841. *The Cyclodehydration of Anils. Part III.** *The Alternative Hydrolytic Reaction.*

By T. G. Bonner and Mary Barnard.

Anils of acetylacetone are slowly hydrolysed in aqueous sulphuric acid at acidities slightly lower than those which bring about cyclodehydration to the corresponding quinoline compound.[1] A correlation between the rate of the hydrolysis and the activities of the hydrogen ion and water in the medium has been found for 4-(2 : 3-dimethylanilino)pent-3-en-2-one which suggests a simple bimolecular mechanism.

It is concluded that cyclodehydration proceeds through the diprotonated anil, and hydrolysis through the neutral anil.

Anils of acetylacetone are very rapidly hydrolysed to the primary aromatic amine and ketone in dilute aqueous acids and use is made of this fact to stop cyclodehydration of the anil to a substituted quinoline in concentrated sulphuric acid by diluting the mixture with water.[1] At some intermediate acidity, therefore, a change occurs in the nature of the reaction between the anil and its acid environment. The two most important solvent properties affecting the point at which the transition from cyclodehydration to hydrolysis can occur are (i) the activity of protons measured by Hammett's acidity function H_0 and (ii) the activity of water, obtained from the ratio of the vapour pressure of pure water to the vapour pressure of water over the sulphuric acid–water mixture (p/p_0). The medium or range of media where the change of reaction takes place should vary with the particular anil selected since proton-accepting capacity and reactivity (whether in cyclodehydration or hydrolysis) will depend on the constitution of the anil.

Previous work on the hydrolysis of anils appears to be confined to aqueous-alcoholic solutions. It has been shown[2] that hydrolysis of 4 : 4′-disubstituted benzylideneanilines in acetate-buffered 50% aqueous methanol is a first-order reaction with respect to the benzylideneaniline. Catalysis by water or bases was negligible in comparison with acid-catalysis and at pH 3 the rate of hydrolysis became immeasurably fast. The abnormally slow acid hydrolysis of *N*-(*p*-dimethylaminobenzylidene)aniline was attributed to the formation of its less reactive conjugate acid. Another study[3] of the hydrolysis of benzylideneaniline over the pH range 6—13 indicated that below pH 11 catalysis by the hydroxyl ion was negligible, the only effective catalyst being the H_3O^+ ion; the formation of an intermediate, *N*-(α-hydroxybenzyl)aniline was postulated and evidence for it from ultraviolet and infrared absorption spectra was claimed. Measurement[4] of the rates of hydrolysis and formation of the product of condensation of a substituted benzaldehyde and *p*-toluidine has shown that practically all substituents in the *m*- and the *p*-position in the benzaldehyde portion of the anil reduce the rate of hydrolysis relatively to that of benzylidene-*p*-toluidine. This is typical of a side-chain reaction dependent mainly on the inductive effect of nuclear substituents in which either attack by an electrophilic reagent or proton addition to the side chain takes place before reaction.

Preliminary work on the anils of acetylacetone showed that hydrolysis was immeasurably rapid in 2—3N-sulphuric acid. The more acidic ranges were therefore explored for a measurable rate of hydrolysis since at the point where cyclodehydration becomes significant the hydrolysis must be relatively slow. It was found that 4-(2 : 3-dimethylanilino)pent-3-en-2-one gave a measurable rate of cyclodehydration in the range 70—81% sulphuric acid. Below 70% H_2SO_4 the cyclodehydration was too slow for measurement.

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* Part II, *J.*, 1955, 2358.

[1] Bonner, Thorne, and Wilkins, *J.*, 1955, 2351.

[2] Willi and Robertson, *Canad. J. Chem.*, 1953, **31**, 363.

[3] Kastening, Holleck, and Melkonian, *Z. Electrochem.*, 1956, **60**, 130.

[4] Bloche-Claude, *Compt. rend.*, 1954, **239**, 804.

