THE STEREOCHEMISTRY OF SOME REACTIONS OF BROMINE WITH
THE SILVER SALTS OF OPTICALLY ACTIVE CARBOXYLIC ACIDS.

Being a Thesis submitted to the University of
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by

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Abstract of Thesis.

A number of reactions in which "positive" bromine is an intermediate reagent have been investigated and optically active compounds have been used in order to study the mechanisms of some of these reactions.

The preparation and resolution of 2-ethylhexanoic and \( \alpha \)-phenylpropionic acids and the preparation of \( \alpha \)-(p-nitro-phenyl)-propionic acid are described. The reactions of the silver salts of these acids with two equivalents of bromine have been investigated; from optically active silver 2-ethylhexanoate specimens of optically active 3-bromoheptane were obtained. A reaction mechanism in accord with this result is proposed.

Attempts to effect an asymmetric synthesis by the addition of \((+)-\) and \((-)-2\)-ethylhexanoyl hypobromite to styrene, followed by alkaline hydrolysis, yielded optically inactive phenyl glycol.

The bromine cation formed by the addition of silver nitrate to acidic solutions of bromine, effected substitution in the phenyl nucleus of \( \alpha \)-phenylpropionic acid. When bromine cations were allowed to react in the presence of acetate ions with styrene and cyclo-hexene, the quantities of the corresponding bromo-acetates which were formed were substantially
greater, and the quantities of the dibromides less, than those formed in parallel experiments in which bromide ions were not removed.
The work described in this Thesis has been carried out at Battersea Polytechnic under the direction of Dr. J. Kenyon, F.R.S. The author wishes to thank Dr. Kenyon for his continued interest in the progress of this work, Dr. C. L. Arcus for his invaluable advice and criticism, and the Department of Scientific and Industrial Research for a Maintenance Allowance.
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HISTORICAL INTRODUCTION.

The literature concerning the stereochemistry of the reactions of halogens with metallic salts of carboxylic acids consists only of five papers, published during the past three years; the chemical nature of these reactions, however, has been studied fairly fully over a much longer period of time, the earliest experimental results being published by Féligot (C.r. 1836 3 9.) who, by allowing bromine to react with silver benzoate, prepared m-bromo-benzoic acid.

The first mention of the interaction of bromine with the silver salts of carboxylic acids to yield alkyl bromides appears to have been made by Borodine (Ann. 1861 119 123.), who, having obtained monobromovaleric and monobromobutyric acids by passing bromine vapour over the silver salts of valeric and butyric acids respectively, attempted to prepare monobromoaetic acid in the same way. His experiment yielded, in place of the expected acid, only a mixture of gases which, on further investigation, were found to be methyl bromide and carbon dioxide, the reaction being formulated thus:

\[ \text{CH}_3\cdot\text{COOAg} + \text{Br}_2 = \text{CH}_3\text{Br} + \text{CO}_2 + \text{AgBr}. \]

Very shortly after this Schützenberger (Ann. 1861 120 113.) postulated that compounds of the type R.\(\text{COO}\)X, where R
is an alkyl radical and X is a halogeno- or cyano- group, could be prepared by reaction between a metallic carboxylate and a mixed halogen compound and quoted as examples:

\[ \text{CH}_3\text{COONa} + \text{ICl} = \text{CH}_3\text{COOI} + \text{NaCl} \]
\[ \text{CH}_3\text{COOAg} + \text{ICN} = \text{CH}_3\text{COOCH} + \text{AgI}. \]

the metallic ion being replaced in each case by the more electropositive ion of the mixed halogen.

As evidence as to the possibility of this reaction, he claimed to have prepared acetyl hypochlorite (\(\text{CH}_3\text{COOCl}\)) and from it the corresponding hypobromite and hypoiodite. By passing chlorine monoxide through anhydrous acetic acid at a low temperature, followed by the removal of excess reagent by warming to \(30^\circ\), he obtained a liquid of empirical formula \(\text{C}_2\text{H}_3\text{O}_2\text{Cl}\), i.e. monochloroacetic acid. The properties of this compound were, however, rather different to those of chloroacetic acid and the formula \(\text{CH}_3\text{COOCl}\) was assumed for this product. The following reactions were given as examples:

\[ \text{CH}_3\text{COOCl} + \text{H}_2\text{O} = \text{HClO} + \text{CH}_3\text{COOH} \]

\[ \text{CH}_3\text{COOCl} \xrightarrow{\text{violently}} (\text{CH}_3\text{CO})_2\text{O} + \text{Cl}_2 + \text{O}_2 \]

\[ 2\text{CH}_3\text{COOCl} + \text{I}_2 = 2\text{CH}_3\text{COOI} + \text{Cl}_2 \]

\[ 2\text{CH}_3\text{COOI} \xrightarrow{\text{at } 100^\circ} \text{CH}_3\text{COOCH}_3 + \text{CO}_2 + \text{I}_2. \]
He also heated dry sodium acetate with iodine monochloride and obtained a mixture of sodium chloride and the postulated "essigsaurer Jod" or acetyl hypiodite, from which, however, the latter could not be separated, although the reactions given above were noted. Reaction with excess of iodine monochloride yielded methyl chloride, carbon dioxide, iodine and sodium chloride. Sodium butyrate was found to react in a similar manner.

By dissolving bromine in acetyl hypochlorite the production of the hypobromite was claimed, although the product exploded after 1-2 hours. Attempts to prepare the sulphur analogues by reaction of the hypochlorite with sulphur, and of sodium acetate with sulphur dichloride, resulted only in the formation of acetic anhydride, sulphur dioxide and sulphur, this being taken to illustrate the instability of acetyl hyposulphite. The reaction of sodium benzoate with iodine monochloride gave iodobenzene, carbon dioxide, sodium chloride and higher iodinated compounds.

This work of Schützenberger suffered severe criticism by Aronheim (Ber. 1879 12 26.) who showed that the supposed "essigsaurer Chlore" was probably merely a mixture of acetic anhydride and chlorine monoxide. Grandmougen (Rev. Chim. Ind. 1931 42 332.) agreed with Aronheim and suggested a possible structural formula for a mixed compound, i.e.:
He similarly postulated that the corresponding iodo-compound was a mixture of acetic anhydride and iodine dioxide or possibly of the structure, \( \text{I}(\text{OOC(CH}_2)_2)\), this being analogous to iodine iodate, \( \text{I}(	ext{IO}_3)_2 \).

Birnbaum and Reinherz (Ber. 1883 15 456.) heated silver benzoate with iodine at 100° and obtained, after a vigorous reaction, a mixture of iodo-benzoic acid, \( p \)-iodo-diphenyl and benzoic acid. Using silver salicylate under similar conditions the resultant products were mono- and di-iodosalicylic acids, together with free salicylic acid.

Cofman (J.C.S. 1919 115 1040.), having shown that the iodination of phenols was due to hypiodous acid or iodine hydroxide, \( \text{IOH} \), in which the iodine atom may be positive, proposed the following mechanism for Birnbaum's reaction, assuming a trace of water to be present:

\[
\begin{align*}
\text{HO.C}_6\text{H}_4\text{COOAg} + \text{I}_2 + \text{H}_2\text{O} & = \text{HO.C}_6\text{H}_4\text{COOH} + \text{AgI} + \text{HOI} \\
\text{HO.C}_6\text{H}_4\text{COOH} + \text{HOI} & = \text{HO.C}_6\text{H}_4\text{I}\text{COOH} + \text{H}_2\text{O}.
\end{align*}
\]

Simonini (Monatshefte, 1892 13 320.), however, by heating silver acetate with iodine to 100° obtained methylacetate in 50% yield, together with some acetic acid but no unsaturated compounds. The corresponding esters were similarly
obtained by the use of the silver salts of butyric and caproic acids.

Wieland and Fischer (Ann. 1925 446 49.) carried out experiments similar to those of Simonini and proposed a free radical mechanism for the decomposition of their postulated intermediate compound. They gave two possible structures for this intermediary:

\[
\begin{align*}
\text{(A)} & \quad \left[ Ag\cdot OOC.R \right] I \\
\text{(B)} & \quad \left[ I\cdot OOC.R \right] Ag
\end{align*}
\]

of which (A) was the more probable, since the addition of iodine caused no precipitation of silver iodide.

The formation and decomposition of the complex were given as follows:

\[
2R\cdot COOAg + I_2 = (R\cdot COO)_2AgI + AgI
\]

\[
(R\cdot COO)_2AgI \rightarrow 2R\cdot COO^- + AgI
\]

\[
R\cdot COO^- \rightarrow R^- + CO_2
\]

\[
R\cdot COO^- + R^- = R\cdot COOR.
\]

Prevost (C.r. 1933 196 1129.) claimed to have isolated a complex of silver benzoate with iodine, formed by crystallisation of the components from benzene. The solution was not stable in moist air, but the dry yellowish-white solid
appeared quite stable. An important property of this complex was its ability to react with an olefine to give a di-ester. That this reaction occurred in two stages was proved by the isolation of the intermediate mono-ester-mono-bromide by addition of the silver benzoate-bromine complex to stilbene in the cold, reaction at higher temperatures leading to the formation of the di-ester, (C.r. 1933 197 1661.):

$$2R_2COOAg + I_2 = (R_2COO)_2AgI + AgI$$
$$R_2COOAg + R'.CH:CH.R' = R_2COO.CHR'.CHR'.Ag + AgI$$
$$R_2COO.CHR'.CHR'.I + R_2COOAg = R_2COO.CHR'.CHR'.OOCR + AgI.$$  

This property of addition to double bonds is also possessed by acyl hypohalites and it is this reaction which has been largely used in proof of their separate existence. Brunel (Ann. Chim. et Phys. 1905 (8) 6 229.) by adding certain mercuric salts and iodine alternately to cyclohexene obtained several disubstituted cyclohexanes, among them being 2-iodo-cyclohexyl acetate,

$$C_6H_5 + HgCl_2 + I_2 = C_6H_5Cl + HgCl$$
$$C_6H_5 + HgCl + I_2 = C_6H_5Cl + HgI_2$$
$$23C_6H_5 + Hg(CH_3COO)_2 + 2I_2 = 23C_6H_5I(CH_3COO) + HgI_2.$$  

The first convincing proof of the separate existence of acyl hypohalites came from Birkensbach, Goubeau and Berninger (Ber. 1932 65 1339.) who, having found that the
reaction of iodine with silver perchlorate in organic media led to substitution, apparently due to the formation of iodine perchlorate. (Birkenbach and Goubeau, Ber 1932 65 393.), decided to treat a series of silver salts with iodine and cyclohexene in order to determine whether the formation of mixed halogen compounds of the type IClO₄ was a general result of these reactions. It had already been shown, (Birkenbach et al., Ber. 1931 64 218, 961.), that the interaction of silver perchlorate or silver cyanate with iodine and cyclohexene resulted in 2-ido-cyclohexyl perchlorate and 2-ido-cyclohexyl isocyanate respectively being obtained. The series of silver salts used consisted of the chloride, nitrate, nitrite, iodate, periodate, cyanide, acetate and benzoate. Only in the case of the nitrate did no reaction occur; with the iodate and periodate, much oxidation occurred thus preventing the isolation of the addition compounds, while the use of silver cyanide resulted only in the formation of cyanogen iodide which does not add to double bonds. The reactions of the chloride, nitrite, acetate and benzoate were analogous to that of the perchlorate.

That it was not the molecular intermediate of Simonini, Wieland and Fischer, or Prevost (loc. cit.) which took part in this reaction was proved by Birkenbach, Goubeau and Berninger (loc. cit.) by allowing silver acetate to react with iodine in pure ether at -80°, removing excess silver.
salts by filtration and only then adding the filtrate to cyclohexene. From the resultant solution 2-iodo-cyclohexyl acetate was obtained as before. The filtrate having been proved to be silver-free, the acetyl hypohalite must have been present in the free state, possibly stabilised by the low temperature, by excess iodine or by the solvent, ether.

Bockemüller and Hoffmann (Ann. 1935 519 165.), in a study of the properties of acyl hypohalites, investigated their decarboxylation to alkyl halides, addition to double bonds, oxidative powers, power of halogenation and general stability. The following additional evidence for the structure $R.COOR'$ was found: the reaction of silver butyrate with bromine in carbon tetrachloride and filtration to remove silver salts yielded a solution which liberated iodine from acidified potassium iodide and had a bromine content equal to one-half that of a solution of bromine of the same oxidising power,

\[ \text{i.e. } Fr.COOR + 2\text{H}I \rightarrow Fr.COOR + \text{HBr} + \text{I}_2 \]

as compared with \[ Fr_2 + 2\text{H}I = 2\text{HBr} + \text{I}_2 \]

Further confirmation was found in that the butyryl hypobromite so prepared on addition to cyclohexene yielded 2-bromo-cyclohexyl butyrate.

Additions of several hypohalites to cyclohexene were
carried out by Uschakow and Tchistow (Ber. 1923 63 824.) with results similar to those above. The preparative uses of the decarboxylation of acyl hypohalites to the corresponding halides were studied by Lüttringhaus and Schade (Ber. 1941 74 1565; Chem. Abs. 1943 37 74.) and by Hunsdiecker and Hunsdiecker (Ber. 1942 75 291; U.S. Pat. 2176181 1939.) details of which will be given later.
THE BROMINATIVE DECARBOXYLATION OF SILVER CARBOXYLATES.

Introduction

The reaction of silver and mercuric salts of carboxylic acids with bromine under anhydrous conditions to yield the alkyl or aryl bromide containing one atom of carbon less than the original acid has been known for some considerable time and the reaction is generally thought to proceed through the formation of an intermediate acyl hypohalite (vide Historical Introduction), which then decarboxylates to give the halide:

\[ \text{R} \cdot \text{COOAg} + \text{Br}_2 \rightarrow \text{R} \cdot \text{COOBr} + \text{AgBr} \]

\[ \text{R} \cdot \text{COOBr} \rightarrow \text{RBr} + \text{CO}_2 \]

The work described in the present section is directed to the elucidation of the mechanism of this degradation.

The silver salt-bromine reaction has been reviewed by Kleinberg (Chem. Rev. 1947 40 331.) who illustrated its complexity by listing the variables which influence the course of the reaction:

(i) The nature of the silver salt
(ii) The silver salt:halogen ratio
(iii) The temperature of reaction
(iv) The presence or absence of other reactive compounds
(v) The solvent in which the reaction occurs.

The use of equivalent quantities of silver salt and halogen results in the formation of a complex intermediate which may be thermally decomposed to yield the ester of the acid with the lower alcohol, or may be combined with an unsaturated compound to give the di-ester of the corresponding glycol.

\[
eq g. \quad 2R.COOAg + I_2 = (R.COO)_2AgI + AgI
\]

\[
(R.COO)_2AgI \rightarrow \text{R.COOOR + CO}_2 + \text{AgI}\]

That the iodine is present as a positive ion has been shown by hydrolysis which yields, together with the acid and silver iodide, silver iodate. Addition to olefines occurs by a two-stage process of which the product of the first step may sometimes be isolated,

\[
(R.COO)_2Ag^X^+ + \text{R'CH:CHR''} = \text{R'CH-CHR''} + \text{R.COOAg}
\]

\[\text{R.COOAg + R'CH-CHR''} = \text{AgX + R'CH-CHR''}\]

Dicarboxylic acids under these conditions yield cyclic anhydrides, carbon monoxide and carbon dioxide, together with the silver halide.

The more interesting reaction is that between one
equivalent of silver salt and two equivalents of bromine and it is in this reaction that the acyl hypobromite is formed. The greater part of the work on this reaction has been performed on aliphatic or substituted aliphatic acids, although Bockemüller and Hoffmann (Ann. 1935 319 105.) obtained bromobenzene from silver benzoate in 80% yield and Dauben and Tilles (J. Amer. Chem. Soc. 1950 72 3135.) obtained several substituted bromobenzenes from the corresponding benzoic acids.

Kleinberg (loc. cit.) and also Runshiecker, Runshiecker and Vogt (U.S.Pat. 2176181 1939.) list the following types of reaction, the silver salts being used in each case:

1) Fatty acids give alkyl halides.

2) α-Hydroxy acids give hydrogen halide compounds of aldehydes.

3) Hydroxy acids (not α-) give hydroxyalkyl halides.

4) Poly-hydroxy acids (one α-) give hydrogen halide compounds of hydroxyaldehydes.

5) α-Halo-fatty acids give 1,1-dihalo-hydrocarbons.

6) N-fold halogenated fatty acids give N+1-fold halo-hydrocarbons.

7) Dicarboxylic acids give dihalides.

8) Ester acids give halogenated acid esters.
9) α-Keto-acids give acyl halides, one carbon atom poorer.

10) Cycloalkane carboxylic acids give corresponding cycloalkane halides.

11) α-Amino-acids give alkylidene-imine hydrohalides.

12) Other amino-acids give halo-alkylamines.

The second important reaction of acyl hypohalites is their addition to carbon-carbon double bonds; this leads to the production of the ester of the olefine-halohydrin.

\[ \text{R'CH:CHR''} + \text{R.COOBr} = \text{R'CH-CHR''} \]
\[ \text{R.COO} \times \text{Br} \]

which on alkaline hydrolysis yields the corresponding glycol. That the halogen atom in acyl hypohalites is associated with a positive charge was shown by Carlsone (Über eine neue Klasse von Verbindungen des positiv einwertige Jods. Verlag von S. Hirzel. Leipzig. 1932.) who stabilised an acyl hypohalite by coordination with pyridine. The resulting complex liberated iodine from acidified potassium iodide and with water yielded iodine and pyridine iodate, while reaction with phenol in acidic solution gave iodophenol, this reaction having been shown by Cofman (J.C.S. 1919 1040.) to be due to hypoiodous acid, in which the iodine occurs as a positive ion.
Bockemilier and Hoffmann (loc. cit.) found that acyl hypohalites were capable of halogenating solvents containing replaceable hydrogen atoms. The reaction in general follows the course:

\[ R.COOX + R'X \rightarrow R.COOH + R'X \]

e.g. \( CH_2.COOAg + Br_2 + CH_2Cl_2 \rightarrow CH_2Br + CO_2 + AgBr + CHCl_2 \)

They also found that silver stearate yielded higher brominated products together with the expected heptadeacyl bromide.

The hydrolysis of the hypohalites was found to occur very readily; a trace of moisture added to a solution of a hypohalite changed the colour from pale yellow to dark brown with the formation of hydrohalic and halic acids:

\[ R.COOX + H_2O = R.COOH + HOX \]

\[ 3HOX = 2HX + H_2O_3 \]

**Reaction Mechanisms**

A free radical mechanism has been proposed by Price (Mechanisms of Reactions at Carbon-Carbon Double Bonds. 1946 55.) for the decomposition of the acyl hypohalites to the halides:

\[ Br_2 \rightarrow 2Br^{-} \]

\[ R.COOAg + Br^{-} \rightarrow AgBr + R.COO^{-} \]

\[ R.COO^{-} \rightarrow R^{-} + CO_2 \]

\[ R^{-} + Br_2 \rightarrow RBr + Br^{-} \]
On this assumption it is obvious that if the radical \( R^- \)
were asymmetrical, then the use of an optically active siliver salt, \( R^ {-} \text{COOAg} \), would result in the production of an alkyl bromide devoid of optical activity, due to the temporary intermediate existence of the free radical \( A^- \) and consequent racemisation. The experimental verification of this mechanism has been claimed by Arnold and Morgan (J. Amer. Chem. Soc. 1945 70 4243) who allowed the silver salts of both \((+)-\)
and \((-)-2\)-ethylhexanoic acids to react with bromine and obtained completely inactive specimens of \( 2\)-bromo-\( n \)-heptane. They prepared the silver salts by heating a suspension of silver acetate in carbon tetrachloride with the free acid for 90 minutes under reflux; after cooling the bromine was added and the whole was heated under reflux for a further 7 hours. These conditions appear rather drastic in face of the thermal instability of acyl hypohalites as illustrated by Bockemüller and Hoffmann (loc. cit.) who found that butyryl hypobromite in carbon tetrachloride, for example, is almost completely decomposed in 2 minutes at 0°.

