392. *Reactions of ω-Substituted Acetophenone Derivatives. Part III. Comparison of the Mechanism of Interaction of ω-Halogenoacetophenones and of Benzyl Halides with Primary and Tertiary Bases.*

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IN Part II (Baker, this vol., p. 1148) it was shown that the velocity of reaction of ω-halogenoacetophenones of the type $R{\cdot}C_6H_4{\cdot}CO{\cdot}CH_2X$ with primary and tertiary bases is determined by the resultant of several opposing factors, which were analysed and discussed. Mechanisms involving reaction with the enolic form of the ketone were excluded on *prima facie* grounds, but in an attempt to obtain further evidence on this possibility, the velocities of interaction of similarly substituted benzyl halides, $R{\cdot}C_6H_4{\cdot}CH_2X$, with pyridine and aniline have now been determined under identical conditions (cf. *loc. cit.*, p. 1154). The reactions

$$R{\cdot}C_6H_4{\cdot}CH_2X + NH_2Ph \longrightarrow R{\cdot}C_6H_4{\cdot}CH_2{\cdot}NHPh + HX \quad (A)$$

and

$$R{\cdot}C_6H_4{\cdot}CH_2X + NC_5H_5 \longrightarrow R{\cdot}C_6H_4{\cdot}CH_2{\cdot}\overset{\oplus}{N}C_5H_5\}\overset{\ominus}{X} \quad . \quad (B)$$

are both pseudo-unimolecular in the presence of a large excess of the base, and the values of the coefficients k (in c.c. of $0{\cdot}05N$-silver nitrate; min.^{-1}) for the interaction of various substituted benzyl halides in $0{\cdot}025M$-solution in 90% alcohol with 10 mols. of the base at 30·5° are summarised in Table I.

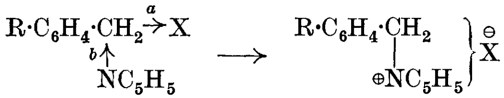
TABLE I.

Reaction of $R{\cdot}C_6H_4{\cdot}CH_2X$ with 10 mols. of (A) aniline and (B) pyridine in $M/40$-solution in 90% alcohol at 30·5°.

	$k \times 10^3$.						Ratio k_I/k_{Br}.	
	X = Cl.		X = Br.		X = I.			
R.	A.	B.	A.	B.	A.	B.	A.	B.
p-MeO	—	$\propto$	—	$\propto$	—	—	—	—
p-Me	—	—	87	9·5	—	—	—	—
H	0·70	0·09	35	4·4	61	5·1	1·74	1·15
m-NO_2	—	—	30·4	1·4	44	1·6	1·45	1·14
p-NO_2	—	—	22·3	1·56	36·2	1·8	1·62	1·16

Before discussing the mechanism of these reactions it is necessary to emphasise the significance of the symbolism used by the author throughout this and other series of papers. Robinson has suggested (this vol., p. 1445, footnote) that the signs + and — applied to inductive (I) and electromeric (T) effects during recent years should be given a direct *electrical* significance and that their previous allocation should, in consequence, be reversed. As used by the author, however, these + and — signs have had, not an electrical, but an *algebraic* significance since they arose out of the terms electron-source and electron-sink, respectively (Ingold and Ingold, J., 1926, 1310; *Ann. Reports*, 1926, **23**, 141). Thus the symbols $+I$ and $+T$ are employed when the group tends to *supply* electrons *to* the nucleus (by inductive and electromeric mechanisms, respectively), the symbols $-I$ and $-T$ being used when the group tends to *withdraw* electrons *from* the nucleus.