It was shown that this anil did not remain stable in the more aqueous media below 70% sulphuric acid since when the acidity was increased considerably above this strength by rapid addition of pure sulphuric acid the yield of cyclodehydration product, 2 : 4 : 7 : 8-tetramethylquinoline was very much less than that obtained when the anil was treated directly with concentrated sulphuric acid. This result was also obtained with other anils and was fully investigated to confirm that it meant a slow hydrolysis of anil to re-form 2 : 3-dimethylaniline and acetylacetone.

EXPERIMENTAL

Media.—Pure sulphuric acid and sulphuric acid–water mixtures were prepared and standardised as described in Part I.[1]

Materials.—4-(2 : 3-Dimethylanilino)pent-3-en-2-one, prepared from 2 : 3-dimethylaniline and acetylacetone by the method of Turner and Roberts[5] and recrystallised twice from light petroleum (b. p. 60—80°), had m. p. 83—84°. An 89% yield of 2 : 4 : 7 : 8-tetramethylquinoline was obtained when 1 g. of this was treated with 10 ml. of concentrated sulphuric acid;[1] the m. p. of the product after crystallisation twice from light petroleum (b. p. 40—60°) was 30—31° (Found: C, 84·3; H, 8·3; N, 7·6. Calc. for $C_{13}H_{15}N$: C, 84·3; H, 8·1; N, 7·6%)

Behaviour of 4-(2 : 3-*Dimethylanilino*)*pent*-3-*en*-2-*one in Acid.*—In 2N-sulphuric acid hydrolysis to the amine and acetylacetone was virtually complete in a few minutes, colorimetric analysis of the acetylacetone by the method described in Part I indicating a 99·3% recovery. A much slower hydrolysis in 60% sulphuric acid was established by maintaining overnight at 25° a solution of 0·2 g. of anil in this medium and then adding 15 ml. of pure sulphuric acid to convert the unchanged anil very rapidly into the quinoline derivative. (It was confirmed that the cyclodehydration of this anil is immeasurably fast in the medium formed under these conditions.) 2 ml. portions of the solution were removed at hourly intervals: the acetylacetone content remained constant and corresponded to 71% hydrolysis at equilibrium. When the solution in 60% sulphuric acid was kept at 25° for 1½ hr. instead of overnight before addition of the 100% sulphuric acid, only 20% hydrolysis occurred.

Both the acetylacetone and the 2 : 3-dimethylaniline in separate solution in 60% sulphuric acid were quantitatively recoverable on dilution with water. If a mixture of these solutions, however, is kept at 25° overnight and then pure sulphuric acid added, the recovery of acetylacetone is only 74%, indicating that some anil had been formed. No product other than quinoline compound was found. In order to establish that the acetylacetone and amine form the anil only in the 60% sulphuric acid and do not condense together on addition of the pure sulphuric acid, the following experiments were carried out on a 10 ml. sample of a solution of acetylacetone in 60% sulphuric acid:

(*a*) 2 ml. of the solution were made up to 10 ml. with pure sulphuric acid; (*b*) 0·5 g. of 2 : 3-dimethylaniline was added to the remaining 8 ml. of the original solution; a 2 ml. aliquot portion was immediately removed, made up to 10 ml. with pure sulphuric acid, and kept at room temperature for 24 hr.; (*c*) the residual solution of acetylacetone and amine in 60% sulphuric acid from (*b*) was kept at room temperature for 24 hr., and a 2 ml. aliquot portion then removed and made up to 10 ml. with pure sulphuric acid. On analysis of these three solutions, 100% recovery of the acetylacetone was evident in (*a*) and (*b*) but only 67% in (*c*). The anil is therefore formed in (*c*) but not in (*b*).

