601. *Quantitative Aspects of the Base-catalysed Halogenation of Aliphatic Ketones. Part III.*[1] *Comparison of Bromination and Iodination.*

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Work on the base-catalysed iodination of aliphatic ketones has been extended to a study of bromination. The two reactions are similar but the greater stability of hypobromous acid enables less stringent conditions to be employed to obtain the limiting uptake of bromine. Nevertheless, with methyl ketones, reaction rarely gives quantitative yields of bromoform and a fatty acid; bromination of the non-methyl group (leading to the formation of bromo-acids) and of bromoform to carbon tetrabromide occur as side reactions. With non-methyl ketones, a highly complex reaction occurs and the main process appears to be oxidation of the substrate.

Previous papers [1,2] reported an investigation of the base-catalysed iodination of some aliphatic ketones, and it is now believed that the principal iodinating species is hypoiodous acid.[3] In view of the different properties of hypoiodites and hypobromites,[4] it was thought of interest to carry out a parallel study of the bromination of these ketones.

EXPERIMENTAL

The experimental methods were similar to those used in the iodination experiments.[2]

Kinetic Measurements.—Since the reactions are relatively rapid, rate measurements were made in Y-tubes. To prevent bromine vapour from distilling into the alkali–ketone mixture, a separate flask containing the standard bromine solution was placed in the thermostat until the required temperature was attained, and the bromine solution was pipetted into the empty limb of the Y-tubes immediately before the solutions were mixed. Reaction was stopped by pouring the reaction mixture into 10% potassium iodide solution containing just sufficient hydrochloric acid for neutralisation of the alkali, and the liberated iodine was immediately titrated with thiosulphate.

Measurement of Bromine Consumption.—The procedure was the same as with iodine except that 1 ml. of 10% potassium iodide solution was added immediately before acidification; the resulting iodine was rapidly titrated with thiosulphate.

Identification of Acid Reaction Products.—After removal of excess of bromine, organic acids were separated from other products by extraction into ether followed by aqueous ammonia. The ammoniacal solution was analysed for the anions of fatty acids by paper-chromatography.[5]

Quantitative Analysis of Reaction Products.—Excess of halogen was removed with thiosulphate, and the organic constituents were extracted into ether (8 × 5 ml.). Acid products were separated from neutral products by shaking with 0·1N-aqueous sodium hydroxide (3 × 5 ml.) and then extracted back into ether (3 × 5 ml.) after acidification. Both the ethereal solutions were separately analysed for bromine content by the sodium–alcohol method.[6]

RESULTS

Kinetic Measurements.—(a) *Methyl ketones.* Measurements were made of the rates of bromination of acetone, ethyl methyl ketone, methyl *iso*propyl ketone, and *tert.*-butyl methyl ketone. With the alkali present in large excess, the rate of bromine consumption obeys a first-order kinetic law. The velocity constants are substantially the same as those for iodination (Table 1). The slightly higher bromination rates are probably attributable to the greater

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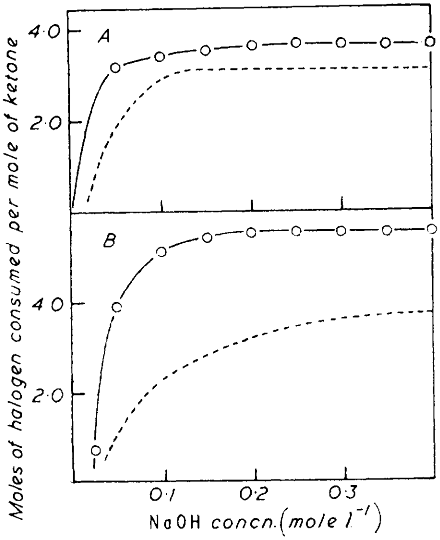
[1] Part I, Cullis and Hashmi, *J.*, 1957, 1548.
[2] Part II, *idem*, *J.*, 1956, 2512.
[3] Morgan, Bardwell, and Cullis, *J.*, 1950, 3190.
[4] Kretzschmar, *Z. Elektrochem.*, 1904, **10**, 798.
[5] Hashmi and Cullis, *Analyt. Chim. Acta*, 1956, **14**, 336.
[6] Drogin and Rosanoff, *J. Amer. Chem. Soc.*, 1916, **38**, 711.

halogen consumption found with bromine (cf. Table 3). It is difficult to apply a correction for this, since the higher bromine uptake is due, at least in part, to slow further bromination of bromoform (cf. Fig. 2).

