Calculation of Results.

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

$kt = 2.303 (\log (a-x) - \log a)$. Where a is the initial concentration of the anil, x the amount of quinoline compound at time t.

All concentrations were expressed in moles litres of solution; k was expressed in $min.^{-1}$ k was obtained graphically by plotting $\log V_A$ against time t (where V_A = equivalent volume of standard acetylacetone solution and $\log V_A$ differs from $\log (a - x)$ by a constant amount ($\bar{3}.3325$), and the slope of the resultant straight line found.

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

Typical duplicate results were:-

Expt. No. 11 and 12. Cyclisation of the anil in 91.1% H_2SO_4 at 25°C.

k = .0212

.0212

Expt. No. 24 and 25. Cyclisation of the anil in 87.6% H_2SO_4 at 25°C.

k = .00742

.00741.

(See Graphs 3 (a) (b) (c) (d).).

8. Kinetic Results:-

All experiments were carried out at 25°c. The initial concentration of the anil in sulphuric acid was 0.1002- 0.1005m.

Expt. No.	% H_2SO_4	Initial concentration of anil.	k .
8	93.1	0.1005 M	0.428
11	91.1	0.1003 M	0.0212
14	89.2	0.1005 M	0.0123
31	89.0	0.1004 M	0.0106
25	87.6	0.1003 M	0.00742
18	86.3	0.1005 M	0.00445
28	85.5	0.1003 M	0.00330
21	84.5	0.1005 M	0.00239

(See Graph 3(e)).

IV Discussion of Results.

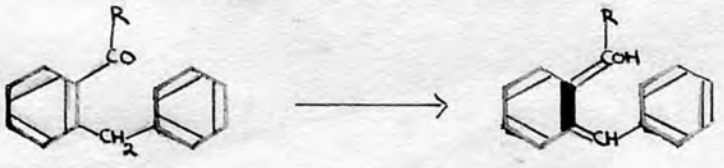
1. Mechanism of cyclisation reactions:-

In investigating the rate of cyclisation of β-p-(toluidino)-propenylmethyl ketone to 2:4:6-trimethylquinoline, it was anticipated that the reaction mechanism would have certain features in common with other acid-catalysed cyclisations, and these are considered first.

A mechanism of cyclisation reactions proposed by Berliner[43] is based on the behaviour of carbonyl compounds in strongly acidic media and upon the concept of cyclodehydration as essentially an internal aromatic substitution. For example he considered the cyclisation of o-benzylphenyl ketones to 9-alkyl or 9-aryl substituted anthracenes or substituted 1:2-benzyl anthracenes by refluxing with 34% hydrobromic acid and acetic acid, a reaction which had previously been recorded by Bradsher[44].

(I) (II)

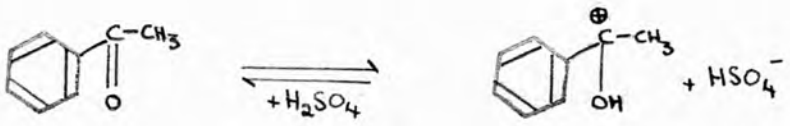
Prior to Berliner's paper, Bergmann had suggested that, as a first step in such hydrocarbon synthesis, enolisation was essential,



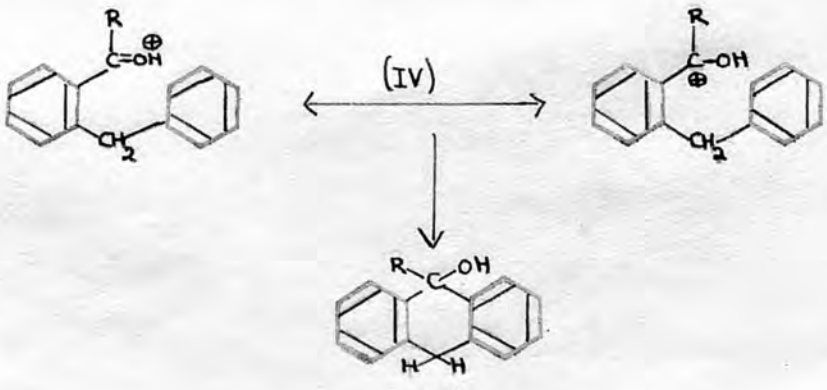
(III)

but Berliner believed that the neutral enol III, even if it were formed by acid-catalysed enolisation, would not undergo cyclisation, and that ionic fragments play an important part as reaction intermediates even in cases where the initial and final products are non-ionic in character. He therefore proposed a mechanism based on the addition of a proton to the carbonyl oxygen followed by an electrophilic substitution reaction.

Previous work of Hantzch and Hammett[45] had shown that in sulphuric acid carbonyl compounds form salts as in the case of acetophenone.

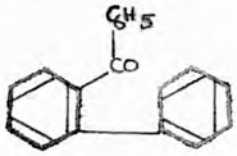


A proton is transferred from the acid to the carbonyl group and the conjugate acid of the ketone is positively charged. Berliner therefore suggested that the first step in the cyclisation may be the formation of the conjugate acid (IV), which is the hybrid of the two resonant forms $>C=\overset{\oplus}{O}H_2$ $>\overset{\oplus}{C}-OH$. Ring closure being an electrophilic attack by the carbon atom on the opposite ortho position, forming a compound which readily suffers dehydration.

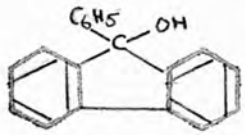


(V)

This mechanism does not require enolisation and no active hydrogen is necessary; in fact a similar cyclisation can be accomplished with a compound which has no hydrogen atom available for enolisation. (Schelnk and Bergmann)[46].

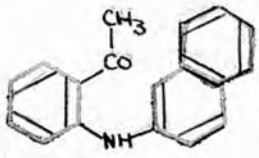


2-phenylbenzophenone

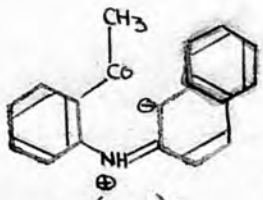


9-phenylfluorenol.

Berliner noted that cyclisation proceeds with greater ease in the acridine series; e.g. if the secondary amine o-acetylphenyl - 2 - naphlhylamine (VI) is dissolved in glacial acetic acid and a few drops of concentrated sulphuric acid are added, the reaction is completed after a short heating, whereas much longer periods are needed in the case of hydrocarbons.



(VI)



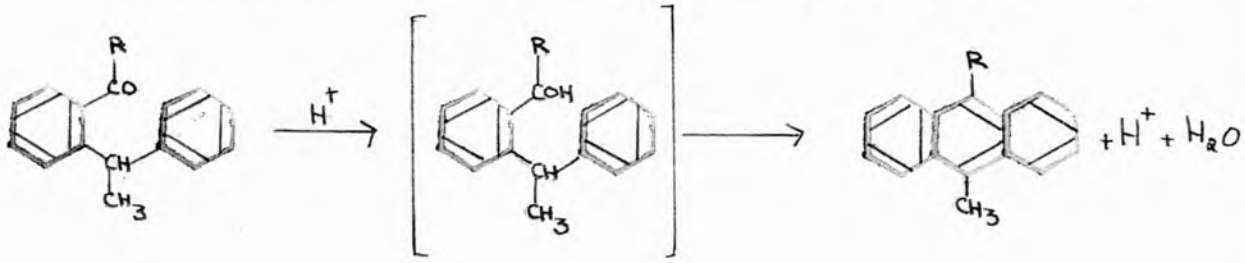
(VII)

The amine group is much more strongly ortho-para-directing than the methylene group and an equivalent structure (VII) can be written with a true negative charge in the ortho position. The secondary amino group in this medium is apparently not basic enough to form the meta-directing ammonium ion. If, however, only sulphuric acid

is used, heating to a higher temperature and for longer periods becomes necessary.

