

CLIV.—*The Relation of the Velocity of Chlorination of Aromatic Compounds to Constitution. Part I. Chlorination of Anilides.*

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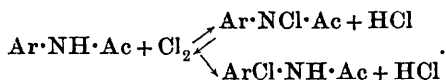
ALTHOUGH it is well known that differences exist in the "readiness" with which anilides are chlorinated or brominated, no systematic study of the relation between the velocities of substitution and constitution has been made.

The investigation is beset with numerous difficulties. The forma-

tion of the compound of hydrogen bromide and bromine: $\text{HBr} + \text{Br}_2 \rightleftharpoons \text{HBr}_3$, especially in anhydrous solvents, obscures the process of bromination (*Brit. Assoc. Reports*, 1910, p. 85; Orton and Jones, *Proc.*, 1909, **25**, 305; Jones, this vol., 392). The similar compound of chlorine and hydrogen chloride, if produced at all under analogous conditions, is at such low concentrations as to have no detectable effect on chlorination. Hence we have, in the first place, confined our attention to chlorination.

The process of chlorination is very greatly affected by the medium in which it takes place. For reasons which will appear in what follows, a true comparison of the speeds of chlorination can best be made in glacial acetic acid. Orton and Jones (*Trans.*, 1909, **95**, 1456) have shown that in acetic acid of various dilutions there exists an equilibrium between chlorine, anilide, chloroamine, and hydrogen chloride: $\text{Ar}\cdot\text{NH}\cdot\text{Ac} + \text{Cl}_2 \rightleftharpoons \text{Ar}\cdot\text{NCl}\cdot\text{Ac} + \text{HCl}$. In glacial acetic acid the right hand side of the system cannot be detected, but as the medium is diluted, it becomes perceptible; for example, in 95 per cent. acetic acid it forms 20 per cent. of the system; in 75 per cent. acetic acid, 80 per cent.; and finally, in 50 per cent. acetic acid, only a trace of free chlorine is present. These numbers refer to 2:4-dichloroacetanilide, but although in dilute acetic acids there is considerable difference between anilides, in glacial acetic acid the constitution of the anilide has little effect. This equilibrium is attained with extreme rapidity, but in one or two selected instances the velocity of the opposing reactions has been indirectly measured (*Brit. Assoc. Reports*, *loc. cit.*).

This reversible formation of chloroamine complicates greatly the process of chlorination in the nucleus, *C*-chlorination, in dilute acetic acid. When chlorine is added to an aqueous acetic solution of an anilide which is capable of *C*-chlorination, such as *p*-chloroacetanilide, two reactions, both extremely fast, take place, irreversible *C*-chlorination and reversible *N*-chlorination:

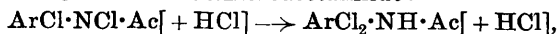


The proportion of the two changes, and hence their relative velocities, can be very easily measured by estimations of the free chlorine (by aspiration) and of the chloroamine (by titration) (Orton and Jones, *loc. cit.*). It varies with the composition of the medium and the constitution of the anilide: thus for *p*-chloroacetanilide, the ratio, *N*-chlorination/*C*-chlorination, in 30 per cent. acetic acid, is 0.93:1; in 50 per cent., 1.25:1; in 65 per cent., 1.55:1, whilst for acetanilide, in the same concentrations of acetic acid, 0.082:1, 0.08:1, and 0.083:1.

The absence of *N*-chlorination, and the fact that *C*-chlorination is slowest in glacial acetic acid, allows of direct measurement of the speeds of *C*-chlorination, and a comparison of different anilides in this medium, which has therefore been chosen for a study of the effect of constitution of anilides.

In selecting a method of experiment, it must be remembered, as shown in the foregoing, that the same velocity of chlorination is found when the reacting system is prepared from chlorine and anilide, or chloroamine and hydrochloric acid, since chloroamines and hydrogen chloride in glacial acetic acid react quantitatively and instantly, forming chlorine and anilide. For a similar reason, as a very convenient way of adding given quantities of chlorine, an anilide, the speed of chlorination of which is under investigation, may be treated with the molecular proportions of hydrogen chloride and some chloroamine, such as acetylchloroamino-2:4-dichlorobenzene, the anilide corresponding with which is not chlorinated in the nucleus at an appreciable rate. This last procedure is in every way to be preferred, for the preparation of standard solutions of chlorine in glacial acetic acid, or the preparation of chloroamines often difficult to purify, is avoided. Moreover, the simplification of the manipulation lessens the opportunity for the introduction of small quantities of water, which has a powerful accelerating effect on the velocity of chlorination. We have put these three methods of operating to a thorough experimental test, and have shown that the value of the velocity coefficient is independent of the procedure, and, further, of the order in which the three reagents are mixed.

