149. *Reactions of ω-Substituted Acetophenone Derivatives. Part II. The Mechanism of the Interaction of ω-Halogenoacetophenones with Primary and Tertiary Bases.*

By JOHN WILLIAM BAKER.

IN Part I (Baker, J., 1931, 2416) it was shown that in the side-chain nitration of ω-halogenoacetophenones the attack is by a negative-centre seeking reagent and is facilitated by an accession of electrons to the side chain (Ingold and Rothstein's type A_2; J., 1928, 1219). On the other hand, in the replacement of the halogen by basic groups (OH, NR_2, etc.), it was tentatively suggested

(1) that the electrostriction of positive centre-seeking groups to the ω-carbon atom is an important stage in the mechanism, and (2) that the reaction appears to be facilitated, not so much by the ease of anionisation of the halogen (— *I* effect), as by the positive character of this atom (compare, *inter alia*, Bennett and Berry, J., 1927, 1676), *i.e.*, the reaction is one requiring a recession of electrons from the side chain. For the purpose of a quantitative study, with a view to prescribe more exactly the mechanism of the replacement of the ω-halogen in derivatives of the type Ar·CO·CHRX by positive-centre seeking groups, it is necessary to employ a reaction which goes smoothly to completion with a measurable velocity without the occurrence of any complicating side reactions. Such a reaction is available in the interaction of ω-halogenoacetophenones with primary (aniline, A) and tertiary (pyridine, B) amines.

$$R\cdot C_6H_4\cdot CO\cdot CHR'X + NH_2Ph \longrightarrow R\cdot C_6H_4\cdot CO\cdot CHR'\cdot NHPh + HX \quad (A)$$

$$R\cdot C_6H_4\cdot CO\cdot CHR'X + NC_5H_5 \longrightarrow R\cdot C_6H_4\cdot CO\cdot CHR'\cdot \overset{\oplus}{N}C_5H_5\}\overset{\ominus}{X} \quad (B)$$

This communication describes an investigation of the effect of varying the polar nature of the groups R, R′, and X on the velocity of these two reactions. Matheson and Humphries (J., 1931, 2514) have already shown that reaction (A) is pseudo-unimolecular in the presence of a large excess of aniline, and the same is found to be true for reaction (B). Hence these pseudo-unimolecular velocity coefficients have been determined for the interaction of various ω-halogenoacetophenones in 0·025*M*-solution in 90% alcohol with 10 molecular proportions of the base at 30·5°, the reactions being followed by titration of the halide ion present, as described by Matheson and Humphries (*loc. cit.*).

The results are summarised in the following tables. The value of the pseudo-unimolecular velocity coefficient, *k*, is calculated in c.c. of 0·05*N*-silver nitrate, time being in minutes.

TABLE I.

Reaction of $R\cdot C_6H_4\cdot CO\cdot CH_2X$ *with pyridine* (10 *mols.*) *in* M/40-*solution in* 90% *alcohol at* 30·5°.

	$k \times 10^3$.		Ratio k_X/k_{Cl}.	
X.	R = H.	R = *m*-NO_2.	R = H.	R = *m*-NO_2.
Cl	0·11	0·15	1	1
Br	6·5	11·3	59 *	75
I	5·0	8·2	45·5	54·6

* Clarke (J., 1910, **97**, 416) found $k_{Br}/k_{Cl} = 54$.

TABLE II.

Values of k × 10^3 *for the interaction of* R·C_6H_4·CO·CHR′X *with aniline* (10 *mols.*) *in* M/40-*solution in* 90% *alcohol at* 30·5°.

	R′ = H.			R′ = Me.	R′ = NO_2.
R.	X = I.	X = Br.	X = Cl.	X = Br.	X = Br.
p-MeO	10	—	—	—	—
p-Me	11	11·4	—	—	—
H	14·8	14·5	0·15	0·7	—
m-NO_2	47	44	—	2·6	—
p-NO_2	41·4	35	—	—	0·025

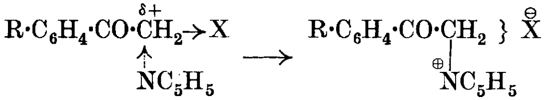
Discussion of Results.

