538. *Elimination Reactions. Part II.* Base-catalysed Ionisation and Substitution Reactions of Ketones and Nitroparaffins.*

By H. M. E. Cardwell.

Two opposing rules of orientations of base-catalysed substitution reactions of ketones are observed. These rules correspond to the Hofmann and the Saytzeff type of control of the preliminary elimination reaction. It is shown, by analysis of kinetic data from the nitroparaffins, that these rules may be due to the fact that alkyl groups inductively hinder the loss of a proton to a base, but that once this has occurred they stabilise the resulting ion in a resonant or hyperconjugative manner.

Hughes (*Nature*, 1941, **147**, 813) has pointed out that the rates of base-catalysed iodination of acylbenzenes (Table I) as determined by Evans and Gordon (*J.*, 1938, 1434) indicate that alkyl groups act in an inductive manner and hinder the loss of a proton to a base. The large decrease in rate of loss of a proton caused by replacement of one hydrogen atom by Me, the slight decrease in rate on replacing Me by Et, and the further sharp decrease in rate on replacing the second hydrogen atom by Me are entirely and only consistent with this explanation.†

Table I.

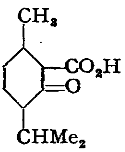
Rates of AcO^-*-catalysed iodination of* $Ph\cdot CO\cdot CHR_1R_2$.

R_1, R_2 =	H, H	H, Me	H, Et	Me, Me
Rate	238	37	29	7

(The rate for $Ph\cdot CO\cdot CH_3$ has been adjusted to the rate of ionisation of $CH_3\cdot NO_2$ so that the figures are directly comparable with those given in Table II.)

Tautomerism in ketones is therefore very similar to elimination reactions of sulphonium salts; under basic conditions the Hofmann rule is operative in ionisation of ketones and bimolecular elimination reactions of sulphonium salts; but on crossing the mechanistic border to acid-catalysed enolisation of ketones and to unimolecular elimination reactions of sulphonium salts Saytzeff's rule becomes operative.

There are a number of base-catalysed substitution reactions of ketones which follow Hofmann's rule of orientation of substitution. For instance, excellent yields of carboxylic acids ($Alk\cdot CH_2\cdot CO_2H$ from $\cdot CO\cdot CH_3$ *via* $\cdot CO\cdot CHal_3$) are obtained on base-catalysed iodination of alkyl methyl ketones (Simonsen, *J.*, 1922, **121**, 2292; Semmler and Schiller, *Ber.*, 1927, **60**, 1591). Many base-catalysed aldol condensations conform to this type of orientation; for instance, aromatic aldehydes condense preferentially on the CH_3 group of *n*-alkyl methyl ketones (Harries and Warunis, *Annalen*, 1903, **330**, 257; Warunis and Lekos, *Ber.*, 1910, **43**, 654; Zafiriadis, *Compt. rend.*, 1950, **230**, 452). The aldol condensation is, however, a reversible reaction, and the orientation of condensation is sensitive to the experimental conditions used. Carboxylation also follows Hofmann's rule. In this reaction the ketone is converted rapidly and irreversibly into the sodium enolate by treatment with a slight excess of sodium triphenylmethide in ether and is then treated with carbon dioxide. The latter reaction also appears to be very rapid. Using this technique, Levine and Hauser (*J. Amer. Chem. Soc.*, 1944, **66**, 1768) found that the product was solely $CH_2R\cdot CO\cdot CH_2\cdot CO_2H$ from the ketones $CH_2R\cdot CO\cdot CH_3$ (R = Me, Et, *n*-C_5H_{11}, and Pr^i). With sodamide in ether the enolate does not appear to be produced immediately and irreversibly, for Gardner, Perkin, and Watson (*J.*, 1910, **97**, 1756) found that (−)-menthone and (+)-*iso*menthone both gave a carboxy-(+)-*iso*menthone (I), indicating that inversion had occurred [with (−)-menthone] at the $\cdot CHPr^i\cdot$ asymmetric centre (see note added in proof, p. 2444).



(I.)

