88. *Mechanism of Aromatic Side-chain Reactions with Special Reference to the Polar Effects of Substituents. Part IX. The* ortho-*Effect in the Reaction of Phenacyl Bromides with Pyridine.*

By John W. Baker.

The reaction $C_6H_4R{\cdot}CO{\cdot}CH_2Br + NC_5H_5 \longrightarrow C_6H_4R{\cdot}CO{\cdot}CH_2{\cdot}\overset{+}{N}C_5H_5\}\overset{-}{Br}$ in 0·25M-solution in dry acetone is bimolecular and is facilitated by electron recession from the side chain to the aromatic nucleus (cf. Baker, J., 1933, 1128).

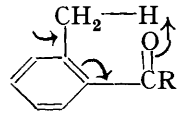
The bimolecular velocity coefficients (*k*) for phenacyl bromide and its *p*- and *o*-methyl and 2 : 4-dimethyl derivatives decrease in the order given, although the depression in the value of *k* caused by such substitution is relatively small. The 2 : 4 : 6-trimethyl derivative (in which both ortho-positions are substituted), however, fails to undergo detectable reaction under the given experimental conditions (20°) even after five days. An explanation of these results is advanced on the basis of the occurrence of resonance between the carbonyl group and the *o*-methyl substituent (cf. Baker, J., 1935, 1844; Dippy, Evans, Gordon, Lewis, and Watson, J., 1937, 1421).

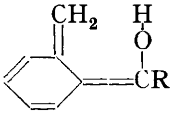
Although substitution by a nitro-group in the *p*-position in phenacyl bromide *increases* the reaction velocity about 2·5 times, similar substitution in the *o*-position *reduces* the velocity to about one-third of that of the unsubstituted parent. In this case it seems probable that a direct effect of the negative end of the nitro-group dipole on the $-CO{\cdot}CH_2Br$ side chain is involved, since any chelation is unlikely.

In a recent paper Dippy, Evans, Gordon, Lewis, and Watson (J., 1937, 1421) suggested that an alkyl group might form a hydrogen bond with an electron-donating group such as carbonyl in the *o*-position, and cited as one example the fact that *o*-toluic acid is appreciably stronger than either its *m*- or its *p*-isomeride or than benzoic acid itself.

The postulate that resonance occurs between structures of the types (I) and (II) is, of course, a direct corollary to the mechanism of the mesomeric effect of alkyl groups suggested by Baker and Nathan (J., 1935, 1844). The presence of the essential conjugated system is clearly indicated in (I). The existence of such chelation, arising from resonance phenomena, had been postulated by the author to explain some earlier results obtained in kinetic investigations of the reaction between various alkylphenacyl bromides and pyridine, data which it now seems desirable to put on record.

(I.)





(II.)

It was shown (Baker, J., 1933, 1128) that, in 90% alcohol as a solvent, the reaction $C_6H_4R{\cdot}CO{\cdot}CH_2Br + NC_5H_5 \longrightarrow C_6H_4R{\cdot}CO{\cdot}CH_2{\cdot}\overset{+}{N}C_5H_5\}\overset{-}{Br}$ is almost certainly bimolecular, and that it is facilitated by substituents (*e.g.*, *p*-nitro-) which increase electron recession from the side chain to the aromatic nucleus. These conclusions have now been confirmed in dry acetone as a solvent. The following table gives the values of the bimolecular velocity coefficients for the reaction between various substituted phenacyl bromides and pyridine, both 0·025M, in that solvent.

Reaction between $C_6H_4R{\cdot}CO{\cdot}CH_2Br$ *and* C_5H_5N *in* 0·025M-*solution in dry acetone*

R.	$10^3 \times k$ (l./g.-mol.-sec.). 20°.	40°.	*E* (Arrhenius), kg.-cals.
H	0·79	2·83	11·7
p-Me	0·74	2·62	11·6
o-Me	0·55	—	—
2 : 4-Me₂	0·50	1·82	11·8
2 : 4 : 6-Me₃	(Too slow to be measured.)		—
p-Bu$^\gamma$	0·57	2·00	11·5
p-NO₂	*ca.* 1·9	—	—
o-NO₂	,, 0·24	—	—

