355. *An Investigation of the Course of the Reformatsky Reaction.*

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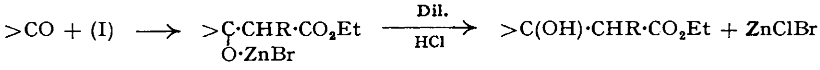
Evidence additional to that adduced by Dain (*J. Russ. Phys. Chem. Soc.*, 1896, **28**, 593) has been provided for the production of intermediate compounds in the course of the Reformatsky synthesis of β-hydroxy-esters. Solid products have been isolated which have been shown to be derived from the components zinc, α-halogeno-ester, and ketone or aldehyde. The product which is deposited after the interaction of zinc and the α-halogeno-ester alone is now regarded as formed by self-condensation of the transitory primary intermediate product. This may be precipitated alongside the secondary intermediate product, and so, after hydrolysis, yield a β-ketonic ester as impurity in the final product of the synthesis.

In the Reformatsky reaction an α-halogeno-carboxylic ester, usually the bromo-ester, is condensed with an aldehyde or ketone, in the presence of zinc, to give a β-hydroxy-ester. The reaction is carried out in two stages: first, the reactants are refluxed in a non-hydroxylic solvent and then the product is hydrolysed by cold dilute acid. Reformatsky (*J. pr. Chem.*, 1896, **54**, 469) postulated a course whereby the α-halogeno-ester forms, with the zinc, a primary intermediate (I), which with the aldehyde or ketone forms a secondary intermediate (II), which can be hydrolysed to the β-hydroxy-ester:

$$\text{Br·CHR·CO}_2\text{Et} + \text{Zn} \longrightarrow \text{BrZn·CHR·CO}_2\text{Et} \qquad \text{(I.)}$$



$$>\text{CO} + \text{(I)} \longrightarrow >\underset{\text{O·ZnBr}}{\text{C}}\text{·CHR·CO}_2\text{Et} \xrightarrow[\text{HCl}]{\text{Dil.}} >\text{C(OH)·CHR·CO}_2\text{Et} + \text{ZnClBr}$$

(II.)

Experimental confirmation was obtained by Dain (*J. Russ. Phys. Chem. Soc.*, 1896, **28**, 543) who isolated a yellow solid from a mixture of zinc and ethyl α-bromo*iso*butyrate which gave a bromine analysis in fair agreement with the formula (I). Comparable results were obtained with zinc and ethyl α-bromo*iso*valerate, but no other tests were carried out to prove the identity of these solids.

From a mixture of zinc, benzaldehyde, and ethyl α-bromopropionate Dain isolated a yellow solid giving a bromine analysis which signified a secondary intermediate (II), the identity being confirmed by hydrolysis with dilute acid to the expected β-hydroxy-ester. Similar observations were made when using the α-bromo-*iso*butyrate and -*iso*valerate.

Little further investigation has since been made of the solids formed during Reformatsky reactions although their occurrence has been mentioned incidentally by several workers. The widely varying yields from case to case and the unreactivity of certain ketones in the reaction have led to studies of the by-products. Hann and Lapworth (*Proc. Chem. Soc.*, 1903, **19**, 189) claimed to have isolated ethyl γ-bromoacetoacetate from reactions employing ethyl bromoacetate, and presumed it to be formed by the action of the primary intermediate on the carbethoxyl group of unchanged bromo-ester. This observation was not confirmed by Hussey and Newman (*J. Amer. Chem. Soc.*, 1948, **70**, 3024) who, nevertheless, isolated unhalogenated β-ketonic carboxylic esters, and simple esters (the reduced α-bromo-esters), from reactions with and without a ketone. Zeltner (*Ber.*, 1908, **41**, 589; *J. pr. Chem.*, 1908, **78**, 97) found that where the zinc was replaced by magnesium no β-hydroxy-esters were formed : instead, reduced esters and β-ketonic esters were isolated. The β-ketonic esters were considered by Zeltner to be formed by the condensation of two molecules comparable with Reformatsky's primary intermediate (I). Hussey and Newman (*loc. cit.*) offer a less convincing explanation of the production of β-ketonic esters, and the formation of the reduced ester is considered to arise from a reaction of the enolic form of the ketone (cf. Newman, *J. Amer. Chem. Soc.*, 1940, **62**, 870; 1942, **64**, 2131), a view which is however inconsistent with facts such as the formation of methyl crotonate in the Reformatsky reaction involving methyl γ-bromocrotonate and benzaldehyde (Jones, O'Sullivan, and Whiting, *J.*, 1949, 1415).