Bradsher[47,6] has also proposed a mechanism similar to that of Berliner.

Berliner[35] later measured the rates of cyclisation of some ortho-acyl substituted 1:1 di-phenylethanes to alkyl anthracenes.



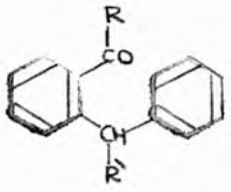
The reaction was carried out at 133-134°C in a mixture of boiling acetic and hydrobromic acids and was followed by precipitation and weighing of the product at fixed time intervals. The reaction was first order with respect to the cyclising compounds and the effect of the group R on the rate was as shown below.

R.	Methyl	Ethyl	n-Propyl	n-Butyl	n-Pentyl	n-Hexyl	Phenyl	Benzyl.
$K(min)^{-1}$	4.6	1.8	0.99	0.35	0.36	0.36	0.16	0.91.

The influence of the groups was interpreted in terms of the inductive effect of the alkyl groups stabilising the carbonium ion, the effect decreasing to a limiting value with increasing length of carbonium chain. The possibility of steric effects was not ruled out.

Bradsher and Vingiello[48] later measured the rates of

cyclisation of similar types of compounds VIII.



VIII

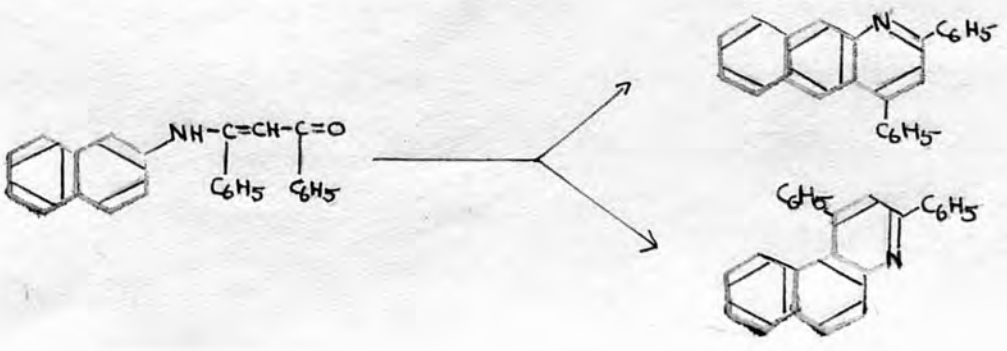
They carried out the reaction in glass-stoppered tubes in a thermostat at 117.5°C and corrected the weight of product isolated to allow for solubility in the cyclising medium. The following results were obtained.

R	H	CH_3	C_2H_4	$C_6H_5CH_2$	p-$CH_3C_6H_4$	p-BrC_6H_4	p-ClC_6H_4	p-FC_6H_4
R	H	H	H	H	H	H	H	H
$K(hr)^{-1}$ $\times 10^{-2}$	540	70	30	23	4.2	4.2	4.1	2.8

R	C_6H_5	C_6H_5	C_6H_5
R	H	CH_3	C_6H_5
K	4.4	13	13

They deduced that steric factors as well as electronic factors may play an important part in determining the rate of cyclisation.

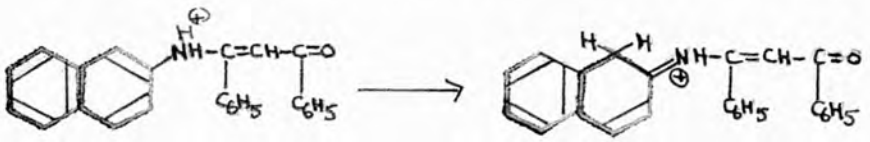
An interesting case of cyclisation to form a heterocyclic ring was considered by Huisgen[49]. He found that the anil of dibenzoylmethane and β-naphthylamine in cold concentrated sulphuric acid gives the linear-type condensation product IX in tenfold excess over the angular-type product X.



(IX)

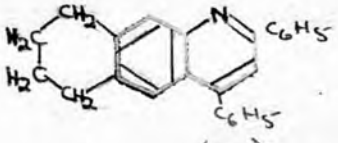
(X)

This result is surprising in view of the known higher reactivity of the (1) position in the naphthalene ring and, to account for it, Huisgen postulated that blocking of position (1) occurred as a result of salt formation in concentrated acid solution XI.



(XI)

Angular ring closure is obviously not possible in the structure XI. Confirmation of this view is provided by the fact that using a hydrogen-free condensing agent, zinc chloride, and heating to 200°C a 60% yield of the angular diphenylbenzylquinoline is obtained, without detectable quantities of the linear isomer. Huisgen further observed that in simple benzene derivatives the salt structure XI is not possible so that, as might be expected, the anil of β-aminotetralin and dibenzoylmethane is cyclised to the same tetramethylene diphenylquinoline XII with either zinc chloride or concentrated sulphuric acid.



(XII)

The linear condensation product is in agreement with the usually preferred p-substitution as against o-substitution (Waters) 50.

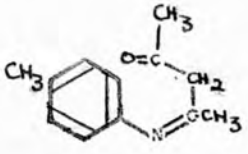
As in the kinetic studies, carried out by Berliner, and Bradsher and Vingiello, the rate of cyclisation of β-p-(toluidino)-

propenylmethyl ketone to 2:4:6-trimethylquinoline is found to be first order with respect to the cyclising compound. The reaction proceeds at a measurable rate at 25°C and the plots of log (a-x) against t for different media at that temperature are reasonable straight lines as shown in graph 3. The rate constant increases with increasing acidity as shown in graph 4 and no medium with a maximum rate was found, the rate being immeasurably fast at all higher acidities up to and including absolute sulphuric acid.

Before considering in greater detail the mechanism of this cyclisation reaction it is necessary to discuss the tautomeric structures which can be used to represent the anil and to decide in what form it undergoes reaction.

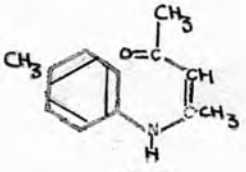
2. Tautomerism of Anils.

Anils of primary aromatic amines and acetylacetone are usually represented in two tautomeric forms.



XIII

Ketimine form.

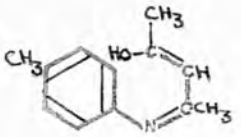


XIV

Enimine form.

in which the ketimine form represents conjugation of the side chain double bond with the aromatic ring, while the enimine form represents a conjugation between C = C and C = O confined to the side chain.

An extension of the conjugation of XIII is possible by enolisation of the keto group (see XV).



(XV)

but on the other hand conjugation of the unshared electrons of the N atom with the ring is presumably less likely than in the enimine form.

The study of this type of tautomerism to decide between the alternative structures where possible, has been extensively undertaken by V. Auwers and coworkers. Their investigations have included the measurement of the molecular refractivity and dispersivity of many schiffs bases including XIII above [51,52]. The observation of molecular exaltation in individual compounds was taken to indicate the existence of the compound in that tautomeric form in which conjugation between a C = C double bond and a C = O group occurred.