Considering first the simpler reaction (B). This involves two phases, precisely similar to those discussed in connexion with the corresponding reaction with ω-halogenoacetophenones, *viz.*, (*a*) the anionisation of the halogen, and (*b*) the co-ordination of the basic nitrogen atom, by means of its unshared electron pair, to the adjacent methylene group.



$$\begin{array}{c}R\cdot C_6H_4\cdot CH_2\overset{a}{\rightarrow}X\\ {\scriptstyle b}\uparrow\\ NC_5H_5\end{array}\longrightarrow\left.\begin{array}{c}R\cdot C_6H_4\cdot CH_2\\ |\\ \oplus NC_5H_5\end{array}\right\}\overset{\ominus}{X}$$

The experimental results (Table I) at once diagnose the reaction as being of the opposite type to that with ω-halogenoacetophenone derivatives. The latter reaction is facilitated by the introduction of a nitro-group ($-I$, $-T$) into the nucleus, *i.e.*, by a recession of electrons from the side chain, indicating that phase (*b*) is of major importance in determining the velocity of reaction. With substituted benzyl halides, however, the velocity is retarded by a *p*-nitro- and is accelerated by a *p*-methyl ($+I$) substituent, *i.e.*, it is one requiring an accession of electrons to the side chain. Hence in this case, phase (*a*), *viz.*, the anionisation of the halogen, is the main factor in determining the velocity. It follows that the present results can throw very little direct light on the original point at issue, *viz.*, the possibility of interaction of the ketone derivatives through the enolic phase, a mechanism which is still, therefore, not definitely excluded.

When the substitutents R are arranged in order of decreasing electron availability, an exact parallel with the ω-halogenoacetophenone reactions is found in the occurrence of a minimum value for the velocity with a *m*-nitro-substituent.

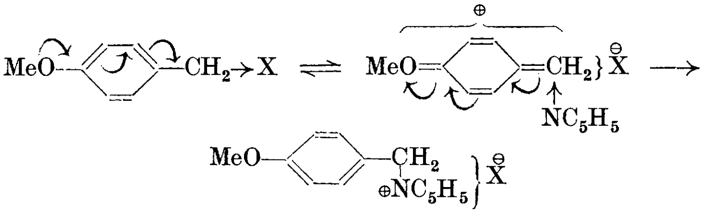
$$p\text{-Me}>\text{H}>\underset{\text{minimum}}{m\text{-NO}_2}<p\text{-NO}_2$$

$$+I\text{——increasing }-I\longrightarrow$$

Hence it would appear that phase (*b*), although of very minor importance, does, to some extent affect the velocity, since the very powerful electron-attraction of the *p*-nitro-substituent, whilst strongly inhibiting phase (*a*), tends to facilitate phase (*b*).

Alteration of the nature of the halogen atom X (R being constant) introduces a striking anomaly, for, since the velocity is determined mainly by the ease of anionisation of the halogen (*a*), it would be expected to increase, *ceteris paribus*, in the order of electron affinity of the halogens, *i.e.*, in the order of increasing $-I$ effects: $I < Br < Cl$. The experimental order (which is in accord with general experience regarding quaternary-salt formation) is, however, the exact opposite, *viz.*, $Cl < Br < I$. This result suggests that it is necessary to consider whether the ease of separation of a halogen atom as a negative ion is necessarily the same as the order of anionic stabilities of the halide ions, but further discussion of this point is deferred until more experimental evidence has been accumulated. It is certainly difficult to see how the reaction under discussion could proceed *via* the initial union of the halogen with the base in a manner similar to that postulated by Bennett (*Ann. Reports*, 1929, **26**, 139) to account for the anomalous results observed in the interaction of chlorides of type $R(CH_2)_nCl$ with potassium iodide.

The other point of special interest is the very great increase in velocity (too great to be measured) caused by the introduction of a *p*-methoxy-group. The almost instantaneous formation of a quaternary salt, which occurs in this case, suggests that a totally different mechanism is involved, and it is tentatively suggested that reaction occurs between the pyridine and an *ionised* (salt) form of the *p*-methoxybenzyl halide which results from the powerful $+T$ effect of the *p*-methoxyl substituent.