With other substituting reagents (alkyl halides, alkyl sulphates, diethylaminobutanone methiodide) substitution occurs on the most substituted carbon atom. For instance, with the following cyclic ketones substitution occurs on the carbon atom marked * (Cornubert, Humeau,

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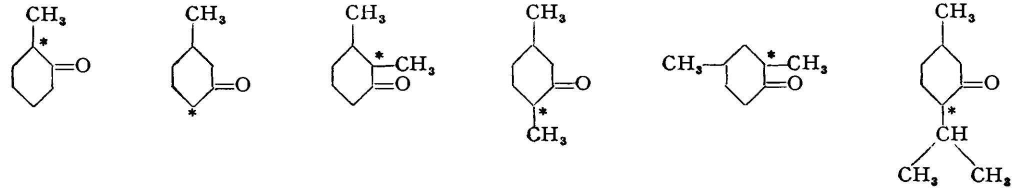
* Part I, preceding paper.

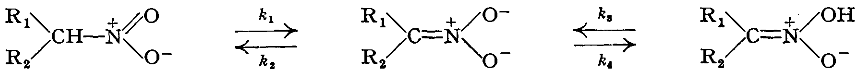
† This paper is restricted, as is the previous paper, to saturated acyclic or monocyclic ketones containing no hetero-substituent other than the single carbonyl oxygen atom. The use of rate data from the acetophenones therefore presents an anomaly which it is hoped to resolve in a later paper.

Bihan, and Maurel, *Bull. Soc. chim.*, 1931, **49**, 1260). This is substitution in accordance with the extended Saytzeff rule given in the preceding paper.



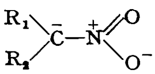
A clue to the origin of these opposed rules of orientation of substitution is given by the observation that the reactions following Hofmann's rule are rapid, whilst those following Saytzeff's rule are slow, but the most convincing evidence comes from kinetic data (Table II) on rates of ionisation and equilibrium concentrations of ions of the nitroparaffins (Maron and La Mer, *J. Amer. Chem. Soc.*, 1938, **60**, 2588; Turnbull and Maron, *ibid.*, 1943, **65**, 212; Bell and Swarzenbach, private communication).

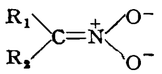
TABLE II.



Serial No.	R_1, R_2 =	H, H (i).	Me, H (ii).	Et, H (iii).	Me, Me (iv).
1	k_1	238	39	29	2·1
2	k_1/k_2	$6·2 \times 10^{-11}$	$3·5 \times 10^{-9}$	$1·1 \times 10^{-9}$	$2·1 \times 10^{-8}$
3	$10^{-8}k_2$	3840	112	263	1
4	$10^6k_3/k_4$	600	39	15	7·7

The variations in rates of ionisation (serial No. 1) of the nitroparaffins and ketones (Table I) on change of the alkyl substituents are almost identical; the inductive effect of alkyl substituents is therefore operative to the same extent in both reactions. The figures for the equilibrium constants (serial No. 2), however, reveal the paradox that 2-nitropropane (iv), which of the series most slowly loses a proton, is the strongest acid. The figures in serial No. 3 resolve this paradox, for they show that the extra Me in $\mathrm{CHMe{:}\overset{+}{N}{<}^{O^-}_{O^-}}$ stabilises this ion relative to $\mathrm{CH_2{:}\overset{+}{N}{<}^{O^-}_{O^-}}$, and that Et is less effective than Me as a stabiliser. This clearly is a resonance or hyperconjugative effect, for the normal order of this effect (2Me > Me + H > Et + H >2H) is observed. Alkyl substituents will stabilise the two systems $\mathrm{{>}C{:}\overset{+}{N}{<}^{O^-}_{O^-}}$ and $\mathrm{{>}C{:}\overset{+}{N}{<}^{OH}_{O^-}}$ in an equivalent manner; hence it is not surprising that their effect on k_3/k_4 (serial No. 4) is largely inductive. The effect of alkyl groups on the rates of addition of a proton to carbon in the mesomeric ion may be expressed in a slightly different manner. In the mesomeric

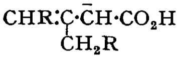
(A.) 

 (B.)

system (A) $\rightleftharpoons$ (B), it is usually assumed that (B) makes a much larger contribution than (A), but it is quite reasonable to assume that variations in the substituents R_1 and R_2 will vary the electron distribution in the mesomeric ion, and this variation may be expressed by saying that the relative contributions made by (A) and (B) are varied. The larger the contribution made by (A) the greater will be the rate of addition of a proton to carbon. Replacement of a hydrogen atom by Et will increase the relative contribution made by (B), an effect that will be accentuated by replacement of Et by Me. The above system is analogous to the three carbon system:

(A.) 