Measurement of the Rate of Hydrolysis.—Kinetic measurements were carried out at 25° in a thermostat controlled within ±0·02°. The reaction vessel was a 50 ml. conical flask with a B24 neck. The anil was weighed into a B24 socket cap, the amount taken providing a 0·1M-solution when dissolved in 25 ml. of the medium. The medium was contained in a tared 25 ml. graduated flask and after being made up to the mark in the thermostat at 25° it was transferred to the reaction vessel in the thermostat. The 25 ml. flask was weighed in order to calculate the exact volume of medium used. To start the reaction, the reaction vessel was removed from the thermostat and the filled socket cap inserted. The medium and reactant were brought into contact at zero time by vigorous shaking and after complete dissolution had occurred (1—2 min.) the flask was returned to the thermostat. Six to eight 2 ml. samples were removed from the reacting mixture in the course of each experiment. Each sample was run into 7 ml. of pure

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[5] Turner and Roberts, *J.*, 1927, 1832.

sulphuric acid in a 10 ml. graduated flask cooled in ice, and the solution made up to the mark at room temperature with pure sulphuric acid. This was left for 2 hr. to ensure complete conversion of unhydrolysed anil into the quinoline derivative. A 2 ml. sample was then run into 20 ml. of ice-cold water, neutralised, and made up to 50 ml. in 0·1N-sulphuric acid, and its acetylacetone content determined colorimetrically. The rate constant, k, was obtained from the kinetic equation for a reversible reaction in which a first-order hydrolysis is opposed by a second-order recombination of the products

$$kt(2a - x_e) = 2{\cdot}3x_e \log [ax_e + x(a - x_e)]/a(x_e - x)$$

where a is the initial concentration of anil, and x and x_e are the concentrations of anil at time t and at equilibrium respectively. The plot of $\log [ax_e + x(a - x_e)]/a(x_e - x)$ against t was a good straight line for all experiments. A typical duplicate result is shown in Fig. 1. Rates of hydrolysis over the range 52—62% sulphuric are given in the Table.

FIG. 1.

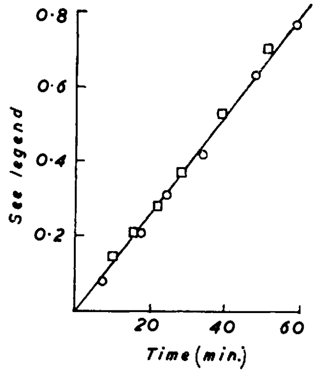

FIG. 2.

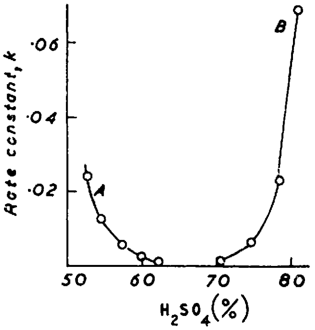

FIG. 1. *Hydrolysis of* 4-(2 : 3-*dimethylanilino*)*pent*-3-*en*-2-*one in* 52·8% H_2SO_4. $k = 0{\cdot}0241$ min.$^{-1}$. *Ordinate*: $\log [ax_e + x(a - x_e)]/a(x_e - x)$.

FIG. 2. 4-(2 : 3-*Dimethylanilino*)*pent*-3-*en*-2-*one*: *A*, *hydrolysis*; *B*, *cyclodehydration.*

Rates of hydrolysis of 4-(2 : 3-*dimethylanilino*)*pent*-3-*en*-2-*one* (*initial concn.* 0·1M) *at* 25°.

H_2SO_4 (%)	10^3k (min.$^{-1}$)	$\log k + H_0$	$\log p/p_0$	$\log k - H_0 - \log p/p_0$
62·4	0·962, 0·973	−7·63	−0·88	2·49
60·1	2·25, 2·27	−6·96	−0·76	2·46
57·7	5·34	−6·34	−0·66	2·46
54·9	12·7, 12·4	−5·64	−0·58	2·42
52·8	24·1, 24·1	−5·14	−0·50	2·40
60·1 *	5·33, 5·38			

* M-$(NH_4)_2SO_4$ present.

