56. *The Halogenation of Phenolic Ethers and Anilides. Part IV. The Chlorination of Some* p-*Substituted Anilides.*

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IN Part I (Orton and Bradfield, J., 1927, 986) the directive influence of the acylamido-group was discussed in the light of modern theories, and from a combined study of the proportions of the *o*- and *p*-isomerides formed on chlorination and the velocities of substitution it was found that these groups (R·CO·NH) could be arranged in the order (for R) : Et>Pr,Bu>Ph>Me>H. Except for a transposition of the benzamido- and the acetamido-group this order agrees with the sequence to be anticipated from a consideration of the ionisation constants of the corresponding carboxylic acids.

Additional rate measurements published subsequently (Bradfield and B. Jones, J., 1928, 3073) established the interesting fact that the *p*-toluenesulphonamido-group has a more powerful directing influence than the acetamido-group, the same order being observed in the depressed reactivities of the corresponding methylated acyl derivatives. The combined data from the study of the unsubstituted anilides then give the following order of directive power:

$$\mathrm{Et{\cdot}CO{\cdot}NH > Pr{\cdot}CO{\cdot}NH, Bu{\cdot}CO{\cdot}NH > Ph{\cdot}CO{\cdot}NH > C_7H_7{\cdot}SO_2{\cdot}NH > Me{\cdot}CO{\cdot}NH >}$$
$$\mathrm{Ph{\cdot}SO_2{\cdot}NH > H{\cdot}CO{\cdot}NH > C_7H_7{\cdot}SO_2{\cdot}NMe > CCl_3{\cdot}CO{\cdot}NH > Me{\cdot}CO{\cdot}NMe.}$$

The greater reactivity of the *p*-toluenesulphonanilide than of the acetanilide in nitration was independently observed by Bell (J., 1928, 2770; 1929, 2784), but he appears to have overlooked the fact that the explanation of these differences had already been recorded by Orton and Bradfield (*loc. cit.*).

Measurements have now been extended to anilides in which the *p*-position is occupied by halogen or by a carboxy- or nitro-group, the medium being the "99% acetic acid" containing 1 c.c. of water per 100 c.c. of solution.

TABLE I.

*Velocity coefficients for the chlorination of substances of the type p-*NHAc·C_6H_4X *in 99% acetic acid, at 20°.*

$[Cl_2] = 0{\cdot}02M$; $[HCl] = 0{\cdot}05M$.

Concn. of anilide, mols./l.		0·02	0·06	0·10	Concn. of anilide, mols./l.		0·02	0·06	0·10
Mol. proptn. of anilide		1	3	5	Mol. proptn. of anilide		1	3	5
		Velocity coefficients.					Velocity coefficients.		
Group X.	Group Ac.				Group X.	Group Ac.			
p-Cl	C_2H_5·CO	—	—	0·950	*p*-Br	C_2H_5·CO	—	—	1·043
,,	CH_3·CO	0·365	0·411	0·465	,,	CH_3·CO	0·418	—	0·528
,,	C_6H_5·CO	0·305	—	—	,,	C_7H_7·SO_2	—	—	0·362
,,	C_7H_7·SO_2	0·294	—	0·311	,,	C_6H_5·SO_2	—	0·227	—
,,	C_6H_5·SO_2	0·205	0·204	—	*p*-CO_2H	C_2H_5·CO	0·719	—	0·885
,,	CCl_3·CO	—	—	0·00117 *	,,	C_6H_5·SO_2	—	0·199	—

* Concn. of anilide = 0·20*M*.

TABLE II.

Velocity coefficients for the chlorination of p-*bromo-, -chloro-, and -nitro-acetanilide in 99% acetic acid at 20°.*

	p-Bromo- and *p*-chloro-acetanilide. $[Cl_2] = 0{\cdot}01M$; $[HCl] = 0{\cdot}05M$.		*p*-Nitroacetanilide. $[Cl_2] = 0{\cdot}04M$; $[HCl] = 0{\cdot}05M$.	
Concn. of anilide, mols./l.	0·01	0·02	0·02	0·05
Mol. proptn. anilide	1	2	0·5	1·25
p-Br	0·400	—	0·00897	0·00887
p-Cl	0·351	0·349		

Attempts to determine the constitutional influence of groups upon reactivity from comparative velocities are almost invariably complicated by the influence of solvents upon reaction kinetics, and as a result there is a tendency at present to regard large differences of velocity as alone significant (Conant and Hussey, *J. Amer. Chem. Soc.*, 1925, **47**, 480; Lapworth, J., 1931, 1964; Williams and Hughes, *ibid.*, p. 3125). Yet from an exhaustive study of side-chain reactions, Williams (J., 1930, 37) has shown that as far as reactions in polar solvents are concerned "the regularities in the effect of substituents over-shadow specific solvent effects." In the case of the phenolic ethers (Bradfield and B. Jones, J., 1928, 1006, 3073; 1931, 2903) there can be no doubt that the striking regularities observed are to be attributed directly to constitutional changes in the groups X and OR. On the other hand, it was to be anticipated that hydrochloride formation would modify the directing influence of the acylamido-groups. With a single exception, an increase in the proportions of hydrogen chloride to anilide decreases the velocity coefficient, the relative directive powers of the groups varying with the initial concentration of the reactants. The directive powers of the acetamido- and the *p*-toluenesulphonamido-group are 100 : 84 when the molar proportions of anilide, chloride and hydrogen chloride are 2 : 2 : 5, but 100 : 67 when these are in the ratio 10 : 2 : 5. A change of solvent also affects the directive powers. In 40% acetic acid, Orton, Soper, and Williams (J., 1928, 998) found the ratio of the velocities of chlorination of *p*-bromo- and *p*-chloro-acetanilide to be Br : Cl = 84 : 100, while the present measurements give Br : Cl = 113 : 100. In spite of these effects, however, the velocity coefficients determined under identical conditions give the relative directing influence of the various acylamido-groups under the particular set of conditions selected.