The occurrence of maxima in the values of the velocity coefficients in series obtained by varying the polar character of one or other of the substituent groups uniformly in one direction, immediately suggests that the velocity of the reactions is determined by the resultant of several opposing factors, and interpretation of the results necessitates detailed theoretical consideration of the effects of the variable groups on possible stages in the mechanism of the reaction.

The existence of two types of electronic displacement, namely, the conjugative and the general polar effects, was first recognised by Robinson (Allan, Oxford, Robinson, and Smith, J., 1926, 406, and references there cited). The first, which involves covalency changes and occurs in the polarisation of conjugated systems, has since been termed the electromeric effect and designated by the symbols ± *T*; the second, in which no such change in covalency occurs and which is propagated by electrostatic induction, has been called the inductive effect and denoted by the symbols ± *I* (Ingold and Shaw, J., 1927, 836; compare *Ann. Reports*, 1926, **23**, 133; 1927, **24**, 151). To these must be added the direct effect (± *D*), resulting from the transmission of polar effects by direct action through space (Ingold and Vass, J., 1928, 417; Lapworth and Robinson, *Mem. Manchester Phil. Soc.*, 1928, **72**, No. 4, 1). It is an open question whether the total polar effect of any atom or group can be subdivided in the clear-cut manner postulated above (compare Lapworth and Manske, J., 1928, 2533), but, in the absence of precise knowledge of the real physical processes involved, it appears to the author that, at this stage, such a division is desirable as a working hypothesis. This is especially so since experimental evidence (such as that given in this communication) indicates that, in any particular reaction, one or other of the postulated effects is of major importance.

From such a standpoint, reaction (B), involving simple quaternary-salt formation with pyridine, is the most straightforward and will be considered first.

This reaction involves (1) the co-ordination of the pyridine molecule with the ω-carbon atom of the acetophenone derivative by means of the unshared electron pair on the nitrogen atom, and (2) the separation of the halogen as a negative halide ion :



$$\mathrm{R\cdot C_6H_4\cdot CO\cdot}\underset{\substack{\uparrow\\ \mathrm{NC_5H_5}}}{\overset{\delta+}{\mathrm{C}}}\mathrm{H_2\rightarrow X} \longrightarrow \mathrm{R\cdot C_6H_4\cdot CO\cdot}\underset{\substack{\oplus|\\ \mathrm{NC_5H_5}}}{\mathrm{C}}\mathrm{H_2}\ \}\ \overset{\ominus}{\mathrm{X}}$$

The first stage will be facilitated by any factor which augments the positive charge on the ω-carbon atom (and *vice versa*). Hence, with any given halogen, the velocity should be greater the more strongly the group R attracts electrons, *i.e.*, it will be facilitated when R is a group of the polar type $-I$; with R constant, the velocity should, for the same reason, be greater the greater the electron affinity ($-I$ effect) of the halogen atom X, *i.e.*, it should increase in the order I<Br<Cl. But the second stage, which involves the ease of anionisation of the halogen, would also be expected to increase in the same order. Thus, theory suggests that the velocity of this reaction will be increased by substitution of an electron-attracting group in the phenyl nucleus, and, *ceteris paribus*, in the order I<Br<Cl. The former of these conclusions is confirmed by the consistently greater velocity coefficients for the reaction with *m*-nitro-ω-halogenoacetophenones relative to that of the corresponding unsubstituted derivatives (Table I). With regard to the second conclusion, the predicted order for the three halogens is confirmed in the case of Br>I, but chlorine presents a striking anomaly, for which only a tentative explanation can be advanced. Of the three halogens studied, chlorine has the most powerful inductive ($-I$, $-D$) effect (moreover, it is an element which *may* be capable of expanding its octet to a larger electron group).* Possibly, therefore, the external field of attraction of the chlorine atom itself for the molecule of the basic reagent is so powerful that the latter is largely prevented from attack at the ω-carbon atom, at which point alone is consummation of the reaction possible by subsequent separation of the halogen as a halide ion. From this point of view, investigation of the corresponding fluorine derivatives (even more powerful $-I$ effect, but with no possibility of octet expansion) would be of interest; so far, however, attempts to prepare ω-fluoroacetophenones have been unsuccessful.