The speed of chlorination in glacial acetic acid is independent of the quantity of hydrogen chloride, provided that the acid is in excess of one molecular proportion. When a chloroamine is used as chlorinating agent, and but a relatively small proportion of hydrogen chloride, 1/20—1/10th gram-molecular proportion, added, the concentration of the chlorine in the system remains constant at 1/20—1/10th gram-molecular proportion during the main part of the reaction. Hence the reaction is apparently of the first order. Moreover, since the quantity of chlorine produced in the system is equivalent to the hydrogen chloride added, the speed of chlorination is proportional to the concentration of the acid. When the chlorination is carried out by treatment of the isomeric chloroamine with a small proportion of hydrogen chloride (1/20—1/10th gram-mol.), for example, the conversion of acetylchloroamino-*p*-chlorobenzene into 2:4-dichloroacetanilide:



the speed of chlorination is proportional to the *square* of the concen-

tration of the hydrogen chloride added, for now quantities equivalent to the hydrogen chloride, of both the reacting substances, anilide and chlorine, are produced in the system. These relations only hold in glacial acetic acid, for in the diluted media chloroamine and hydrogen chloride can co-exist.

Experiment has shown that hydrogen chloride may be present in excess to the extent of 8—10 molecular proportions without affecting the character or speed of the chlorination. This behaviour is in marked contrast to the effect of hydrogen bromide on bromination (*loc. cit.*); addition of sufficient excess of hydrogen bromide, 4 gram-molecular proportions, will bring the bromination of acetanilide in glacial acetic acid to a standstill.

The reaction is naturally a simple change of the second order. Whatever view be held as to the mechanism of substitution, the first step is the interaction of separate molecules of anilide and chlorine. There appear to be no disturbing effects produced by change of concentration, or during the course of the reaction. Frequently, of course, a chloroanilide is produced in the reaction, which is itself capable of chlorination. Notwithstanding the fact that its concentration exceeds that of the original anilide for the second half of the reaction, the unchlorinated (or less chlorinated) anilide reacts so much more rapidly (about 200 times) with chlorine than the chlorinated anilide that the effect of the consecutive reaction is scarcely perceptible, even towards the end of the change.

Results: (i) *Acyl Groups*.—The formyl group shows its usual influence; the speed of chlorination reaches a maximum with the propionyl group, but falls off very slightly with increasing length of the acyl chain; the branch chain in *isovaler*anilide has an obvious depressing effect on the velocity.

	k_{II}		k_{II}
Formanilide	4.95	Stearanilide	64
Acetanilide	40	<i>iso</i> Valeranilide	57
Propionanilide	72	Oxanilide	2
Butyranilide	64.5	Benzanilide	42

(ii) The effect of the presence of chlorine in the ortho- or para-positions respectively is well shown by the following numbers:

	k_{II}		k_{II}
Acetanilide	40	Benzanilide	42
<i>o</i> -Chloroacetanilide	0.079	<i>p</i> -Chlorobenzanilide	0.16
<i>p</i> -Chloroacetanilide	0.21		

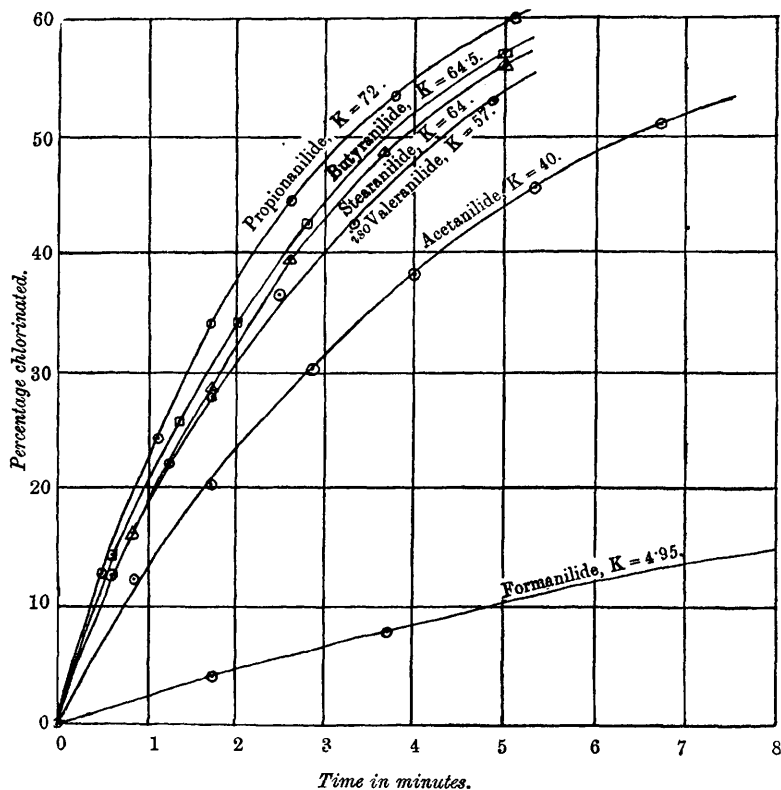
The striking effect of the chlorine atom in the ortho-position is noteworthy. The chlorination of 2:4-dichloroacetanilide in glacial acetic acid cannot be detected at the ordinary temperature; *s*-trichloroacetanilide is produced at 150—160°, but the yield is

poor, as the attack of chlorine on the acetic acid solvent is then considerable.

