Asymmetric Syntheses involving

keto-esters.

- by -

Doreen M. Bovey.

A Thesis submitted for the degree
of Doctor of Philosophy in the
University of London.

ProQuest Number: 10097953

ProQuest 10097953

A B S T R A C T.

Asymmetric syntheses involving keto-esters

by Doreen M. Bovey.

The partial asymmetric syntheses performed by McKenzie involving Grignard reactions on optically active α -keto-esters.

$$R \cdot CO \cdot CO_2 R'_* \xrightarrow[\text{+ DECOMPOSITION}]{R''MgX} R - \underset{\underset{OH}{|}}{\overset{\overset{R''}{|}}{C}} - CO_2 R'_* \xrightarrow{\text{HYDROLYSIS}} R - \underset{\underset{OH}{*|}}{\overset{\overset{R''}{|}}{C}} - CO_2 H$$
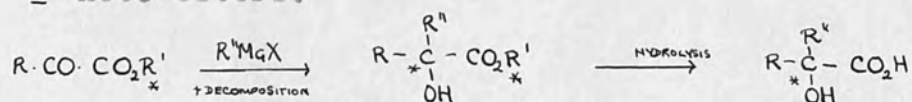
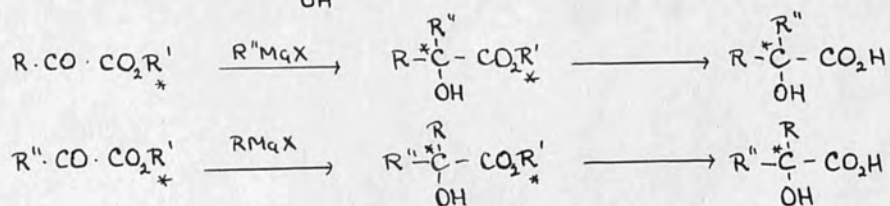are discussed, and a mechanism for the course of such syntheses is proposed. The reaction is probably influenced primarily by asymmetry in the electromagnetic field in the neighbourhood of the α-carbonyl group, induced by the asymmetric field in the optically active centre, and also by the differing free energies of intermediate diastereoisomeric Grignard complexes formed during the reaction. The resultant asymmetric synthesis is therefore directed by a combination of these effects, and not by any single force of "asymmetric induction" as originally postulated by McKenzie. This hypothesis is substantiated by reference to the two complementary syntheses of $R - \underset{\underset{OH}{|}}{\overset{\overset{R''}{|}}{C}} - CO_2H$, i.e,

$$R \cdot CO \cdot CO_2 R'_* \xrightarrow{R''MgX} R - \underset{\underset{OH}{|}}{\overset{\overset{R''}{*|}}{C}} - CO_2 R'_* \longrightarrow R - \underset{\underset{OH}{|}}{\overset{\overset{R''}{*|}}{C}} - CO_2 H$$

$$R'' \cdot CO \cdot CO_2 R'_* \xrightarrow{RMgX} R'' - \underset{\underset{OH}{|}}{\overset{\overset{R}{*|}}{C}} - CO_2 R'_* \longrightarrow R'' - \underset{\underset{OH}{|}}{\overset{\overset{R}{*|}}{C}} - CO_2 H$$

as the sign of rotation of the product and the degree of
asymmetric synthesis are shown to depend on both the
above factors.

The effect of increasing the separation between
the asymmetric and reaction centres in such syntheses
has been studied by performing Grignard reactions on the
homologous series of $(-)$-menthyl ketoesters,
$Ph \cdot CO \cdot (CH_2)_n \cdot CO_2 C_{10}H_{19}$. Asymmetric synthesis takes place
when $n = 2$ or 3, and the relationship between the
hydroxy-acids and their corresponding lactones formed
in these reactions has been investigated. Laevorotatory
acids, giving dextrorotatory lactones of higher specific
rotation than the parent compound were obtained, the
degree of asymmetric synthesis being only slightly
dependent on the conditions of reaction.

No optical activity could be detected in the
hydroxy-acids formed when $n = 4$ or 8, probably because
the electromagnetic induction effect is dissipated along
the methylene chain, and the difference in free energy
between the diastereoisomeric Grignard complexes is
too small to effect any observable asymmetric synthesis.

C O N T E N T S.

INTRODUCTION — SECTION I.

When the study of the chemistry of carbon compounds first became a distinct branch of Chemistry, it was thought that the synthesis of natural products was only possible in living organisms - hence the designation, "Organic Chemistry". Soon, however, several natural products were synthesised in the laboratory but they differed from the natural compounds in one important respect; while the chemical properties of the natural and synthetic products were identical, the natural compounds were usually optically active and the synthetic material inactive.

All such natural products contain a carbon atom having four different groups attached to it, and since these groups have a tetrahedral configuration round the central carbon atom, the compound is capable of existing in two forms, known as optical isomers or antipodes, which are mirror images of each other :
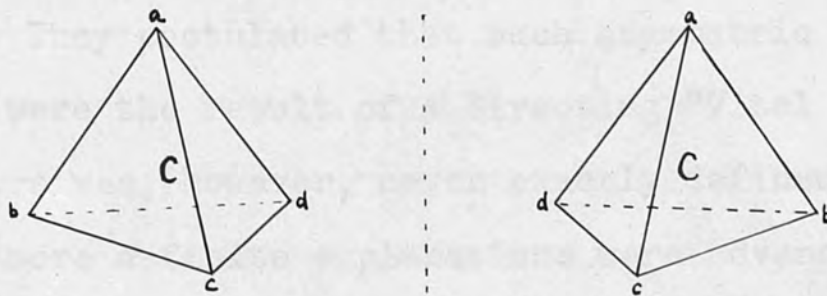
Solutions of each of these forms have the property of rotating the plane of plane polarised light, one

form being dextro- and one laevo-rotatory. Thus a
mixture of equal proportions of both forms will be
optically inactive, and is known as racemic.

Under ordinary laboratory conditions the synthesis
of chemical compounds takes place under the influence
of highly symmetrical physical and chemical forces;
both antipodes of any compound capable of exhibiting
optical activity are therefore yielded in equimolecular
proportions, and the resulting product is inactive.
The synthesis of natural products, however, takes
place under conditions which usually give one antipode
only. This distinction led Pasteur, in 1880, to
postulate that this formation of one isomer only of an
asymmetric compound must be a prerogative of life
itself, and although he later modified his views
and expressed the opinion that asymmetric syntheses
might be performed in the laboratory under the
influence of asymmetric forces not then known, there
were many who thought that this would never be
achieved. They postulated that such asymmetric
syntheses were the result of a directing "Vital Force",
whose nature was, however, never exactly defined.

Some more definite explanations were advanced,
of which two were later substantiated. Van't Hoff,
in 1894, suggested that the asymmetric force causing
natural asymmetric syntheses might be the partially

elliptically polarised light reflected from the surface of the sea. This affords an example of "absolute asymmetric synthesis", which is defined as the synthesis of an optically active compound from a symmetrical one under the influence of asymmetrical physical forces only, without the intermediate use of any optically active chemical compound. The earliest attempts in laboratory absolute asymmetric syntheses failed because the forces employed were not truly asymmetric. Either the forces themselves were not asymmetric (for instance, Boyd ,(Inaug. Dissert. Heidelberg 1896) reduced benzoylformic acid in a homogeneous magnetic field, which has an axis of symmetry perpendicular to the lines of force) or, if asymmetric, were not essential to the reaction.

The only certain examples of an absolute asymmetric process so far reported have been photo-chemical decompositions using circularly polarised light.

An explanation of the formation of (+)-glucose in plants was advanced by Emil Fischer, also in 1894 (Berichte, 1894, 27, 3231). He suggested that the glucose was produced by the condensation of formaldehyde (formed from carbon dioxide and water), each stage in the reaction taking place under the directing influence of the chlorophyll in the cells.

The chlorophyll, known to be optically active, formed
a loose additive complex during the reaction and was
regenerated at the end. The postulation of an optically
active intermediate compound is the basis of the
accepted definition of "partial asymmetric synthesis".
This was given by Marckwald in 1904 (Berichte. 37, 1368)
as the synthesis of optically active compounds from
compounds of symmetrical structure by the intermediate
use of optically active chemical compounds, but without
any analytical separation.

In the class of partial asymmetric synthesis two
main divisions may be noted, according to the nature
of the optically active intermediate used. Enzymes,
which are optically active compounds of high molecular
weight and unknown constitution have been used, and
often yield products of high optical purity. Fischer
suggested that the optical purity of natural
asymmetric compounds might be due to action by enzymes,
which in addition to causing actual asymmetric
synthesis, will often cause the decomposition of the
two antipodes in a racemic mixture at such widely
different rates, that a product of nearly 100% purity
may be isolated. Enzymes are usually found to be
specific to one reaction or type of reaction.

Among optically active intermediates of known
constitution which have been used, those which have

found the widest application are the alcohols
(-)-menthol, (-)-borneol, active amyl alcohol and
sec-octyl alcohol, although alkaloids such as
quinine and acids such as (+)-tartaric and
(+)-camphosulphonic have been used. In general the
use of these intermediates in partial asymmetric
synthesis does not give a high degree of optical
purity in the product, and great care must be exercised
to eliminate the possibility of optical activity arising
from incomplete removal of the intermediary, or from
side products.

The present work has been concerned with the
study of partial asymmetric synthesis by the Grignard
reaction on optically active keto-esters, and previous
work in this field will be considered in detail.

Asymmetric syntheses involving keto-esters.

Optically active alcohols have been widely used
as the intermediate in attempted partial asymmetric
syntheses as they are easy to introduce into, and
eliminate from, the molecule undergoing reaction. The
particular examples under consideration are those in
which reactions are performed on an optically active
keto-ester, i.e. $R \cdot CO_2 R'$ where R'_* is optically active
and R contains a carbonyl group.

$$R \cdot CO_2R'$$

<center>*</center>

$$R'' \cdot CO_2R' \qquad\qquad\qquad R'' \cdot CO_2R'$$
$$(+) \qquad\qquad\qquad\qquad\qquad (-)$$

<center>I   II</center>
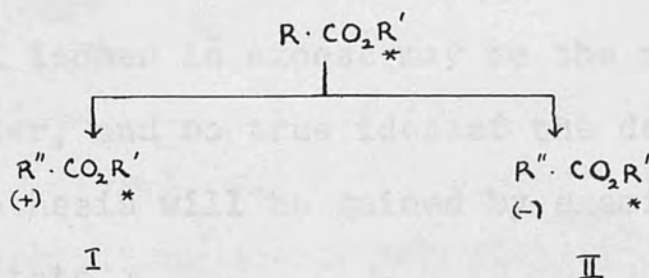
If any asymmetric synthesis takes place, there will
be formed in the reaction unequal proportions of the
diastereoisomerides I and II. At this stage care must
be exercised to ensure that no analytical separation
of the diastereoisomerides takes place. This may
occur since I and II will not, in general, be equally
soluble in solvents, and all extractions have to be
carried out several times to ensure that they are
complete. The ester is then saponified and the optically
active alcohol removed, usually by ether extraction of
the alkaline hydrolysate.

$$R'' \cdot CO_2R' \xrightarrow{\text{NaOH}} R'' \cdot CO_2Na + R'OH$$
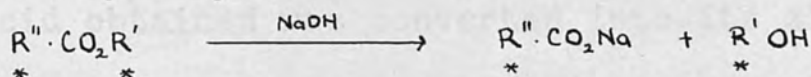
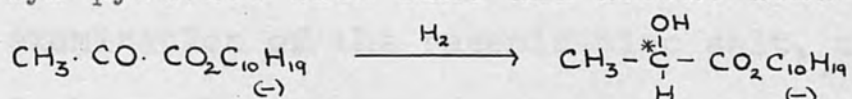If asymmetric synthesis has taken place there will
be unequal proportions of the optical isomers of the
sodium salt of the acid $R'' \cdot CO_2H$ in solution. In
order to isolate all the acid present, the alkaline
solution should be acidified with mineral acid and
extracted with ether. If the acid is merely
precipitated and (assuming it to be solid) filtered
off, there is the possibility that the racemic acid

or the optical isomer in excess may be the more soluble in water, and no true idea of the degree of asymmetric synthesis will be gained by examination of the precipitate.

If the acidified mixture is extracted several times with ether, all the acid will be extracted.

The first attempt at partial asymmetric syntheses involving keto-esters was reported by Kipping, in 1900, (Proc. 1900, 16, 226) who reduced (-)-bornyl benzoylformate and pyruvate, but he did not obtain any optically active product.

Cohen and Whiteley (J. 1901, 79, 1305) reduced (-)-menthyl pyruvate with zinc and acetic acid:

$$CH_3 \cdot CO \cdot CO_2 C_{10} H_{19} \xrightarrow{\ H_2\ } CH_3 - \overset{OH}{\underset{H}{\overset{*}{C}}} - CO_2 C_{10} H_{19}$$
$$(-) \qquad\qquad\qquad\qquad (-)$$

The (-)-menthyl lactate was hydrolysed and the lactic acid obtained was converted into its zinc salt, which was found to be optically inactive in aqueous solution. However, it was only after crystallisation of this salt from water that the product was examined polarimetrically, so that even if asymmetric synthesis had taken place it might have been missed owing to crystallisation of a racemate from the solution. This was proved by McKenzie in 1905 (J. 1905, 81, 1373), when he reduced (-)-menthyl pyruvate with aluminium amalgam. After hydrolysis of the (-)-menthyl lactate and removal of (-)-menthol, he converted the acid

into its zinc salt and allowed this to crystallise
from water. This salt, dissolved in dilute hydrochloric
acid (to liberate free lactic acid) was optically
inactive, but the mother liquor was distinctly
dextrorotatory. After acidification with hydrochloric
acid, the solution was laevorotatory, indicating a
partial asymmetric synthesis of (-)-lactic acid.
Asymmetric synthesis was also accomplished by reduction
of (-)-menthyl pyruvate with zinc and glacial acetic
acid, and, although to a smaller degree, when the
reduction was carried out with sodium amalgam. The
failure of Cohen and Whiteley to detect any asymmetric
synthesis in this reaction was therefore probably due
to their examination of the racemic zinc salt, and
neglect of the mother liquors.

The reduction of (-)-menthyl benzoylformate with
aluminium amalgam by McKenzie in 1904 (J. 1904, 1249)
did not at first afford conclusive evidence of
asymmetric synthesis. Unequal proportions of
(-)-menthyl-(-)-mandelate and (-)-menthyl-(+)-mandelate
were obtained, as shown by the specific rotation of
the products, the (-)-menthyl- (-)-mandelate being in
excess. Only r-mandelic acid was obtained after
hydrolysis, because the alcoholic potash used to
saponify the ester also caused racemisation. This
difficulty was later overcome (McKenzie and Humphreys

J. 1909, 95, 1105) by acetylation of the (–)-menthyl

mandelate before saponification. A laevorotatory

mandelic acid was then obtained, as expected. Further

experiments in the reduction of optically active

α-keto esters were carried out by McKenzie and

co-workers, in the course of which optically active

lactic acid was obtained by the reduction of

(–)-menthyl pyruvate (loc. cit), (–)-bornyl pyruvate

(McKenzie and Wren, J. 1906, 89, 688) which gave a

laevorotatory product, and (+)-amyl pyruvate (McKenzie

and Miller, J.1909, 95, 544) which gave a dextrorotatory

acid. Comparison of these experiments showed that the

greatest degree of asymmetric synthesis was obtained by

reduction of the (–)-menthyl ester.

The larger part of McKenzie's work on partial

asymmetric synthesis was concerned with the Grignard

reaction between an alkyl or aryl magnesium halide and

an optically active α-keto ester, the conditions

being usually chosen so that the ester group was not

appreciably attacked by the reagent.

$$R \cdot CO \cdot CO_2 R'_* \xrightarrow[+\ DECOMPOSITION]{R''MgX} R - \overset{R''}{\underset{OH}{\overset{*}{C}}} - CO_2 R'_* \left[+ R - \overset{R''}{\underset{OH}{\overset{*}{C}}} - \overset{R''}{\underset{R''}{C}} - OH + R'OH \right]$$

$$\downarrow$$

$$R - \overset{R''}{\underset{OH}{\overset{*}{C}}} - CO_2 H$$
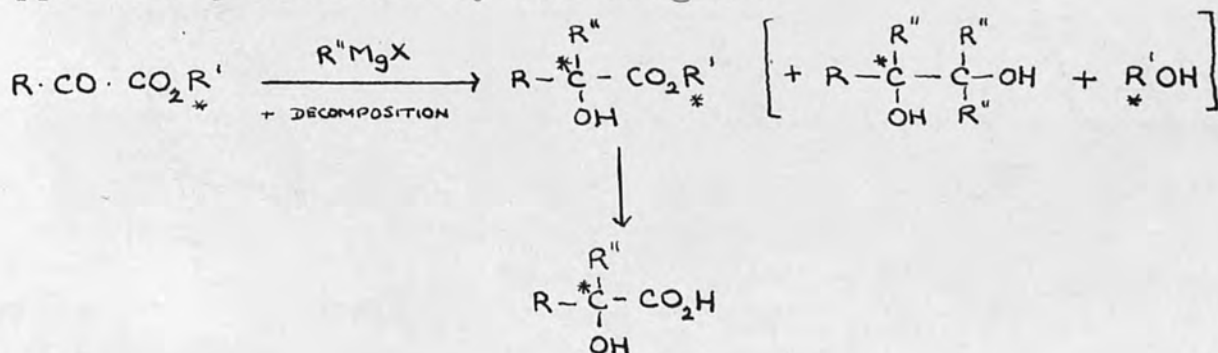
The keto-esters used were benzoylformates, anisoylformates, ⍺-naphthoylformates and pyruvates, which will be considered under separate headings.

Grignard reactions using benzoylformates.

Grignard reactions carried out using (-)-menthyl, (-)-bornyl and (-)-β-octyl benzoylformates usually yielded laevorotatory substituted glycollic acids.

$$Ph \cdot CO \cdot \underset{*}{CO_2R'} \xrightarrow[\text{DECOMPOSITION}]{R''MgX \; +} \; Ph - \overset{R''}{\underset{OH}{\overset{*}{C}}} - \underset{*}{CO_2R'} \xrightarrow{\text{HYDROLYSIS}} Ph - \overset{R''}{\underset{OH}{\overset{*}{C}}} - CO_2H$$
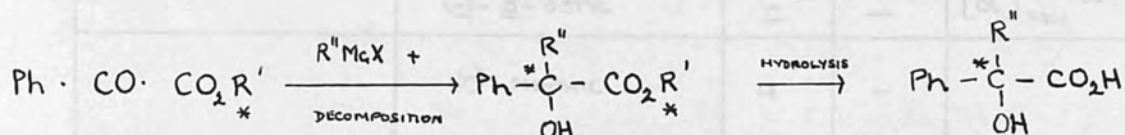
The particular reactions carried out and the sign of rotation of products obtained are given in Table A. It is impossible in all cases to compare the degree of asymmetric synthesis obtained by the action of one reagent on different esters since McKenzie did not always give the specific rotations of the acids he obtained.

TABLE A.

GRIGNARD REACTIONS USING BENZOYLFORMATES

GRIGNARD REAGENT USED.	ESTER USED	REFERENCE	SIGN OF ROTATION OF PRODUCT	SPECIFIC ROTATION OF PRODUCT.
CH$_3$MgI	(−)-MENTHYL	a. b.	−	$[\alpha]_D^{18} = -8.5°$
	(−)-BORNYL	b.	−	$[\alpha]_D^{15} = -1.9°$
	(−)-β-OCTYL	c.	−	$[\alpha]_{5461}^{25} = -6.6°$
C$_2$H$_5$MgBr	(−)-MENTHYL	a	−	
	(−)-BORNYL	b	−	$[\alpha]_D^{17} = -4.2°$
	(+)-BORNYL	e	+	
iso-C$_4$H$_9$MgI	(−)-MENTHYL	b	−	$[\alpha]_D^{11} = -5°$
	(−)-BORNYL	{ b / d	+ / −	$[\alpha]_D^{14} = +0.97°$
α-C$_{10}$H$_7$MgBr	(−)-MENTHYL	b	−	
	(−)-BORNYL	b	+	
	(+)-β-OCTYL	c	−	$[\alpha]_{5461}^{25} = -0.46°$
n-C$_3$H$_7$MgI	(−)-MENTHYL	b	−	$[\alpha]_D = -1.96°$
tert-C$_4$H$_9$MgI	(−)-MENTHYL	b	−	$[\alpha]_D^{16} = -0.7°$

REFERENCES.

a. McKenzie, J. 1904, **87**, 1249.
b. McKenzie, J. 1906, **89**, 365.
c. Mc. Kenzie & Ritchie. Biochem. Z. 1931, **237**, 1.
d. Ritchie, Ph.D. Thesis; St Andrews, 1932, p.128
e. McKenzie & Mitchell. Biochem. Z. 1929, **208**, 456, 471.