The significance of the results obtained by Arnold and Morgan has been questioned by Doering and Farber (J. Amer. Chem. Soc. 1949 71 1514) because the brominative decarboxylation of the silver salt of \( \text{bicyclo-(2.2.2.2)-octane-2-carboxylic acid (I)} \) yielded, in place of the expected \( 2\)-bromo-\( \text{bicycle-(2.2.2)-octane (II)} \), the isomeric
2-bromo-bicyclo-(1.2.3.)-octane (III). The structure of the latter they proved by reduction to bicyclo-(1.2.3.)-octane and by hydrolysis to bicyclo-(1.2.3.)-octane-2-ol. Having studied the effect of silver bromide and of silver acetate and bromine on a specimen of (II) in carbon tetrachloride, and finding that this was converted into (III) in good yield, they postulated that the silver bromide reacted with the halide in such a way as to weaken the carbon-bromine bond and that the alkyl bromide isolated may not have been that originally formed in the decarboxylation. In consequence of this observation, the rearrangement accompanying the decarboxylation of (I) may not, without further experimental evidence, provide the basis of a reaction mechanism, and similarly no conclusion about the mechanism of the reaction should be drawn from the optical inactivity of the 2-bromo-n-heptane obtained by Arnold and Morgan from optically active 2-ethylhexanoic acid, in the absence of any observations on the optical stability or otherwise of the bromide in the presence of bromine and silver bromide.
An alternative reaction mechanism to that suggested by Price (loc. cit.) was proposed by Aros, Campbell and Kenyon (J.C.S. 1949 1510.) following the preparation of an optically active specimen of (+)-α-phenylethyl bromide by the reaction of silver (+)-α-phenylpropionate with two equivalents of bromine in carbon tetrachloride, the retention of optical activity being 43\%. They showed that the (+)-acid and the (+)-bromide have opposite configurations, whence the reaction proceeds with inversion and racemisation, and proposed a bimolecular substitution reaction by the electrophilic reagent, positive bromine. The suggested mechanism of the reaction is as follows:

α-Phenylpropionyl hypobromite is first formed and two molecules of this react according to equation (i) to yield α-phenylethyl bromide, carbon dioxide and two ions which combine to regenerate a molecule of the hypobromite,

\[
(\text{Ph})_2\text{CH COO}^-\text{Br} + (\text{Ph})_2\text{CH COO}^-\text{Br} \rightarrow (\text{Ph})_2\text{CH COO}^-\text{Br}^- + \text{Br}^- + \text{Br}^+ + \text{CO}_2
\]

followed by CHPhMe.CO^- + Br^+ → CHPhMe.COBr.

Molecular bromine may also react by a similar mechanism to yield α-phenylethyl bromide, carbon dioxide and ions which combine to give bromine,

\[
\text{Br}^-\text{Br} \rightarrow \text{Br}^-\text{Br}^- + \text{Br}^- + \text{Br}^-\text{CHPhMe} + \text{CO}_2 + \text{Br}^+
\]
followed by \( \text{Br}^- + \text{Br}^+ \rightarrow \text{Br}_2 \).

Finally, a small concentration of bromine cations may either be set up by reactions (i) or (ii), or may exist in equilibrium with the hypobromite or with bromine, and the reaction may then proceed by (iii), in which \( \alpha \)-phenylethyl bromide and carbon dioxide are formed and bromine cations are regenerated:

\[
(iii) \quad \text{Br}^+ + \text{C}_6\text{H}_5\text{CH}_2\text{Br} \rightarrow \text{Br}^- + \text{C}_6\text{H}_5\text{CO}_2\text{Br} + \text{Br}^+
\]

All the reactions (i), (ii) and (iii) result in the production of \( \alpha \)-phenylethyl bromide with inversion of configuration; in each case the attack by \( \text{Br}^+ \) proceeds by means of an electrophilic bimolecular substitution reaction \((S\_E2)\) through the transition complex:

\[
\begin{align*}
\text{Me} & \quad \text{H} \\
\text{Br}^+ & \quad \text{C} \quad \text{C} \quad \text{O} \quad \text{O} \quad \text{Br}^+
\end{align*}
\]

in which the \( \text{Br}-\text{C} \) bond forms simultaneously with the loosening of the \( \text{C}-\text{CO}_2\text{Br} \) bond.

The configuration of the \( \alpha \)-phenylethyl bromide resulting from such reactions would be completely inverted; the bromide obtained experimentally was inverted but also partially racemised. The possibility of a subsidiary reaction mechanism in which a planar \( \alpha \)-phenylethyl fragment is formed or one which involves retention of configuration was not
overlooked by these workers but it appeared most likely that
the racemisation was due to the action of bromine and silver
bromide on the completely inverted (+)-α-phenylethyl bromide
during the period elapsing between its formation and its
isolation. This was believed to be the first established
example of this class of replacement reaction.

Following upon this difference of opinion between
Arnold and Morgan on the one hand, and Arcus, Campbell and
Kenyon on the other, Bell and Smyth (J.C.S. 1949 2372.)
published results they had obtained by the brominative
decarboxylation of three optically active carboxylic acids.
By treatment of the silver salts of (+)- and (-)-2-ethyl-
hexanoic, (+)-α,α'-diphenylsuccinic, and (-)-benzylethyl-
acetic acids with two equivalents of bromine in carbon
tetrachloride, they obtained the corresponding bromides,
3-bromo-n-heptane, 1,2-dibromo-1,3-diphenyl-ethane, and
2-bromo-1-phenyl-n-butane, in each case the product being
devoid of optical activity. As a result of a similar
experiment on the silver salt of (+)-benzylethylacetic acid
(\(\int_\text{5461}^0 +30.9^\circ\)), however, the specimen of 2-bromo-1-phenyl-
n-butane obtained possessed a negative rotation in alcoholic
solution, \(\int_\text{5461}^0 -2.85^\circ\) (c,14.37:1,1.). The reason for this
difference in behaviour shown by the degradation of the
silver salts of (+)- and of (-)- benzylethylacetic acid
was obscure to these workers as the reactions occurred under
apparently identical conditions. Although the results quoted in this paper might have been held to favour the free radical mechanism for the replacement, as proposed by Price (loc. cit.), the authors state that they subscribe to the views expressed by Arcus, Campbell and Kenyon. Attempts to apply this reaction to optically active diphenic acids were abandoned as silver diphenate would not decarboxylate smoothly to give the required dibromo-diphenyl.

The Racemisation of Optically Active Alkyl Bromides.

In an attempt to elucidate the cause of the partial racemisation which occurred during their silver salt-bromine reaction, Arcus, Campbell and Kenyon performed several subsidiary experiments, and much further work on the racemisation of \( \alpha \)-phenylethyl bromide was carried out by Arcus and Boyd (J.C.S. 1951 ...). The former workers discovered that after heating under reflux for one hour a solution of the optically active bromide in carbon tetrachloride together with silver bromide and bromine (0.7 equivalent), the recovered bromide was racemised to the extent of 99.8\%. During this experiment the evolution of hydrogen bromide was noted, indicating the occurrence of bromination. From a similar experiment in which silver bromide but no bromine was used, there was obtained, after heating for three hours, \( \alpha \)-phenylethyl bromide which was racemised only to the extent
of 0.6%. Similar experiments in which bromine (2.0 equivalent) but no silver bromide was used, gave, after three and nineteen hours heating respectively, 38.4% and 99.0% racemisation. Thus racemisation is rapid when bromine and silver bromide are present together, slower with bromine alone and very slight with silver bromide alone.

Two possible mechanisms for this silver bromide catalysed racemisation of α-phenylethyl bromide were proposed by Arcus, Campbell and Kenyon; the first that of a bimolecular halogen exchange reaction, which has been shown to be the mechanism of the racemisation of the bromide by lithium bromide in acetone (Hughes, Juliusberger, Scott, Topley and Weiss, J.C.S. 1936 1173); the second, a free radical reaction:

\[ \text{RBr} + \text{Br}_2 \rightarrow \text{R}^- + \text{Br}_2 + \text{Br}^- \]
\[ \text{R}^- + \text{Br}^- \rightarrow \text{RBr} \]

A more detailed examination of the racemisation of α-phenylethyl bromide has been carried out by Arcus and Boyd (loc. cit.) in the hope that a kinetic study would lead to some conclusions regarding its mechanism. By repeating the experiments on the racemisation of the bromide by silver bromide alone at 73.4°, they found that, whereas a three-month old specimen of dry, powdered silver bromide (0.65 g.) shaken with a solution of the (-)-bromide (0.8 g.) in carbon tetrachloride (8 ml.) caused negligible racemisation during
two hours, freshly prepared silver bromide caused 39% race-
misation during the same time (2 g AgBr in 10 ml. 10% 
solution of the bromide), and in a similar experiment with 
another freshly prepared specimen of silver bromide 22% 
racemisation occurred during one hour and thereafter no 
further racemisation occurred. Thus it appears that since 
in the silver salt-bromine reaction the silver bromide is 
formed in situ, its effect as a racemisation catalyst may be 
considerable. The speed of racemisation of α-phenylethyl 
bromide by silver bromide and bromine was confirmed by 
Arcus and Boyd, who also noticed the evolution of hydrogen 
bromide and were able to isolate from the reaction mixture 
a white solid, subsequently identified as styrene dibromide. 
Styrene dibromide was also formed during racemisation by 
bromine alone, which caused a carbon tetrachloride solution 
of the bromide to lose 40% of its rotatory power in four 
hours.

From these results it appears that the racemisation of 
α-phenylethyl bromide in the presence of bromine and silver 
bromide involves the combined action of hydrogen bromide 
and styrene dibromide, together with the added reagents. 
These various factors could not be isolated as the action of 
bromine on the organic bromide necessarily involves the 
formation of hydrogen bromide and styrene dibromide but
the optical stability of the bromide was studied in the presence of the following substances (all experiments being conducted by shaking in carbon tetrachloride solution at 73.4°): (i) hydrogen bromide; (ii) styrene dibromide; (iii) silver bromide; (iv) hydrogen bromide and styrene dibromide; (v) hydrogen bromide and silver bromide; (vi) hydrogen bromide and charcoal; (vii) hydrogen bromide and powdered glass; (viii) hydrogen bromide and potassium bromide; (ix) hydrogen bromide and silica. As a result of these experiments it was found that only in (ii) did no racemisation occur. (On attempting to recover the optically active bromide by distillation in the presence of styrene dibromide racemisation, 39% in a test experiment, occurred.)

The rate of racemisation by bromine in the presence of silver bromide was found to be seven times as rapid as that caused by bromine alone. The velocity of racemisation by hydrogen bromide and silver bromide was 320 times as great as that by hydrogen bromide alone; the presence of charcoal and of powdered glass increased this latter rate by 140 and 130 times respectively.

Reactions of Bromine with Silver Carboxylates

The effect of silver bromide on the racemisation of \(\alpha\)-phenylethyl bromide by bromine and by hydrogen bromide is very striking and on this account it was decided to attempt
the brominative decarboxylation of the silver salt of an optically active acid with the removal of the silver bromide formed at the earliest opportunity, thus enhancing the possibility of obtaining an optically active product. By conducting the experiments at relatively low temperatures it was hoped to delay the decomposition of the acyl hypobromite until after the removal of the silver bromide by filtration, thus allowing the alkyl bromide little contact with the racemisation catalyst. The acids chosen for use in these experiments were 2-ethylhexanoic acid, as used by Arnold and Morgan and also by Bell and Smyth, α-phenylpropionic acid, used by Arcus, Campbell and Kenyon, and also α-(p-nitrophenyl)-propionic acid, the reason for the choice of which will appear later.

Owing to the instability of acyl hypohalites to moisture all reagents must be thoroughly dried. The drying of the carbon tetrachloride was accomplished by allowing it to stand over calcium chloride, distilling and then maintaining over phosphorus pentoxide, followed by distillation from this reagent. The solvent was then kept over fresh phosphorus pentoxide. Bromine was dried as described in Organic Syntheses (1940 20 92.), by shaking twice with an equal volume of concentrated sulphuric acid, followed by distillation from phosphorus pentoxide. The silver salts proved more obdurate and required drying in vacuo over daily changes of phosphorus
pentoxide for a period of two to three weeks; they were then finely ground and stored in dark-brown bottles.

The 2-ethylhexanoic acid used was prepared and resolved by the method of Kenyon and Platt (J.C.S. 1939 633.) and some of their specimens were also used. The silver salts of the (+)-, (+)- and (-)- acids were prepared by the method described by Arcus, Campbell and Kenyon (loc. cit.) for silver α-phenylpropionate.

The experiment of Arnold and Morgan was repeated with inactive 2-ethylhexanoic acid in order to obtain a specimen of the bromide, but this drastic procedure was not applied to any of the optically active acids.

The production of 3-bromo-n-heptane from silver 2-ethylhexanate was accomplished by adding a solution of dry bromine in carbon tetrachloride to a stirred suspension of the silver salt in the same solvent at room temperature. After stirring for 2½ hours, the silver bromide was removed by filtration and the filtrate was heated under reflux for 2½ hours to decompose the acyl hypobromite. After the removal of acidic products by treatment with sodium carbonate, distillation yielded the bromide in 20% yield. The hypobromite appeared to commence to decompose before the addition of bromine was complete. Accordingly, in the experiments with optically active acids the time and temperature of reaction were
diminished in successive experiments, and the optical activity of the resultant bromide progressively increased.

The first run in which silver (+)-2-ethylhexanoate was used was conducted between 10-10°C and for a total time of three hours, the silver bromide being removed after two hours. This gave (+)-3-bromo-n-heptane, $\alpha_D^{24}+0.27^0$ (1,2; homogeneous) in 34% yield, the optical purity of the acid used being 92%. Redistillation of this product gave a specimen of rotation $\alpha_D^{23}+0.05^0$ (1,0.5; homogeneous); the difference of rotation of the two specimens is within the limits of experimental error and thus, although the rotation is rather low, it is none the less a real value.

The silver salt of the (-)-acid was next used and the reaction mixture was cooled to between 0-10°C; stirring was stopped after a total time of 55 minutes, and, after filtration, the mixture was not heated but merely freed from acid with sodium carbonate, dried and distilled. The bromide obtained in this way possessed a rotation of similar magnitude to that of the (+)-bromide, but as in this case the optical purity of the acid was only 62%, a slight increase in retention of asymmetry is indicated; the yield also was higher, $\alpha_D^{23}+0.05^0$. 1,0.5; homogeneous. 60% yield.

In a final experiment, the silver salt of (+)-2-ethyl-
hexanoic acid of 95\% optical purity was employed. The reaction mixture was cooled in a freezing mixture, kept at a temperature below -10\°, during the addition of the bromine-carbon tetrachloride solution (15 minutes) and for a further 15 minutes thereafter. The cold product was then quickly filtered by suction through sintered glass, care being taken to exclude moisture, and the filtrate heated under reflux for 20 minutes. As a result of this experiment a specimen of (+)-3-bromo-n-heptane was obtained the rotation of which was three times that of the previous specimens, \( \alpha_{D}^{21^\circ} = +0.18^\circ \) (1,0.5; homogeneous).

In order to correlate the results of these three experiments more clearly the table below shows the calculated rotations of the specimens of 3-bromo-n-heptane, (l,l; homogeneous), on adjustment of the optical purity of each specimen of acid used to 100\%, the maximum value quoted by Kenyon and Platt (J.C.S. 1939 633.) being taken as standard:

(1) \( \alpha_{D} +0.13^\circ \); (ii) \( \alpha_{D} -0.15^\circ \); (iii) \( \alpha_{D} +0.39^\circ \).

The purity of the specimens of 3-bromo-n-heptane obtained in these experiments was established by their refractive indices, boiling points, and bromine content. All bromine analyses on these specimens were carried out by the method given in detail in the experimental portion of this thesis.
From these results it appears likely that the acyl hypobromite decomposes by routes similar to those proposed by Areus, Campbell and Kenyon (loc. cit.) for \( \alpha \)-phenylpropionyl hypobromite, but that the racemisation of the optically active bromide so formed is far more rapid in the presence of silver bromide and bromine than that of \( \alpha \)-phenylethyl bromide, although it probably proceeds by a similar mechanism. This would explain the failure of Arnold and Morgan to obtain an optically active product as their procedure involved heating the bromide with silver bromide and bromine for seven hours, which would apparently cause complete racemisation.

The proposed mechanism for the formation of the optically active 3-bromo-\( \eta \)-heptane is as follows, it being assumed that inversion occurs as in the production of \( \alpha \)-phenylethyl bromide:

2-Ethylhexanoyl hypobromite is first formed and two molecules of this compound react according to equation (1) to yield 3-bromo-\( \eta \)-heptane, carbon dioxide and two ions which combine to regenerate one molecule of 2-ethylhexanoyl hypobromite:

\[
\text{EtCH}_2\text{CO}^-\text{Br} + \eta\text{Bu}^\text{CH}(-\text{CO}^-\text{Br}) \rightarrow \text{EtCH}_2\text{CO}^-\text{Br} + \eta\text{Bu}^- + \text{CO}_2
\]

followed by \( \eta\text{Bu}^\text{CH}_2\text{CO}^- + \text{Br}^+ \rightarrow \eta\text{Bu}^\text{CH}_2\text{CO}^-\text{Br} \)
Molecular bromine may also react by a similar mechanism to yield 3-bromo-n-heptane, carbon dioxide, and ions which combine to regenerate bromine:

\[
\text{(i) } \text{Br}^+ + \text{n-Bu}^- \xrightarrow{\text{CH}_2\text{COO}^-} \text{Br}^- + \text{Br}^- + \text{CO}_2 + \text{Br}^+
\]

followed by \( \text{Br}^- + \text{Br}^+ \rightarrow \text{Br}_2 \)

Finally a small concentration of bromine cations may be either set up by reactions (i) and (ii) or may exist in equilibrium with the hypobromite or with bromine, and reaction may then proceed by (iii) in which 3-bromo-n-heptane and carbon dioxide are formed and bromine cation is regenerated:

\[
\text{(iii) } \text{Br}^+ + \text{n-Bu}^- \xrightarrow{\text{CH}_2\text{COO}^-} \text{Br}^- + \text{Br}^- + \text{CO}_2 + \text{Br}^+
\]

When the experiments leading to the production of optically active 3-bromo-n-heptane had been completed, it was decided to attempt to repeat the conversion of silver \( \alpha \)-phenylpropionate to \( \alpha \)-phenylethyl bromide (Arcus, Campbell and Kenyon, loc. cit.) under milder conditions, in the hope of achieving a higher retention of asymmetry.

\( \alpha \)-Phenylpropionaldehyde is now commercially available and its oxidation to \( \alpha \)-phenylpropionic acid by various methods was investigated. The method outlined by Arcus and Kenyon (J.C.S. 1933 916.), oxidation with potassium permanganate in acetone in the presence of magnesium sulphate.
gave the best yield (40%) of the acid, together with a large quantity of resinous matter and also some acetophenone. The latter possibly arises from the oxidation of a condensation product of the aldehyde with the solvent, acetone:

\[
\text{PhMeCH.CHO} + \text{CH}_3\text{COCH}_3 \rightarrow \text{PhMeCH.CH.CHCOCH}_3 \rightarrow \text{PhMeCH.CH.CH}_2\text{COCH}_3
\]

\[
\text{PhMeCH.CH}_2\text{COCH}_3 \rightarrow \text{PhMeCO} + \text{OHC.CH}_2\text{COCH}_3 \rightarrow \text{resin.}
\]

A far better yield of the acid was obtained by the hydrolysis of \(\alpha\)-phenylpropionitrile, which was produced by the action of dimethyl sulphate on the sodio-derivative of benzyl cyanide, obtained by treating an ethereal solution of the nitrile with sodamide (Campbell and Kenyon, J.C.S. 1946 25.). The success of this reaction, however, depends on the quality of the sodamide employed, for unless this is fresh no reaction occurs. The acid was resolved by means of strychnine, using the method of Raper (J.C.S. 1923 123 2557.) which had also been employed by Arcus and Kenyon (loc. cit.).