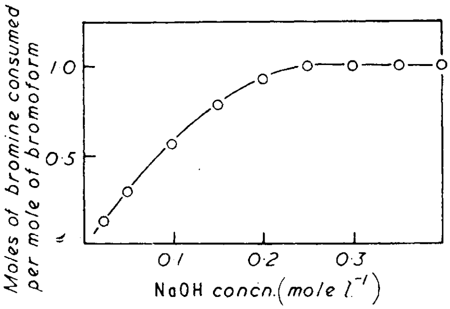
(b) *Non-methyl ketones.* In measurements of the rate of bromination of non-methyl

FIG. 1. *The influence of alkali concentration on halogen consumption.*



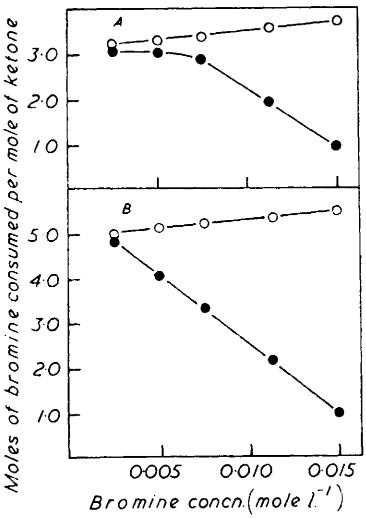
Temp. = 25°; [Ketone] = 0·0025M.
A, $CH_3{\cdot}CO{\cdot}CH_2{\cdot}CH_3$, [Bromine] = 0·012M.
B, $CH_3{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}CH_3$, [Bromine] = 0·0156M.
(The broken lines represent the iodine consumption with [Iodine] = 0·01M.)

FIG. 2. *The influence of alkali concentration on the bromination of bromoform.*



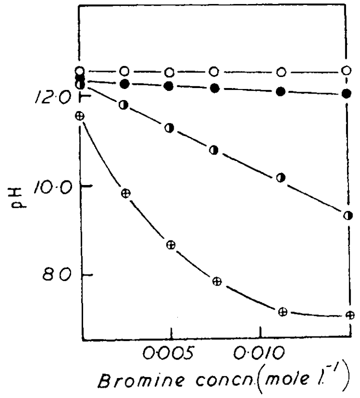
Temp. = 25°; [Bromoform] = 0·0025M; [Bromine] = 0·012M.
Reaction time = 24 hr.

FIG. 3. *The influence of bromine concentration on bromine consumption.*



Temp. = 25°; [Ketone] = 0·0005M; [NaOH] ● = 0·02M, ○ = 0·08M.
A, $CH_3{\cdot}CO{\cdot}CH_2{\cdot}CH_3$. *B*, $CH_3{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}CH_3$.

FIG. 4. *The influence of bromine concentration on the* pH *of reaction mixtures.*



Temp. = 25°; [NaOH] ⊕ = 0·005M, ◑ = 0·02M, ● = 0·08M, ○ = 0·32M.

TABLE 1. *Rate of halogenation of some methyl ketones.*

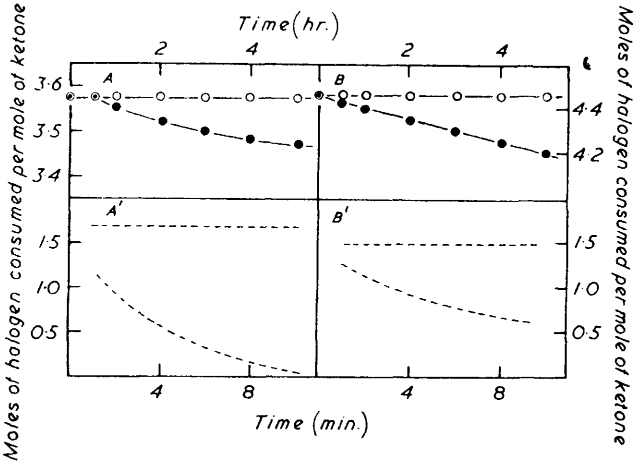
Temp. = 25°; [Ketone] = 0·0025M; [Bromine] = 0·0105M; [Iodine] = 0·01M; [NaOH] = 0·1M.