The results of experiments using methyl
magnesium iodide do, however, show that the power of
the optically active intermediates to cause asymmetric
syntheses decreases in the order

$$(-)-\text{MENTHYL} \quad > \quad (-)-\beta-\text{OCTYL} \quad > \quad (-)-\text{BORNYL}.$$
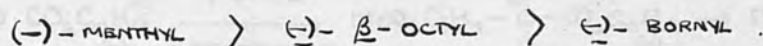
Laevorotatory acids were obtained from reactions
with laevorotatory esters in all cases except the
reaction with α-naphthyl magnesium bromide, and some
doubt in connection with iso-butyl magnesium iodide.
Mc Kenzie (b) originally reported a dextrorotatory acid
having $[\alpha]_D^{14} = +0.97°$ in alcohol $[l=2, c=25.7]$, but
the experiment was repeated by Ritchie twice (d) and
both times a slightly laevorotatory acid was obtained.

Conversely, it might be expected that the use of
a dextrorotatory ester would cause excess of the
$(+)$-isomer of the glycollic acid in the product of
reaction, and this was found in the reaction between
$(+)$-bornyl benzoylformate and ethyl magnesium
bromide (e) but in the only other example reported by
McKenzie (c), the reaction between $(+)-\beta$-octyl
benzoylformate and α-naphthyl magnesium bromide,
a laevorotatory acid was obtained.

Grignard reactions involving p-anisoylformates.

$(-)$-Menthyl-p-anisoylformate was the only ester used
and treatment with both methyl (McKenzie and Ritchie,
Biochem. Z. 1932, 250, 376) and phenyl (Ritchie unpublished)

magnesium halides gave a laevorotatory product.

In the former reaction (−)-methylanisoylglycollic
acid was prepared optically pure by crystallisation of
the slightly active acid from benzene.

$$MeO\cdot C_6H_4\cdot CO\cdot CO_2C_{10}H_{19} \xrightarrow[+ \text{ DECOMPOSITION}]{MeMgI} MeO\cdot C_6H_4-\overset{Me}{\underset{OH}{\overset{*}{C}}}-CO_2C_{10}H_{19} \rightarrow MeO\cdot C_6H_4-\overset{Me}{\underset{OH}{\overset{*}{C}}}-CO_2H$$
$$(-)\qquad\qquad\qquad\qquad\qquad (-)\qquad\qquad\qquad\qquad (-)$$

Most substituted glycollic acids yielded the
racemic compound on crystallisation of a slightly active
acid, the excess of the (+)-or (−)-isomer remaining in
solution, but in the above case the excess (−)-acid
present crystallised first, and after repeated
crystallisation was obtained optically pure.

A reaction using excess methyl magnesium iodide
was carried out, so that a glycol was produced:

$$MeO\cdot C_6H_4\cdot CO\cdot CO_2C_{10}H_{19} \xrightarrow[+ \text{ DECOMPOSITION}]{MeMgI} MeO\cdot C_6H_4-\overset{Me}{\underset{OH}{\overset{*}{C}}}-\overset{Me}{\underset{Me}{C}}-OH + C_{10}H_{19}OH$$
$$(-)\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad (-)$$

Since the reaction with the ketonic group should take
place before the ester group is attacked, an asymmetric
synthesis should result. This was in fact found,
(McKenzie and Ritchie, loc. cit) and a laevorotatory
glycol was obtained.

Grignard reactions using α-naphthoylformates.
(McKenzie and Ritchie, Biochem. Z. 1931, 231, 412)
Grignard reactions using these esters were found to
give laevorotatory glycollic acids.

$$\alpha\text{-}C_{10}H_7\cdot CO\cdot CO_2R' \xrightarrow[+ \text{ DECOMPOSITION}]{R''MgX} \alpha\text{-}C_{10}H_7-\overset{R''}{\underset{OH}{\overset{*}{C}}}-CO_2R' \rightarrow \alpha\text{-}C_{10}H_7-\overset{R''}{\underset{OH}{\overset{*}{C}}}-CO_2H$$

TABLE B.   GRIGNARD   REACTIONS   USING   α-NAPHTHOYL FORMATES.

GRIGNARD REAGENT USED	ESTER USED	SIGN OF ROTATION OF PRODUCT	SPECIFIC ROTATION OF PRODUCT
MeMgI	(−)- MENTHYL	−	$[\alpha]_{5790}^{25} = -10.0°$
	(−)- BORNYL	−	$[\alpha]_{5461}^{25} = -3.5°$
EtMgBr	(−)- MENTHYL	−	$[\alpha]_{5790}^{25} = -6.8°$
PhMgBr	(−)- MENTHYL	−	$[\alpha]_{5461}^{25} = -9.2°$

Grignard reactions using pyruvates.

The reaction between optically active pyruvates and Grignard reagents was found to give, with one exception, a laevorotatory product when a (+)-keto ester was used, and a dextrorotatory acid from a (−)-keto ester (see table C).

α-Naphthyl magnesium bromide is again seen to give results which are in opposition to those obtained with other Grignard reagents, but in general the use of a laevorotatory aliphatic α-keto-ester gives a dextrorotatory glycollic acid, while a laevorotatory aromatic keto-ester gives a laevorotatory product.

The asymmetric synthesis of the acid $R-\overset{R''}{\underset{OH}{\overset{*}{C}}}-CO_2H$ may obviously be accomplished in two ways:
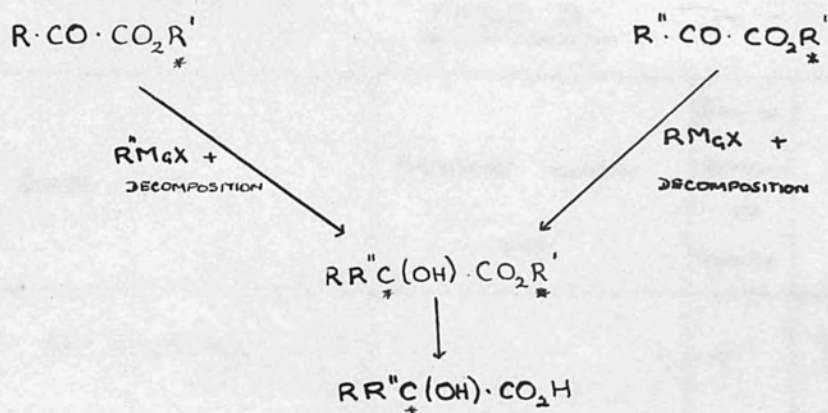
TABLE C.

Grignard reactions using pyruvates.

Grignard reagent used.	Ester used	Reference	Sign of rotation of product	Specific rotation of product
C_2H_5MgBr	(−) − Menthyl	b	+	
	(−) − Bornyl	f	+	
C_6H_5MgBr	(−) − Menthyl	b	+	$[\alpha]_D^{16} = +5.4°$
	(−) − Bornyl	f	+	
	(−)−β−Octyl	d	+	$[\alpha]_{5461}^{25} = +1.8°$
iso − C_4H_9MgI	(−) − Menthyl	f	+	
	(−) − Bornyl	f	+	
α − $C_{10}H_7MgBr$	(−) − Menthyl	f	+	
	(−) − Bornyl	f	−	
	(+)−β−Octyl	d	−	$[\alpha]_{5461}^{25} = −0.4°$
p−MeO·C_6H_4MgBr	(−) − Menthyl	g	+	$[\alpha]_{5461}^{25} = +9.4°$

REFERENCES

f. McKenzie & Wren. J. 1906, 89, 688

g. McKenzie & Ritchie. Biochem. Z. 1932, 250, 376.

$$R \cdot CO \cdot CO_2R' \qquad\qquad R'' \cdot CO \cdot CO_2R'$$

$$\underset{\text{DECOMPOSITION}}{\overset{\overset{*}{R}MgX \ +}{}} \qquad\qquad \underset{\text{DECOMPOSITION}}{\overset{\overset{*}{R}MgX \ +}{}}$$

$$R R'' C(OH) \cdot CO_2 R'$$

$$R R'' C(OH) \cdot CO_2 H$$

A study of McKenzie's results shows that these two routes usually furnish optically active acids which have opposite signs of rotation. This is shown in Table D, the only exceptions being in reactions involving α-naphthyl magnesium bromide.

TABLE D.

| Ester Used.	Grignard Reagent Used.	Sign of Rotation of Product	Specific Rotation of Product
Ph·CO·CO$_2$C$_{10}$H$_{19}$ (−)		−	$[\alpha]_D^{18} = -8.3°$
Ph·CO·CO$_2$C$_{10}$H$_{17}$ (−)	CH$_3$MgI	−	$[\alpha]_D^{15.5} = -1.9°$
Ph·CO·CO$_2$C$_8$H$_{17}$ (−)		−	$[\alpha]_{5461}^{25} = -6.6°$
Me·CO·CO$_2$C$_{10}$H$_{19}$ (−)		+	$[\alpha]_D^{16} = +5.4°$
Me·CO·CO$_2$C$_{10}$H$_{17}$ (−)	C$_6$H$_5$MgBr	+	
Me·CO·CO$_2$C$_8$H$_{17}$ (−)		+	$[\alpha]_{5461}^{25} = +1.8°$
p-MeO·C$_6$H$_4$·CO·CO$_2$C$_{10}$H$_{19}$ (−)	CH$_3$MgI	−	$[\alpha]_{5461}^{25} = -15.9°$
Me·CO·CO$_2$C$_{10}$H$_{19}$ (−)	p-MeO·C$_6$H$_4$MgBr	+	$[\alpha]_{5461}^{25} = +9.4°$
α-C$_{10}$H$_7$·CO·CO$_2$C$_{10}$H$_{19}$ (−)		−	$[\alpha]_{5790}^{25} = -10.0°$
α-C$_{10}$H$_7$·CO·CO$_2$C$_{10}$H$_{17}$ (−)	CH$_3$MgI	−	$[\alpha]_{5461}^{25} = -3.5°$
Me·CO·CO$_2$C$_{10}$H$_{19}$ (−)		+	
Me·CO·CO$_2$C$_{10}$H$_{17}$ (−)	α-C$_{10}$H$_7$MgBr	[−]	
α-C$_{10}$H$_7$·CO·CO$_2$C$_{10}$H$_{19}$ (−)	C$_6$H$_5$MgBr	−	$[\alpha]_{5461}^{25} = -9.2°$
Ph·CO·CO$_2$C$_{10}$H$_{19}$ (−)		[−]	
Ph·CO·CO$_2$	α-C$_{10}$H$_7$MgBr	+	

This partial asymmetric synthesis of both isomers
of an optically active compound by different routes has
been observed by Roger (J. 1939, 108) in the asymmetric
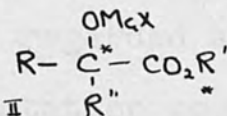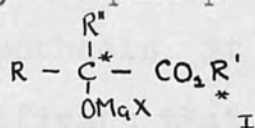synthesis of (+)- and (-)-ethyl benzoin from (-)mandelic
acid.

$$Ph - \overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle OH}{|}}{C}} - CO_2H$$

(-)

$$Ph - \overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle OH}{|}}{C}} - CO - Et$$

(-)

PhMgBr

$$Ph - \overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle OH}{|}}{C}} - \overset{\overset{\displaystyle OH}{|}}{\underset{\underset{\displaystyle Ph}{|}}{C}}{}^{*}Et$$

OXIDATION

$$Ph - \overset{\overset{\displaystyle }{\|}}{\underset{\underset{\displaystyle O}{}}{C}} - \overset{\overset{\displaystyle OH}{|}}{\underset{\underset{\displaystyle Ph}{|}}{C}}{}^{*}Et$$

(+)

$$Ph - \overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle OH}{|}}{C}} - CO - Ph$$

(-)

EtMgBr

$$Ph - \overset{\overset{\displaystyle H}{|}}{\underset{\underset{\displaystyle OH}{|}}{C}} - \overset{\overset{\displaystyle OH}{|}}{\underset{\underset{\displaystyle Et}{|}}{C}}{}^{*}Ph$$

OXIDATION

$$Ph - \overset{\overset{\displaystyle }{\|}}{\underset{\underset{\displaystyle O}{}}{C}} - \overset{\overset{\displaystyle OH}{|}}{\underset{\underset{\displaystyle Et}{|}}{C}}{}^{*}Ph$$

(-)
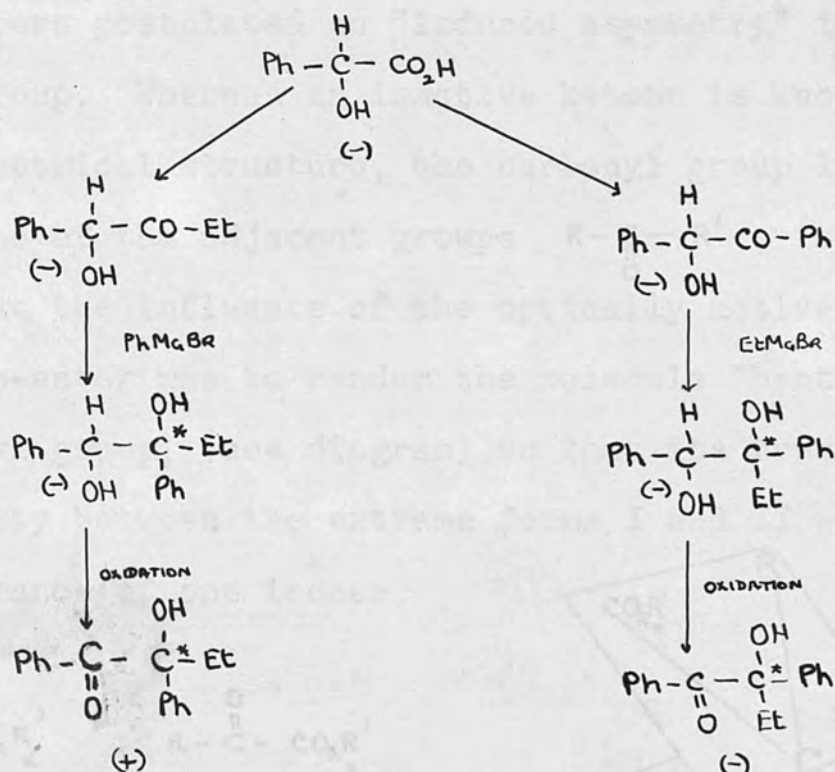
Roger offered no explanation of this, but Partridge
(J. 1939, 1201) later suggested that, assuming "the ketonic
double bond opens in the same sense" in each synthesis,
the production of optical isomers was "a necessary
consequence of the order in which the phenyl and ethyl
group have been embodied". He also pointed out the
similarity in the production of optical antipodes of
ethyl benzoin and of (+)-and (-)-methyl anisyl glycollic
acids, obtained by McKenzie and Ritchie (loc. cit), but

he offered no explanation of the mechanism of asymmetric synthesis.

Ritchie's original explanation of of the asymmetric synthesis of glycollic acids from optically active α-keto esters postulated an "induced asymmetry" in the carbonyl group. Whereas an inactive ketone is known to have a symmetrical structure, the carbonyl group lying in the plane of the adjacent groups $R-\underset{\underset{O}{\|}}{C}-R'$, it was thought that the influence of the optically active group in the keto-ester was to render the molecule "bent" at the carbonyl group, (see diagram) so that its true structure lay between the extreme forms I and II with a preponderance of one isomer:

$$R-\underset{\underset{O}{\|}}{C}-\underset{*}{CO_2R'} \qquad R-\underset{\|}{\overset{O}{C}}-\underset{*}{CO_2R'}$$

$$\text{I} \qquad\qquad \text{II}$$
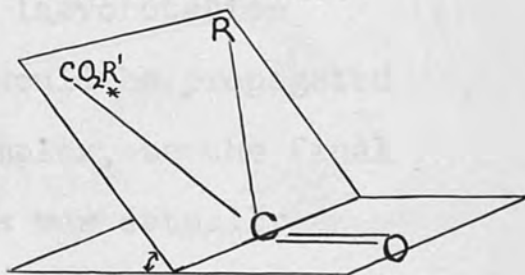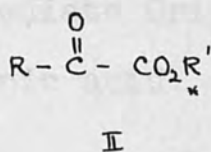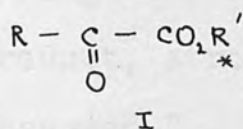
As a direct result of this, on treatment with a Grignard reagent, unequal proportions of the diastereoisomerides

$$R-\underset{\underset{OMgX}{|}}{\overset{R''}{\underset{*}{C^*}}}-\underset{*}{CO_2R'} \qquad R-\underset{\underset{R''}{|}}{\overset{OMgX}{\underset{*}{C^*}}}-\underset{*}{CO_2R'}$$

$$\text{I} \qquad\qquad\qquad \text{II}$$

would be formed and the glycollic acid finally obtained would be optically active. This hypothesis was apparently substantiated by the observed property of α-ketoesters of mutarotating in ethyl alcoholic solution since this mutarotation was attributed to the induction of asymmetry

in the carbonyl group. If the numerical value of the
rotation increased (i.e. a negative rotation decreased
or a positive one increased) a positive rotation was said
to have been induced in the carbonyl group. On this
basis, it was predicted, and found, that a dextrorotatory
glycollic acid was formed by a Grignard reaction on the
ester. If the numerical value of the rotation of the
ester in alcohol decreased, as with (-)-menthyl
benzoylformate, for instance, a negative rotation was
supposed to have been "induced" in the carbonyl group.
In Ritchie's words (Asymmetric Synthesis and Asymmetric
Induction, p.105) "This would lead us to expect that in
the asymmetric synthesis ......, the laevorotation
initiated at the α-carbonyl group would be propagated
through the intermediate Grignard complex, to the final
product, atrolactinic acid: and this was actually
observed."

In spite of the remarkable agreement between
prediction and experimental observation obtained with
this hypothesis, it cannot be regarded as probable. It
is significant that the mutarotation could only be
observed in alcohol and not in ether or any other
non-hydroxylic solvent. Ritchie himself suggests (loc.
cit.) that this mutarotation may be due to simple
solvation, with the formation of a hemi-acetal:

$$Ph \cdot CO \cdot CO_2C_{10}H_{19} \xrightarrow{\text{EtOH}} \underset{\underset{OH}{\overset{*|}{C}}}{Ph - \overset{Et}{\underset{|}{C}} - CO_2C_{10}H_{19}} \quad (-)$$

This seems more likely in the light of later work by Turner and Jamison (J. 1941, 538) and Turner and Glazer (J. 1949, S.169).

