537. *Elimination Reactions. Part I. Acid-catalysed Enolisation and Substitution Reactions of Ketones.*

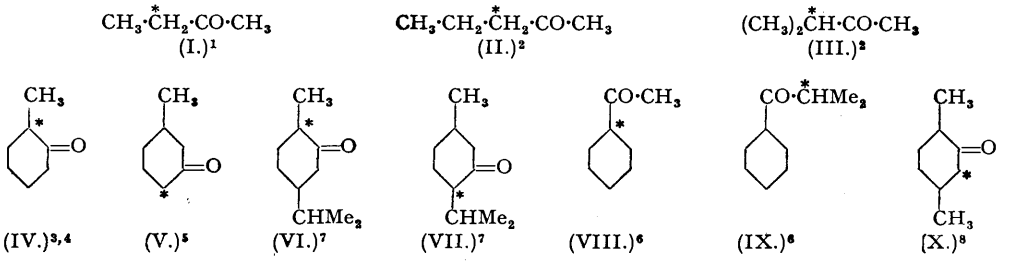
By H. M. E. Cardwell and A. E. H. Kilner.

Determination of the velocities of production of the isomeric enols from a series of simple alkyl ketones has revealed that orientation of enolisation is controlled by the ability of alkyl groups to be hyperconjugated with the developing double bond in the transition state. The orientation of enolisation largely controls the orientation of substitutions. Rules for the orientation of enolisation are given, and are identical with the modified Saytzeff rule for the dehydrohalogenation of alkyl halides.

There is a pronounced alternation in the hyperconjugative property of *n*-alkyl groups, Me>H; Pr^n>Et; *n*-amyl>Bu^n.

In the acid-catalysed halogenation of ketones it has been clearly demonstrated (Lapworth, *J.*, 1904, **85**, 30 : Bell, " Acid–Base Catalysis," Oxford Univ. Press, 1941) that the rate-controlling step is the enolisation of the ketone. The orientation of halogenation of unsymmetrical ketones should therefore parallel the orientation of enolisation.

The halogenation of the ketones (I)—(X) is described in the literature; in the majority of cases only the monohalogeno-ketone predominantly formed has been isolated, the asterisks indicating the preferred position of substitution. With the exception of the chlorination of

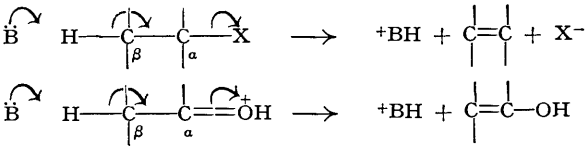


[1] Catch, Elliott, Hey, and Jones, *J.*, 1948, 272. [2] Catch, Hey, Jones, and Wilson, *J.*, 1948, 276. [3] Godchot and Bedos, *Compt. rend.*, 1925, **181**, 919. [4] Borrel and Cornubert, *Bull. Soc. chim.*, 1928, **43**, 804. [5] Godchot and Bedos, *Compt. rend.*, 1924, **178**, 1374. [6] Faworsky, *J. pr. Chem.*, 1913, **88**, 641. [7] Kötz and Steinhorst, *Annalen*, 1911, **379**, 1. [8] Kötz, Blendermann, *et al.*, *Annalen*, 1913, **400**, 47, 55.

2 : 5-dimethyl*cyclo*hexanone (X) all the above halogenations conform to the following rule : " In the acid-catalysed enolisation (halogenation) of an unsymmetrical saturated ketone (acyclic or monocyclic) the proton will be lost most readily from the carbon atom whose adjacent carbon atoms carry the largest number of hydrogen atoms." The rule may be illustrated by 2- and 3-methyl*cyclo*hexanone (IV and V) ; in (IV) there are five hydrogen atoms on the carbon

atoms adjacent to position 2, and two hydrogen atoms adjacent to position 6; in (V) there are one and two hydrogen atoms respectively adjacent to the corresponding positions: substitution in the 2-position in the former and in the 6-position in the latter is, therefore, expected. In the anomalous case (X) the structure of the product was not conclusively established (see Godchot and Bedos, *loc. cit.*).

The above rule is similar to the extended Saytzeff rule (Dhar, Hughes, Ingold, Mandour, Maw, and Woolf, *J.*, 1948, 2093) for the orientation of dehydrohalogenation of alkyl halides:



The similarity of the two reactions has been noticed by Hughes (*Nature*, 1941, **147**, 813) and by Hauser and Adams (*J. Amer. Chem. Soc.*, 1944, **66**, 345), and the latter have suggested that alkyl substituents must be exerting the same type of influence (Baker–Nathan or hyperconjugative) in both reactions. To test this conclusion, we have determined the proportions of the isomeric monobromo-ketones formed in the acid-catalysed bromination of the following methyl ketones (Pr^i, Bu^n, Bu^i, Bu^s, *n*-amyl, and *n*-hexyl) by the method used by Catch *et al.* (*loc. cit.*) for ethyl methyl and methyl *n*-propyl ketones. Fractional distillation under reduced pressure was used to separate the bromo-ketones, the actual percentages being determined by interpolation on the graph of weight of distillate against boiling point. In all cases the bromomethyl ketones were more lachrymatory and higher-boiling than the bromomethylene ketones. Crystalline derivatives (anilino-compounds from the bromomethyl ketones, and thiazoles from the bromomethylene ketones) were prepared in most cases. Authentic specimens of the bromomethyl ketones (except those from *n*-amyl methyl and *n*-hexyl methyl ketones were prepared (for comparative purposes) by the action of diazomethane followed by hydrogen bromide on the appropriate acid bromides.

The results of these investigations (including the two ketones studied by Catch *et al.*) are given in Table I (cols. ii and iii) together with relative rates of iodination at 25° (col. iv) as determined by Dawson *et al.* (*J.*, 1910, **97**, 2048; *J.*, 1911, **99**, 1740) (the rate figures for *n*-amyl and *sec.*-butyl methyl ketones were kindly provided by Dr. J. Shorter). The itemised rates given in cols. (v)—(viii) are used in the discussion.

It is difficult to estimate the accuracy of these analyses. In all cases, but in particular for *n*-hexyl methyl ketone, the proportion of bromomethyl ketones may have been underestimated. These ketones are sensitive to traces of acids and, as the dibromo-ketones decompose when heated with liberation of hydrogen bromide, it was essential to strip the crude reaction

TABLE I.

		Percentage of:		Rate of iodination ($COMe_2$ = 100).	Rate of formation of enols: >C:C(OH)·CH₃.		>CH·C(OH):CH₂.	
Ser. no.	Ketone. (i.)	>CBr·CO·CH₃. (ii).	>CH·CO·CH₂Br. (iii.)	(iv.)	cols. (ii) × (iv). 100 (v.)	Statistically corrected. (vi.)	cols. (iii) × (iv). 100 (vii.)	Statistically corrected. (viii.)
1	H·CH_2·COMe	50	50	100	50	50	50	50
2	Me·CH_2·COMe	73 *	27	104	76	104	28	28
3	Et·CH_2·COMe	63	37	94	59	89	35	35
4	Pr^n·CH_2·COMe	77	23	110	85	127	25	25
5	Bu^n·CH_2·COMe	60	40	96	58	86	37	37
6	Am^n·CH_2·COMe	80	20	106	85	127	21	21
7	Pr^i·CH_2·COMe	52	48	86	45	67	41	41
8	Me_2CH·COMe	76	24	69	52	156	17	17
9	MeEtCH·COMe	78	22	48·3	38	114	10	10
10	Bu^t·COMe	—	100	46	—	—	46	46
11	Me·CH_2·COEt	50	50	82	41	62	41	62

* Beets (*Rec. Trav. chim.*, 1950, **69**, 307) found 74% of this chloro-ketone in the monochloro-ketones.

mixture from most of the dibromo-ketones before fractionation. In this process significant quantities of the bromomethyl ketones may have been left in the dibromo-ketone fraction. As illustrative of the sensitivity of the bromomethyl ketones we quote three fractionations of

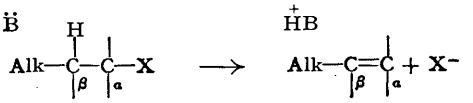
the bromoketones from *n*-amyl methyl ketone. A fractionation at 30 mm. resulted in complete pyrolysis of the bromomethyl fraction, a second fractionation on a new sample at 23 mm. gave 83% of 3-bromoheptan-2-one, but examination of the fraction presumed to be 1-bromoheptan-2-one showed a strong acid reaction, anomalously high refractive index, and abnormally low bromine content. Evidently pronounced decomposition had still occurred. Repetition of the fractionations on a new sample, at 5 mm., gave 60% of the bromomethylene ketone, and both bromo-ketones gave a neutral reaction, normal refractive indices, and excellent analyses. Despite this experimental difficulty, we consider that the analyses (except that for *n*-butyl methyl ketone) are accurate to within $\pm 3\%$.

