486. *Quantitative Aspects of the Base-catalysed Halogenation of Aliphatic Ketones. Part I. Iodination of Methyl Ketones.*

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The base-catalysed iodination of some aliphatic methyl ketones has been investigated. In practice, reaction does not occur quantitatively according to the equation: $CH_3{\cdot}COR + 3I_2 + 4NaOH = CHI_3 + R{\cdot}CO_2Na + 3NaI + 3H_2O$. Acetone, ethyl methyl ketone, methyl *n*-propyl ketone and *n*-butyl methyl ketone take up more than the theoretical amount of iodine, while methyl *iso*propyl ketone and *tert.*-butyl methyl ketone consume less than this quantity, even when the optimum conditions are attained for high iodine uptake.

The factors controlling the extent of iodine consumption include the concentrations and the rate and order of addition of the reactants. It is shown that there is a competition between reactions involving iodination of the organic compound and those resulting in decomposition of the active iodinating species.

Analytical methods have been devised which enable the fate of the consumed iodine to be determined. From all the ketones studied, iodinated organic acids are formed as well as the predicted fatty acids. With the least reactive ketones, less highly iodinated neutral products are found in addition to iodoform. The mechanisms of the reactions leading to the formation of these abnormal products are discussed.

When methyl ketones react with iodine in alkaline solution the principal reaction occurring is generally represented by the equation (1). This reaction has been much used for the

$$CH_3{\cdot}COR + 3I_2 + 4NaOH = CHI_3 + R{\cdot}CO_2Na + 3NaI + 3H_2O \quad . \quad . \quad (1)$$

determination of methyl ketones and related compounds.

Kramer[1] devised a gravimetric procedure which is still occasionally employed,[2] but is in general only suitable for semi-quantitative work. Messinger's volumetric method[3] has been much more widely used. This has been extensively studied and modified in order to yield the most accurate results.[4] Even under optimum conditions, however, it seems that reaction does not occur quantitatively according to equation (1). For example, Hatcher and Mueller[5] found that the reaction never gave theoretical yields of iodoform. The method is also said to give high results in the determination of acetone[6, 7] and ethyl methyl ketone,[8] and low results with methyl *iso*propyl ketone.[6]

In this paper, the quantitative aspects are discussed of the base-catalysed iodination of a number of methyl ketones. It is established that in no case does the overall reaction proceed strictly according to equation (1), though with acetone the extent of side reactions is small enough not to exclude the use of Messinger's method for the quantitative analysis of this ketone.

EXPERIMENTAL

Materials.—The purest available commercial samples of the ketones were used. Acetone was further purified by the sodium iodide method. The other ketones were dried (K_2CO_3) and then fractionated through a 1-m. column, the middle fractions of constant physical properties being retained. Attempts to determine the concentration of ketone solutions by the hydroxylamine method[9] invariably led to low results. Hence all ketone solutions were prepared by weight according to Goodwin's procedure.[4] All other reagents were " AnalaR " materials or of comparable purity and were further purified where necessary by conventional methods.

Kinetic Measurements.—Since the reactions are relatively fast, rate measurements were made in Y-tubes, the sodium hydroxide and ketone solutions originally being in one limb and the iodine solution in the other. Reaction was stopped by pouring the reaction mixture into a slight excess of hydrochloric acid and the liberated iodine was immediately titrated with thiosulphate.

Measurement of Total Halogen Consumption.—Two of the reactant solutions were run into a conical flask, and the third solution was added with continuous shaking of the flask. After 1 hr., the mixture was acidified, and the liberated iodine titrated with thiosulphate.

The order of mixing of the reagents was usually ketone–alkali–iodine, and to ensure that, as far as possible, the iodine solution was added at a standard rate, the same (25 ml.) pipette was used throughout for its delivery.

Identification of Acid Reaction Products.—Excess of halogen was titrated with thiosulphate, and the organic constituents were extracted with ether (3 × 5 ml.). The combined ethereal extracts were washed with aqueous ammonia (3 × 5 ml.), and the ammonia layer was analysed for the anions of fatty acids and halogenated organic acids by a paper-chromatographic method.[10]

Quantitative Analysis of Reaction Products.—(a) *Neutral and acid iodinated products.* After removal of excess of halogen with thiosulphate, the acidified reaction mixture was shaken with ether (8 × 5 ml.). The combined ethereal extracts were further shaken with 0·1N-aqueous sodium hydroxide (3 × 5 ml.). The alkaline layer was acidified with halogen-free nitric acid and organic acids were extracted with ether (3 × 5 ml.). Both the ethereal solutions (containing neutral and acid organic products respectively) were separately analysed for total halogen content by a modification of Drogin and Rosanoff's sodium–alcohol method.[11]

To test the efficiency of extraction, pure samples of iodoform, iodoacetic acid, and β-iodopropionic acid were analysed for halogen, and it was found that almost all the organically bound iodine ($\gtrdot$ 98%) could be determined (Table 1).