Turner and Jamison (loc. cit) first pointed out that the observed mutarotation could be explained on the basis of a slow hemiacetal formation, and later (Quarterly Reviews, 1948, 1, 299) suggested that an immediate formation of hemiacetal might take place, followed by first order asymmetric transformation of the two possible diastereoisomers. Turner and Glazer (loc.cit) showed that the first of these hypotheses was correct, and therefore, since no mutarotation phenomena are observed in non-hydroxylic solvents, there is no reason to suppose that the ketonic group in the ester assumes an asymmetric configuration. Turner and Jamison (loc.cit) also suggested that in asymmetric syntheses involving the Grignard reaction the intermediate complex was possibly formed which

$$\underset{CO_2R'\,*}{\overset{R}{\underset{}{}}}\overset{\delta_+}{C}=\overset{\delta}{O}\cdots\overset{\delta_+}{\underset{X}{Mg}}\overset{\delta}{\overset{R''}{}}$$

decomposed to give

$$\underset{CO_2R'\,*}{\overset{R}{\underset{}{}}}\overset{*}{\underset{}{C}}\overset{R''}{\underset{OMgX}{}} .$$

Unequal proportions of the two diastereoisomerides of the latter compound would be formed, owing to the different energy changes involved in each decomposition

(the diastereoisomeride with the lower free energy would
obviously be formed in excess). The same idea was
expressed by Turner and Harris (Quarterly Reviews 1947,
I, 330) in 1947 when they postulated that in the addition
of a compound XY to a carbonyl group in the ketone

$R - \underset{*}{C} - R'$ (R containing a centre of fixed asymmetry),
   $\overset{\|}{O}$

X^- approached the positive end of the polarised carbonyl
group:

$X^- \qquad \overset{*R}{\underset{R'}{\overset{|}{\underset{|}{C}}}} = \overset{?}{O} \qquad \longrightarrow \qquad X \cdots\cdots \overset{*R}{\underset{R'}{\overset{|}{\underset{|}{C}}}} \overset{\delta+}{\underset{}{}} \overset{\delta-}{=} \overset{}{O}$
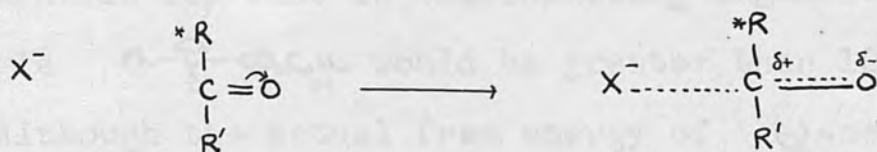
thus making two tetrahedral arrangements of groups
possible before the addition of Y^+:
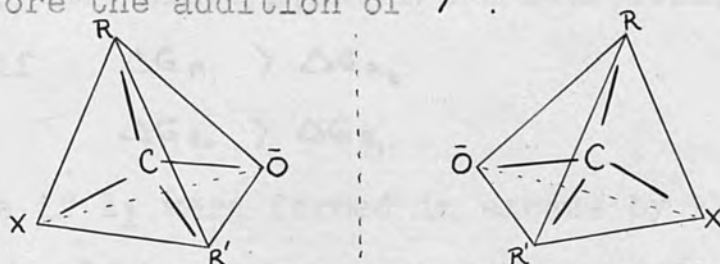
Since the energy changes involved in the formation
of these two structures are unequal, unequal proportions
of each would be present, and the addition of Y^+ would

give an excess of one diastereoisomer of $X - \overset{*R}{\underset{R'}{\overset{|}{\underset{|}{C'''}}}} - OY$.

If this were the only influence directing the
asymmetric synthesis, one would expect that the same
diastereoisomer (the one with the lower free energy)
of the compound would be formed, regardless of the
route of synthesis. For instance, application to
Grignard reactions on α-ketoesters would lead us to
expect that the same diastereoisomer of (-)-menthyl
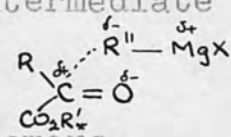
phenylmethylglycollate (and therefore the same isomer of phenylmethylglycollic acid) would be formed in excess, whether it was produced by the reaction of PhMgBr on (−)-menthylpyruvate, or MeMgBr on (−)-menthyl benzoyl-formate: this is shown in the accompanying diagrams,

ΔG being the change in free energy involved in each reaction (the keto-ester has been drawn in a tetrahedral configuration for ease in the following argument; in fact the angle $Ph-\overset{O}{\underset{\parallel}{C}}-CO_2C_{10}H_{19}$ would be greater than $109° 28'$).

Although the actual free energy of (−)-menthyl pyruvate and (−)-menthyl benzoylformate are not the same, it is obvious that since A_1 and B_2 are identical, (as are A_2 and B_1), if $\Delta G_{A_1} > \Delta G_{A_2}$

then $\Delta G_{B_2} > \Delta G_{B_1}$

and therefore if A_1 were formed in excess by the first reaction, B_2 would be in excess by the second.

There is also the possibility that the intermediate complex formed in the Grignard reaction may be $\underset{CO_2R'_*}{\overset{R''-MgX}{\underset{\|}{C}=O}}$ which is capable of existing in two diastereoisomers. (see Turner and Reid, J.1949, 3365   ). Since the formation of this complex is reversible, asymmetric transformation may take place to give the diastereoisomer of lower free energy in excess and irreversible decomposition to the complex $\underset{CO_2R'}{\overset{R\quad R''}{\underset{*}{C}}-OMgX}$
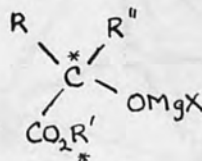
I. Reaction between (-)-menthyl pyruvate and
phenyl magnesium bromide.
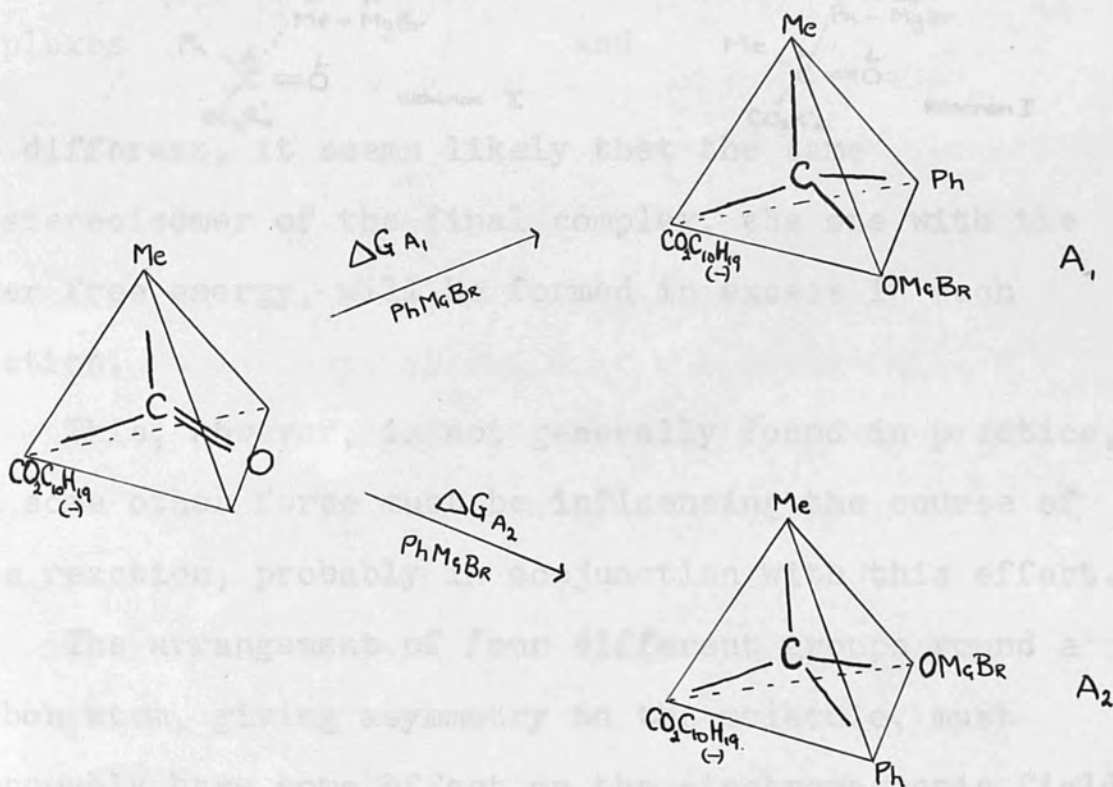
II. Reaction between (-)-menthyl benzoylformate and
methyl magnesium bromide.
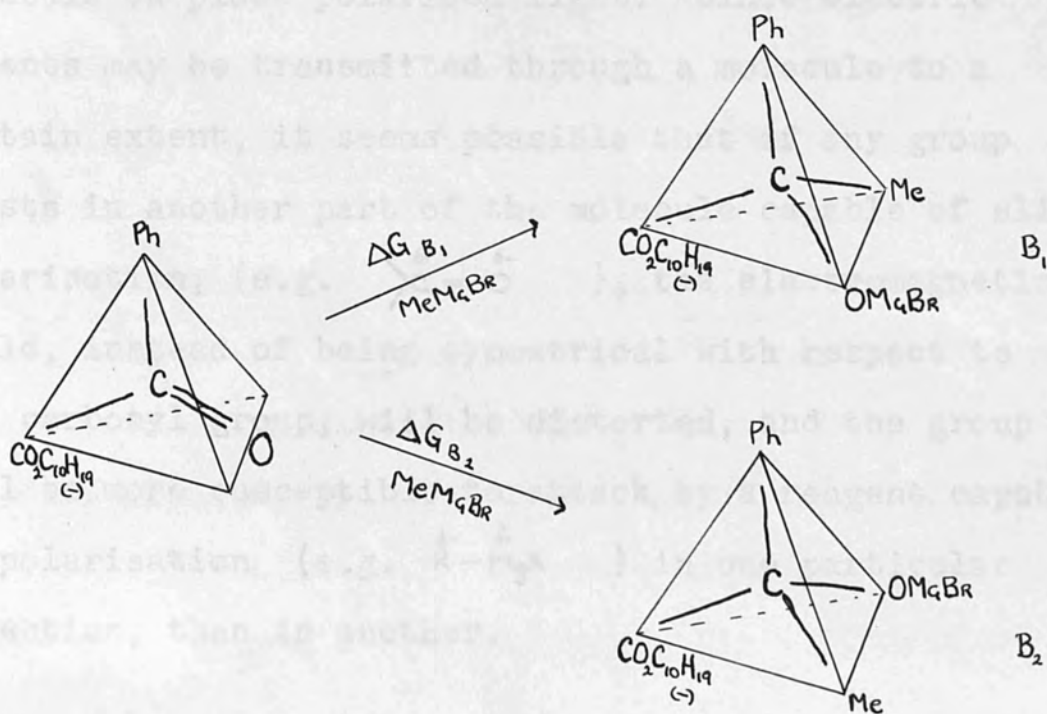
will result in asymmetric synthesis.   Although the

complexes $Ph \underset{\delta+}{\overset{\delta-}{C}} \cdots \underset{\delta+}{\overset{\delta-}{Me}} - MgBr$ and $Me \underset{\delta+}{\overset{\delta-}{C}} \cdots \underset{\delta+}{\overset{\delta-}{Ph}} - MgBr$

$\overset{\delta+}{C} = \overset{\delta-}{O}$ REACTION II $\overset{\delta+}{C} = \overset{\delta-}{O}$ REACTION I

$CO_2R'_*$ $CO_2R'_*$
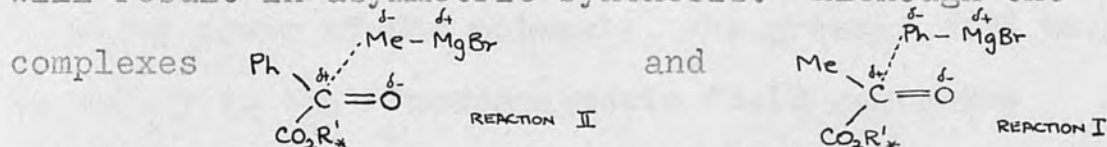
are different, it seems likely that the same

diastereoisomer of the final complex, the one with the

lower free energy, will be formed in excess in each

reaction.

This, however, is not generally found in practice,

and some other force must be influencing the course of

this reaction, probably in conjunction with this effect.

The arrangement of four different groups round a

carbon atom, giving asymmetry to the molecule, must

presumably have some effect on the electromagnetic field

in the neighbourhood of that atom. The asymmetry in

this field is probably connected with the effect of the

molecule on plane polarised light. Since electric

effects may be transmitted through a molecule to a

certain extent, it seems possible that if any group

exists in another part of the molecule capable of slight

polarisation, (e.g. $\overset{\delta+}{C} = \overset{\delta-}{O}$), the electromagnetic

field, instead of being symmetrical with respect to

the carbonyl group, will be distorted, and the group

will be more susceptible to attack by a reagent capable

of polarisation (e.g. $\overset{\delta-}{R} - \overset{\delta+}{Mg}X$) in one particular

direction, than in another.

It is suggested that the greater the optical rotatory power of the molecule, the greater will be the asymmetry in the electromagnetic field round the asymmetric carbon atom, and therefore the greater will be the power of inducing asymmetry in other parts of the molecule. Thus using (-)-menthol, (-)-borneol, (-)-β-octyl and (-)-amyl alcohols as the asymmetric intermediates, the degree of asymmetric synthesis brought about by each should bear the same relation as the specific rotation of each, i.e:

(-)-menthol ⟩ (-)-borneol and (-)-β-octyl ⟩ (-)-amyl

The liquid and solid alcohols cannot really be compared. Also, the use of dextrorotatory intermediates would be expected to cause asymmetric synthesis in the opposite sense to laevorotatory ones.

The degree of asymmetric synthesis in any particular reaction will depend, of course, on the conditions of reaction, but under similar conditions the above effect should be noted.

It should be emphasised that a displacement of the oxygen atom of the carbonyl group, so that the carbon-oxygen bond is no longer in the plane of the rest of the molecule is not proposed. This type of displacement was the effect postulated by McKenzie and Ritchie, but this cannot now be considered probable. The asymmetric

induction effect is concerned solely with the carbon-oxygen bond of the carbonyl group, and it is the electromagnetic field round this group which is asymmetric. The idea of these asymmetric syntheses being directed by asymmetry induced in the carbon-oxygen bond of the carbonyl group was first put forward by Tiffeneau and Levy (Bull. Soc. chim. 1927, (IV) 11, 1351) although they expressed it as "one bond" of the carbonyl group breaking more easily than the other. This is founded on older conceptions of chemical bonding between atoms, but the basic idea is similar. The same opinion was presumably held by Partridge (loc. cit) although he did not discuss the point in detail.

In reactions at the carbonyl group of d-keto esters, therefore, the effect of the optically active group will be that instead of proceeding symmetrically, and resulting in a compound with the oxygen atom equally distributed between positions a and b (see diagram), the reaction will take place asymmetrically, the carbonyl group being attacked preferentially in one particular direction, and the resulting compound will show the oxygen atom predominating at a or b.
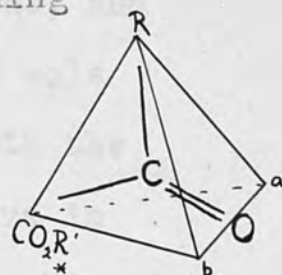
Since the induced asymmetry is concerned solely

with the effect of the centre of fixed asymmetry in the
ester group, there is no reason to suppose that the
nature of the group R will have any marked effect on
this asymmetry. The carbonyl group in (-)-menthyl
pyruvate and (-)-menthyl benzoylformate would be
attacked preferentially by a Grignard reagent in the
same way, and reference to the diagrams previously drawn
will show that if A, is produced in excess by reaction I,
B, will be in excess in the second reaction. As these
two compounds are diastereoisomerides, this hypothesis
does describe the practical results.

If, as seems likely, the group R has little effect
on the degree of induced asymmetry at the carbonyl group,
it would be expected that both reactions I and II would
give roughly equal degrees equal degrees of asymmetric
synthesis. This is not confirmed by experiment, and
therefore this inductive effect cannot be the sole
influence operating. It is suggested that both the
directive forces so far described are effective in
determining the course of the reaction, the combination
of which may give rise to several possibilities:

a) if they both operate in the same sense one
would expect asymmetric synthesis to occur to an equal
degree, and in the same sense, in both reactions I and II.
This is not found practically, and may therefore be

presumed to be incorrect.

b) if they both operate in opposite senses there are three possibilities:

(i) if the inductive effect were the greater, asymmetric synthesis would take place in opposite senses in I and II, but would be greater in the reaction giving the diastereoisomer with the lower free energy.

(ii) if the inductive effect were the weaker, asymmetric synthesis would take place in the same sense in I and II, giving in both cases the diastereoisomer of lower free energy, but the degree of asymmetric synthesis would be greater when the inductive effect would also give this isomer.

(iii) if both effects are almost equal, the degree of asymmetric synthesis in either sense might be so small as to be unobservable.

In general, it has been found that asymmetric syntheses involving Grignard reactions on α-keto esters conform to the conditions of b) (i).

Using (-)-menthyl esters there are no exceptions to this rule, showing that the power of the (-)-menthyl group to induce asymmetry in the carbonyl group is the deciding factor in the course of every reaction. The degree of asymmetric synthesis obtained was greater when in the ester $R \cdot CO \cdot CO_2 C_{10}H_{19}$, R was C_6H_5- , $MeO \cdot C_6H_4-$, or

α- $C_{10}H_7$— , and MeMgI was the reagent (giving a
(−) -rotatory product) than when R was Me, and the
Grignard reagents were C_6H_5MgBr, p-$MeO \cdot C_6H_4 \cdot MgBr$ or
α-$C_{10}H_7MgBr$ (giving a dextrorotatory product). This
means that the diastereoisomer with the lower free
energy was in each case

$$R \underset{CO_2C_{10}H_{19}}{\overset{(-)}{\underset{(-)}{\diagup}} C} \overset{(-) \; OMgBr}{\underset{Me}{\diagdown}}$$
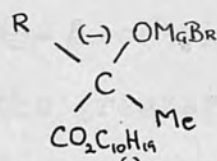
where R = C_6H_5- , p - $MeO \cdot C_6H_4-$, or α-$C_{10}H_7-$. If
the energy changes were the deciding factor in any of
these reactions, the laevorotatory glycollic acid
would be obtained, regardless of the route of synthesis.

Using (−)-bornyl esters, the conditions of b) (i)
were generally operative, except in the reactions
giving α-naphthylmethyl glycollic acid. Here, as
predicted in the previous argument, the laevorotatory
acid is obtained from both routes of synthesis, the
degree of asymmetric synthesis being the greater in the
reaction between MeMgBr and (−)-bornyl-α-naphthoylformate,
also as expected.

The reaction between α-naphthyl magnesium
bromide and (−)-bornyl benzoylformate also gives results
at variance with results given by other Grignard
reagents and this ester, but unfortunately the
complementary reaction (PhMgBr on (−)-bornyl-α -
naphthoylformate) was not performed, and so a true

.test of the hypothesis cannot be made.

A few reactions performed with ⊕- and ⊖-β-octyl benzoylformate and pyruvate show that the asymmetric synthesis of phenylmethylglycollic acid takes place as expected. ⊖-β-Octyl benzoylformate and MeMgI give a laevorotatory product, and ⊖-β-octyl pyruvate and PhMgBr a dextrorotatory one, the greater degree of asymmetric synthesis taking place in the former reaction.

It would be expected that Grignard reactions on ⊕-β-octyl benzoylformate would give ⊕-rotatory glycollic acids, but unfortunately the only reaction reported was using α-naphthyl magnesium bromide, when a laevo-rotatory product was obtained. Using ⊕-octyl pyruvate and the same reagent, a laevorotatory product was obtained, as expected. As the complementary reactions of PhMgBr and MeMgBr on ⊕-β-octyl-α-naphthoyl formate have not been performed, no definite conclusions may be drawn, but this does show the greater inductive power of the β-octyl group over the ⊖-bornyl group, which has been noted before.

From a study of these Grignard reactions, it seems probable, therefore, that the asymmetric influence of the optically active group is the deciding factor in determining the course of the reaction except where the asymmetric influence is weak. Then the introduction

of a large group into the molecule (i.e. the α-naphthyl group) causes such a difference in the free energies of of the possible products, that this becomes the controlling factor.

It is impossible to obtain an accurate idea of the effect of different Grignard reagents on one ester since, as has already been pointed out, the glycollic acids have not all been resolved; however it does seem that the action of methyl magnesium bromide gives the greatest degree of asymmetric synthesis.

The mutarotation of optically active α-keto esters in alcoholic solution provides an analogous case, since it has been shown to be due to slow hemiacetal formation (Turner and Glazer loc. cit). The mechanism of the reaction depends, however, on the percentage of water present in the alcohol (Turner and Jamison loc. cit).

The power of an asymmetric group to cause asymmetric synthesis must depend on two main factors,

a) the power of the optically active group itself to induce asymmetry at the reaction centre, and

b) the separation between the asymmetric and reaction centres.

The factor a) has already been discussed, and has been studied in several reactions, but the factor b)

has not been investigated fully. Only isolated examples

may be quoted, and no true comparisons made. When the

asymmetric and reaction centres are adjacent, as in the

synthesis of the ethyl benzoins:

$$Ph-\overset{\overset{H}{|}}{\underset{\underset{OH}{|}}{C}}-CO-Ph \xrightarrow{\text{EtMgBr}} Ph-\overset{\overset{H}{|}}{\underset{\underset{OH}{|}}{C}}-\overset{\overset{OH}{|}}{\underset{\underset{Et\,(-)}{|}}{C^{*}}}-Ph \xrightarrow{\text{OXIDATION}} Ph-CO-\overset{\overset{OH}{|}}{\underset{\underset{Et\,(-)}{|}}{C^{*}}}-Ph$$
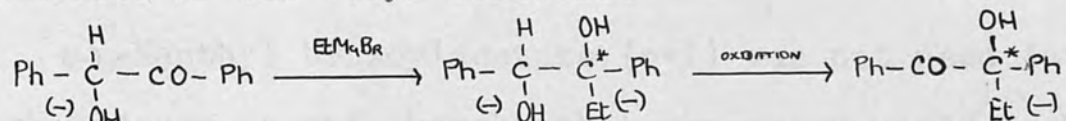
it is not surprising that the inductive effect may be so

great as to cause practically complete formation of one

isomer.