Theoretical analysis of the reaction of ω-halogenoacetophenones

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* This suggestion receives support from recent accurate measurements of the dipole moment of carbon tetrachloride (private communication from Dr. F. R. Goss).

with primary bases such as aniline (reaction A) is more complicated, since, in this case, only a portion of the basic reagent becomes attached to the ω-carbon atom, whilst the halogen is eliminated as hydrogen halide. It will be convenient to consider first the effect of the substituent groups R and R′ for any given halogen derivative, and afterwards to discuss the case when R and R′ are constant and the nature of the halogen is varied.

With any given halogen, arguments similar to those employed above indicate that if R and R′ are groups which have a strong attraction for electrons ($-I$ type) they will (1) increase the $\delta +$ charge on the ω-carbon and hence facilitate the initial electrostriction of the negatively polarised portion of the reagent molecule, and (2) decrease the ease of anionisation of the halogen and thus tend to inhibit the completion of the reaction. When R and R′ are groups of the opposite polar type ($+I$) they will obviously tend to increase electron availability in the side chain, with the resultant reversal of these effects.

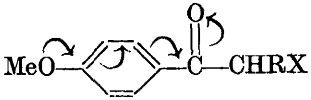
The results summarised in Table II indicate that the electrostriction of the negatively polarised portion of the reagent molecule is of primary importance, substitution in the nucleus of the electron-repelling methyl group decreasing the velocity of reaction, whilst substitution of the strongly electron-attracting nitro-group largely increases the velocity, *providing the effect be not too powerful.* After a certain point, the inhibitory effect of the powerfully electron-attracting group on the anionisation of the halogen atom becomes important, with the result that a maximum occurs at some point in the series. With the groups studied, this maximum occurs at the *m*-nitro-derivative, the series, arranged in order of increasing $-I$ effects of the substituent groups R and R′, being

$$\omega\text{-Me} < (p\text{-Me},\ p\text{-MeO}) < \text{H} < \underset{\text{(maximum)}}{m\text{-NO}_2} > p\text{-NO}_2 \gg p\text{-di-NO}_2$$

$$\text{Decreasing } +I \rightarrow \vdots \leftarrow \text{ Increasing } -I \longrightarrow$$

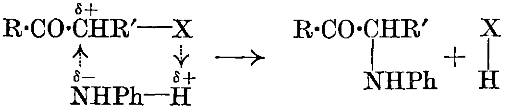
Under the experimental conditions employed, the reaction is almost completely inhibited by substitution of groups of opposite polar types, *viz.*, methyl (tends to neutralise the $\delta +$ charge on the carbon, although it increases the ease of anionisation of the halogen) and nitro- (prevents the anionisation of the halogen, although largely increasing the positive charge on the ω-carbon), in the ω-position. The possibility of steric effects cannot, of course, be disregarded in these cases.

The closely similar values of the velocity coefficients observed with a *p*-Me($+I$) and *p*-MeO (weak $-I$, $+T$) substituent, suggest that the electromeric effect ($+T$), although probably of secondary importance, cannot be neglected, since it more than counteracts the slightly facilitating influence of the weak $-I$ effect.



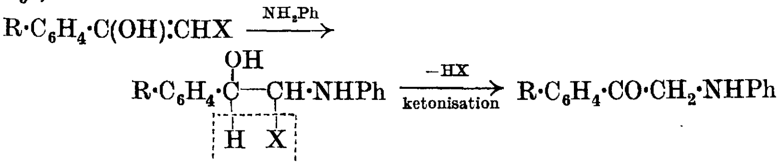
It will obviously tend to satisfy the $-T$ effect of the carbonyl group and thus diminish the polar effect of the latter group as a whole in inducing a positive charge on the ω-carbon atom.

