

## 842. The Cyclodehydration of Anils. Part IV.<sup>1</sup> Substituent Effects.

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Substituent effects have been studied in the cyclodehydration of substituted 4-anilinopent-3-en-2-ones to the corresponding 2:4-dimethylquinolines in strongly acidic aqueous media. The *m*-halogeno-derivatives all cyclise faster than the unsubstituted compound, in accord with stabilisation of the transition complex by electron-release from the halogen atom.

Additivity of substituent effects has been studied for both cyclodehydration and hydrolysis of disubstituted 4-anilinopent-3-en-2-ones and compared with the additivity of  $pK_a$  values of the anilinium ions. The enhanced interaction of the substituents in 2:3-disubstituted derivatives in particular is noted and discussed.

THE correlation reported previously<sup>2</sup> between the rate constant,  $k$ , for cyclodehydration of acetylacetone anils to 2:4-dimethylquinolines and Hammett's acidity function,  $H_0$ , given by the equation:

$$\log k + H_0 = \text{Constant} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

was established for the anils of aniline and *p*-toluidine over the range aqueous 85–97% sulphuric acid. The ratio of the rate constants for these two anils  $k_{Me}/k_H$  is reasonably constant over the range of medium common to both compounds. This is expected since the mechanism of ring closure should be independent of the constitution of the anil. The ratio is most conveniently evaluated from the difference in the mean values of the sum,  $\log k + H_0$ , for the cyclodehydration of each compound over the range of media studied. This gives  $k_{Me}/k_H = 6$  which is in accord with the activating effect of a methyl group *meta* to the point of electrophilic substitution in the benzene ring. A much greater activating effect with measurable rates of cyclodehydration requiring more aqueous sulphuric acids should be found for 4-*m*-toluidinopent-3-en-2-one where the methyl group is *para* to the point of ring closure. The most acid medium in which the cyclodehydration of the

TABLE I. Rates of cyclodehydration of 4-(2:3-dimethylanilino)pent-3-en-2-one (initial concn. 0.05M) at 25°.

H <sub>2</sub> SO <sub>4</sub> (%)	10 <sup>2</sup> $k$ (min. <sup>-1</sup> )	$\log k + H_0$	$\log k + C_0$	HClO <sub>4</sub> (%)	10 <sup>2</sup> $k$ (min. <sup>-1</sup> )	$\log k + H_0$
80.8	6.92, 6.97	-8.31	-15.54	71.4	11.1, 11.5	-9.02
78.6	2.26, 2.23	-8.31	-15.42	69.4	6.52, 6.52	-9.03
74.8	0.592, 0.586	-8.36	-15.03	66.7	1.09, 1.07	-8.92
70.5	0.135, 0.140	-8.39	-14.54	63.6	0.164, 0.164	-8.91

*m*-methylanilino-compound could be accurately measured was 83% sulphuric acid. The ratio  $k_{Me}/k_H$  calculated from the corresponding  $\log k$  and  $H_0$  values was then *ca.* 700. The 3:4- and 2:3-dimethylanilino-compounds similarly gave high values for this ratio ( $k/k_H = 1180$  and 430 respectively). As the latter anil proved to be the most convenient for a study of the hydrolysis,<sup>1</sup> it was used also for a more extensive study of the cyclodehydration. The rate of cyclodehydration of this anil was measured in the range 70–80% aqueous sulphuric acid and also in aqueous perchloric acid. The results given in Table I show that equation (1) is obeyed in these more aqueous solutions and that the lack of correlation between the rate constant and the acidity function,  $C_0$  (ref. 3) (or  $J_0$ ; ref. 4), previously noted<sup>1</sup> is confirmed. The plot of  $\log k$  against  $H_0$  was a good straight line for both media with a slope of -1.09 for sulphuric acid and of -0.92 for perchloric acid. It can be concluded that over a considerable range of aqueous acidic media (from  $H_0 = -5.5$

<sup>1</sup> Part III, preceding paper.

<sup>2</sup> Bonner, Thorne, and Wilkins, *J.*, 1955, 2351.

<sup>3</sup> Deno, Jaruzelski, and Schriesheim, *J. Amer. Chem. Soc.*, 1955, 77, 3044.