The anomalous effect of *o*-methyl substituents is immediately apparent. Substitution by a methyl group in one *o*-position causes a greater decrease in reaction velocity than does similar substitution in the *p*-position; but whereas the effect of simultaneous *op*-substitution, in the 2 : 4-dimethyl derivative, is approximately that anticipated on an additive basis, the introduction of methyl substituents into both *o*-positions so greatly reduces the reaction velocity that, under the standard conditions used, the 2 : 4 : 6-trimethyl derivative exhibits no appreciable reaction even after 5 days.* Since the centre of reaction is the terminal side-chain bromomethyl group, it seems improbable that a purely spatial inhibition is under observation, and the enormous difference in velocity between the 2 : 4-dimethyl and the 2 : 4 : 6-trimethyl compound seems too great to be explained purely on the basis of the simple inductive effect of an additional methyl group. The intimate mechanism of the formation of the quaternary salt is unknown, but the most feasible explanation of these results is derived from the assumption that the carbonyl group, with its intrinsic capacity for polarisation in the sense $\overset{\frown}{C{=}O}$, is essentially involved. This view receives confirmation from the observation (Thomson and Stevens, J., 1932, 70) that phenylbromomethylsulphone (in which the sulphone group should activate the adjacent $\cdot CH_2Br$ group towards a nucleophilic reagent, but in which electromeric polarisation is excluded) does not react with either benzyldimethylamine or piperidine. In the *p*-methylphenacyl derivative the contribution of structures of the type $\overset{+}{H}CH_2{:}C_6H_4{:}C\overset{-}{O}\cdot CH_2Br$ to the mesomeric wave-function is probably very small, a conclusion which is confirmed by the greater retarding effect of a *p-tert.*-butyl substituent. In compounds where one *o*-methyl group is present, however, structures of the type (II; R = CH_2Br) are readily formed when the side-chain carbonyl group is correctly orientated to the *o*-substituent: when both *o*-positions are substituted by methyl groups, the formation of the chelate ring is possible no matter what may be the rotational orientation of the side chain, the number of possible structures between which resonance may occur is increased and so, in this case, structures of type (II) may assume major importance. The incidence of such resonance when *o*-methyl substituents are present would greatly reduce the assumed mechanistic function of the carbonyl group † and so inhibit the reaction.

Further evidence for such interaction between the carbonyl and methyl groups is provided by the suppression of normal carbonyl activity in 2 : 4 : 6-trimethylacetophenone. Although the 2 : 4-dimethyl and the 2 : 4 : 5-trimethyl derivative readily form oximes and semicarbazones, the 2 : 4 : 6-trimethyl compound fails to react with hydroxylamine, hydrazine hydrate (Bouveault, *Compt. rend.*, 1897, **124**, 158), phenylhydrazine (Baum, *Ber.*, 1895, **28**, 3209), or semicarbazide (this communication) under the conditions ordinarily employed for the preparation of these derivatives. Neither the carbonyl group nor the bromine atom in 2 : 4 : 6-trimethylphenacyl bromide reacts with semicarbazide acetate in

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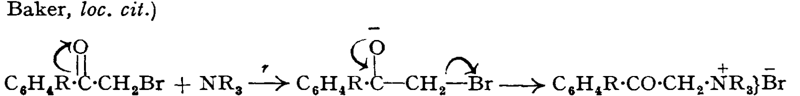
* The value of k is of the order of 10^{-6}—10^{-7}. Reaction readily occurs when the bromide is warmed with excess of pyridine without solvent.

† Examples of two *possible* mechanisms which require such polarisation of the carbonyl group and are in harmony with experimental observations are:

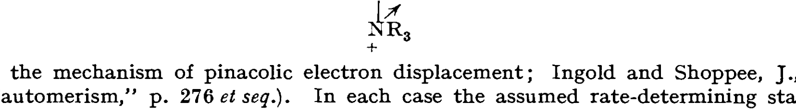
(1)



$$C_6H_4R\cdot CO\cdot CH_2Br + NR_3 \rightleftharpoons C_6H_4R\cdot\overset{O}{\overset{\|}{C}}-CH_2-\underset{10e}{\overset{-}{Br}}-\overset{+}{N}R_3 \xrightarrow{r} C_6H_4R\cdot\overset{\overset{-}{O}}{\overset{|}{C}}{=}CH_2 + \overset{+}{N}R_3-\overset{-}{Br} \longrightarrow C_6H_4R\cdot CO\cdot CH_2\cdot\overset{+}{N}R_3\}\overset{-}{Br}$$

