297. *Quantitative Aspects of the Base-catalysed Halogenation of Aliphatic Ketones. Part II.*[1] *Iodination of Non-methyl Ketones.*

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Base-catalysed iodination of three aliphatic non-methyl ketones has been studied. The factors controlling the extent of iodine consumption are similar to those found with methyl ketones, though more stringent conditions must be satisfied to achieve the maximum halogen uptake.

Analysis of products shows that, in contrast to the behaviour of methyl ketones, the halogen effects considerable oxidation, and only a small proportion of the consumed iodine is converted into organic form.

METHYL ketones react rapidly with iodine in alkaline solution to give iodoform as the main product. Non-methyl ketones are also readily iodinated and the uptake of iodine is sometimes higher than with methyl ketones, although comparatively little iodoform is produced. An earlier study of some quantitative aspects of the base-catalysed iodination of methyl ketones [1] has now been extended to some non-methyl compounds.

EXPERIMENTAL

Purified commercial samples of diethyl ketone and di*iso*propyl ketone were used. A specimen of pure *n*-butyl ethyl ketone was kindly supplied by Dr. H. M. E. Cardwell. All ketone solutions were prepared by weight.[2]

The experimental methods were similar to those used with methyl ketones.[1]

RESULTS

Kinetic Measurements.—As with methyl ketones, a plot of $\log_{10} (T_t - T_\infty)$ against t (where T_t and T_∞ are the thiosulphate titres after times t and infinity respectively) gives a straight line, indicating that the reaction obeys an overall first-order kinetic law. The velocity constants shown in Table 1 are calculated from results in the range 0—50% of completed reaction. Comparison with the corresponding values for methyl ketones [1] shows that the non-methyl ketones are generally much less reactive.

TABLE 1. *Rates of iodination of some non-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)
Diethyl ketone	3·31	Di*iso*propyl ketone	2·30
n-Butyl ethyl ketone	3·64	(Acetone)	(16·80)

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[1] Part I, Cullis and Hashmi, *J.*, 1956, 2512.

[2] Goodwin, *J. Amer. Chem. Soc.*, 1920, **42**, 39.

With all three ketones, the rate of iodination is independent of iodine concentration, indicating that the rate-determining step involves ketone and alkali only. The relationship between rate and alkali concentration is of the form: rate $= k_0 + k_{OH^-}[OH^-]$, where k_0 presumably represents the " spontaneous " (solvent-catalysed) rate of iodination. Thus for diethyl ketone:

$$k\ (\text{sec.}^{-1}) = 1{\cdot}90 \times 10^{-3} + 1{\cdot}52 \times 10^{-2}[OH^-]$$

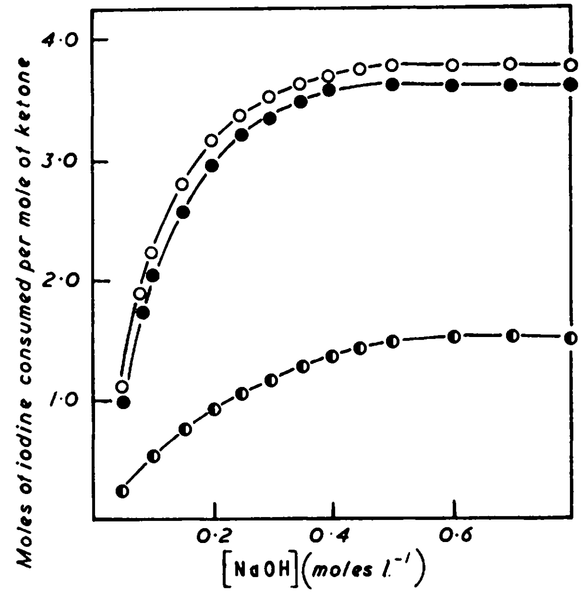


FIG. 1. *The influence of alkali concentration on iodine consumption by non-methyl ketones.*

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

○, Et_2CO (3·77). ●, $Et{\cdot}CO{\cdot}Bu^n$ (3·60). ◐, Pr^i_2CO (1·52).