<sup>4</sup> Gold and Hawes, *J.*, 1951, 2102.

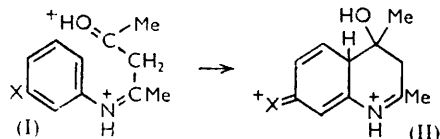
to -9.1) the cyclodehydration proceeds by a rate-determining internal electrophilic substitution of the diprotonated form of the anil which is present in fractionally small amount.<sup>1</sup>

*Halogen Substituents.*—It has been noted<sup>5</sup> that while 4-*m*-chloroanilinopent-3-en-2-one cyclises in concentrated sulphuric acid to 7-chloro-2:4-dimethylquinoline the corresponding *p*-chloro- and 3:5-, 2:5-, and 2:4-dichloro-anils fail to react. Since halogen deactivates the benzene nucleus to attack by electrophilic reagents, the rate of cyclo-

TABLE 2. Rates of cyclodehydration of *m*-halogenoanils in 93.8% sulphuric acid at 25°.

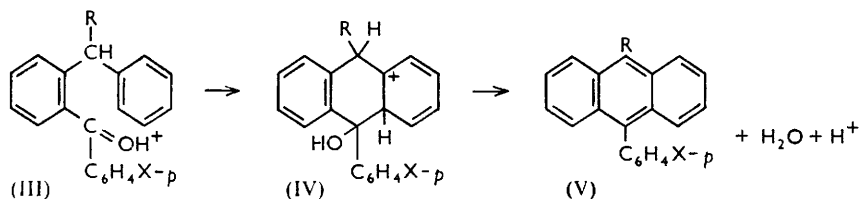
4-Anilinopent-3-en-2-one	<i>m</i> -F	<i>m</i> -I	<i>m</i> -Cl	<i>m</i> -Br	H
10 <sup>2</sup> <i>k</i> (min. <sup>-1</sup> ) .....	4.16	1.90	0.83	0.696	0.371

dehydration for the *m*-chloroanil should be less than for the unsubstituted anil. However, this was not found to be the case, as the results in Table 2 show. The experimental result for 4-anilinopent-3-en-2-one is halved to allow for the fact that there are two identical points of ring closure in this compound compared with one only in its *meta*-substituted derivatives. In all four *m*-halogenoanils, the halogen atom activates the *para*-position relative to hydrogen, the order being F > I > Cl > Br > H. Activation is readily explicable in terms of the stabilisation of the transition complex by operation of the electromeric effect of halogen. The diprotonated side chain in the anil (I) can transfer one



of its positive charges to the halogen atom, X, in forming the intermediate (II) which must resemble closely the transition state in the reaction. The quinoline produced results from loss of a molecule of water and a proton from this intermediate. The inhibitory inductive effect is clearly still operative since the rate of cyclodehydration of the corresponding *m*-toluidine anil is several hundred times greater still. The inductive effect, however, is secondary to the polarisability of the halogen atoms under the influence of the strong electrical field in the cyclic transition state.

Another cyclisation in which the effect of halogen has been studied is the conversion of



2-benzyl-4'-halogenobenzophenones to 9-*p*-halogenophenylanthracenes (V) in hydrobromic-acetic acid.<sup>6</sup> Here the rate of cyclisation is hardly affected by *p*-halogeno- (or even *p*-methyl) substituents and this is in accord with the formation of a transition state in which the electromeric effect cannot operate, as shown in (III) and (IV).

The similarity in operation of the polarisability effect of halogens in other electrophilic substituents is shown by a comparison of the rates of cyclodehydration with the partial rate factors for *para*-substitution in nitration and halogenation of the corresponding halogenobenzenes.<sup>7</sup> As shown in the Figure a linear relation exists between log *k* (cyclodehydration) and log *f<sub>p</sub>* in both cases, the sole exception being the fluorine substituent in

<sup>5</sup> Turner and Roberts, *J.*, 1927, 1836.