With the secondary ketones (Nos. 8 and 9, Table I) our results differed so markedly from those of previous workers that we tested and confirmed them by a chemical method of analysis (see p. 2440). Catch, Hey, Jones, and Wilson (*loc. cit.*) stated that the bromination product of methyl *iso*propyl ketone contained no significant quantity of bromomethyl ketone, but examination of their results revealed that they discarded the fraction containing this isomer under the impression that it consisted solely of dibromo-ketones. The discrepancy between our results and those of Bartlett and Stauffer (*J. Amer. Chem. Soc.*, 1935, **57**, 2580) for *sec.*-butyl methyl ketone cannot be resolved so easily. These authors measured the rates of iodination and racemization of the optically active ketone. They concluded that the relative rates of formation of $CMeEt{:}CMe{\cdot}OH$ and $CHMeEt{\cdot}C(OH){:}CH_2$ (overall rate = 100) were 18 and 82, whilst Table I gives 78 and 22, respectively. The two results can only be reconciled if it is assumed that the ketone used by the American authors, $[\alpha]_D^{25}$ +8·15°, was of very low optical purity.

The results in general are in conformity with our rule. In particular, serial Nos. 2, 3, and 7 illustrate a decrease in percentage of $R{\cdot}CHBr{\cdot}CO{\cdot}CH_3$ as the number of hydrogen atoms on the α-carbon atom in the group R decreases. But it is evident (from serial Nos. 2—6) that other factors are of importance. It is shown below that the full significance of these results only becomes apparent when the percentages are coupled with the rate figures to give the relative rates at which the various enols are formed.

Discussion.

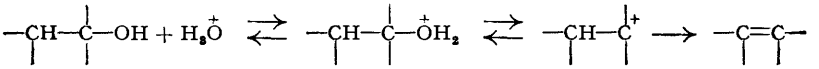
1. *The Mechanistic Basis of Hofmann's and Saytzeff's Rules of Orientation.*—Before analysing the results given in Table I it is necessary to define briefly the factors which determine the type of influence exerted by alkyl substituents in elimination reactions. Hughes and Ingold (*Trans. Faraday Soc.*, 1941, **37**, 657) have concluded that the type of influence exerted by a β-alkyl substituent (see scheme below) depends on whether the β-proton is loosened before, with, or after heterolysis of the C–X bond :



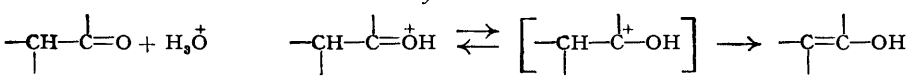
Where X is loosened before the proton, the transition state is highly unsaturated and the alkyl substituent facilitates the elimination reaction by hyperconjugation with the developing double bond; this is the basis of Saytzeff's rule that the most substituted olefin is formed in dehydrohalogenations of alkyl halides. Where, however, the proton is loosened before heterolysis of the C–X bond takes place, the effect of the alkyl substituent is largely inductive or electrostatic, and by increasing the strength of the C–H bond it reduces the rate of elimination; this is the basis of Hofmann's rule that the least substituted olefin is formed in the decomposition of quaternary ammonium hydroxides.

An acid-catalysed enolisation can be written in a manner which is precisely analogous to a unimolecular dehydration of an alcohol :

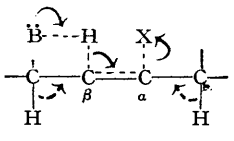
Unimolecular dehydration of an alcohol :



Acid-catalysed enolisation :



In the former reaction (and in the unimolecular elimination reactions of halides and sulphonium salts) the extreme unsaturation of the C^+ sextet results in extreme hyperconjugative control by alkyl substituents. There is, however, an essential difference between the two reactions: in the former, heterolysis of the $C-\overset{+}{O}H_2$ bond is rate controlling whilst, in the latter, the corresponding step is largely imaginary, as $C=\overset{+}{O}H$ and $\overset{+}{C}-OH$ are but two canonical forms of a resonance hybrid to which the former must make much the larger contribution. In acid-catalysed enolisation, therefore, loss of the β-proton and heterolysis of one of the C–O bonds are probably simultaneous (Bell, *op. cit.*). The effect of alkyl substituents on the rate of acid-catalysed enolisation of ketones should therefore be very similar to the effect of such substituents on rates of elimination, where loss of the proton and heterolysis of the C–X bond are known to be simultaneous. The bimolecular dehydrohalogenation of alkyl halides is such a reaction (Hughes and Ingold, *loc. cit.*; Skell and Hauser, *J. Amer. Chem. Soc.*, 1945, **67**, 1661). In this reaction β-alkyl substituents facilitate the elimination by hyperconjugation with the double bond (Dhar, Hughes, Ingold, Mandour, Maw, and Woolf, *J.*, 1948, 2093). In the accompanying diagram (after Dhar *et al.*) the dotted arrows indicate the hyperconjugation or overlap of the C–H bonding orbitals with the developing π-orbital of the double bond. As a C–H orbital overlaps more effectively than a C–C orbital with the developing π-orbital, it is clear that the order of effectiveness of alkyl substituents in facilitating elimination should be Me > Et > Pr^i > Bu^t (3, 2, 1, and 0 C–H bonds, respectively), and that an α-alkyl substituent should be as effective as a β-substituent in facilitating elimination.



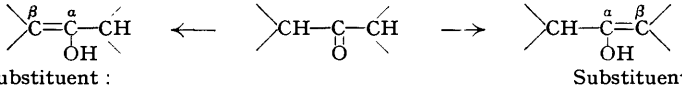
2. *Comparison of Acid-catalysed Enolisation and Bimolecular Dehydrohalogenations.*—A direct comparison of rates of acid-catalysed enolisation and of bimolecular dehydrohalogenations will now be made; for despite the obvious differences between these reactions the effect of alkyl groups on rates of reaction should be very similar in the two cases. The species whose rates of elimination reactions will be compared are $-\overset{|}{C}H-\overset{|}{C}-Br$ and $-\overset{|}{C}H-\overset{|}{C}=\overset{+}{O}H$. The comparison therefore will only be valid if the basicities of the ketones under consideration and hence the concentrations of the oxonium intermediates are approximately the same. The only available evidence (Gordy, *J. Chem. Physics*, 1939, **7**, 93; Gordy and Stanford, *ibid.*, 1940, **8**, 170) suggests that simple alkyl ketones do indeed have approximately the same basicity.

For the purpose of comparison the relative rates at which the enols $CHR{:}CMe{\cdot}OH$ and $CH_2R{\cdot}C({:}CH_2){\cdot}OH$ are formed have been calculated from the figures given in Table I in the following manner. Ethyl methyl ketone for instance iodinates at a rate of 104 (acetone = 100); the proportion of $Me{\cdot}CHBr{\cdot}CO{\cdot}CH_3$ in the monobromo-ketone fraction was 73%; the relative rate of formation of $CHMe{:}CMe{\cdot}OH$ is therefore $73 \times 104/100 = 76$, and that of $CH_2Me{\cdot}C({:}CH_2){\cdot}OH$ is $27 \times 104/100 = 28$. Relative rates of olefin formation have been calculated in a similar manner from the experimental results of Dhar, Hughes, and Ingold (*J.*, 1948, 2058).

The resulting relative rates are given in Table II (after Dhar *et al.*). In this table the figures on the left are for the rate of production of $\cdot\overset{\beta}{C}H{:}\overset{\alpha}{C}X{\cdot}CH_3$ (X = OH or H) and on the right for $\cdot\overset{\alpha}{C}H_2{\cdot}\overset{\beta}{C}X{:}CH_2$; in each case the nature of the alkyl groups on the α- and β-carbon atoms is

TABLE II.