The purpose of our investigation was to determine afresh the composition of the solid deposits which separate in Reformatsky reactions and, also, to ascertain whether they are truly intermediates.

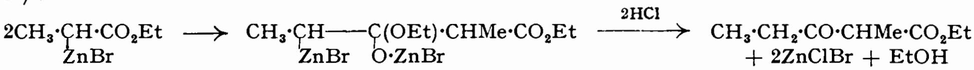
A boiling mixture of benzophenone, ethyl bromoacetate, and zinc in benzene deposited a yellow solid, zinc and bromine analyses of which indicated a formula $BrZn{\cdot}O{\cdot}CPh_2{\cdot}CH_2{\cdot}CO_2Et$, *i.e.*, a secondary intermediate of Reformatsky's type (II) (see Table). This solid gave an almost quantitative yield of the appropriate β-hydroxy-ester, whereas no trace of such an ester could be isolated from the remainder of the reaction mixture, and it thus appears to be a true intermediate.

No solid separated from a boiling mixture of benzaldehyde, ethyl α-bromopropionate, and zinc in benzene, although an unsatisfactory deposit was produced on addition of light petroleum (b. p. 60—80°). A stable yellow solid was eventually obtained from these reactants on three months' storage without a solvent, and the zinc and bromine analyses of the product agreed well with formula (II). Experience with benzaldehyde, ethyl bromoacetate, and zinc was similar; although this solid gave, after hydrolysis, cinnamic acid as expected, analyses were not as satisfactory as in the previous cases owing to contamination with metallic zinc.

Benzophenone and ethyl α-bromopropionate (unlike benzophenone and ethyl bromoacetate) failed to give a deposit when refluxed with zinc in benzene but yielded a pale yellow solid when this solution was diluted with light petroleum. This compound, when treated with cold dilute acid, yielded the appropriate ethyl β-hydroxy-ββ-diphenyl*iso*butyrate, but the analyses for *both* zinc and bromine were high. Acetophenone or *cyclo*hexanone with ethyl bromoacetate and zinc yielded similar " impure " solid intermediates (see Table). The reason for these high analyses became apparent when the condensation of 1-benzoylnaphthalene with ethyl α-bromopropionate was attempted. When these two components were heated with zinc in benzene the metal dissolved but after hydrolysis about 90% of the initial ketone was recovered. In a similar

		Formula of expected	Found, %.		Required, %.	
Ester.	CO-compound.	product.	Zn.	Br.	Zn.	Br.
$CH_2Br{\cdot}CO_2Et$	$COPh_2$	$C_{17}H_{17}O_3BrZn$	15·7	19·1	15·8	19·3
,, ...	Ph·CHO	$C_{11}H_{13}O_3BrZn$	21·5	20·6	19·3	23·6
,, ...	COPhMe	$C_{12}H_{15}O_3BrZn$	21·3	26·0	18·6	22·7
,, ...	*cyclo*Hexanone	$C_{10}H_{17}O_3BrZn$	22·5	27·2	19·7	24·2
$CHMeBr{\cdot}CO_2Et$	Ph·CHO	$C_{12}H_{15}O_3BrZn$	18·7	22·6	18·6	22·7
,, (2 expts.)	$COPh_2$	$C_{18}H_{19}O_3BrZn$	18·2, 18·7	22·5, 21·6	15·3	18·7

experiment the solid which separated during reaction was isolated and found to contain about twice the amount of bromine required for the secondary intermediate (II). Further, the same solid was obtained from a reaction in which the ketone was omitted, and when treated with dilute acid, it yields the β-ketonic ester, ethyl α-propionylpropionate. The most obvious explanation is the condensation of two molecules of the primary intermediate (I) (cf. Zeltner, *loc. cit.*, who suggested that similar compounds are produced in the reaction of magnesium with a bromo-ester):



$$2\mathrm{CH_3\cdot\underset{ZnBr}{CH}\cdot CO_2Et} \longrightarrow \mathrm{CH_3\cdot\underset{ZnBr}{CH}—\underset{O\cdot ZnBr}{C}(OEt)\cdot CHMe\cdot CO_2Et} \xrightarrow{2\mathrm{HCl}} \mathrm{CH_3\cdot CH_2\cdot CO\cdot CHMe\cdot CO_2Et} + 2\mathrm{ZnClBr} + \mathrm{EtOH}$$

(III.)

