CCCCXXX.—*The Chlorination of Anilides. Part VII. The Constitutional Influence of the Acyl Group upon Side-chain Reactivity.*

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A new method for the analysis of solutions containing both chloroamine and free chlorine was applied by Orton, Soper, and Williams (J., 1928, 998) to show that *N*-chlorination and *C*-chlorination of anilides are simultaneous side reactions, and subsequently (Williams, J., 1930, 37) to investigate the effects of substituents upon the rates of *N*-chlorination of acetanilides and acetobenzylamides in 40% acetic acid at 18°. This investigation has now been extended to an examination of the constitutional influence of the acyl group on the kinetics of chlorination. The reactions may be summarised by the equations

$$\mathrm{Ar{\cdot}NHAc} + \mathrm{Cl_2} \begin{array}{l} \nearrow \ \mathrm{Ar{\cdot}NClAc} + \mathrm{HCl} \\ \searrow \ \mathrm{Cl{\cdot}(Ar{-}H){\cdot}NHAc} + \mathrm{HCl} \end{array}$$

The unsubstituted acylanilides are frequently chlorinated too rapidly for the convenient measurement of reaction velocities (Table I), so the chloro-substituted anilides have been employed (Table II). The medium is, in all cases, 40% acetic acid (6·90 *N*), and the temperature 18° ± 0·01°. In the tables, k_N and k_C are second-order velocity coefficients for *N*- and *C*-chlorination respectively, and each value is the mean of at least three determinations.

The mean deviation from the mean is estimated to be in most instances about ± 2%, and exceeds ± 6% only with chloroform-anilides (see Experimental). A dash in the tables indicates that the reaction in question is too slow for accurate measurement in comparison with the other (simultaneous) reaction taking place. The word " rapid " signifies that the reactions are of the same order of rapidity as with acetanilide, or possibly even faster. The rates of reaction for acetanilide were determined by special methods by Orton, Soper, and Williams (*loc. cit.*).

TABLE I.

Chlorination of $C_6H_5{\cdot}NHAc$.

Ac–.	k_N.	k_C.	k_N/k_C.
H·CO–	—	Rapid	0·175
$CH_3{\cdot}CO$–	96	11,000	0·00873
$CCl_3{\cdot}CO$–	—	149	—

TABLE II.

(*a*) Chlorination of *o*-$Cl{\cdot}C_6H_4{\cdot}NHAc$.

Ac–.	k_N.	k_C.	$K_a \times 10^5$ for Ac·OH.	Ac–	k_N.	k_C.	$K_a \times 10^5$ for Ac·OH.
H·CO–	1170	—	21·4	$CH_2Cl{\cdot}CO$–	112	—	155
$CH_3{\cdot}CO$–	286	—	1·85				

(*b*) Chlorination of *p*-$Cl{\cdot}C_6H_4{\cdot}NHAc$.

H·CO–	425	—	21·4	$CH_2Cl{\cdot}CO$–	29·3	36·4	155
Me·CO–	115	135	1·85	$CCl_3{\cdot}CO$–	—	Very slow, cf. Table I	Strong
Et·CO–	72	167	1·4				
$Pr^{\alpha}{\cdot}CO$–	78	169	1·5	Ph·CO–	28·3	57·2	6·6
$Pr^{\beta}{\cdot}CO$–	35	163	1·5	$Ph{\cdot}SO_2$–	Rapid	—	Strong

The value for the ratio k_N/k_C is determined by measuring the final chloroamine titre at the end of the reaction, and that given in Table I for formanilide is possibly not exact (although consistent results were obtained with the initial concentration ratio $[Ar{\cdot}NHAc]/[Cl_2]$ varying from 5·5/1 up to 25/1), owing to the chance of formation of the chloroamines of the primary products of nuclear chlorination (Orton, Soper, and Williams, *loc. cit.*; see also Soper, *J. Physical Chem.*, 1927, **31**, 1192). It is nevertheless certain from the evidence with other compounds that this ratio is much higher for formanilide than for acetanilide; the replacement of the acetyl group by the formyl group facilitates *N*-chlorination. This effect is seen again in both sections of Table II.

The last column in Table II gives the ionisation constants at 25° for the acids Ac·OH (Scudder, " The Electrical Conductivity and Ionisation Constants of Organic Compounds," London, 1914; Landolt–Börnstein, " Tabellen," Berlin, 1923–31).

Discussion of Results.

Uncertainties with regard to the influence of solvents upon reaction kinetics impose limitations upon the use of comparative rate measurements to determine the constitutional influence of groups upon reactivity. Although, when a standard substance (in the present instance, chlorine) is made to react with a series of compounds under fixed conditions, the only variable is apparently constitution, and differing rates of reaction may in the last resort be ascribed to the imposed variations in constitution, yet *specific* mutual actions between solvent and solute may operate as "intermediate" independent variables, and thus obscure the direct relation between constitution and change of reactivity. Conant and Hussey (*J. Amer. Chem. Soc.*, 1925, **47**, 480) and Lapworth (this vol., p. 1964) have expressed the view that only *large* differences of velocity are of significance in relation to changes of constitution.