Relative rates of enol and olefin production:



Substituent:						Substituent:		
Serial no.	β.	α.	Rate.	Ketone.	Rate.	α.	β.	Serial no.
1	H	Me	50	Me·COMe	50	Me	H	1
2	Me	Me	(114) 76	Et·COMe	28	Et	H	2
3	Et	Me	(89) 59	Pr·COMe	35	Pr	H	3
4	Me	Et	(62) 41	Et·COEt	41 (62)	Et	Me	4
				Alkyl halide.				
5	H	Me	50	Me·CHBrMe	50	Me	H	5
6	Me	Me	115	Et·CHBrMe	26	Et	H	6
7	Et	Me	80	Pr·CHBrMe	33	Pr	H	7
8	Me	Et	79	Et·CHBrEt	79	Et	Me	8

specified. In addition to the figures for enol-production rate we have given in parentheses figures corrected statistically for the number of hydrogen atoms on the carbon atom from which the proton is lost (*i.e.*, the rate of production of $CH_3{\cdot}CH{:}C(OH){\cdot}CH_3$ is 76. This figure is corrected by multiplying by $\frac{3}{2}$ to allow for the fact that there are three potential protons in the CH_3 group of acetone and only two in the CH_2 group of ethyl methyl ketone. The main justification for this correction (which was first suggested by Dr. Shorter, but see also Bell, Gelles, and Möller, *Proc. Roy. Soc.*, 1949, *A*, **198**, 308) is the extraordinary parallelism that results between the olefin and enol production rates. In effect, we are postulating that where a strong base OH^- is necessary to extract a proton (bimolecular elimination reaction) the probability factor is high, but that where only a weak base (solvent molecule) is necessary (acid-catalysed enolisation) the probability factor is low. [On this reasoning, application of a statistical correction would be appropriate in the unimolecular elimination reaction of alkyl halides, sulphonium salts, etc., where a weak base (solvent molecule) is sufficient to remove the proton.]

The detailed arguments used by Dhar *et al.* for the lower half of the table are repeated below with suitable minor modifications so that they now apply to both halves of the table: "Comparing serial nos. 1, 5 and 2, 6, one sees (left-hand column) that in agreement with theory, the extra β-methyl in 2 and 6 accelerates the formation of $CHMe{:}CXMe$ (X = H or OH) compared with the lower homologue, whereas (right-hand column) the replacement of α-Me by α-Et retards, as it should, the formation of $CEtX{:}CH_2$. Comparing serial nos. 2, 6 and 3, 7, we find (left), again in agreement with theory, that the replacement of a β-Me by β-Et retards the formation of $CHEt{:}CXMe$ compared with $CHMe{:}CXMe$, whereas (right) the replacement of α-Et by α-Pr, which in theory should have little effect, actually slightly accelerates the formation of $CXPr{:}CH_2$ in comparison with $CEtX{:}CH_2$."

Comparing serial nos. 3, 7 and 4, 8 (left) a discrepancy between the two halves of the table is apparent. In the elimination reaction, interchange of Me and Et substituents between the α- and β-positions has no effect on the rate of production of the particular olefins, whereas with the ketones the combination of α-Me–β-Et is more effective than the combination α-Et–β-Me. Such a discrepancy is not unexpected, as the transition state in enol production (where the oxygen atom is still firmly bound to the carbon) must be less symmetrical than the transition state in olefin production (where the bromide ion is only partially bound to carbon). Indeed, serial nos. 3 and 4 still provide convincing evidence that the alkyl groups are acting in a hyperconjugative manner, for if their effect was inductive serial no. 3 would show a lower rate than serial no. 4.

The above analysis establishes the common mechanistic basis of bimolecular dehydrogalogenations and acid-catalysed enolisations, and reveals that our empirical rule of orientation of enolisation reactions is founded on the ability of alkyl groups to facilitate the reaction by hyperconjugation with the developing double bond in the transition state. Orientation according to the Saytzeff rule is more extreme in dehydrohalogenations than in enolisations, for only in the latter is the orientation affected by the number of potential protons available. For instance, although the substituents are acting *quantitatively* in the same manner (see Table II, serial nos. 2 and 6) in the two reactions given below the orientation is more pronounced in the elimination reaction:

$$(73\%)\ CH_3{\cdot}CH{=}\underset{\displaystyle OH}{C}{\cdot}CH_3 \longleftarrow CH_3{\cdot}CH_2{\cdot}\overset{\displaystyle +OH}{C}{\cdot}CH_3 \longrightarrow CH_3{\cdot}CH_2{\cdot}\underset{\displaystyle OH}{C}{=}CH_2\ (27\%)$$

$$(81\%)\ CH_3{\cdot}CH{=}CH{\cdot}CH_3 \longleftarrow CH_3{\cdot}CH_2{\cdot}\underset{\displaystyle Br}{CH}{\cdot}CH_3 \longrightarrow CH_3{\cdot}CH_2{\cdot}CH{=}CH_2\ (19\%)$$

In the next example (Hughes, Ingold, and Mandour, *J.*, 1948, 2090), we also observe a more pronounced orientation in the elimination reaction:

$$(76\%)\ (CH_3)_2C{=}\underset{\displaystyle OH}{C}{\cdot}CH_3 \longleftarrow (CH_3)_2CH{\cdot}\overset{\displaystyle +OH}{C}{\cdot}CH_3 \longrightarrow (CH_3)_2CH{\cdot}\underset{\displaystyle OH}{C}{=}CH_2\ (24\%)$$

$$(82\%)\ (CH_3)_2C{=}CH{\cdot}CH_3 \longleftarrow (CH_3)_2CH{\cdot}\underset{\displaystyle I}{CH}{\cdot}CH_3 \longrightarrow (CH_3)_2{\cdot}CH{\cdot}CH{=}CH_2\ (18\%)$$

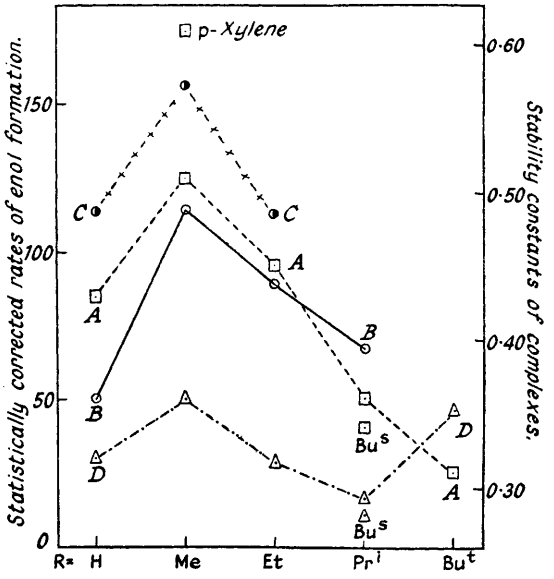
When the necessary statistical correction is applied to the methyl *iso*propyl ketone figures, the expected proportion of $(CH_3)_2C{:}CH{\cdot}CH_3$ in the olefin mixture becomes $\frac{76 \times 3}{76 \times 3 + 24} \times 100 = 90\%$—significantly higher than that observed. Hence, paradoxically, although the Saytzeff

orientation is more extreme in the elimination reaction, the substituents are acting in a more extreme hyperconjugative manner in the enolisation.

3. *Comparison of the Effect of Alkyl Groups on Acid-catalysed Enolisation, and on Degree of Complex Formation between Alkylbenzenes and Picric Acid.*—(a) *Introduction.* A detailed comparison between elimination reactions of alkyl bromides and enolisation reactions of ketones cannot be extended further as no data are available for alkyl bromides corresponding to the other ketones which have been investigated. The comparison with dehydrohalogenations having established that alkyl groups are acting in a hyperconjugative manner in enolisation, there is no longer any need to restrict the comparison to reactions of the same mechanistic type. Instead, any reaction may be selected in which the groups with which we are concerned (Me to n-C_6H_{13}; Pr^i and Bu^t) have been shown to act in a hyperconjugative manner. The only reaction which fulfils these requirements is that between picric acid and alkylbenzenes, which has been studied by Anderson and Hammick (*J.*, 1950, 1089).