A repetition of the experiment of Arcus, Campbell and Kenyon was carried out on silver (+)-\(\alpha\)-phenylpropionate but this resulted in the production of none of the required \(\alpha\)-phenylethyl bromide. A second attempt led to no better result, and a series of reactions between different preparations of silver salt and of bromine under various conditions yielded none of the expected product; the only compound isolated from the intractable products being identified as
α-phenylethyl α-phenylpropionate, i.e. the ester of the acid with the alcohol containing one carbon atom less. Other products appear to be mono- or di-bromo-derivatives of this ester, possibly some styrene dibromide and a little free bromo-α-phenylpropionic acid, together with some free α-phenylpropionic acid.

The reasons for the failure of these attempts to prepare α-phenylethyl bromide by the silver salt-bromine reaction are not clear; it is well known that the absence of moisture is essential to the production of reasonable yields of the bromide and this condition was observed in the preparation of the reagents as far as was possible. The silver salt was, in all cases, dried over phosphorus pentoxide in vacuo for long periods, and in later experiments it was dried to constant weight over phosphorus pentoxide at 70° and 1.5 mm. The carbon tetrachloride was redried before almost every experiment by fractionation from phosphorus pentoxide and the bromine was dried as already mentioned. The ground-glass jointed apparatus used was dried in an oven at 100° for three hours, then quickly assembled with calcium chloride tubes at every outlet.

Despite all the precautions enumerated above, the appearance of water in the reflux condenser was noticed, its presence becoming obvious as the reaction proceeded.
That this water was not present in the reagents originally was shown by heating under reflux the silver salt and the bromine in carbon tetrachloride in separate flasks, and in neither case was any trace of moisture apparent, while during the reactions on the same specimens the quantity of water appearing was comparatively large.

In view of these observations it appears possible that the water is formed by some side-reaction and that it is as a result of this that the experiments have failed to yield any α-phenylethyl bromide. Another possible contributory cause of the failure of these experiments, may be the physical state of the silver salt. It has been observed by Arcus and Boyd (loc. cit.) that freshly-prepared silver bromide is a more efficient catalyst in the racemisation of α-phenylethyl bromide than is a specimen which has been stored for some time. The formation of the ester in this silver salt-bromine reaction may also occur at the surface of the silver salt and be similarly affected by the age or state of the surface:

\[ \text{PhMeCH}_2\text{COOAg} + \text{PhMeCHBr} \rightarrow \text{PhMeCH}_2\text{COOH} + \text{AgBr}. \]
\[ \text{PhMeCH}_2\text{COOAg} + \text{PhMeCHBr} \rightarrow \text{PhMeCH}_2\text{COOH} + \text{AgBr}. \]

The bromination of the ester and acid probably occurs thus:

\[ R\text{COOBr} + R'\text{H} \rightarrow R\text{COOH} + R'\text{Br}, \]

and the formation of styrene dibromide is known to occur on
heating α-phenylethyl bromide with bromine:

\[
\text{PhMeCHBr} + \text{Br}_2 = \text{PhMeCHBrCH}_3\text{Br} + \text{HBr}.
\]

The hydrogen bromide liberated in this reaction would react with the silver salt, setting free the acid which could then be brominated as indicated above:

\[
\text{PhMeCHCOAg} + \text{HBr} = \text{PhMeCHCOOH} + \text{AgBr}
\]

\[
\text{PhMeCHCOOH} + \text{PhMeCHCOOBr} = \text{Br}_2\text{C}_6\text{H}_4\text{CHMeCOOH} + \text{PhMeCHCOOH}
\]

In view of the failure of these experiments no reactions with optically active acids were performed. The reaction is being reinvestigated by Dr. A. Campbell.

That the acyl hypobromite acts preferentially as a brominating agent in cases in which a low yield of the bromide is obtained, was postulated by Dauben and Tilles (J. Amer. Chem. Soc. 1950 72 3185). They allowed bromine to react with the silver salts of several aromatic acids and found that the yield of bromide varied with the substituents in the aromatic nucleus, and ranged from 68% from m-nitrobenzoic acid to 0% from m-methoxybenzoic acid; in the latter reaction only brominated acidic compounds, including 3-methoxy-5-bromo-benzoic acid, were isolated. They also showed that the addition of anisole to acetyl hypobromite at -20° resulted in the formation of p-bromo-anisole. Papa, Schwenk and Klingsberg (J. Amer. Chem. Soc.
1950 72 2623.) have shown that silver \(\text{-}(m\text{-methoxyphenyl})\)-propionate reacts with bromine to yield only \(\text{-}(2\text{-bromo-5-methoxyphenyl})\)-propionic acid, and also that acids of the type \(\text{Ar.CHR.CO}_2\)H when added to a silver acetate-bromine mixture in acetic acid readily give nuclearily substituted bromo-compounds.

Barnes and Prochaska (J. Amer. Chem. Soc. 1950 72 3188.) also carried out experiments on the reaction of bromine with the silver salts of aromatic acids and stated that the course of the reaction was determined by the nuclear substituents. They consider the reaction to proceed through free radicals and proposed two paths:

\[
\begin{align*}
\text{HBr} & \rightarrow \text{Br}_2 + \text{R-} + \text{CO}_2\text{H} - \text{Br}_2 \rightarrow \text{R-} + \text{CO}_2\text{H} + \text{HBr} \\
\text{O=O-OBr} & \rightarrow \text{Br-} + \text{R-} + \text{CO}_2 \rightarrow \text{CO}_2 + \text{R-} + \text{Br-}.
\end{align*}
\]

The relative importance of these two paths depends upon the ease of bromination of the free acid, which is assumed either to be present as a small impurity in the silver salt or to be formed by a trace of moisture according to the equation:

\[
6\text{C}_6\text{H}_5\text{CO}_2\text{Ag} + 3\text{H}_2\text{O} + \text{Br}_2 = 5\text{AgBr} + \text{AgBrO}_3 + 6\text{C}_6\text{H}_5\text{CO}_2\text{H}.
\]
If the bromination is rapid, the hydrogen bromide liberated would quickly decompose the hypobromite:

\[ \text{RCOOBr} + HBr = \text{RCOOH} + Br_2 \]

and also set free the acid from the salt, thus effectively competing with the decarboxylation to the bromide. They found that the yield of bromide is also affected by variation in the temperature of reaction and by the rate of addition of the bromine solution. This latter point bears out the observations of Bockemüller and Hoffmann (loc. cit.) who found that by treating silver adipate in boiling carbon tetrachloride with a constant excess of bromine, 1,4-dibromo-n-butane was the chief product, but that by adding the bromine slowly to the boiling solution, the yield of dibromide was depressed and the main product was 6-valerolactone. They also noted that the decomposition at room temperature of benzoyl hypobromite gave bromo-substituted phenyl benzoates.

Barnes and Prochaska (loc. cit.) also stated that there is no direct relationship between the ease of decarboxylation of the acid and the yield of the bromide. They compared 4-methoxy-3-bromobenzoic acid with 3-nitrobenzoic acid, which are at opposite extremes in ease of decarboxylation, and found that they both gave the same yield of substituted bromobenzene by the silver salt-bromine reaction. Working
with compounds such as phenylacetic acid, they found that the entry of a nitro-group into the nucleus increased the yield of the bromide, possibly by discouraging substitution in both the nucleus and the side-chain.

In view of these latter experiments it was decided to carry out the silver salt-bromine reaction using \(\alpha-(p\)-nitrophenyl\)-propionic acid in the hope of obtaining the required \(\alpha-(p\)-nitrophenyl\)-ethyl bromide in reasonable yield.

Attempts to prepare this acid from \(p\)-nitrobenzyl cyanide by methods analogous to that used in the preparation of \(\alpha\)-phenylpropionic acid met with no success because the sodio-derivative of the nitrile did not appear to be formed. \(\alpha-(p\)-Nitrophenyl\)-propionitrile was, however, prepared by the method of Opolski, Kowalski and Filewski (Ber. 1916 49 2232.), by which \(\alpha\)-phenylpropionitrile was nitrated with fuming nitric acid. Acid hydrolysis of the nitrile yielded the acid which separated from methylene chloride-cyclohexane as pale yellow rhombs m.p. 86-87\(^\circ\). The silver salt of this acid was prepared in 85\% yield by the addition of a solution of silver nitrate in distilled water to a solution of the acid in aqueous ammonia, excess ammonia having been removed by heating, and this was finally dried by heating at 70\(^\circ\) and 2 mm. for 6 hours.
A solution of bromine in carbon tetrachloride was added dropwise during fifteen minutes to a stirred suspension of this silver salt in carbon tetrachloride, at room temperature. Although the precipitation of silver bromide appeared to be almost instantaneous, a slight bromine colouration persisted after heating under reflux for three hours. The hot mixture was then filtered, and the cooled filtrate was washed successively with sodium meta-bisulphite solution, sodium carbonate solution and with water. (From these washings 0.5 g. of the acid, m.p. 85-87°, was recovered.) The solution was dried with anhydrous magnesium sulphate and the solvent was evaporated, leaving a residual viscous oil; this was taken up in ether, the evaporation of which gave a pale-yellow crystalline solid m.p. 28-30°. This solid was dissolved in ligroin, from which separated a small amount of a colourless compound, m.p. 124-126°, which was insoluble in light petroleum and contained no bromine, and the analysis of which indicated it to be α-(p-nitrophenyl)-ethyl α-(p-nitrophenyl)-propionate. Evaporation of the solvent from the filtrate yielded colourless plates of α-(p-nitrophenyl)-ethyl bromide, m.p. 34-35°, in 50% yield.

The entry of a nitro-group into the para-position in the aromatic nucleus has, therefore, increased the yield of the bromide. It is intended to extend this work to the reaction with optically active silver α-(p-nitrophenyl)-propionate.
THE ADDITION REACTIONS OF ACYL HYPOCHLORITES.

Introduction.

The addition of acyl hypochlorites across carbon-carbon double bonds, analogous to the behaviour of the halogens from which they are derived, has already been mentioned; this property was first observed by Brunel (Ann. Chim. et Phys. 1905 (8) 6 229.) and was later extensively studied by Berninger and co-workers, Ushakov and Tshistow, and others.

\[ R'COOAg + Br_2 \to R'COOBr + AgBr \]
\[ RCH=CHR + R'COOBr \to RCH=CHR \]
\[ R'COOBr \]

The following descriptions are representative of the experimental procedures used in carrying out this reaction. Bockemüller and Hoffmann (Ann. 1935 519 165.) and Birkenbach, Goubeau and Berninger (Ber. 1932 65 1339.) added two equivalents of the halogen to the silver carboxylate suspended in an inert solvent such as ether or carbon tetrachloride, removed the silver halide by filtration, and then added the unsaturated compound. In all experiments the olefin employed was cyclohexene and the 2-halo-cyclohexyl esters were obtained in 30-40% yield. The former workers also prepared 2.3-dichloropropyl acetate by adding silver acetate to a solution of chlorine in carbon tetrachloride, filtering off the silver chloride, and then adding allyl chloride; only a
low yield was obtained in this case, however. Uschakov and Tchistow (Ber. 1935 68 324.) obtained similar yields of 2-bromo-cyclohexyl esters by the alternate addition of small quantities of solutions of bromine and of cyclohexene in carbon tetrachloride to a stirred suspension of the silver salt in the same solvent. The simultaneous production of the dihalide was observed in most experiments.

Asymmetric Synthesis

The production of optically active acyl hypobromites as illustrated in the previous section, coupled with their powers of addition to olefines, led to a consideration of the possibility of effecting an asymmetric synthesis with their aid. The addition of an optically active acyl hypobromite to an olefine, such as styrene, might result in one configuration of the new asymmetric centre being formed in larger quantity than the other; removal of the optically active acyl group by hydrolysis would then yield an optically active glycol.

The classical definition of asymmetric synthesis was given by Marckwald (Ber. 1904 37 1368.) translated literally as follows: "Asymmetric syntheses are such, that from compounds of symmetrical constitution by the intermediate use of optically active substances, but without any analytical separation, optically active products result."
The view that "the production of single asymmetric molecules is the prerogative of life" was held by Japp (Nature 1898 53 452.) in opposition to the opinion of Van't Hoff that the use of an unsymmetrical physical force could result in the formation of optically active compounds. Many attempts to effect such syntheses were made, but satisfactory results were not obtained until Kuhn and Brown (Naturwiss 1929 17 227.) achieved the asymmetric-photochemical decomposition of externally compensated compounds by circularly polarised light.

Fischer (Ber. 1901 34 629.) attempted to prepare optically active salicylaldehyde cyanhydrin from helicin in the following way:

\[
\text{CHO} \cdot (\text{CHO})_4 \cdot \text{CH}_2\text{O} \cdot \text{C}_6\text{H}_4 \cdot \text{CHO} \rightarrow \text{CHO} \cdot (\text{CHO})_4 \cdot \text{CH}_2\text{O} \cdot \text{C}_6\text{H}_4 \cdot \text{C} \quad \text{CN}
\]

helicin \quad \text{helicin cyanhydrin}

\[
\text{CHO} \cdot (\text{CHO})_4 \cdot \text{CH}_2\text{OH} + \text{OH} \cdot \text{C}_6\text{H}_4 \cdot \text{C} \quad \text{CN}
\]

glucose \quad \text{salicylaldehyde cyanhydrin}

The desired product could not, however, be isolated; analogous attempts by Fischer and by other investigators resulted in similar lack of success.

Three years later Marchwald (Ber. 1904 37 349.) reported a successful asymmetric synthesis by purely chemical means; he prepared the mono-brucine salt of ethylmethyalmalonic acid
and heated this to 170°, whereby carbon dioxide was evolved and the brucine salt of ethylmethylacetic acid was formed. Removal of the brucine left an acid having a negative rotation, found to contain a 10% excess of the \( \text{L} \)-over the \( \text{D} \)-isomer.

\[
\text{Et} \overset{\text{COOH}}{\text{Brucine}} \xrightarrow{\text{heat}} \text{Et} \overset{\text{COOH}}{\text{Brucine}} \xrightarrow{\text{Me} \overset{\text{COOH}}{\text{H}} \text{Me} \overset{\text{O}}{\text{Me}}} \xrightarrow{\text{Et}} \overset{\text{COOH}}{\text{H}}
\]

In this same year, 1904, the first of a series of undoubted asymmetric syntheses was reported by McKenzie (J.C.S. 1904 85 1249). A first attempt to obtain an optically active mandelic acid by the reduction of \((-\text{-})\)-menthyl benzoylformate was unsuccessful because, although an excess of \((-\text{-})\)-menthyl \((-\text{-})\)-mandelate over \((-\text{-})\)-menthyl \((+\text{-})\)-mandelate was produced, hydrolysis of the resultant ester mixture by alcoholic potash caused racemisation, and the resultant acid was optically inactive. Later, McKenzie and Humphries (J.C.S. 1909 93 1105) showed that by acetylating the reduced ester mixture, and then saponifying, the optically active mandelic acid could be obtained:

\[
\begin{align*}
\text{Ph} \overset{\text{CO} \overset{\text{O}}{\text{COOR}}}{} & \overset{\text{SN}}{\xrightarrow{\text{Ph} \overset{\text{CHOH}}{\text{COOR}}}{} \overset{\text{Ac} \overset{\text{O}}{\text{O}}}{\xrightarrow{\text{Ph} \overset{\text{CHOAc}}{\text{COOR}}}{} \overset{\text{Ph} \overset{\text{CHOH}}{\text{COOH}}}{}
\end{align*}
\]

In a similar manner McKenzie et al. (J.C.S. 1905 87 1373; ibid 1906 89 683; ibid 1909 93 544) obtained optically active lactic acids from the \((-\text{-})\)-menthyl, \((-\text{-})\)-bornyl, and \((-\text{-})\)-amyl
esters of pyruvic acid, by reduction and hydrolysis:

\[
\text{CH}_3\text{COO}^- + \text{MgX} \rightarrow \text{CH}_3\text{CH}_2\text{COO}^-\text{MgX}
\]

McKenzie and co-workers (J.S. 1904 85 1373; ibid. 1909 95 544; Biochem. Z. 1931 231 412; ibid. 1931 237 1; ibid. 1932 250 376.) also investigated the reaction of optically active esters of α-ketonic acids with Grignard reagents, and found that hydrolysis of the resultant complexes yielded optically active hydroxy acids:

\[
e.g. \quad \text{PhCOO}^- \rightarrow \text{PhCO}^- \rightarrow \text{PhCOOH}
\]

\[(R = (-)-menthyl, (-)-bornyl, (-)- and (+)-2-octyl.)
(R' = Me, Et, \text{Pr}, i-\text{Pr}, \text{Ph}.)\]

The mechanism of these latter asymmetric syntheses has been discussed by Ritchie (Asymmetric Synthesis and Asymmetric Induction. St. Andrews Univ. Publ. 1933 No. 36.) in the light of the hypothesis of asymmetric induction. He assumes that the addition of the solvent, ether, to the ester gives rise to the production of the two possible diastereoisomerides (A') and (B') in unequal amounts, (A') being in excess, and the configuration adopted by the α-carbonyl group in each is maintained in the intermediates (A) and (B) and also in the atrolactic acid finally obtained:
An alternative mechanism for these asymmetric reactions has been proposed more recently by Reid and Turner (J.C.S. 1949 3365.). It is admitted that in the reaction between the Grignard reagent and the keto-ester, the two diastereoisomerides are formed in unequal quantities, but, since they are not interconvertible, it is stated that "mechanistic difference must be sought at the stage of the two corresponding transition states, from which they are formed irreversibly." The two transition states (A') and (B'), below, formed reversibly from the reagents, must have different energies, since they are of the nature of diastereoisomers. Thus a mechanism is possible whereby the reaction with the lower activation energy can be followed preferentially and an "asymmetric reaction" may result. The process is represented thus:
The "equilibrium" between the two transition states bears a formal resemblance to that between two diastereoisomerides undergoing first-order asymmetric transformation.

In the same paper, a description is given of the preparation of (+)-(S)-hydroxy-β-phenylbutyric acid by means of a Reformatsky reaction between acetophenone and (−)-menthyl bromoacetate in the presence of zinc. The mechanism is shown diagrammatically in a manner similar to that above for the Grignard reaction, to which it is similar. This appears to be the first example of such an asymmetric synthesis in which the "fixed centre of asymmetry" is not in the compound containing the carbonyl group; such a reaction could not be explained on the hypothesis of induced asymmetry in the carbonyl group.
It appears that in all asymmetric syntheses of this type that the first stage consists of the production of two diastereoisomerides in unequal quantities. In order to arrive at an asymmetric synthesis as defined by Marckwald, it is necessary to remove the original asymmetric centre, leaving the new asymmetric centre in an optically active state. Methyl magnesium iodide reacts with (-)-benzoic to yield only one of the two possible diastereoisomerides (A) and (B), whence the addition appears entirely unsymmetrical, but this is not regarded as an asymmetric synthesis according to the above definition because the original asymmetric centre is not removed:

\[
\begin{align*}
\text{(A)} & : \text{Ph} & \text{H}-\text{C}-\text{OH} & \text{Me}-\text{CH}_2\text{I} & \text{Ph} & \text{H}-\text{C}-\text{OH} \\
\text{(B)} & : \text{Ph} & \text{H}-\text{C}-\text{OH} & \text{Me}-\text{C}-\text{OH} & \text{Ph} & \text{H}-\text{C}-\text{Me}
\end{align*}
\]

By the addition of bromine in chloroform to (+)-\(\gamma\)-phenyl-\(\alpha\)-methylallyl alcohol, Kenyon and Partridge (J.C.S. 1936 1313) obtained a solid product which they were able to separate by fractional crystallisation into two compounds of different melting point and crystalline form. The less soluble compound on oxidation with chromic anhydride in acetic acid gave optically pure (+)-1,2-dibromo-1-phenyl-3-butanone, while the more soluble product under similar conditions yielded the corresponding (-)-ketone, also in the optically pure state. By conducting the bromination and oxidation without employing
crystallisation or other form of separation of the intermediate dibromo-alcohols, the dibromo-ketone was obtained in an optically active state; the rotatory power depended on the temperature at which the addition of bromine had been carried out, the highest value being 41.5° of that of the optically pure compound. In this experiment two new centres of asymmetry were formed, followed by the destruction of the original centre by oxidation.

\[
\text{CH}_2\text{CHOH.CH}=\text{CH}.\text{Ph} \xrightarrow{\text{Br}_2} \text{CH}_2\text{CHOH.CHBr.CHBr}.\text{Ph} \xrightarrow{\text{O}_{2H}} \text{CH}_2\text{CO.CHBr.CHBr}.\text{Ph}
\]

A similar series of reactions carried out on (+)-ethyl-vinylcarbinol, also resulted in the production of an optically active ketone, (Partridge, Ph.D. Thesis, London, 1937.)

\[
\text{C}_2\text{H}_5\text{CHOH.CH}=\text{CH}_2 \xrightarrow{\text{Br}_2} \text{C}_2\text{H}_5\text{CHOH.CHBr.CH}_2\text{Br} \xrightarrow{\text{O}_{2H}} \text{C}_2\text{H}_5\text{CO.CHBr.CH}_2\text{Br}
\]

although the use of optically active phenylvinylicarbinol in the same way (Strauss, M.Sc. Thesis, London, 1951.) yielded an inactive dibromo-ketone. To account for the inactivity of the dibromo-propiophenone so formed, it was postulated that keto-enol tautomerism might occur with consequent racemisation of the active product, this being favoured by the presence of the phenyl group with which conjugation could occur.
The use of 3-phenyl-a-ethylallyl alcohol in a similar series of reactions by Waddan (Ph.D. Thesis. London. 1951.) resulted in the production of an optically active ketone, in agreement with the results of Kenyon and Partridge which it resembles in that new centres of asymmetry were produced at both the 6 and 8 carbon atoms.