When the asymmetric and reaction centres are

separated, as, for example, in McKenzie's synthesis,

both possible diastereoisomerides are formed, with one

in excess.

No work has been reported in which the distance

between the reaction and asymmetric centres has been

steadily increased, as for example, by a methylene

chain ($-CH_2-$)$_n$, the asymmetric intermediate and the

general type of reaction remaining the same. This has

been done in the present work by performing Grignard

reactions on (-)-menthyl keto-esters, the carbonyl group

and ester group being separated by a methylene chain,

e.g. $R \cdot CO \cdot (CH_2)_n \cdot CO_2 C_{10} H_{19}$.

(-)-Menthyl esters were used because (-)-menthol had

been shown to give the greatest degree of asymmetric

synthesis of all the readily available active alcohols.

The group R was the phenyl group, and reactions were

performed using methyl and ethyl magnesium bromides.
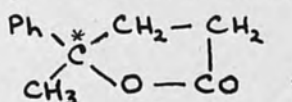
(The complementary reactions between phenyl magnesium bromide and $Me \cdot CO \cdot (CH_2)_n \cdot CO_2C_{10}H_{19}$ were undertaken by another worker).

(−)-Menthyl benzoylacetate (n=1) was not used in this work because it was thought that the ester would probably react in the enol-form, $C_6H_5-C(OH)=CH \cdot CO_2C_{10}H_{19}$ and after decomposition of the Grignard complex, the original ester would be recovered. McKenzie (J.1906, 89, 382) has shown that this occurs in the reaction between (−)-menthyl acetoacetate and EtMgBr.

McKenzie (J. 1906, 89, 382) also carried out the reaction between phenyl magnesium bromide and (−)-menthyl laevulinate, $CH_3 \cdot CO \cdot (CH_2)_2 \cdot CO_2C_{10}H_{19}$ and obtained a slightly laevorotatory product, thought to be the lactone

$$Ph \underset{CH_3}{\overset{*}{C}} \overset{CH_2-CH_2}{\underset{O-CO}{\diagup}}$$

The reaction between MeMgBr and (−)-menthyl benzoylpropionate has not previously been described, but would be expected to give the acid $C_6H_5-\overset{Me}{\underset{OH}{\overset{|}{\underset{|}{C}}}}-(CH_2)_2 \cdot CO_2H$ which would easily lactonise. By analogy with the results obtained by McKenzie, the lactone would be expected to be dextrorotatory.

Increasing the chain length between the asymmetric and reaction centres would be expected to decrease the inducing effect of the optically active group. The difference in free energy between the two diaster-

-eoisomerides of $C_6H_5 - \overset{\underset{\displaystyle OH}{\overset{\displaystyle CH_3}{\underset{|}{\overset{|}{*C}}}}}{} - (CH_2)_n \cdot CO_2C_{10}H_{19}$ would probably not
change much with increase in n, and therefore the increase
in n would be expected to cause a decrease in the degree
of asymmetric synthesis. Since, when $n = 0$, a
laevorotatory acid is obtained, the glycollic acids
obtained would probably be laevorotatory. No predictions
may be made regarding the relation between the optical
activities of acids and their lactones (when n = 2 or 3)
at this stage.

When n becomes large it seems probable that the two
effects will balance, and the degree of asymmetric synthesis
will be so small, if present, as to be non-detectable.

S E C T I O N II.

a). Preparation of (±)-menthyl benzoylformate.

b). Preparation of (±)-menthyl-β-benzoylpropionate.

c). Preparation of (±)-menthyl-γ-benzoylbutyrate.

d). Preparation of (±)-menthyl-δ-benzoylvalerate.

e). Preparation of (±)-menthyl-ω-benzoylpelargonate.

S E C T I O N IIa

Benzoylformic acid.

Benzoylformic acid, $Ph \cdot CO \cdot CO_2H$, has been described frequently in the literature, but was most conveniently prepared by McKenzie (J, 1904, 1247) by the oxidation of acetophenone with hot alkaline permanganate solution. The mixture of benzoylformic and benzoic acids so obtained was separated through their differing solubilities in water.

$$Ph \cdot CO \cdot CH_3 \xrightarrow{KMnO_4} Ph \cdot CO \cdot CO_2H + Ph \cdot CO_2H$$
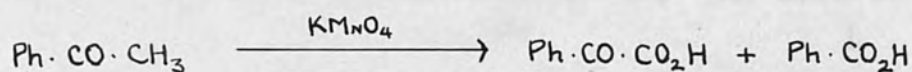
McKenzie's method was later modified by Jamison and Turner, (private communication) and their method was used by the author.

(-)-Menthylbenzoylformate.

(-)-Menthylbenzoylformate was prepared by the Fischer-Speier method (Section Va) and was crystallised from alcohol. The ester was found to have m.p. 73°- 73.5° and $[\alpha]_{5461}^{25} = -52.3°$ in absolute alcohol $[l = 2, c = 2.38]$ 15 minutes after wetting the solid. McKenzie (J.1904, 1249) gives m.p. 73-74°, Jamison and Turner (J.1941, 538) give $[\alpha]_{5461}^{18.8} = -51.6°$ in 99% alcohol $[l = 2, c = 3.5175]$ three minutes after wetting the solid.

SECTION IIb.

β-Benzoylpropionic acid.

β-Benzoylpropionic acid has been described frequently in the literature, and only the more important methods of synthesis will be given here. The acid was first reported by Matsmoto (Ber. $\underline{8}$, 1145) in 1875, who prepared it, m.p. 115°, by prolonged heating of a mixture of cinnamaldehyde hydrochloric acid and prussic acid.

$$Ph \cdot CH = CH \cdot CHO \xrightarrow{HCN} Ph \cdot CH = CH - \underset{OH}{\overset{H}{\underset{|}{C}}} - CN \xrightarrow{HCl} Ph \cdot CH = CH - \underset{OH}{\overset{H}{\underset{|}{C}}} - CO_2H$$

$$\downarrow$$

$$Ph \cdot CO \cdot (CH_2)_2 \cdot CO_2H$$
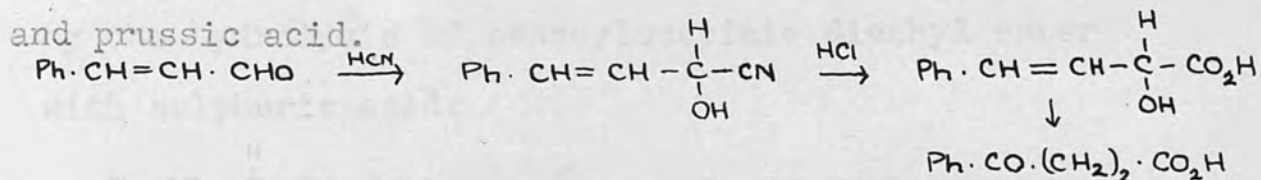
The final stage in the reaction, i.e. the conversion of α-hydroxy-γ-phenylcrotonic acid into β-benzoylpropionic acid, which is effected by boiling with dilute hydrochloric acid, has been investigated by a number of workers, notably Fittig (Annalen 1898, $\underline{299}$, 5   ), Erlenmeyer (Annalen 1904, $\underline{333}$, 196) and Bougault (Ann. Chim. Phys. 1908, (8), $\underline{15}$, 573). The mechanism proposed for the change is of interest as it provides an explanation of the production of β-benzoylpropionic acid in some other reactions.

$$Ph \cdot CH = CH \cdot CH(OH) \cdot CO_2H \xrightarrow{-H_2O} Ph \cdot CH = C = CH \cdot CO_2H$$

$$\downarrow + 2H_2O$$

$$Ph \cdot CH(OH) \cdot CH(OH) \cdot CH_2 \cdot CO_2H$$

$$\downarrow -H_2O$$

$$Ph \cdot C(OH) = CH \cdot CH_2 \cdot CO_2H$$

$$\downarrow$$

$$Ph \cdot CO \cdot CH_2 \cdot CH_2 \cdot CO_2H$$
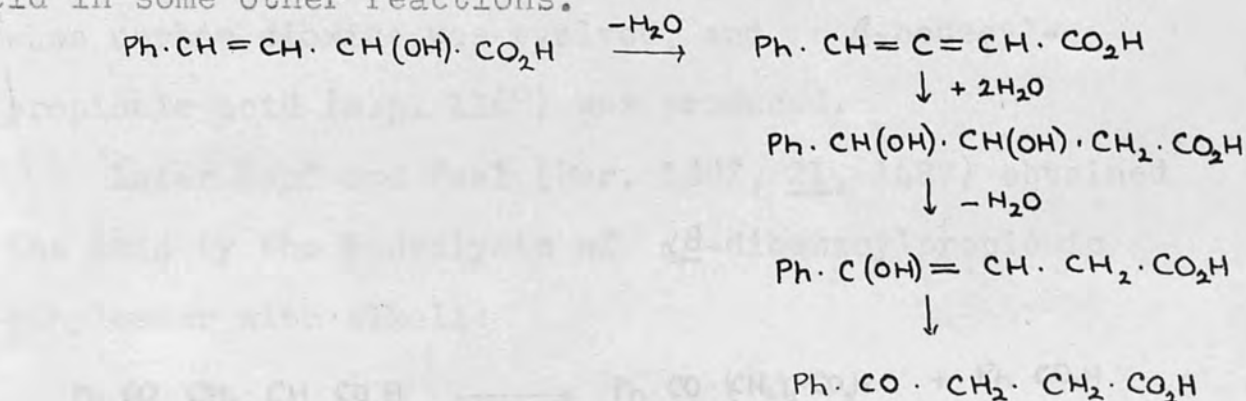
As may be predicted from this mechanism, β-benzoyl propionic acid is the final product of the hydrolysis of $Ph \cdot CH(Br) \cdot CH(Br) \cdot CH_2 \cdot CO_2H$ (Fittig et al. Annalen, 268, 74) and $Ph \cdot CH = C = CH \cdot CO_2H$ or $Ph \cdot CH = CH - CH(OH) \cdot CCl_3$ (Drboglaw, $\cancel{X}$ 1900, 32, 230).

Perkin, in 1885, (J. 47, 276) obtained the acid by the hydrolysis of benzoylsuccinic diethyl ester with sulphuric acid:
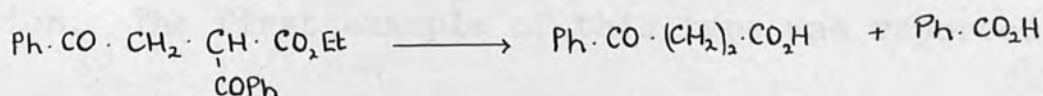
$$Ph \cdot CO - \overset{H}{\underset{CO_2Et}{C}} - CH_2 \cdot CO_2Et \longrightarrow Ph \cdot CO \cdot (CH_2)_2 \cdot CO_2H$$
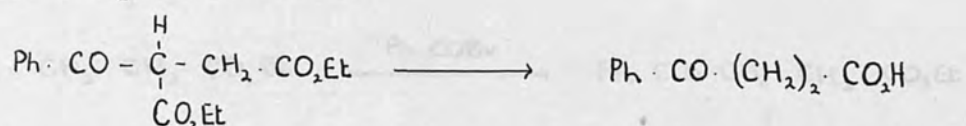
and a similar method was used by Klobb (Ann. Chim. Phys. VII 10, 191) and Bougault (Ann. Chim. Phys. 1908, VIII, 15, 506) who hydrolysed the alkyl-ester-nitrile of benzoyl-iso-succinic ester:

$$Ph \cdot CO \cdot CH_2 \cdot \overset{}{\underset{CN}{CH}} - CO_2Et \longrightarrow Ph \cdot CO \cdot CH_2 - \overset{H}{\underset{CO_2H}{C}} - CO_2H \longrightarrow Ph \cdot CO \cdot (CH_2)_2 \cdot CO_2H$$
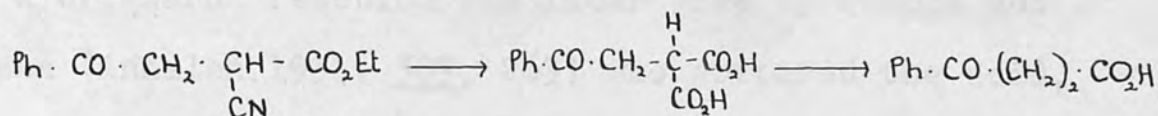
Kues and Paal (Ber. 1885, 18, 3352) carried out the final stage of this last reaction by heating β-benzoyl-iso-succinic acid above its melting point, when carbon dioxide was evolved, and β-benzoyl-propionic acid (m.p. 116°) was produced.

Later Kapf and Paal (Ber. 1888, 21, 1487) obtained the acid by the hydrolysis of $\alpha\beta$-dibenzoylpropionic ethylester with alkali:

$$Ph \cdot CO \cdot CH_2 \cdot \overset{}{\underset{COPh}{CH}} \cdot CO_2Et \longrightarrow Ph \cdot CO \cdot (CH_2)_2 \cdot CO_2H + Ph \cdot CO_2H$$

The condensation of benzaldehyde and fumaric acid or
malic acid also yields β-benzoylpropionic acid
(Mayrhofer and Nemeth, Monatsh,1903, 24, 81).

$$Ph \cdot CHO \;+\; \underset{CO_2H}{\overset{CO_2H}{CH=CH}} \longrightarrow Ph-\underset{OH}{\overset{H}{C}}-\underset{CO_2H}{C}=CH-CO_2H \xrightarrow{-CO_2} Ph \cdot CO \cdot (CH_2)_2 \cdot CO_2H$$
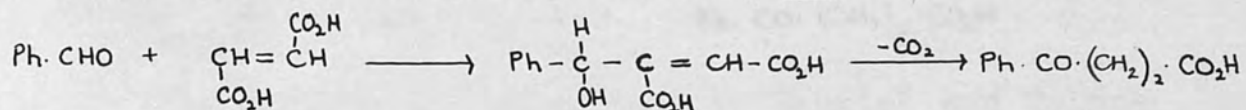
In 1906, R. Meyer and Togel (Annalen.1906, 347, 88)
prepared the acid (m.p. 116°) by a Grignard reaction
between benzoyl bromide and β-carbethoxyethyl magnesium
iodide.

$$MgI \cdot CH_2 \cdot CH_2 \cdot CO_2Et \xrightarrow{Ph \cdot COBr} Ph \cdot CO \cdot CH_2 \cdot CH_2 \cdot CO_2Et$$

$$\downarrow \text{HYDROLYSIS}$$

$$Ph \cdot CO \cdot CH_2 \cdot CH_2 \cdot CO_2H$$

A Grignard reaction was later used by Komppa and
Rohrmann (Annalen.1934, 509, 263) who prepared the acid,
from succinic anhydride and phenyl magnesium bromide, the
glycol $Ph_2C(OH) \cdot (CH_2)_2 \cdot CPh_2OH$ also being formed.

$$PhMgBr + (CH_2)_2\overset{CO}{\underset{CO}{\diagup\diagdown}}O$$

$$Ph \cdot CO \cdot (CH_2)_2 \cdot CO_2H \qquad\qquad Ph_2C(OH) \cdot (CH_2)_2 \cdot CPh_2OH.$$
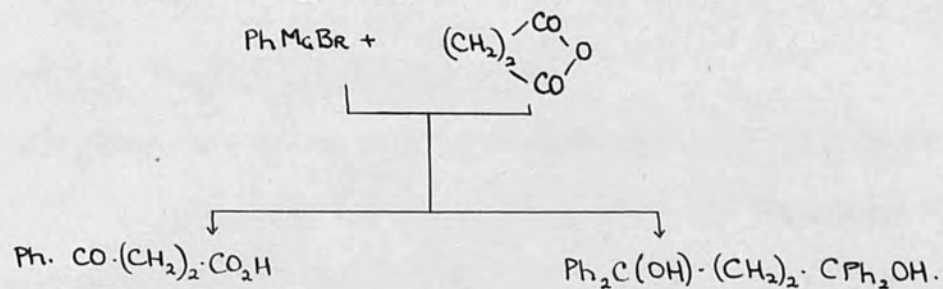
The methods of synthesis which have found the
widest application are those utilising the Friedel-Crafts
reaction. The first example of this type was reported

by Burcker (Ann. Chim. Phys. (V), 26, 435) who performed the reaction between succinic anhydride and benzene in presence of aluminium chloride.

$$(CH_2)_2 \overset{CO}{\underset{CO}{\diagdown}} O + C_6H_6 \xrightarrow{AlCl_3} Ph \cdot CO \cdot (CH_2)_2 \cdot CO_2H$$
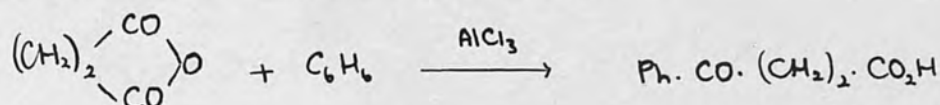
This method was later used by Gabriel and Colman (Ber. 1899, 32, 398), Kugel, (Annalen.1898, 299, 50) who obtained an acid of m.p. 116°, Borsche (Ber.1914, 47, 1110) and Kohler and Englebrecht (J.Amer. Chem.Soc. 1919, 41, 768, acid m.p. 116.5°).

More recently, Papa, Schwenk and Hankin (J. Amer. Chem. Soc. 1947, 69, 3078) prepared the acid, m.p. 113°-114° in 84% yield by a Friedel-Crafts reaction between β-carbethoxypropionyl chloride and benzene, followed by hydrolysis of the resultant ethyl β-benzoylpropionate:

$$C_6H_6 + Cl \cdot CO \cdot (CH_2)_2 \cdot CO_2Et \longrightarrow Ph \cdot CO \cdot (CH_2)_2 \cdot CO_2Et \longrightarrow Ph \cdot CO \cdot (CH_2)_2 \cdot CO_2H$$

In the present work the method of Kohler and Englebrecht (loc. cit). was used, and the acid was obtained in 95% yield, m.p. 116°.

(-)-Menthyl-β-benzoylpropionate

(-)-Menthyl-β-benzoylpropionate has not been previously reported. It was prepared by Fischer - Speier esterification of the acid (Section Va) and crystallised easily in hard, large prisms from light petroleum b.p. 60° - 80°. The ester was found to have m.p. 92°, and $[\alpha]_{5461}^{25} = -62.1°$ in chloroform (1 = 2,

<u>c</u> = 1.715). Chloroform was used as a solvent in the
determination of the specific rotation, as the ester
was insufficiently soluble in alcohol.

S E C T I O N   IIc.

Ɣ -Benzoylbutyric acid.

Ɣ-Benzoylbutyric acid, like its homologues, has
been prepared by Friedel-Crafts reactions, and was first
described by Auger (Ann. Chim. Phys. (VI), $\underline{22}$, 360) in
1891. He obtained the acid as a crystalline solid
m.p. 125° - 126°, by the reaction between glutaryl
chloride and benzene in presence of aluminium chloride.
Dibenzoyl propane was also formed at the same time ;

$$C_6H_6 \ + \ Cl \cdot CO \cdot (CH_2)_3 \cdot COCl$$

$$Ph \cdot CO \cdot (CH_2)_3 \cdot CO_2H \qquad\qquad Ph \cdot CO \cdot (CH_2)_3 \cdot CO \cdot Ph$$
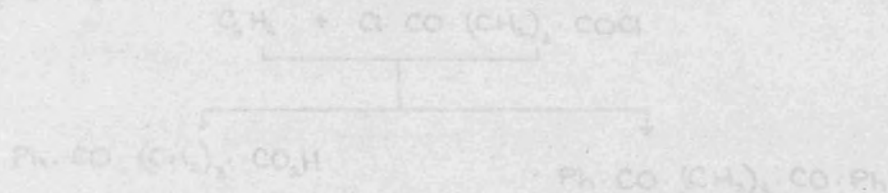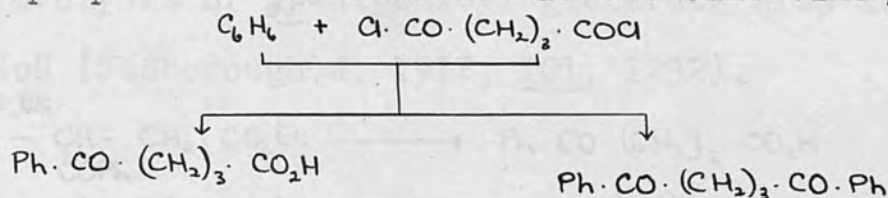
The reaction between Ɣ-carbethoxy butyryl
chloride, $Cl \cdot CO \cdot (CH_2)_3 \cdot CO_2Et$ and benzene to give ethyl-
benzoylbutyrate, without the formation of any diketone,
has not been reported, presumably owing to the relative
inaccessibility of the parent acid.