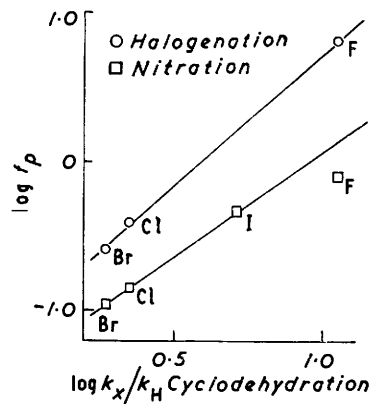
<sup>6</sup> Bradsher and Vingiello, *J. Amer. Chem. Soc.*, 1949, **71**, 1434.

<sup>7</sup> de la Mare, *J.*, 1954, 4450.

nitration. This is further evidence for the efficacy of the nitronium ion as an electrophilic reagent, since it does not evoke the full operation of the polarisability of the fluorine atom. The view that halogenation by means of the less effective halogen molecule is more powerfully electron-demanding<sup>8</sup> clearly applies to the cyclodehydration.

A recent example of activation by a *p*-fluorine substituent has been found in the solvolysis of halogenobenzyl toluene-*p*-sulphonates in aqueous acetone.<sup>9</sup> The sequence of decreasing rate constants, *p*-F > H > *p*-Cl > *p*-I > *p*-Br, demonstrates the superior conjugating effect of fluorine in stabilising the transition state in this reaction, but it is evident that for the other halogens the balance of conjugative and inductive effects is not identical with that of the cyclodehydration. In the correlation found between the rate constants of the solvolysis and of nitration of the corresponding halogenobenzenes, only the *p*-fluoro-substituent showed a considerable deviation. It was suggested that this was due to the decreased availability of the non-bonding electrons of the fluorine atom in the nitration by hydrogen-bonding with the highly acidic medium. The similar deviation

Comparison of rates of halogenation, nitration, and cyclodehydration at the para-position to halogen.



evident in the correlation of the rates of cyclodehydration and nitration shown in the Figure does not support this proposal since in this case the medium is the same for both reactions.

The complete failure of 4-*p*-chloroanilinopent-3-en-2-one to cyclise was confirmed and it is evident that in this compound and the dichloroanils referred to above the deactivating inductive effect of halogen *meta* to the point of ring closure predominates.

*Additivity of Substituted Effects.*—Before considering the effects of substituents in the cyclodehydration of disubstituted anils, it is convenient to review the additivity of these effects in the acid dissociation constants of the corresponding anilinium ions. Substituent effects will be additive if the experimental value for  $pK_a^{X,Y}$  fits equation (2):

$$pK_a^{X,Y} = pK_a^X + pK_a^Y - pK_a^H \quad . \quad . \quad . \quad . \quad . \quad (2)$$

Previous results<sup>10,11</sup> show that the biggest deviation from additivity occurs with 2:6-xylidine where the lower  $pK_a$  value indicates that the amine is less basic than if the effects of the two methyl groups were strictly additive. In contrast, the 2:3-xylidine is a stronger base than expected. Steric hindrance of resonance in the base is frequently invoked to account for the increased basicity of an aromatic amine when bulky substituents such as methyl are introduced in the *ortho*-positions<sup>12</sup> but the lower basicity of *o*-toluidine compared with aniline and the *m*- and *p*-toluidines is in contradiction to the operation of

<sup>8</sup> de la Mare and Waters, *Ann. Reports*, 1953, **50**, 127.

<sup>9</sup> Fang, Kochi, and Hammond, *J. Amer. Chem. Soc.*, 1958, **80**, 563.

<sup>10</sup> Beale, *J.*, 1954, 4495.

<sup>11</sup> Gillois and Rumpf, *Bull. Soc. chim. France*, 1954, **21**, 112.

<sup>12</sup> Hammett and Paul, *J. Amer. Chem. Soc.*, 1934, **56**, 827; Wheland, "Resonance in Organic Chemistry," Chapman and Hall Ltd., London, 1955, p. 372.

this factor; in this case, the difference has been attributed to a sterically hindered solvation of the *o*-toluidinium ion.<sup>13</sup> The latter effect would account for the decreased basicity of 2 : 6-xylidine and the former for the increase in 2 : 3-xylidine but it is difficult to predict which of the two effects would predominate in any given compound. Similar differences in behaviour have also been observed between 2 : 5- and 2 : 3-dimethyl derivatives of benzene of the type  $\text{XYC}_6\text{H}_3\text{R}$  where  $\text{R} = \text{NO}_2$ <sup>14</sup> or  $\text{CO}_2\text{H}$ ,<sup>15</sup> in that the introduction of the 3-methyl but not the 5-methyl substituent increases the influence of the 2-methyl substituent on the interaction between the group R and the benzene ring. For the remaining compounds in Table 3 it is evident that the substituent effects are reasonably additive.