The Attempted Asymmetric Synthesis of Phenyl Glycol.

All the above-mentioned asymmetric syntheses have been achieved by the addition of a reagent incapable of exhibiting optical activity to an optically active compound containing a double bond, followed by the removal of the original centre of optical activity. It was therefore decided to attempt an asymmetric synthesis in the reverse way, by the addition of an optically active reagent to a symmetrical unsaturated compound.

For this purpose the acyl hypobromites appeared to be possible reagents and that resulting from the action of bromine on the silver salts of (+)- and (-)-2-ethylhexanoic acid was chosen for this attempt, the unsaturated material being styrene. It was anticipated that the addition might take place, under the influence of the optically active centre
in the hypobromite, in an unsymmetrical manner, resulting in the production of the two possible diastereoisomeric bromo-esters in unequal amounts,

\[
\text{Ph.CH:CH}_2 + \text{R.COOBr} \rightarrow (A) \quad \text{Ph} \quad \text{C} \quad \text{CH}_2 \text{Br} \quad \text{H} \quad \text{OOC.R} \\
\text{B) \quad Ph} \quad \text{C} \quad \text{CH}_2 \text{Br} \quad \text{H} \quad \text{OOC.R.}
\]

\[
(+) \quad (-) \quad (+) \quad (+)
\]

The removal of the original centre of optical activity by hydrolysis (this also resulting in the replacement of the bromine atom by a hydroxyl group) would then lead to an optically active product, i.e. assuming (A) to be formed in excess,

\[
\text{Ph} \quad \text{C} \quad \text{CH}_2 \text{Br} \quad \text{H} \quad \text{OOC.R} \quad \text{NaOH} \rightarrow \text{Ph} \quad \text{C} \quad \text{CH}_2 \text{OH} + \text{R.COONa} + \text{NaBr.}
\]

\[
(-) \quad (+) \quad (-) \quad (+)
\]

With a view to obtaining an insight into the preparation of these bromo-esters, 2-bromo-1-phenylethyl acetate was prepared by adding first a solution of bromine in carbon tetrachloride to a stirred suspension of silver acetate in carbon tetrachloride cooled to below \(-10^\circ\), followed by the addition of a solution of freshly-distilled styrene in the same solvent. After further stirring, filtration and distillation yielded the bromo-ester in good yield.

The addition of acyl hypohalites across carbon-carbon double bonds usually occurs in the same direction as that of
the corresponding hypohalous acid, or the opposite way to the hydrohalic acid, e.g.,

\[
\text{Ph.CH:CH}_2 + \text{HBr} = \text{Ph.CHBr.CH}_3
\]
\[
\text{Ph.CH:CH}_2 + \text{HOBr} = \text{Ph.CHOH.CH}_2\text{Br}
\]
\[
\text{Ph.CH:CH}_2 + \text{CH}_3\text{COOBr} = \text{Ph.CH.CH}_3\text{Br}. \text{COO.CH}_3
\]

By the acetylation of styrene bromohydrin, Marvel and Moon (J. Amer. Chem. Soc. 1940 62 40.) prepared 2-bromo-1-phenyl-ethyl acetate having b.p. 105-107°/3 mm., and \(n_D^{20} 1.5380\), while the corresponding constants for the product obtained as described above were, b.p. 98-100°/0.3 mm., and \(n_D^{25} 1.5339\). Analysis of this compound gave good values for carbon and hydrogen contents but the bromine-content was slightly higher than calculated, possibly due to the presence of a little styrene dibromide. The presence of the latter, as will be shown later, elevates the refractive index of the specimen and this may account for the slight discrepancy between the values recorded.

Attempts to replace the bromine atom in the bromo-ester by heating under reflux with sodium benzoate in alcohol, failed to yield the required 1-acetoxy-2-benzoxy-phenylethane in isolable amount. Hydrolysis with alcoholic potash yielded no styrene oxide, the only product isolated and identified being phenyl glycol, in low yield. Hydrolysis with aqueous
sodium hydroxide solution resulted in the production of phenyl glycol in 60% yield; it was identified by analysis and by the preparation of the crystalline dibenzoate.

The use of silver 2-ethylhexanoate in place of silver acetate in the silver salt-bromine-styrene reaction led to the formation of the corresponding ester of styrene bromohydrin. This compound also showed little or no reaction with sodium benzoate, or with silver benzoate and gave only a very low yield of phenyl glycol when hydrolysis by means of aqueous potassium carbonate solution was attempted. The use of sodium hydroxide for the hydrolysis, however, gave the glycol in 60-70% yield.

In the light of these preceding experiments, use was then made of the silver salts of both the (+) and the (-) forms of 2-ethylhexanoic acid. The (-)-acid was first used and gave a 35% yield of (-)-2-bromo-1-phenyl 2-ethylhexanoate together with some styrene dibromide. The acid used was 75% optically pure and the resulting bromo-ester had b.p. 150-154°/1 mm., n D 1.5080, and α D 17°-0.61° (1.0.5); its composition was verified by analysis.

In order to convert this (-)-bromo-ester to the glycol it was heated under reflux with 2N sodium hydroxide solution until all oily droplets had disappeared, this requiring 10.5 hours. The mixture was then cooled, saturated with potassium
carbonate and extracted with ether. This extract was dried with potassium carbonate; its rotation was measured and gave in a 2 dm. tube the value $\alpha_D^{14^0} -0.02^0$ (c.5.9). Addition of ligroin to this ethereal solution gave the glycol in 74% yield as colourless needles m.p. 64-65° and $\alpha_D^{15^0} 0.09^0$ (c.5.7; 1.2; in ether.). The acid was recovered from the hydrolysis in 83% yield and was found to be racemised to the extent of 40%. (Kenyon and Young, J.C.S. 1949 216., studied the rates of racemisation of esters of disubstituted acetic acids in the presence of sodium ethoxide, and found that when equimolecular amounts of (+)-ethyl 2-ethylhexanoate and sodium ethoxide in alcohol are maintained at 80° for 20 minutes, the product is completely racemised.)

The silver salt of the (±)-acid (93% optically pure) similarly gave the (±)-bromo-ester in 60% yield; it had b.p. 152-156°/ 1.5 mm., $n_D^{25^0} 1.5081$, $\alpha_D^{17.5^0} +0.88^0$ (1.0.5). Hydrolysis of this product with 3N sodium hydroxide solution required 10 hours for completion and the ethereal extract of the reaction mixture was optically inactive. The phenyl glycol so obtained was recrystallised from ether-ligroin (65% yield of recrystallised material). The acid recovered from the hydrolysis was 36% racemised.

In explanation of the lack of optical activity of the glycol obtained in these experiments and the consequent failure of the attempted asymmetric synthesis, the following
points arise. Either the enantiomers of the new asymmetric centre were formed in equal amounts, or else one of them was formed in excess and racemisation during hydrolysis led to the formation of optically inactive phenyl glycol. The most probable course of hydrolysis in aqueous alkali is considered, from the results of Winstein (described in a later section, p. 66.), to be as follows:

\[
\begin{align*}
\text{Br} & \quad \text{Br}^- \\
\text{Ph-CH-CH}_2 & \quad \text{Ph-CH-CH}_2^+ \\
O \quad \text{C}=O & \quad O \quad \text{C}=O \\
R & \quad R
\end{align*}
\]

(the last step occurring by normal alkaline hydrolysis with acyl-oxygen fission.)

since the valencies of the asymmetric carbon atom are not disturbed, no racemisation should occur during hydrolysis.

Other possible mechanisms of hydrolysis may be briefly reviewed. It is possible that in the second step, above, the hydroxyl ion attaches itself to C\(_\alpha\), giving the α-ester; this would result in inversion, but not in racemisation. S\(_\text{N}2\) hydrolysis of the bromide appears unlikely because the bromo-ester failed to react with sodium benzoate in alcohol; S\(_\text{N}1\) hydrolysis of the bromide without the above 'vicinal effect' is possible. Since heating with aqueous potassium carbonate gave only a low yield of phenyl glycol, it is
concluded that the ester-linkage does not readily undergo alkyl-oxygen fission; alkaline hydrolysis of the ester-linkage by normal acyl-oxygen fission (independently of the hydrolysis of the bromide), which is a possibility, would not cause racemisation.

If, contrary to the present conclusion, the bromo-ester were 2-bromo-2-phenylethyl 2-ethylhexanoate, the above conclusions on hydrolysis would still apply, except that if $S_N1$ hydrolysis of the bromide, without the 'vicinal effect', occurred, there would be extensive, but probably not complete racemisation. However, the most probable course of hydrolysis in aqueous alkali would be as represented above, but with the phenyl group attached to $C_\beta$.

The course of the addition reaction, involving two stages, is set out in the attached diagram (p. 54.). The second stage, in which 2-bromo-1-phenylethyl 2-ethylhexanoate is formed by an $S_N2$-type reaction, is not essentially concerned in the asymmetric synthesis, which can occur only in Stage I when the stereoisomeric cations (i)' and (ii)' are formed via the intermediate diastereoisomeric critical complexes (i) and (ii). It is concluded from the experimental result that the asymmetry of the $\alpha$-carbon atom of the acyl hypobromite causes no appreciable difference in the rates of formation and of decomposition of (i) and (ii). The lack of influence is attributed to the distance, due to the
interposition of the -CO.O- grouping, between the asymmetric carbon atom and the styrene-bromine complex. This situation contrasts with that of the successful addition of bromine to \((-\text{phenyl-}\alpha\text{-methylallyl alcohol, in which the asymmetric centre was adjacent to the olefinic group undergoing addition.}\)
SOME REACTIONS INVOLVING THE BROMINE CATION.

(a) Substitution Reactions.

Introduction.

The use of acyl hypobromites in the experiments described in the preceding pages led to the awakening of an interest in the uses of "positive bromine" in other reactions, with a view to further stereochemical studies. The production of bromine cations in aqueous media and their use in substitution reactions have been studied by Waters et al. (J.C.S. 1950 573; Nature 1949 164 446; ibid. 1950 165 401).

They discovered that solutions containing the highly reactive bromine cation could readily be obtained by the addition of silver or mercuric salts to solutions of bromine in water or acetic acid, in the presence of either nitric or sulphuric acid. The addition of potassium bromate to acidic solutions of bromine also produced bromine cations and these solutions were active brominating agents.

These results are based on the following reactions:

\[ \text{Br}_2 + \text{H}_2\text{O} \rightarrow \text{H}^+ + \text{Br}^- + \text{HOBr} \]
\[ \text{HOBr} + \text{H}^+ \rightarrow \text{H}_2\text{O} + \text{Br}^+. \]

The bromine cations formed in this way have a strong tendency to combine with bromine anions to regenerate bromine,
but a considerable concentration of bromine cations may be obtained by the removal of bromine anions,

(a) as insoluble silver bromide,
(b) as feebly dissociated mercuric bromide,
or (c) by the addition of bromate ions, thus:

$$6H^+ + BrO_3^- + 5Br^- \rightarrow 3Br_2 + 3H_2O.$$  

Benzene, chlorobenzene and bromobenzene were brominated in this way in 2N nitric acid. For the bromination of benzoic acid and methyl benzoate more concentrated nitric acid was required, whilst nitrobenzene, 2,4-dinitrotoluene and \( m \)-dinitrobenzene needed 90% sulphuric acid for successful reaction to occur. The yields of mono-brominated products obtained by these reactions were quite high, being in the range 60-80%.

The Object and Course of the Investigation.

In view of the ease of preparation of bromine cations in solution, attempts were made to use such solutions to effect substitution reactions of the type,

$$\begin{align*}
\text{C}_2\text{H}_5 && & \text{C}_2\text{H}_5 \\
\text{H-C-COOH} + \text{Br}^+ & \rightarrow & \text{RCC-C-Br} + \text{H}^+ \\
\text{C}_4\text{H}_9 && & \text{C}_4\text{H}_9
\end{align*}$$
To this end experiments were performed with two acids, 2-ethylhexanoic and \( \alpha \)-phenylpropionic, in each of which the asymmetric carbon atom is tertiary, and it was hoped that reaction, as outlined above, might occur. In practice reaction did not take this course; no brominated acidic materials were isolated in the experiments on the purely aliphatic acid, and bromination of the \( \alpha \)-phenylpropionic acid took place in the aromatic nucleus.

The first experiment with 2-ethylhexanoic acid was carried out in 3N sulphuric acid; a solution of silver nitrate in water was added to a stirred mixture of the organic acid with two equivalents of bromine in the sulphuric acid. Immediate precipitation of silver bromide occurred and during three hours further stirring the colour of bromine gradually faded and finally disappeared, the oily droplets in the aqueous medium possessing, however, a red colouration. Extraction with ether and distillation yielded two main fractions, one consisting largely of the original acid, and the other of a liquid of lower boiling point and higher refractive index. The analysis of the latter material corresponded approximately to that of a mono-bromo-derivative of 3-heptyl 2-ethylhexanoate.

A similar experiment was carried out in 6N nitric acid when a small quantity of bromine-containing material was obtained; this boiled over a range of 60° and possessed a
refractive index considerably higher than that of the original acid (the latter formed the bulk of the total product). The bromine-content of this fraction was rather low and no structure could be assigned to it.

From the reaction of the same quantities of 2-ethylhexanoic acid, bromine and silver nitrate in a mixture of glacial acetic acid and nitric acid, 70% of the original acid was recovered and a little brominated material was isolated.

In an attempt to identify the products of these reactions, all fractions of corresponding boiling points were combined and subsequently separated into neutral and acidic fractions by treatment with sodium carbonate solution and extraction with ether. The only acidic material obtained in this way was the original 2-ethylhexanoic acid of which about 50% of the total used in the three experiments was recovered.

The neutral material isolated from the low-boiling fractions was separated by distillation into two parts, one (a) having b.p. 71-81⁰/21 mm., and the other (b) having b.p. 120-124⁰/21 mm. Analyses of these fractions showed that the former contained 44.6% bromine and the latter only 18.5%, but owing to the small quantities available it was impossible to purify the products further and no definite structural formulae could be assigned on the basis of the analytical results. The latter do indicate, however, as the
Table below illustrates, that the compounds are probably brominated derivatives of the ester formed by the loss of one carboxyl group between two molecules of the acid, possibly together with hydroxy derivatives of this bromo-ester, formed by hydrolysis of the brominated material.

The higher boiling neutral product (c), also, could not be identified; its bromine-content was approximately midway between those of the other two products (a) and (b). The table below shows the empirical formulae of these three products, calculated from the analytical results on the basis of \( C = 15 \). (The empirical formula of the ester from which it is postulated that they are derived is \( C_{15}H_{20}O_2 \).)

(a) \( C_{15}H_{29}S_0.5Br_2.4 \)
(b) \( C_{15}H_{29}O_4.5Br_0.8 \)
(c) \( C_{15}H_{26}O_4Br_1.4 \)

A similar attempt to brominate \( \alpha \)-phenylpropionic acid by means of the bromine cation was more successful, although reaction did not occur in the desired position. The gradual addition of an aqueous solution of silver nitrate to a stirred mixture of the acid, bromine and dilute sulphuric acid, resulted in the complete decolourisation of the reaction mixture and there was isolated a very viscous product, the analysis of which corresponded closely with that of a mono-brominated derivative of \( \alpha \)-phenylpropionic
acid. That the bromine atom had entered the aromatic
nucleus in preference to the replacement of the tertiary
hydrogen atom in the side-chain, was shown by the failure
of alcoholic potash to remove the bromine. Oxidation with
potassium permanganate yielded p-bromobenzoic acid apparently
mixed with some of the ortho- isomer, from which the pure
p-acid was separated by recrystallisation; no evidence for
the presence of benzoic acid was obtained.

Since these attempts to prepare α-bromo-acids did not
succeed, no experiments with optically active materials
were made.
(b) Addition Reactions.

Introduction.

The classical picture of the addition of halogens to olefinic double bonds involves the simultaneous addition of the two atoms of the halogen molecule to the unsaturated carbon atoms, but the discovery by McKenzie (J.C.S. 1912 101 1196.) that such additions occur predominantly in the trans-positions, exploded this theory of the mechanism of the reaction. The addition of bromine to maleic acid was found to yield racemic dibromosuccinic acid, while from a similar reaction of the halogen with fumaric acid, the chief product was meso-dibromosuccinic acid.

If the two atoms of a bromine molecule were to add simultaneously across the unsaturated bond in maleic acid (I), they must attach themselves on the same side of the plane of the molecule so that the two halves of the dibromo-succinic acid molecule would be mirror images of one another and the internally compensated meso- form would result. Similarly fumaric acid (II) would yield the racemic acid,

\[
\begin{align*}
(I) & \quad H-C-COOH \quad \parallel \quad H-C-COOH \\
& \quad H-C-COOh \quad \parallel \quad HOOC-C-H
\end{align*}
\]

The ready formation of an anhydride from maleic acid shows that in this acid, (I), the two carboxyl groups are adjacent.
whereas the only anhydride obtainable from fumaric acid, with much more difficulty, is that of maleic acid, fumaric anhydride being unknown. Thus the configurations of the acids are known and those of the resulting dibromosuccinic acids were proved by the resolution of the racemic mixture.

Hence the actual addition must have occurred in a trans-manner, the two atoms adding separately, one in front of, and the other behind, the plane of the molecule. This method of addition is not possible so long as the bromine atoms remain united and, therefore, the reaction must proceed in at least two stages.

That these steps involve ionic intermediates when the addition occurs in polar solvents, was indicated by the results of Terry and Eichelberger (J. Amer. Chem. Soc. 1925 47 1067.) and of Francis (J. Amer. Chem. Soc. 1925 47 2340.). The former workers studied the addition of bromine to maleate and fumarate ions in aqueous solutions and found that, together with the expected dibromosuccinic acids, a bromohydrin of the composition, HOOC\(\cdot\)CHBr\(\cdot\)CHOH\(\cdot\)COOH, was also formed. The presence in solution of a high concentration of bromide ions inhibited the production of this latter compound and it was also found that the presence of a high concentration of chloride ions resulted in the final isolation of much chloro-bromosuccinic acid. Francis (loc. cit.) studied the reaction of ethylene with bromine and iodine in aqueous
solution and found the addition of sodium chloride to result in the production of chlorobromo- and chloroiodo-ethanes, while 2-bromoethyl nitrate was found to be a product of the addition of bromine to ethylene in the presence of nitrate ions.