The Friedel-Crafts reaction between glutaric
anhydride and benzene has, however, been performed,
(Organic Syntheses, II, p.82) and the acid, m.p. 125° -126°
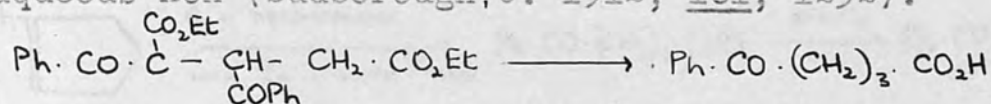was obtained in 80-85% yield.

Wislecenus and Kuhn (Annalen 1898, $\underline{302}$, 218)
prepared the acid by the hydrolysis of the reaction
product of benzoylacetic ester and methylene iodide in
presence of sodium ethoxide:

$Ph \cdot CO \cdot CH_2 \cdot CO_2Et$

$$Ph \cdot CO \cdot CH_2 \cdot CO_2Et \quad | \quad CH_2 \quad | \quad I \quad | \quad CH_2 \quad | \quad I \quad | \quad Ph \cdot CO \cdot CH_2 \cdot CO_2Et \xrightarrow{NaOEt}$$

$$Ph \cdot CO \cdot \underset{|}{CH} - CO_2Et$$
$$| \atop CH_2$$
$$Ph \cdot CO \cdot CH - CO_2Et$$

$$\downarrow$$

$$Ph \cdot CO \cdot (CH_2)_3 \cdot CO_2H + Ph \cdot CO_2H .$$
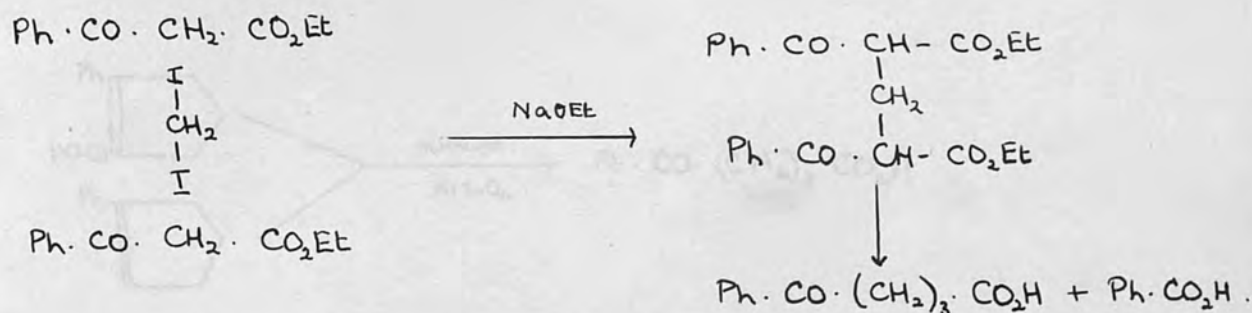
The acid has also been obtained by the ketonic hydrolysis of ᴅ-benzoyl glutaric ester (Fichter and Bauer, Ber. 1898, <u>31</u>, 2001),

$$Ph \cdot CO - \overset{CO_2Et}{\underset{H}{C}} - (CH_2)_2 \cdot CO_2Et \longrightarrow Ph \cdot CO \cdot (CH_2)_3 \cdot CO_2H$$
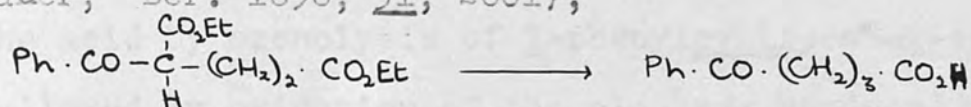
and by hydrolysis of ᴅβ-dibenzoyl glutarate with 10% aqueous KoH (Sudborough, J. 1912, <u>101</u>, 1232).

$$Ph \cdot CO \cdot \overset{CO_2Et}{\underset{COPh}{C}} - CH - CH_2 \cdot CO_2Et \longrightarrow Ph \cdot CO \cdot (CH_2)_3 \cdot CO_2H$$

The main line of synthesis of γ-benzoyl butyric acid has been by the oxidation of a suitable phenyl <u>cyclo</u>-pentane derivative, which reaction is similar to that performed in the phenyl <u>cyclo</u>hexane series to give <u>δ</u>-benzoyl valeric acid.
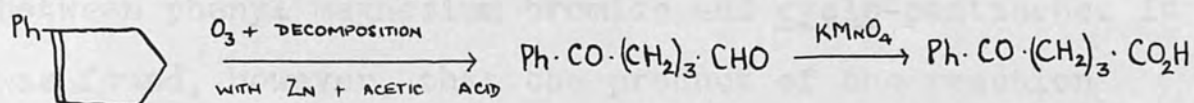
The first synthesis of this type was carried out by Bauer in 1912 (Comptes. rend. <u>155</u>, 289) who oxidised 1-benzoyl-2-phenyl-<u>cyclo</u>pent-<u>1</u>-ene with aqueous permanganate.

$$\underset{Ph \cdot CO}{\overset{Ph}{\diagup}} \quad \xrightarrow{KMnO_4} \quad Ph \cdot CO \cdot (CH_2)_3 \cdot CO_2H + Ph \cdot CO_2H$$
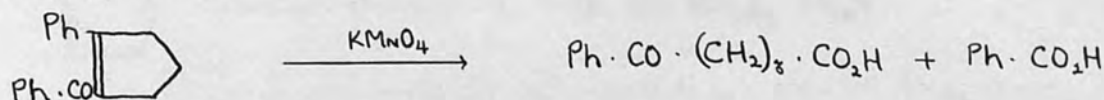
In the following year he obtained the acid, m.p. 125°, by the oxidation of <u>2</u>-phenyl-<u>cyclo</u>pent-<u>1</u>-ene carboxylic acid, and <u>1</u>-phenyl-<u>cyclo</u>pent-<u>1</u>-ene with alkaline permanganate solution (Comptes rend.1913,<u>156</u>,1685).

Ph
HO·CO
Ph

$$\text{(structures)} \xrightarrow[\text{KMnO}_4]{\text{ALKALINE}} Ph \cdot CO \cdot (CH_2)_3 \cdot CO_2H$$
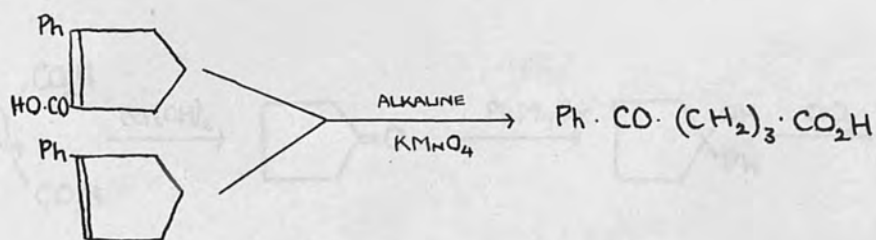
This last method was used by Fuson et al. (J. Amer. Chem. Soc. 1943, 56, 235) who also prepared the acid by ozonolysis of 1-phenylcyclopent-1-ene followed by oxidation of the aldehyde produced with 5% alkaline permanganate:
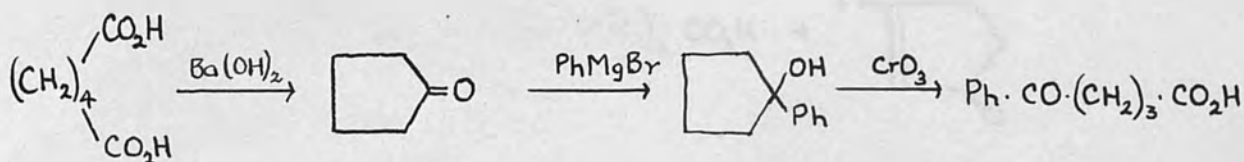
Ph

$$\xrightarrow[\text{WITH ZN + ACETIC ACID}]{O_3 + \text{DECOMPOSITION}} Ph \cdot CO \cdot (CH_2)_3 \cdot CHO \xrightarrow{\text{KMnO}_4} Ph \cdot CO \cdot (CH_2)_3 \cdot CO_2H$$

The acid was also obtained, though in poorer yield by the decomposition of the ozonide with water.

The most recent method synthesis has been reported by Fieser and Szmuszkovicz (J.Amer. Chem. Soc. 1948, 70, 3352) who used a solution of chromic anhydride in glacial acetic acid for the oxidation of 1-phenyl-cyclopentan-1-ol. The acid was obtained in 76% yield, m.p. 126°.

OH
Ph

$$\xrightarrow{\text{CrO}_3} Ph \cdot CO \cdot (CH_2)_3 \cdot CO_2H$$
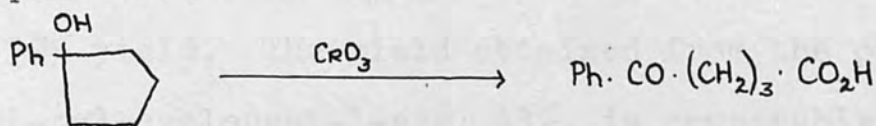
As this last method appeared to yield the best results, it was attempted in the present work, in spite of the restriction on the scale of the preparation imposed by the large volumes of solution incurred. The following synthesis was therefore attempted:

$(CH_2)_4 \Big\langle \begin{array}{c} CO_2H \\ CO_2H \end{array} \xrightarrow{Ba(OH)_2} \;\;\bigcirc\!\!=\!\!O\;\; \xrightarrow{PhMgBr} \;\;\bigcirc\!\!\Big\langle \begin{array}{c} OH \\ Ph \end{array}\;\; \xrightarrow{CrO_3} \; Ph \cdot CO \cdot (CH_2)_3 \cdot CO_2H$

Cyclopentanone was prepared by the distillation
of a mixture of adipic acid and crystalline barium
hydroxide (Organic Syntheses I, 192).

The preparation of 1-phenylcyclopentan-1-ol (Zelinsky,
Ber, 1925, 58, 2755) was attempted by a Grignard reaction
between phenyl magnesium bromide and cyclo-pentanone. It
was found, however, that the product of the reaction
dehydrated on distillation in vacuo, 1-phenyl-cyclo-pent-
1-ene, b.p. 84° /4 m.m., m.p. 23°, being obtained in 77%
yield. This was oxidised by chromic anhydride in glacial
acetic acid, the general method of Fieser and
Szmuszkovicz (loc. cit.) being slightly modified. These
authors did not describe this particular reaction
although the analogous one using 1-phenyl-cyclohex-1-ene
was performed, the δ-benzoylvaleric acid being obtained
in 39% yield. The yield obtained from the oxidation of
1-phenyl-cyclopent-1-ene, 43%, is comparable, and is
expectedly lower than that resulting from the oxidation
of the tertiary alcohol, owing to the greater formation
of unsaturated ketone.

$$\text{Ph} \overset{\text{CrO}_3}{\longrightarrow} \text{Ph} \cdot \text{CO} \cdot (\text{CH}_2)_3 \cdot \text{CO}_2\text{H} \quad + \quad \text{Ph}$$
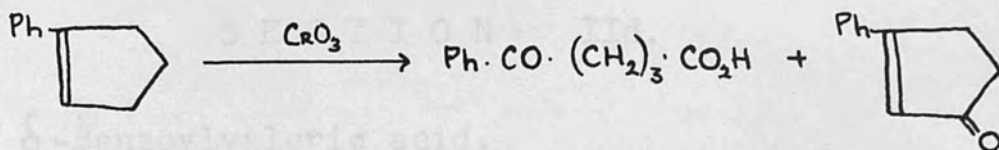
1-Phenylcyclopent-1-en-3-one was isolated from the reaction mixture and identified by its semicarbazone m.p. 223-224° (Fieser loc. cit. gives m.p. 226° - 227°). γ-Benzoylbutyric acid, crystallised from water, was found to have m.p. 126.5° - 127°.
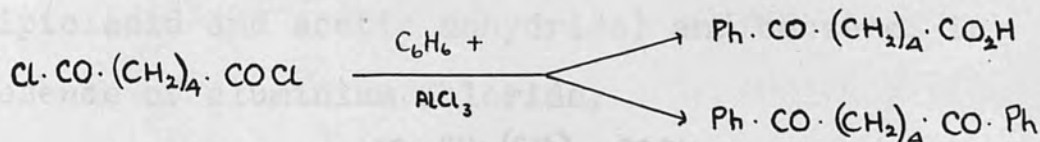
(-)-Menthyl-γ-benzoylbutyrate.

(-)-Menthyl-γ-benzoylbutyrate has not been previously described. It was prepared by the Fischer-Speier method (Section Va) and was isolated as a solid after removal of excess of menthol by steam distillation, by cooling in ice. The ester crystallised in colourless prisms, m.p. 19° - 19.5°, from light petroleum b.p. 40° - 60°, cooled in a CO_2/EtOH bath. After five crystallisations, (-)-menthyl-γ-benzoyl butyrate was found to have $\left[\alpha\right]_{5461}^{25} = -59.9°$ in alcohol (l = 2, c = 1.570).
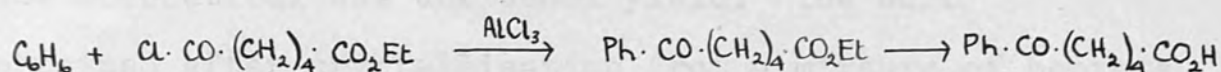
S E C T I O N   IId.

δ-Benzoylvaleric acid.

Two main lines of synthesis have been developed for the preparation of δ-benzoylvaleric acid. The first, involving a Friedel-Crafts reaction between benzene and a suitable derivative of adipic acid (which will give the requisite side chain of four methylene groups) was originally employed by Bauer in 1912 (Comptes rend. 155, 289). He carried out the reaction between benzene and adipoyl chloride in presence of aluminium chloride, but the yield he obtained was necessarily low owing to the simultaneous formation of dibenzoylbutane.
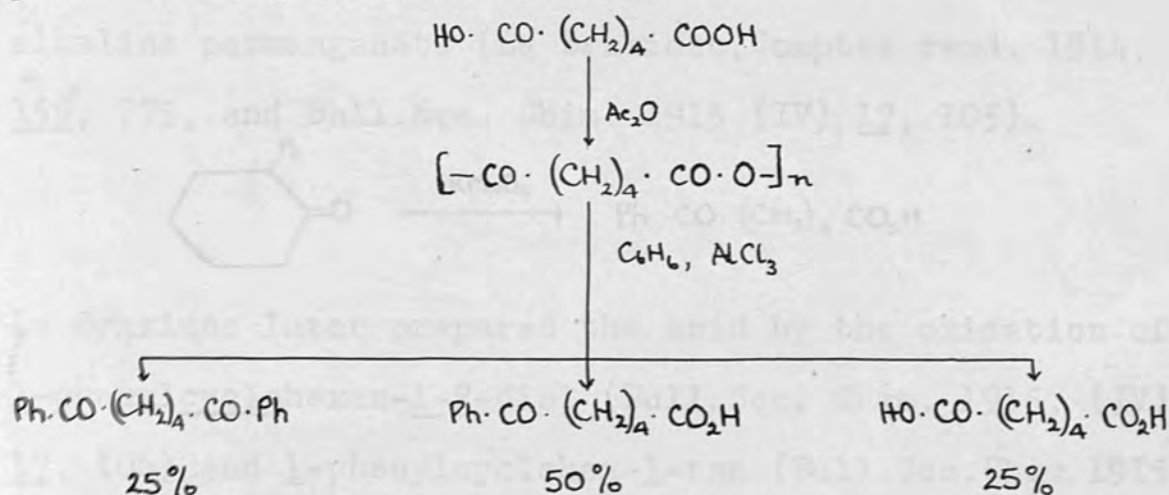
$$CL \cdot CO \cdot (CH_2)_4 \cdot CO\,CL \xrightarrow[ALCl_3]{C_6H_6 +} \begin{array}{l} Ph \cdot CO \cdot (CH_2)_4 \cdot CO_2H \\ Ph \cdot CO \cdot (CH_2)_4 \cdot CO \cdot Ph \end{array}$$

This method was also used by Borsche and Wollemann (Ber. 1912, 45, 3715) who prepared the acid m.p. 70° – 72°, and dibenzoylbutane m.p. 107°.

The formation of dibenzoylbutane as a side product was avoided by Raper and Wayne (Biochem. J. 1928, 22, 193) who used δ-carbethoxyvaleryl chloride in a Friedel-Crafts reaction with benzene and aluminium chloride.

Mlle S. Grateau (Comptes. rend. 1930, 191, 947) also used this method, and claimed an 80% yield of acid m.p. 70° - 71°. The most recent recorded user of this synthesis has been by Papa, Schwenk and Hankin (J. Amer. Chem. Soc. 1947, 69, 3018) who obtained an acid m.p. 70° - 71° in 78% yield, after hydrolysis of the ethyl δ-benzoylvalerate which is the primary product of the reaction.

$$C_6H_6 + Cl\cdot CO\cdot(CH_2)_4\cdot CO_2Et \xrightarrow{AlCl_3} Ph\cdot CO\cdot(CH_2)_4\cdot CO_2Et \longrightarrow Ph\cdot CO\cdot(CH_2)_4\cdot CO_2H$$

A modification of this type of synthesis was introduced by Hill in 1932 (J. Amer. Chem. Soc. 1932, 69, 4105) and involves a Friedel-Crafts reaction between adipic polymeric anhydride (prepared from adipic acid and acetic anhydride) and benzene, in presence of aluminium chloride.

$$HO\cdot CO\cdot(CH_2)_4\cdot COOH$$

$$\downarrow Ac_2O$$

$$[-CO\cdot(CH_2)_4\cdot CO\cdot O-]_n$$

$$C_6H_6, AlCl_3$$

$Ph\cdot CO\cdot(CH_2)_4\cdot CO\cdot Ph$	$Ph\cdot CO\cdot(CH_2)_4\cdot CO_2H$	$HO\cdot CO\cdot(CH_2)_4\cdot CO_2H$
25%	50%	25%

It may be shown theoretically that the yield of δ-benzoylvaleric acid can never exceed 50%, and 25% each of adipic acid and dibenzoyloctane are

yielded at the same time. Hill claimed a yield of

acid, m.p. 71°, of 75% of the theoretical.

This method of synthesis was adopted in the

present work as being less laborious than the synthesis

using δ-carbethoxyvaleryl chloride, and likely to

afford a greater overall yield. The results claimed

by Hill could not, however, be achieved and 30-40% of

the theoretical was the usual yield. The acid

obtained after crystallisation from a mixture of benzene

and light petroleum b.p. 60° - 80° had m.p. 76°, and

was probably purer than that prepared by Hill (m.p.71°).

