276. *The Influence of Nuclear Substituents upon Side-chain Reactions. Part II. Factors controlling the Velocities of Acid-catalysed Prototropy of Nuclear-substituted Acetophenones.*

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The discoveries that certain reactions proceed in solution with nearly the same speeds and energies of activation as in the gaseous phase (*e.g.*, the decomposition of chlorine monoxide, Moelwyn-Hughes and Hinshelwood, *Proc. Roy. Soc.*, 1931, *A*, **131**, 177), and that the velocities of a number of reactions in solution are approximately those predicted by the collision theory in its simplest form (Moelwyn-Hughes, *Chem. Reviews*, 1932, **10**, 241) while, in some cases at least, a speed smaller than that calculated is a characteristic of the reaction itself (Moelwyn-Hughes and Hinshelwood, J., 1932, 230), have led to the representation of the speeds of bimolecular reactions in solution by the equation $k = PZe^{-E/RT}$, where Z is the collision frequency as given by the kinetic theory, and P, which varies over a wide range, is a probability factor including all necessary conditions other than activation. The marked influence of nuclear substituents upon the reaction velocities of benzene derivatives may clearly arise from changes in E, in P, or in both.

The results of Bradfield, Jones, and their collaborators (J., 1928, 1006, 3073; 1931, 2903, 2907; *Chem. and Ind.*, 1932, **51**, 254) indicated that, in the chlorination of a series of phenolic ethers of general formula $RO{\cdot}C_6H_4X$ or $RO{\cdot}C_6H_3Me{\cdot}X$, the factor P remains unchanged within the limits of experimental error; the postulate that differences in velocity are to be ascribed to changes in the energy of activation was both necessary and sufficient for the explanation of their observations. The same work also showed that the relative effects of the groups OR were independent of the nature of X, and *vice versa*; the conclusion was thus reached that substituent groups contribute additively to the energy of activation, which may be represented as the sum of a series of terms, $E = E_0 + e_1 + e_2 + \ldots.$, where E_0 is the value relating to the unsubstituted compound, and e_1, e_2, etc., are the contributions (positive or negative) of the substituents.

Somewhat later, Nathan and Watson (J., 1933, 217, 890) measured the velocities of acid-catalysed prototropic change of a series of *p*-substituted acetophenones and ω-chloroacetophenones, using Lapworth's bromination method. They regarded the observed velocities as a measure of the relative speeds at which the catalyst reacted with the carbonyl oxygen, and, in the light of Bradfield's results, assumed that the influence of the substituent upon this reaction consisted entirely in a change of the energy of activation. They further reviewed the available data for 13 other side-chain reactions on the basis of the same assumption (J., 1933, 1248). The investigation here described was undertaken with the object of testing the correctness or otherwise of these postulates.

During the progress of the present work, Williams and Hinshelwood (J., 1934, 1079) reported their demonstration that, in the benzoylation of anilines in benzene solution, the energy of activation is the only factor which is changed to an important extent by the introduction of *p*-substituents either in the amine or in the acid chloride. The result was particularly striking, since it referred to a reaction for which the value of P was of the order 10^{-7}. An examination of Cain and Nicoll's data (J., 1902, **81**, 1434) for the decomposition of diazo-compounds led them to a similar conclusion for this reaction also. Still more recently, Hinshelwood and Legard's investigation of the kinetics of esterification (this vol., p. 587) for six different acids and four alcohols has shown that here again variations in velocity depend upon different energies of activation, although replacement of the undissociated acid by hydrogen ion as catalyst leads to important changes in other factors; even steric hindrance is connected with changes in E. It has therefore been proved, in several cases, that differences in the reaction velocities of a series of similarly-constituted compounds are to be ascribed mainly to changes in the energy of activation. McKay (*Chem. and Ind.*, 1934, **53**, 870) has pointed out that changes in E are to be anticipated, on theoretical grounds, when the observed effects can be ascribed to polar influences.