A quantitative comparison of the directive powers of the various acylamido-groups in the unsubstituted and *p*-substituted series is not possible, since, owing to the lower reactivity of the latter series the measurements were not all carried out at the same concentration. From Table I the following series of diminishing directive powers is obtained:

$$\mathrm{Et{\cdot}CO{\cdot}NH > Me{\cdot}CO{\cdot}NH > Ph{\cdot}CO{\cdot}NH > C_7H_7{\cdot}SO_2{\cdot}NH > Ph{\cdot}SO_2{\cdot}NH \gg CCl_3{\cdot}CO{\cdot}NH}.$$

In both the *p*-chloro- and the *p*-nitro-series the theoretical sequence Me·CO·NH> Ph·CO·NH is found, and in the *p*-chloro- and *p*-bromo-series the order $C_7H_7{\cdot}SO_2{\cdot}NH >$ Me·CO·NH observed in the unsubstituted anilides is reversed.

In view of the basic character of anilides and the acid nature of the reaction medium, it is not to be expected that ratios of the type $k^{OR_1}_{p\text{-}X}/k^{OR_2}_{p\text{-}X}$ and $k^{OR}_{p\text{-}X_1}/k^{OR}_{p\text{-}X_2}$ obtained in the present series would show the same constancy as appeared in the data for the phenolic ethers. Nevertheless, the values given in Tables III and IV (compiled from the velocity coefficients in Col. 5, Table I) agree sufficiently well to justify the extension of this treatment to the chlorination of anilides, but a more detailed knowledge as to the extent of hydrochloride formation in solution would be necessary in order to analyse these results further.

Finally, a comparision of the relative directive influences of bromine, chlorine, and the carboxyl group in *p*-substituted phenolic ethers and anilides is made in Table VI. With the anilides, all three groups display similar effects, whereas in the ethers the deactivation due to the carboxyl group becomes much more pronounced.

TABLE III.

Relative directive effects of the groups NHAc *in compounds of the type* $p\text{-NHAc}{\cdot}C_6H_4X$. *Values of* $100k^{\mathrm{NHAc}}_{\mathrm{X}}/k^{\mathrm{NH{\cdot}CO{\cdot}CH_3}}_{\mathrm{X}}$.

X.	Ac =	$-CO{\cdot}CH_3$.	$-CO{\cdot}C_2H_5$.	$-SO_2{\cdot}C_7H_7$.
p-Cl		100	205	67·1
p-Br		100	198	68·7

TABLE IV.

Relative directive effects of the groups -Cl, -Br, *and* $-CO_2H$ *in compounds of the type* $p\text{-NHAc}{\cdot}C_6H_4X$. *Values of* $100k^{\mathrm{NHAc}}_{\mathrm{X}}/k^{\mathrm{NHAc}}_{p\text{-Cl}}$.

Ac.	X =	Cl.	Br.	CO_2H.
$CO{\cdot}C_2H_5$		100	110	93·1
$CO{\cdot}CH_3$		100	114	—
$SO_2{\cdot}C_7H_7$		100	116	—
$SO_2{\cdot}C_6H_5$		100	111	97·4

TABLE V.

Effect of relative concentrations of anilide, chlorine, and hydrogen chloride on the ratio $100k^{\mathrm{NH{\cdot}CO{\cdot}CH_3}}_{p\text{-Br}}/k^{\mathrm{NH{\cdot}CO{\cdot}CH_3}}_{p\text{-Cl}}$.

Mol. proptn. anilide : Cl_2 : HCl.	*p*-Cl.	*p*-Br.
2 : 2 : 5	100	115
10 : 2 : 5	100	114
1 : 1 : 5	100	114

TABLE VI.

Relative directive powers of the groups Br, Cl, CO_2H, *and* NO_2 *in compounds of the type* $p\text{-NHAc}{\cdot}C_6H_4X$ *and* $p\text{-OR}{\cdot}C_6H_4X$.

	Medium.	X =	Br.	Cl.	CO_2H.	NO_2.
Phenyl ethers	99% Acetic acid		102·5	100	36	0·25
Anilides	,, ,, ,,		113	100	95	2·17
Acetanilide	40% ,, ,,		84	100	—	—

EXPERIMENTAL.

The velocity coefficients were determined by the method described in the earlier papers (Orton and Bradfield, J., **1927**, 986; Bradfield and B. Jones, J., **1928**, 3073), each value recorded being the mean of those obtained from at least two individual experiments. Some difficulty was experienced initially in determining the starch–iodide end-point owing to the precipitation of the anilide when portions of the reaction mixture were run into aqueous potassium iodide, but this was overcome by titrating in the presence of enough carbon tetrachloride to dissolve the precipitate.

The anilides, prepared by standard methods from the corresponding amino-compounds and the acyl chloride or anhydride, were repeatedly recrystallised from ethyl alcohol or acetic acid.

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An extension of the study of phenolic ethers is in progress in this laboratory.

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