The test of additivity in the cyclodehydration reaction is obtained by replacing the  $\text{pK}_a$  terms in equation (2) by the logarithms of the rate constants of cyclodehydration and assuming that the value of the acid dissociation constant of the diprotonated anilinoanil  $\text{AH}_2^{++}$  is not greatly affected by nuclear substituents. The results in Table 4 show that an additivity of substituent effects in the cyclodehydration is found only for the 2 : 4-di-

TABLE 3.  $\text{pK}_a$  values of disubstituted anilines.

Aniline	Found	Calc.	Diff.	Aniline	Found	Calc.	Diff.
2 : 6-Dimethyl .....	3.95	4.26	-0.31	3 : 4-Dimethyl .....	5.17	5.23	-0.06
2 : 3-Dimethyl .....	4.70	4.57	+0.13	2 : 5-Dimethyl .....	4.53	4.57	-0.04
2 : 4-Dimethyl .....	4.89	4.91	-0.02	5-Chloro-4-methyl ...	4.05	4.09	-0.04

methylanilino-anil and the 3-chloro-4-methylanilino-anil. The largest deviations occur in the 2 : 3- and the 3 : 4-dimethyl compound, and are in the direction of greatly decreased rates of reaction. In both cases this effect can be interpreted as steric inhibition by the adjacent methyl group of the full operation of the electromeric effect of the 3-methyl substituent. This would reduced to some degree the stabilisation of the transition complex by the resonance structure corresponding to (II).

The peculiarity of the 2 : 3-disubstituted anils is analogous to the unusual effect on the basicity of the adjacent methyl groups in 2 : 3-xylidine, to which reference has been made above. This effect is also evident in the hydrolysis of the anils. The hydrolysis

TABLE 4. Additivity of substituent effects.

4-Anilinopent-2-en-2-one	$\log k^X$	$\log k^Y$	Cyclodehydration		$\log k^{X,Y}$		Diff.
			$\log k^H$	Calc.	Found	Diff.	
2 : 3-Dimethyl .....	-1.99	0.41	-2.43	0.85	0.20	-0.65	
2 : 4-Dimethyl .....	-1.99	-1.58	-2.43	-1.14	-1.14	0	
3 : 4-Dimethyl .....	0.41	-1.58	-2.43	1.26	0.64	-0.62	
3-Chloro-4-methyl .....	-2.08	-1.58	-2.43	-1.23	-1.27	-0.04	
3-Chloro-2-methyl .....	-1.99	-2.08	-2.43	-1.64	-2.00	-0.36	
Hydrolysis							
4-Anilinopent-3-en-2-one	$\log k^X$	$\log k^Y$	$\log k^H$	Calc.	$\log k^{X,Y}$		Diff.
2 : 3-Dimethyl .....	-2.17	-1.56	-1.34	-2.39	Found	Diff.	
2 : 4-Dimethyl .....	-2.17	-1.74	-1.34	-2.57	-2.65	-0.26	
3 : 4-Dimethyl .....	-1.56	-1.74	-1.34	-1.96	-2.57	0	
					-1.90	+0.06	

Rates of cyclodehydration were determined in 93.8% sulphuric acid at 25°, except those of the *m*-methyl, 2 : 3-dimethyl, and 3 : 4-dimethyl compounds. The last three were measured in 74.8% sulphuric acid and the values in the 93.8% acid calculated from equation (1). All rates of hydrolysis were determined in 60.1% sulphuric acid at 25°.

rates given in Table 4 show that while the effects of methyl groups in the 2- and the 4-position are additive, the rate of hydrolysis of the 2 : 3-dimethylanilino-compound is less than expected. It has been suggested that the enhanced effect of the 2-methyl substituent on an adjacent side chain due to the repulsion of a 3-methyl substituent operates by reducing the coplanarity of the side chain with the benzene ring.<sup>15</sup> This

<sup>13</sup> Brown and Cahn, *J. Amer. Chem. Soc.*, 1950, **72**, 2939.