RESULTS AND DISCUSSION

Ionisation of Anils in Sulphuric Acid.—Previous investigation [1] of the cyclodehydration of the acetylacetone anils from aniline and *p*-toluidine in the range 85—97% sulphuric acid established that the kinetic results satisfied the relation [6] $\log k + H_0 =$ Constant, where k is the rate constant for the cyclodehydration and H_0 the Hammett acidity function for the corresponding medium. Accordingly, it was concluded that reaction proceeded through a positively charged anil formed in fractionally small amount. The cyclodehydration of 4-(2 : 3-dimethylanilino)pent-3-en-2-one conforms with this result, since rates of

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[6] Hammett and Deyrup, *J. Amer. Chem. Soc.*, 1932, **54**, 2721; Hammett and Paul, *ibid.*, 1934, **56**, 830.

cyclodehydration measured over the range 70—80% sulphuric acid fitted the above equation (see Fig. 2 and following paper). It is evident however that in these strongly acid media, an anil may be almost entirely present in the monoprotonated form,[7] and in this case the result obtained would suggest that the cyclodehydration occurs in a diprotonated anil present in fractionally small amount, the bulk of the anil being present in a stable monoprotonated form. The relation deduced[1] would then be $\log k + H_+ =$ Constant, where H_+ is an acidity function evaluated in the same way as H_0 but by means of bases carrying a single charge which form a doubly positively charged conjugate acid. As the H_+ acidity function had not then been evaluated, this equation could not be tested but recently[8] it has been shown that H_0 and H_+ are parallel functions of medium composition. The original result therefore satisfies both the above equations. Evidence in favour of complete monoprotonation of anils in these media was sought by determining the lowering of freezing point of a solution of an anil in pure sulphuric acid. The anil selected was 4-*p*-chloroanilinopent-3-en-2-one which was found[5] to be stable but incapable of cyclisation in the concentrated acid. A spectroscopic examination of this anil in pure sulphuric acid showed that it remained unchanged during the time taken to determine the freezing point. No special apparatus was employed for the f. p. determination and the method used[9] of comparing the *i*-factor with that of a neutral compound known to form its conjugate acid quantitatively in pure sulphuric acid was found to be adequate. The neutral compound used was benzoic acid and a satisfactory value of 2·07 was found for the *i*-factor for this solution. The *i*-factor for the depression of f. p. by the anil under the same conditions was found to be 2·05. If this result is general for anils of this type, it can be concluded that over the range of sulphuric acid media where measurable rates of cyclodehydration are found, the anil is almost entirely present as a stable monoprotonated form, the ring closure occurring through a diprotonated form. The decrease in rate of this reaction as the acidity of the medium is reduced is due to the decreasing degree of formation of this species from the monoprotonated form. Further decrease in acidity will eventually result in the appearance of the neutral anil and at that point it is likely that very little, if any, of the diprotonated species will be present. An alternative mechanism to the rate-determining ring closure which would give the same correlation of $\log k$ and H_+ is one in which a rate-determining elimination of water from the diprotonated anil is followed by rapid ring closure. There are however no theoretical grounds for assuming that the diprotonated anil would eliminate water at a measurable rate. Any species directly formed by elimination of water would be highly unstable and likely to give rise to products other than the quinoline derivative. No evidence has been found for any other product.

Mechanism of Hydrolysis of Anils.—The results in the Table show that the highest acidity at which a measurable rate of hydrolysis is obtained is about 63% sulphuric acid and that the hydrolysis becomes more rapid as the acidity of the medium is decreased by further addition of water. Ammonium sulphate is also known to decrease the acidity of sulphuric acid solutions and its addition in molar concentration to one of the media more than doubles the rate of hydrolysis. Since this salt reduces acidity without increasing the water content of the medium, its effect corresponds to altering an equilibrium in the direction of forming a large proportion of the species actually undergoing the hydrolysis. Increasing the water content of the solution could have the same effect but it is difficult to separate the extent of this effect on the rate from that due to the increasing concentration of water as a reactant in the hydrolysis. If it is assumed that the species undergoing hydrolysis is the neutral anil the marked increase in rate of hydrolysis shown in Fig. 2 would follow from the rapid change which is known to occur in the ionisation ratio $[AH^+]/[A]$ for a base A and its conjugate acid AH^+ in the appropriate range of sulphuric acid–water mixtures.

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[7] Professor F. A. Long, personal communication.

[8] Bonner and Lockhart, *J.*, 1957, 364.

[9] Williams and Hardy, *J.*, 1953, 2560.