The formation of picric acid complexes is dependent on the electron density in the nucleus of the alkylbenzenes. This electron density is increased by (*a*) the inductive electron-release

FIG. 1.



A. *Stability constant of the complex* PhR–*Picric acid.*
B. *Rate of formation of* $R{\cdot}CH{:}C(OH){\cdot}CH_3$.
C. ,, ,, $R{\cdot}CMe{:}C(OH){\cdot}CH_3$.
D. ,, ,, $R{\cdot}C(OH){:}CH_2$.

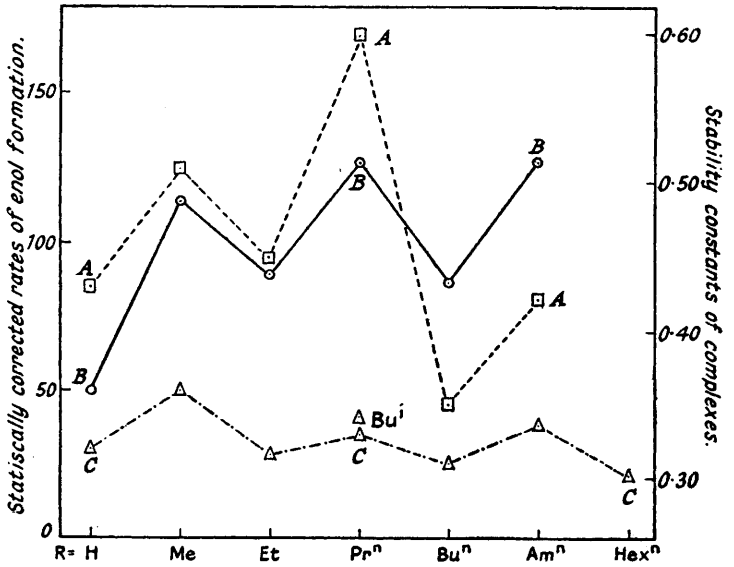
of alkyl groups where $Bu^t > Pr^i > Et > Me > H$, and may be increased (*i.e.*, by polarisation demand of a reagent) by (*b*) the hyperconjugative release of electrons where $Me > Et > Pr^i > Bu^t > H$. The inductive effect should be very little affected by the electron-accepting power of the acid component of the complex. The hyperconjugative effect, however, is a polarisability effect and should vary with the cationoid nature of the acid component. Davies and Hammick (*J.*, 1938, 763) observed that the degree of complex formation between tetranitromethane and PhR varied with R as follows: $R = Bu^t > Et > Me > Pr^i > H$. This order was interpreted as indicative of an inductive effect coupled with a hyperconjugative effect. With the more powerfully cationoid reagent (picric acid) (Anderson and Hammick, *loc. cit.*) the order was $R = Me > Et > H > Pr^i > Bu^t$; with the exception of the position of hydrogen in the series this is the normal hyperconjugative order for the ability of alkyl groups to donate electrons to an unsaturated system. This therefore is clearly a polarisability or hyperconjugative effect.

(b) *Branched alkyl groups.* In Fig. 1 are plotted the statistically corrected rates for the production of $CHR{:}C(OH){\cdot}CH_3$ ($R = H$ to Pr^i) and for $R{\cdot}C(OH){:}CH_2$ ($R = H$ to Bu^t) (the value for acetaldehyde, 30·4, is a revised figure provided by Dr. J. Shorter, who has asked us to correct that, 38·8, given in error in *J.*, 1950, 3425). In addition, stability constants are

plotted for the complexes PhR–picric acid (R = H to Bu^t). The enolisation rates for variations in the β-group closely parallel the stability constants, and we have no doubt that $CHBu^t{:}C(OH){\cdot}CH_3$ will be formed at a low rate from *tert.*-butylacetone (this will be investigated). With α-groups, however, we note that $Bu^t{\cdot}C(OH){:}CH_2$ is formed at an anomalously high rate from pinacone. It is unlikely that this anomaly is due to a high basicity in pinacone.* The anomaly, however, is not peculiar to pinacone, for *tert.*-butyldimethylcarbinyl halides ($Bu^t{\cdot}CMe_2{\cdot}Hal$) show an abnormally high rate of unimolecular solvolysis and elimination, the product being largely olefin (Shorter and Hinshelwood, *J.*, 1949, 2412; Brown and Fletcher, *J. Amer. Chem. Soc.*, 1949, **71**, 1845; 1950, **72**, 1223; Hughes, Ingold, Martin, and Meigh, *Nature*, 1950, **166**, 679). The structural similarity between these halides and pinacone suggests that the same factors, at present unknown, are operative in both cases.

It was noted earlier that methyl *iso*propyl ketone (Me + Me hyperconjugation) gave less bromopropyl ketone (RR'CBr·COMe) than did *sec.*-butyl methyl ketone (Me + Et hyperconjugation). Itemised rate figures resolve this anomaly, for they show that the bromoketone (R = R' = Me), rate 52, is formed considerably faster than the ketone (R = Me,

FIG. 2.



A. Stability constant of the complex PhR–*picric acid.*
B. Rate of formation of $R{\cdot}CH{:}C(OH){\cdot}CH_3$.
C. ,, ,, $R{\cdot}C(OH){:}CH_2$.

R' = Et), rate 38. The orientation anomaly is therefore due to the high rate of formation of $Pr^i{\cdot}C(OH){:}CH_2$, and not, as might be inferred in the absence of rate figures, to a high rate of formation of $CMeEt{:}CMe{\cdot}OH$. The rate of formation of this enol is indeed a little lower than expected, if it is assumed that the introduction of a β-methyl group produces the same effect on passing from $CH_2Et{\cdot}COMe$ (59) to $CHEtMe{\cdot}COMe$ as it does on passing from $CH_2Me{\cdot}COMe$ (76) to $CHMe_2{\cdot}COMe$ (52). On this basis the calculated rate of formation of $CMeEt{:}CMe{\cdot}OH$ is 52 × 59/76 = 40, a little higher than the observed value of 38.

The above figures are for relative rates; the resulting statistically corrected rates of formation of $CRMe{:}CMe{\cdot}OH$ (R = H, Me, Et) are plotted in Fig. 1. The fact that this graph roughly parallels the equivalent graph for $CHR{:}CMe{\cdot}OH$, which it certainly would not in the absence of the statistical correction, supports the earlier suggestion that the electronic effects of β-substituents cannot be rationalized until this correction is applied.

* If pinacone had a higher basicity by virtue of the strong inductive effect of the *tert.*-butyl group than the other ketones investigated in this paper, then $COPr^i_2$ with its two Pr^i groups might also be expected to enolise at a faster rate than might be deduced from the partial rates for acetone and $COMePr^i$. These partial rates (Table I, Serial Nos. 1 and 8, cols. v and vii) suggest that the rate for $COPr^i_2$ should be 2(52 × 17)/50 = 35. Dr. J. Shorter, however, finds that the rate is 12·6. This suggests either that $COPr^i_2$ has a *weaker* basicity than the other ketones or, far more likely, that the rate of formation of $Pr^i{\cdot}C(OH){:}CH_2$ is abnormally large.

(c) n-*Alkyl groups. The Alternation effect.* In Fig. 2, graphs (similar to those in Fig. 1) are given for the effect of *n*-alkyl groups. The similarity between the variations in rates of enolisation and in stability constants of picric acid complexes is remarkable. In both cases a striking alternation in the effect of *n*-alkyl groups, Me > H; Pr^n > Et and Bu^n; Am^n > Bu^n and *n*-C_6H_{13}, is observed. This alternation was not expected at the start of this investigation, but in retrospect we may recall that Dhar *et al.* noted that $CHPr^n{:}CH_2$ was formed more rapidly than $Et\cdot CH{:}CH_2$ from the corresponding secondary bromides (Table II, serial nos. 6 and 7). In addition, the very slight alternation in overall rates of iodination of the *n*-alkyl methyl ketones (Table I, col. iv, serial nos. 1—6) might have been noted. The alternation in overall rates is slight because each increase in rate of production of $R\cdot\overset{\beta}{C}H{:}\overset{\alpha}{C}Me\cdot OH$ (R = Me, Pr^n, *n*-amyl) over the next lower homologue (R = H, Et, Bu^n) is compensated by a decrease in rate of production of $H\cdot\overset{\beta}{C}H{:}\overset{\alpha}{C}R\cdot OH$ (R = Et, Bu^n, *n*-C_6H_{13}) over the next lower homologue (R = Me, Pr^n, *n*-amyl). That an alternation in overall rate is still observable, despite these compensating alternations in partial rates, is due to the fact that, α- and β-groups being largely equivalent, the combination α-Me–β-R always shows a larger rate than the combination α-R–β-H.