Considering now the effect of varying the halogen substituent, we see that the relevant conclusions already drawn in the case of the reaction with tertiary bases (p. 1151) will apply equally to the analogous reaction with primary bases, facilitation of the reaction running parallel to the $-I$ effects of the halogens, Cl>Br>I. But, in this case, cognisance must be taken of a second factor, since the halogen is eliminated not simply as a halide ion but as a hydrogen halide. There is considerable evidence to show that the unshared halogen electrons have an affinity for a positive charge ($+T$ effect; compare, *inter alia*, Ingold and Vass, J., 1928, 2262), and hence they may, independently of the other stages in the reaction, exert a definite attraction for the positively polarised hydrogen atom of the attacking aniline molecule:



Such an affinity for a positive field will increase in the order of the $+T$ effects, *viz.*, I>Br>Cl, which is the *reverse* of that deduced for facilitation of the other processes involved in the mechanism of the reaction. Thus the experimental velocity order for the three ω-halogen derivatives will depend on the relative importance of these antagonistic processes of control. The results obtained (Table II) lend some support to the view that, at least with iodine (which is known to form stable iodinium salts), this last-discussed factor is by no means negligible. Thus, under the same conditions of concentration and temperature, the velocity of reaction with the weaker base, aniline, is more than twice as great as is that with the stronger base, pyridine, in spite of the fact that electrostriction of the unshared electron pair of the nitrogen will occur the more readily the stronger the base. Again, in qualitative agreement with the results of Matheson and Humphries (*loc. cit.*) for the reaction of phenacyl bromide and iodide with aniline, the velocity of reaction with the ω-iodo-compound is, in most cases, slightly greater than with the corresponding ω-bromo-derivative, in spite of the smaller electron affinity (− *I* effect) of the former halogen. This velocity order (I>Br) is exactly the opposite of that obtained in the reaction with pyridine (Br>I) in which no elimination of hydrogen halide is involved. The anomalous position of chlorine is, however, again evident.

Mechanisms involving reaction with the enolic form of the ketone, *e.g.*,



$$R{\cdot}C_6H_4{\cdot}C(OH){:}CHX \xrightarrow{NH_2Ph}$$

$$R{\cdot}C_6H_4{\cdot}\overset{OH}{\underset{H}{C}}-\underset{X}{CH}{\cdot}NHPh \xrightarrow[\text{ketonisation}]{-HX} R{\cdot}C_6H_4{\cdot}CO{\cdot}CH_2{\cdot}NHPh$$

have been excluded from the foregoing discussion, since they would be less readily applicable to the reaction with pyridine and, *a priori*, it seems reasonable to assume that the mechanisms of reaction with tertiary and with primary bases are of closely similar types. It is intended to elucidate this point by an analogous investigation of benzyl and β-phenylethyl halides.

EXPERIMENTAL.

Preparation of Materials.—Phenacyl halides. These were prepared by the usual methods and purified by repeated crystallisation from alcohol and finally from ligroin (b. p. 40—60°) or from ether–ligroin. The chloride, bromide, and iodide had m. p. 56°, 50°, and 30° respectively.

ω-Halogeno-*m*-nitroacetophenones were prepared as described in Part I (*loc. cit.*) and after purification had m. p. 102—103° (chloride), 96° (bromide) and 96° (iodide). ω-Bromo-*p*-nitro- and ω*p*-dinitroacetophenones were also prepared as described previously; m. p.'s, 99° and 89—90° respectively.

ω-Bromo-*p*-methylacetophenone, prepared by bromination of *p*-tolyl methyl ketone (Kunckell, *Ber.*, 1897, **30**, 577), was converted by the action of aqueous-alcoholic potassium iodide in the usual manner into ω-*iodo*-p-*methylacetophenone*, m. p. 44°, crystallising from ligroin (b. p. 40—60°), containing a little ether, in clusters of slender prisms (Found: C, 41·8; H, 3·6. C_9H_9OI requires C, 41·6; H, 3·5%).

ω-*Iodo*-p-*methoxyacetophenone.* Although replacement of the chlorine in ω-chloro-*p*-methoxyacetophenone * by bromine could not be effected even by prolonged heating with potassium bromide either in aqueous alcohol or in nitromethane, the ω-*iodo*-derivative was readily obtained by warming with aqueous-alcoholic potassium

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* The author desires to express his thanks to Prof. G. T. Morgan and Dr. G. R. Davies of the Chemical Research Laboratory, Teddington, for the kind gift of this material.

iodide; crystallised from ligroin (b. p. 40—60°) containing a little ether, it had m. p. 61° (Found: C, 40·0; H, 3·4. $C_9H_9O_2I$ requires C, 39·1; H, 3·3%).