The second line of synthesis of δ-benzoylvaleric

acid involves the oxidation of a phenylcyclohexane or

phenylcyclohexene derivative. The first recorded example

was the oxidation of 1-phenylcyclohexan-2-one with

alkaline permanganate (Le Brazidec, Comptes rend. 1914,

159, 775, and Bull.Soc. Chim. 1915,(IV),17, 105).

$$\text{Ph} \cdot \text{CO} \cdot (\text{CH}_2)_4 \cdot \text{CO}_2\text{H}$$
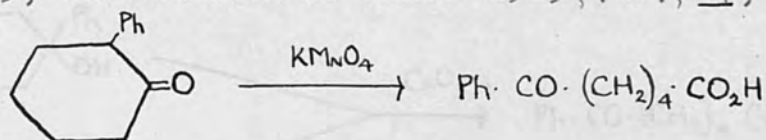
Le Brazidec later prepared the acid by the oxidation of

1-phenylcyclohexan-1-2-diol (Bull.Soc. Chim. 1915, (IV)

17, 106) and 1-phenylcyclohex-1-ene (Bull.Soc.Chim.1915,

(IV), 17, 102).

$$Ph \cdot CO \cdot (CH_2)_4 \cdot CO_2H$$
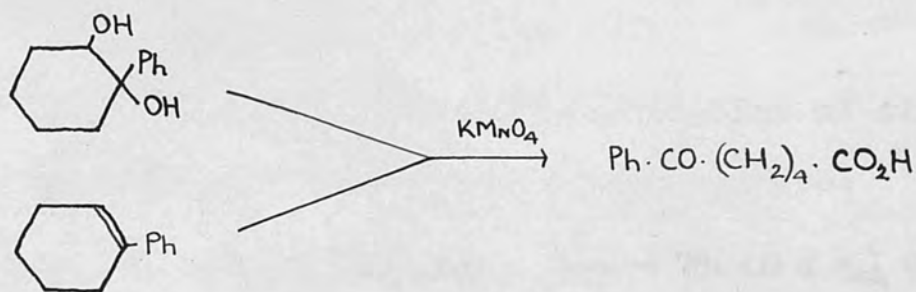
This last method was also used by Bauer and
Friedman in 1914 (Ann. Chim. Phys. (IX), 1, 383) who
reported the acid as having m.p. 78°, and by von Auwers
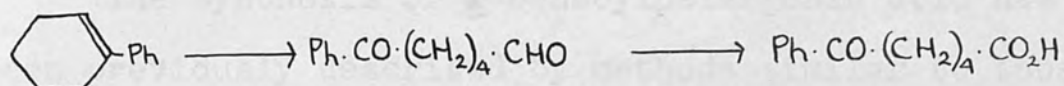and Trepmann (Ber. 1915, 48, 1217) who obtained an acid
of m.p. 77° - 78°.

The most recent work on this synthesis has been
carried out by Fieser and Szmuszkovicz (J. Amer. Chem.
Soc. 1948, 70, 3352) who used a solution of chromic
anhydride in glacial acetic acid as the oxidising agent.
Using this method, 1-phenylcyclohexan-1-ol and
1-phenylcyclohex-1-ene were both oxidised to
δ-benzoylvaleric acid, m.p. 126° the former in 80%
yield, and the latter in only 39% yield.

$$Ph \cdot CO \cdot (CH_2)_4 \cdot CO_2H +$$
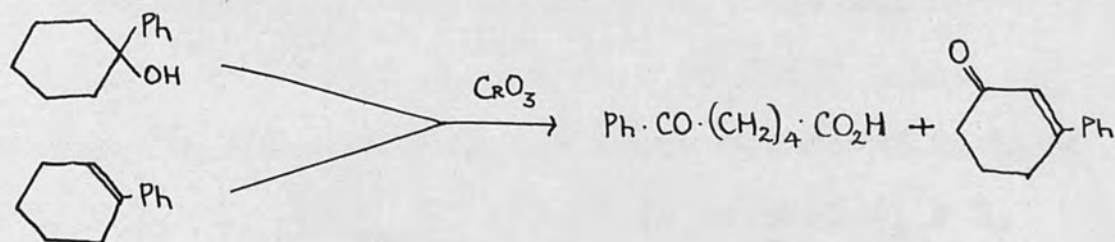
1-Phenylcyclohex-1-en-3-one was obtained as a
byproduct in both cases, the yield being greater in the
reaction with 1-phenylcyclohex-1-ene.

Fieser and Szmuszkovicz (loc. cit.) also prepared
the acid by the ozonolysis of 1-phenylcyclohex-1-ene

in ethereal solution, followed by oxidation of the
resulting aldehyde with alkaline permanganate:

$$\text{Ph} \longrightarrow \text{Ph} \cdot \text{CO} \cdot (\text{CH}_2)_4 \cdot \text{CHO} \longrightarrow \text{Ph} \cdot \text{CO} \cdot (\text{CH}_2)_4 \cdot \text{CO}_2\text{H}$$

The disadvantage of this synthesis is that although
a good yield of pure acid may be obtained from the
oxidation of 1-phenylcyclohexan-1-ol, the scale on which
the reaction may be performed is limited, owing to the
large volumes of solution involved. As described in the
previous section (Section IIc), a similar synthesis was
used to prepare γ-benzoylbutyric acid, but it was felt
in the case of δ-benzoylvaleric acid that Hill's method
provided a shorter route to the considerable weight of
acid required.

(-)-Menthyl-δ-benzoylvalerate.

(-)-Menthyl-δ-benzoylvalerate has not been
previously reported. It was prepared in 85% yield by
the Fischer-Speier method (Section Va), and was
crystallised from ether cooled in a Co_2/EtOH bath.
After five crystallisations the ester was found to have
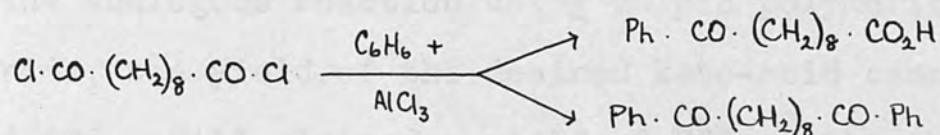m.p. 50° and $[\alpha]_{5461}^{25} = -59.5°$ in alcohol ($\underline{l} = 2$,
$\underline{c} = 1.650$).
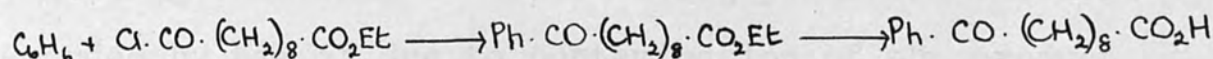
S E C T I O N   IIe.

ω-Benzoylpelargonic acid:

The synthesis of ω-benzoylpelargonic acid has
been previously described by methods similar to those
used for the preparation of δ-benzoylvaleric acid.

Auger, in 1891, first prepared the acid by a
Friedel-Crafts reaction between sebacyl chloride and
benzene in presence of aluminium chloride (Ann. Chim.
Phys. 1891, (6), 22, 364). The acid, m.p. 78° - 79°
was obtained together with the expected dibenzoyloctane.

$$Cl \cdot CO \cdot (CH_2)_8 \cdot CO \cdot Cl \xrightarrow[\text{AlCl}_3]{\text{C}_6\text{H}_6 +} \begin{array}{l} Ph \cdot CO \cdot (CH_2)_8 \cdot CO_2H \\ Ph \cdot CO \cdot (CH_2)_8 \cdot CO \cdot Ph \end{array}$$

This method was also used by Borsche and Wollemann
(Ber. 1911, 44, 3185) who recorded a melting point of
85-86°.

Later, Raper and Wayne (Biochem. J. 1928, 22, 193,
acid m.p. 84°) and Papa, Schwenk and Hankin (J. Amer.
Chem. Soc. 1947, 69, 3018) used ω-carbethoxynonoyl
chloride in a Friedel-Crafts reaction with benzene and
thus lessened the possibility of formation of dibenzoyl
octane.

$$C_6H_6 + Cl \cdot CO \cdot (CH_2)_8 \cdot CO_2Et \longrightarrow Ph \cdot CO \cdot (CH_2)_8 \cdot CO_2Et \longrightarrow Ph \cdot CO \cdot (CH_2)_8 \cdot CO_2H$$

This reaction is analogous to that involving β-carbethoxy-
propionyl chloride (Section IIb) and δ-carbethoxy-valeryl

chloride (Section IId) and the yield claimed is comparable (80%). The acid obtained by Papa et al. (loc. cit) had the rather low melting point of 78-79°, and may possible have been contaminated with sebacic acid formed by hydrolysis during the reaction.

Hill (J. Amer. Chem. Soc. 1932, 54, 4105) carried out the Friedel-Crafts reaction between sebacic polymeric anhydride and benzene, in presence of aluminium chloride. As has been already stated (Section IId) in connection with the analogous reaction using adipic polymeric anhydride, the yield of the desired keto-acid cannot exceed 50%. Hill claimed a yield of 78% of the theoretical, of an acid m.p. 77° - 78°.

In the present work this method of synthesis was first attempted as it had been found to give satisfactory results using adipic polymeric anhydride (Section IId). Using sebacic polymeric anhydride, however, it was found that the ω-benzoylpelargonic acid was badly contaminated with sebacic acid, which could not be completely removed by extraction with boiling water, as advocated by Hill. It is suggested that the low melting point for the acid recorded by him is due to contamination of the product with sebacic acid. Presumably, in the synthesis using adipic polymeric anhydride, the greater solubility of adipic acid in water precluded the contamination of the
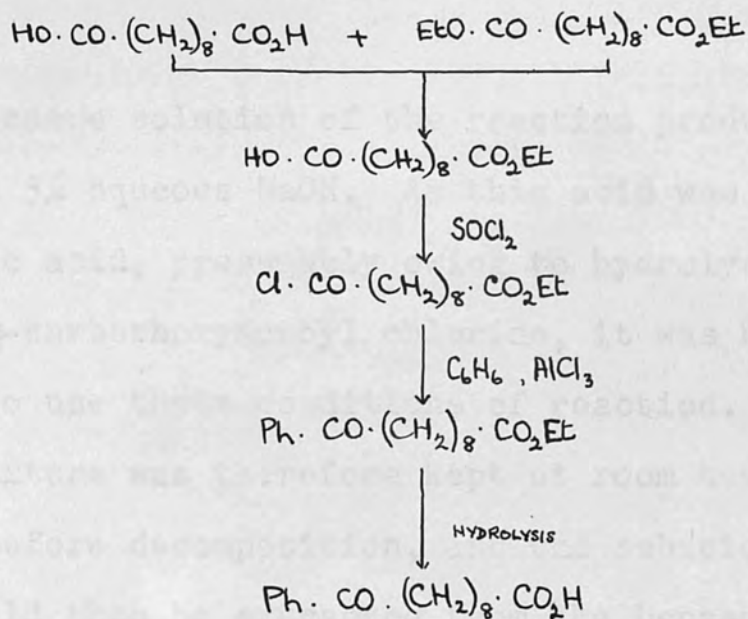
$\underline{\delta}$-benzoyl-valeric acid in this way.

It was thought, however, that the $\underline{(-)}$-menthyl esters of $\underline{\omega}$-benzoylpelargonic acid and sebacic acid might be separable by fractional distillation, and the crude acid was therefore esterified by the Fischer-Speier method (Section Va). After removal of the excess of $\underline{(-)}$-menthol by steam distillation, the crude product was freed from unchanged acids by washing with 10% aqueous Na_2CO_3, and was distilled in vacuo. No dimenthyl sebacate (b.p. 256° /20 mm.) was obtained, and sebacic acid (b.p. 243° /10 mm.) was found as a contaminant in the $\underline{(-)}$-menthyl-$\underline{\omega}$-benzoylpelargonate (b.p. 262°/5 mm.) presumably owing to the decomposition of $\underline{(-)}$-menthyl sebacate during the distillation. Although the sebacic acid could be removed by washing an ethereal solution of the distillate with 10% aqueous Na_2CO_3 and distilling the ether-soluble residue, this method of synthesis was considered unsatisfactory, and it was deemed advisable to prepare the $\underline{\omega}$-benzoylpelargonic acid in a pure state before esterification.

The following synthesis was then adopted:

$$HO \cdot CO \cdot (CH_2)_8 \cdot CO_2H \quad + \quad EtO \cdot CO \cdot (CH_2)_8 \cdot CO_2Et$$

$$\downarrow$$

$$HO \cdot CO \cdot (CH_2)_8 \cdot CO_2Et$$

$$\downarrow \quad SOCl_2$$

$$Cl \cdot CO \cdot (CH_2)_8 \cdot CO_2Et$$

$$\downarrow \quad C_6H_6 , AlCl_3$$

$$Ph \cdot CO \cdot (CH_2)_8 \cdot CO_2Et$$

$$\downarrow \quad HYDROLYSIS$$

$$Ph \cdot CO \cdot (CH_2)_8 \cdot CO_2H$$

Ethyl hydrogen sebacate (b.p. $183°/5$ mm) was
prepared in 65% yield by the reaction between sebacic
acid, diethylsebacate (b.p. $170°/7$ mm. Organic
Syntheses. II, 277) and alcohol, in solution in di-n-
butyl ether (Organic Syntheses II, 276).

ω-Carbethoxynonoyl chloride, b.p. $165°/10$ m.m.
was prepared by the action of thionyl chloride on the
half-ester.

A Friedel-Crafts reaction was carried out to
obtain ethyl-ω-benzoylpelargonate, the method of Papa,
Schwenk and Hankin (loc. cit.) being somewhat modified.
It was found that using their method, in which the
reaction mixture was heated on a water bath for three
hours, the ethyl-ω-benzoyl-pelargonate hydrolysed,
giving ω-benzoylpelargonic acid which was extracted

when the benzene solution of the reaction product was washed with 5% aqueous NaOH. As this acid was contaminated with sebacic acid, presumably owing to hydrolysis of unreacted ω-carbethoxynonoyl chloride, it was not thought advisable to use these conditions of reaction. The reaction mixture was therefore kept at room temperature overnight before decomposition, and the sebacic acid present could then be extracted from the benzene solution before hydrolysis of the ethyl ω-benzoylpelargonate. A yield of 92% of acid was obtained, which, recrystallised from a mixture of benzene and light petroleum, b.p. 60°-80°, had m.p. 83°.

The acid was characterised as its semicarbazone m.p. 153° - 154°, and 2:4-dinitrophenylhydrazone, m.p.144°.

(−)-Menthyl-ω-benzoylpelargonate.

This ester had not been previously reported, and was prepared by the Fischer-Speier method (Section Va) in 79% yield. The ester was solidified after removal of excess of menthol, by cooling in ice, and was crystallised from alcohol. After five crystallisations it was found to have m.p. 37° - 38° and $[\alpha]_{5461}^{25} = -51.00°$ in alcohol ($l = 2$, $c = 2.255$). The ester was found to have b.p. 262°/5 m.m., but the ester was not purified by distillation as slight decomposition occurred; the

distillate was always found to smell slightly of menthol, whereas the pure ester was odourless.

SECTION III

a) Reactions using (-)-menthyl benzoylformate.

b) Reactions using (-)-menthyl-β-benzoylpropionate.

c) Reactions using (-)-menthyl-γ-benzoylbutyrate.

d) Reactions using (-)-menthyl-δ-benzoylvalerate.

e) Reactions using (-)-menthyl-ω-benzoylpelargonate.

S E C T I O N   III

a) Reactions using (–)-menthyl benzoylformate.

b) Reactions using (–)-menthyl-β-benzoylpropionate.

c) Reactions using (–)-menthyl-γ-benzoylbutyrate.

d) Reactions using (–)-menthyl-δ-benzoylvalerate.

e) Reactions using (–)-menthyl-ω-benzoylpelargonate.

S E C T I O N   IIIa.

(-)-Menthylbenzoylformate.

McKenzie's work on the Grignard reaction between
(-)-menthylbenzoylformate and methyl magnesium iodide
(J. 1904, 1247) has already been discussed (Section I).
In connection with the present work it seemed advisable
to perform Grignard reactions on (-)-menthyl benzoyl-
formate under conditions comparable with those to be
later used in reactions with other keto-esters.

To this end, reactions were carried out using
methyl magnesium bromide (1.25 mols.) as the reagent:

$$Ph.CO.CO_2C_{10}H_{19} \xrightarrow[\text{+ DECOMPOSITION}]{MeMgBr} Ph - \overset{Me}{\underset{OH}{\overset{*|}{C}}} - CO_2C_{10}H_{19} \longrightarrow Ph - \overset{Me}{\underset{OH}{\overset{*|}{C}}} - CO_2H$$

$$(-) \qquad\qquad\qquad\qquad\qquad (-)$$
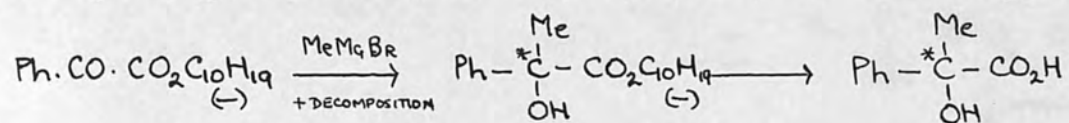
After hydrolysis of the hydroxy-ester and removal
of menthol (see Section Va) the α-phenylactic acid
(91% yield) was found to have $[\alpha]^{25}_{5461} = -9.38$

$$[\alpha]^{25}_{5480} = -8.10° \text{ IN ALCOHOL } [\underline{l}=2, \underline{c} = 12.40]$$
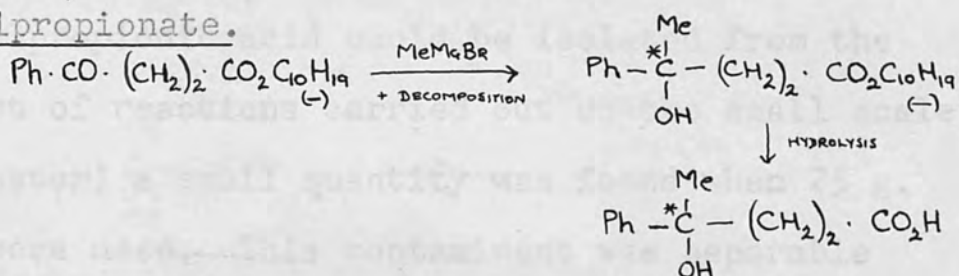
McKenzie (loc. cit), using 1.0 mols of methyl magnesium
iodide obtained an acid having $[\alpha]^{20}_{D} = -8.3°$ in alcohol,
($\underline{l}$ = 4, $\underline{c}$ = 6.718).

Since the change of Grignard reagent and different
conditions of reaction appeared to effect little change
in results from those previously obtained, this reaction
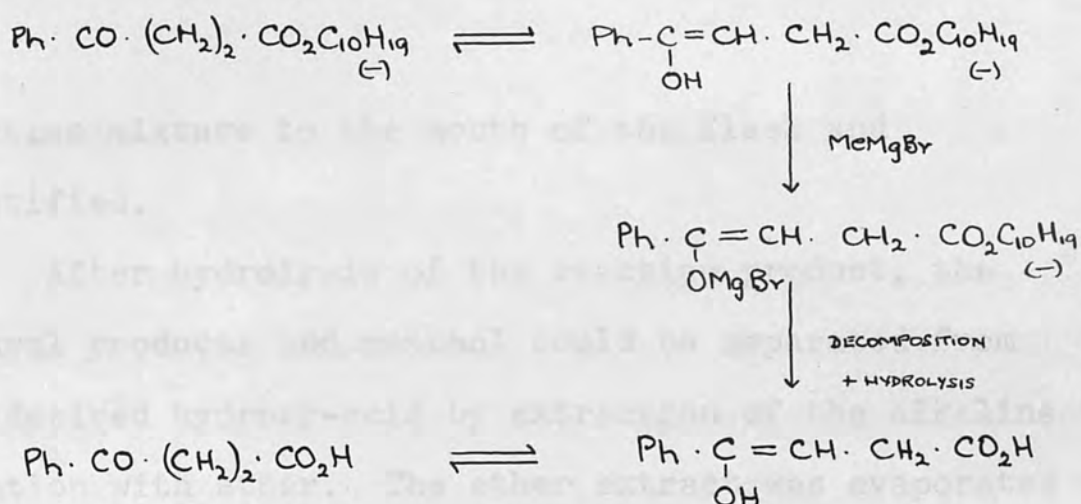was not further investigated.

S E C T I O N   IIIb.

(–)-Menthyl-β-benzoylpropionate.