The approximate constancy of factors other than the energy of activation cannot, however, be postulated for a given reaction of *any* series of similar compounds, for there is definite proof that substituent groups may have so profound an effect that a change even in reaction mechanism occurs. Thus, the hydrolysis of methyl and ethyl halides in aqueous alcohol proceeds by a bimolecular mechanism, while *iso*propyl and *tert.*-butyl halides undergo unimolecular hydrolysis (Gleave, Hughes, and Ingold, this vol., p. 236; Hughes and Ingold, *ibid.*, p. 244; Hughes, *ibid.*, p. 255; *J. Amer. Chem. Soc.*, 1935, **57**, 708), and similar observations have been made upon the series benzyl chloride, benzylidene chloride, and benzotrichloride (Olivier and Weber, *Rec. trav. chim.*, 1934, **53**, 869). Indeed, the velocities of hydrolysis of certain substituted benzyl and benzylidene chlorides in neutral and in alkaline solution indicate an influence of *nuclear* substituents upon the mechanism (Olivier and Weber, *loc. cit.*). It is, nevertheless, a tempting speculation that the influence of nuclear substituents upon the reaction velocities of benzene derivatives, when it is of a polar character (compare McKay, *loc. cit.*) and when the reaction is not particularly susceptible to complications such as changes in mechanism, may, in general, be due almost entirely to changes in the energy of activation; no definite conclusion will be possible, however, until many more, accurate experimental data are available regarding the kinetics of the reactions of benzene derivatives.

The present communication deals with the acid-catalysed prototropy of a series of *m*- and *p*-substituted acetophenones. We have measured the velocities of bromination (= velocity of prototropic change) at four temperatures, using $0{\cdot}1M$-solutions in 75% acetic acid in presence of $0{\cdot}5M$-hydrochloric acid. The observed velocities are recorded in cols. 2—5 of the table below, and the values of E (determined in the usual manner) in the last column. The velocities are in every case the mean of those found by two or more (sometimes several) concordant determinations, and we believe them to be accurate within ± 1%.

If the well-known formula for Z (Moelwyn-Hughes, " Kinetics of Reactions in Solution," Oxford, 1933) is substituted in the expression $k = PZe^{-E/RT}$, and P is assumed constant, the equation reduces to

$$E = c - 2{\cdot}303RT \,.\, \log k \Big/ \left[\left(\frac{\sigma_1 + \sigma_2}{2}\right)^2 \left(\frac{1}{M_1} + \frac{1}{M_2}\right)^{\frac{1}{2}}\right] = c - 2{\cdot}303RT \,.\, \log k/z,$$

where c is a comprehensive constant, and σ_1 and σ_2 are the molecular diameters and M_1 and M_2 the molecular weights of the reacting species (compare Nathan and Watson, *loc. cit.*, p. 891). The plot of E against $\log k/z$ is therefore a straight line with slope $2{\cdot}303RT$. The values of $\log k/z$ are given in cols. 6—9 of the table; they are obtained by combining with the velocity coefficients in cols. 2—5 the values of z recorded by Nathan and Watson or calculated by their method.