(b) *Iodoform.* After reaction was complete, the iodine liberated on acidification was titrated with thiosulphate. The organic constituents were extracted with chloroform (20 ml.). The

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[1] Kramer, *Ber.*, 1880, **13**, 1000.
[2] Hennion and Pillar, *J. Amer. Chem. Soc.*, 1950, **72**, 5317.
[3] Messinger, *Ber.*, 1888, **21**, 3366.
[4] See, *e.g.*, Goodwin, *J. Amer. Chem. Soc.*, 1920, **42**, 39.
[5] Hatcher and Mueller, *Trans. Roy. Soc. Canada*, 1929, **23**, 35.
[6] Dal Nogare, Norris, and Mitchell, *Analyt. Chem.*, 1951, **23**, 1473.
[7] Haughton, *Ind. Eng. Chem. Anal.*, 1937, **9**, 167.
[8] Cassar, *Ind. Eng. Chem.*, 1927, **19**, 1061.
[9] Marasco, *ibid.*, 1926, **18**, 701.
[10] Hashmi and Cullis, *Analyt. Chim. Acta*, 1956, **14**, 336.
[11] Drogin and Rosanoff, *J. Amer. Chem. Soc.*, 1916, **38**, 711.

chloroform layer was shaken with 0·2% aqueous hydroxylamine hydrochloride to remove carbonyl compounds,[6] then dried and diluted to exactly 25 ml. with fresh solvent. The iodoform content was determined by a spectroscopic absorption method,[6] the optical density being measured at 3470 Å with a Unicam SP 500 spectrophotometer fitted with 2-cm. quartz cells.

TABLE 1.

Compound	Weight of iodine (%) Found	Weight of iodine (%) Calc.	Extraction (%)
Iodoform	95·41	96·70	98·7
Iodoacetic acid	67·30	68·28	98·6
β-Iodopropionic acid	62·17	63·50	98·0

Related iodo-compounds, *e.g.*, methylene iodide, were also found to absorb to some extent at the wavelength used, but the absorption is much less than that due to iodoform itself (< 10%). The possible interference of such compounds was therefore neglected.

RESULTS

Kinetic Measurements.—The higher methyl ketones show similar kinetic behaviour to acetone.[12, 13] With the alkali present in large excess, the iodine disappears according to a first-order kinetic law. Plots of $\log_{10}(T_t - T_\infty)$ against t (where T_t and T_∞ are the thiosulphate titres after times t and infinity, respectively) are linear over at least the first half of the reaction, after which the rate tends to fall off less rapidly.

The rates of halogenation in Table 2 are not, however, proportional to the rates of disappearance of ketone and should, strictly speaking, be multiplied by a " statistical " factor to allow for the different amounts of iodine consumed by the various ketones (Fig. 1). Such a correction is difficult to apply in practice since the conditions obtaining in the rate experiments are not those under which the limiting uptake of halogen is achieved. In any case, multiplication of the observed rates of halogenation by the appropriate factors would not alter qualitatively the order of reactivity of the ketones studied.

TABLE 2. *Rates of iodination of some methyl ketones.*

Temp. = 25°; [Ketone] = 0·0025M; [Iodine] = 0·01M; [NaOH] = 0·1M.

Ketone	Vel. const. (k) (sec.$^{-1}$ × 10^3)	Ketone	Vel. const. (k) (sec.$^{-1}$ × 10^3)
Acetone	16·80	*n*-Butyl methyl ketone	8·08
Ethyl methyl ketone	9·01	Methyl *iso*propyl ketone	7·16
Methyl *n*-propyl ketone	8·56	*tert.*-Butyl methyl ketone	3·41

The initial rates of halogenation are directly proportional to the hydroxyl-ion concentration (Table 3) and independent of the concentration of iodine (Table 4).

TABLE 3. *Influence of alkali concentration on the rates of iodination of some methyl ketones.*

Temp. = 25°; [Ketone] = 0·0025M; [Iodine] = 0·01M.

Ethyl methyl ketone [NaOH] (M)	Vel. const. (k) (sec.$^{-1}$ × 10^3)	k/[OH$^-$]	*tert.*-Butyl methyl ketone [NaOH] (M)	Vel. const. (k) (sec.$^{-1}$ × 10^3)	k/[OH$^-$]
0·1	9·01	90·1	0·1	3·41	34·1
0·2	17·40	87·0	0·2	6·62	33·1
0·3	26·20	87·3	0·3	9·99	33·3

TABLE 4. *Influence of iodine concentration on the rate of iodination of some methyl ketones.*

Temp. = 25°; [Ketone] = 0·0025M; [NaOH] = 0·1M.

Ethyl methyl ketone [Iodine] (M)	Vel. const. (sec.$^{-1}$ × 10^3)	*tert.*-Butyl methyl ketone [Iodine] (M)	Vel. const. (sec.$^{-1}$ × 10^3)
0·01	9·01	0·01	3·41
0·02	8·80	0·02	3·61
0·03	9·00	0·03	3·45

Factors Controlling the Extent of Iodine Consumption.—(a) *Influence of alkali concentration.* A fixed volume of iodine solution was added to various ketone–alkali solutions. The uptake of

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[12] Bartlett, *J. Amer. Chem. Soc.*, 1934, **56**, 967.
[13] Bell and Longuet-Higgins, *J.*, 1946, 636.

iodine increases with alkali concentration (Fig. 1), reaching a limiting value only in presence of a comparatively large excess of hydroxyl ions, *i.e.*, 8—15 times that required according to equation (1).