Analyses for the intermediate (two samples; Found: Zn, 27·1, 27·9; Br, 31·8, 30·8. $C_{10}H_{18}O_4Br_2Zn_2$ requires Zn, 26·5; Br, 32·4%) agree with the suggested formula (III) if contamination with a little metallic zinc is postulated.

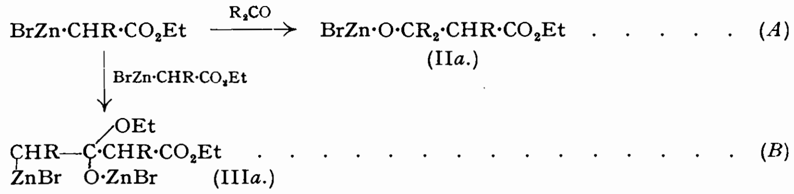
Attempts to produce a β-ketonic ester complex from ethyl bromoacetate and zinc have, so far, only yielded tars, although the existence of such a complex is highly probable since Hussey and Newman (*loc. cit.*) have isolated ethyl acetoacetate from appropriate Reformatsky reactions. Moreover, we have been able to isolate ethyl α-*iso*butyryl*iso*butyrate after hydrolysis of the solid product deposited when zinc reacts with ethyl α-bromo*iso*butyrate, and also the solid analysed correctly.

The formation of these β-ketonic ester complexes explains the high zinc and bromine contents of some of the isolated β-hydroxy-ester complexes. Co-precipitation of the former complex with the latter will cause both the zinc and the bromine content of the resultant deposit to exceed those theoretically required by the pure β-hydroxy-ester complex. Purification by crystallisation has not been possible, owing to the insolubility in suitably inert solvents. It is true that some of these complexes have been isolated by precipitation from apparent solution in benzene but it is thought that these are very fine suspensions rather than true solutions.

The β-ketonic ester complexes were isolated by us by the method employed by Dain for his so-called "primary intermediates" (I). It is reasonably certain, therefore, that Dain's compounds were the β-ketonic ester complexes analogous to (III).

We believe, therefore, that the primary intermediate is soluble and has a rather transitory existence, and that the reactions involved are:

$$\mathrm{R\cdot CHBr\cdot CO_2Et} + \mathrm{Zn} \rightleftharpoons \mathrm{BrZn\cdot CHR\cdot CO_2Et}\quad \text{(I.)}$$



$$\begin{tikzcd} \mathrm{BrZn\cdot CHR\cdot CO_2Et} \arrow[r, "\mathrm{R_2CO}"] \arrow[d, "\mathrm{BrZn\cdot CHR\cdot CO_2Et}"] & \underset{\text{(II}a.)}{\mathrm{BrZn\cdot O\cdot CR_2\cdot CHR\cdot CO_2Et}} \quad . \; . \; . \; . \; . \; . \; (A) \\ \mathrm{\underset{ZnBr}{CH}R—\underset{O\cdot ZnBr}{C}\overset{OEt}{\diagup}\cdot CHR\cdot CO_2Et}\quad \text{(III}a.) & . \; . \; . \; . \; . \; . \; . \; . \; . \; . \; (B) \end{tikzcd}$$

$$\text{(II}a) \xrightarrow{\mathrm{HX}} \mathrm{HO\cdot CR_2\cdot CHR\cdot CO_2Et} + \mathrm{ZnBrX}$$

$$\text{(III}a) \xrightarrow{2\mathrm{HX}} \mathrm{CH_2R\cdot CO\cdot CHR\cdot CO_2Et} + 2\mathrm{ZnBrX} + \mathrm{EtOH}$$

The amount of β-ketonic ester formed as a by-product will depend on the relative rates of the competing processes (*A*) and (*B*); if a sterically hindered ketone is used, *e.g.*, 1-benzoyl-naphthalene, the reaction (*B*) may be dominant [in some cases Hussey and Newman (*loc. cit.*) have shown that the main product can be the β-ketonic ester]. Also, the complex (III*a*) may react further with the ester, and thus lead to the tars produced in many Reformatsky reactions.