(cf. Baker, *loc. cit.*)

(2)



$$C_6H_4R\cdot\overset{O}{\overset{\|}{C}}\cdot CH_2Br + NR_3 \xrightarrow{r} C_6H_4R\cdot\overset{\overset{-}{O}}{\overset{|}{\underset{\underset{+}{N}R_3}{C}}}-CH_2-Br \longrightarrow C_6H_4R\cdot CO\cdot CH_2\cdot\overset{+}{N}R_3\}\overset{-}{Br}$$

(cf. the mechanism of pinacolic electron displacement; Ingold and Shoppee, J., 1928, 365; Baker, "Tautomerism," p. 276 *et seq.*). In each case the assumed rate-determining stage is marked *r*. In any mechanism which involves direct attack at the carbonyl group it is obvious that purely spatial inhibitory effects may also be involved.

aqueous alcohol, but 2 : 4-dimethylphenacyl bromide readily affords a *semicarbazido*-derivative, the bromine evidently being more reactive than the carbonyl group.

Another significant example of the *ortho*-effect is provided by the relative velocities of reaction of the *o*- and *p*-nitrophenacyl bromides with pyridine. Owing to the insolubility of the quaternary salts, the values of the velocity coefficients for these two isomerides are less accurate, but there is no doubt that whereas in the *p*-position the nitro-group exerts its expected electron-attracting effect and increases the reaction velocity, yet an *o*-nitro-substituent actually reduces the velocity considerably. Although the formation of a five-membered chelate ring between an *o*-nitro-substituent and a carboxyl anion may be postulated (Dippy *et al.*, *loc. cit.*), it is difficult to assume such chelation involving a carbonyl group. Direct co-ordination of the doubly-linked oxygen (as donor) to the nitrogen as acceptor is unlikely in view of the charge distribution involved, and any other type of five-membered chelate ring necessitates tercovalent carbon.

It would thus appear that the retarding effect of an *o*-nitro-substituent must arise, in this reaction at least, from the electron-repelling effect of the negatively charged oxygen atoms of the nitro-group acting directly through the medium upon the seat of reaction in the side chain (cf. Bennett, *Chem. and Ind.*, 1935, **54**, 1008; Baker, J., 1936, 399), an effect which outweighs the electron-attractive effect (transmitted through the bonds) of the positive end of the dipole.

EXPERIMENTAL.

Preparation of Materials.—*o-Methylacetophenone.* *o*-Toluoyl chloride (38 g.) was added dropwise to a solution of methylzinc iodide (0·25 g.-mol.) in benzene–ethyl acetate cooled in a freezing mixture. After being kept for 1 hour at room temperature, the reaction mixture was decomposed with ice and dilute sulphuric acid, and the ketone extracted with ether. The extract was washed with aqueous sodium carbonate and water and dried over sodium sulphate. Fractional distillation of the residue from the dried ethereal solution gave 26 g. of the ketone, b. p. 93—94°/13 mm. The semicarbazone, crystallised from alcohol, had m. p. 206° (lit., m. p. 203°; 192°). Bromination of the ketone was effected by the dropwise addition of 16 g. of bromine to 13·4 g. of the ketone, without solvent, on the steam-bath. After isolation in the usual manner, repeated fractional distillation gave the ω-*bromo*-compound, b. p. 113·5°/1·7 mm. (Found : C, 51·7, 50·4; H, 4·4, 4·3; Br, 38·5. C_9H_9OBr requires C, 50·7; H, 4·2; Br, 37·6%).

2 : 4-Dimethylphenacyl bromide, m. p. 44·2—44·6°, and 2 : 4 : 6-trimethylphenacyl bromide, m. p. 57° (Found : C, 54·3; H, 5·6; Br, 33·2. Calc. for $C_{11}H_{13}OBr$: C, 54·8; H, 5·4; Br, 33·2%), were prepared by the method of Jacobs and Heidelberger (*J. Biol. Chem.*, 1915, **21**, 458). *p*-*tert*.-Butylacetophenone, b. p. 97—98°/0·8—0·9 mm., prepared by Verley's method (*Bull. Soc. chim.*, 1898, **19**, 73), gave a *semicarbazone*, m. p. 231—232° (decomp.) after crystallisation from 96% alcohol (Found : C, 67·5; H, 8·3. $C_{13}H_{19}ON_3$ requires C, 66·9; H, 8·2%). Bromination of the ketone (8 g.) was effected by the dropwise addition of 7·9 g. of dry bromine in carbon tetrachloride solution. The solution was evaporated in a vacuum to remove most of the solvent and hydrogen bromide, and the bromide was isolated in the usual manner. Repeated fractional distillation gave p-tert.-*butylphenacyl bromide*, b. p. 127°/0·5 mm., which, however, does not seem to be pure (Found : Br, 33·2, 30·1. $C_{12}H_{15}OBr$ requires Br, 31·4%).