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

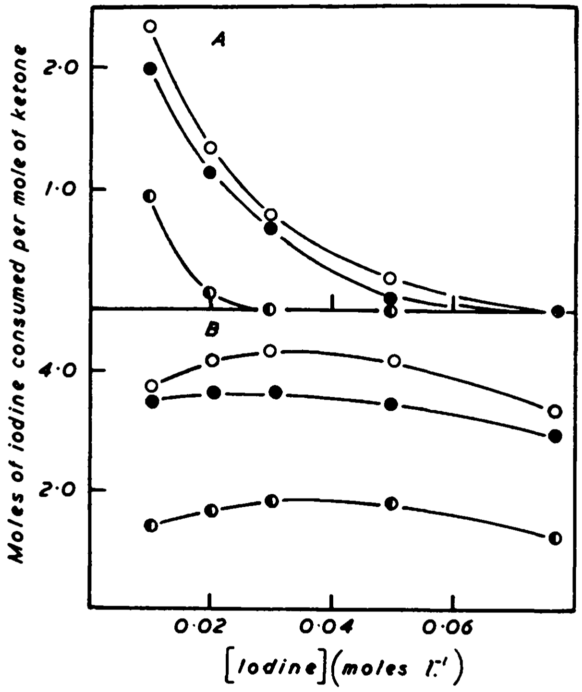


FIG. 2. *The influence of iodine concentration on iodine consumption by non-methyl ketones.*

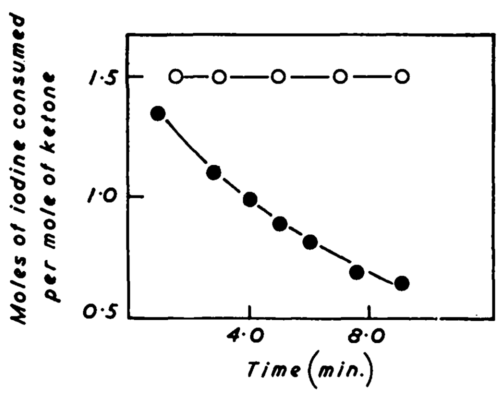
Temp. = 25°. [Ketone] = 0·0025M.

A, [NaOH] = 0·1M. *B*, [NaOH] = 0·4M. ○, Et_2CO. ●, $Et{\cdot}CO{\cdot}Bu^n$. ◐, Pr^i_2CO.

The rate of exchange of deuterium with heavy water is much greater for diethyl ketone than for acetone.[3] The water-catalysed enolisation process [negligible with acetone where k_{OH^-} is large ($16{\cdot}8 \times 10^{-2}$ l. mole^{-1} sec.$^{-1}$)] therefore becomes significant with diethyl ketone for which k_{OH^-} is much smaller.

Factors controlling the Extent of Iodine Consumption.—(a) *Influence of reagent concentrations.* The uptake of iodine increases with alkali concentration (Fig. 1), but the limiting iodine consumption is reached at much higher concentrations ([NaOH] $\geqslant$ 0·5M) than with methyl ketones ([NaOH] = 0·08—0·15M). At low alkali concentrations, excess of iodine has a markedly unfavourable influence on halogen uptake [Fig. 2(*A*)]; at a higher pH, the iodine consumption at first increases but subsequently falls again [Fig. 2(*B*)]. Separate experiments show that the decrease may be attributed partly to a lowering of pH and partly to an increase in potassium iodide concentration.

FIG. 3. *The influence of the order of mixing of the reagents on iodine consumption by diethyl ketone.*

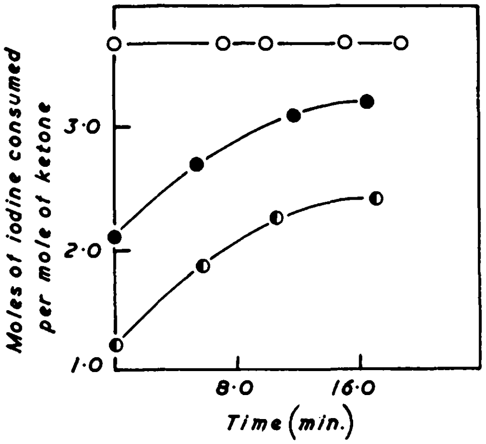


Temp. = 25°. [Ketone] = 0·0025M. [Iodine] = 0·01M. [NaOH] = 0·05M.