$\mathrm{\bar{C}HR{\cdot}\underset{CH_2R}{C}{:}CH{\cdot}CO_2H}$

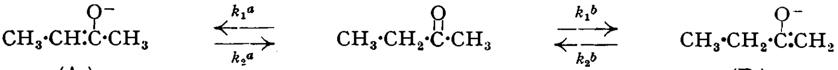
 (B.)

$\mathrm{CHR{:}\underset{CH_2R}{C}{\cdot}\bar{C}H{\cdot}CO_2H}$

and the rate data for k_2 (cols. i—iii) may be compared with the proportions of αβ- (addition of H^+ to A) and βγ- (addition of H^+ to B) unsaturated acids obtained on equilibration of these systems. The percentages of αβ-unsaturated compound were: R = H, 100; Me, 5; Et, 33 (Kon and May, *J.*, 1927, 1549; Hughes *loc. cit.*; de la Mare, Hughes, and Ingold, *J.*, 1948, 17).

With ketones, experimental difficulties have so far precluded the measurements of rates of ionisation and equilibrium concentrations of enolate ions. The assumption that alkyl groups act qualitatively in the same manner in base-catalysed reactions of nitroparaffins and ketones is, however, strengthened by the observation that it provides a satisfactory explanation of the opposed rules of orientation of substitution reactions observed earlier.

The argument will be restricted to saturated acyclic and monocyclic ketones, as in the previous paper, and will be concerned solely with the first stage of ionisation, *i.e.*, removal and addition of a proton from and to carbon.



$$CH_3{\cdot}CH{:}\overset{O^-}{C}{\cdot}CH_3 \underset{k_2^a}{\overset{k_1^a}{\leftrightarrows}} CH_3{\cdot}CH_2{\cdot}\overset{O}{\overset{\|}{C}}{\cdot}CH_3 \underset{k_2^b}{\overset{k_1^b}{\rightleftarrows}} CH_3{\cdot}CH_2{\cdot}\overset{O^-}{C}{:}CH_2$$

(A.) (B.)

In the particular case of ethyl methyl ketone, by analogy with the nitroparaffins, k_1^b will be greater than k_1^a, but k_2^b will be much greater than k_2^a. If, therefore, a substituting reagent is used which reacts with the enolate ion as soon as it is formed, the product will be largely $CH_3{\cdot}CH_2{\cdot}CO{\cdot}CH_2X$ ($k_1^b > k_1^a$) (Hofmann-type rule). If, however, conditions are used which allow equilibration of the enolate ions before substitution takes place, the orientation may be controlled by the ratio of k_1^a/k_2^a to k_1^b/k_2^b, and by analogy with the nitro-paraffins the former will be larger. The product will therefore be largely $CH_3{\cdot}CHX{\cdot}CO{\cdot}CH_3$, and orientation of substitution will approximate to that required by Saytzeff's rule.*

The above ideas may be used in the selection of the optimum experimental conditions for obtaining substitution according to the Hofmann- or the Saytzeff-type rule. Clearly, the cationoid reactivity of the attacking reagent is of supreme importance; where it is highly reactive, and where the substitution is irreversible, orientation will follow the Hofmann rule regardless of the experimental conditions used.

In these cases it is often possible to use a weak base in a solvent which can provide the proton necessary for equilibration of the enolate ions, but if the ion is attacked as soon as it is formed, the rate of formation of the ions will control orientation of substitution.