It is perhaps significant that pure, redistilled *colourless* *p*-methoxybenzyl bromide, when kept in the dark, develops a claret colour, which is immediately destroyed by addition of either dry alcohol or water (? hydrolysis of the salt form) but not by dissolution in dry nitromethane. In the last solvent the colour first deepens and then vanishes when the solution is warmed, but reappears on cooling and, moreover, it is destroyed by addition of anhydrous sodium acetate.

In reaction (A), in which the elimination of hydrogen halide is involved, it has already been suggested (*loc. cit.*, p. 1153) that, in addition to the two phases (*a*) and (*b*) involved in reaction (B), a third factor (*c*), *viz.*, the attraction of the unshared halogen electrons for the positively polarised portion of the attacking aniline molecule, may also influence the velocity of the reaction.

In complete harmony with the results obtained (*ibid.*) in the case of ω-halogenoacetophenone derivatives, the effect of this third factor is again evident, for the velocity of reaction of benzyl halides (Table I) with the weaker base, aniline, is at least ten times as great as that with the stronger base, pyridine; whilst the ratio k_I/k_{Br} for the aniline series is also greater than it is for the pyridine series, in agreement with the increasing order of $+T$ effects of the halogens, I>Br>Cl.

Ingold (*Ann. Reports*, 1928, **25**, 146; Ingold and Patel, *J. Indian Chem. Soc.*, 1930, **7**, 95) has already pointed out that the rate-determining phase in side-chain halogen reactions is dependent on the nature of the medium in which the reaction occurs (*e.g.*, the hydrolysis of benzyl halides in acid and alkaline media). It now appears that, generalising from a comparison of the reaction of bases with side-chain halogen in derivatives of the two types $R{\cdot}C_6H_4{\cdot}CO{\cdot}CH_2X$ and $R{\cdot}C_6H_4{\cdot}CH_2X$, the mechanism even in the *same* solvent and under identical experimental conditions is determined by the nature of the group to which the halogen is attached. In the ω-halogenoacetophenones the positive charge induced by the carbonyl group on the adjacent methylene group predisposes the reaction to proceed *via* an initial electrostriction of the basic nitrogen atom to this methylene group, whilst in the benzyl halides the absence of such positive field would appear to destine the reaction to proceed *via* the initial anionisation of the halogen atom.

EXPERIMENTAL.

Preparation of Materials.—The various benzyl halides were prepared by standard methods, and purified by fractional distillation or crystn. from EtOH or ligroin. The specimens used had the following consts.: CH_2PhCl, b. p. 179°/749 mm.; CH_2PhBr, b. p. 199°/749 mm.; CH_2PhI, m. p. 24°; *p*-$MeC_6H_4{\cdot}CH_2Br$, m. p. 36°; *p*-$MeO{\cdot}C_6H_4{\cdot}CH_2Cl$, m. p. 38°; *p*-$MeO{\cdot}C_6H_4{\cdot}CH_2Br$, b. p. 104°/1—1·5 mm.; *m*-$NO_2{\cdot}C_6H_4{\cdot}CH_2Cl$, m. p. 47°; *m*-$NO_2{\cdot}C_6H_4{\cdot}CH_2Br$, m. p. 57—58°; *m*-$NO_2{\cdot}C_6H_4{\cdot}CH_2I$, m. p. 83—84°; *p*-$NO_2{\cdot}C_6H_4{\cdot}CH_2Br$, m. p. 100°; *p*-$NO_2{\cdot}C_6H_4{\cdot}CH_2I$, m. p. 128°. $CHMePhBr$, b. p. 94°/16 mm., was also prepared, but although this gave a pseudo-unimolecular velocity coeff. with C_5H_5N ($k \times 10^3 = 3{\cdot}7$), yet the product obtained after evaporation in a vac. at room temp. was C_5H_5N,HBr (Found : Br, 49·2. Calc. : Br, 50·0%. Calc. for $C_{13}H_{14}NBr$: Br, 30·3%), elimination of HBr being the sole reaction.

p-*Methoxybenzylpyridinium bromide* (Found : Br, 28·6%. $C_{13}H_{14}ONBr$ requires Br, 28·6%) was obtained in the usual manner by the action of C_5H_5N on *p*-MeO·C_6H_4·CH_2Br in EtOH solution; it crystallises from dry EtOH in fine needles, m. p. 162—163° (decomp.).