The molecular refractivity of β-anilinopropenylmethylketone was measured by V. Auwers and Suzemihl (loc:cit:) using both the pure compound and its solution in methylnaphthalene. Using the calculated value for the molecular refractivity for the enimine form $C_6H_5NH.C(CH_3)=CH.COOEH_3$, the exaltation values were 3.5 for the pure compound and 3.35 in solution. They concluded that this must be the structure of the compound since there is here conjugation between the C = C bond and the C = O group and in addition between the N atom and the benzene ring. However in this case the evidence is not conclusive

since if the calculated values of the molecular refractivity for the two tautomeric structures XIV and XV are compared, the difference between them is only 0.135 compared with the exaltation of 3.5 for the pure compound. i.e. bothstructures satisfy the high exaltation found. The calculated values for the two structures differ only in the contribution of the N and O atoms which are differently bound in each case.

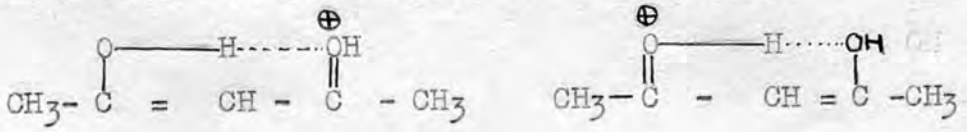
These are indicated below:-

			M
XIV	$C_6H_5 - NH - \underset{\underset{CH_3}{\vert}}{C} = CH - \underset{\underset{CH_3}{\vert}}{C} = O$.	Secondary N	2.499
		= O	2.211
			4.710
XV	$C_6H_5 - N = \underset{\underset{CH_3}{\vert}}{C} - CH = \underset{\underset{CH_3}{\vert}}{C} - OH$	- N =	3.05*
		- O -	1.525
			4.575

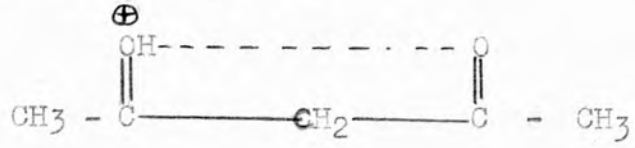
*V. Auwers and Suzemihl Ber 1930. 63 B p.1076. other values are taken from Gilman's "Organic Chemistry" John Wiley and Sons 2nd. 1943 Vol II p.1751.

3. The Nature of the anil in sulphuric acid solutions.

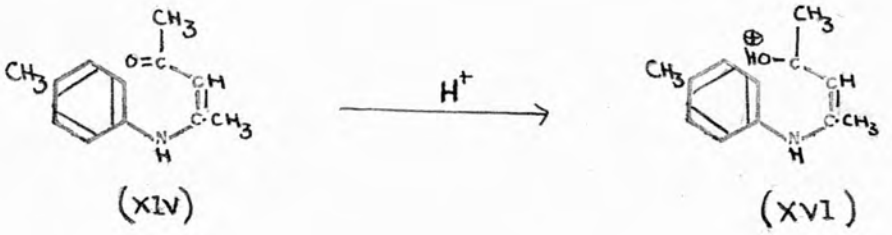
In considering the mechanism of the cyclisation of the β-(p-toluidino)propenylmethyl ketone to 2:4:6 - trimethylquinoline in concentrated sulphuric acid, it can be assumed that reaction occurs in a cationic species. Of some relevance in this connection is the observation made by Schwarzenbach and Witter[53] that acetylacetone has an enol content of about 75% in concentrated sulphuric acid, although it is only about 15.5% enolised in water. This is attributed to the resonance stabilisation of the enolic cation[54] as shown



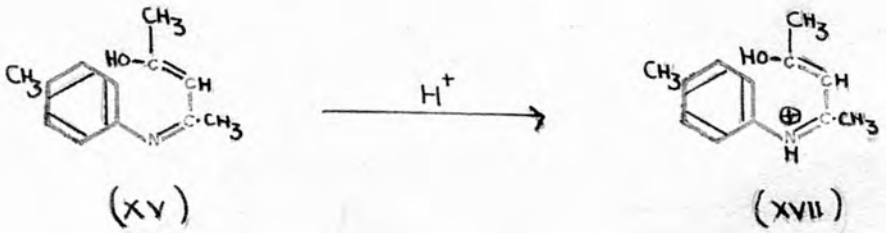
The ketonic cation cannot be stabilised in this way, only the structure shown being possible.



considering the anil in concentrated sulphuric acid and assuming first that there is only a single proton uptake, either tautomeric form XIV or XV can give structures analogous to the enolic cation of acetylacetone.



(XIV) (XVI)



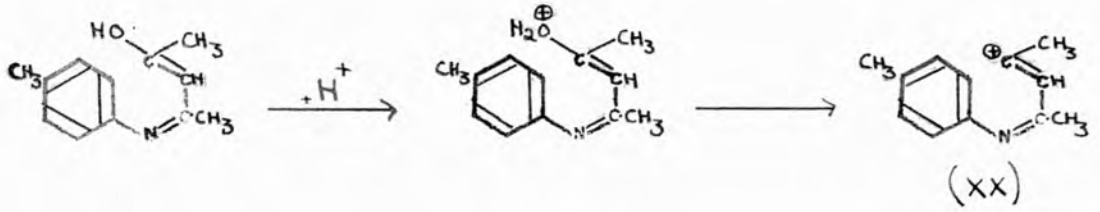
(XV) (XVII)

XVI and XVII are resonance structures which can be written for the cation, two other contributing structures are XVIII and XIX.

(XVIII) (XIX)

Location of the proton on the N atom of structure XIV would not permit such charge spreading as in XVI.

The cyclisation reaction can thus be assumed to proceed through the cationic form represented by structures XVI to XIX. An alternative, but remote possibility, however is that the anil ionises in sulphuric acid by the following steps.



(XX)

An experimental test can decide between these alternatives based upon whether the rate constant k_1 is related to Hammett's acidity function H_o[54(a)] or to the J_o function defined by Gold and Hawes[55]. The correlation of k_1 with H_o depends on the cyclisation proceeding through the cation represented by the structures XVI to XIX and with J_o on the cation represented by XX.

Let $[A]_T$ = total anil concentration

$[AH^+]$ = concentration of cation represented by structures XVI to XIX.

$[A^+]$ = concentration of cation represented by structure XX

$[A]$ = concentration of unionised anil.

k_1 = experimental velocity coefficient for a given medium.

k = theoretical velocity coefficient, assumed constant over the range of media considered.

4. Relation between k_1 and H_o

Experimentally in any given medium the reaction is first order with respect to the anil.

$$\text{Experimental rate} = k_1 [A]_T$$

If the reaction proceeds through the cation represented by structures XVI to XIX.

$$\text{Theoretical rate} = k . [\overset{+}{A}H]$$

Equating these rates:-

$$\frac{k}{k_1} = \frac{[A]_T}{[AH^+]} = 1 + \frac{[A]}{[AH^+]} \qquad (1)$$

assuming that the anil can be treated as a Hammett - type base (i.e. if B represents the base, it takes up a simple proton to form BH^+ without further change).

$$H_o = pK_a + \log \frac{[A]}{[AH^+]}$$

where pK_a is the negative logarithm of the dissociation constant of the acid AH^+ ad defined by Hammett (loc: cit:).

$$\text{Let } H_o = -\log h_o$$

$$\text{then } -\log h_o = -\log K_a + \log \frac{[A]}{[AH^+]}$$

$$\text{or } \frac{K_a}{h_o} = \frac{[A]}{[AH^+]}$$

substituting in (1) for $\frac{[A]}{[AH^+]}$

$$\frac{k}{k_1} = 1 + \frac{K_a}{h_o} \qquad (2)$$

5. Relation between k_1 and J_o .

Assuming that the reaction proceeds through the cation represented by the structure XX, a similar treatment to that above gives first:-

$$\frac{k}{k_1} = \left| + \frac{[A]}{[A^+]} \right. \qquad (3)$$

assuming that the anil ionising in this form can be treated as a triphenylcarbonol-type compound (or as nitric acid which ionises in sulphuric acid to give the dehydrated cation NO_2^+)

$$J_o = pK + \log \frac{[A]}{[A^+]} \qquad pk = -pk_A$$

Where pK_A is the negative logarithm of $\frac{[A^+]}{[A]} \cdot \frac{(H_2O)}{h_o}$ as defined by Gold and Hawes (loc:cit:).