*Bromination of Substituted Acetophenones.**

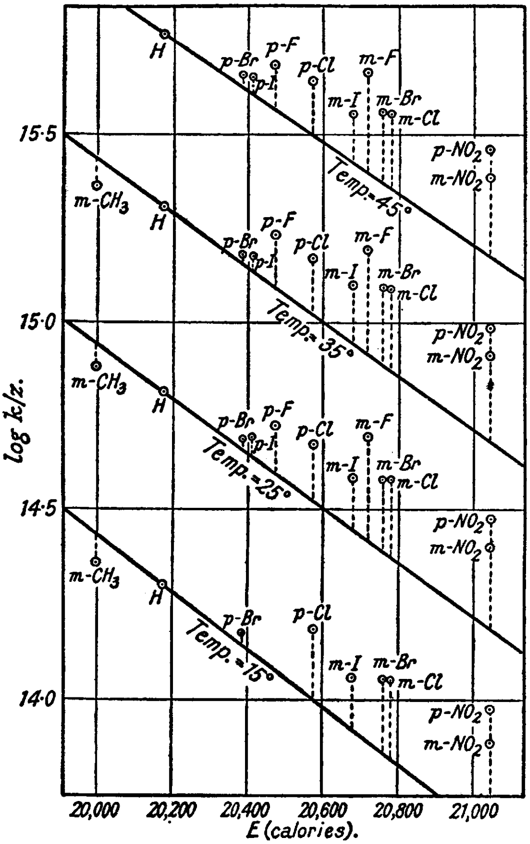
Substituent.	Velocities.				Values of $\log k/z$.				
	k_{15°.	k_{25°.	k_{35°.	k_{45°.	15°.	25°.	35°.	45°.	E(cals.).
m-CH_3	0·0891	0·297	0·890	—	14·356	14·879	15·355	—	20,000
H	0·0750	0·244	0·754	2·18	14·300	14·812	15·302	15·764	20,180
m-I	0·0445	0·150	0·484	1·41	14·049	14·576	15·085	15·549	20,680
m-Br	0·0436	0·147	0·479	1·40	14·048	14·576	15·089	15·555	20,760
m-Cl	0·0430	0·146	0·471	1·385	14·044	14·575	15·083	15·552	20,780
m-F	—	0·165	0·524	1·54	—	14·687	15·189	15·657	20,720
m-NO_2	†0·0298	0·099	0·320	0·955	13·876	14·397	14·907	15·382	21,040
p-I	—	0·195	0·597	1·76	—	14·690	15·176	15·646	20,410
p-Br	0·0580	0·185	0·569	1·74	14·172	14·676	15·164	15·649	20,390
p-Cl	†0·0571	0·182	0·567	1·68	14·181	14·670	15·164	15·636	20,570
p-F	—	0·179	0·573	1·63	—	14·722	15·228	15·682	20,470
p-NO_2	†0·0368	0·118	0·379	1·14	13·969	14·474	14·980	15·459	21,040

* The velocity coefficients are expressed as fall of $N/50$-thiosulphate titre per minute for 20 c.c. of $0{\cdot}1M$-ketone solutions in presence of $0{\cdot}5M$-hydrochloric acid. They have not been reduced to the customary units, since the concentration of hydrogen ion is uncertain and the units do not affect the argument. Certain of the values for 25° differ somewhat from those found previously (Nathan and Watson, *loc. cit.*), and we attribute this mainly to the development of improved methods of preparation and purification of the compounds (see Experimental). The velocities marked thus † have been neglected in computing E, as they deviate rather seriously from the Arrhenius straight line; the deviations have been confirmed by several independent measurements. The plot of $\log k$ against $1/T$ for the remaining values gives excellent straight lines.

In the figure, the values of E are plotted against those of $\log k/z$, and through the points referring to unsubstituted acetophenone straight lines are drawn with the theoretical slope $2{\cdot}303RT$; this procedure is identical with that adopted by Williams and Hinshelwood (*loc. cit.*). The points do not fall on the lines, as would be the case if the equation were strictly applicable, *i.e.*, if Nathan and Watson's assumptions were both correct. The deviations from the theoretical lines are of a very different order of importance from the small divergences reported by Williams and Hinshelwood, and it is evident that an explanation must be sought, due attention being paid to the fact that the measured change occurs in more than one stage.

The obvious method of attack upon the problem is to examine Nathan and Watson's postulates in the light of the observations now recorded, and two alternatives may be considered : (1) that the measured velocities actually represent the relative speeds at which the ketones react with the acid catalyst, but that the effect of a substituent upon this reaction involves a change in factors other than the energy of activation; (2) that the observed velocities are *not* a true measure of the speeds of reaction of ketone and catalyst.