With alkyl halides and sulphates it is necessary to convert the ketone completely into the enolate ion (to minimise aldol type condensation) before substitution takes place, as the unchanged ketone is a more reactive cationoid reagent than the halides or sulphates. These conditions do not, in general, favour equilibration, for they involve the use of strong bases (sodium triphenylmethide, sodamide, or sodium *tert.*-alkoxides) in aprotic solvents; but once a small amount of the ketone has been alkylated, the resulting alkyl ketone can act as a proton source and allow equilibration of the small amount of enolate ion in solution. With the more reactive alkylating agents (*e.g.*, methyl sulphate) it should prove possible to increase the cationoid reactivity sufficiently, by use of a solvent of high dielectric constant, for orientation of substitution to follow the Hofmann-type rule. Clearly, the new solvent must not be one which increases significantly the possibility of equilibration of the ions or of self-condensation of the ketone. The only solvents which satisfy these conditions are the highly basic solvents such as liquid ammonia. In conformity with these ideas, but quite independently, Dr. Friedmann in these laboratories has recently discovered that methyl sulphate reacts rapidly with the sodium enolate of 2-methyl*cyclo*hexanone in liquid ammonia at $-70°$ to give 80% of 2 : 6- and only 20% of 2 : 2-dimethyl*cyclo*hexanone. This is almost a complete inversion of the orientation found in the slow alkylation with this reagent in ether.

An adequate test of these ideas would clearly involve much work, but they are put forward now in the hope that they will facilitate the choice of the optimum experimental conditions for the preparation of particular substituted ketones.

[*Added in proof, July 5th,* 1951.] The preparation of (—)-2-carbomethoxymenthone by successive treatment of (—)-menthone with ethereal sodium triphenylmethide, carbon dioxide, and ethereal diazomethane has shown that these reactions are rapid and largely irreversible under the conditions used. Analysis of the mixture of keto-esters prepared in this way from an unsymmetrical ketone therefore gives a rough measure of the relative rates of loss of a proton from the two reactive positions.

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* The more stable ion of any pair should be the least reactive not only to a proton but to most cationoid reagents. Hence, change over to Saytzeff-type orientation of substitution should not occur at once on passing from zero to first-order reactions with respect to the cationoid substituting reagent. A correlation between rules of substitution and cationoid reactivity of the reagents would be explicable in terms of probability factors and activation energies (Birch, Faraday Soc. Discussion " The Labile Molecule," 1947, p. 247, 262; Dewar, *ibid.*, p. 261; " Electronic Theory of Organic Chemistry," Oxford Univ. Press, 1949, p. 103) but it would not be easy to deduce in this manner that substitution with unreactive cationoid reagents would approximate to the Saytzeff-type rule.

(—)-2-*Carbomethoxymenthone*.—(—)-Menthone (5 g.; $[\alpha]_D^{20}$ $-22{\cdot}9°$) in dry ether (20 c.c.) was treated with slightly less than one equiv. of ethereal sodium triphenylmethide. The ethereal suspension of the sodium enolate was immediately run on excess of chopped solid carbon dioxide. When evolution of carbon dioxide had ceased the mixture was twice extracted with ice-cold water. The combined aqueous extracts were extracted five times with ether, and were acidified with ice-cold 2N-sulphuric acid. The liberated (—)-2-carboxymenthone was extracted with ether. The ethereal extract was rapidly clarified with magnesium sulphate and then (95 c.c.) gave a rotation of $-2{\cdot}21°$ in a 3-dm. tube (from the amount of methyl ester subsequently obtained the acid must have had a minimum $[\alpha]_D$ of $-24{\cdot}1°$). The menthone obtained from this acid by decarboxylation had $[\alpha]_D^{20}$ $-20{\cdot}4°$, indicating that negligible reversion had taken place at the ·CHPr^i· asymmetric centre. The ethereal solution (90 c.c.) of the acid was esterified with ethereal diazomethane and then washed rapidly with 2N-sulphuric acid, water, aqueous sodium hydrogen carbonate, and water. After drying ($MgSO_4$) and removal of the ether the residue (2·92 g.) was distilled. (—)-2-*Carbomethoxymenthone* distilled as a colourless oil with a sweet menthone-like odour, b.p. 122—124°/6—7 mm., $[\alpha]_D^{20}$ $-29{\cdot}0°$ (*c*, 6 in methanol) (Found: C, 67·3; H, 9·5. $C_{12}H_{20}O_3$ requires C, 67·9; H, 9·4%). The ester gave a deep green colour with methanolic ferric chloride. On addition of a few drops of concentrated sulphuric acid to a solution of the ester (628·6 mg.) in methanol (10 c.c.) the rotation (1-dm. tube) changed from $-1{\cdot}82°$ to $+0{\cdot}37°$ in 6 days but mutarotation was not complete when this note was submitted.

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