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

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

FIG. 4. *The influence of the rate of addition of iodine on iodine consumption by diethyl ketone.*



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.).]

(b) *Order and rate of addition of the reagents.* The iodine uptake decreases if the alkali and iodine are mixed and set aside before the ketone is added, but if the ketone and alkali are " premixed " the consumption of iodine is independent of the time which elapses before the iodine is run in (Fig. 3). The total halogen uptake is increased by slow addition of iodine (Fig. 4), particularly at low alkali concentrations.

Identification of reaction products. Paper-chromatographic analysis shows that, as with methyl ketones, iodinated organic acids are formed in addition to unsubstituted fatty acids (Table 2). The nature of the acid products indicates the positions in the ketone molecule at which C–C bond cleavage takes place.

With diethyl ketone and *n*-butyl ethyl ketone, yellow crystals of iodoform, m. p. and mixed m. p. 119° (lit., m. p. 119°), separated from the reaction mixture.

Quantitative Analysis of Reaction Products.—(a) *Neutral and acid iodinated products.* The results in Table 3 show that with all three compounds the percentage of consumed iodine extracted is remarkably low (usually 20—40%). Since the extraction procedure is highly efficient (>98%),[1] all the iodine taken up is clearly not organically-bound. This implies that most of the consumed halogen is used for oxidation purposes according to the process $I_2 + 2e = 2I^-$, and is thereby converted into inorganic form. With diethyl ketone and *n*-butyl ethyl

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[3] Gordon and McNesby, unpublished results.

ketone, the major part of the organically bound iodine is present in neutral form, while with di*iso*propyl ketone the iodinated products consist mainly of iodo-acids [α-iodo*iso*butyric acid (α-iodo-α-methylpropionic acid)].

(b) *Iodoform.* Analysis shows that all the iodine in neutral organic form is present as iodoform, though with di*iso*propyl ketone the quantity formed is very small (Table 4).

TABLE 2. *Acids formed in the base-catalysed iodination of some non-methyl ketones.**

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

	Acids formed	
Ketone	Fatty acids	Iodo-acids
$\mathrm{Et} \vert \mathrm{CO{\cdot}Et}$	$\mathrm{Me{\cdot}CO_2H}$, 0·38 (0·39) $\mathrm{Et{\cdot}CO_2H}$, 0·47 (0·48)	$\mathrm{Me{\cdot}CHI{\cdot}CO_2H}$, 0·55 (0·55)
$\mathrm{Et} \vert \mathrm{CO} \vdots \mathrm{Bu^n}$	$\mathrm{Me{\cdot}CO_2H}$, 0·38 (0·39) $\mathrm{Et{\cdot}CO_2H}$, 0·47 (0·48) $\mathrm{Bu^n{\cdot}CO_2H}$, 0·68 (0·68)	$\mathrm{Me{\cdot}CHI{\cdot}CO_2H}$, 0·55 (0·55) $\mathrm{Pr^n{\cdot}CHI{\cdot}CO_2H}$, 0·71 (0·72 for isomeric $\mathrm{Pr^i{\cdot}CHI{\cdot}CO_2H}$)
$\mathrm{Pr^i} \vert \mathrm{CO{\cdot}Pr^i}$	None	$\mathrm{Me_2CI{\cdot}CO_2H}$, 0·64 (0·65)

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

TABLE 3. *Influence of iodine concentration on the iodinated products formed from non-methyl ketones.*

Temp. = 25°; [Ketone] = 0·0025M; [NaOH] = 0·5M.