Bromination of *o*-nitroacetophenone in acetic acid according to Gevekoht's procedure (*Annalen*, 1883, **221**, 327) gave mainly the ωω-dibromo-derivative, m. p. 85°. The monobromo-compound was obtained by the addition of slightly less than 1 mol. of bromine to the ketone, both in solution in dry ligroin (b. p. 40—60°), gently warmed on a steam-bath. After evaporation of the solvent, the product was washed in ethereal solution with aqueous sodium bicarbonate and water, and dried with sodium sulphate. The residue from the dried ethereal solution was distilled under reduced pressure and the distillate, which crystallised, was further purified by crystallisation from cold ligroin (b. p. 40—60°) as described by Gevekoht. The sample used had m. p. 55·2°.

The samples of *p*-methyl- and *p*-nitro-phenacyl bromides were those used in an earlier investigation (Baker, J., 1932, 1148). They were again purified by crystallisation before use.

The following quaternary salts were isolated in the course of the investigation : o-*Nitrophenacylpyridinium bromide*, decomp. *ca.* 260° (Found : * Br′, 25·2. $C_{13}H_{11}O_2N_2Br$ requires Br′, 26·1%); o-*methylphenacylpyridinium bromide*, m. p. 182° (Found : * Br′, 27·1. $C_{14}H_{14}ONBr$ requires Br′, 27·4%); and 2 : 4 : 6-*trimethylphenacylpyridinium bromide*, decomp. *ca.* 280° (Found : * Br′, 24·4. $C_{16}H_{18}ONBr$ requires Br′, 25·0%), which was obtained by warming

2 : 4 : 6-trimethylphenacyl bromide with excess of pyridine without solvent, the salt which crystallised out being washed with dry acetone.

Action of Semicarbazide Acetate.—Under the ordinary conditions of semicarbazone formation, 2 : 4 : 6-trimethylacetophenone (von Meyer and Molz, *Ber.*, 1897, **30**, 1271) gave no semicarbazone when kept for a month. Dilution of the aqueous-alcoholic solution only reprecipitated the unchanged ketone. Addition of an alcoholic solution of the ω-bromo-compound to a solution of semicarbazide acetate gave, within a few minutes, a copious crystalline precipitate, which after crystallisation from dilute alcohol had m. p. 57° either alone or mixed with the original ω-bromo-compound. Similarly treated, 2 : 4-dimethylphenacyl bromide gave a bromine-free precipitate of the ω-*semicarbazido*-compound, m. p. 175—176°, after crystallisation from dilute alcohol (Found : N, 15·8. $C_{11}H_{15}O_2N_3,C_2H_6O$ requires N, 15·7%).

Velocity Measurements.—The kinetic measurements were carried out by the micro-technique previously described (Baker and Nathan, J., 1935, 1840). The values of the velocity coefficients were determined from the slope of the straight line obtained by plotting $x/(a-x)$ against time for 5—7 independent determinations of x. In the case of the *o*-nitro-compound, in which early crystallisation of the salt occurred, 2 c.c. samples of the reaction mixture were sealed in separate tubes kept in the thermostat, so that the whole sample could be broken into water for titration of the bromide ion formed. With 2 : 4 : 6-trimethylphenacyl bromide and pyridine, both 0·025M in dry acetone, no appreciable bromide ion could be detected in a sample taken after the reaction mixture had been kept in a thermostat at 20° for 5 days.

The bimolecular character of the reaction is confirmed by the following data obtained with various proportions of phenacyl bromide (C_a) and pyridine (C_p) :

C_a, M.	0·025	0·025	0·0125
C_p, M.	0·014	0·025	0·025
$10^3 \times k$	0·78	0·79	0·79

All analyses, except those marked with an asterisk, are by Dr. G. Weiler.

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