An alternation in the hyperconjugative property of *n*-alkyl groups has been predicted on theoretical grounds (Mulliken, Rieke, and Brown, *J. Amer. Chem. Soc.*, 1941, **63**, 41; Dewar, "Electronic Theory of Organic Chemistry," Oxford Univ. Press, 1949, p. 157). Crudely, we can picture every C–C bond as having an element of unsaturation; the strong hyperconjugative property of a methyl group with its three C–H bonds will therefore be more effectively transmitted by an even number of C–C bonds, as in

$$H_3C-\underset{\delta}{CH_2}\overset{\cdots}{=}\underset{\gamma}{CH_2}-\underset{\beta}{CH_2}\overset{\cdots}{=}\underset{\alpha}{CH_2}-\underset{OH}{C}=CH_2$$

than by an odd number of carbon atoms, as in

$$H_3C-\underset{\gamma}{CH_2}-\underset{\beta}{CH_2}-\underset{\alpha}{CH_2}-\underset{OH}{C}=CH_2$$

Such an effect should result in a slightly increased electron density in the α–β and γ–δ bonds, with consequent shortening of these bonds in the first example, whereas in the second example the electron density and bond lengths (α–β and β–γ) should be the same. The effect, however, would probably be too small for detection by existing methods. Where, however, the weakly conjugative H_3C– group is replaced by the strongly conjugative O=C(OH)· group the effect becomes large enough for its detection. For instance, Morrison and Robertson (*J.*, 1949, 980, 987, 993, 1001) found that the bond lengths in adipic acid alternated in length as shown below:

$$O=\underset{OH}{C}\overset{1{\cdot}52}{-\!-}\underset{\delta}{CH_2}\overset{1{\cdot}49}{\cdots}\underset{\gamma}{CH_2}\overset{1{\cdot}54}{-\!-}\underset{\beta}{CH_2}\overset{1{\cdot}49}{\cdots}\underset{\alpha}{CH_2}\overset{1{\cdot}52}{-\!-}\underset{OH}{C}=O$$

A similar alternation in bond lengths was observed in two other even-numbered dicarboxylic acids, succinic and sebacic. In glutaric acid, however, all the C–C bonds were of the same length as shown below:

$$O=\underset{OH}{C}\overset{1{\cdot}53}{-\!-}\underset{\gamma}{CH_2}\overset{1{\cdot}53}{-\!-}\underset{\beta}{CH_2}\overset{1{\cdot}53}{-\!-}\underset{\alpha}{CH_2}\overset{1{\cdot}53}{-\!-}\underset{OH}{C}=O$$

The variations in electron density associated with these variations in bonds length are clearly displayed in the electron contour maps given by Morrison and Robertson.

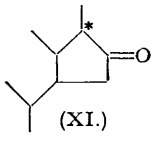
This pronounced difference between the odd- and even-numbered carboxylic acids is probably responsible for the well-known alternation in melting points, the more conjugated acids (even series) having the higher melting points. In conformity with these ideas, the alternation in melting points is much smaller but still observable in the monocarboxylic acids. The analogy which Anderson and Hammick drew between these melting points and the stability constants of picric acid complexes is therefore valid, and these very varied phenomena are all reflections of the fundamental alternation in hyperconjugative properties of *n*-alkyl groups.

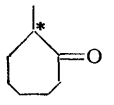
This theory of alternation also explains the high rate of formation of $(CH_3)_2CH\overset{\cdots}{=}CH_2\cdot C(OH){:}CH_2$ (Fig. 2), where the effect of both methyl groups is transmitted through the C–C bond.

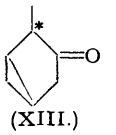
4. *Other Acid-catalysed Substitution Reactions.*—The general rules which have been developed in this paper can be applied directly to any substitution reaction where the reagent reacts with the enol as soon as it is formed. In reactions where enolisation is not rate-controlling, orientation of substitution will be influenced by the relative concentrations of the isomeric enols at equilibrium. As an alkyl substituent will stabilise the enol in a hyperconjugative manner in the same way as it lowers the energy of the transition state leading to the enol, the concentrations of the enols should be proportional to their rates of formation. (In this respect acid-catalysed substituent reactions are quite different from base-catalysed reactions; see following paper.)

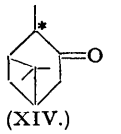
For instance, Shorter and Hinshelwood (*J.*, 1950, 3276) have studied the oxidation of acetone by ceric acid, and Shorter (*J.*, 1950, 3425) has studied this reaction for other aliphatic ketones. Enolisation is a prior step to oxidation, but the enols are not oxidised as soon as they are formed. With higher alkyl ketones oxidation appears to take place almost exclusively on the enol $R\cdot\overset{|}{C}{:}CMe\cdot OH$, and the rates of oxidation are proportional to the rates of production of these enols as determined in this paper. This can only mean that the equilibrium concentrations of these enols are proportional to their rates of production, as we have already suggested.

Numerous acid-catalysed oxidations of ketones are recorded by Simonsen and Owen (" The Terpenes," Vols. I and II, Cambridge, 1947 and 1949). The compounds VI, VII, and (XI)—(XIV) undergo oxidation fission between the carbon atom marked * and the carbonyl group.

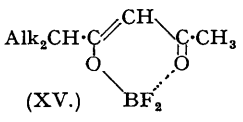

(XI.)


(XII.)


(XIII.)


(XIV.)

In addition, Fileti and Ponzio (*J. pr. Chem.*, 1897, **55**, 186) found that $CH_2Me\cdot CO\cdot CH_2Pr^i$ on oxidation by nitric acid gave $Me\cdot CO\cdot CO\cdot CH_2Pr^i$, whilst $CH_2Me\cdot CO\cdot CH_2Et$ gave a mixture of $Me\cdot CO\cdot CO\cdot CH_2Et$ and $CH_2Me\cdot CO\cdot COEt$. All these results suggest that enolisation, as predicted by our rule, is a prior and orientating step in the oxidation. The orientation of acid-catalysed aldol condensations may also be predicted successfully from our rules. The orientation of acylation of ketones with acetyl chloride or acetic anhydride (catalysed by boron trifluoride) (Hauser and Adams, *loc. cit.*) also follows the Saytzeff-type rule, but with secondary ketones $CHAlk_2\cdot CO\cdot CH_3$ the reversibility of the reaction and the fact that $CHAlk_2\cdot CO\cdot CH_2\cdot CO\cdot CH_3$ can form a complex of the type (XV) (Morgan and Tunstall, *J.*, 1924, **125**, 1963) whilst the isomer $CH_3\cdot CO\cdot CAlk_2\cdot CO\cdot CH_3$ cannot, results in more acylation on the CH_3 group than would be expected.


(XV.)

5. *Effect of Other Groups.*—The above arguments * could naturally be extended to ketones containing more polar and unsaturated groups in the same way that Dhar *et al.* have extended their arguments on elimination reactions. Such an extension, however, is complicated by the fact that such groups have marked effects on the basicity of the ketones and in some cases make the halogenation of the enol reversible. A discussion of these topics will therefore be reserved for a later occasion, as will the effect of acid catalysts other than the hydroxonium ion on the orientation of enolisation.

Conclusions.

1. In saturated aliphatic and monocyclic ketones the orientation of acid-catalysed enolisation is controlled by the ability of α- and β-alkyl substituents to stabilise the transition state in a hyperconjugative manner.

2. The orientation of enolisation owing to the operation of the above factor, is slightly obscured by the fact that the rate of enolisation is proportional to the number of potential protons available.