(iii) Chlorine offers a marked contrast to the methyl group:

	k_{II}		k_{II}
Acetanilide	40	Benzanilide	42
Aceto- <i>o</i> -toluidide	9	Benzo- <i>o</i> -toluidide	5.7
Aceto- <i>p</i> -toluidide	77	Benzo- <i>p</i> -toluidide	70
<i>p</i> -Chloroacetanilide	0.21	<i>p</i> -Chlorobenzanilide	0.16

FIG. 1.



The methyl group in the *para*-position causes an increase in the speed of chlorination; but the influence of position is well shown, in that k_{II} for the chlorination of aceto-*o*-toluidide is only 1/4th that of k_{II} for acetanilide.

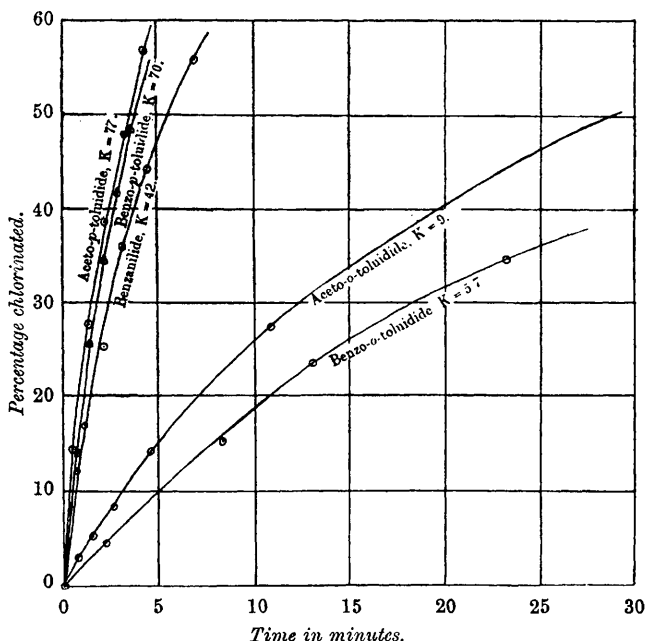
These numbers give also an opportunity of contrasting the acetyl and benzoyl groups. Although benzanilide is chlorinated slightly more rapidly than acetanilide, in the case of the corresponding

derivatives the acetyl compounds are chlorinated about $1\frac{1}{2}$ times as fast as the benzoyl compounds.

(iv) Measurements of the chlorination of anisidides and phenetidides show that the mere occupation of the ortho- or para-positions is not a decisive factor. Aceto-*o*-anisidide and aceto-*o*-phenetidide are chlorinated more rapidly than the para-derivatives.

	k_{II}		k_{II}
Acetanilide	40	Aceto- <i>p</i> -toluidide.....	77
Aceto- <i>o</i> -anisidide	60	Aceto- <i>o</i> -phenetidide	90
Aceto- <i>p</i> -anisidide	57	Aceto- <i>p</i> -phenetidide	85

FIG. 2.



The ethoxyl group is more favourable to chlorination than the methoxyl; the methyl group occupies an intermediate position.

(v) The cumulative effect of methyl groups is illustrated in the series:

	k_{II}		k_{II}
Acetanilide	40	Aceto- <i>p</i> -toluidide.....	77
Aceto- <i>o</i> -toluidide	9	Aceto- ψ -cumidide	630
Aceto- <i>m</i> -xylylide.....	9		

The introduction of a methyl group in the para-position with respect to the group NHAc in aceto-*o*-toluidide, as illustrated in aceto-*m*-xylylide, has no effect, whilst the introduction of an ortho-

methyl group in aceto-*p*-toluidide reduces the value of k_{II} to 1/9th 77 to 9. The introduction of a third methyl group, as in ψ -cumidide, is, however, accompanied by a very large rise in the value of k_{II} from 9 to 630.

(vi) The naphthalides are chlorinated at a very high speed.

	k_{II}		k_{II}
Acetanilide	40	Formanilide	4.95
Aceto- α -naphthalide	550	Formo- α -naphthalide	365
Aceto- β -naphthalide	"instantaneous chlorination."		