Francis accounted for these results by the hypothesis that the initial step in the reaction consists of the addition of a bromine cation,

\[
R\begin{array}{c}C\equiv C\end{array}R' + Br-Br \rightarrow \left[\begin{array}{c}R-\hat{C}\equiv C\end{array}R\right]^+ + Br^- \\
\]

followed by a nucleophilic attack on this positive ion by the negative ions present in the solution.

Ingold (Chem. Rev. 1934 15 270.) suggested that the addition of chlorine to an unsaturated compound occurs by the following stages:

\[
Cl_2 \rightarrow (\delta-)Cl-Cl(\delta+)\\
(\delta-)Cl-Cl(\delta+) \rightarrow Cl^- Cl \\
\rightarrow Cl Cl \rightarrow Cl Cl
\]

Kinetic studies of the addition of hydrogen bromide and hydrogen chloride to cyclohexene and 3-hexene by O'Connor, Baldinger, Hennion (J. Amer. Chem. Soc. 1939 61 1454.) showed that these reactions proceed with
greater velocity in non-polar solvents such as toluene and heptane, than in donor solvents such as ether, dioxane, etc. This supports Ingold's theory that the more electropositive portion of the molecule adds first, and that this step is rate-determining, because addition in donor solvents is hindered by the solvent molecules forming temporary coordinate linkages with the hydrogen halides.

Roberts and Kimball (J. Amer. Chem. Soc. 1937 59 947.) postulated a three-membered ring structure for the intermediate positive ion in order to explain the stereochemical specificity of the addition reaction:

\[
\begin{align*}
R-C=O & \quad \text{+ Br}_2 \quad \rightarrow \quad [R-C-Br]^+ \\
\end{align*}
\]

The attachment of the bromine ion to one carbon atom only would allow free rotation about the carbon-carbon bond and hence both maleic and fumaric acids should yield the same product or mixture of products on reaction with bromine.

That trans-addition results in an inversion of configuration of one, but not both, of the carbon atoms of the intermediate complex, was also shown by Roberts and Kimball. As shown in the diagram attached (A. p. 67.), this inversion occurs during the second step, the reaction of the bromide ion with the cyclic bromonium intermediate.
The existence of a cyclic intermediate of this type was also demonstrated by Winstein and Lucas (J. Amer. Chem. Soc. 1939 61 2845.) by the conversion of optically active specimens of erythro- and threo-3-bromo-2-butanol into meso- and dl-2,3-dibromobutane respectively, by treatment with fuming hydrobromic acid, as illustrated in the attached diagram (B. p. 67.). The most convincing way of accounting for the distinct course of reaction and the formation of a single, different product in each case, and the resultant loss of optical activity in both cases, is to postulate the formation of an intermediate of the form shown. Winstein and Buckles (J. Amer. Chem. Soc. 1942 64 2780.) studied the reaction of silver acetate in dry acetic acid with threo- and erythro-2-acetoxy-3-bromobutane and with meso- and dl-2,3-dibromobutane, and found retention of configuration to be the predominant occurrence. These steric results were believed to be due to the neighbouring bromine atom or acetoxy group participating in the process, with the production of the intermediates:

(i) \( \begin{align*} &\text{Br} \\ &\text{C} \end{align*} \)

and

(ii) \( \begin{align*} &\text{O} \\ &\text{C} \end{align*} \)

The same conclusion can also be drawn from the results obtained by Bartlett and Tarbell (J. Amer. Chem. Soc. 1937
A. 

cis- 

\[ \text{Br}_2 \rightarrow \text{C} \equiv \text{C} \text{CH}_3 \] 

(i) ONLY POSSIBLE STRUCTURE (SYMmetrical) 

\[ \text{Br}_2 \rightarrow \] 

\[ \text{C} \equiv \text{C} \text{C} \text{H}_3 \] 

\[ \text{Br}_2 \rightarrow \] 

\[ \text{C} \equiv \text{C} \text{C} \text{H}_3 \] 

\[ \text{Br}_2 \rightarrow \] 

\[ \text{d}-2,3\text{-DIBROMOBUTANE} \] 

and 

\[ \text{d}-2,3\text{-DIBROMOBUTANE} \] 

trans- 

\[ \text{Br}_2 \rightarrow \text{C} \equiv \text{C} \text{CH}_3 \] 

\[ \text{Br}_2 \rightarrow \] 

\[ \text{C} \equiv \text{C} \text{C} \text{H}_3 \] 

\[ \text{Br}_2 \rightarrow \] 

\[ \text{d}-2,3\text{-DIBROMOBUTANE} \] 

and 

\[ \text{d}-2,3\text{-DIBROMOBUTANE} \] 

B. 

optically active 

\[ \text{Br}_2 \rightarrow \text{C} \equiv \text{C} \text{CH}_3 \] 

\[ \text{Br}_2 \rightarrow \] 

\[ \text{C} \equiv \text{C} \text{C} \text{H}_3 \] 

\[ \text{Br}_2 \rightarrow \] 

\[ \text{d}-2,3\text{-DIBROMOBUTANE} \] 

\[ \text{d}-2,3\text{-DIBROMOBUTANE} \] 

optically active 

\[ \text{Br}_2 \rightarrow \text{C} \equiv \text{C} \text{CH}_3 \] 

\[ \text{Br}_2 \rightarrow \] 

\[ \text{C} \equiv \text{C} \text{C} \text{H}_3 \] 

\[ \text{Br}_2 \rightarrow \] 

\[ \text{d}-2,3\text{-DIBROMOBUTANE} \] 

\[ \text{d}-2,3\text{-DIBROMOBUTANE} \]
on the addition of halogens to dimethylmaleic acid and dimethylfumaric acid in alkaline solutions, halo-lactones resulting.

Supporting evidence as to the ionic nature of these addition reactions may be drawn from the results of Stewart and Edlund (J. Amer. Chem. Soc. 1923 45 1014.) who found that the addition of bromine to ethylene was a surface-catalysed reaction. Norrish (J.C.S. 1923 123 306.) found that this reaction proceeded nearly thirty times as quickly on a surface of stearic acid than on one of paraffin wax, thus showing that a polar catalyst assists in the reaction. Williams (J.C.S. 1932 1747, 1758.) found the rate of reaction to decrease with increasing temperature, indicating that the reaction was not a direct combination of the two components but depended upon the formation of an intermediate product which was less stable at higher temperatures. The fact that the presence of water accelerated the reaction led to the hypothesis that the active intermediate may be a hydrated bromine molecule, the positive ion of which is reactive.

The Entry of "Foreign Ions"

As has already been mentioned, the addition of a halogen to an unsaturated compound in polar solvents leads to the production of other compounds besides those normally formed by such addition reactions in non-polar solvents.
The preparation of bromohydrins in good yield by the interaction of olefins with bromine in aqueous solutions has been demonstrated by Read et al. (J.C.S. 1917 111 240; ibid. 1920 117 1214, etc.). That this reaction does not occur through the formation of hypobromous acid,

\[ \text{Br}_2 + \text{H}_2\text{O} = \text{HBr} + \text{HOBr} \]

\[ \text{C}_2\text{H}_4 + \text{HOBr} = \text{BrCH}_2\text{-CH}_2\text{OH} \]

was shown by Francis (J. Amer. Chem. Soc. 1925 47 2340) who found that alteration of the hypobromous acid concentration by working in acidic solutions did not affect the rate of reaction, and furthermore, hypobromous acid itself was found to be less reactive in the production of bromohydrins than was bromine water. The reaction was therefore formulated thus:

\[ \text{C}_2\text{H}_4 \rightarrow \text{CH}_2\text{-CH}_2; \quad \text{Br}_2 \rightarrow \text{Br} + \text{Br} \]

\[ \text{Br}^+ + \text{CH}_2\text{-CH}_2 \rightarrow \text{BrCH}_2\text{-CH}_2^+ \]

\[ \text{BrCH}_2\text{-CH}_2^+ + \text{X}^- \rightarrow \text{BrCH}_2\text{-CH}_2\text{X} \quad (\text{X} = \text{Br, OH, etc.}) \]

Backer and Strating (Rec. Trav. Chim. 1934 53 525) on addition of chlorine and of bromine to 2,3-dimethyl-2-butene-1,4-sulphone in glacial acetic acid obtained the 3-acetoxyl-4-halo-addition compound in 10-20% yield,
Similarly, Bockemüller and Hoffmann (Ann. 1935 519 165.) found that when the addition of chlorine to allyl chloride was carried out in homogeneous solution in carbon tetrachloride in light, the only product was 1,2,3-trichloropropene. When, however, the reaction was performed in acetic acid solution there was obtained, together with the trichloropropene, about 20% of a higher boiling product which was subsequently identified as 2,3-dichloropropyl acetate. The formation of this ester they attributed to the following reactions:

\[
\begin{align*}
\text{CH}_3\text{COOH} + \text{Cl}_2 & \rightarrow \text{CH}_3\text{COCl} + \text{HCl} \\
\text{CH}_2\text{CH} = \text{CHCl} + \text{CH}_3\text{COOCl} & \rightarrow \text{CH}_2\text{CHClCH}_2\text{Cl} + \text{CH}_3\text{COO} \cdot \text{CH}_3
\end{align*}
\]

and on the basis of this reaction they commenced their study of the reactions of acyl hypohalites already mentioned.

The addition of bromine to stilbene in methanol solution was studied by Bartlett and Tarbell (J. Amer. Chem. Soc. 1936 58 466.) who isolated two products,

Ph.CHBr.CHBr.Ph and Ph.CHBr.CHMe.Ph

(I) (II)
The possibility that (II) might have arisen by direct addition of methyl hypobromite was disposed of by a kinetic study of the reaction, the rate being of the first order in stilbene and independent of the acidity of the solution. Methyl hypobromite could arise by the reaction:

\[
\text{Br}_2 + 2\text{CH}_3\text{OH} \rightarrow \text{CH}_3\text{OB}r + \text{Br}^- + \text{CH}_2\text{OH}^+.
\]

If this were rate determining, then the rate would be independent of the stilbene concentration; if the addition of the hypobromite were rate determining, then the rate of addition, which would be proportional to the concentration of hypobromite, would vary inversely as the hydrogen ion concentration. The relative amounts of (I) and (II) were found to vary with varying concentrations of bromide ions in a way consistent with the assumption that the intermediate complex could react in either of two ways:

\[
\begin{align*}
\left[\text{Ph.CH-CH.Ph}\right]^+ + \text{Br}^- & \rightarrow \text{Ph.CHBr.CHBr.Ph} \\
\left[\text{Ph.CH-CH.Ph}\right]^+ + \text{CH}_2\text{OH} & \rightarrow \text{Ph.CHBr.CHMe.PH} + \text{H}^+
\end{align*}
\]

The total rate of reaction is decreased by the addition of bromide ions in a way that can be accounted for by the production of a tri-bromide ion which reacts at a rate one hundred times slower than does bromine:

\[
\text{Br}_2 + \text{Br}^- \rightarrow \text{Br}_3^-
\]
Weber, Hennion and Vogt (J. Amer. Chem. Soc. 1939 61 1457.) on passing chlorine and ethylene through acetic acid, acetic anhydride or methyl acetate, found that in each case the main products were ethylene dichloride and 2-chloroethyl acetate, some glycol diacetate also being formed.

Additions to Styrene and Cyclohexene.

That it is the bromine cation which first takes part in the addition of a halogen to an olefinic bond is apparent from the experiments described above. The production of high concentrations of active bromine cations in aqueous solutions has already been described (Derbyshire and Waters, J.C.S. 1950 573.) and it was decided to attempt to use a modification of this method in order to effect the preparation of bromo-esters preferentially to the dibromides, by the addition of bromine to a mixture of the olefine and the silver salt of the carboxylic acid together with the free acid in sulphuric acid solution.

To this end a solution of bromine (2 equivalents) in glacial acetic acid was added slowly to a vigorously stirred mixture of silver acetate, acetic acid and styrene in 6N sulphuric acid. Filtration and extraction, followed by distillation of the extract, yielded a product which consisted

\[
\text{Ph.CH.CH.PH} + \text{Br}_3^- \rightarrow \frac{\text{Ph.CH-CH.PH}}{\text{Br}}^+ + 2\text{Br}^-
\]
substantially of 2-bromo-1-phenylethyl acetate. The latter was contaminated with a little styrene dibromide, the presence of which considerably elevates the refractive index of the bromo-ester. Hydrolysis with aqueous sodium hydroxide gave phenyl glycol in 90% yield.

A similar experiment performed in the absence of the silver salt resulted in the production of styrene dibromide together with some of the bromo-ester. Further experiments in the absence of silver bromide but with the addition of sodium bromide and also by adding the bromine undiluted with acetic acid, gave (in comparison with the first experiment) greater yields of the dibromide and less of the bromo-ester; a small quantity of the latter appeared to be produced in each case. Pure styrene dibromide was subjected to hydrolysis with aqueous sodium hydroxide and gave only 20% of the theoretical yield of phenyl glycol.

As a result of adding a solution of bromine in acetic acid to a stirred mixture of cyclohexene, silver acetate, acetic acid and sulphuric acid in a manner similar to the above, there was obtained a mixture of approximately equal quantities of 2-bromocyclohexyl acetate and 1,2-dibromocyclohexane. From the lower boiling fraction, containing mainly dibromide, there separated on cooling colourless needles which after recrystallisation from ether, had
m.p. 124-126°. This compound contained no bromine and analysis gave the empirical formula C₆H₁₀O; it is postulated that the compound may be C₁₂H₂₀O₂, or octahydrodiphenylene dioxide. Both fractions from this addition reaction rapidly darkened after distillation, becoming first pale blue, then green, violet and finally black.

A similar experiment in which the silver acetate was omitted gave mainly the dibromide, only a little of the bromo-ester being formed.

The results of these experiments are shown below in tabular form. In each case a mixture of the bromo-ester and the dibromide was obtained, the separation of the components of which was difficult to achieve completely; the yields of bromo-ester are therefore given as a calculated percentage of the total product, the calculation being based on the analytical results and the weights of the products obtained.

<table>
<thead>
<tr>
<th>Unsaturated Compound used</th>
<th>Conditions of Reaction</th>
<th>% Yield of Bromo-ester</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Styrene</td>
<td>Silver acetate present</td>
<td>70</td>
</tr>
<tr>
<td>2. Styrene</td>
<td>Silver acetate absent</td>
<td>25</td>
</tr>
<tr>
<td>3. Styrene</td>
<td>As 2. Sodium bromide added</td>
<td>15</td>
</tr>
<tr>
<td>4. Styrene</td>
<td>As 2. Bromine added undiluted</td>
<td>10</td>
</tr>
<tr>
<td>5. Cyclohexene</td>
<td>Silver acetate present</td>
<td>50</td>
</tr>
<tr>
<td>6. Cyclohexene</td>
<td>Silver acetate absent</td>
<td>20</td>
</tr>
</tbody>
</table>
The results of these experiments indicate that the removal of bromide ions as silver bromide enhances the possibility of the formation of the bromo-ester, whilst the addition of such ions has the opposite effect; thus they are in complete agreement with the theory that the addition of halogens to unsaturated compounds in polar solvents is ionic in character.
EXPERIMENTAL SECTION.

(i) Introductory Notes.

(a) In all experiments involving bromine, apparatus with ground glass joints was used.

(b) Dry bromine was obtained by shaking commercial bromine twice with an equal volume of concentrated sulphuric acid, followed by distillation from phosphorus pentoxide.

(c) Carbon tetrachloride was first dried over calcium chloride and distilled, then dried over phosphorus pentoxide, distilled from the same reagent, and stored in a stoppered bottle containing phosphorus pentoxide.

(d) Styrene was kept over anhydrous sodium sulphate and was distilled (a little hydroquinone having been added) immediately before use.

(e) All refractive indices were taken with an Abbé refractometer, maintained at 25°.
(ii) The Preparation and Resolution of Acids.

(a) 2-Ethylhexanoic Acid

1. 2-Ethylhexanoic acid.

A mixture of 2-ethylhexanol (Commercial, b.p. 181-182°, 130 g.) and a solution of sodium hydroxide (30 g.) in water (300 ml.) contained in a five-litre three-necked flask fitted with a mercury-sealed stirrer, a reflux condenser and a wide-bore dropping funnel, was vigorously stirred during the addition of potassium permanganate (340 g.) in water (3 l.). After the addition was complete the hot mixture was stirred for twelve hours. Dilute sulphuric acid (100 ml., 1:1) was then added and sulphur dioxide was passed through the stirred mixture until all the precipitated manganese dioxide had dissolved, the acid which separated then being extracted with ether. This ethereal extract was extracted with excess sodium bicarbonate solution, leaving the unoxidised alcohol in the ethereal solution, whence it was recovered by distillation. The aqueous alkaline extract was acidified with hydrochloric acid, extracted with ether, the extract dried overnight with anhydrous sodium sulphate and, after evaporation of the solvent, the residual acid was distilled under reduced pressure. 2-Ethylhexanoic acid, 76 g. (65% yield on the alcohol oxidised) b.p. 132-135°/26 mm., 224-226°/760 mm., nD 1.4216 was obtained. Twenty grams of
2-ethylhexanol, b.p. 181-183°, were recovered.

2. (-)-2-Ethylhexanoic acid.

Quinine (234 g.) was added to a hot solution of 2-ethylhexanoic acid (103 g.) in aqueous acetone (1100 ml., 50%). The resulting white, fluffy salt was recrystallised seven times from aqueous acetone to give needles (84 g.), m.p. 107-108°, having $[\alpha]_D^{20} +120.3°$ (c, 5; 1, 2 in 99% alcohol). Decomposition with ice-cooled hydrochloric acid yielded (-)-2-ethylhexanoic acid (23.5 g.), b.p. 118-120°/ 16 mm., having $[\alpha]_D^{17} -7.95°$, $d_4^{17} 0.9079$, and $n_2^20 1.4231$.

3. (+)-2-Ethylhexanoic acid.

The combined filtrates from the first four recrystallisations of the quinine salt were decomposed with hydrochloric acid and yielded 2-ethylhexanoic acid (50 g.), b.p. 125-130°/ 21 mm., having $d_4^{20} +6.55°$ (1, 2). This was combined in warm aqueous acetone (700 ml., 50%) with cinchonidine (102 g.) and the resulting salt was recrystallised five times from aqueous acetone. The cinchonidine salt of the (+)-acid (57 g.), m.p. 67-69°, $[\alpha]_D^{19} +63.0°$ (c, 5; 1, 2 in 99% alcohol.), on decomposition with hydrochloric acid, yielded (+)-2-ethylhexanoic acid (17.2 g.), b.p. 117-119°/ 15 mm., $[\alpha]_D^{17} +8.89°$ (1, 0.5), $d_4^{17} 0.9081$, $n_2^20 1.4231$. 
(b). \( \alpha \)-Phenylpropionic Acid.

1. Oxidations of \( \alpha \)-Phenylpropionaldehyde to the Acid.

(i) With neutral potassium permanganate.

\( \alpha \)-Phenylpropionaldehyde (Commercial, b.p. 90°/17 mm. 200 g.) was dissolved in acetone and water (400 ml. + 150 ml.) contained in a three-necked flask fitted with a mercury-sealed stirrer and a reflux condenser. To this vigorously stirred solution was gradually added a finely-ground mixture of potassium permanganate (150 g.) and magnesium sulphate heptahydrate (118 g.) during one hour, the reaction being moderated occasionally by placing cold water round the flask. After a further two hours' stirring, the mixture was cooled and then sulphur dioxide was passed through it, with stirring, until the manganese dioxide had completely dissolved. The product was extracted from the pink solution with ether and, after evaporation of the solvent, was mixed with an excess of aqueous sodium bicarbonate solution (130 g. in 500 ml.). The undissolved oil was extracted from this solution with ether, dried and distilled. The alkaline solution was acidified with hydrochloric acid, extracted with ether, the extract dried with anhydrous sodium sulphate and fractionally distilled. Yield of \( \alpha \)-phenylpropionic acid 86 g. (38%), b.p. 152-153°/17 mm. Equivalent, found by titration with standard sodium hydroxide solution, 151.2.
for $C_9H_{10}O_2$, 150.2.