Let $J_o = - \log j_o$

$$- \log j_o = - \log K + \log \frac{[A]}{[A^+]}$$

$$\frac{K}{j_o} = \frac{[A]}{[A^+]}$$

substituting in (3) for $\frac{[A]}{[A^+]}$

$$\frac{k}{k_1} = + \frac{K}{j_o} \qquad (4)$$

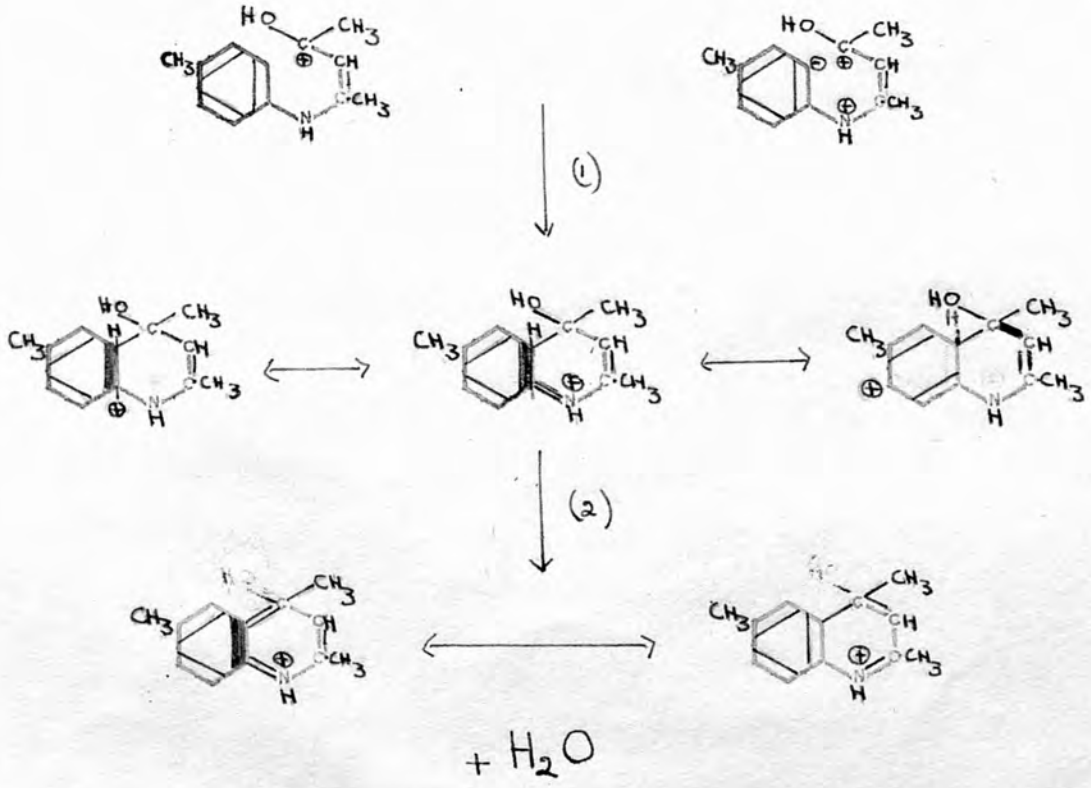
From equations (2) and (4) it is evident that a plot of $\frac{1}{k_1}$ against $\frac{1}{h_o}$ and against $\frac{1}{j_o}$ for the range of media studied should distinguish between the alternative mechanisms, since in only one case should the plot give a straight line relationship.

Values of h_o were obtained from the tables for H_o given by Deno and Taft[56] and of j_o from results of the ionisation of triarylcarbinol indicators in sulphuric acid-water mixtures given by Murray and Williams[57] and from values of J_o given by Gold and Hawes (loc:cit:).

The plot of $\frac{1}{k_1}$ against $\frac{1}{h_o}$ gives a straight line, that of $\frac{1}{k_1}$ against $\frac{1}{j_o}$ a smooth curve (graph 5). It can be concluded therefore that cyclisation occurs through the cation represented by structures XVI to XIX.

6. The mechanism of the cyclisation reaction:-

The cyclisation reaction can presumably be regarded as proceeding through the following steps:-

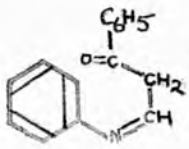


Since the product is obtained in the form of the quinoline cation, the final step does not involve the expulsion of a proton as is usually the case in electrophilic substitution of aromatic compounds, but the removal of a molecule of water.

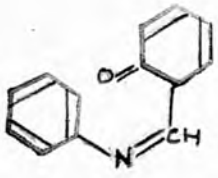
7. Anils failing to cyclise:-

In the first section reference was made to certain anils which fail to cyclise under suitable conditions. Among these are a small number, not substituted in the nucleus, which have in common the absence of a methyl group attached to the carbon atom of the sidechain adjacent to the N atom.

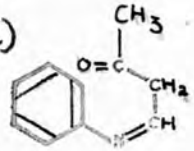
These anils are:-

(a) 

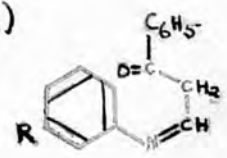
2-formyl acetophenone (Claisen & Fischer[36]).

(b) 

2-formyl cylcohexanone (Borsche[58])

(c) 

formylacetone (Thiele[18]).

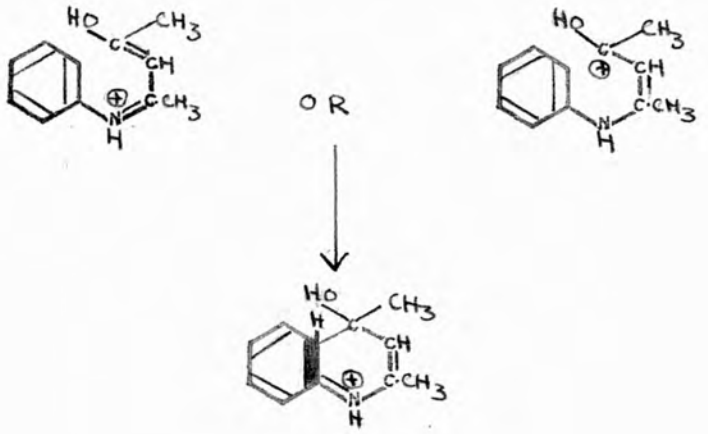
(d) 

(R=H) - this gives a very poor yield on attempted cyclisation, but with R = OMe, a very good yield is obtained under mild conditions.

dibenzoylmethane (Lempert and Robinson[40]).