	Vel. const. (*k*) (10^{-3} sec.$^{-1}$)	
	Bromination	Iodination
Acetone	17·20	16·80
Ethyl methyl ketone	9·43	9·01
Methyl *iso*propyl ketone	7·30	7·16
tert.-Butyl methyl ketone	3·65	3·41

ketones, the halogen concentrations were higher than in the corresponding iodination experiments to accommodate the greater consumption of bromine. The rates of bromination of diethyl ketone, *n*-butyl ethyl ketone and di*iso*propyl ketone are similar to the corresponding iodination rates (Table 2), but there is no evidence of close quantitative agreement. The higher bromination rates can probably be ascribed to the greater bromine uptake (cf. Table 3).

The rates of bromination of all the ketones studied are independent of halogen concentration.[7] With methyl ketones, the velocity is proportional to the hydroxyl-ion concentration, though with non-methyl ketones the behaviour is more complex.

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



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

○ Ketone and sodium hydroxide mixed, bromine added after time *t*.
● Bromine and sodium hydroxide mixed, ketone added after time *t*.

A, $CH_3{\cdot}CO{\cdot}CH_2{\cdot}CH_3$, [Bromine] = 0·012M.
B, $CH_3{\cdot}CH_2{\cdot}CO{\cdot}CH_2{\cdot}CH_3$, [Bromine] = 0·0156M.

(The broken lines represent the iodine consumption with [Iodine] = 0·01M. The upper curves in *A'* and *B'* refer to experiments in which the iodine was added last, and the lower curves refer to experiments in which the ketone was added last.)

Factors Controlling the Extent of Bromine Consumption.—(a) *Influence of alkali concentration.* The uptake of bromine by both methyl and non-methyl ketones increases with alkali concentration. Although, as with iodine, a stoicheiometric excess of alkali must be used to achieve the limiting uptake of bromine, the bromine consumption is considerably higher than the iodine uptake, especially at low alkali concentrations. Some typical results are shown in Fig. 1, and the numbers of moles of bromine and iodine consumed per mole of ketone after 1 hr. are given in Table 3. Still more bromine is consumed, if the reaction is allowed to proceed for more than 1 hr. This is clearly due to the slow further bromination of bromoform to carbon

TABLE 2. *Rates of halogenation of some non-methyl ketones.*

Temp. = 25°; [Ketone] = 0·0025M; [Bromine] = 0·03M; [Iodine] = 0·01M; [NaOH] = 0·1M.

	Vel. const. (k) (10^{-3} sec.$^{-1}$)	
	Bromination	Iodination
Diethyl ketone	3·60	3·31
n-Butyl ethyl ketone	3·98	3·64
Di*iso*propyl ketone	2·45	2·30

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

tetrabromide [8, 9] which, as blank experiments show, is complete after about 24 hr. provided sufficient alkali is present (Fig. 2).

TABLE 3. *Limiting consumption of halogen by ketones.*

Temp. = 25°; [Ketone] = 0·0025M; [Bromine] = 0·012M (methyl ketones), 0·0156M (non-methyl ketones); [Iodine] = 0·01M. Reaction time = 1 hr.

Ketone	Moles of halogen consumed per mole of ketone	
	Bromine	Iodine
Acetone	3·50	3·02
Ethyl methyl ketone	3·70	3·12
Methyl *n*-propyl ketone	3·68	3·15
n-Butyl methyl ketone	3·70	3·02
Methyl *iso*propyl ketone	3·43	2·65
tert.-Butyl methyl ketone	3·05	2·35
Diethyl ketone	5·52	3·77
n-Butyl ethyl ketone	5·20	3·60
Di*iso*propyl ketone	1·92	1·52

TABLE 4. *Acids formed in the base-catalysed bromination of ketones.**

Temp. = 25°; [Ketone] = 0·0025M; [Bromine] = 0·015M; [NaOH] = 0·4M.