The alkali-insoluble material (44 g.) had b.p. 90-92°/17 mm.,
$n^25_0$ 1.5305. A viscous gum (56 g.) remained in the distillation
flask.

**Identification of the Alkali-insoluble Product**

The alkali-insoluble liquid obtained in (i) above was
found to be a carbonyl compound but it was not $\alpha$-phenyl-
propionaldehyde, as the following figures prove:

<table>
<thead>
<tr>
<th></th>
<th>The CO compound</th>
<th>$\alpha$-Phenyl-propionaldehyde</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semi-carbazone, m.p.</td>
<td>195-197°</td>
<td>152°</td>
</tr>
</tbody>
</table>
| 2,4-dinitrophenyl-
  hydrazone, m.p.         | 188-190°        | 117-119°                         |
| Refractive indices, $n^25_0$ | 1.5305           | 1.5168                           |

It reacted with bromine in warm carbon tetrachloride
with the evolution of hydrogen bromide and the formation of
a very lachrymatory material.

Oxidation of the carbonyl compound (44 g.) with acidic
sodium dichromate (as in (ii) below) yielded: benzoic acid,
10 g., m.p. 121°, unchanged compound 22 g., b.p. 90°/18 mm.,
and a gummy residue, 10 g.

Semi-carbazone of the compound, found: C, 61.1; H, 6.2; N, 22.8%

Calculated for $C_9H_{10}O_2$: C, 61.0; H, 6.3; N, 22.7%

The empirical formula of the compound is hence: $C_9H_{10}O_2$, or
possibly, $C_9H_6\cdot CO\cdot CH_2$. The semi-carbazone of the compound was found to have m.p. 195-197° alone, and when mixed with an authentic specimen of acetophenone semi-carbazone of m.p. 196-197°. The compound was therefore acetophenone.

(ii) With acidic sodium dichromate.

To a vigorously stirred mixture of $\alpha$-phenylpropion-aldehyde (40 g.) and dilute sulphuric acid (109 ml., 1:2 w/w) contained in a three-necked flask fitted with a reflux condenser and heated on a steam-bath, was added finely-ground sodium dichromate (27.5 g.) during one hour, after which the stirring and heating were continued for two hours. After cooling, the mixture was extracted with ether and the product purified by treatment with sodium bicarbonate solution. The neutral and acidic ethereal extracts so obtained were dried and distilled. There was obtained:

$\alpha$-phenylpropionic acid 5 g. (23%), b.p. 152°/17 mm.,
a-phenylpropionaldehyde (20 g.), b.p. 94-97°/22 mm.,
(semi-carbazone m.p. 149-150°),
and a viscous gum (11 g.).

(iii) With acidic potassium permanganate.

A stirred mixture of $\alpha$-phenylpropionaldehyde (23.5 g.) and dilute sulphuric acid (8.5 ml. concentrated in water, 50 ml.) was heated on a steam-bath during the addition of
powdered potassium permanganate (16.5 g.) during thirty minutes. After a further two hours' heating and stirring, the mixture was cooled and sulphur dioxide was passed through it to dissolve the precipitate. The product was extracted with ether and purified as above. It yielded:

- α-phenylpropionic acid (3 g., b.p. 151-152°/ 17 mm.),
- phenylpropanaldehyde (15 g., b.p. 90-95°/ 20 mm.),
- 1 gums (10 g.).

(iv) With alkaline potassium permanganate.

Whilst α-phenylpropanaldehyde (40 g.) was being added dropwise to a stirred solution of sodium carbonate (18 g.) in water (100 ml.), powdered potassium permanganate (35 g.) was added in small portions during one hour. After two hours' warming, with stirring, on a steam-bath, the mixture was cooled, filtered, acidified with sulphuric acid and extracted with ether. The acid so obtained was purified as before and distilled; yield of α-phenylpropionic acid, b.p. 150-153°/ 17 mm. 4 g. (10%). A pitch-like resin (25 g.) was also formed.

2. α-Phenylproponitrile.

To a stirred solution of benzyl cyanide (140 g.) in dry ether (300 ml.) contained in a three-necked flask fitted with a mercury-sealed stirrer, a reflux condenser and a large-bore dropping funnel, was added carefully, in small portions, a
suspension of sodamide (47 g.) in dry ether (150 ml.) during thirty minutes. The mixture was heated under reflux, with stirring, for three hours and then cooled in an ice-bath. Dimethyl sulphate (170 g.) was added to this cooled, stirred mixture during four hours, after which stirring was continued at room temperature for eight hours. Water (500 ml.) was then added, the ethereal layer separated and dried with anhydrous sodium sulphate. The ether was evaporated and the residual \(\alpha\)-phenylpropionitrile purified by distillation under reduced pressure. Yield 120 g. (76\%), b.p. 116-118°/ 20 mm.

2. \(\alpha\)-Phenylpropionic acid.

In a flask fitted with a two-way adaptor, one bearing a reflux condenser and the other a tap funnel, was placed a mixture of water (105 ml.), glacial acetic acid (125 ml.) and concentrated sulphuric acid (140 ml.). To this was added \(\alpha\)-phenylpropionitrile (120 g.) and the spontaneous refluxing which occurred was maintained by heating for four hours. The solution was then cooled, the upper layer separated, washed with water and taken up in an excess of sodium hydroxide solution (3N.). The alkaline solution was extracted with ether and acidified with hydrochloric acid. The liberated \(\alpha\)-phenylpropionic acid was extracted with ether, dried with anhydrous sodium sulphate and distilled; it (112 g., 82\%) had b.p. 158-160°/ 22 mm., \(n_\text{D}^0\) 1.5210
4. (+)-α-Phenylpropionic acid.

Strychnine (200 g.) was added to a hot solution of α-phenylpropionic acid (90 g.) in aqueous alcohol (900 ml., 75%). From the resulting solution, after allowing to stand in a refrigerator for four days, strychnine α-phenylpropionate (130 g.) separated in large rhombs. Concentration of the filtrate to half-bulk yielded a further crop of salt (35 g.). Fractional crystallisation to the fifth crops yielded a main crop (V, 65 g.) and a secondary crop (E, 40 g.). Decomposition of these crops of salt with ammonia yielded two specimens of (+)-α-phenylpropionic acid, both of which solidified on standing, forming large glassy rhombs.

(i) (+)-α-Phenylpropionic acid (from V) 16.0 g., b.p. 148-149°C/15 mm., m.p. 29°C, $\alpha_D^{16} +51.52° (1,0.5)$.

(ii) (+)-α-Phenylpropionic acid (from E) 11.0 g., b.p. 144-146°C/14 mm., m.p. 23-29°C, $\alpha_D^{16} +46.15° (1,0.5)$.

5. (-)-α-Phenylpropionic acid.

The concentrated, combined filtrates from the first three recrystallisations of the strychnine salt were decomposed with ammonia and the α-phenylpropionic acid was liberated by acidification, extraction and distillation. It (33.5 g.) had $\alpha_D^{20} -32.5° (1,0.5)$, b.p. 152-154°C/18 mm. After standing for three days in a refrigerator this acid crystallised as large colourless prisms. These were allowed to melt partially
at about 25° and the liquid, which had $c_0^{20\circ} = -27.9\circ$ (1,0.5), was drained off. The crystals were melted, allowed to recrystallise and the process was repeated, the liquid this time having $c_0^{17\circ} = -28.2\circ$ (1,0.5). The remaining crystals (10 g.) when melted had $c_0^{17\circ} = -39.32\circ$ (1,0.5).
(c) $\alpha$-(p-Nitrophenyl)-propionic Acid.

1. $\alpha$-(p-Nitrophenyl)-propionitrile.

Fuming nitric acid (300 ml., d. 1.49) was added drop-wise to stirred $\alpha$-phenylpropionitrile (48 g.), cooled to $-10^\circ$ in a freezing mixture, during four hours. The mixture was allowed to stand for two days and then poured into crushed ice and water (2.5 l.). The next day the semi-solid mass was extracted with ether, the extract washed well with water and dried with anhydrous magnesium sulphate. Light petroleum (b.p. 40-60°) was added when the required $\alpha$-(p-nitrophenyl)-propionitrile separated as pale yellow rhombs, m.p. 73-74°, (13 g., 25%). Concentration of the filtrate gave a second crop of yellow crystals, these having m.p. 50-60°, while complete removal of the solvent left an intractable brown oil (30 g.), which was not examined further.

2. $\alpha$-(p-Nitrophenyl)-propionic acid.

The nitrile (12.6 g.) prepared as above, was heated under reflux with concentrated hydrochloric acid (50 ml.) for four hours. On cooling the oily layer solidified; this was filtered off, treated with sodium carbonate solution and the insoluble nitrile was removed by filtration. Acidification of the alkaline solution gave the acid (5.9 g.) m.p. 84-85°. The recovered nitrile (6 g.) was heated under reflux with sulphuric acid (50 ml., 70%) for thirty minutes,
after which treatment as above gave a further 5.1 g. of the acid, m.p. 84-85°. The acid separated from methylene chloride-cyclo-hexane as pale yellow rhombs m.p. 86-87°, (9.0 g. 70%).
(iii) The Brominative Decarboxylation of Silver Carboxylates.

(a) Silver 2-Ethylhexanoate.

1. Silver Acetate.

Sodium hydroxide solution (300 ml., N.) was added to distilled glacial acetic acid (20 g., b.p. 119°) and the solution was titrated with the alkali until just alkaline to phenolphthalein. This solution was added dropwise with stirring to a solution of silver nitrate (55 g.) in distilled water (100 ml.). The precipitated silver salt was filtered at the pump, washed with water, alcohol and ether. Drying over phosphorus pentoxide in vacuo yielded silver acetate (50 g., 92%).

2. Silver 2-Ethylhexanoate.

2-Ethylhexanoic acid (29.0 g.) was added to warm aqueous sodium hydroxide solution (180 ml. N.) and this solution was then titrated with the caustic soda until just alkaline to phenolphthalein. The solution was added dropwise with stirring to one of silver nitrate (32.6 g.) in warm distilled water (300 ml.). The precipitated silver 2-ethylhexanoate was washed by decantation with cold water, filtered at the pump, washed with more water, then with acetone and finally with ether. The product was dried over calcium chloride in vacuo, finely ground in a mortar and then dried.
over phosphorus pentoxide in vacuo. Yield of silver 2-ethylhexanoate 44 g. (93%).


The silver salts of specimens of the optically active acids were prepared similarly and were obtained in 92-98% yield. All specimens of silver salt were obtained as slightly pink, rather sticky solids, which required prolonged drying, and were stored in dark brown bottles.

4. 3-Bromo-n-heptane (I).

Method of Arnold and Morgan. (J. Amer. Chem. Soc. 1948 70 4248.)

A mixture of finely-powdered, dry silver acetate (14.5 g.), 2-ethylhexanoic acid (12.0 g.) and dry carbon tetrachloride (240 ml.) was heated under reflux on a steam-bath for ninety minutes. The mixture was then cooled to room temperature, a solution of dry bromine (4.5 ml.) in carbon tetrachloride (19 ml.) was added, slowly at first and then rapidly, and the suspension was heated under reflux for seven hours. After cooling, the silver salts were removed by filtration through sintered glass, the filtrate was well shaken with an aqueous solution of sodium meta-bisulphite containing caustic soda (15 ml.) and dried with anhydrous sodium sulphate. The carbon tetrachloride was evaporated and the residue fractionally distilled twice under reduced pressure. 3-Bromo-n-heptane
was thus obtained in 30% yield (4.5 g.), b.p. 55-58°/ 20 mm., 
\( n^o_{D} = 1.4477 \).

5. 3-Bromo-n-heptane, (ii).

A mixture of finely-powdered, dry silver 2-ethyl-
hexanoate (15.0 g.) and dry carbon tetrachloride (150 ml.)
was contained in a three-necked flask, fitted with a
mechanical stirrer, a dropping funnel and a reflux condenser
carrying a tube containing a mixture of soda-lime and calcium
chloride. To the suspension formed by vigorously stirring this
mixture was added a solution of dry bromine (8.0 g.) in carbon
tetrachloride (30 ml.) during fifteen minutes, after which
the mixture was stirred for two and a half hours, during
the first hour of which the bromine colouration faded and
disappeared, while a fine precipitate of silver bromide was
formed. The latter was filtered off using a sintered glass
funnel and the solution was heated under reflux for two and
a half hours. It was then cooled, washed with sodium meta-
bisulphite solution (20 ml., 20%), sodium carbonate solution
(20 ml., 20%) and water. The carbon tetrachloride solution
was dried overnight with anhydrous sodium sulphate, the
solvent removed by distillation and the residue fractionally
distilled under reduced pressure. Yield of silver bromide
11 g. (100%). Yield of 3-bromo-n-heptane 3.3 g., (30%),
b.p. 65-67°/ 23 mm., \( n^o_{D} = 1.4482 \). Found, Br, 44.2% .
Calculated for C\(_7\)H\(_{15}\)Br, Br 44.6%.
Silver (+)-2-ethylhexanate was prepared as previously described from a specimen of the (+)-acid with $\beta^D_{D} = 8.23^\circ$, (1.05; 92% optically pure). The dry, powdered silver salt (19.3 g.) was mixed with dry carbon tetrachloride (200 ml.) in a three-necked flask, fitted with a stirrer, a dropping funnel, a reflux condenser and a drying tube, and cooled in iced water to 10-15°. During the vigorous stirring of this mixture, a solution of dry bromine (13.4 g.) in carbon tetrachloride (35 ml.) was added during fifteen minutes, followed by further stirring for two and a half hours, the liquid by then being colourless. After removal of the precipitated silver bromide by filtration through sintered glass, the filtrate was heated under reflux for one hour. The solution was then cooled, shaken well with a solution of sodium meta-bisulphite (20 ml., 20%), washed with sodium carbonate solution (25 ml., 20%) and with water. The solution was dried with anhydrous sodium sulphate, the solvent evaporated and the residue fractionally distilled three times. Yield of silver bromide 14.3 g. (100%).

Twice distilled (+)-3-bromo-n-heptane: 4.6 g. (34%).

b.p. 63-65°/24 mm., $n^D_5 = 1.4482$, $a^D_5 = 0.27^\circ$ (1.2; homogeneous).

Thrice distilled (+)-3-bromo-n-heptane: 3.2 g., b.p. 63-65°/22 mm.

$\text{Br}_3$ 1.4482, $a^D_5 = 0.06^\circ$ (1.05; homogeneous).

Found, Br, 44.6%. Calculated for C$_7$H$_5$Br, Br, 44.6%. 
7. \((-\)-3-bromo-\(n\)-heptane.

Silver \((-\)-2-ethylhexanoate was prepared from the \((-\)-acid having \(\alpha_D^{27} = -3.49^0\) (1.05), \(\alpha_D^{27} = -7.6^0\) (82\% optically pure) as already described. Using the same apparatus as in the previous experiment but with cooling to 0-10\(^0\), a solution of dry bromine (4.9 g.) in carbon tetrachloride (20 ml.) was added during 10 minutes to a vigorously stirred suspension of the silver salt (8.0 g.) in dry carbon tetrachloride (100 ml.). Stirring was continued until all colour of bromine had disappeared, 45 minutes. The solution was freed from silver bromide by filtration, shaken well first with a solution of sodium meta-bisulphite (20 ml., 20\%), then with one of sodium carbonate (25 ml., 20\%), washed with water and dried with anhydrous sodium sulphate. The solvent was evaporated and the residue fractionally distilled under reduced pressure. Yield of silver bromide 6 g. (100\%).

Yield of once-distilled bromide, 3.4 g. (60\%), b.p. 63-70\(^0\)/25 mm.

Redistilled \((-\)-3-bromo-\(n\)-heptane: 2.73 g., b.p. 66-68\(^0\)/26 mm.,
\(\alpha_D^{20} -0.07^0\) (1,0.5; homogeneous)

Thrice distilled \((-\)-3-bromo-\(n\)-heptane: 2.10 g., \(n_D^{25} = 1.4481,\)
b.p. 66-68\(^0\)/26 mm., \(\alpha_D^{20} -0.06^0\) (1,0.5; homogeneous)

Found, Br, 44.5\%. Calculated for \(C_7H_{16}Br\), Br, 44.6\%. 

8. (+)-3-bromo-n-heptane. (ii).

Silver (+)-2-ethylhexanoate was prepared from a specimen of (+)-2-ethylhexanoic acid with $d_2^{22°} +15.07°$ (1.2; 93° optically pure) by the method already given. Apparatus as in experiment (i) was set up, the flask this time being cooled in a freezing mixture to between -15° and -10°. To the well-stirred, cooled suspension of the silver salt (10.0 g.) in dry carbon tetrachloride (100 ml.) was added an ice-cooled solution of dry bromine (6.2 g.) in carbon tetrachloride (25 ml.), during fifteen minutes. After fifteen minutes further stirring, the cold mixture was filtered by suction through a sintered glass funnel, with the exclusion of moist air. The filtrate was then heated under reflux for thirty minutes, cooled, washed with sodium meta-bisulphite solution (20 ml., 20%), sodium carbonate solution (25 ml., 20%) and water. After drying the solution with anhydrous sodium sulphate and evaporation of the solvent, the residual (+)-3-bromo-n-heptane was purified by distillation under reduced pressure. Yield of (+)-3-bromo-n-heptane, 2.5 g., (35%) b.p. 64-70°/ 25 mm., $n_d^{25°} 1.4484$, $d_2^{10} +0.19°$ (1.0.5).

Redistilled (+)-3-bromo-n-heptane: 1.5 g., b.p. 65-67°/ 25 mm. $n_d^{25°} 1.4482$, $d_2^{10} +0.18°$ (1.0.5)

Found. C, 47.1; H, 8.8; Br, 44.6%.

Calculated for $C_7H_{15}Br$: C, 46.9; H, 8.4; Br, 44.6%.
(b) Silver α-Phenylpropionate.

1. Silver α-Phenylpropionate.

To α-phenylpropionic acid (30 g.) was added aqueous sodium hydroxide solution (175 ml., N) and the resulting mixture was titrated with the alkali until just alkaline to phenolphthalein. This solution was warmed to about 50°C and to it was added, dropwise with stirring, a warm solution of silver nitrate (34 g.) in distilled water (200 ml.). The precipitated silver α-phenylpropionate was cooled, washed with water by decantation, filtered, washed with water, acetone and ether in turn and then dried in vacuo over phosphorus pentoxide. It was finely ground, stored in a dark bottle and re-dried before use as required. Yield 50 g. (97%).

2. Reactions of Silver α-Phenylpropionate with Bromine.

To a well-stirred suspension of silver α-phenylpropionate (10.5 g.) in dry carbon tetrachloride (80 ml.), boiling under reflux on a steam-bath, was added a solution of dry bromine (6.4 g.) in the same solvent (20 ml.) during fifteen minutes. The mixture was heated until all the bromine colour had disappeared (1.5 hours) and then for a further hour. After cooling to room temperature the silver bromide was filtered off, using a sintered glass filter. The filtrate was
shaken with sodium bicarbonate solution, washed with water, dried with anhydrous sodium sulphate and after evaporation of the solvent, the residue was distilled under reduced pressure, no clear-cut fraction being obtained. Product, a yellow oil, 4.0 g., b.p. 90-210°/17 mm., n\text{D}^{25} 1.5460. From the bicarbonate washing an acidic product (0.5 g.) was recovered.

(ii)

Experiment (i) was repeated, the bromine solution being added during one hour and the total time of heating being four hours. Treatment as before yielded an oil (4.5 g.) b.p. 100-210°/27 mm., n\text{D}^{25} 1.5471. An acidic product (0.5 g.) was recovered from the washings.