The formation of reduced esters is explained by the above scheme as caused by hydrolysis of the primary intermediate (I) which has not undergone reaction (*A*) or (*B*).

EXPERIMENTAL.

Reformatsky reactions were conducted, and solid intermediate products separated, as described below; the procedures varied in detail, although 0·1 molar quantities of the organic reactants were generally employed and 0·1 atomic proportion of zinc.

The α-bromo-esters and liquid aldehydes and ketones were dried and distilled before use. The zinc foil or shavings were freshly cleaned by successive washings with 2·5% hydrochloric acid, distilled water, alcohol, and ether, and dried for 1 hour at 100°. In the condensations where a solvent was employed the initial reaction was allowed to subside before the whole was refluxed on a steam-bath.

Benzophenone and Ethyl Bromoacetate.—Benzophenone (18·2 g.), ethyl bromoacetate (16·5 g.), and zinc (6·5 g.) were heated in a mixture of benzene (40 ml.) and toluene (35 ml.). Reaction occurred with some vigour and almost all the zinc dissolved in 2 hours; a solid gradually separated during the reaction. When the mixture had cooled the supernatant liquid was removed by means of a filter-tube, and the residual solid washed several times with dry benzene. Finally the pale yellow solid was removed as a suspension in benzene, recovered on a sintered-glass filter, and dried in a vacuum-desiccator, the whole operation being conducted in dry air (for analysis see Table).

This solid (5·2 g.) gave ethyl β-hydroxy-ββ-diphenylpropionate (3·3 g., 97%).

Benzophenone and Ethyl α-Bromopropionate.—Benzophenone (18·2 g.), ethyl α-bromopropionate (18·2 g.), and zinc (6·5 g.) were refluxed in benzene (25 ml.) for 1½ hours. The bulk of the zinc dissolved, leaving a clear liquid which was passed through a sintered-glass filter and poured slowly into light petroleum (b. p. 60—80°) (30 ml.). A white solid separated which was washed with further light petroleum and dried in a vacuum-desiccator (for analysis see Table).

Hydrolysis with 2N-sulphuric acid gave ethyl β-hydroxy-ββ-diphenyl*iso*butyrate.

Benzaldehyde and Ethyl Bromoacetate.—Benzaldehyde (10·6 g.), ethyl bromoacetate (16·5 g.), and zinc (6 g.), in a flask closed with a cork and wax, were kept at 0° for 12 hours and then at room temperature for 18 months, whereafter they comprised a yellow paste and a little unchanged zinc. Addition of benzene (10 ml.) produced a thick yellow suspension capable of being poured from the residual zinc. Further dilution of this liquid with benzene produced a yellow viscous material, but by addition of light petroleum (b. p. 60—80°) to this, a few ml. at a time, a pale yellow solid was obtained which was filtered off and washed with further light petroleum in a current of dry air (for analysis see Table).

Treatment first with 2N-sulphuric acid and then with 10% aqueous potassium hydroxide yielded cinnamic acid.

Benzaldehyde and Ethyl α-Bromopropionate.—Benzaldehyde (10·6 g.), ethyl α-bromopropionate (18·2 g.), and zinc (6·5 g.) were heated for 1 hour in benzene (30 ml.). A brisk reaction occurred and most of the zinc dissolved, to give a clear liquid from which no solid settled. This liquid was passed through a sintered-glass filter and poured slowly into light petroleum (b. p. 60—80°) (30 ml.), whereupon a deep yellow solid separated which, however, decomposed in a few minutes although out of contact with moist air.

The same quantities of reactants, in the absence of the solvent, were then set aside as in the case of benzaldehyde and ethyl bromoacetate; after 3 months all of the zinc had been digested. The resultant yellow paste was diluted with anhydrous ether, and on addition of light petroleum (b. p. 60—80°) a pale yellow solid was recovered (for analysis see Table).