These difficulties were discussed in a previous paper (Williams, *loc. cit.*), and it was shown by tabulation of a large number of different side-chain reactions that, in polar solvents at least, the regularities in the effects of substituents over-shadow specific solvent effects, since the reactions can be correlated and classified fairly consistently by means of the electronic theories. In this field, therefore, it is probable that provisional rough conclusions may be drawn from velocity measurements.

It is evident from the foregoing tables that the presence of a methyl substituent in the acyl group retards *N*-chlorination; the effect is especially marked in *p*-chloro*iso*butyranilide. The presence of chlorine in the side chain also retards *N*-chlorination. A difficulty in interpretation thus arises, for previous work on the effects of substituents (J., 1930, 37) has shown that both the foregoing substituents, when present in the *nucleus*, enhance the rate of *N*-chlorination. The conclusion was then drawn that *N*-chlorination (like *C*-chlorination) is facilitated by the transmission of a negative charge to the atom to which the replaceable hydrogen is attached, and that the significant stage in the process is the attachment of an incipiently positive chlorine component. From this point of view, the accelerating influence of nuclear substituted chlorine had to be ascribed to predominating tautomeric effect ($+ T$; Ingold, *Ann. Reports*, 1927, **24**, 151) and it was, in fact, found that, when the reacting atom was not directly attached to the nucleus, as in the acetobenzylamides, nuclear chlorine depressed the reaction rate ($- I$). By a process of reasoning similar to that employed by Orton and Bradfield (J., 1927, 986), it would appear, if the reactive form of the anilide is assumed to be the normal form Ar·NH·CO·R, that the rates of *N*-chlorination of acylanilides should decrease with increasing ionisation constants of the corresponding fatty acids. Table II shows that this expectation is justified with the ω-chloro-compounds, which suggests that the retarding influence of chlorine in the acyl group is due to its normal inductive effect ($-I$). On the other hand, k_N for the ω-methyl-substituted anilides *increases* with increasing ionisation constant of the acid, although the values for k_C are, actually, inversely parallel to the K_a values * and are also parallel to the velocity coefficients for nuclear chlorination observed with glacial acetic acid media, in which no *N*-chlorination occurs (Orton and King, J., 1911, **99**, 1369; Orton and Bradfield, *loc. cit.*). The latter fact suggests that, when *N*- and *C*-chlorination both take place, they may do so by independent mechanisms, involving different forms of the anilide. A like parallelism is found on comparing k_C from Table II (*b*) with the figures of Bradfield and Jones (J., 1928, 1006) for the effect of increasing chain length in a group R upon the rate of nuclear chlorination of compounds of the form *p*-Cl·C_6H_4·OR.

The retarding influence of the phenyl group in Table II (*b*), as seen in k_N for *p*-chlorobenzanilide, is consistent with the previous observation (J., 1930, 37) that the rate of *N*-chlorination increases steadily in the series: acetanilide, acetobenzylamide, aceto-β-phenylethylamide, acetamide. The case of *p*-chlorobenzenesulphonanilide is scarcely comparable with the others and demands special treatment (compare Orton and Bradfield, *loc. cit.*).

At present it is only possible to offer speculative suggestions to account for the behaviour of the ω-methyl group in *N*-chlorination, and detailed discussion is reserved pending further experiments. One possibility, which covers many of the facts, is attack by a chlorine molecule at the nitrogen and/or the hydrogen atom of an *aci*-form of the anilide, with formation of an *N*-chloro-derivative. Substituents may then accelerate reaction either by increasing the negativeness of the nitrogen, or by increasing the positiveness of the oxygen and so facilitating the separation of a proton. The nature of the effect of a substituent may then depend on its position, according to whether its influence is felt most strongly at the nitrogen or at the oxygen atom. But there are several ways in which a chlorine molecule may attack an anilide molecule to form a chloroamine, and it is possible that the introduction of a substituent alters, not only the ease of attack according to a particular formulation, but also the mode of attack itself. Pryde and Soper (this

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* The absence of a value of k_C for *p*-chloroformanilide in Table II means only that *C*-chlorination is too slow in comparison with *N*-chlorination to be distinguished with certainty from accidental loss of chlorine. It does not necessarily follow that k_C for this compound is less than that for chloroaceto-*p*-chloroanilide.

vol., p. 1510) have found that the interpretation of some results for the rates of interaction of anilides with hypochlorous acid is facilitated by the assumption that an *O*-chloro-derivative is formed; and Soper and Smith (J., 1928, 138) have discussed this formulation for chloroamines in explaining a somewhat similar anomaly of the methyl group, *viz.*, the fact that it decreases the hydrolysis constant of a chloroamine when present in the benzene nucleus and raises it when in the acyl group.