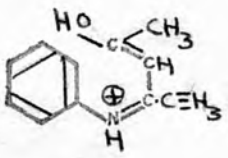
The corresponding compounds with a methyl group in place of the hydrogen of the methine group cyclise readily to the corresponding 2-quinaldine derivatives. The influence of the methyl group might be interpreted as facilitating the formation of the transition state since, as can be seen below, the formation of the transition state

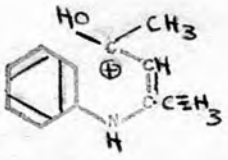
requires the appearance ofan α/β-double bond. The capacity of the methyl group for hyperconjugation with this bond would help the lower energy of formation



However one might expect that the replacement of the methyl group by a phenyl group would be even more effective in such a case, but this is not so, since it has been found experimentally that (d) R= H cyclises in very poor yield. The explanation here may be concerned with the relative stabilities of the structures (e) and (f) on the one hand and (g) and (h) on the other.

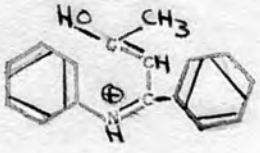
(e)

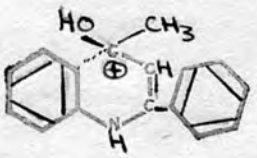




(f)

(g)





(h)

The conjugation between the two phenyl groups in (g) should be much stronger than that between the phenyl and methyl group in (e) and similarly that between the phenyl group and the $\alpha\beta$-double-bond in (h) much stronger than that between the methyl group and the $\alpha\beta$-double-bond in (f). Further a larger amount of energy should required to obtain (h) from (g) than (f) from (e), since the former involves a difference between two relatively large quantities while the latter involves a difference between two smaller quantities (e) should, therefore, attain the transition state more readily than (g)

References.

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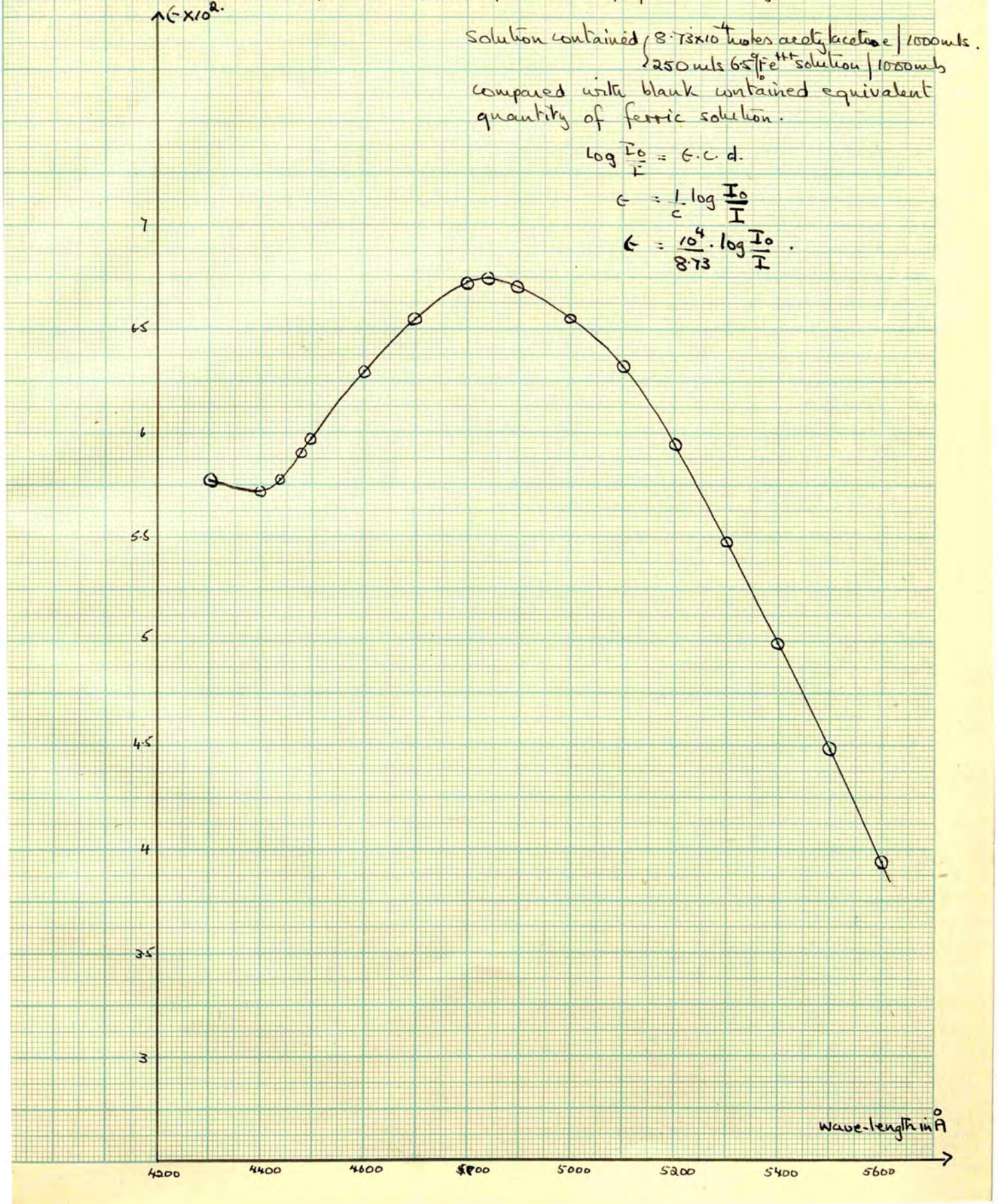
Graph 1.

Graph 1. (P.25) Graph of extinction coefficient ϵ against wave-length. for absorption spectrum of ferric acetylacetonate solution.



solution contained { 8.73×10^{-4} moles acetylacetone / 1000 mls. 250 mls 6.5×10^{-5} Fe^{+++} solution / 1000 mls