Ketone	Acids formed	
	Fatty acids	Bromo-acids
$CH_3{\cdot}CO\vdots{\cdot}CH_3$	$CH_3{\cdot}CO_2H$ 0·38 (0·39)	$CH_2Br{\cdot}CO_2H$ 0·45 (0·44)
$CH_3{\cdot}CH_2{\cdot}CO\vdots{\cdot}CH_3$	$CH_3{\cdot}CH_2{\cdot}CO_2H$ 0·48 (0·48)	$CH_3{\cdot}CHBr{\cdot}CO_2H$ 0·52 (0·52)
$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CO\vdots{\cdot}CH_3$	$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$ 0·58 (0·57)	$CH_3{\cdot}CH_2{\cdot}CHBr{\cdot}CO_2H$ 0·60 (0·61)
$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CO\vdots{\cdot}CH_3$	$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$ 0·68 (0·68)	$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CHBr{\cdot}CO_2H$ 0·70 (0·70)
$(CH_3)_2CH{\cdot}\vdots CO\vdots{\cdot}CH_3$	$(CH_3)_2CH{\cdot}CO_2H$ 0·57 (0·57)	$(CH_3)_2CBr{\cdot}CO_2H$ 0·60 (0·61) $CH_2Br{\cdot}CO_2H$ 0·45 (0·45)
$(CH_3)_3C{\cdot}\vdots CO\vdots{\cdot}CH_3$	$(CH_3)_3C{\cdot}CO_2H$ 0·69 (0·69)	$CH_2Br{\cdot}CO_2H$ 0·44 (0·45)
$CH_3{\cdot}CH_2{\cdot}CO\vdots{\cdot}CH_2{\cdot}CH_3$	$CH_3{\cdot}CO_2H$ 0·38 (0·39) $CH_3{\cdot}CH_2{\cdot}CO_2H$ 0·47 (0·48)	$CH_3{\cdot}CHBr{\cdot}CO_2H$ 0·52 (0·53)
$CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}\vdots CO\vdots{\cdot}CH_2{\cdot}CH_3$	$CH_3{\cdot}CO_2H$ 0·38 (0·39) $CH_3{\cdot}CH_2{\cdot}CO_2H$ 0·47 (0·48) $CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$ 0·68 (0·68)	$CH_3{\cdot}CHBr{\cdot}CO_2H$ 0·52 (0·53) $CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}CHBr{\cdot}CO_2H$ 0·70 (0·70)
$(CH_3)_2{\cdot}CH{\cdot}CO\vdots{\cdot}CH(CH_3)_2$	No fatty acids detected	$(CH_3)_2{\cdot}CBr{\cdot}CO_2H$ 0·61 (0·60)

* 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.

(b) *Influence of bromine concentration.* Equal volumes of different bromine solutions were added to a standard ketone–alkali mixture. From the typical results in Fig. 3 it will be seen that at high alkali concentrations, the consumption of halogen increases slightly with bromine concentration. However, at low alkali concentrations, a large excess of bromine has an unfavourable effect. The decrease in halogen uptake is probably due to depletion of the hydroxyl ion as a result of the reaction : $Br_2 + OH^- = HBrO + Br^-$. Control experiments show a decrease in pH when relatively large amounts of bromine are added to solutions of sodium hydroxide (Fig. 4). The effect is naturally most marked at low alkali concentrations

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[8] Dehn, *J. Amer. Chem. Soc.*, 1909, **31**, 1227.

[9] Fuson and Bull, *Chem. Rev.*, 1934, **15**, 275.

and vanishes when a large excess of sodium hydroxide is present. Addition of bromide ions has no effect on bromine uptake; in this respect, bromination differs from iodination, in which the halogen uptake is decreased by iodide ions, which accelerate disproportionation of hypoiodous acid.[10]

(c) *Order of mixing of reagents.* The consumption of halogen is slightly decreased when the alkali and bromine solutions are mixed and set aside before the ketone is added (Fig. 5). The observed effect is not nearly as pronounced as with iodine.

(d) *Rate of addition of bromine.* The uptake of bromine is increased by slow addition of the halogen, especially at low alkali concentrations. Again the observed effects are not as marked as with iodine.

Identification of Reaction Products.—(a) *Acids.* The R_F values of the fatty acids and brominated organic acids found are given in Table 4. The acids generally correspond to those formed on iodination, indicating that the course of bromination of these ketones is similar to that of iodination.

(b) *Carbon tetrabromide.* With all ketones except di*iso*propyl ketone, colourless crystals separated from the reaction mixtures after long standing, especially when the sodium hydroxide concentration was greater than 0·2M. The liquid was decanted and the crystals were repeatedly washed with water and were recrystallised from alcohol. The m. p.s of the various samples of carbon tetrabromide lay in the range 90—91° (lit., m. p. 90·1°).

Quantitative Analyses of Reaction Products.—Analytical data for the bromination products of methyl and non-methyl ketones are shown in Table 5. The results obtained with methyl ketones show a marked contrast with those for non-methyl ketones. With the former, almost all the bromine taken up is in organically bound form, while with the latter the percentage extraction of the halogen consumed is quite low. These findings are similar to those for iodination and suggest that with non-methyl ketones the halogen performs considerable oxidation of the organic substrate.