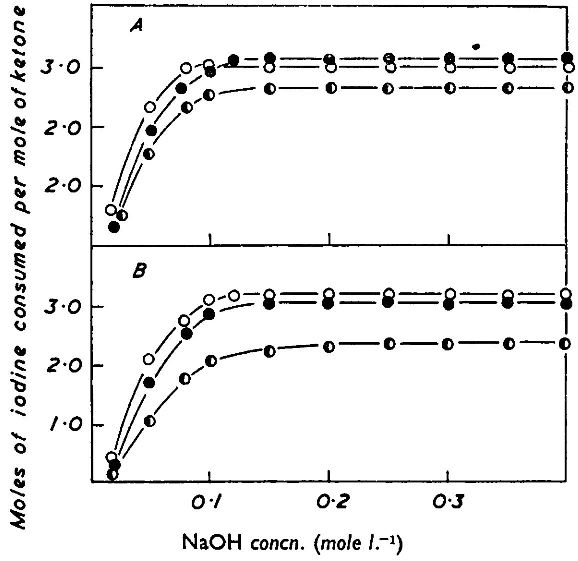


FIG. 1. *The influence of alkali concentration on consumption of iodine by methyl ketones.*

Temp. = 25°; [Ketone] = 0·0025M; [Iodine] = 0·01M.

A. ○ $(CH_3)_2CO$ (3·02)
● $CH_3{\cdot}CO{\cdot}CH_2{\cdot}CH_3$ (3·12)
◐ $CH_3{\cdot}CO{\cdot}CH(CH_3)_2$ (2·65)
B. ○ $CH_3{\cdot}CO{\cdot}[CH_2]_2{\cdot}CH_3$ (3·15)
● $CH_3{\cdot}CO{\cdot}[CH_2]_3{\cdot}CH_3$ (3·02)
◐ $CH_3{\cdot}CO{\cdot}C(CH_3)_3$ (2·35)

(The figures against each ketone represent the number of moles of iodine consumed per mole of ketone when excess of alkali is present.)

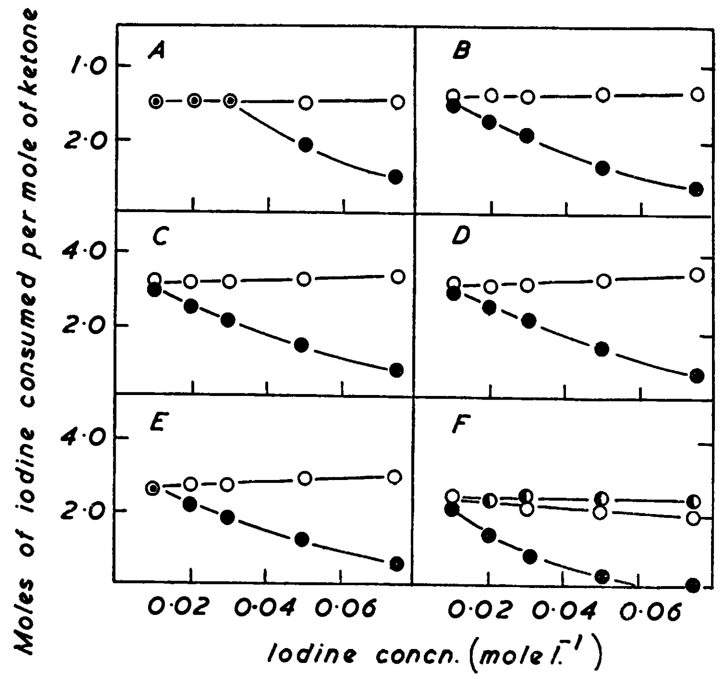


FIG. 2. *The influence of iodine concentration on consumption of iodine by methyl ketones.*

Temp. = 25°;
[Ketone] = 0·0025M.

[NaOH] : ● = 0·1M;
○ = 0·4M; ◐ = 1·0M.