(iia)

The products of experiments (i) and (ii) were combined and distilled under reduced pressure, two fractions being taken:

- Fraction 1: 3 g., b.p. 90-182°/20 mm.,
- Fraction 2: 2 g., b.p. 182-194°/20 mm.,
- Residue: 3 g.

Both fractions deposited crystals on cooling; these were filtered off and recrystallised from aqueous alcohol when large transparent rhombs, m.p. 73° separated. Sodium fusion tests showed the absence of bromine.
Found: C, 79.3; H, 6.9%. α-Phenylethyl α-phenylpropionate, C\textsubscript{17}H\textsubscript{18}O\textsubscript{2} requires: C, 80.3; H, 7.1%.

Hydrolysis of this ester (1.1 g.) with potassium hydroxide (0.5 g.) in diethylene glycol (3 ml.) yielded an alcohol, the phenyl urethane of which had m.p. 88-89° alone, and when mixed with an authentic specimen of the phenyl urethane of α-phenylethyl alcohol (m.p. 89°). The acid obtained from this hydrolysis was converted to its silver salt and ignited. Found; Ag, 42.6, 42.4%. Calculated for silver α-phenylpropionate, C\textsubscript{9}H\textsubscript{8}O\textsubscript{2}Ag, Ag, 42.0%.

Sodium fusions on the oily filtrates from the crystals of the ester gave positive tests for bromine.

(iii)

Silver α-phenylpropionate (9.0 g.), contained in the reaction flask, was heated at 100° and 17 mm. for three hours whilst connected to a flask containing phosphorus pentoxide. The former was allowed to cool in a vacuum desiccator, dry carbon tetrachloride (45 ml.) was added and to this cold, stirred suspension was quickly added dry bromine (5.4 g.). The stirred mixture was then heated under reflux for three hours. Treatment of the product as in experiment (i) yielded a similar result. The product (3 g., b.p. 100-190°/22 mm.) deposited crystals m.p. 60-70° on cooling. After recrystallisation from alcohol these had m.p. 72-73° alone, and when mixed with the ester from (iia).
To a suspension of silver α-phenylpropionate (10.5 g.), dried over phosphorus pentoxide at 70° and 1.5 mm. for three hours, in carbon tetrachloride (50 ml.) boiling under reflux on a steam-bath, was added, with vigorous stirring, dry bromine (6.2 g.) during ten minutes. After 4½ hours' further stirring and refluxing, the mixture was cooled, filtered, the filtrate washed with sodium meta-bisulphite solution, sodium carbonate solution, and water, dried with anhydrous sodium sulphate and distilled. There was obtained:

Fraction 1., b.p. below 147°/1.5 mm., 1.0 g.

Fraction 2., b.p. 148-154°/1.5 mm., 2.0 g.

Fraction 2. yielded crystals m.p. 50-60°; m.p. 72-74° after recrystallisation from alcohol.

From the washings there was obtained 1.0 g. of acidic material.

Dry bromine (6.4 g.) was added during five minutes to a stirred suspension of silver α-phenylpropionate (10.8 g.), dried as in (iv), in carbon tetrachloride (50 ml.) heated under reflux in an oil-bath at 100-105°. After stirring for one hour, during which water appeared in the condenser, the mixture was cooled and filtered through sintered glass. The filtrate was washed with sodium meta-bisulphite and sodium carbonate solutions, dried with anhydrous sodium sulphate and distilled under reduced pressure, after the removal of
Fraction 1. b.p. below 146°/1.5 mm., 1.0 g.
Fraction 2. b.p. 146-152°/1.5 mm., 1.5 g.
Acidic material (1.5 g.) was recovered from the washings.

(vi)

To dry carbon tetrachloride (150 ml.) contained in a three-necked flask, provided with a mechanical stirrer, a dropping funnel and a calcium chloride tube, cooled in a freezing mixture at below -15°, was added silver a-phenylpropionate (10.5 g.). This suspension was vigorously stirred during the rapid (3 minutes) addition of a solution of dry bromine (6.4 g.) in carbon tetrachloride (25 ml.), and for a further ninety minutes, the temperature of the cooling-bath being maintained below -15°. The mixture was then allowed to attain room temperature and finally heated under reflux for thirty minutes, stirring being continued throughout.

When cold, the precipitated silver bromide was removed by filtration through sintered glass and the filtrate was washed with sodium meta-bisulphite and sodium carbonate solutions, to remove excess bromine and free a-phenylpropionic acid respectively. After having been dried with anhydrous magnesium sulphate, the carbon tetrachloride was evaporated and the residue fractionated in vacuo.

Fraction 1. b.p. below 123°/0.7 mm., 0.2 g., nD25° 1.5548
Fraction 2. b.p. 120-136°/ 0.7 mm., 1.0 g., \( n^25_D 1.5520 \)

Fraction 3. b.p. 136-150°/ 0.7 mm., 1.7 g., \( n^25_D 1.5494 \)

From the aqueous washings 2.0 g. of acidic material was recovered.

(vii)

To a solution of dry bromine (6.2 g.) in carbon tetrachloride (150 ml.), warmed in an oil-bath at 50-60°, was added, with vigorous stirring, a suspension of silver \( \alpha \)-phenylpropionate (10.2 g.), which had been dried over phosphorus pentoxide at 70° and 2 mm. for five hours, in carbon tetrachloride (50 ml.), during five minutes. The oil-bath temperature was raised to 110° and so maintained for two hours, the solvent being allowed to reflux with vigorous stirring meanwhile. The mixture when cool was treated as for (vi).

Fraction 1. b.p. below 102°/ 16 mm., 0.1 g., \( n^25_D 1.5512 \)

Fraction 2. b.p. 102-190°/ 16 mm., 2.2 g., \( n^25_D 1.5510 \)

Residual tar, 1.0 g.

Recovered acidic material, 2.3 g.
Silver α-(p-Nitrophenyl)-propionate.

1. Silver α-(p-Nitrophenyl)-propionate.

α-(p-Nitrophenyl)-propionic acid (7.65 g.) was dissolved in aqueous ammonia (55 ml., 0.76 N) and excess ammonia was removed by warming. To this solution was added, with stirring, a solution of silver nitrate (6.6 g.) in water (50 ml.). The precipitated silver salt was filtered at the pump, washed well with water, acetone and with ether and dried in vacuo over phosphorus pentoxide. A yield of 10.5 g. (85%) was obtained.

2. α-(p-Nitrophenyl)-ethyl bromide.

To a suspension of the above silver salt (10.5 g.) in carbon tetrachloride (200 ml.) was added, dropwise with stirring, a solution of dry bromine (5.3 g.) in carbon tetrachloride (50 ml.) during fifteen minutes. The stirred mixture was then heated under reflux for three hours, after which the precipitated silver bromide was removed by the filtration of the hot suspension through a sintered glass funnel. The filtrate was cooled, washed with sodium metabisulphite and sodium carbonate solutions, and then with water. (Acidification of these washings yielded α-(p-nitrophenyl)-propionic acid (0.5 g.) m.p. 85-87°). This solution was dried with anhydrous magnesium sulphate and the solvent
evaporated, leaving a viscous oil (6.0 g.). This oil was dissolved in ether, light petroleum (b.p. 40-60°) was added, and the solvents were allowed to evaporate when a pale yellow solid, m.p. 28-30°, separated. This was dissolved in ligroin, from which separated α-(p-nitrophenyl)-ethyl α-(p-nitrophenyl)-propionate (0.5 g.) as a colourless solid having m.p. 124-126°. Found: C, 53.7; H, 5.0; N, 8.1%. C₁₇H₁₆O₂N₂ requires, C, 59.3; H, 4.7; N, 8.1%.

From the ligroin filtrate there were obtained on evaporation, colourless plates of α-(p-nitrophenyl)-ethyl bromide (4.0 g., 50%) having m.p. 34-35°. Found: C, 42.2; H, 3.6; N, 6.1; Br, 34.9%. C₁₇H₁₆O₂Br requires, C, 41.8; H, 3.5; N, 6.1; Br, 34.8%.
(iv) The Attempted Asymmetric Synthesis of Phenyl Glycol.

1. 2-Bromo-1-Phenylethyl Acetate.

In a 500 ml. three-necked flask, fitted with a mechanical stirrer, a dropping funnel and a calcium chloride tube, cooled in a freezing mixture at between -18° and -10°, was placed some finely-powdered dry silver acetate (33.4 g.). To this was added dry carbon tetrachloride (250 ml.) and whilst this mixture was being stirred, a solution of dry bromine (32.0 g.) in carbon tetrachloride (50 ml.) was added during five minutes. After ten minutes further stirring, during which the bromine colouration disappeared, a solution of freshly-distilled styrene (21 g., b.p. 145°) in carbon tetrachloride (25 ml.) was added during five minutes, and the resulting mixture was stirred for one hour, the temperature of the cooling-bath being maintained below -10°. The precipitated silver bromide and excess silver acetate were filtered off, using a sintered glass filter, the filtrate was washed with sodium bicarbonate solution, dried with anhydrous magnesium sulphate, and the solvent removed by distillation. The residue was fractionally distilled under reduced pressure and there was obtained a colourless oil which became yellow on standing. The yield of 2-bromo-1-phenylethyl acetate was 29.1 g. (60%), having b.p. 100-104°/ 0.6 mm., nD25 1.5391. A portion was redistilled for analysis, the
remainder was used in the following experiments. The redistilled portion (3.0 g.) had b.p. 98-100\(^{\circ}\) / 0.3 mm.,
\(n_d^{25\circ} 1.5389\). (Marvel and Moon, J. Amer. Chem. Soc. 1940 62 45.
describe 2-bromo-1-phenylethyl acetate, b.p. 105-107\(^{\circ}\) / 3 mm.,
\(n_d^{20\circ} 1.5380\). Found, C, 49.2; H, 4.6; Br, 33.3\% Calculated
for \(C_{10}H_{11}O_2Br\), C, 49.4; H, 4.6; Br 32.8\%.

2. Reactions of 2-Bromo-1-phenylethyl acetate.

(i) With sodium benzoate.

A solution of 2-bromo-1-phenylethyl acetate (1.5 g.) in alcohol (15 ml.) was heated under reflux with sodium benzoate (1.33 g., 1.5 mols.) for 12 hours. The mixture was then cooled, diluted with water (20 ml.), extracted with ether and the extract dried with anhydrous sodium sulphate. The presence of bromine in the aqueous layer was shown by acidification with nitric acid, filtration and the addition of silver nitrate, but the ethereal extract yielded only a white crystalline solid m.p. 120-121\(^{\circ}\), identified as benzoic acid, and an oil b.p. 156-160\(^{\circ}\) / 18 mm. containing bromine (sodium fusion) and apparently the original compound. The required 1-acetoxy-2-benzoyl-1-phenylethane was not observed.

(ii) With alcoholic potassium hydroxide.

To some of the ester (6.2 g.) was added alcoholic caustic potash solution (60 ml., \(N\), when a white precipitate immediately appeared (potassium bromide) and the solution
became yellow. The mixture was heated under reflux for 2.5 hours, cooled, diluted with water (60 ml.), and extracted with ether. The extract was dried with anhydrous sodium sulphate and after removal of the solvent, the residue was distilled under reduced pressure; there was obtained:

Fraction 1. b.p. below 82°/35 mm., 0.84 g., \( n^D_{25} 1.5401 \)
Fraction 2. b.p. 82-95°/35 mm., 0.34 g., \( n^D_{25} 1.5366 \)
Residue, 0.5 g., which, after recrystallisation from ether-ligroin, yielded phenyl glycol m.p. 64-65° (0.25 g.).

The aqueous extract was saturated with carbon dioxide, concentrated to about 15 ml. and extracted with ether. After drying this extract, light petroleum (b.p. 60-80°) was added, when colourless needles of phenyl glycol (0.5 g.) m.p. 64-65.5° separated. Found, C, 69.4; H, 7.4%. Calculated for \( \text{C}_8\text{H}_{10}\text{O}_2 \), C, 69.3; H, 7.3%.

No evidence for the presence of styrene oxide (which has b.p. 84-85°/15 mm.) was observed.

(iii) Hydrolysis with sodium hydroxide.

The bromo-ester (1.8 g.) was heated under reflux with aqueous caustic soda solution (20 ml., N) for three hours and the cooled mixture was extracted with ether. The aqueous extract was saturated with potassium carbonate and again extracted with ether. The extracts were combined, dried with anhydrous sodium sulphate and ligroin was added, when white needles of phenyl glycol (0.6 g., 60%) m.p. 64-65° alone and
when mixed with the specimen above, separated. Its di-
benzoate had m.p. 93-94°. (Milas and Sussman, J. Amer. Chem.
Soc. 1937 59 2346, give m.p. 65-66° and m.p. 92-93° respectively)

**3. 2-Bromo-1-phenylethyl 2-ethylhexanoate.**

To a well-stirred suspension of finely-ground silver
2-ethylhexanoate (6.0 g.) in dry carbon tetrachloride (75 ml.)
maintained at between -15° and -10°, was added a solution of
dry bromine (3.2 g.) in carbon tetrachloride (15 ml.) during
ten minutes. The stirring was continued until the bromine
colouration had disappeared and the suspension had become
very fine and creamy, when a solution of freshly-distilled
styrene (2.1 g.) in carbon tetrachloride (15 ml.) was added
during five minutes. After a further thirty minutes'
stirring in the cooling-bath below -10°, the mixture was
allowed to reach room temperature and then filtered twice
through sintered glass to remove the fine deposit of silver
bromide and obtain a clear, colourless solution. The solvent
was evaporated, the residue warmed to 80° at 24 mm. to remove
excess of styrene and then distilled under reduced pressure
to yield two fractions, pale yellow oils which darkened on
standing.

*Fraction 1. b.p. 100-140°/ 1-5 mm., 1.4 g., n_D 1.4776.*
*Fraction 2. b.p. 135-145°/ 2-3 mm., 1.5 g., n_D 1.5060.*

(i) Sodium fusions.
Sodium fusions indicated the presence of bromine in both fractions of the product of experiment 3.

(ii) Hydrolysis using aqueous caustic soda. (a).
The bromo-ester (Fraction 2., 0.7 g.) was heated under reflux with aqueous caustic soda solution (10 ml., 3N) for three hours. The solution was cooled, saturated with potassium carbonate and extracted repeatedly with ether. After drying the ethereal extract with anhydrous sodium sulphate, ligroin was added and from this solution colourless needles of phenyl glycol (0.25 g., 66.5°) m.p. 63-65°, separated.

(iii) Hydrolysis using aqueous potassium carbonate.
The remainder of fraction 2. (0.3 g.) was heated under reflux with a solution of potassium carbonate (0.6 g.) in water (10 ml.) for twelve hours. The solution was then cooled, saturated with potassium carbonate and extracted with ether. The extract yielded a small quantity of phenyl glycol (0.05 g. m.p. 60-63°) together with unchanged bromo-ester.

(iv) Hydrolysis using aqueous caustic soda. (b).
The residual ester from (iii) was treated as in (ii) above and yielded phenyl glycol (0.25 g., 60°) m.p. 63-65°.
5. (-)-2-Bromo-1-phenylethyl 2-ethylhexanoate

Silver (-)-2-ethylhexanoate was prepared from a specimen of the (-)-acid having b.p. 123-125°/17 mm., $c^D_{15}^{15} = 2.95^0$, $[a]_{D}^{15} = 6.9^0$ (1.0.5, 75% optically pure). To a well-stirred suspension of this finely-powdered, dry silver salt (14.8 g.) in dry carbon tetrachloride (150 ml.), cooled in a freezing mixture to between -15° and -10°, was added a solution of dry bromine (9.3 g.) in carbon tetrachloride (25 ml.) during ten minutes. Stirring was continued until the bromine colouration had gone, five minutes, whereupon a solution of freshly-distilled styrene (6.3 g., b.p. 145°) in the same solvent (25 ml.) was quickly added, after which the mixture was briskly stirred for a further thirty minutes, the cooling-bath temperature being maintained below -10°. The mixture was then allowed to reach room temperature, the silver bromide was filtered off, using a sintered glass filter, the filtrate shaken twice with sodium bicarbonate solution (25 ml., 20%) and dried with anhydrous sodium sulphate. The solvent was removed by distillation, any excess styrene present was removed by heating, at 17 mm., in an oil-bath at 170°, and the residue was fractionally distilled under reduced pressure. Together with the (-)-2-bromo-1-phenylethyl 2-ethylhexanoate, some styrene dibromide was obtained:

the styrene dibromide (1.9 g.), b.p. 110-125°/1 mm., m.p. 69-71°, formed, after recrystallisation from aqueous alcohol,
white plates having m.p. 73° alone, and when mixed with an authentic specimen of styrene dibromide (m.p. 73°).

The \(-\)-ester (6.6 g., 35%), was obtained as a colourless, viscous oil which turned yellow on standing, having b.p. 150-154°/1 mm., \(n^o_{D} 1.5080\), \(d^o_{D} 0.61^o (1.0.5)\). Found, C, 53.8; H, 7.3; Br, 24.3%. \(C_{16}H_{25}O_2Br\) requires, C, 58.7; H, 7.1; Br, 24.4%.

6. Phenyl Glycol. (i).

A portion of the above \((-\)\)-2-bromo-1-phenylethyl 2-ethylhexanoate (3.3 g.) was heated under reflux with aqueous sodium hydroxide solution (30 ml., 2N) until all oily droplets had disappeared, 10.5 hours. The solution was cooled, saturated with potassium carbonate and extracted with ether, the extracts being dried with potassium carbonate. The aqueous extract was acidified with hydrochloric acid, extracted with ether and the extract dried with anhydrous sodium sulphate. The rotation of the first ethereal extract was measured, after which the solvent was allowed to evaporate, the phenyl glycol so obtained being recrystallised from ether-ligroin. The acid recovered from the second extraction was distilled and its rotation measured.

Yield of phenyl glycol 1.0 g. (74%), m.p. 60-62°; after recrystallisation m.p. 64-65°.

Rotation of ethereal extract: \(d^o_{D} 0.02^o (c, 5.9; 1,2)\)
Rotation of recrystallised glycol: $\alpha_D^{15^\circ} 0.00^\circ$ (c, 3.7; 1.2, in ether)

Yield of recovered (-)-acid 1.25 g. (83%), b.p. 223$^\circ$, $\alpha_D^{15^\circ} -1.80^\circ$ (1.0.5, homogeneous), whence the acid had undergone 40% racemisation.

7. (+)-2-Bromo-1-phenylethyl 2-ethylhexanoate.

From a specimen of (+)-2-ethylhexanoic acid having b.p. 118-121$^\circ$/15 mm., $\alpha_D^{22^\circ} +15.07^\circ$ (1,2; 93% optically pure) was prepared the silver salt in 99% yield. A suspension of this silver salt (15.2 g.) in carbon tetrachloride (150 ml.), cooled in a mixture of ice and salt at between -20$^\circ$ and -10$^\circ$, was vigorously stirred during the addition of an ice-cooled solution of dry bromine (9.5 g.) in carbon tetrachloride (25 ml.). When all colour of bromine had disappeared, ten minutes, a solution of freshly-distilled styrene (6.3 g.) in the same solvent (25 ml.) was added and the stirring continued for thirty minutes, cooling below -10$^\circ$ being maintained meanwhile. The reaction mixture was allowed to attain room temperature, the silver salts were removed by filtration, the filtrate shaken twice with sodium bicarbonate solution (25 ml., 20%) and then dried with anhydrous sodium sulphate. The solvent was evaporated, excess styrene removed by warming to 100$^\circ$ at 15 mm., and the residue distilled under reduced pressure. Yield of styrene dibromide 0.9 g., m.p. 73$^\circ$. 
The bromo-ester (12.0 g., 60%) had b.p. 152-156°/1.5 mm.,
\(n^D_2 1.5031, \alpha^D_2 17.5° + 0.88° (1,0.5)\). Found, C, 58.9; H, 7.0;
Br, 24.4%. \(\text{C}_18\text{H}_{23}\text{O}_2\text{Br}\) requires, C, 58.7; H, 7.1; Br, 24.4%.