As may be seen from the reactions of alkyl iodides (*e.g.*, Segaller, J., 1914, **105**, 106; Haywood, J., 1922, **121**, 1904; Conant *et al.*, compare *Ann. Reports*, 1929, **26**, 137), the influence of increasing chain-length upon reaction speed is usually progressive up to about the fourth carbon atom, after which there is little further change. This is borne out by the results in Table II (*b*). But with regard to symmetry in the effect of a substituent group introduced in turn on either side of the reacting bond, there are few data available for comparison with the present results for *N*-chlorination. Ingold (J., 1930, 1032) has shown that the effect of change in constitution in X or Y in the hydrolysis of compounds of the form

$$X{\cdot}CH_2{\cdot}CO{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}Y \text{ and } X{\cdot}CO{\cdot}O{\cdot}CH_2{\cdot}Y$$

is the same whether the substituent is present in X or in Y. From the data of Norris (*Z. physikal. Chem.*, 1927, **130**, 662) for the reaction $p\text{-}NO_2{\cdot}C_6H_4{\cdot}COCl + ROH = p\text{-}NO_2{\cdot}C_6H_4{\cdot}CO_2R + HCl$, it appears that the effects of substituents in the benzene nucleus and of varying chain-length in the alcohol ROH are self-consistent, although the same may not be true when the nitrobenzoyl chloride is replaced by a diphenylchloromethane derivative (Norris and Banta, *J. Amer. Chem. Soc.*, 1928, **50**, 1804).

EXPERIMENTAL.

Materials.—Certain of the anilides were pure specimens prepared in the Chemical Laboratory, University College, Bangor. For these we are greatly indebted to the late Prof. K. J. P. Orton and to Dr. A. E. Bradfield. The longer-chain anilides and ω-chloroacetanilides were made by the action of the acyl chloride upon the amine and were repeatedly recrystallised from dilute acetic acid, alcohol, or water. Other materials were prepared and purified as previously described by Orton, Soper, and Williams (*loc. cit.*). All reaction media were tested for stability to chlorine.

Control of Reaction Medium.—In order to ensure that the medium conditions in the present experiments were identical with those in the previous work, velocity measurements were made with substances whose velocity coefficients had been determined previously. The results were as follows: For aceto-β-phenylethylamide, $k_N = 210$, 200; old value 205. For aceto-*p*-chlorobenzylamide, $k_N = 99, 97$; old value 99. Tests with the latter compound were repeated periodically with the different samples of medium, always with satisfactory results.

Velocity Measurements.—Alternate portions of the reaction mixture were analysed at known time intervals (*a*) for chlorine by titration with $N/500$-thiosulphate, and (*b*) for chloroamine by removal of chlorine with saturated *p*-cresol solution, and subsequent titration. Precautions and controls were applied just as before, except that it was found advantageous as an additional precaution in certain cases to keep all analysis flasks in a light-tight box. The velocity coefficients were calculated as usual from the equations

$$k_N + k_C = \frac{2\cdot303}{t(a-b)}\log_{10}\left[\frac{b}{a}\cdot\frac{a-(x+y)}{b-(x+y)}\right]; \quad \frac{k_N}{k_C} = \frac{y}{x}.$$

The individual experiments in the present series differed in no way from those described previously, and reference may be made to the earlier papers for examples worked out in full. No deviations were observed from the conclusion established by Orton, Soper, and Williams that Wegscheider's test (constancy of the ratio k_N/k_C) is fulfilled in the interaction of chlorine with anilides in aqueous acetic acid, so that *N*- and *C*-chlorination are true side reactions.

Particular care was required with formanilide derivatives, as these were found to decompose rather easily in solution. Any warming caused marked decomposition, accompanied, sometimes by the appearance of colour, and always by an abnormally high initial consumption of chlorine to form a nuclear-chlorinated derivative. It was found necessary to make up solutions by dissolving the anilide in glacial acetic acid and then diluting to 40% concentration. Expt. 72 is an example of one of the final results with *p*-chloroformanilide.

Expt. 72. *p*-Chloroformanilide = $0\cdot000984M$. $Na_2S_2O_3$ = $1\cdot028N/500$. Chlorine = $0\cdot000645M$. HCl = $0\cdot01M$.

Time, mins. ...	0	0·88	1·80	2·70	3·53	4·37	5·20	6·00	6·47
Titre, c.c.	1·41	5·70	3·11	5·58	3·91	5·48	4·33	5·48	5·06

From curves constructed from these data, we find :

k_N at one-minute intervals	—	463	473	471	460
Change, %	49·2	61·9	71·0	77·0	81·3

Mean k_N (corrected for accidental chlorine loss) = 424.
Mean of four experiments, $k_N = 425 \pm 10\%$.

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