TABLE 5. *Bromination products of some ketones.*

Temp. = 25°; [Ketone] = 0·0025M; [Bromine] = 0·012M (methyl ketones), 0·0156M (non-methyl ketones); [NaOH] = 0·4M.

	Moles of bromine per mole of ketone				
	Found				
Ketone	Neutral	Acid	Total	Consumed	Extraction (%)
Acetone	3·28	0·13	3·41	3·48	98·0
Ethyl methyl ketone	3·33	0·29	3·62	3·70	97·9
Methyl *n*-propyl ketone	3·35	0·25	3·60	3·70	97·4
n-Butyl methyl ketone	3·30	0·25	3·55	3·60	98·6
Methyl *iso*propyl ketone	3·10	0·22	3·32	3·40	98·3
tert.-Butyl methyl ketone	2·85	0·22	3·07	3·11	98·3
Diethyl ketone	0·49	0·20	0·69	5·52	12·5
n-Butyl ethyl ketone	0·68	0·30	0·98	5·20	18·9
Di*iso*propyl ketone	0·17	0·40	0·57	1·92	30·2

DISCUSSION

Nature of the Brominating Species.—The bromination and iodination of ketones have many features in common. By analogy with iodination, the brominating species is probably hypobromous acid. This is 300 times more stable than hypoiodous acid,[4] and there is only a relatively small tendency for the acid to disproportionate. In the present study of the bromination of ketones, the results are in agreement with the greater stability of hypobromous acid, and to achieve high uptake of bromine it is not necessary to control the experimental conditions as strictly as in iodination.[1,2] Thus the bromine consumption reaches a limiting value at lower alkali concentrations, and the effect of the order of mixing of the reagents is much less marked for bromination. Further the unfavourable effect of

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[10] Li and White, *J. Amer. Chem. Soc.*, 1943, **65**, 335.

excess of halogen at low alkali concentrations is not apparent unless comparatively large quantities of bromine are added, because the pH remains high enough to stabilise hypobromous acid.

Methyl Ketones.—Under the experimental conditions used, the bromoform produced is further brominated to carbon tetrabromide; thus the theoretical limiting molar uptake of bromine with methyl ketones is 4·0. However, the molar consumption of bromine (measured after 1 hr.) is always less than the above value, since conversion of bromoform into carbon tetrabromide is slow.

The analytical results show that a small proportion of the consumed bromine is in acid form, while the major part is found as bromoform and carbon tetrabromide. The bromo-acids identified in the products correspond with the iodo-acids found on iodination, and their formation indicates some attack on the non-methyl group during halogenation in addition to the normal attack on the methyl group.

Non-methyl Ketones.—To achieve the limiting uptake of bromine, the same experimental conditions should be used as with methyl ketones. This suggests that the brominating species is again hypobromous acid.

The molar consumption of bromine is considerably greater than that of iodine. However, the analytical results show that only 10—30% of the bromine consumed is organically bound. With the non-methyl compounds, hypobromous acid thus appears to be an even more powerful oxidising agent than hypoiodous acid.[11] The various fatty acids and bromo-acids identified in the products correspond with the acids found on iodination and this no doubt indicates an essential similarity in reaction mechanism.

Conclusion: Use of Methods involving Base-catalysed Halogenation for the Quantitative Analysis of Methyl Ketones.—Iodination processes are generally unsatisfactory for the determination of methyl ketones (with the possible exception of acetone), since the experimental conditions must be very carefully adjusted in order to maintain an adequate supply of hypoiodous acid. Even if this is done, however, the occurrence of some halogenation of the non-methyl group (simultaneously with attack of the methyl group) and of some premature hydrolysis of intermediate iodo-ketones ensures that reaction rarely occurs according to the overall equation:

$$CH_3{\cdot}COR + 3I_2 + 4NaOH = CHI_3 + R{\cdot}CO_2Na + 3NaI + 3H_2O$$

On account of the greater stability of hypobromous acid than of hypoiodous acid, it might be expected that the use of bromine would reduce the stringency of the conditions needed to maintain a sufficient supply of the halogenating species. This is found to be the case, but nevertheless bromination is no more satisfactory than iodination as a basis of methods for the determination of methyl ketones. For, in addition to the continued occurrence of the side reactions referred to above, there is the added complication that in alkaline solution bromoform is slowly further halogenated to carbon tetrabromide.

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[11] Cf. Latimer, "Oxidation Potentials," Prentice-Hall Inc., New York, 1952.