3. The most stable enol is produced most rapidly; hence the orientation of substitution is very largely controlled by the orientation of enolisation, and is almost independent of the substituting reagent, provided that subsequent reactions (*e.g.*, dehydration in the aldol condensation) are equally ready for the two possible primary products.

* All previous arguments applied only to saturated acyclic or monocyclic ketones containing no hetero-atom other than the single carbonyl oxygen atom.

4. As α- and β-substituents exert approximately equal effects, the modified Saytzeff rule given earlier can be further refined and expressed as follows: In the dehydrohalogenation of saturated aliphatic halides and in the acid-catalysed enolisation of saturated aliphatic ketones, the double bond (in olefin or enol) will preferentially be established between those carbon atoms whose adjacent carbon atoms carry the largest number of hydrogen atoms.

5. There is a well-marked alternation in the hyperconjugative ability of *n*-alkyl groups to release electrons: $Pr^n > Et$ and Bu^n, $n\text{-}C_5H_{11} > Bu^n$ and $n\text{-}C_6H_{13}$.

Experimental.

(M.p.s are uncorrected. Analyses are by Drs. Weiler and Strauss and Mr. F. C. Hall.)

Preparation of Ketones.—*n*-Butyl and *sec.*-butyl methyl ketones were prepared by the action of *n*-butyl- and *sec.*-butyl-magnesium bromides on acetic anhydride (Newman and Smith, *J. Org. Chem.*, 1948, **13**, 592). *iso*Butyl methyl ketone was prepared by oxidation of *sec.*-hexyl alcohol. Methyl *iso*propyl ketone was prepared by the method of Whitmore, Evers, and Rothrock (*Org. Synth.*, Coll. Vol. II, p. 408). *n*-Amyl and *n*-hexyl methyl ketones were commercial samples.

The ketones were fractionated through a 60-cm. column (packed with Fenske helices) and had the following physical constants: *n*-Butyl methyl ketone, b. p. 125—126°/760 mm.; *iso*butyl methyl ketone, b. p. 114·5°/744 mm.; *sec.*-butyl methyl ketone, b. p. 115—117°/760 mm.; methyl *iso*propyl ketone, b. p. 93—94°/760 mm., *n*-amyl methyl ketone, b. p. 149·5°/750 mm.; *n*-hexyl methyl ketone, b. p. 169—170°/750 mm.

Bromomethyl ketones. Authentic specimens of some of these ketones were prepared by the action of hydrogen bromide on the diazo-ketones, which were prepared from *n*-valeroyl, *iso*valeroyl, and α-methylbutyryl bromides and diazomethane (Catch, Elliott, Hey, and Jones, *J.*, 1948, 278).

Bromination.—The ketones were brominated at 40—50° with bromine in the presence of potassium chlorate (*idem, ibid.*, p. 272). In each case, the monobromo-ketones were roughly stripped of unchanged ketone and dibromo-ketones by distillation under reduced pressure.

Fractionation of the Bromo-ketones.—The fractionating assembly was a copy of that used by Catch *et al.* (*loc. cit.*), except that the packed section of the column was 60 cm. long. (Drawings of the assembly were kindly provided by Dr. Catch.)

(a) *Monobromo-ketones from* n-*Butyl Methyl Ketone.*—The monobromo-ketones (b. p. 65—125°/45 mm.; 147 g.) on fractionation at 40 mm. (reflux ratio 20 : 1) gave the following fractions (total 112 g.): (i) b. p. to 82·5° (4·8 g.); (ii) b. p. 82·5—85·5° (2·2 g.); (iii) b. p. 85·5—87·5° (58·3 g.); (iv) b. p. 87·5—88·5° (3·1 g.); (v) b. p. 88·5—91·0° (4·8 g.); (vi) b. p. 91—92° (4·2 g.); (vii) b. p. 92·0—93·0° (1·7 g.); (viii) b. p. 93·0—95·0° (2·4 g.); (ix) b. p. 95·0—98·0° (7·4 g.); (x) b. p. 98·0—100·0° (3·8 g.); (xi) b. p 100·0—103·0° (5·8 g.); (xii) b. p. 103·0—106·0 (3·2 g.); (xiii) b. p. 106·0—110·0° (2·2 g.); (xiv) b. p 110·0°/25 mm. (8·5 g.).

Fractions (iii) and (iv) on redistillation gave 3-*bromohexan*-2-*one* (36·8 g.), b. p. 82°/30 mm., n_D^{20} 1·4591 (Found: Br, 44·4. $C_6H_{11}OBr$ requires Br, 44·6%). 2-*Amino*-4-*methyl*-5-n-*propylthiazole* (prepared from the bromo-ketone and thiourea in 97% yield) crystallised from light petroleum (b. p. 40—60°) in colourless needles, m. p. 45—45·5° (Found: C, 54·1; H, 7·6. $C_7H_{12}N_2S$ requires C, 53·8; H, 7·7%). The *picrate* of the thiazole crystallised from acetone in yellow needles, m. p. 218—220° (decomp.) (Found: C, 40·8; H, 4·0. $C_7H_{12}N_2S,C_6H_3O_7N_3$ requires C, 40·5; H, 3·9%). 3-*Anilino*-*hexan*-2-*one* (prepared from the above bromo-ketone and aniline) was a yellow oil, b. p. 106°/1·0 mm., n_D^{20} 1·5399 (Found: C, 74·6; H, 9·4. $C_{12}H_{17}ON$ requires C, 75·5; H, 9·0%).

Fractions (vi)—(xi) on redistillation gave 1-bromohexan-2-one (13·2 g.), b. p. 96°/30 mm., n_D^{20} 1·4649, analysis (Found: Br, 43·4. Calc. for $C_6H_{11}OBr$: Br, 44·6%) indicating that some decomposition had occurred: our specimen from *n*-valeroyl bromide had b. p. 98—99°/33 mm., n_D^{22} 1·4612 (Catch *et al.* give b. p. 108°/50 mm., $n_D^{15·5}$ 1·4486). 2-*Amino*-4-n-*butylthiazole* (prepared from the above bromo-ketone and thiourea) was a viscous, pale yellow liquid, b. p. 110—111°/1·0 mm., n_D^{21} 1·5515 (Found: C, 53·4; H, 8·0. $C_7H_{12}N_2S$ requires C, 53·8; H, 7·7%). The *picrate* of the thiazole crystallised from acetone in pale yellow needles, m. p. 214—216° (decomp.) (Found: C, 41·0; H, 4·0. $C_7H_{12}N_2S,C_6H_3O_7N_3$ requires C, 40·5; H, 3·9%). 1-*Anilinohexan*-2-*one* crystallised from acetone in colourless needles, m. p. 74·5—75° (Found: C, 75·1; H, 8·8. $C_{12}H_{17}ON$ requires C, 75·5; H, 9·0%).

The thiazole picrate and anilino-compounds did not depress the m. p.s of these compounds prepared from a sample of 1-bromohexan-2-one prepared by the diazomethane method.

(b) *Monobromo-ketones from* iso*Butyl Methyl Ketone.*—The monobromo-ketones (b. p. 60—113°/45 mm.; 268 g.) on fractionation at 60 mm. (reflux ratio 20 : 1) gave the following fractions (total 245 g.): (i) b. p. to 55·0° (21·9 g.); (ii) b. p. 55·0—83·0° (0·25 g.); (iii) b. p. 83·0—88·5° (0·6 g.); (iv) b. p. 88·5—89·0° (7·15 g.); (v) b. p. 89·0—90·5° (70·7 g.); (vi) b. p. 90·5—93·0° (19·1 g.); (vii) b. p. 93·0—96·0° (4·9 g.); (viii) b. p. 96—98° (7·3 g.); (ix) b. p. 98—102° (59·7 g.); (x) b. p. 102—105° (24·7 g.); (xi) b. p. 105—108° (4·55 g.); (xii) b. p. 108—115° (3·5 g.); (xiii) b. p. 115—125° (4·1 g.); (xiv) column stripped at 30 mm. (16·9 g.).