A, $(CH_3)_2{\cdot}CO$; *B*, $CH_3{\cdot}CO{\cdot}C_2H_5$
C, $CH_3{\cdot}CO{\cdot}[CH_2]_2{\cdot}CH_3$
D, $CH_3{\cdot}CO{\cdot}[CH_2]_3{\cdot}CH_3$
E, $CH_3{\cdot}CO{\cdot}CH(CH_3)_2$
F, $CH_3{\cdot}CO{\cdot}C(CH_3)_3$

(b) *Influence of iodine concentration.* Equal volumes of different iodine solutions were run into a standard ketone–alkali solution. When sufficient alkali is present to achieve limiting consumption of a fixed amount of halogen, the uptake of iodine generally increases slightly with iodine concentration; at lower alkali concentrations, the iodine consumption decreases markedly when a large excess of the halogen is added (Fig. 2). This decrease might be due to depletion of the hydroxyl-ion concentration as a result of the reaction : $I_2 + OH^- = HIO + I^-$. Measurements show an appreciable decrease in the pH of solutions of sodium hydroxide when large amounts of iodine are added; this effect is naturally most marked at low alkali concentrations (Fig. 3). Any factor which reduces the hydroxyl-ion concentration also tends to decrease the extent of iodine consumption (compare Fig. 1). On the other hand, the observed behaviour might be attributable to concurrent alterations in the concentration of potassium iodide, for the different iodine solutions were prepared by dilution with water of a stock solution of iodine in aqueous potassium iodide. Separate experiments show that at low alkali concentrations an

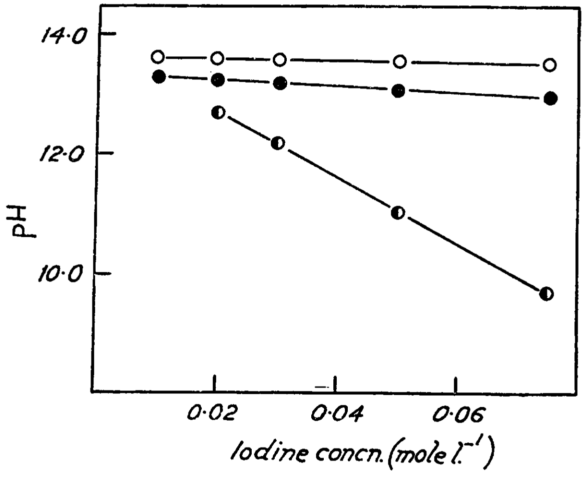
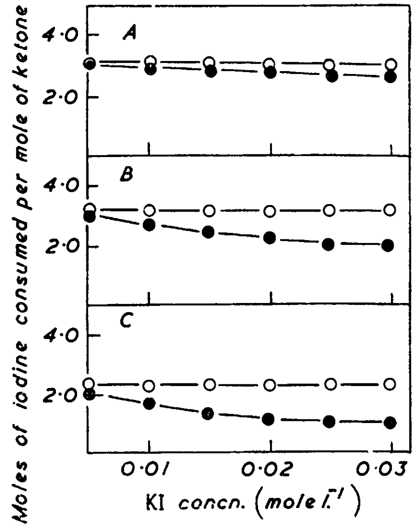


FIG. 3. *The influence of iodine concentration on the* pH *of reaction mixtures.*

Temp. = 25°. [NaOH] : ◐ = 0·1M ; ● = 0·4M ; ○ = 0·5M.

FIG. 4. *The influence of potassium iodide concentration on consumption of iodine by methyl ketones.*

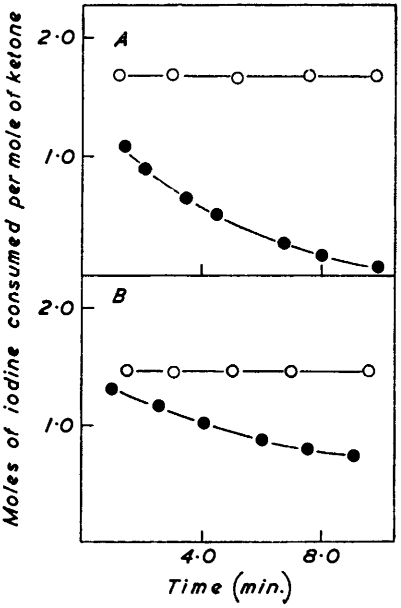


Temp. = 25°; [Ketone] = 0·0025M; [Iodine] = 0·01M.

[NaOH] : ● = 0·1M; ○ = 0·4M.

A, $(CH_3)_2CO$
B, $CH_3{\cdot}CO{\cdot}C_2H_5$
C, $CH_3{\cdot}CO{\cdot}C(CH_3)_3$

FIG. 5. *The influence of the order of mixing of the reagents on consumption of iodine.*



Temp. = 25°; [Ketone] = 0·0025M; [Iodine] = 0·01M; [NaOH] = 0·05M.

○ Ketone and sodium hydroxide mixed, iodine added after time *t*.

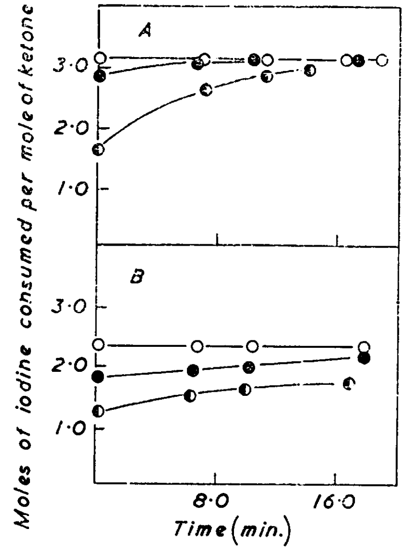
● Iodine and sodium hydroxide mixed, ketone added after time *t*.