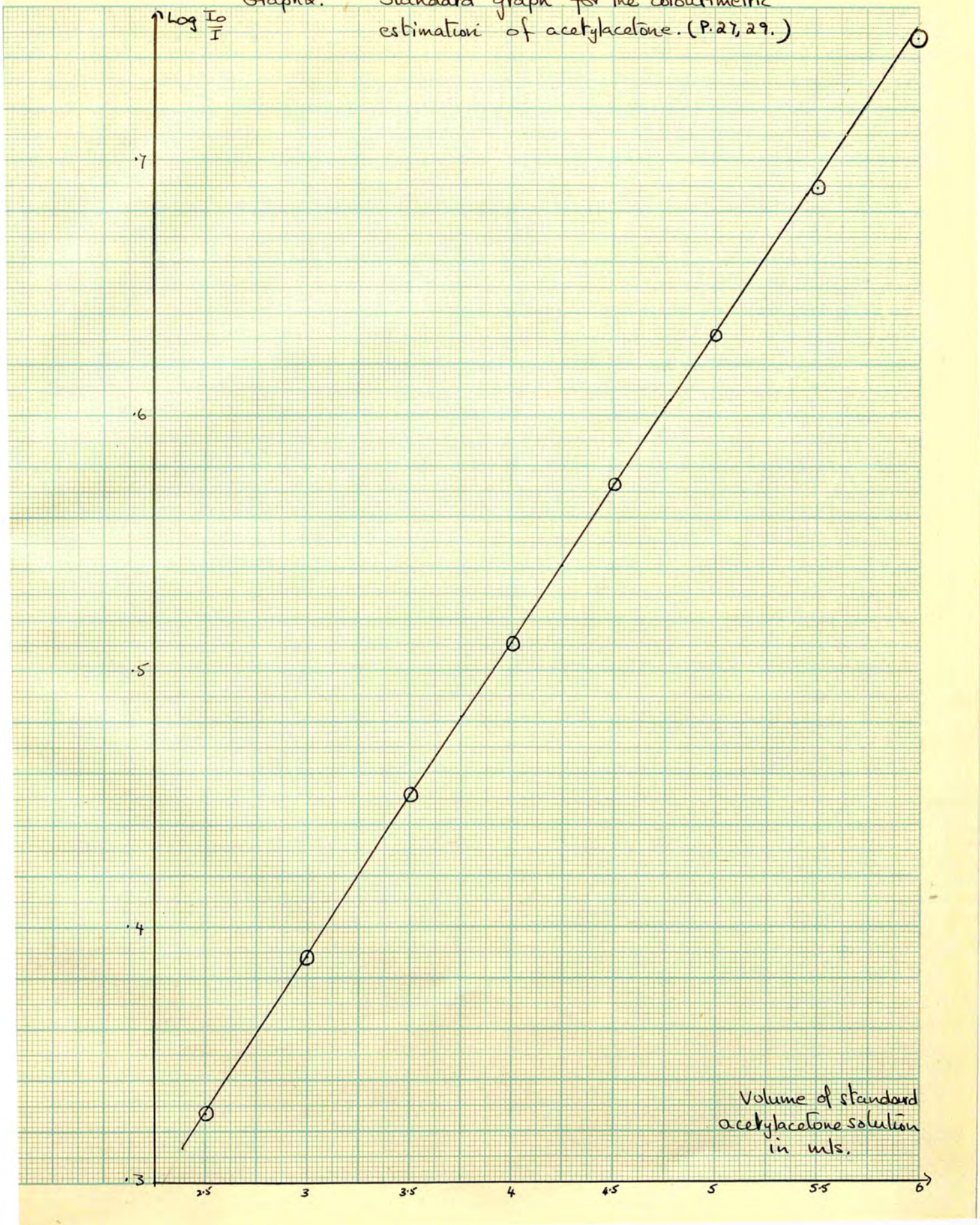
compared with blank contained equivalent quantity of ferric solution.

$$\log \frac{I_0}{I} = \epsilon . c . d.$$

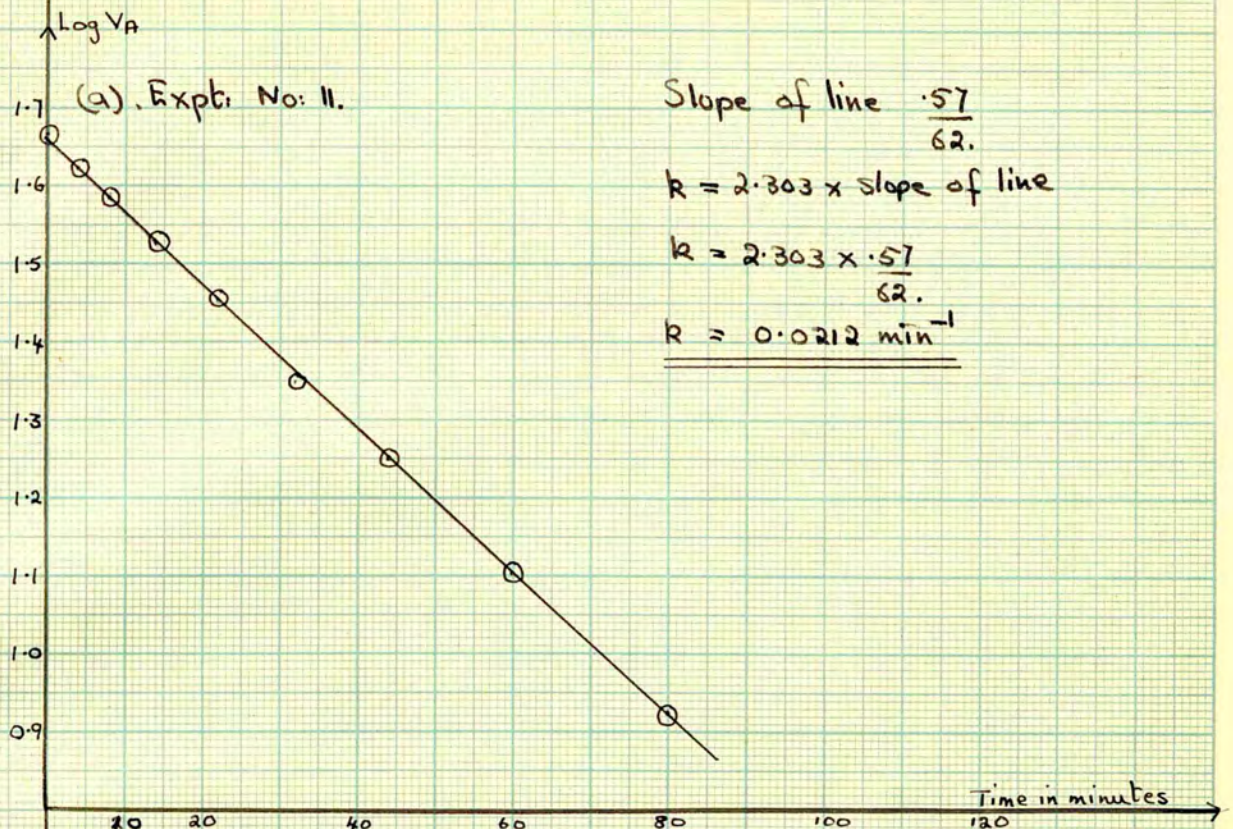
$$\epsilon = \frac{1}{c} \log \frac{I_0}{I}$$

$$\epsilon = \frac{10^4}{8.73} . \log \frac{I_0}{I} .$$

Graph 2. Standard graph for the colourimetric estimation of acetylacetone. (P. 27, 29.)



Graph 3 (a) and (b). The cyclisation of the anil in 91·1% H_2SO_4. (P.37)