Fractions (v) and (vi) on redistillation gave 3-*bromo*-4-*methylpentan*-2-*one* (81·1 g.), b. p. 57—59°/13 mm., n_D^{19} 1·4619. This sample gave the folowing b. p.s: 79°/40 mm.; 88°/60 mm.; 95°/80 mm.; 102°/100 mm. (Found: Br, 44·2. $C_6H_{11}OBr$ requires Br, 44·6%). 2-*Amino*-4-*methyl*-5-iso*propyl*-*thiazole* (prepared from the above bromo-ketone and thiourea) crystallised from light petroleum (b. p. 40—60°) in yellow needles, m. p. 72—73° (Found: C, 53·8; H, 7·5. $C_7H_{12}N_2S$ requires C, 53·8; H, 7·7%). The *picrate* crystallised from acetone in pale yellow needles, m. p. 210° (decomp.) (Found:

C, 40·4; H, 3·9. $C_7H_{12}N_2S,C_6H_3O_7N_3$ requires C, 40·5; H, 3·9%). 3-*Benzoyloxy*-4-*methylpentan*-2-*one* (prepared from the bromo-ketone and potassium benzoate) crystallised from light petroleum (b. p. 40—60°) in colourless needles. m. p. 35—36° (Found : C, 71·0; H, 7·2. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·2%). A mixture with the isomeric 1-benzoyloxy-4-methylpentan-2-one (m. p. 34—35°, see below) melted at 30°.

Fractions (vii)—(x) on redistillation gave 1-bromo-4-methylpentan-2-one (76·1 g.), b. p. 69—71°/15 mm., n_D^{19} 1·4638. This sample gave the following b. p.s : 94°/40 mm.; 105°/60 mm.; 113·5°/80 mm.; 122°/100 mm. Analysis (Found : Br, 46·0. Calc. for $C_6H_{11}OBr$: Br, 44·6%) indicated that it was contaminated with some dibromo-ketone. A specimen prepared from *iso*valeroyl bromide had b. p. 76—78°/19 mm., n_D^{20} 1·4620. Catch *et al.* (*loc. cit.*) give b. p. 101—102°/50 mm., n_D^{17} 1·4595. A sample of this ketone on treatment with thiourea gave a 97% yield of 2-*amino*-4-iso*butylthiazole*, b. p. 111—112°/1·5 mm., n_D^{20} 1·5441 (Found : C, 54·1; H, 7·6%). The *picrate*, m. p. 201—202° (decomp.) (Found : C, 40·9; H, 4·2. $C_7H_{12}N_2S,C_6H_3O_7N_3$ requires C, 40·5; H, 3·9%), did not depress the m. p. of a sample of the picrate prepared from the thiazole (b. p. 111—112°/1·5 mm., n_D^{20} 1·5438) which in turn had been prepared from authentic 1-bromo-4-methylpentan-2-one. 1-*Anilino*-4-*methylpentan*-2-*one* (prepared from the bromo-ketone and aniline) crystallised from ether in colourless plates, m. p. 54·5—55° alone or mixed with an authentic specimen prepared *via* the diazo-ketone (Found : C, 75·7; H, 8·9. $C_{12}H_{17}ON$ requires C, 75·5; H, 8·9%). 1-*Benzoyloxy*-4-*methylpentan*-2-*one* (from the bromo-ketone and potassium benzoate) solidified after distillation, b. p. 154°/5 mm., and then crystallised from light petroleum (b. p. 40—60°) or acetone at −50°, in needles, m. p. 34—35° (Found : C, 71·2; H, 7·3. $C_{13}H_{16}O_3$ requires C, 70·9; H, 7·3%).

(c) *Monobromo-ketones from* sec.-*Butyl Methyl Ketone*.—The monobromo-ketones from *sec.*-butyl methyl ketone (b. p. 50—108°/30 mm.; 142 g.) on fractionation at 35 mm. (reflux ratio 20 : 1) gave the following fractions (total 112 g.) : (i) b. p. up to 64·0° (3·0 g.); (ii) b. p. 64·0—69·0° (3·1 g.); (iii) b. p. 69·0—71·0° (9·0 g.); (iv) b. p. 71·5—72·5° (50·8 g.); (v) b. p. 72·5—73·0° (2·1 g.); (vi) b. p. 73·0—74·5° (2·4 g.); (vii) b. p. 74·5—81·0° (4·7 g.); (viii) b. p. 81·0—85·0° (2·6 g.); (ix) b. p. 85·0—89·0° (3·3 g.); (x) b. p. 89·0—91·0° (4·4 g.); (xi) b. p. 91·0—93·0° (4·4 g.); (xii) b. p. 93·0—95·0° (5·6 g.); (xiii) b. p. 95·0—100·0° (3·2 g.); (xiv) column stripped at 18 mm. (13·7 g.).

Fractions (iv) on redistillation gave 3-*bromo*-3-*methylpentan*-2-*one* (48·6 g.), b. p. 65°/24 mm., 69°/30 mm., 74°/39 mm., 80·5°/50 mm., n_D^{21} 1·4634 (Found : Br, 45·1. $C_6H_{11}OBr$ requires Br, 44·6%). 3-*Anilino*-3-*methylpentan*-2-*one* had b. p. 125°/1·5 mm., n_D^{20} 1·5476 (Found : C, 75·1; H, 9·1. $C_{12}H_{17}ON$ requires C, 75·5; H, 9·0%).

Fractions (v)—(xiii) were refluxed for 3 hours with thiourea (22·4 g.), ethanol (50 c.c.), and water (50 c.c.). To the cooled product 2N-aqueous sodium hydroxide (150 c.c.) was added and the mixture was refluxed for ½ hour. The mixture was cooled, acidified with dilute hydrochloric acid, and extracted several times with ether. The evil-smelling ethereal layer on distillation gave impure 3-mercapto-3-methylpentan-2-one, b. p. 75—77°/27 mm., n_D^{20} 1·4602 (2·6 g.) (Found : C, 57·1; H, 9·8. $C_6H_{12}OS$ requires C, 54·1; H, 9·2%). This compound was so offensive that further purification was not attempted. Pure 3-bromo-3-methylpentan-2-one on similar treatment with thiourea gave 5·1 g. of the mercapto-ketone (38·6%). The low yield indicated that this method was not suitable for quantitative determination of tertiary bromo-ketones; but, on the assumption that the yield was the same in the two experiments, fraction (v)—(xiii) contained about 9·0 g. of 3-bromo-3-methylpentan-2-one making the total quantity of this bromo-ketone 65—66 g. (56—57 g. estimated from the graph). The aqueous layer was then made alkaline with aqueous sodium hydroxide, and extracted with ether. Distillation of the ethereal solution gave 2-*amino*-4-sec.-*butylthiazole* as a colourless viscous liquid, b. p. 109—111°/2 mm., n_D^{21} 1·5558 (13·8 g.) (Found : C, 53·7; H, 7·9. $C_7H_{12}N_2S$ requires C, 53·8; H, 7·7%). The *picrate* crystallised from acetone in yellow needles, m. p. 183—185° (decomp.) (Found : C, 40·3; H, 3·7. $C_7H_{12}N_2S,C_6H_3N_3O_7$ requires C, 40·5; H, 3·9%). The thiazole prepared from pure 1-bromo-3-methylpentan-2-one (diazomethane method) had b. p. 110°/1·5 mm., n_D^{20} 1·5562; the picrate had m. p. 188—189° (decomp.). A mixture with the picrate from the crude ketones showed no depression.

On the assumption that the yield of the thiazole from the bromomethyl ketone was 93—97% (as in similar cases), these fractions must have contained 16—17 g. of 1-bromo-3-methylpentan-2-one. Interpolation from the graph of weight of distillate against boiling point gave 18—19 g., whilst direct determination by application of the thiazole method to a portion of the crude ketones before distillation gave 18·7 g.

(d) *Monobromo-ketones from Methyl* iso*Propyl Ketone*.—The monobromo-ketones from this ketone (b. p. 75—120°/150 mm.; 172 g.) on fractionation at 150 mm. (reflux ratio 20 : 1) gave the following fractions (total 130 g.) : (i) b. p. to 80·0° (2·8 g.); (ii) b. p. 80·0—83·0° (1·4 g.); (iii) b. p. 83·0—83·5° (38·6 g.); (iv) b. p. 83·5—84·0° (38·8 g.); (v) b. p. 84·0—90·0° (3·4 g.); (vi) b. p. 90·0—96·0° (1·9 g.); (vii) b. p. 96·0—103·0° (3·7 g.); (viii) b. p. 103·0—105·5° (24·5 g.); (ix) b. p. 105·5—119·0° (5·7 g.); (x) column stripped at 60 mm. (9·4 g.).