A, $CH_3{\cdot}CO{\cdot}C_2H_5$
B, $CH_3{\cdot}CO{\cdot}C(CH_3)_3$

excess of potassium iodide decreases the uptake of a fixed amount of iodine (Fig. 4); the decrease is most marked with the least reactive ketones. This is a specific effect of iodide ions, since additions of other salts, *e.g.*, potassium sulphate, do not influence iodine consumption.

(c) *Order of mixing of reagents.* Two of the reactant solutions were mixed and the third solution was added after various times. The extent of halogen consumption is greatly decreased when the alkali and iodine are mixed and set aside before the ketone is added (Fig. 5). On the other hand, when either the alkali and ketone or the ketone and iodine are "pre-mixed," the amount of iodine consumed is independent of the time which elapses before the third component is added.

FIG. 6. *The influence of the rate of addition of iodine on consumption of iodine.*



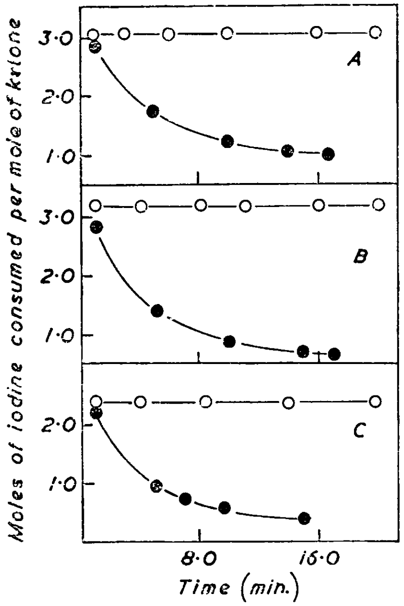
Temp. = 25°; [Ketone] = 0·0025M; [Iodine] = 0·01M.

[NaOH] : ◐ = 0·05M; ● = 0·1M; ○ = 0·4M.

[The abscissæ represent the time, *t*, taken for the addition of a fixed volume of iodine solution (25 ml.).]

A, $CH_3 \cdot CO \cdot C_2H_5$
B, $CH_3 \cdot CO \cdot C(CH_3)_3$

FIG. 7. *The influence of the rate of addition of alkali on consumption of iodine.*



Temp. = 25°; [Ketone] = 0·0025M; [Iodine] = 0·01M.

[NaOH] : ● = 0·4M; ○ 4·0M.

[The abscissæ represent the time, *t*, taken for the addition of a fixed volume of alkali solution (40 ml.).]

A, $(CH_3)_2CO$
B, $CH_3 \cdot CO \cdot C_2H_5$
C, $CH_3 \cdot CO \cdot C(CH_3)_3$

(d) *Rate of addition of reagents.* Fixed volumes of iodine solution were added slowly with constant agitation to "pre-mixed" ketone–alkali solutions, and the rate of addition of the iodine was varied to extend over different periods of time. The iodine uptake is increased by slow addition of the halogen, the effect being most pronounced when the alkali : ketone ratio is comparatively small (Fig. 6). The reverse effect is found when the alkali is added last, its slow addition causing the consumption of iodine to decrease (Fig. 7).

(e) *Influence of ketone structure.* The important fact emerges from Fig. 1 that with acetone the limiting molar consumption of iodine corresponds almost exactly to the theoretical value of 3·0 according to equation (1). With the higher homologues, however, the corresponding value may be appreciably greater or less than 3·0. In general, the number of moles of iodine consumed per mole of ketone, $CH_3 \cdot COR$, is greater or less than 3·0 according to whether R is a straight-chain or branched-chain alkyl group.

Identification of Acid Reaction Products.—The results in Table 5 show that, in addition to the fatty acids predicted according to equation (1), their α-iodo-derivatives are formed wherever possible. With methyl *iso*propyl ketone and *tert.*-butyl methyl ketone, the nature of the acid products suggests that some fission occurs across both the C–C bonds adjacent to the carbonyl group.

Quantitative Analysis of Reaction Products.—(a) *Neutral and acid iodinated products.* Table 6 shows some analytical results for the products of reaction mixtures containing different initial iodine concentrations; in all cases, sufficient alkali was present to achieve the limiting uptake of a fixed amount of iodine. The total extraction of organically bound iodine may be compared with the values obtained during standardisation of the analytical method (Table 1). Almost all the consumed iodine is evidently converted into organic form; the major part of the halogen is in neutral form and only a small proportion is found as iodo-acids. Where the molar iodine

TABLE 5. *Acids formed in the base-catalysed iodination of some methyl ketones.*.*

Temp. = 25°; [Ketone] = 0·0025M; [Iodine] = 0·01M; [NaOH] = 0·4M.