Velocity Measurements.—These were carried out exactly as described in the corresponding determinations of ω-halogenoacetophenones (*loc. cit.*) except that, owing to the greater reactivity of the benzyl halides with H_2O–EtOH–$AgNO_3$, the sample (10 c.c.) was run into 5—10 c.c. of distilled H_2O, extracted with 20 c.c. of Et_2O, and the extract repeatedly washed with distilled H_2O to dissolve out all the ionised halogen compound. The combined H_2O extracts were run into 10 c.c. of 0·05*N*-$AgNO_3$, and the excess titrated with 0·05*N*-NH_4NCS (Volhard method).

Full details are given only in the first case in each series. The pseudo-unimolecular velocity coeff. was calc. in terms of c.c. of 0·05*N*-$AgNO_3$, the time being in mins.

Interaction of Benzyl Halides of Type R·C_6H_4·CH_2X.

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

CH_2PhBr (0·4275 g./100 c.c.).

Time, mins.	*N*/20-$AgNO_3$, c.c.	$a - x$.	10^3k.	Time, mins.	*N*/20-$AgNO_3$, c.c.	$a - x$.	10^3k.
10	0·26	4·74	(5·3)	90	1·69	3·31	4·6
20	0·44	4·56	4·6	155	2·39	2·61	4·2
40	0·79	4·21	4·3	185	2·78	2·22	4·4
60	1·15	3·85	4·2	∞	5·0	—	—
						Mean	4·4

Compound.	Concn., g./100 c.c.	No. of detmtns.	10^3k. Mean.	Max.	Min.
Ph·CH_2Cl	0·3162	5	0·093	0·094	0·090
Ph·CH_2I	0·5450	6	5·10	5·14	5·01
m-NO_2·C_6H_4·CH_2Br	0·5400	6	1·36	1·43	1·28
m-NO_2·C_6H_4·CH_2I	0·6575	7	1·6	2·0	1·4
p-NO_2·C_6H_4·CH_2Br	0·5400	7	1·56	1·61	1·50
p-NO_2·C_6H_4·CH_2I	0·6575	5	1·8	2·1	1·7
p-Me·C_6H_4·CH_2Br	0·4625	6	9·5	9·7	9·2

With *p*-MeO·C_6H_4·CH_2Cl the reaction was complete when the first reading ($t = 1$ min.) was taken. A blank experiment in which no C_5H_5N was added gave only a very faint turbidity with $AgNO_3$.

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

CH_2PhBr (0·4275 g./100 c.c.).

Time, mins.	*N*/20-$AgNO_3$, c.c.	$a - x$.	10^3k.	Time, mins.	*N*/20-$AgNO_3$, c.c.	$a - x$.	10^3k.
5·5	8·80	3·80	(50)	30	6·77	1·77	35
12·3	8·11	3·11	39	35	6·51	1·51	34
25	7·08	2·08	35	40	6·30	1·30	33
						Mean	35

Compound.	Concn., g./100 c.c.	No. of detmtns.	10^3k. Mean.	Max.	Min.
$Ph\cdot CH_2Cl$	0·3162	6	0·70	0·73	0·69
$Ph\cdot CH_2I$	0·5450	6	61	70	54
m-$NO_2\cdot C_6H_4\cdot CH_2Br$	0·5400	6	30·4	31·4	29·7
m-$NO_2\cdot C_6H_4\cdot CH_2I$	0·6575	6	44	47	42
p-$NO_2\cdot C_6H_4\cdot CH_2Br$	0·5400	7	22·3	23·1	20·7
p-$NO_2\cdot C_6H_4\cdot CH_2I$	0·6575	6	36·2	37·3	34·8
p-$Me\cdot C_6H_4\cdot CH_2Br$	0·4625	4	87	94	81

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