An inspection of the figure reveals a significant feature of the observations. Although the points depart very considerably from the theoretical straight lines, they are nevertheless located *around* the lines in a systematic manner, those referring to the electron-repulsive methyl substituent lying on one side, and those for the remaining (electron-attractive) groups on the opposite side, this deviation being greatest for the highly polar nitro-substituent. Thus, an electron-repulsive group gives values of k/z which are *lower*, and electron-attractive substituents values *higher*, than those anticipated on the basis of Nathan and Watson's postulates. Moreover, for any given compound, the divergence from the straight line is identical at the four temperatures, within the limits of error in the experimental determination of k and the calculation of z. Clearly, the factor responsible for the deviation is independent of temperature, or nearly so.



The regularity noted above does not, of course, exclude the first alternative (variation in P for the attack of the catalyst), but it leads to a very reasonable interpretation on the basis of the second. Some years ago the view was expressed (Hughes, Watson, and Yates, J., 1931, 3322) that "the velocity of a catalysed keto–enol change is dependent in a dual manner upon the influence of substituent groups, and due consideration must be given to the effect of the group (i) in facilitating the ionisation of the proton, and (ii) in promoting co-ordination with the catalyst," and the explanation here suggested involves the application of this view to the mechanism of acid-catalysed prototropy first put forward by Lapworth and Hann (J., 1902, **81**, 1513) and recently given a more precise physical significance (Watson, Nathan, and Laurie, *J. Chem. Physics*, 1935, **3**, 170). It is now generally recognised that in ketones and aldehydes quantum-mechanical resonance occurs between the normal and semipolar structures (Pauling and Sherman, *ibid.*, 1933, **1**, 606; McKay, *loc. cit.*), a phenomenon which Ingold has termed "mesomerism" (J., 1933, 1120; *Chem. Reviews*, 1934, **15**, 232). The normal structure is the main participant, and hence the actual configuration of the carbonyl group may be represented by $>\text{C}=\text{O}$ with a tendency ($>\overset{\curvearrowright}{\text{C}=\text{O}}$) towards $>\overset{\oplus}{\text{C}}-\overset{\ominus}{\text{O}}$. Watson, Nathan, and Laurie have suggested that in a fruitful collision with an acid catalyst energy is communicated to the group, and the semipolar form becomes the main participant in the resonance state. An immediate transformation now occurs either (*a*) regenerating the original form, or (*b*) producing the enol ion:

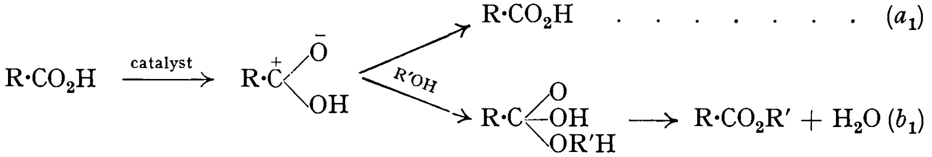
$$\text{(a.)}\quad >\text{CH}-\underset{\text{X}}{\overset{\oplus}{\text{C}}}-\overset{\ominus}{\text{O}} \rightarrow >\text{CH}-\underset{\text{X}}{\text{C}}=\text{O} \qquad >\text{CH}-\underset{\text{X}}{\overset{\oplus}{\text{C}}}-\overset{\ominus}{\text{O}} \rightarrow >\text{C}=\underset{\text{X}}{\text{C}}-\overset{\ominus}{\text{O}}\quad \text{(b.)}$$

The rate of prototropic change will, on this view, depend both upon the speed of reaction of ketone and catalyst and upon the proportion of the energised form which undergoes transformation (*b*). In process (*a*), a pair of electrons, initially the sole property of the oxygen atom, moves in the direction of the curved arrow and enters the carbon–oxygen double bond, whereas in process (*b*) a similar movement occurs, electrons from C_α approaching carbonyl carbon until they are shared by both atoms; changes in X (in this case the introduction of substituents into the acetophenone nucleus) will probably influence these electronic transferences to an approximately equal extent (compare Nathan and Watson, J., 1933, 217). In process (*b*), however, the electron pair concerned is initially shared by C_α

and a proton, and, prior to or concurrently with the movement indicated by the curved arrow, the removal of this proton (by an acceptor in the medium) must occur. An electron-attractive substituent in X will *increase*, and an electron-repulsive substituent will *decrease* the facility of this process, with a resulting change in the extent to which transformation (*b*) occurs, and therefore in the proportion of enol formed. The influence of the substituent here will therefore be opposed to its influence upon the initial attack of the ketone by the catalyst, and the relationships illustrated in the figure, *viz.*, velocities higher than anticipated for nitroxyl and halogens, and lower for methyl, are exactly those which would be predicted.