In the case of aceto- β -naphthalide at a concentration of 1/240 gram-molecule per litre, it is impossible to detect free chlorine after mixing.

EXPERIMENTAL.

The procedure which has been found most suitable in making the measurements of the velocity is as follows: A quantity of the anilide (0.00041 gram-molecule) is dissolved in about 15 c.c. of glacial acetic acid, and placed in a stoppered flask. One molecular proportion of acetylchloroamino-2:4-dichloroacetanilide, the source of the chlorine, is dissolved in about 85 c.c. of glacial acetic acid in a 100 c.c. stoppered measuring flask. Both these solutions are allowed to attain the temperature of the bath, 16°. One molecular proportion of hydrogen chloride, in the form of the constant boiling aqueous (22 per cent.) solution (0.058 c.c.), is then added, from a burette graduated to 1/50ths, to the solution of the chloroamine; and then the solution of the anilide immediately introduced. The total volume of the mixture was as nearly as possible 100 c.c., and hence the concentrations of the reacting substances, 0.0041 gram-molecule per litre. The reacting solution was carefully shielded from light in a closed bath kept in a dark room.

Volumes of 10 c.c. were withdrawn by a pipette at appropriate intervals, and added to a 5 per cent. potassium iodide solution; the iodine set free was titrated with *N*/50-thiosulphate.

In the case of anilides with a low solubility in glacial acetic acid, such as oxanilide and stearanilide, the anilide was dissolved in a larger volume of acid, 80–85 c.c., and the chloroamine in the smaller volume (20–15 c.c.). These are mixed, and the hydrogen chloride added finally.

When the speed was low the concentrations were raised to 0.025 gram-molecule per litre.

The anilides were either the purest material supplied by Kahlbaum or prepared from anilines obtained from the same source. They were recrystallised two or three times before use. The *o*-chloroaniline was prepared in the laboratory, and purified by

recrystallising the hydrochloride as described in the following paper (this vol., p. 1381).

Two determinations at least were made of the speed of chlorination, and the anilide was always recrystallised again before the second measurement. The values given for k_{II} in the foregoing are the mean of two concordant experiments.

For the highly dilute solutions which are required for these very speedy reactions, it is essential that the glacial acetic acid should be free from substances which react with chlorine. We used either the special "K" acid supplied by Kahlbaum, or an acid prepared by ourselves by distillation of a good commercial acid from phosphoric oxide. In all cases the acid was shown to be stable to bromine or chlorine (Orton, Edwards, and King, this vol., p. 1178).

Since the speed of chlorination in glacial acetic acid is very sensitive to the addition of water, increasing in a direct ratio, it was very important that the medium should be kept of constant composition throughout the whole series of experiments. We aimed at using an acid melting at 16.3° , that is, it contained 0.14 per cent. of water, as such an acid was far easier to obtain than an absolute acetic acid. Moreover, the addition of a trace of water obviously produces far less effect on the velocity than with an absolute acid. The high or irregular speeds which were occasionally observed could generally be ascribed to accidental entrance of small quantities of water during the manipulations.

The following figures are typical examples of the whole series of experiments. Concentrations are 0.0041, except where otherwise stated:

<i>Formanilide.</i>			<i>Acetanilide.</i>		
Time (minutes).	Percentage chlorinated.	k_{II} .	Time (minutes).	Percentage chlorinated.	k_{II}
5.0	8.8	4.75	0.8	12.3	—
14.3	21.4	4.75	1.7	20.3	40
26.3	33.4	4.75	2.8	30.8	40
40.3	43.5	4.77	4.0	38.2	39
57.6	53.5	5.00	5.3	45.6	39
81.7	62.5	5.10	6.7	51.1	39

<i>Propionanilide.</i>			<i>Stearanilide.</i>		
Time (minutes).	Percentage chlorinated.	k_{II} .	Time (minutes).	Percentage chlorinated.	k_{II} .
0.5	12.9	74	0.8	16.1	63
1.1	24.4	73	1.7	28.6	59
1.7	34.1	72	2.6	39.5	57
2.7	44.5	74	3.7	48.7	57
3.8	53.6	74	5.0	56.0	56
5.1	60.0	73	6.4	62.4	57

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o-Chloroacetanilide ; conc. 0·025.

Time (minutes).	Percentage chlorinated.	k_{II} .
60·0	10·0	0·074
184·1	24·8	0·072
360·1	40·8	0·076
606·2	53·2	0·075
1007·5	65·3	0·074

p-Chlorobenzanilide ;

Time (minutes).	Percentage chlorinated.	k_{II} .
69·5	5·6	—
179·2	10·6	0·165
361·4	19·3	0·165
575·2	27·8	0·167
651·0	29·8	0·165
871·2	36·6	0·165

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