Fractions (iii) and (iv) on redistillation gave 3-bromo-3-methylbutan-2-one (70 g.), b. p. 78°/100 mm., 82°/120 mm., 86°/140 mm., 90°/150 mm., 93·5°/160 mm., n_D^{20} 1·4575 (Catch *et al.* give b. p. 83—84°/150 mm., n_D^{16} 1·4590) (Found : Br, 47·4. Calc. for C_5H_9OBr : Br, 48·5%).

Fraction (viii) on redistillation gave 1-bromo-3-methylbutan-2-one (20 g.), b. p. 93°/75 mm., 101°/100 mm., 107—108°/125 mm., n_D^{20} 1·4635 (Found : Br, 46·7. Calc. for C_5H_9OBr : Br, 48·5%). The low bromine analysis indicated that this sample certainly contained very little dibromo-ketone. Catch *et al.* (*loc. cit.*) record b. p. 86°/50 mm., $n_D^{14\cdot5}$ 1·4467.

A sample of the above bromomethyl ketone on treatment with thiourea gave 2-*amino*-4-iso*propylthiazole*, a pale yellow oil, b. p. 105—107°/0·5 mm., n_D^{20} 1·5616 (Found : C, 50·4; H, 7·2. $C_6H_{10}N_2S$

requires C, 50·7; H, 7·1%). The *picrate* crystallised from acetone in yellow needles, m. p. 209—211° (decomp.) (Found: C, 39·6; H, 3·7; N, 19·2. $C_6H_{10}N_2S,C_6H_3O_7N_3$ requires C, 38·8; H, 3·5; N, 18·9%).

50 G. of the stripped brominated mixture were treated with thiourea and worked up as already described for the bromination product of *sec.*-butyl methyl ketone (p. 2440). The yield of 2-amino-4-*iso*propylthiazole was 10·0 g., which is equivalent to 24% of 1-bromo-3-methylbutan-2-one in the mixture (the reaction being assumed to afford a 97% yield). This figure agrees well with that obtained by interpolation from the graph (*viz.*, 25%).

(e) *Monobromo-ketones from* n-*Amyl Methyl Ketone.*—The monobromo-ketones (b. p. 50—89°/7 mm.; 535 g.) were fractionated at 4 mm. through a 160-cm. column packed with Fenske helices. The following fractions (total 491 g.) were collected: (i) b. p. 25—54° (6·5 g.); (ii) b. p. 54—61·5° (8·9 g.); (iii) 61·5—64° (246·8 g.); (iv) 64—67·5° (6·5 g.); (v) 67·5—71° (4·5 g.); (vi) 71—74° (5·6 g.); (vii) 74—77·5° (6·3 g.); (viii) 77·5—78·5° (117·9 g.); (ix) 78·5—79·0° (48·3 g.); (x) 79·0° (30·9 g.); (xi) 79—85° (9·3 g.).

Fraction (iii) consisted of 3-*bromoheptan*-2-*one*, n_D^{18} 1·4610 (Found: C, 43·8; H, 7·1; Br, 41·5. $C_7H_{13}OBr$ requires C, 43·5; H, 6·7; Br, 41·5%). The small forerun indicated that the preliminary stripping from unchanged ketone was too thorough. The stripping (82 g.) was therefore analysed (Found: Br, 22·39, 22·05%). This fraction therefore contained up to 44 g. of monobromo-ketone, largely 3-bromoheptan-2-one, making the total quantity of this ketone, 290 g. A sample of this bromo-ketone on treatment with thiourea gave 2-*amino*-5-n-*butyl*-4-*methylthiazole*, colourless needles, m. p. 41—42°, from light petroleum (b. p. 40—60°) (Found: C, 56·2; H, 8·0. $C_8H_{14}N_2S$ requires C, 56·5; H, 8·2%). The *picrate* crystallised from acetone in yellow needles, m. p. 192—193° (decomp.) (Found: C, 43·3; H, 4·7. $C_8H_{14}N_2S,C_6H_3O_7N_3$ requires C, 42·1; H, 4·3%). 3-*Anilinoheptan*-2-*one*, a yellow oil, had b. p. 132°/1·0 mm., n_D^{20} 1·5449 (Found: C, 77·2; H, 9·2. $C_{13}H_{19}ON$ requires C, 76·1; H, 9·3%).

Fractions (viii)—(x) consisted of 1-bromoheptan-2-one, n_D^{18} 1·4650 (Found: C, 43·8; H, 7·1; Br, 41·3. Calc. for $C_7H_{13}OBr$: C, 43·5; H, 6·7; Br, 41·5%). Catch *et al.* record b. p. 96°/14 mm., n_D^{18} 1·4645. A sample of this bromo-ketone on treatment with thiourea gave 2-*amino*-4-n-*amylthiazole*, a pale yellow oil, b. p. 134°/1·5 mm., n_D^{20} 1·5429 (Found: C, 56·2; H, 8·1; N, 15·9. $C_8H_{14}N_2S$ requires C, 56·5; H, 8·2; N, 16·5%). The *picrate* crystallized from acetone in yellow needles, m. p. 183—184° (decomp.) (Found: C, 42·5; H, 4·0; N, 17·9. $C_8H_{14}N_2S,C_6H_3O_7N_3$ requires C, 42·1; H, 4·3; N, 17·5%). 1-*Anilinoheptan*-2-*one* crystallized from light petroleum (b. p. 60—80°) in colourless elongated plates, m. p. 73—74° (Found: C, 76·0; H, 9·3; N, 7·0. $C_{13}H_{19}ON$ requires C, 76·1; H, 9·2; N, 6·8%).

(f) *Monobromo-ketones from* n-*Hexyl Methyl Ketone.*—The monobromo-ketones (506 g.; b. p. 56—93°/3 mm.) were fractionated at 2—3 mm. through a 200-cm. column packed with Fenske helices. The following fractions (total 477 g.) were collected: (i) b. p. 32·0° (72·0 g.); (ii) b. p. 32·0—61·0° (9·3 g.); (iii) b. p. 61·0—61·5° (3·9 g.); (iv) b. p. 61·5—63·5° (299·9 g.); (v) b. p. 63·5—67·5° (13·0 g.); (vi) b. p. 67·5—71·5° (1·9 g.); (vii) b. p. 71·5—76·0° (4·4 g.); (viii) b. p. 76·0—77·4° (4·4 g.); (ix) b. p. 77·4—79·0° (53·7 g.); (x) b. p. 79·0—84·0° (18·8 g.).

Fraction (i) consisted of unchanged *n*-hexyl methyl ketone, n_D^{20} 1·4150. Fraction (iv) consisted of 3-*bromo-octan*-2-*one*, n_D^{20} 1·4615 (Found: Br, 37·6. $C_8H_{15}OBr$ requires Br, 38·6%). On treatment with thiourea it gave 2-*amino*-5-n-*amyl*-4-*methylthiazole*, a colourless, waxy solid, m. p. 26—27° (from light petroleum, b. p. 40—60°, at a low temperature) (Found: C, 59·1; H, 8·8; N, 15·3; S, 17·2. $C_9H_{16}N_2S$ requires C, 58·7; H, 8·7; N, 15·2; S, 17·4%).

Fractions (viii)—(x) consisted largely of 1-*bromo-octan*-2-*one*. The preliminary stripping from dibromo-ketones had evidently been a little too efficient, and the proportion of the bromomethyl ketone was almost certainly underestimated. Fraction (ix) had n_D^{19} 1·4660 (Found: C, 46·2; H, 7·5; Br, 40·2. $C_8H_{15}OBr$ requires C, 46·3; H, 7·2; Br, 38·6%). 1-*Anilino-octan*-2-*one* crystallized from light petroleum (b. p. 60—80°) in colourless elongated plates, m. p. 67—68° (Found: N, 6·2. $C_{14}H_{21}ON$ requires N, 6·4%).

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