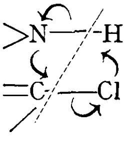
Although, therefore, our results show very definitely that the changes in velocity are not accounted for quantitatively by the contributions of the substituents to the energy of activation, it is not necessary to assume a variation in the proportion of fruitful collisions between activated molecules of ketone and catalyst. An adequate interpretation is found on the view that the observed velocities are not a true measure of the relative speeds of the initial reaction, and that the apparent changes in a " *P* factor " have their origin in a subsequent stage.

We wish further to point out the possibility that certain other observations may be capable of an interpretation on similar lines. The prototropy of acetone under the influence of different acid catalysts has recently been studied by Smith (J., 1934, 1744), and his value of 0·15 for *P* when hydrogen ion is the catalyst is in good agreement with the values 0·15 and 0·29 for acetophenone and *p*-nitroacetophenone respectively, obtained from our results by calculating *P* in the usual manner, the assumption being made that the concentration of hydrogen ion is equal to that of hydrogen chloride introduced. Smith finds an increase in *P* with increasing acid strength of the catalyst, and this is to be anticipated on the view presented above if it be supposed that the transformations (*a*) and (*b*) occur while the catalyst molecule remains linked to carbonyl oxygen, for increasing acidity of the catalyst (reaching a maximum for the solvated hydrogen ion) will lead to increasing facility of removal of the α-proton and hence increasing proportion of enol formed. It may be tentatively suggested, indeed, that the variations of *P* in esterification reactions (Hinshelwood and Legard, *loc. cit.*) may also arise in the second stage of a sequence such as the following (compare Lowry, J., 1925, 1381) :



The large increase in *P* on changing from a non-ionic catalyst to hydrogen ion would then receive an interpretation akin to that suggested above with reference to the prototropy of acetone (b_1 favoured strongly), while the rising *P* values on passing from primary to secondary and tertiary alcohols would be anticipated, since the unshared electrons of the alcoholic oxygen become progressively more prone to co-ordination at a positive centre. Further, the simultaneous rise in *E* and *P* found in most cases would be attributed to the opposite effects of constitutional variations upon the two stages of the reaction, as in the case of the substituted acetophenones already discussed. For a series of acids, the sequence is not obvious, but here the catalyst and the reactant molecule are both changing, and the relationships may be further obscured by the resonance of the carbethoxyl group and other complicating factors.

We suggest, therefore, that the variable *P* term found in certain catalytic processes may be due to the occurrence of the reaction in consecutive stages, *E* being determined by the initial stage of the process and *P* mainly (or entirely) by a subsequent stage. On the other hand, the *P* factor in a straightforward bimolecular reaction such as the benzoylation of aniline doubtless represents the proportion of the collisions between activated molecules that lead to reaction; the essentials of this change may probably be written as in the inset, and stringent conditions of orientation in such a case are not unexpected. It is significant that *P* does not here vary with the introduction of substituents.



EXPERIMENTAL.