	Acids formed	
Ketone	Fatty acids	Iodo-acids
$CH_3{\cdot}CO\vdots CH_3$	$CH_3{\cdot}CO_2H$ 0·38 (0·39)	$CH_2I{\cdot}CO_2H$ 0·50 (0·50)
$CH_3{\cdot}CH_2{\cdot}CO\vdots CH_3$	$CH_3{\cdot}CH_2{\cdot}CO_2H$ 0·48 (0·48)	$CH_3{\cdot}CHI{\cdot}CO_2H$ 0·54 (0·55)
$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CO\vdots CH_3$	$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$ 0·56 (0·57)	$CH_3{\cdot}CH_2{\cdot}CHI{\cdot}CO_2H$ 0·64 (0·62)
$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CO\vdots CH_3$	$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$ 0·68 (0·68)	$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CHI{\cdot}CO_2H$ 0·73 (0·72—for isomeric α-iodo*iso*valeric acid)
$(CH_3)_2{\cdot}CH\vdots CO\vdots CH_3$	$(CH_3)_2CH{\cdot}CO_2H$ 0·57 (0·57)	$(CH_3)_2CI{\cdot}CO_2H$ and $CH_2I{\cdot}CO_2H$ 0·64 (0·63) 0·51 (0·50)
$(CH_3)_3C\vdots CO\vdots CH_3$	$(CH_3)_3C{\cdot}CO_2H$ 0·69 (0·70)	$CH_2I{\cdot}CO_2H$ 0·51 (0·50)

* R_F values of acids present in products are given together with the corresponding values determined for the known acids. The developing solvent contained 30% v/v of aqueous ammonia (*s.g.* 0·88) and 70% v/v of *n*-propyl alcohol.

TABLE 6. *Influence of iodine concentration on the iodinated products formed from methyl ketones.*

Temp. = 25°; [Ketone] = 0·0025M; [NaOH] = 0·4M.

	Moles of iodine per mole of ketone				
	Found				
[Iodine] (mole l.$^{-1}$)	Neutral	Acid	Total	Consumed	Extraction (%)
Acetone					
0·01	2·90	0·06	2·96	3·01	98·2
Ethyl methyl ketone					
0·0075	2·80	0·11	2·91	3·00	97·4
0·01	2·93	0·13	3·06	3·12	98·0
0·03	2·93	0·13	3·06	3·14	98·0
0·075	2·93	0·21	3·15	3·23	98·0
Methyl *n*-propyl ketone					
0·0075	2·80	0·13	2·93	3·00	98·0
0·01	2·93	0·13	3·06	3·13	98·0
0·03	2·93	0·16	3·09	3·16	98·0
0·075	2·93	0·35	3·28	3·35	98·1
n-Butyl methyl ketone					
0·0075	2·80	0·13	2·93	3·00	98·0
0·01	2·80	0·16	2·96	3·02	98·1
0·03	2·93	0·16	3·09	3·15	98·0
0·075	2·93	0·47	3·40	3·47	98·2
Methyl *iso*propyl ketone					
0·0075	2·46	0·11	2·57	2·66	97·2
0·01	2·46	0·11	2·57	2·65	97·2
0·03	2·55	0·11	2·66	2·71	98·3
0·075	2·74	0·14	2·88	2·96	97·5
tert.-Butyl methyl ketone					
0·0075	2·20	0·08	2·28	2·34	98·0
0·01	2·18	0·09	2·27	2·34	97·3
0·03	2·05	0·09	2·14	2·20	97·2
0·075	1·84	0·09	1·93	1·98	98·4

uptake is greater than 3·0, the increase in halogen consumption with iodine concentration is accounted for by an increase in the quantity of iodo-acids. Where less than the theoretical amount of iodine is taken up, the variations appear to be controlled mainly by the quantity of neutral halogenated products. With reaction solutions containing insufficient alkali to cause the limiting amount of iodine to be taken up, neutral and acid reaction products are formed concurrently in a more or less constant ratio, even when the total extent of iodination is small (Table 7). This suggests that the iodo-acids are formed as an integral part of the main reaction involving iodination of the ketone followed by C–C bond fission, and not by a slow subsequent halogenation of the fatty acids first formed. Experiment indeed shows that no appreciable direct iodination of the fatty acids occurs under the experimental conditions used.

TABLE 7. *Influence of alkali concentration on the iodinated products formed from methyl ketones.*

Temp. = 25°; [Ketone] = 0·0025M; [Iodine] = 0·01M.

	Moles of iodine per mole of ketone				
	Found				
[NaOH] (mole l.$^{-1}$)	Neutral	Acid	Total	Con- sumed	Extrac- tion (%)
Ethyl methyl ketone					
0·05	1·63	0·07	1·70	1·73	98·2
0·08	2·46	0·11	2·57	2·61	98·9
0·10	2·80	0·12	2·92	2·99	98·7
0·40	2·93	0·13	3·06	3·12	98·0

	Moles of iodine per mole of ketone				
	Found				
[NaOH] (mole l.$^{-1}$)	Neutral	Acid	Total	Con- sumed	Extrac- tion (%)
tert.-Butyl methyl ketone					
0·05	0·91	0·05	0·96	0·99	98·1
0·08	1·67	0·06	1·73	1·77	98·0
0·10	1·98	0·08	2·06	2·09	98·7
0·40	2·18	0·09	2·27	2·34	97·3

TABLE 8. *Iodoform present in the neutral iodinated products.*

Temp. = 25°; [Ketone] = 0·0025M; [Iodine] = 0·01M; [NaOH] = 0·4M.