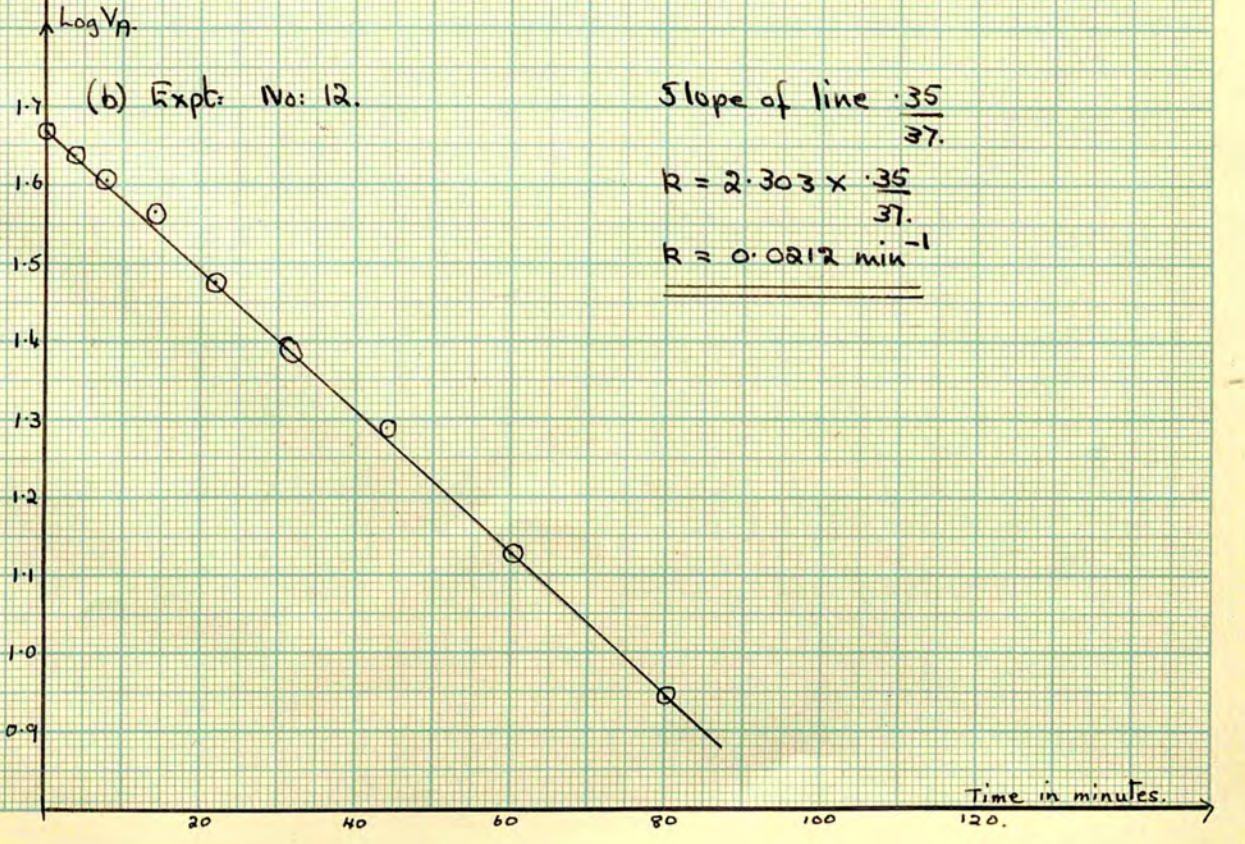
(a). Expt: No: 11.

Slope of line $\frac{\cdot 57}{62.}$

$k = 2{\cdot}303 \times$ slope of line

$k = 2{\cdot}303 \times \frac{\cdot 57}{62.}$

$k = 0{\cdot}0212\ min^{-1}$



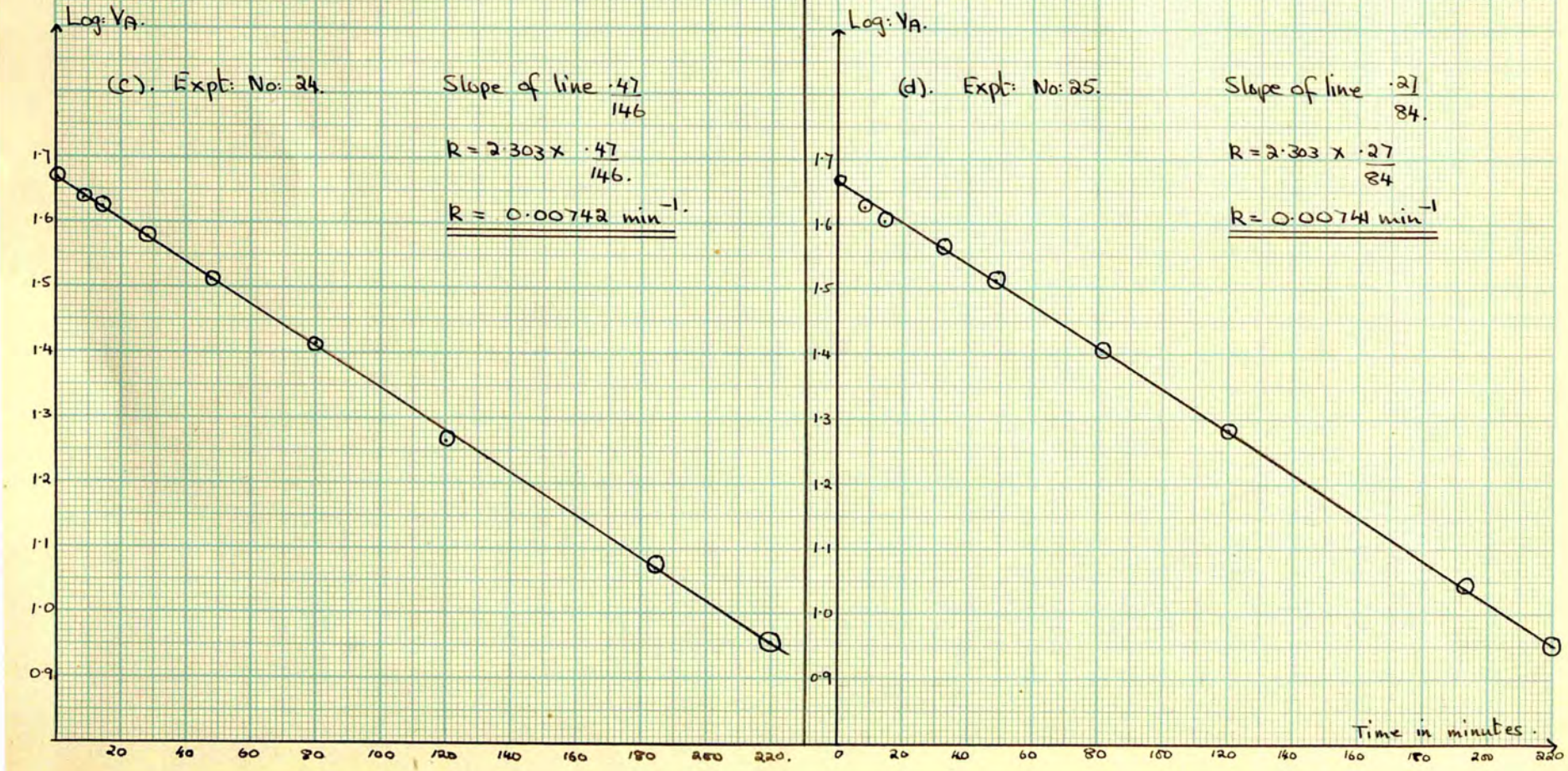
(b) Expt: No: 12.