Preparation of Materials.—Acetophenone, distilled under reduced pressure, had m. p. 19·6° (Morgan and Lammert, *J. Amer. Chem. Soc.*, 1924, **46**, 881, give 19·655° ± 0·002°).

m-Nitroacetophenone was prepared by a modification of the method of Mayer and English (*Annalen*, 1918, **417**, 82; compare Rupe, Braun, and Zembruski, *Ber.*, 1901, **34**, 3522; also " Organic Syntheses," Vol. X, 74). Acetophenone (48 g.) was dissolved in concentrated sulphuric acid (260 g.), cooled by ice and ammonium chloride. A mixture of concentrated nitric (58 g.) and sulphuric (180 g.) acids was added, with strong cooling and vigorous shaking, as rapidly as was consistent with a temperature of − 5°. The mixture was further shaken for ½ hour and poured on ice, *m*-nitroacetophenone separating as a pale yellow solid (64 g.). It was dissolved in glacial acetic acid, shaken three times with charcoal, filtered, and crystallised. The sample used for the measurements was further recrystallised from aqueous acetic acid, and obtained as cream-coloured crystals, m. p. 79·5° (" Organic Syntheses," *loc. cit.*, gives 76—78°).

m-Aminoacetophenone was obtained by reduction of *m*-nitroacetophenone with iron (Morgan and Moss, *J. Soc. Chem. Ind.*, 1923, **42**, 462T). When iron filings were employed, difficulty was encountered in the filtration, and this was overcome by the use of coarse iron chippings. Yield of crude product, 89%; m. p. 94° (Morgan and Moss record 92—93°; and Elson, Gibson, and Johnson, J., 1930, 1130, 98—99° for the pure compound).

m-*Chloroacetophenone.* *m*-Aminoacetophenone (40 g.) in concentrated hydrochloric acid (50 c.c.) diluted with water (190 c.c.) was diazotised at 0° with sodium nitrite (21 g.), and treated with cuprous chloride [copper sulphate (50 g.) and sodium chloride (24 g.) in water (100 c.c.) treated with concentrated hydrochloric acid (200 g.) and copper turnings (26 g.) until colourless, and hydrochloric acid added until the total weight was 405 g.]. The mixture was heated on a water-bath, and after steam-distillation the product was extracted with ether and the extract washed with alkali, acid, and water, and dried over calcium chloride. On distillation under reduced pressure, the *m*-chloroacetophenone was obtained as a colourless oil, b. p. 113°/11 mm. (Found: Cl, 22·5. Calc.: Cl, 22·95%); yield, 45%. The specimen was further fractionated before the measurements. [Wahl and Rolland (*Ann. Chim.*, 1928, **10**, 29) describe it as a yellow liquid, b. p. 227—229°.]

m-Bromoacetophenone, prepared from *m*-aminoacetophenone as described by Elson, Gibson, and Johnson (who give b. p. 127°/14 mm., 131°/16 mm.; *loc. cit.*), was a colourless oil, b. p. 110°/8 mm.; yield 30% (Found: Br, 39·7. Calc.: Br, 40·1%).

m-*Iodoacetophenone.* *m*-Aminoacetophenone (40 g.) was diazotised, and potassium iodide (66 g.) added, the mixture being thereafter treated as for *m*-chloroacetophenone. The product was an oil having a light colour, b. p. 128·5°/8 mm.; yield 30% (Found: I, 50·8. Calc.: I, 51·6%).

m-Fluoroacetophenone was prepared by the method of Balz and Schiemann (*Ber.*, 1927, **60**, 1186; compare " Organic Syntheses," XIII, 46). *m*-Aminoacetophenone (60 g.) was diazotised, and the solution added to a well-cooled and stirred solution of hydrofluoboric acid (200 g. of 40% solution). The thick creamy precipitate of borofluoride was collected and dried for a long period. It decomposed at 83°, and the residue, after steam-distillation, extraction with ether, drying, and fractionation, gave *m*-fluoroacetophenone as a colourless oil, b. p. 81°/9 mm. (Found: C, 68·9; H, 5·16. Calc.: C, 69·5; H, 5·07%).

m-*Methylacetophenone.* Calcium *m*-toluate was precipitated by calcium chloride from a solution of the ammonium salt, dehydrated at 120°, and mixed with anhydrous calcium acetate (50% excess). The mixture was heated under carefully controlled conditions, and the product steam-distilled, extracted with ether, and twice fractionated under reduced pressure. It was a colourless oil, b. p. 96°/10 mm. (Auwers, *Annalen*, 1915, **408**, 243, gives 109°/12 mm.; Klages and Lickroth, *Ber.*, 1899, **32**, 1560, give b. p. *ca.* 110°/16 mm.) (Found: C, 79·7; H, 7·8. Calc.: C, 80·6; H, 7·5%).