<sup>14</sup> van Helden, Verkade, and Wepster, *Rec. Trav. chim.*, 1954, **73**, 39.

<sup>15</sup> Dippy, Hughes, and Laxton, *J.*, 1954, 1470.

would clearly result in the increased basicity of 2 : 3-xylylidine. The slower hydrolysis of the 2 : 3-dimethylanilino-compound found experimentally would also be expected since the greater electron-density in the neighbourhood of the azomethine bond would hamper the nucleophilic attack by water. The reduced rate of cyclodehydration of 4-(2-chloro-3-methylanilino)pent-3-en-2-one has a similar explanation if it is assumed that there is an increase in the repulsion between the chlorine and the methyl substituent due to the side chain which decreases the conjugation of the 3-methyl group with the ring and reduces the contribution of the resonance structure corresponding to (II).

In the hydrolysis methyl groups in all positions reduce the rate, in contrast to their activating effect in cyclodehydration, and this is in accord with the mechanism proposed in the preceding paper of nucleophilic attack by water on the carbon atom of the side chain adjacent to the nitrogen atom. As might be expected in a side-chain reaction, the results for the hydrolysis of both the monosubstituted and the disubstituted anils (except the 2 : 3-dimethylanil) fit the Hammett equation:<sup>16</sup>

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

where  $k$  and  $k_0$  are the rate constants for the substituted and unsubstituted anils respectively,  $\rho$  is a constant characteristic of the reaction, and  $\sigma$  a constant characteristic of the substituent. The plot of  $\log k/k_0$  against Hammett's original  $\sigma$  values is a straight line and the value of  $\rho$  from the slope is 1.91. The fact that  $\rho$  is positive indicates a reaction facilitated by a low electron-density at the reaction site. No similar correlation of rate constant with the  $\sigma$  values recently proposed<sup>17</sup> for electrophilic aromatic substitution was found for the cyclodehydration.

TABLE 5. Activation energies ( $\pm$  ca. 300 cal.) in cyclodehydration.

H <sub>2</sub> SO <sub>4</sub> (%)	4- <i>p</i> -Toluidinopent-3-en-2-one		4-Anilinopent-3-en-2-one	
	$E_A$ (cal.)	$\log_{10} A$	$E_A$ (cal.)	$\log_{10} A$
94.9	15,900	10.4	17,400	10.9
91.2	16,500	10.4	15,600	9.1
86.8	17,300	10.5	—	—

*Constants of the Arrhenius Equation.*—Rates of cyclodehydration of both anilino- and *p*-toluidino-anils were measured over the range 0—50° in different media to evaluate the constants,  $A$  and  $E$ , of the equation  $\log k = \log A - E/RT$  which are given in Table 5. Reproducible results could not be obtained for the anilinoanil in 86.8% sulphuric acid, possibly because of some hydrolysis in this medium.

#### EXPERIMENTAL

*Media.*—Pure sulphuric acid and sulphuric acid–water mixtures were prepared and standardised as described in Part I.<sup>2</sup> Perchloric acid–water mixtures were prepared from “AnalaR” perchloric acid and similarly standardised.

*Materials.*—Acetylacetone was dried over potassium carbonate and distilled. The majority of aromatic amines were obtained from B.D.H. or Light and Co. and were recrystallised or distilled under reduced pressure. *m*-Iodoaniline was obtained by reduction of *m*-nitroaniline. 3-Chloro-4-methylaniline was prepared from 2-methyl-5-nitroaniline by diazotisation and treatment with cuprous chloride.<sup>18</sup> 4-Chloro-3-methylaniline was obtained by the action of sodium chlorate and concentrated hydrochloric acid on aceto-*m*-toluidide.<sup>19</sup>

The anils were prepared by boiling under gentle reflux a 1 : 1.1 mixture<sup>3</sup> of the aromatic amine and acetylacetone. Most anils were obtained in 60—70% yield by this method and were crystallised from light petroleum (b. p. 40—60°). The following substituted 4-anilinopent-2-en-4-ones do not appear to have been described previously: *m*-fluoro-, m. p. 35—36°; *p*-fluoro-,

<sup>16</sup> Hammett, *Chem. Rev.*, 1935, **17**, 125; Taft, “Steric Effects in Organic Chemistry,” ed. by Newman, Chapman and Hall Ltd., London, 1956, p. 556; Brown and McDaniel, *J. Org. Chem.*, 1958, **23**, 420.