	Moles of iodine per mole of ketone				
	Found				
[Iodine] (mole l.$^{-1}$)	Neutral	Acid	Total	Consumed	Extraction (%)
Diethyl ketone					
0·0075	0·18	0·05	0·23	3·00	8·1
0·01	0·53	0·07	0·60	3·82	15·9
0·03	0·87	0·12	0·89	4·54	21·6
0·075	0·70	0·10	0·80	3·55	22·4
n-Butyl ethyl ketone					
0·0075	0·80	0·20	1·00	3·00	33·7
0·01	0·75	0·33	1·08	3·60	30·1
0·03	0·86	0·30	1·16	3·68	31·8
0·075	0·85	0·34	1·19	3·02	39·5

	Moles of iodine per mole of ketone				
	Found				
[Iodine] (mole l.$^{-1}$)	Neutral	Acid	Total	Consumed	Extraction (%)
Di*iso*propyl ketone					
0·0075	0·06	0·36	0·42	1·46	29·3
0·01	0·06	0·36	0·42	1·46	29·3
0·03	0·12	0·58	0·70	1·84	38·0
0·075	0·06	0·38	0·44	1·24	36·8
Diacetyl					
0·01	—	—	1·07	2·66	40·5

TABLE 4. *Iodoform present in the neutral iodinated products.*

Temp. = 25°; [Ketone] = 0·0025M; [Iodine] = 0·01M; [NaOH] = 0·5M.

	Moles of iodine per mole of ketone	
Ketone	Neutral organic form (found by total halogen analysis)	Iodoform (found by spectroscopic absorption)
Diethyl ketone	0·53	0·48
n-Butyl ethyl ketone	0·75	0·71
Di*iso*propyl ketone	0·06	0·05

DISCUSSION

The base-catalysed iodination of methyl ketones proceeds mainly according to equation (1). The corresponding reaction for non-methyl ketones follows a somewhat different course and is rarely accompanied by the production of more than small quantities of iodoform.

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

The factors controlling iodine uptake are similar to those operative with methyl ketones, though comparison shows that with non-methyl compounds much more stringent conditions are required to achieve the limiting uptake of halogen. Since the extent of iodine consumption depends on a balance between the rates of halogenation of the ketone and of disproportionation of hypoiodite to iodate, the necessity of retarding the latter process should be greater with the comparatively unreactive non-methyl ketones. Thus the favourable effect of alkali concentration (Fig. 1), the unfavourable influence of excess of iodine (Fig. 2), and the need for slow addition of the iodine to the pre-mixed ketone–alkali solution (Fig. 4) are even more in evidence with non-methyl ketones as factors controlling the halogen consumption.

The base-catalysed iodination of non-methyl ketones is mechanistically more complex than the corresponding process for methyl ketones. A marked difference is provided by the analytical results, which show that with non-methyl ketones only a small percentage of the consumed iodine is converted into organic form.

Levine and Stephens[4] studied the reaction of propiophenone with sodium hypobromite. Successive bromination at the CH_2 group yields 2 : 2-dibromopropiophenone, which is then hydrolysed to 1-phenylpropane-1 : 2-dione. The latter in presence of sodium hypobromite suffers oxidative fission across the CO–CO bond to give a high yield (>90%) of benzoic and acetic acids. The main overall reaction is thus :

$$Ph{\cdot}CO{\cdot}CH_2{\cdot}CH_3 + 3Br_2 + 8NaOH = Ph{\cdot}CO_2Na + Me{\cdot}CO_2Na + 6NaBr + 5H_2O \quad . \quad (2)$$

and all the consumed halogen reappears in inorganic form. An analogous reaction with aliphatic non-methyl ketones may be responsible for the observed low conversion of consumed halogen into organic form. It is of interest to consider individually the results obtained with the three ketones studied.