8. Phenyl Glycol (II).

The (+)-2-bromo-1-phenylethyl 2-ethylhexanoate (3.3 g.)
obtained as above (7.) was hydrolysed by heating under reflux
with aqueous sodium hydroxide (40 ml., 3N) until a clear
yellow solution was obtained, ten hours. The solution was
cooled, saturated with potassium carbonate, extracted with
ether and the extract dried with potassium carbonate. The
(+)-2-ethylhexanoic acid was recovered from the aqueous
extract by acidification, extraction and distillation. The
rotation of the ethereal extract of phenyl glycol was
measured, then ligroin was added and crystallisation allowed
to proceed.

Yield of phenyl glycol 0.9 g. (65%), m.p. 63-65°, after
recrystallisation from ether-ligroin m.p. 64.5-65.5°.

Rotation of ethereal extract: \(\alpha^D_2 0.00° (c,5; 1,2)\)

The (+)-acid recovered (1.2 g., 50%) had b.p. 233-225°,
\(\alpha^D_2 +2.40° (1,0.5)\), whence the acid had undergone 36%
racemisation.
(v) Some Reactions of the Bromine Cation.

(a) Substitution Reactions.

1. 2-Ethylhexanoic acid in dilute sulphuric acid.

To a well-stirred mixture of 2-ethylhexanoic acid (7.2 g.) and bromine (8.0 g.) in dilute sulphuric acid (150 ml., 3N) was added a solution of silver nitrate (8.5 g.) in distilled water (50 ml.) during fifteen minutes. Immediate precipitation of silver bromide occurred and during three hours' further stirring, the bromine colour faded and the oil, which was originally floating on the surface, appeared as red droplets among the precipitate. The mixture was filtered through sintered glass and both the filtrate and the precipitate were extracted with ether. The combined extracts were dried with anhydrous sodium sulphate and fractionally distilled. Yield of silver bromide 9.3 g., (100%). Yield of oil 9.0 g.

Fraction 1. b.p. below 132°/ 23 mm., 3.1 g., nD 1.4380

Fraction 2. b.p. 132-134°/ 23 mm., 3.1 g., nD 1.4290

The residue consisted of 2.0 g. of an intractable black solid. Sodium fusions on both fractions gave positive tests for bromine.

Fraction 1; found, C, 55.2; H, 9.2; Br, 22.1%.

C₁₅H₂₉O₂Br requires, C, 56.1; H, 9.1; Br, 24.9%.

Fraction 2. consisted mainly of the original acid (b.p. 130°/ 22 mm., nD 1.4246.
2. 2-Ethylhexanoic acid in Dilute Nitric acid.

A solution of silver nitrate (8.5 g.) in water (50 ml.) was added dropwise during thirty minutes to a stirred mixture of 2-ethylhexanoic acid (7.2 g.), bromine (8.0 g.) and dilute nitric acid (200 ml., 6N). The mixture was stirred for a further five hours and extracted with ether. The extract, after being washed with sodium meta-bisulphite solution to remove excess bromine, was dried with anhydrous sodium sulphate and distilled.

Fraction 1. b.p. 70-130°/25 mm., 1.9 g., nD^25 1.4419
Fraction 2. b.p. 131-134°/25 mm., 4.6 g., nD^25 1.4351.

Sodium fusions were carried out on both fractions; fraction 1. gave a positive bromine reaction, while fraction 2. gave only a very slight bromine reaction.

Fraction 1. (0.1510 g.) was heated on a steam-bath with caustic soda solution (10 ml., 3N) for 1.5 hours, and the bromide determined by Volhard's method; the estimation was repeated. Found, Br, (1) 18.2%, (ii) 18.2%.

3. 2-Ethylhexanoic acid in Acetic acid and Nitric acid.

2-Ethylhexanoic acid (7.2 g.) and bromine (8.0 g.) were dissolved in glacial acetic acid (150 ml.) to which was added concentrated nitric acid (33 ml.) and water (25 ml.). This mixture was vigorously stirred during the dropwise addition, thirty minutes, of a solution of silver nitrate
(8.5 g.) in water (50 ml.) and for a further three hours.
The precipitated silver bromide was filtered off, water
(200 ml.) was added to the filtrate, which was then extracted
with ether. The extract was washed with sodium meta-bisulphite
solution to remove bromine, then with water and, after being
dried with anhydrous sodium sulphate, fractionally distilled.

Fraction 1. b.p. below 120°/24 mm., 2.2 g., \( n^D_{20} 1.3791 \)
Fraction 2. b.p. 123-135°/24 mm., 3.8 g., \( n^D_{20} 1.4241 \)
Fraction 3. b.p. 135-138°/24 mm., 1.2 g., \( n^D_{20} 1.4285 \)
Residue, 1.2 g. of black tar.

Fraction 1. contained acetic acid, which crystallised on
cooling.

4. Investigation of the Products of Experiments 1., 2., and 3.

(i) Low-boiling fractions.

The three fractions "1." obtained in these experiments
above were combined, treated with sodium carbonate solution
and extracted with ether. After drying the extract with
anhydrous sodium sulphate and removing the solvent by
distillation, fractionation of the residue yielded two
fractions of alkali-insoluble compounds. Acidification and
extraction of the aqueous extract gave a very small amount of
an acidic substance (0.1 g., \( n^D_{20} 1.4235 \)), probably 2-ethyl-
hexanoic acid.

Neutral material, fraction 1. b.p. 71-81°/21 mm., 0.2 g.,
Fraction 2. b.p. 120-124°/ 21 mm., 1.2 g., \( n_D^{15^0} 1.4435 \).
Fraction 1. found, C, 41.7; H, 6.9; Br, 44.6%.

Empirical formula (assuming C_15). \( C_{15}H_{29.5}Br_8.4 \).

Fraction 2. found, C, 52.2; H, 8.5; Br, 18.5%.

Empirical formula (C=15), \( C_{15}H_{290.4}Br_0.8 \).

(ii) High-boiling fractions.

All fractions "2" and "3" were combined and treated as in (i) above. Acidic and neutral materials were again separated. The acidic material (10.0 g.) b.p. 131-132°/ 24 mm., \( n_D^{25^0} 1.4250 \), was 2-ethylhexanoic acid (b.p. 132-135°/ 26 mm., \( n_D^{25^0} 1.4256 \)). The neutral material (1.0 g.) had b.p. 127-132°/ 24 mm., \( n_D^{25^0} 1.4678 \). Found, C, 47.0; H, 6.9; Br, 29.4%.

Calculated formula (C=15), \( C_{15}H_{20}O_4Br_1.4 \).

5. \( \alpha \)-Phenylpropionic acid in Dilute Sulphuric acid.

To a well-stirred mixture of \( \alpha \)-phenylpropionic acid (7.5 g.), bromine (8.0 g.) and dilute sulphuric acid (150 ml., 2N) was added dropwise during one hour a solution of silver nitrate (8.5 g.) in water (50 ml.). After stirring for a further hour, the silver bromide was filtered off, the colourless filtrate and its residue were both extracted with ether, the extract was dried, and the solvent evaporated, leaving a very viscous oil, 10.0 g. This was taken up in sodium carbonate solution which, after shaking with ether (this extract yielding nothing), was acidified and the
liberated acid extracted with ether. The extract was dried with anhydrous magnesium sulphate, the solvent evaporated and the residue distilled in vacuo.

Fraction 1. b.p. 120-137°/1 mm., 1.4 g.
Fraction 2. b.p. 136-141°/1 mm., 4.8 g., n° 1.5594.
Fraction 3. b.p. 140-144°/1 mm., 1.2 g.
Residue 1.5 g.

Fraction 2. Found, C, 47.7; H, 4.1%. Equivalent 237.2.

C₉H₅O₂Br requires, C, 47.2; H, 4.0%. Equivalent 239.0.

All fractions gave positive tests for bromine.

Fraction 2 (0.05 g.) was heated with alcoholic potassium hydroxide (5 ml., N) for fifteen minutes. The solution was then cooled, acidified with nitric acid and silver nitrate solution was added. The absence of any precipitate indicated that the bromine had entered the aromatic nucleus.

(a) The Oxidation of Fraction 2.

To a solution of sodium carbonate (5.0 g.) in water (150 ml.), potassium permanganate (10.0 g.) and fraction 2 (2.95 g.) were added and the mixture was heated under reflux for 1.5 hours. After cooling, concentrated hydrochloric acid (25 ml.) was added and sulphur dioxide was passed until all the manganese dioxide had dissolved. The precipitated acid was extracted with ether, dried with anhydrous sodium sulphate and the ether removed by evaporation. The crude material (2.1 g., 50%) after three recrystallisations
from aqueous alcohol yielded white leaflets having m.p. 250-252° alone and when mixed with \( \beta \)-bromobenzoic acid (prepared as below (b)). The filtrates from the crystallisations yielded solids m.p. 130-245°, possibly containing the \( \alpha \)-isomer.

These results show that fraction 2 consists mainly of \( \alpha \)-(\( \beta \)-bromophenyl)-propionic acid, possibly contaminated with a little of the \( \beta \)-bromo-isomer.

(b) \( \beta \)-Bromobenzoic acid

To a solution of sodium carbonate (10.0 g.) in water (200 ml.) was added potassium permanganate (20 g.) and \( \beta \)-bromotoluene (5.0 g., m.p. 27-28°, b.p. 184-185°) and the mixture was heated under reflux for twelve hours. It was then cooled, acidified with hydrochloric acid and the precipitated manganese dioxide was taken into solution by the passage of sulphur dioxide. The liberated acid was extracted with ether and recrystallised from aqueous alcohol when white leaflets (2.9 g., 52%) of \( \beta \)-bromobenzoic acid m.p. 251-253°, were obtained.
1. The Addition of Bromine to Styrene.

(i) In the presence of silver acetate.

To a briskly-stirred suspension of silver acetate (17.0 g.) and freshly-distilled styrene (10.4 g., b.p. 144-145°) in a mixture of dilute sulphuric acid (150 ml., 6N) and glacial acetic acid (50 ml.) was added a solution of bromine (16.0 g.) in glacial acetic acid (75 ml.) during ninety minutes. After stirring for a further thirty minutes the mixture was filtered through sintered glass, the filtrate extracted with ether, the extract washed well with sodium carbonate solution and dried with anhydrous magnesium sulphate. Evaporation of the solvent and fractionation of the residue yielded largely 2-bromo-1-phenylethyl acetate.

Yield of silver bromide 18.7 g. (100%). The organic product, 12.1 g., gave:

Fraction 1. b.p. 84-86°/0.7 mm., 2.7 g., n_D 1.5689
Fraction 2. b.p. 91-93°/0.7 mm., 5.4 g., n_D 1.5595
Fraction 3. b.p. 96-104°/0.7 mm., 2.0 g., n_D 1.5560
Residual orange gum, 3.0 g.

Fraction 2. Found, C, 48.3; H, 4.5; Br, 37.6%.
Calculated for C_10H_11O_2Br, C, 49.4; H, 4.6; Br, 32.8%.
(ii) In the absence of silver acetate.

(a) Conditions as in (i).

To a well-stirred mixture of styrene (10.4 g., b.p. 144-146°), dilute sulphuric acid (150 ml., 6N) and glacial acetic acid (50 ml.) was added a solution of bromine (16.0 g.) in acetic acid (75 ml.) during ninety minutes. The mixture was stirred for a further thirty minutes and then extracted with ether. The extract was washed with sodium carbonate solution to remove acetic acid and was dried with anhydrous magnesium sulphate. Removal of the solvent left an oil which deposited crystals on cooling. These were filtered off and the remaining liquid was fractionally distilled under reduced pressure, more crystals being observed in the fractions so obtained. Yield of crude product 19 g.

The crystals (6.0 g.) had m.p. 68-70° and after recrystallisation from aqueous alcohol formed glistening plates, m.p. 72-73° alone and mixed with authentic styrene dibromide of m.p. 72-73°.

Fraction 1. b.p. 91-95°/1 mm., 5.9 g., deposited needles of styrene dibromide m.p. 72-73° (2 g.) on cooling.

Fraction 2. b.p. 96-97°/1 mm., 3.3 g., nD^25 1.5664, also deposited a small amount of styrene dibromide on cooling.

Fraction 2. Found, C, 46.2; H, 4.4%.

Calculated for C_{10}H_{11}Br, C, 49.4; H, 4.6%.
(b) With added sodium bromide.

Styrene (10.4 g., b.p. 145-146°C) was added to a solution of sodium bromide (20.6 g., 2 mols.) and glacial acetic acid (50 ml.) in dilute sulphuric acid (150 ml., 6N). This mixture was thoroughly stirred whilst a solution of bromine (16.0 g.) in acetic acid (75 ml.) was added dropwise during ninety minutes. Stirring was continued for thirty minutes, after which the mixture was extracted with ether, the extract washed with sodium bicarbonate solution and dried with anhydrous magnesium sulphate. Removal of ether yielded a viscous liquid which deposited crystals of styrene dibromide (9 g.) m.p. 68-71°C, on cooling; after recrystallisation from aqueous alcohol these had m.p. 72-73°C. The residual oil (9 g., nD25 1.5642) yielded more styrene dibromide (3 g., m.p. 69-71°C) on long cooling.

(c) Bromine added undiluted.

Freshly-distilled styrene (10.4 g., b.p. 144-146°C) was added to a solution of glacial acetic acid (50 ml.) in dilute sulphuric acid (150 ml., 6N) and the resulting mixture was vigorously stirred during the simultaneous addition of bromine (16.0 g.) and glacial acetic acid (75 ml.) during 75 minutes. After stirring for another 45 minutes, the product was extracted with ether, the extract washed well with sodium carbonate solution and dried with anhydrous magnesium sulphate. The ether was evaporated and the residue
(21 g.) cooled, whereupon immediate crystallisation occurred. Filtration yielded fine needles of styrene dibromide (14.1 g.) m.p. 71-73°. Recrystallisation from aqueous alcohol gave glistening plates m.p. 72-73°. The filtrate from the needles (6.4 g., \( n_D^{25} = 1.5715 \)) yielded a further crop of the dibromide (2 g., m.p. 71-73°) on cooling in an ice-box. Very little of the bromo-ester appeared to be produced in this experiment.

(iii) The hydrolysis of the product from (i).

Fraction 2 from experiment (i) (1.8 g.) was heated under reflux with aqueous sodium hydroxide solution (10 ml., 3N) for six hours. The mixture was then cooled, extracted with ether, saturated with potassium carbonate and again ether-extracted. The combined extracts were dried with anhydrous sodium sulphate, ligroin was added and crystallisation allowed to proceed. Colourless needles (0.9 g., 90%) of phenyl glycol separated having m.p. 62-64°. After recrystallisation from ether-ligroin they had m.p. 64.5-65.5° and mixed melting point 64-65° with an authentic specimen of the glycol.

(iv) The hydrolysis of styrene dibromide.

Styrene dibromide (12.3 g.) was heated under reflux with sodium hydroxide solution (135 ml. N) for six hours. The mixture was cooled, saturated with potassium carbonate and extracted with ether. After drying with anhydrous
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magnesium sulphate, ligroin was added when, after allowing
to stand for two days, long colourless needles of phenyl
glycol (1.3 g., 20%) separated which, after recrystallisation
from ether-ligroin had m.p. 64-65°.

2. The Addition of Bromine to Cyclohexene.
   (1) In the presence of silver acetate.
   To a vigorously stirred suspension of cyclohexene
   (8.2 g., b.p. 82-83°) and silver acetate (16.7 g.) in a
   mixture of dilute sulphuric acid (150 ml., 6N) and glacial
   acetic acid (50 ml.) was added, during ninety minutes, a
   solution of bromine (16.0 g.) in acetic acid (50 ml.).
   After stirring for a further thirty minutes, the precipitated
   silver bromide was removed by filtration through sintered
   glass and both filtrate and residue were extracted with
   ether. The extracts were combined, washed with sodium
   carbonate solution and dried with anhydrous magnesium sulphate.
   Removal of solvent and distillation of the residue in vacuo
   yielded two fractions, both of which quickly turned pale blue
   and then gradually darkened until within thirty minutes they
   were quite black. Fraction 1 deposited transparent needles on
   cooling. Yield of crude product 13.9 g.
   Fraction 1. b.p. 100-106°/ 20 mm., 5.2 g., nD° 1.5206
   Fraction 2. b.p. 107-112°/ 20 mm., 5.0 g., nD° 1.5183
   Residual tar, 3.0 g.
   The needles from fraction 1 (0.1 g.) had m.p. 124-125° after
recrystallisation from ether. Found, C, 73.5; H, 10.3\%.

\((\text{C}_6\text{H}_{10})_x\) requires, C, 73.4; H, 10.3\%. It is postulated that this compound may be \(\text{C}_{12}\text{H}_{20}\text{O}_2\), i.e. octahydro-diphenylene dioxide.

Fraction 2, found, C, 36.8; H, 5.2; Br, 53.5\%.
Calculated for \(\text{C}_6\text{H}_{15}\text{O}_2\text{Br}\), C, 43.5; H, 5.9; Br, 36.1\%.
Calculated for \(\text{C}_6\text{H}_{10}\text{Br}_2\), C, 29.8; H, 4.2; Br, 66.0\%.

Fraction 2 thus appears to be a mixture of approximately equal proportions of (a) 2-bromo-cyclohexyl acetate, (Bedos, C.r. 1926 183 564, gives b.p. 103-111°/12 mm., \(n^\circ_d 1.4334\)), and (b) 1,2-dibromocyclohexane, (Hofman and Damm, Mitt. Kohlenforschungsinstiut Breslau, 1925 2 109, give b.p. 101°/13 mm., 116°/29 mm., \(n^\circ_d 1.5540\)). Both of these compounds are known to darken when exposed to light and moist air (locc. cit.)

(ii) In the absence of silver acetate.

A solution of bromine (16.0 g.) in glacial acetic acid (75 ml.) was added during sixty minutes to a vigorously stirred mixture of cyclohexene (8.2 g.), dilute sulphuric acid (150 ml., 6N) and acetic acid (50 ml.) at room temperature. After stirring for a further thirty minutes, the mixture was extracted with ether, the extract was washed with sodium metabisulphite and sodium carbonate solutions, then with water and dried with anhydrous magnesium sulphate. Removal of
the solvent, followed by fractional distillation of the residue yielded 1,2-dibromocyclohexane, contaminated with some 2-bromocyclohexyl acetate.

Fraction 1. b.p. 90-94°/15 mm., 7.6 g., 25°, 1.5288
Fraction 2. b.p. 94-97°/15 mm., 4.3 g., 25°, 1.5278
Fraction 3. b.p. 97-99°/15 mm., 2.4 g., 25°, 1.5298.

All fractions were colourless liquids, but all gradually darkened to shades of green, fraction 3 becoming almost black.

Fraction 1. Found, C, 34.7; H, 5.2; Br, 57.0%.
Fraction 3. Found, C, 35.3; H, 4.9; Br, 56.0%.

Calculated for C5H10Br2, C, 29.8; H, 4.2; Br, 66.0%.
Calculated for C6H13O2Br, C, 43.5; H, 5.9; Br, 36.1%.
The Determination of Bromine

A length (25-30 cm.) of stout-walled glass tubing, of about 2 cm. internal diameter, was sealed at one end, and a constriction, thick-walled and suitable for sealing, was made about 5 cm. from the open end. The substance whose bromine content was required (0.15-0.25 g.) was weighed into this tube, aqueous-alcoholic sodium hydroxide solution (20 ml., N/2) was added and the tube was sealed. It was then heated in a steam-bath for twelve hours with occasional shaking, allowed to cool to room temperature, the seal was carefully broken and the contents of the tube were transferred to a conical flask. Nitric acid (10 ml., 6N.) was added followed by silver nitrate solution (25.0 ml., 0.1N) and the excess of the latter was titrated with potassium thiocyanate solution (0.1N), using iron alum as indicator.

The aqueous-alcoholic sodium hydroxide solution contained no halogen either before or after heating in a sealed tube. The solutions were standardised against potassium bromide; the latter was (a) used directly, (b) heated as in the above determination; the values obtained were identical.