<sup>17</sup> Brown and Okamoto, *J. Amer. Chem. Soc.*, 1957, **79**, 1913.

<sup>18</sup> Witt, *Ber.*, 1892, **25**, 86.

<sup>19</sup> Reverdin and Crépieux, *Ber.*, 1900, **33**, 2503.

m. p. 44°; *m*-bromo-, m. p. 37—38°; *m*-iodo-, m. p. 56—57°; 2 : 4-dimethyl-, m. p. 38—40°; 3 : 4-dimethyl-, b. p. 190°/20 mm.; 3-chloro-4-methyl-, m. p. 67—68.5° (Found: N, 6.5; Cl, 16.1.  $C_{12}H_{14}ONCl$  requires N, 6.3; Cl, 15.9%); 4-chloro-3-methyl-, m. p. 46—47° (Found: N, 6.5; Cl, 15.6.  $C_{12}H_{14}ONCl$  requires N, 6.3; Cl, 15.9%); 3-chloro-2-methyl-, m. p. 81—82°.

The corresponding quinoline compounds were obtained from these anils in 89—99% yields by dissolving 1 g. of the anil in 10 ml. of 98% sulphuric acid and keeping the solution at room temperature for several hours before isolating the product.<sup>2</sup> The following substituted quinolines do not appear to have been reported previously: 7-fluoro-2 : 4-dimethyl-, m. p. 45—46°; 7-bromo-2 : 4-dimethyl-, m. p. 46—47°; 7-iodo-2 : 4-dimethyl-, m. p. 54—55°; 2 : 4 : 6 : 7-tetramethyl-, m. p. 79—80° (Found: C, 84.4; H, 8.1; N, 7.7.  $C_{13}H_{15}N$  requires C, 84.3; H, 7.9; N, 7.6%); 7-chloro-2 : 4 : 6-trimethyl-, m. p. 81—82° (Found: N, 7.1; Cl, 17.3.  $C_{12}H_{12}NCl$  requires N, 6.8; Cl, 17.2%); 5-chloro-2 : 4 : 8-trimethyl-, m. p. 54—55°; 6-chloro-2 : 4 : 7-trimethyl-, m. p. 89—90°; 7-chloro-2 : 4 : 8-trimethyl-, m. p. 68—69° (Found: N, 6.8; Cl, 17.9.  $C_{12}H_{12}NCl$  requires N, 6.8; Cl, 17.2%).

*Measurement of Reaction Rates.*—Rates of cyclodehydration in sulphuric acid–water and perchloric acid–water were determined as described in Part I.<sup>2</sup> It was established that neither sodium perchlorate nor any of the amines or quinoline compounds investigated interfered with analysis of the mixtures, in which the acetylacetone obtained from unchanged anil is converted into its ferric salt which is determined colorimetrically. A small refinement was introduced to obtain the reference curve for standard solutions of acetylacetone prepared from the pure ketone. Two reference curves were obtained, the prepared solutions for analysis in one case containing 1.62 g. of sodium sulphate per 40 ml., and in the other case 3.24 g. of sodium sulphate per 40 ml. These are the lower and the upper limit of sodium sulphate concentrations in the solutions obtained for colorimetric analysis from reaction mixtures. While the difference in slopes of the straight lines obtained by plotting the logarithms of the optical density ratio against concentration of acetylacetone was almost negligible, the gradients in both cases were about 3% less than the slope of the reference curve obtained in the absence of added sodium sulphate. The new reference curves were therefore preferred for the evaluation of the experimental results.

Rates of hydrolysis were determined as described in the preceding paper.<sup>2</sup>

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