	Moles of iodine per mole of ketone	
Ketone	Neutral organic form *	Iodoform †
Acetone	2·90	2·91
Ethyl methyl ketone ...	2·93	2·91
Methyl *n*-propyl ketone...	2·93	2·89

	Moles of iodine per mole of ketone	
Ketone	Neutral organic form *	Iodoform †
n-Butyl methyl ketone...	2·80	2·57
Methyl *iso*propyl ketone	2·46	2·23
tert.-Butyl methyl ketone	2·18	1·63

* Found by total-halogen analysis. † Found by spectroscopic absorption

(b) *Iodoform.* The results in Table 8 show that with acetone, ethyl methyl ketone, and methyl *n*-propyl ketone, iodoform is produced in approximately theoretical quantity and accounts for all the neutral organically-bound iodine. With the other ketones, substantial quantities of less highly halogenated neutral iodine compounds are also formed.

DISCUSSION

Nature of the Iodinating Species.—The main course of the base-catalysed iodination of acetone is well established and is believed to consist of three stages : (i) conversion of the ketone into an enolate ion, (ii) progressive iodination of this ion to yield tri-iodoacetone, (iii) hydrolytic fission of the iodo-ketone to give iodoform and acetic acid. The principal iodinating species in (ii) is thought to be hypoiodous acid.[14] With higher methyl ketones, as with acetone, the *rate* of halogenation is normally controlled by (i) (Tables 3 and 4), but the *extent* of iodination appears to depend on the balance between (ii) and a competing process involving disproportionation of hypoiodite to iodate. In order to reduce the rate of disproportionation and hence increase the iodine uptake, it is necessary to effect a high degree of dispersion of the halogenating agent.[14] Thus the iodine should be run into the

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[14] Morgan, Bardwell, and Cullis, *J.*, 1950, 3190.

pre-mixed ketone and alkali (Fig. 5), and it should be added slowly (Fig. 6). The disproportionation of hypoiodite is retarded by hydroxyl ions and accelerated by iodide ions [15, 16] and consequently the extent of iodine consumption is increased by maintaining a high pH (Fig. 1) and decreased by addition of iodide ions (Fig. 4). The use of a high iodine concentration retards (i) by decreasing the effective hydroxyl-ion concentration; this also slows down (ii) and hence favours the disproportionation process so that the iodine uptake is decreased. This factor is predominant at low alkali concentrations or when (i) is relatively slow, and is thus most in evidence with the least reactive ketones (Fig. 2). At high alkali concentrations, an increased concentration of halogen increases the extent to which (ii) can occur by maintaining for a longer period a sufficient supply of hypoiodous acid.

Causes of Abnormal Iodine Consumption.—The iodine uptake will inevitably be low if the conditions are such that disproportionation of hypoiodous acid is rapid compared with enolisation of the ketone. Even if a sufficient concentration of hypoiodous acid is maintained, however, the iodine consumption rarely corresponds to that required by equation (1). Two opposing factors appear to be operative.

(a) *Factors responsible for high iodine consumption.* A high iodine consumption results from the formation of iodo-acids in addition to the normal reaction products predicted by equation (1). The experimental evidence shows that the production of such compounds must be considered as part of the main reaction and that the " extra " iodine is taken up by the ketone before fission of the C–C bond.

In order to obtain a fuller insight into the mechanism of formation of iodo-acids, it is necessary to consider in more detail the rate-determining (enolisation) stage of the reaction. The direction of enolisation of an unsymmetrical ketone depends on the nature of the solvent. In alkaline solution, substitution at a carbon atom slows down reactions dependent on the enolate ion (Table 2), and this, together with other evidence,[17, 18, 19] suggests that enolisation occurs away from the most substituted group, *i.e.*, towards the methyl group in methyl ketones. The enolate ion formed initially may immediately react to give a monoiodo-ketone, $\mathrm{R{\cdot}CH_2{\cdot}CO{\cdot}CH_2I}$, which will be further rapidly iodinated at the substituted methyl group.[20] If, however, the enolate ion persists in solution long enough, it may undergo a tautomeric change :

$$\text{(I)}\quad [\mathrm{R{\cdot}CH_2{\cdot}CO{:}CH_2}]^- \rightleftharpoons [\mathrm{R{\cdot}CH{:}CO{\cdot}CH_3}]^- \quad\text{(II)}$$

(II) is in general stabilised with respect to (I) by hyperconjugation, and if the experimental conditions are such that equilibrium is set up before iodination occurs, substitution will take place to some extent on the " wrong " carbon atom.[21] If this were to happen, iodo-acid would eventually be formed in addition to iodoform. The iodine uptake is, however, the same whether the order of mixing is ketone–alkali–iodine (Fig. 5) or ketone–iodine–alkali (Fig. 7), although under the latter conditions, equilibrium between (I) and (II) is less readily established. Furthermore, if the above tautomeric change were faster than iodination, the corresponding process :

$$\text{(III)}\quad [\mathrm{R{\cdot}CHI{\cdot}CO{:}CH_2}]^- \rightleftharpoons [\mathrm{R{\cdot}CI{:}CO{\cdot}CH_3}]^- \quad\text{(IV)}$$

would be even more rapid, and both direct enolisation and the position of equilibrium would favour (IV) with respect to (III). In other words, any wrongly mono-iodinated compound should, according to the above mechanism, become di-iodinated. In fact, di-iodo-acids are not found among the reaction products.