Hydrolysis of the neutral anil by water to form the amine and acetylacetone would lead to the following kinetic analysis:

Let A and AH^+ represent the neutral anil and its conjugate acid respectively. Assuming that these are the only forms of the anil present and that $[AH^+] \ll [A]$ in the media in which measurable rates of hydrolysis are obtained, we have by the Brønsted treatment:

$$\text{Theoretical rate} = k_0K(\text{A})(\text{H}_2\text{O})/f_\ddagger$$

where k_0 is the theoretical rate constant, K is the equilibrium constant for the equilibrium between the reactants and the transition complex, $f_\ddagger$ is the activity coefficient of the latter, and the parentheses denote activities

$$\text{Experimental rate} = k[\text{A}]_\text{T}$$

where $[\text{A}]_\text{T}$ is the stoicheiometric concentration of anil. Equating the two rate equations we have

$$k[\text{A}]_\text{T} = k_0K[\text{A}](\text{H}_2\text{O})f_\text{A}/f_\ddagger$$

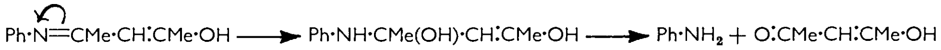
and since $[\text{A}]_\text{T} \approx [\text{AH}^+]$

$$k[\text{AH}^+]/[\text{A}] = k_0K(\text{H}_2\text{O})f_\text{A}/f_\ddagger$$

Taking logarithms and substituting for the term log $[\text{AH}^+]/[\text{A}]$ from the equation $H_0 = \text{p}K_a - \log [\text{AH}^+]/[\text{A}]$, it follows that

$$\log k - H_0 - \log (\text{H}_2\text{O}) = \log k_0Kf_\text{A}/f_\ddagger - \text{p}K_a$$

which is a constant if the activity coefficient ratio $f_\text{A}/f_\ddagger$ is constant over the range of media employed. Since the two species concerned, *i.e.*, the anil and the transition complex, are both neutral this is a reasonable expectation. The above equation was tested by using the known values [6] of H_0 and of log (H_2O) (ref. 10) at 25°. The results given in the Table indicate the constancy attained and at the same time show that the simpler relation $\log k + H_0 = \text{Constant}$ is not obeyed for the hydrolysis. The reaction can be readily represented as a nucleophilic attack by water on the carbon atom of the azomethine bond as shown:



$$\text{Ph·N=CMe·CH:CMe·OH} \longrightarrow \text{Ph·NH·CMe(OH)·CH:CMe·OH} \longrightarrow \text{Ph·NH}_2 + \text{O:CMe·CH:CMe·OH}$$

The stability of the monoprotonated anil can be attributed to the loss of resonance represented in structures (I) and (II) by any similar bonding with a water molecule.

(I) $\text{Ph·}\overset{+}{\text{N}}\text{H:CMe·CH:CMe·OH}$ $\qquad$ $\text{Ph·NH·CMe:CH·CMe:}\overset{+}{\text{O}}\text{H}$ (II)

(III) $\text{Ph·}\overset{+}{\text{N}}\text{H:CH·C}_6\text{H}_4\text{·NMe}_2$ $\qquad$ $\text{Ph·NH·CH=C}_6\text{H}_4\text{·}\overset{+}{\text{N}}\text{Me}_2$ (IV)

An analogous case is provided by the abnormal behaviour on hydrolysis of *N*-(*p*-dimethylaminobenzylidene)aniline previously referred to.[2] Hydrolysis in dilute aqueous acid would require the loss of resonance energy corresponding to the two resonance structures (III) and (IV) of its stable conjugate acid, and in consequence this reaction is extremely slow.

The conjugate acid of the parent benzylideneaniline will only have one stable resonance structure, *i.e.*, that corresponding to (III), and the carbon atom of the azomethine bond will be an electron-deficient centre for attack by water, giving a much faster rate of hydrolysis, as found experimentally.

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[*Received, May* 21*st*, 1958.]

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[10] Gold and Hawes, *J.*, 1951, 2102.