p-Chloro- and *p*-bromo-acetophenone (m. p.'s 20·5° and 51·6° respectively) were prepared by the Friedel–Crafts method (" Organic Syntheses," Coll. Vol., 1932, p. 105, where m. p.'s are given as 20—21° and 49—50·5° respectively). The specimens used previously (Nathan and Watson, J., 1933, 217) had m. p.'s 19·8° and 51·6° respectively.

p-Iodoacetophenone was obtained by a modification of Schweizer's procedure (*Ber.*, 1891, **24**, 551), which gave better results than Nathan and Watson's method. To a solution of dry iodobenzene (40 g.) and freshly-distilled acetyl chloride (16 c.c.) in dry carbon disulphide (60 c.c.), finely-powdered aluminium chloride (20 g.) was added slowly, vigorous ebullition being avoided by cooling. After 15 mins.' shaking, the solvent was distilled off quickly, and the residue poured on ice and then steam-distilled. The unchanged iodobenzene (18 g.) was first collected under iced water. On the appearance of a white solid, the receiver was changed, and the *p*-iodoacetophenone similarly collected. Recrystallised from light petroleum, it was obtained as a white solid, m. p. 85° (compare Schweizer, *loc. cit.*; Nathan and Watson, *loc. cit.*); yield, 40%.

p-Fluoroacetophenone (colourless oil, b. p. 71°/5 mm.; Schiemann and Pillarsky, *Ber.*, 1931, **64**, 1340, give 77—78°/10 mm.) was prepared by the Friedel–Crafts method from fluorobenzene (obtained as in "Organic Syntheses," Vol. 13, 46).

p-Nitroacetophenone was prepared by a modification of Drewsen's method (*Annalen*, 1882, **212**, 160). Bromine was added to ethyl *p*-nitrocinnamate, the product (128 g.) dissolved in absolute alcohol (75 c.c.), and treated with potassium hydroxide, (56 g.) also in alcohol (150 c.c.). The mixture was refluxed for 5 minutes, cooled, acidified with dilute sulphuric acid, and extracted with ether. Drying, removal of ether, and crystallisation from alcohol yielded 70 g. of crude *p*-nitrophenylpropiolic acid. This was stirred slowly into a mixture of sulphuric acid (370 g.) and water (180 c.c.), and maintained at 110° until all had dissolved and frothing ceased. Cooling and pouring into cold water yielded a black solid, which was dried, powdered, and extracted several times with light petroleum; 20 g. of crude *p*-nitroacetophenone thus obtained were purified by being twice shaken in warm light petroleum with animal charcoal, filtered hot, and allowed to crystallise. Yield 12 g.; m. p. 80° (Drewsen records 80—81°; the specimen used by Nathan and Watson had m. p. 78·4°).

Velocity Measurements.—The 75% acetic acid was prepared by diluting 750 c.c. (at the required temperature) of acetic acid, purified by Orton and Bradfield's method (J., 1927, 983), to 1 litre (at required temperature) with pure distilled water containing sufficient hydrochloric acid (previously distilled) to give a 0·5*M*-solution. In preparing the reaction mixtures, 90 c.c. of this medium were added to the weight of ketone required for a 0·1*M*-solution, and the volume made up to 100 c.c. with a solution of bromine of suitable concentration in the same medium. The intial concentrations were: [ketone], 0·1*M*; [HCl], 0·5*M*; [Br_2], 0·005*M*. 20 C.c. were withdrawn at measured time intervals and added to about 50% excess of aqueous potassium iodide. With this procedure there was no measurable liberation of iodine by the bromo-ketone except with *m*- and *p*-iodoacetophenones, where the buffer previously employed by Nathan and Watson was utilised. Titration with *N*/50-thiosulphate led to the data recorded in the table (p. 1169).

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