A more plausible mechanism for the formation of iodo-acids may be constructed if it is assumed that initial attack occurs exclusively at the methyl group and further subsequent

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[15] Skrabal, *Monatsh.*, 1911, **32**, 167, 185; 1912, **33**, 99.
[16] Li and White, *J. Amer. Chem. Soc.*, 1943, **65**, 335.
[17] Simonsen, *J.*, 1922, **121**, 2292.
[18] Semmler and Schiller, *Ber.*, 1927, **60**, 1591.
[19] Levine and Hauser, *J. Amer. Chem. Soc.*, 1944, **66**, 1768.
[20] Cf. Bell and Lidwell, *Proc. Roy. Soc.*, 1940, *A*, **176**, 88.
[21] Cardwell, *J.*, 1951, 2442.

iodination at the same point eventually gives rise to the compound $R\cdot CH_2\cdot CO\cdot CI_3$. This would undergo hydrolytic fission as the predominant, but not necessarily the sole, reaction. It might also enolise to give the ion $[R\cdot CH{:}CO\cdot CI_3]^-$, which would rapidly suffer iodination at the non-methyl group before cleavage takes place. An increase in alkali concentration would increase the rate of hydrolytic fission of the tri-iodo-ketone, but would also accelerate its enolisation and further iodination. Since both processes are presumably of the first order with respect to hydroxyl-ion concentration, the ratio of iodo-acids to iodoform would, on this theory, be largely uninfluenced by the alkali concentration, as is indeed found (Table 7). A mechanism for the formation of iodo-acids, involving iodination at the " wrong " carbon atom *after* rather than before tri-iodination has occurred at the methyl group, therefore seems to be more in accordance with the experimental facts.

With ethyl methyl ketone and methyl *n*-propyl ketone, considerably more iodo-acid is formed than with acetone. This suggests that the tri-iodo-compounds $CH_3\cdot CH_2\cdot CO\cdot CI_3$ and $CH_3\cdot CH_2\cdot CH_2\cdot CO\cdot CI_3$ are relatively more stable towards alkali than tri-iodoacetone, so that they can be halogenated to a greater extent before C–C bond fission takes place.

(b) *Factors responsible for low iodine consumption.* Except with acetone and ethyl methyl ketone, a parallelism exists between rate of iodination (Table 2) and extent of halogen consumption (Fig. 1), the least reactive ketones, such as methyl *iso*propyl ketone and *tert.*-butyl methyl ketone, taking up the smallest amounts of iodine. With these two compounds in particular, less highly iodinated neutral products are formed in addition to iodoform (Table 8). These are not iodo-ketones, since carbonyl compounds were previously removed from the reaction mixture. They must therefore be iodo-paraffins formed by hydrolytic fission of intermediate mono- and di-iodo-ketones.[22] A factor which may encourage premature fission is steric hindrance. Poggi [23] has shown that, during iodination of *tert.*-butyl methyl ketone, the compound $(CH_3)_3C\cdot CO\cdot CHI_2$ can be isolated. Experiments with models confirm that, with the enolate ions $[(CH_3)_3C\cdot CO{:}CI_2]^-$ and $[(CH_3)_2CH\cdot CO{:}CI_2]^-$, steric hindrance makes the introduction of a third iodine atom difficult, so that hydrolysis of the di-iodo-ketones can compete successfully with further iodination. The analytical results show that premature fission sometimes takes place across the " wrong " C–C bond. With methyl *iso*propyl ketone, for example, iodoacetic acid is found among the products (Table 5); after a single iodination on the methyl and *iso*propyl groups, some cleavage must presumably occur according to the equation :

$$(CH_3)_2CI\cdot CO\cdot CH_2I + OH^- = CH_3\cdot CHI\cdot CH_3 + CH_2I\cdot CO_2^-$$

With ketones of low reactivity, it is difficult to maintain a sufficient supply of hypoiodous acid, since the rate of production of enolate ions is small. Attempts to accelerate enolisation by an increase in hydroxyl-ion concentration will also tend to increase the rate of premature hydrolytic fission, so that it may not be easy in practise to achieve a higher iodine consumption.

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[22] Richard and Langlais, *Bull. Soc. chim. France*, 1910, **7**, 462.
[23] Poggi, *Atti Soc. ital. Progresso Sci. XXI Riunione*, 1933, **2**, 376.