Slope of line $\frac{\cdot 35}{37.}$

$k = 2{\cdot}303 \times \frac{\cdot 35}{37.}$

$k = 0{\cdot}0212\ min^{-1}$

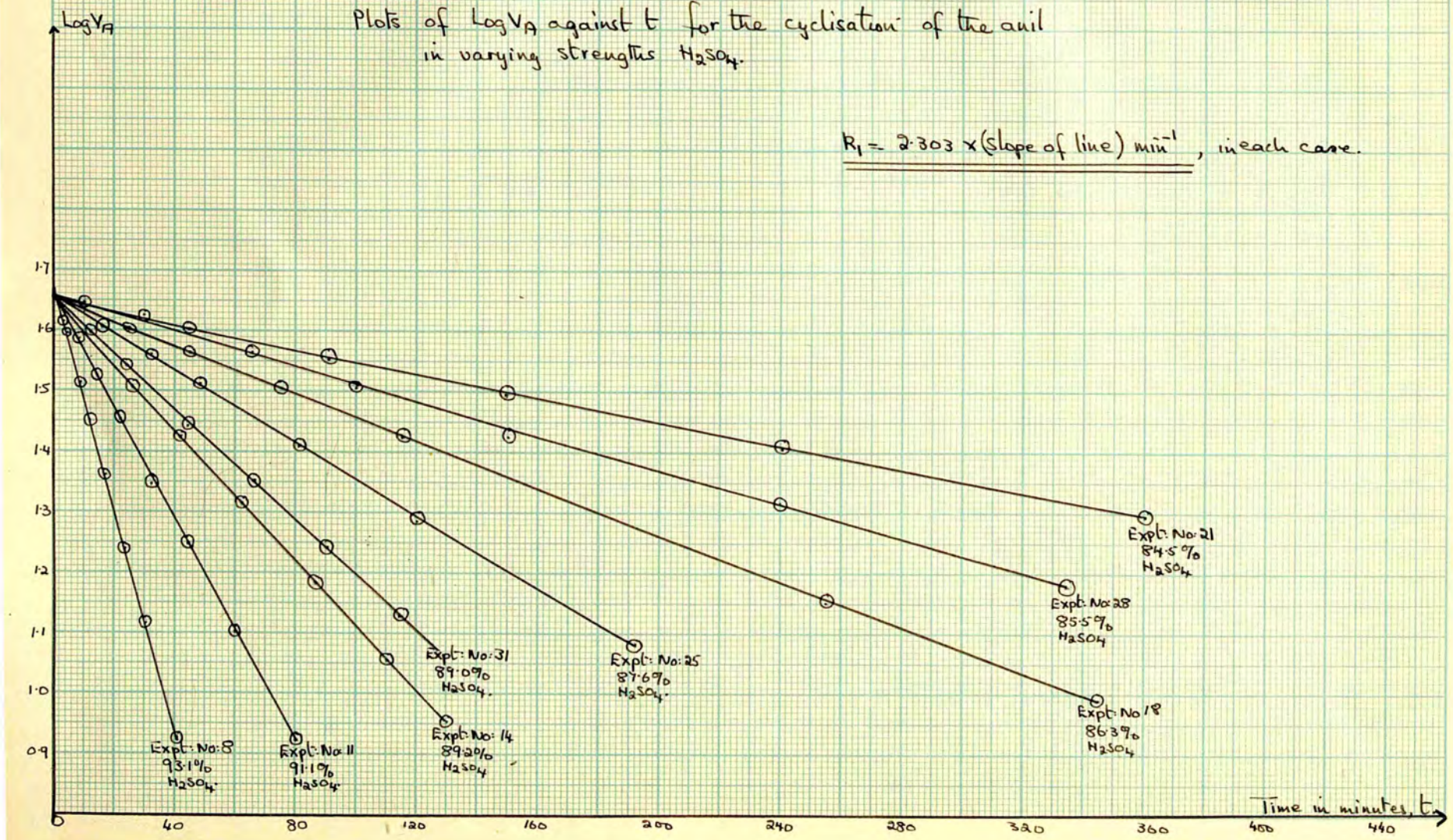
Graph 3 (c) and (d). The cyclisation of the anil in 87·6% H_2SO_4. (P.37).



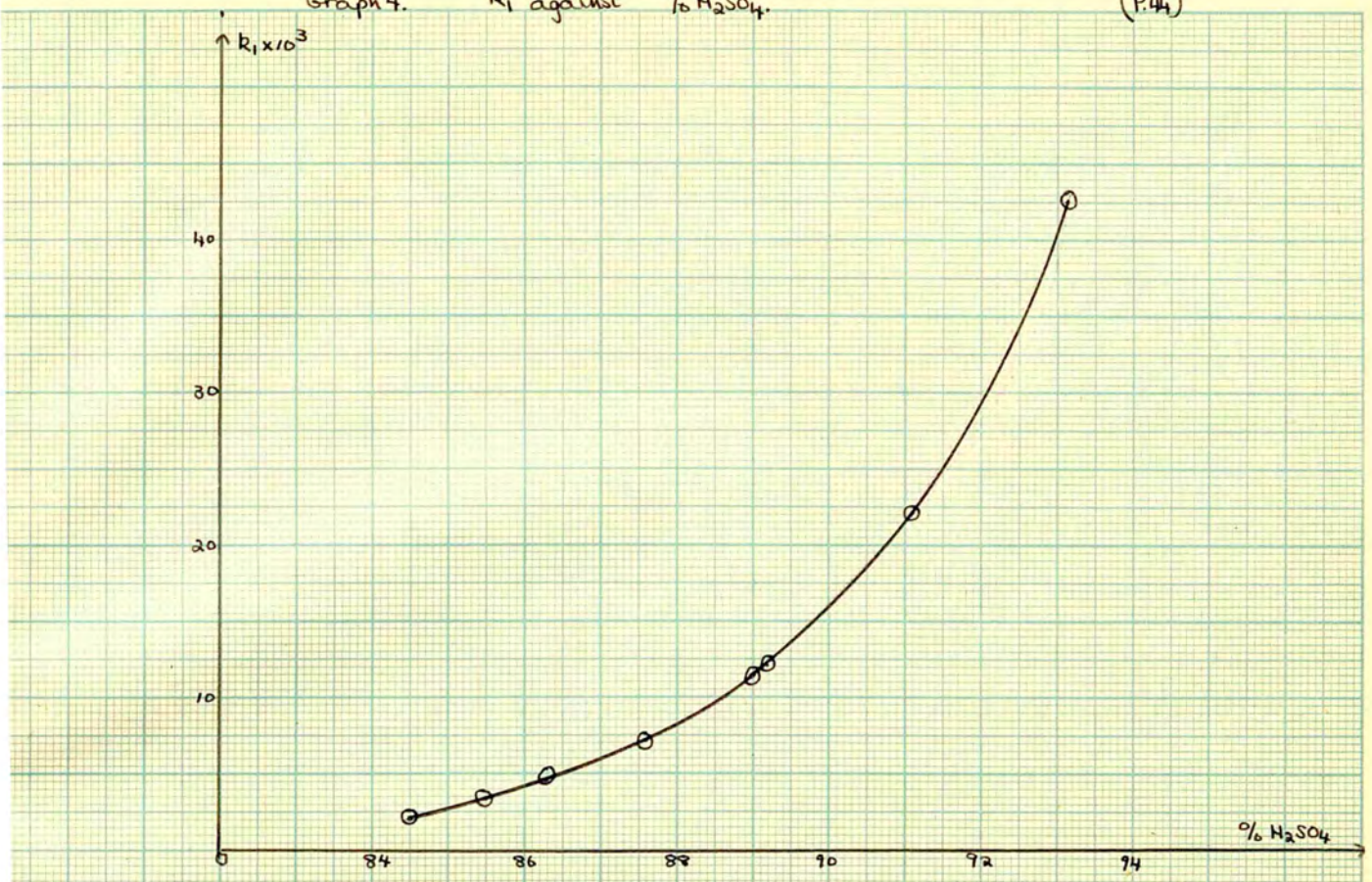
Graph 3 (e).

Plots of $\log V_A$ against t for the cyclisation of the anil in varying strengths H_2SO_4.

$K_1 = 2.303 \times (\text{slope of line}) \text{ min}^{-1}$, in each case.



Graph 4. k_1 against % H_2SO_4. (P.44)



Graph 5. $\frac{1}{k_1}$ against $\frac{1}{h_0}$ } for values in the range of 93·1% – 87·6% H_2SO_4
$\frac{1}{k_1}$ against $\frac{1}{j_0}$ } (P.51)