Partial asymmetric synthesis has been accomplished
in the reactions between both methyl and ethyl magnesium
bromide and (–)-menthylbenzoylpropionate, a preponderance
of the laevo-form of the corresponding hydroxy-acid
occurring in the end product, as predicted. The
corresponding lactone was found to be dextrorotatory.
Reactions between methyl magnesium bromide and (–)-menthyl
β-benzoylpropionate.

$$Ph \cdot CO \cdot (CH_2)_2 \cdot CO_2 C_{10}H_{19} \xrightarrow[\text{+ DECOMPOSITION}]{MeMgBr} Ph - \overset{Me}{\underset{OH}{\overset{*}{C}}} - (CH_2)_2 \cdot CO_2 C_{10}H_{19}$$

$$\downarrow \text{HYDROLYSIS}$$

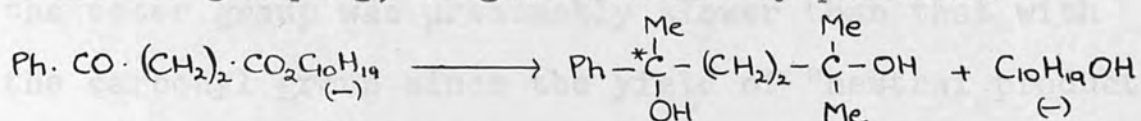$$Ph - \overset{Me}{\underset{OH}{\overset{*}{C}}} - (CH_2)_2 \cdot CO_2 H$$

To enable a direct comparison to be made between
the results of the reaction between methyl magnesium
bromide and (–)-menthylbenzoylpropionate and the analagous
reaction on (–)-menthylbenzoylformate, 1.25 mols. of
Grignard reagent were initially used. It was found,
however, that the end product was badly contaminated with
β-benzoylpropionic acid, either owing to incomplete
reaction of the ester, or owing to its reaction in the
enol form.

$$Ph \cdot CO \cdot (CH_2)_2 \cdot CO_2C_{10}H_{19} \underset{(-)}{\rightleftharpoons} Ph-\underset{\underset{OH}{|}}{C}=CH \cdot CH_2 \cdot \underset{(-)}{CO_2C_{10}H_{19}}$$

$$\downarrow MeMgBr$$

$$Ph \cdot \underset{\underset{OMgBr}{|}}{C}=CH \cdot CH_2 \cdot \underset{(-)}{CO_2C_{10}H_{19}}$$

$$\downarrow \begin{array}{l} DECOMPOSITION \\ + HYDROLYSIS \end{array}$$

$$Ph \cdot CO \cdot (CH_2)_2 \cdot CO_2H \rightleftharpoons Ph \cdot \underset{\underset{OH}{|}}{C}=CH \cdot CH_2 \cdot CO_2H$$

Using excess (2 mols.) of the Grignard reagent, almost complete reaction could be obtained with the keto-form of the ester, but although no trace of β-benzoylpropionic acid could be isolated from the end product of reactions carried out on the small scale (5.g. of ester) a small quantity was found when 25 g. of ester were used. This contaminant was separable by virtue of its greater solubility in slightly acid solution (pH ⇌ 5) over that of ɣ-phenyl-ɣ-hydroxy-valeric acid.

A complication arose, however, using excess Grignard reagent in that reaction also took place at the ester grouping, to give neutral by-products:

$$Ph \cdot CO \cdot \underset{(-)}{(CH_2)_2 \cdot CO_2C_{10}H_{19}} \longrightarrow Ph-\overset{Me}{\underset{\underset{OH}{|}}{\overset{|}{C}}}-(CH_2)_2-\overset{Me}{\underset{\underset{Me}{|}}{\overset{|}{C}}}-OH + \underset{(-)}{C_{10}H_{19}OH}$$

and the product of the reaction was found to smell of menthol. In some cases, by prolonged drying of this product in vacuo, (-)-menthol was sublimed from the

reaction mixture to the mouth of the flask and identified.

After hydrolysis of the reaction product, the neutral products and menthol could be separated from the desired hydroxy-acid by extraction of the alkaline solution with ether. The ether extract was evaporated and steam distilled to remove menthol, (Section Va) and the non-volatile residue was extracted with ether. The product obtained had a somewhat acrid odour, suggesting that decomposition had taken place, possibly with the formation of a tetra-hydro furan derivative:
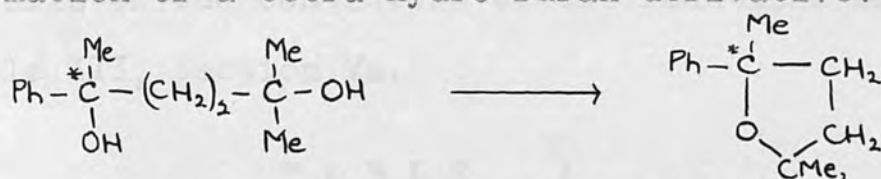
It may be noted that if reaction took place at the carbonyl group before the ester group was attacked, the product might be optically active due to asymmetric synthesis. This was not investigated, however, owing to the difficulty of removing traces of (−)-menthol from the product (Section V). The Grignard reaction with the ester group was presumably slower than that with the carbonyl group since the yield of "neutral products" from the reaction was never more than about 10%.

Some methyl magnesium bromide remained unchanged, its presence being detected by the evolution of gas

(methane) on decomposition of the reaction product with ice.

The reactions using 2 mols. of methyl magnesium bromide were performed under a number of different conditions, to find the optimum conditions for asymmetric synthesis. 5 G. of (-)-menthyl benzoyl propionate were used in these reactions, and the results given in Table A show that the yield of product of the Grignard reaction did not generally vary from 5.20 (3) g. by more than 1%, independent of the conditions of the reaction. Full details of the conditions of the reactions are given in Table III, Section Va.

T A B L E   A.

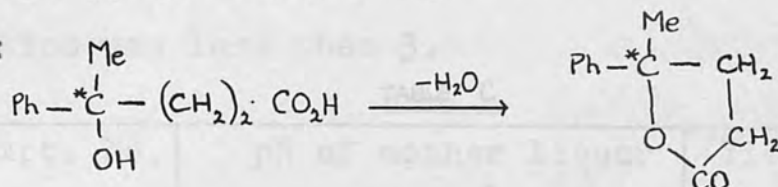| Experiment No.	Yield in g.	Expt. No.	Yield in g.
7	5.23	15	5.20(5)
8	5.20(5)	16	5.19
9	5.13	17	5.22
10	5.20	18	5.25(5)
11	5.18	19	5.06
12	5.15	20	5.25
13	5.19(5)	21	5.23
14	5.19	22	5.25

No significance can be attached to the slight variations
in yield obtained, owing to the difficulties, explained
in Section Va, encountered in the drying of the product.
If the product were subjected to rigorous drying in
vacuo, in an attempt to remove all traces of solvent,
there was the possibility that (-)-menthol, always
present in the product, might sublime, and this might
account for the low yield obtained in some experiments
(e.g. 9 and 19). In addition, the differing conditions
might cause slight variations in the degree of reaction
at the ester group, with consequent variation in the
yield of product obtained.

This last effect is, however, almost negligible,
since the results given in table B show that the yield
of γ-phenylbutyrolactone isolated from the reactions
only varied in general, between 1.30g. and 1.33g.

T A B L E   B.

Expt. No.	Yield of lactone in g.	Expt. No.	Yield of lactone in g.
9	1.34	17	1.34
10	1.30	18	1.23
11	1.29(5)	19	1.33
13	1.30	21	1.32(5)
14	1.27(5)	22	1.30

The product of the reaction after hydrolysis was
found to be a mixture of solid and oil, presumably a
mixture of γ-hydroxy-γ-phenylvaleric acid and its
lactone:

$$Ph-\overset{Me}{\underset{OH}{\overset{*}{C}}}-(CH_2)_2\cdot CO_2H \xrightarrow{-H_2O} Ph-\overset{Me}{\underset{O}{\overset{*}{C}}}\overset{CH_2}{\underset{CO}{|}}\overset{CH_2}{\underset{}{|}}$$

In most experiments this was converted completely
into the lactone by evaporation of its ethereal or
alcoholic solution on a water bath, a drop of dilute
HCl being added when evaporation was nearly complete.
The product was then dried in vacuo, and the lactone
was obtained as a clear yellow oil. The lactone was
prepared as it was found to have a higher specific
rotation than the corresponding acid and was therefore
more accurate for determining the degree of asymmetric
synthesis obtained in each reaction. The lactone
obtained from the reaction was found to be dextro-
rotatory, and the corresponding acid slightly laevo-
rotatory. An aqueous alkaline solution of the potassium
salt of the acid was found to be slightly dextro-rotatory.

Experiments in which the acid was isolated directly
from the alkaline solution after hydrolysis by careful
acidification, showed that, since the acid was moderately
soluble in water, the yield of acid obtained depended on
the pH of the mother liquor. Thus in experiments 8 and

15 (see Table C) the mother liquor was only acidified
to pH 5, and the yield of acid was considerably lower
than that obtained in experiment 7, in which the pH of
the solution was less than 3.

TABLE C

Expt. No.	pH of mother liquor	Yield of acid in g.
8	5	1.00
15	5	1.068
7	3	1.324

In connection with the determination of the specific
rotation of the products obtained from these reactions,
it was decided, in view of the errors involved in such
determinations (see Section V) that variations of less
than $\pm$ 3% were not significant.

The degree of asymmetric synthesis was found to be
dependent to a slight extent on the conditions of the
Grignard reaction. The reaction was presumably complete
after the reaction mixture had been boiled under reflux
for half an hour (experiments 11, 13 and 14) since
boiling under reflux for an additional hour (experiments
9 and 10) effected no change in the yield or degree of
asymmetric synthesis obtained. In all these experiments
the specific rotation of the lactone isolated was found
to be $[\alpha]_{5461}^{25} = +10.2° \pm 0.3°$, which shows a variation

within the limits of experimental error. Full details
of these experiments are given in tables IV and V,
Section Ve.

If the reaction mixture were kept in ice for at
least 40 minutes before decomposition, the specific
rotation of the lactone isolated, $[\alpha]_{5461}^{25}$ was found to
be +9.3° ± 0.2°. Experiments in which the mixture was
kept at 0° for 40 minutes before boiling under reflux
(21 and 22) and those in which the mixture was kept at
0° for 3 hours (17) or 10 hours (18 and 19) with no
subsequent refluxing, gave the same results, showing that
reaction was probably complete after 40 minutes at 0°.

Thus the only dependence of degree of asymmetric
synthesis with conditions found in this reaction was shown
in the slightly higher specific rotation of the lactone
obtained (average $[\alpha]_{5461}^{25}$ = +10.2°) when the reaction mixture
was boiled at ca. 40°, over that obtained (average
$[\alpha]_{5461}^{25}$ = + 9.3°) when the reaction was performed entirely
at 0°.

Reactions on the small scale in which the γ-hydroxy-
-γ-phenylvaleric acid was isolated directly after
hydrolysis of the (-)-menthyl ester (7, 8 and 15) showed
that the acid was slightly laevo-rotatory. Interesting
results were obtained in the preparation of the butyro-
lactone from this acid. When the acid was almost

completely precipitated (experiment 7) by acidification of the solution to pH < 3, the lactone obtained had $[\alpha]_{5461}^{25} = +10.5°$, compatible with the results obtained for the specific rotation of the lactone in other experiments performed under the same conditions (9 and 10). When, however, the acid was only partially precipitated (experiment 15) the lactone obtained had $[\alpha]_{5461}^{25} = +14.5°$, indicating that a preferential precipitation of the (−) -form of the acid had originally taken place (this form being in excess in the product).

To verify this, a reaction was performed (experiment 23, Section Vc, Chart I) using 25 g. of (−)-menthyl-β-benzoylpropionate to obtain sufficient acid for an investigation to be carried out. Approximately 4g. of acid (found to be contaminated with benzoylpropionic acid), having $[\alpha]_{5461}^{25} \simeq -1.25°$ in alcohol, were dissolved in 5% aqueous NaOH and the solution was acidified to pH 5. 1.30 G. of acid having m.p. 109° and $[\alpha]_{5461}^{25} = -4.42°$ were obtained. By acidification of the mother liquor to pH < 3, 1.25g. of an acid m.p. 102° - 103° (contaminated with benzoylpropionic acid) having $[\alpha]_{5461}^{25} = +2.56°$ in alcohol were precipitated. Thus the laevorotatory acid was precipitated preferentially even when the mother liquor must have been dextrorotatory. This was presumably owing to the precipitation of the acid in a crystalline

condition, so that the whole phenomenon is analogous to
a crystallisation. The preponderance of the laevorotatory
acid in solution would ensure a preponderance of the
nuclei of this isomer in the first precipitate formed, and
this would encourage a preferential precipitation of this
form, even when a slight excess of the dextrorotatory form
was present in the solution. After this acid had been
filtered off, the mother liquor, being dextrorotatory,
would by further acidification yield a dextrorotatory
acid.

A lactone was prepared from the first crop of acid,
and was found to have $[\alpha]_{5461}^{25} = +46.8^{\circ}$ in alcohol ($\underline{l} = 2$,
$\underline{c} = 3.475$). Thus the ratio $\dfrac{[\alpha]_{LACTONE}}{[\alpha]_{ACID}} = -10.5$

This ratio was usually found to be approximately -10,
except when the acid and lactone were contaminated with
benzoylpropionic acid. This was apparent in the second
crop of acid obtained, as the lactone prepared from it
had $[\alpha]_{5461}^{25} = -22.2^{\circ}$ in alcohol ($\underline{l} = 2$, $\underline{c} = 5.30$) which
gives the ratio $\dfrac{[\alpha]_{LACTONE}}{[\alpha]_{ACID}} = -9.1$.

It should be emphasised that the acids precipitated were
not optically pure, but merely contained an excess of one
optical isomer over the other. Since the solubilities of
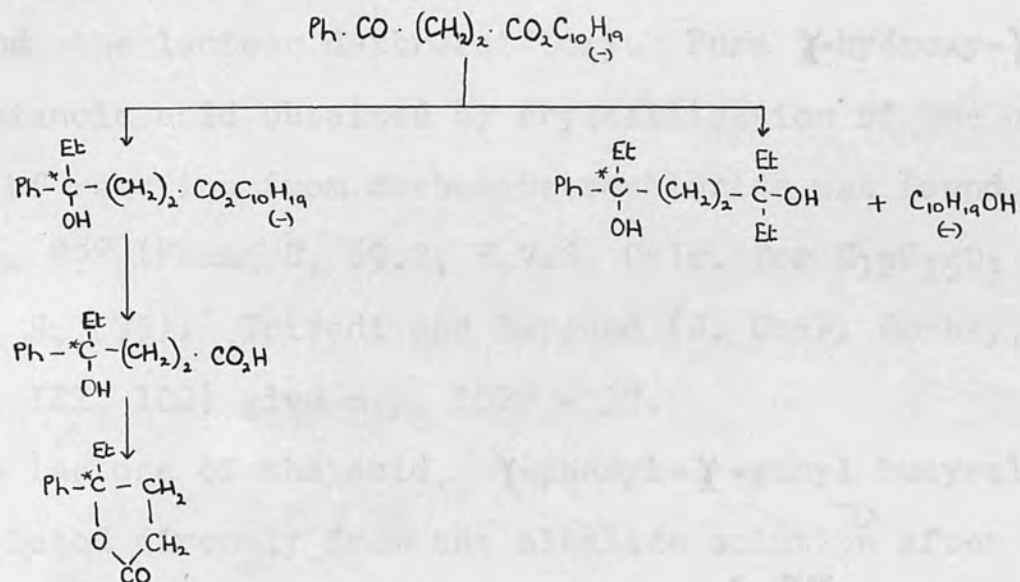both forms of the acid would be identical, the results

just described show only the effect of the presence of
an excess of the nuclei of one optical isomer in contact
with the mother liquor, and the phenomenon is not
comparable with a resolution of diastereoisomerides; nor
is there any possibility of an asymmetric transformation.

In an attempt to use this partial precipitation as
a method of separating the optical isomers of $\underline{Y}$-hydroxy-
$\underline{Y}$-phenylvaleric acid a Grignard reaction (experiment 24)
was carried out on 20 g. of $(\underline{-})$-menthyl-$\underline{\beta}$-benzoylpropionate.
This scale did not prove large enough, however, for a
complete separation to be effected, and the purest acid
obtained, having $[\alpha]_{5461}^{25} = -4.7^\circ$ in alcohol,
m.p. $113^\circ - 115^\circ$, was later found to be only about 80%
optically pure.

The acid was later resolved by a colleague using
brucine, and the dextrorotatory form found to have
$[\alpha]_{5461}^{25} = +5.77^\circ$ in alcohol $(\underline{1} = 2, \underline{c} = 1.194)$, and
m.p. $122^\circ - 122.5^\circ$.

Reactions between (−)-menthyl-β-benzoylpropionate
and ethyl magnesium bromide.

$$Ph \cdot CO \cdot (CH_2)_2 \cdot CO_2 C_{10} H_{19}$$
(−)

$$Ph - \overset{*}{\underset{OH}{C}} - (CH_2)_2 \cdot CO_2 C_{10} H_{19}$$
(−)

$$Ph - \overset{*}{\underset{OH}{C}} - (CH_2)_2 - \overset{Et}{\underset{Et}{C}} - OH + C_{10} H_{19} OH$$
(−)

$$Ph - \overset{Et}{\underset{OH}{C}} - (CH_2)_2 \cdot CO_2 H$$

$$Ph - \overset{Et}{\underset{}{C}} - CH_2$$
$$O \quad CH_2$$
$$CO$$

No reactions between ethyl magnesium bromide and
(−)-menthyl-β-benzoylpropionate were carried out using
1.25 mols. of the Grignard reagent since experience had
shown that incomplete reaction was likely. Using 2 mols.
of the reagent complete reaction was obtained, and, as
in the reaction with methyl magnesium bromide some reaction
at the ester group occurred.

Since the conditions giving optimum asymmetric
synthesis had been found to be addition of the Grignard
reagent to the keto-ester solution over about 10 minutes
followed by boiling under reflux for about half an hour,
all the reactions between ethyl magnesium bromide and
(−)-menthyl benzoylpropionate were carried out in this
manner. The product of the reaction smelt of menthol,
indicating some reaction at the ester grouping, but the
neutral products were not isolated and examined.

γ-Hydroxy-γ-phenylhexanoic acid, or its lactone, were obtained in about 47% yield, the acid being slightly laevo and the lactone dextrorotatory. Pure γ-hydroxy-γ-phenylhexanoic acid obtained by crystallisation of the end product of reaction from carbon tetrachloride was found to have m.p. 89° (Found.C, 69.2, H,7.8, Calc. for $C_{12}H_{16}O_3$ C, 69.2, H,7.75). Trivedi and Nargund (J. Univ. Bombay, 10, part III, 102) give m.p. 102° - 3°.

The lactone of the acid, γ-phenyl-γ-ethyl butyrolactone, when isolated directly from the alkaline solution after hydrolysis was obtained as an oil having $[\alpha]_{5461}^{25} = + 5.26°$ in alcohol ($\underline{1} = 2$, $\underline{c} = 5.325$). If the acid were precipitated first, however, and the lactone prepared from it, the specific rotation was found to be

$$[\alpha]_{5461}^{25} = + 8.47° \text{ in alcohol } (\underline{1} = 2, \underline{c} = 5.90).$$

This suggested that some preferential precipitation of the optically active acid was taking place, as found with γ-hydroxy-γ-phenylvaleric acid, but an experiment performed on a larger scale (Experiment 29, Chart III) showed that although the laevorotatory acid (present in excess in the end product) was precipitated first, the separation did not go so far that the mother liquor became dextrorotatory, as with the methyl homologue. From an alkaline solution of an acid of specific rotation $[\alpha]_{5461}^{25} = - 1.9°$, a first precipitate of acid, m.p. 91° - 93°, $[\alpha]_{5461}^{25} = - 3.76°$ was obtained.

Acidification of the mother liquor gave an acid m.p.
88 - 89°, $[\alpha]^{25}_{5461} = - 0.58°$, and another crop,
m.p. 89-91°, $[\alpha]^{25}_{5461} = - 0.65°$. The excess
laevorotatory acid was therefore precipitated until there
was only a slight preponderance of it over the dextro-
rotatory isomer in the mother liquor, when an acid of
almost constant specific rotation was deposited. Separation
of the acid into its two optical isomers by partial
precipitation was therefore impossible.

The ratio $\dfrac{[\alpha]_{LACTONE}}{[\alpha]_{ACID}}$ was found to be
approximately four, which is considerably lower than
that found with $\underline{Y}$-hydroxy-$\underline{Y}$-phenylvaleric acid and its
lactone.