ω-Bromopropiophenone was prepared by bromination of the ketone in acetic acid (Schmidt, *Ber.*, 1889, **22**, 3251), and purified by distillation in a vacuum, b. p. 137°/15 mm., followed by crystallisation from ligroin (b. p. 40—60°) below 0°.

m-Nitropropiophenone was prepared by nitration of propiophenone in a mixture of nitric (*d* 1·52) and sulphuric (100·4%) acids at – 5° to 0°. The mixture was poured on ice and an excess of potassium hydrogen carbonate, and the neutral product extracted with ether. The residue from the dried ethereal extract crystallised, and, after draining on porous porcelain and crystallisation from alcohol, gave the pure *m*-nitro-derivative, m. p. 98°. Bromination in acetic acid in the usual manner afforded m-*nitrophenyl α-bromoethyl ketone*, m. p. 65° after crystallisation from ether–ligroin (Found: C, 42·1; H, 3·25. $C_9H_8O_3NBr$ requires C, 41·9; H, 3·1%).

Action of Bases on ω-Halogenoacetophenones.—(a) *Qualitative.* In preliminary experiments carried out in order to determine the most suitable bases for quantitative work, the following new derivatives were obtained by the interaction of the appropriate base and acetophenone derivative in absolute-alcoholic solution either by keeping at the ordinary temperature or by gentle warming.

m-*Nitro-ω-anilinoacetophenone* crystallised from ethyl acetate in slender yellow prisms, m. p. 175° (decomp.) (Found: C, 65·6; H, 4·8. $C_{14}H_{12}O_3N_2$ requires C, 65·6; H, 4·7%).

Phenacylpyridinium bromide crystallised from absolute alcohol in stout prisms, m. p. 199—200° (decomp.) (Found: C, 56·3; H, 4·6; Br, by titration, 28·8. $C_{13}H_{12}ONBr$ requires C, 56·1; H, 4·3; Br, 28·8%).

m-*Nitrophenacylpyridinium bromide* crystallised from 96% alcohol in prisms, decomp. 250° (Found: C, 48·3; H, 3·4; Br, by titration, 24·8. $C_{13}H_{11}O_3N_2Br$ requires C, 48·4; H, 3·5; Br, 24·8%).

m-*Nitrophenacylphenyldiethylammonium bromide.* In this case precipitation of the *salt* with ether was necessary. Crystallised from absolute methyl alcohol containing a little ether, it had m. p. 140° (decomp.) (Found: C, 52·0; H, 5·8. $C_{18}H_{21}O_3N_2Br,CH_3{\cdot}OH$ requires C, 53·6; H, 5·9%).

Phenacyltrimethylammonium fluoride was obtained by addition of the exactly equivalent amount of an aqueous solution of silver fluoride to a solution of the quaternary bromide in the same solvent. After separation of the precipitated silver bromide and evaporation of the aqueous solution at the ordinary temperature in a vacuum, the fluoride was obtained in small, extremely hygroscopic crystals.

On gentle warming, the odour of trimethylamine was perceptible, but no pure compound was isolated from the decomposition products.

(b) *Quantitative.* The velocity of reaction of the various ω-halogenoacetophenone derivatives with aniline or pyridine was determined by a method essentially similar to that of Matheson and Humphries (*loc. cit.*).

The reaction vessel consisted of a 300-c.c. wide-mouthed Pyrex flask fitted with a rubber stopper through which passed a condenser, a mercury-sealed stirrer, and a wide stoppered tube, by means of which the reactants were introduced and samples removed. The flask was kept in a thermostat at 30·5° ± 0·1°. Both the reaction mixture and the water in the thermostat were mechanically stirred throughout the experiments. The 90% alcohol used as a solvent was prepared by weighing the requisite amount of distilled water into pure, sodium-dried absolute alcohol. This solvent was used rather than absolute alcohol in order to prevent any alteration in the composition owing to absorption of water, and to minimise the possibility of crystallisation of the quaternary salts formed in the reaction with pyridine. Exactly 0·0025 g.-mol. of the acetophenone derivative was weighed into the reaction vessel and dissolved in 50 c.c. of the 90% alcohol. After it had attained the temperature of the thermostat, 50 c.c. of a 90% alcoholic solution containing exactly 10 mols. of the base (also at the temperature of the thermostat) were added, and the time noted. The course of the reaction was followed by running 10 c.c. of the reaction mixture at intervals into 20 c.c. of *N*/20-silver nitrate, 20 c.c. of water, and a few c.c. of benzene (to dissolve organic matter), adding 2 c.c. of ferric indicator, and titrating the excess of silver nitrate with *N*/20-ammonium thiocyanate solution.