Acetophenone and Ethyl Bromoacetate.—Acetophenone (12 g.), ethyl bromoacetate (16·5 g.), and zinc (6 g.) in benzene (40 ml.) were refluxed; the reaction proceeded with some vigour. Most of the zinc dissolved, leaving a deep-orange liquid which was decanted from unchanged zinc and poured into ether (40 ml.), giving a suspension from which an orange-coloured solid was precipitated by light petroleum (b. p. 60—80°) (40 ml.): this was washed with ether and dried in a vacuum-desiccator (for analysis see Table).

cyclo*Hexanone and Ethyl Bromoacetate.*—*cyclo*Hexanone (9·8 g.), ethyl bromoacetate (16·5 g.), and zinc (6·5 g.) in benzene (50 ml.) were refluxed for 3 hours. After a brisk reaction a white opalescent liquid was left which on addition of light petroleum (b. p. 60—80°) deposited a white solid (for analysis see Table).

1-*Benzoylnaphthalene and Ethyl α-Bromopropionate.*—1-Benzoylnaphthalene (4 g.), ethyl α-bromopropionate (3 g.), and zinc (1·1 g.) in benzene (20 ml.) were refluxed; all the zinc dissolved and a dark orange-coloured liquid remained which was treated with cold 2N-sulphuric acid. From the solid product, *ca.* 3·5 g. of the original ketone were alone recovered.

In a similar experiment an intermediate yellow solid was isolated [Found: Br, 29·8. Calc. for $C_{22}H_{21}O_3BrZn$ (intermediate of type II): Br, 16·7%].

Ethyl α-Bromopropionate and Zinc.—Ethyl α-bromopropionate (36 g.), zinc (13 g.), and benzene (50 ml.) were refluxed for 3 hours, most of the zinc dissolving and leaving an orange-coloured liquid. The liquid was diluted with dry ether (50 ml.); on addition of light petroleum (b. p. 60—80°) a yellow solid was deposited (for analyses see p. 1572).

This solid, hydrolysed with cold 2N-sulphuric acid, gave ethyl α-propionylpropionate, b. p. 200° (Hellon and Oppenheim, *Ber.*, 1877, **10**, 700, give b. p. 199°) (Found: C, 60·3; H, 8·7. Calc. for $C_8H_{14}O_3$: C, 60·7; H, 8·8%).

This ester (5 g.) was converted into the phenylpyrazolone derivative, m. p. (after recrystallisation from 5% alcohol) 108—110° (Hussey and Newman, *loc. cit.*, for 3-ethyl-4-methyl-1-phenyl-5-pyrazolone give m. p. 111°).

*Ethyl α-Bromo*iso*butyrate and Zinc.*—Ethyl α-bromo*iso*butyrate (100 g.), zinc (32·5 g.), and benzene (200 ml.) were refluxed for 2 hours, whereupon all the zinc seemed to have become digested, leaving a pale yellow opalescent liquid from which a pale yellow solid was precipitated by an equal volume of anhydrous ether (Found: Zn, 30·1; Br, 32·8. $C_{12}H_{22}O_4Br_2Zn_2$ requires Zn, 25·1; Br, 30·7%). A similar solid obtained from a mixture of the α-bromo-ester and zinc which had been set aside at room temperature for several months gave on analysis: Zn, 30·4; Br, 33·0%.

This solid, with 2N-sulphuric acid, yielded ethyl α-*iso*butyryl*iso*butyrate, b. p. 200° (Zeltner, *loc. cit.*, gives b. p. 202—203°) (Found: C, 63·1; H, 9·2. Calc. for $C_{10}H_{18}O_3$: C, 64·5; H, 9·7%).

Analyses.—Determinations of zinc and bromine were conducted as follows:

Zinc. The solid was incinerated to zinc oxide (the method used by Dain); or, better, the material was dissolved in acid, and (i) the solution titrated against standard potassium ferrocyanide, with diphenylbenzidine as an indicator, or (ii) the zinc was precipitated as zinc ammonium phosphate and converted into pyrophosphate. The last method was found the most reliable.

Bromine. The solid was dissolved in dilute nitric acid (10%), and the bromine determined by Volhard's method.

Other analyses were conducted by Drs. Weiler and Strauss.

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