(a) *Diethyl ketone.* Initial attack must occur at a CH_2 group, yielding eventually 2 : 2-di-iodopentan-3-one. On hydrolysis, this compound will give pentane-2 : 3-dione which, by analogy with 1-phenylpropane-1 : 2-dione,[4] may undergo oxidation to acetic and propionic acids. Simultaneously, in view of the presence of a $CH_3{\cdot}CO$ group in the intermediate α-diketone, some iodoform will be formed by a normal haloform reaction. The overall reactions may thus include the following :

$$Et_2CO + 3I_2 + 8NaOH = Me{\cdot}CO_2Na + Et{\cdot}CO_2Na + 6NaI + 5H_2O \quad . \quad . \quad . \quad (3)$$

$$Et_2CO + 5I_2 + 8NaOH = CHI_3 + Et{\cdot}CO{\cdot}CO_2Na + 7NaI + 6H_2O \quad . \quad . \quad . \quad . \quad (4)$$

The presence of iodo-acids in the products (including α-iodopropionic acid) suggests that, in addition to the di-iodo-ketone, some of the tri-iodo-compound $CH_3{\cdot}CI_2{\cdot}CO{\cdot}CHI{\cdot}CH_3$ is formed by further iodination of the other methylene group before hydrolysis occurs.

The observed overall iodine uptake (Fig. 1) and the low percentage conversion of consumed iodine into organic form (Table 3) suggest that oxidative fission and a haloform reaction take place concurrently, the former predominating. The widespread occurrence of oxidation with α-diketones is confirmed by analytical measurements with diacetyl (Table 3) ; only about 40% of the consumed iodine is converted into organic form.

(b) n-*Butyl ethyl ketone.* The two α-methylene groups will differ slightly in reactivity, but the wide variety of products (Table 2) suggests that some attack occurs in both positions. The group first halogenated in a particular molecule will preferentially suffer further attack at the same position,[5] forming an αα-di-iodo-ketone. The presence of α-iodo-acids suggests that tri-iodo-ketones are also formed as intermediates. The α-diketones formed on hydrolysis will undergo both oxidative fission, and, when a $CH_3{\cdot}CO$ group is present, a haloform reaction.

The amount of consumed halogen converted into organic form is higher than with diethyl ketone and the difference is mainly accounted for by larger quantities of iodo-acids (Table 3). This implies that with the di-iodo-intermediates from *n*-butyl ethyl ketone, further iodination occurs to a greater extent than with 2 : 2-di-iodopentan-3-one.

(c) *Diisopropyl ketone.* Initial attack must occur at a CH group with the production of a monoiodo-ketone. In order to explain the formation of α-iodo*iso*butyric acid as the

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[4] Levine and Stephens, *J. Amer. Chem. Soc.*, 1950, **72**, 1642.

[5] Bell and Lidwell, *Proc. Roy. Soc.*, 1940, *A*, **176**, 88.

only acid product, this iodo-ketone must undergo fission exclusively across the $CO-CH(CH_3)_2$ bond. Since much of the consumed halogen is converted into inorganic form, an oxidative process of the following type seems to be occurring : *

$$Me_2CI{\cdot}CO{\cdot}Pr^i + I_2 + 2NaOH = Me_2CI{\cdot}CO_2H + Me_2CH{\cdot}OH + 2NaI + H_2O \quad . \quad . \quad (5)$$

Control experiments show that under the conditions employed, no appreciable further halogenation or oxidation of *iso*propyl alcohol takes place.

The above reaction scheme involves conversion of half the consumed iodine into organic form, and the other half into inorganic form. In practice, only about 30% of the halogen taken up is organically bound. With propiophenone,[4] 1·7 moles of hypobromite are consumed per mole of benzoic acid formed, while theoretically only 1·0 mole should be used up. By analogy, reaction (5) may also involve the consumption of more than one mole of iodine, so that more than half of the consumed halogen is used up in this way. It seems that oxidation by hypohalites is accompanied by considerable " wastage " of the active oxidising species.

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* The presence of *iso*propyl alcohol among the products was tested with *p*-dimethylaminobenzaldehyde.[6] If a 1% solution of this reagent in concentrated sulphuric acid is mixed with an aqueous solution containing not less than 0·1% of *iso*propyl alcohol, a violet-red colour appears at the interface. Before the test was applied, the alkaline reaction mixture was distilled to separate neutral organic products from iodide ions, which, if present, would be oxidised to iodine, and mask the red colour.

[6] Auterhoff, *Pharm. Zentralhalle*, 1950, **89**, 293.