For economy of space, full details are given only in the first case in each series. The pseudo-unimolecular velocity coefficient was calculated in terms of c.c. of *N*/20-silver nitrate, the time being in minutes.

Interaction of Acetophenone Derivatives of Type R·C_6H_4·CO·CHRX.

(a) *With pyridine* (1·975 g. = 10 mols.).

ω-Bromo-*m*-nitroacetophenone (0·6100 g./100 c.c.).

Time, mins.	C.c. of *N*/20-$AgNO_3$ for halide ion.	$a - x$.	$10^4 k$ (min.$^{-1}$).
4	0·22	4·86	111
10	0·55	4·53	115
18	0·97	4·11	118
30	1·50	3·58	117
45	2·02	3·06	113
65	2·56	2·52	108
105	3·51	1·57	112
245	4·89	0·19	—
∞	5·08	—	—
			Mean 113

Compound.	Conc., g./100 c.c.	No. of detmtns.	10^4 k, min.$^{-1}$. Mean.	Max.	Min.
ω-Iodo-*m*-nitroacetophenone	0·7375	7	82	85	79
ω-Chloro-*m*-nitroacetophenone ...	0·4988	3	1·5	No deviation	
ω-Bromoacetophenone	0·4975	5	65	69	62
ω-Iodoacetophenone	0·6150	5	50	53	48
ω-Chloroacetophenone	0·3863	3	1·1	No deviation	

(b) *With aniline* (2·325 g. = 10 mols.).

ω-Bromoacetophenone (0·4975 g./100 c.c.).

Time, mins.	C.c. of N/20-AgNO$_3$ for halide ion.	$a - x$.	10^3 k (min.$^{-1}$).
2	0·19	4·76	(19)
5	0·40	4·55	17
10	0·75	4·20	16
17	1·09	3·86	15
25	1·48	3·47	14
35	2·07	2·88	16
45	2·22	2·73	13
60	2·67	2·28	13
∞	4·95	—	—
		Mean	15

Compound.	Conc., g./100 c.c.	No. of detmtns.	10^3 k, min.$^{-1}$. Mean.	Max.	Min.
ω-Bromoacetophenone*	0·4975	7	14	16	13
ω-Iodoacetophenone	0·6150	6	15	15·5	14
,, ...	0·6150	7	15	15·5	14
ω-Chloroacetophenone	0·3863	4	0·146	0·149	0·143
ω-Bromo-*p*-methylacetophenone	0·5325	6	11·4	11·7	11·2
ω-Bromo-*m*-nitroacetophenone†	0·6100	6	44	48	40
ω-Bromo-*p*-nitroacetophenone† ...	0·6100	5	35	37	33
ω-Bromo-ω*p*-dinitroacetophenone	0·7225	4	0·025	0·029	0·020
Phenyl α-bromoethyl ketone	0·5325	4	*ca.* 0·7	0·8	0·6
m-Nitrophenyl α-bromoethyl ketone	0·6450	4	2·6	2·7	2·5
ω-Iodo-*p*-methylacetophenone ...	0·6500	6	11	12	10
ω-Iodo-*p*-methoxyacetophenone	0·6900	6	10	11	9
ω-Iodo-*m*-nitroacetophenone	0·7275	6	46	50	44
ω-Iodo-*p*-nitroacetophenone	0·7275	5	41·4	42	40

* Re-determination.

† In the determinations of both the *m*- and the *p*-nitro-derivative, crystallisation of the ω-anilino-compound occurs at an early stage in the reaction. This does not appreciably affect the constancy of the velocity coefficient since the aniline hydrobromide and the reacting materials remain in homogeneous solution.

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