It may be noted that there was a distinct indication
that the higher the optical purity of the acid, the higher
was its melting point (m.p. inactive acid of 89°). This
effect was found with $\underline{Y}$-hydroxy-$\underline{Y}$-phenylvaleric acid, and
suggests that the melting point diagram is of the
form shown in Fig III. It seems
surprising therefore that Trivedi
and Nargund (loc. cit) should have
given the melting point of the
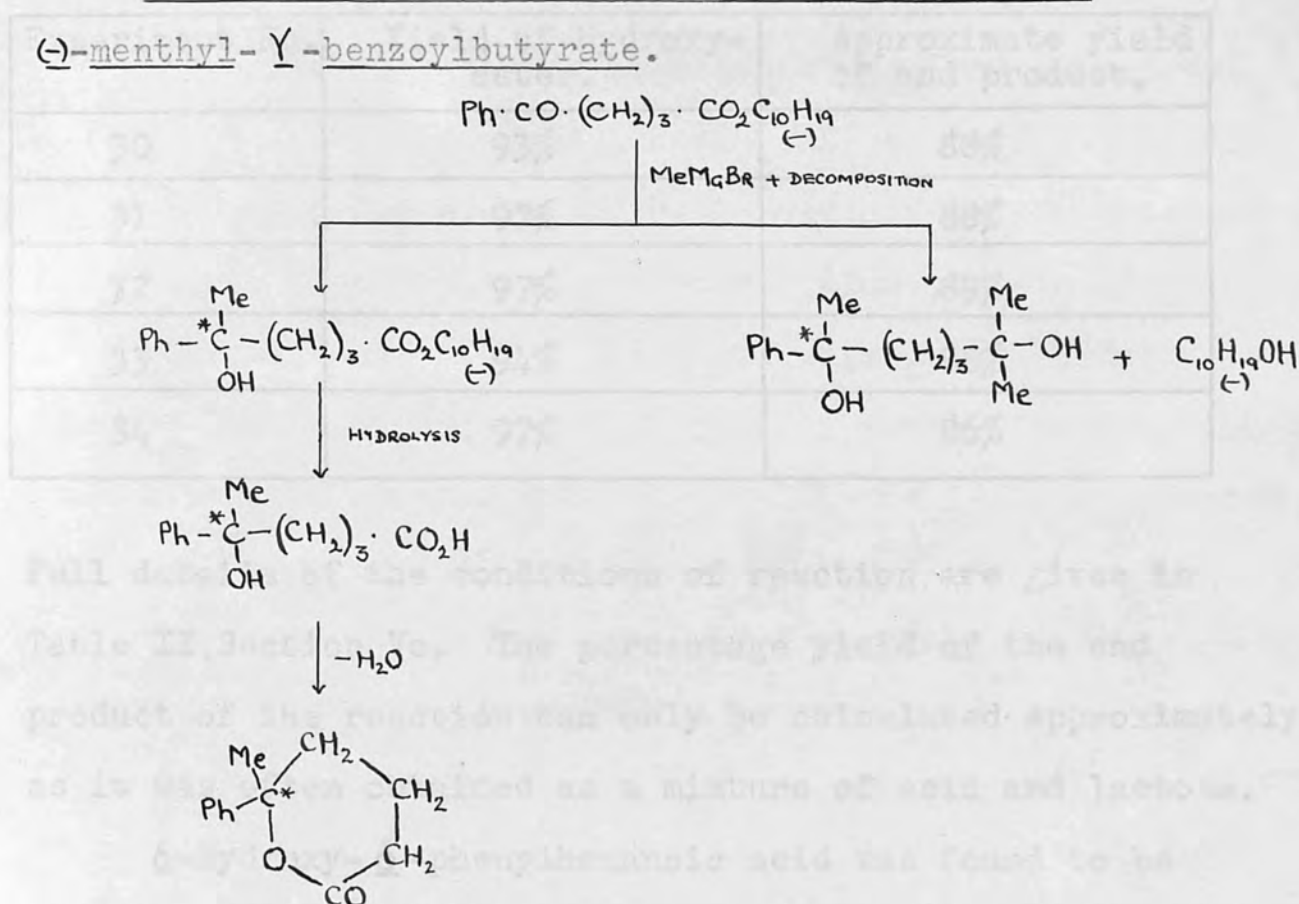acid as 102-3°, since their acid
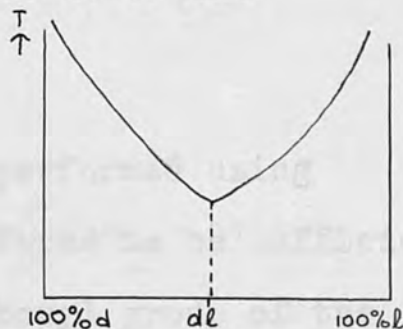
FIG. III.

was presumably optically inactive, being prepared by the
action of methyl magnesium iodide on ethyl-β-benzoylpropionate.

SECTION IIIc.

(-)-Menthyl-γ-benzoylbutyrate.

Partial asymmetric synthesis has been achieved by the Grignard reaction between methyl magnesium bromide and (-)-menthyl-γ-benzoylbutyrate, but none could be detected in the analogous reaction with ethyl magnesium bromide.

Reaction between methyl magnesium bromide and (-)-menthyl-γ-benzoylbutyrate.

$$Ph \cdot CO \cdot (CH_2)_3 \cdot CO_2 C_{10}H_{19}$$
$$(-)$$

MeMgBr + DECOMPOSITION

$$Ph - \overset{*}{\underset{OH}{C}}(Me) - (CH_2)_3 \cdot CO_2 C_{10}H_{19} \quad (-)$$

$$Ph - \overset{*}{\underset{OH}{C}}(Me) - (CH_2)_3 - \underset{Me}{\overset{Me}{C}} - OH \; + \; C_{10}H_{19}OH \quad (-)$$

HYDROLYSIS

$$Ph - \overset{*}{\underset{OH}{C}}(Me) - (CH_2)_3 \cdot CO_2 H$$

$-H_2O$

The Grignard reaction was first performed using 1.25 mols. of the reagent, which was found to be sufficient to cause complete reaction at the carbonyl group of the ester and the γ-benzoylbutyric acid was not found as a contaminant in the δ-hydroxy-δ-phenylhexanoic acid obtained. The product of the Grignard reaction only

smelt faintly of menthol, indicating that the extent of
the reaction of the ester group with the Grignard reagent
was negligible. A yield of 93-97% of hydroxy-ester,

$$Ph-\overset{\overset{Me}{|}}{\underset{\underset{OH}{|}}{\overset{*}{C}}}-(CH_2)_3\cdot CO_2C_{10}H_{19}$$ was obtained, independent of the

conditions of the reaction as shown in Table C.

TABLE   C.

Experiment No.	Yield of hydroxy-ester.	Approximate yield of end product.
30	93%	88%
31	97%	88%
32	97%	89%
33	94%	88%
34	97%	86%

Full details of the conditions of reaction are given in
Table IX, Section Vc. The percentage yield of the end
product of the reaction can only be calculated approximately
as it was often obtained as a mixture of acid and lactone.

&-Hydroxy- & -phenylhexanoic acid was found to be
difficult to convert completely into its lactone, although
slight conversion took place with great ease, and care
was needed to isolate the acid in a pure state. The pure
acid was found to have m.p. 73° - 74° (Found C, 68.8.
H, 7.4. $C_{12}H_{16}O_3$ requires C, 69.2 H, 7.7). Complete
conversion of the acid into the corresponding lactone was

effected by evaporating a solution of the acid in sodium-
dried benzene on a water bath. The evaporation was
repeated two or three times until the product had a
constant specific rotation. The pure lactone was found
to have m.p. 70° - 71°, and crystallised in plates from
alcohol (Found. C,75.5, H,7.13. $C_{12}H_{14}O_2$ requires C,75.8,
H, 7.4.).

The specific rotation of the lactone, and therefore
the degree of asymmetric synthesis taking place, was bound
to be slightly dependent on the conditions of the reaction.
Boiling the reaction mixture under reflux immediately
after the addition of the Grignard reagent resulted in a
lactone having $[\alpha]_{5461}^{25} = +2.9° \pm 0.1°$, but if the reaction
was allowed to proceed entirely at 0°, the lactone isolated
had $[\alpha]_{5461}^{25} = +2.1°$.

The lactone obtained from one experiment (34) was
converted into the corresponding hydroxy-acid which was
found to have m.p. 77° - 79°, 1.05 g. having $\alpha_{5461}^{25} = -0.02°$
in alcohol ($\underline{l} = 2$, $\underline{c} = 5.00$). It will be noted that the
melting point of the mixture of optically active and
inactive acids is higher than that of the dl-acid
(prepared by a Grignard reaction between methylmagnesium
bromide and ethyl-γ-benzoyl butyrate) as was found in
the case of γ-hydroxy-γ-phenyl valeric acid. The
optical rotation of the acid was too low for accurate

observations to be made, and the lactone was therefore always isolated for polarimetric determinations.

To provide some direct comparison with the work carried out on (±)-menthyl-β-benzoylpropionate some reactions were performed using two mols. of methyl magnesium bromide. The Grignard reagent was added to the solution of (±)-menthyl-γ-benzoylbutyrate over a period of ten minutes, and the mixture was then boiled under reflux for half an hour before decomposition. The product of the reaction smelt strongly of menthol, as expected, and 10% of neutral products were isolated in one experiment by the methods already described. The average yield of lactone was 68%, having $[\alpha]_{5461}^{25} = +2.30° \pm 0.10°$.

A resolution of δ-hydroxy-δ-phenylhexanoic acid was attempted using brucine, and by repeated crystallisation, a salt of specific rotation $[\alpha]_{5461}^{25} = -43.1°$ in chloroform, ($\underline{l} = 2$, $\underline{c} = 0.650$), was obtained, unchanged by further crystallisation. Decomposition of this salt and the preparation of the lactone from the acid so obtained, resulted in the isolation of a product having $[\alpha]_{5461}^{25} = +15.67°$ in chloroform ($\underline{l} = 2$, $\underline{c} = 3.695$).

<u>Reaction between (-)-menthyl-γ-benzoylbutyrate and ethyl magnesium bromide.</u>

Ph·CO·(CH₂)₃·CO₂C₁₀H₁₉
(-)

Ph-*C-(CH₂)₃·CO₂C₁₀H₁₉ (with Et and OH)
(-)

Ph-*C-(CH₂)₃-C-OH + C₁₀H₁₉OH
(with Et, OH, Et)
(-)

Ph-C* (with Et, CH₂, CH₂, CH₂, O, Co)
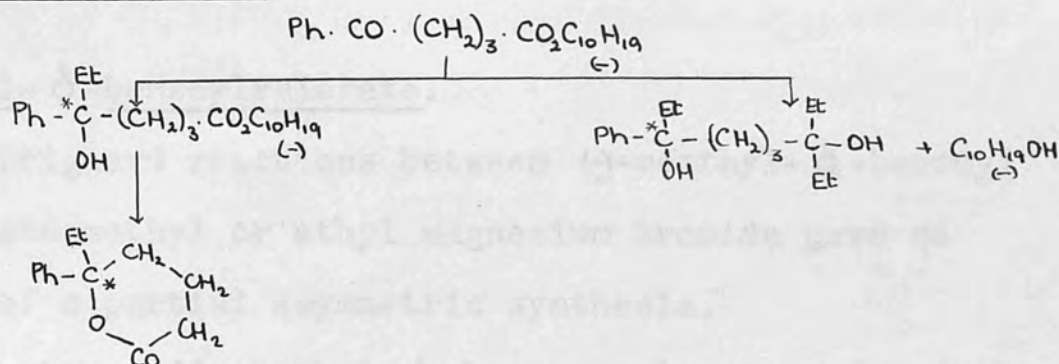
The Grignard reaction was carried out using 1.5 and 2.0 mols. of Grignard reagent under conditions previously found to give maximum asymmetric synthesis, but no activity could be detected in the end product in either case.

Using 1.5 mols. of ethyl magnesium bromide 86% of an optically inactive oil was obtained. From previous experience it was expected that the lactone of the hydroxy-acid would have a higher specific rotation than the acid itself, and the oil was therefore evaporated repeatedly with sodium dried benzene. However, no optical activity was observed in the δ-ethyl-δ-phenylvalerolactone.

When 2 mols. of the Grignard reagent were used, the yield of lactone was 82%. This product was also optically inactive.

S E C T I O N   IIId.

(-)-Menthyl- δ -benzoylvalerate.

The Grignard reactions between (-)-menthyl- δ -benzoyl
valerate and methyl or ethyl magnesium bromide gave no
evidence of a partial asymmetric synthesis.

Reaction between (-)-menthyl- δ -benzoylvalerate and methyl
magnesium bromide.

$$Ph \cdot CO \cdot (CH_2)_4 \cdot CO_2 C_{10}H_{19}$$
$$(-)$$

$$MeMgBr + \text{DECOMPOSITION}$$

$$Ph - \overset{Me}{\underset{OH}{\overset{*1}{C}}} - (CH_2)_4 \cdot CO_2 C_{10}H_{19} \qquad Ph - \overset{Me}{\underset{OH}{\overset{*1}{C}}} - (CH_2)_4 - \overset{Me}{\underset{Me}{C}} - OH + C_{10}H_{19}OH$$
$$(-) \qquad\qquad\qquad (-)$$

$$\downarrow \text{HYDROLYSIS}$$

$$Ph - \overset{Me}{\underset{OH}{\overset{*1}{C}}} - (CH_2)_4 \cdot CO_2H$$
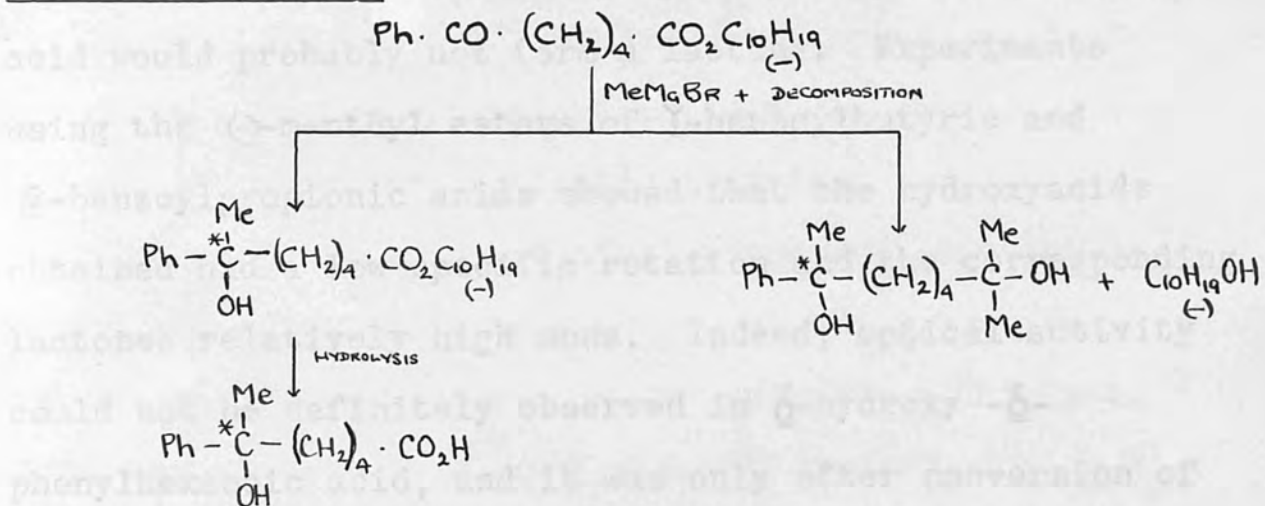
Using $1\frac{1}{4}$ mols. of the Grignard reagent, the
hydroxy-ester was obtained from the reaction mixture in
98% yield. The ϵ-hydroxy- ϵ -phenylheptoic acid was
isolated as a yellow oil, in 98% yield, and was found to
be optically inactive.

Using 2 mols. of the methyl magnesium bromide some
reaction took place at the ester group, and a yield of
only 70% of the hydroxy-acid was obtained. The nature
of the neutral products formed in the reaction was not
investigated.

A reaction using 4 mols. of Grignard reagent resulted in over 50% of the ester undergoing reaction at the ester group, since the yield of hydroxy-acid obtained was only 43%. As in the previous reactions with this ester, no optical activity could be detected in the alcoholic solution of the end product.

The absence of any observable asymmetric synthesis may be due to the fact that ϵ-hydroxy- ϵ-phenylheptoic acid would probably not form a lactone. Experiments using the (-)-menthyl esters of γ-benzoylbutyric and β-benzoylpropionic acids showed that the hydroxyacids obtained had a low specific rotation and the corresponding lactones relatively high ones. Indeed, optical activity could not be definitely observed in δ-hydroxy -δ- phenylhexanoic acid, and it was only after conversion of this acid into its lactone that the asymmetric synthesis could be proved.

Assuming, therefore, that the specific rotation of optically pure ϵ-hydroxy- ϵ-phenylheptoic acid is of the same order as that of δ-hydroxy-δ-phenylhexanoic acid, as is probable, a low degree of asymmetric synthesis in the former acid would be difficult, or even impossible to detect.

It cannot be stated unequivocally, therefore, that asymmetric synthesis of ϵ-hydroxy-ϵ-phenylheptoic acid does not take place in this reaction, but merely that

such a synthesis, if occurrent, is unproven.

Reaction between (-)-menthyl- δ -benzoylvalerate and ethyl magnesium bromide.

$$Ph \cdot CO \cdot (CH_2)_4 \cdot COC_{10}H_{19} \atop (-)$$

$$\underset{\substack{OH}}{\overset{\substack{Et}}{Ph-\overset{*}{C}-(CH_2)_4 \cdot CO_2C_{10}H_{19}}} \atop (-)$$

$$\underset{\substack{OH}}{\overset{\substack{Et}}{Ph-\overset{*}{C}-(CH_2)_4 \cdot CO_2H}}$$

$$\underset{\substack{OH}}{\overset{\substack{Et}}{Ph-\overset{*}{C}-(CH_2)_4}} - \underset{\substack{Et}}{\overset{\substack{Et}}{C}-OH} + \underset{(-)}{C_{10}H_{19}OH}$$
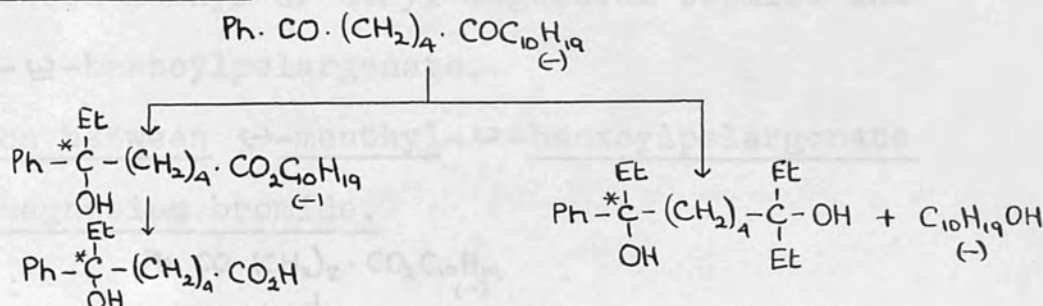
Using 1.25 mols. of Grignard reagent, a yield of 90% of ϵ-hydroxy- ϵ -phenyloctoic acid was obtained as a yellow oil, which was optically inactive.

The use of 2 mols. of ethyl magnesium bromide caused, as expected, some reaction at the ester group and the yield of hydroxy-acid was only 79%. This acid was found to have $\alpha_{5461}^{25} = -0.03°$ in alcohol ($\underline{1} = 2$, $\underline{c} = 12.85$) but this cannot be accounted significant.

S E C T I O N   IIIe.

<u>(-)-Menthyl- ω -benzoylpelargonate.</u>

Asymmetric synthesis was not observed in the Grignard reaction between methyl or ethyl magnesium bromide and (-)-menthyl-ω-benzoylpelargonate.

Reaction between (-)-menthyl- ω -benzoylpelargonate and methyl magnesium bromide.

$$Ph \cdot CO \cdot (CH_2)_8 \cdot CO_2 C_{10}H_{19} \quad (-)$$

$$
\begin{array}{ccc}
& Me & \\
& Ph - \overset{*}{\underset{OH}{C}} - (CH_2)_8 \cdot CO_2 C_{10}H_{19} \ (-) & \\
& & Me \quad Me \\
& & Ph - \overset{*}{\underset{OH}{C}} - (CH_2)_8 - \overset{Me}{\underset{Me}{C}} - OH \ + \ C_{10}H_{19}OH \ (-)
\end{array}
$$

$$
\begin{array}{c}
Me \\
Ph - \overset{*}{\underset{OH}{C}} - (CH_2)_8 \cdot CO_2 H
\end{array}
$$
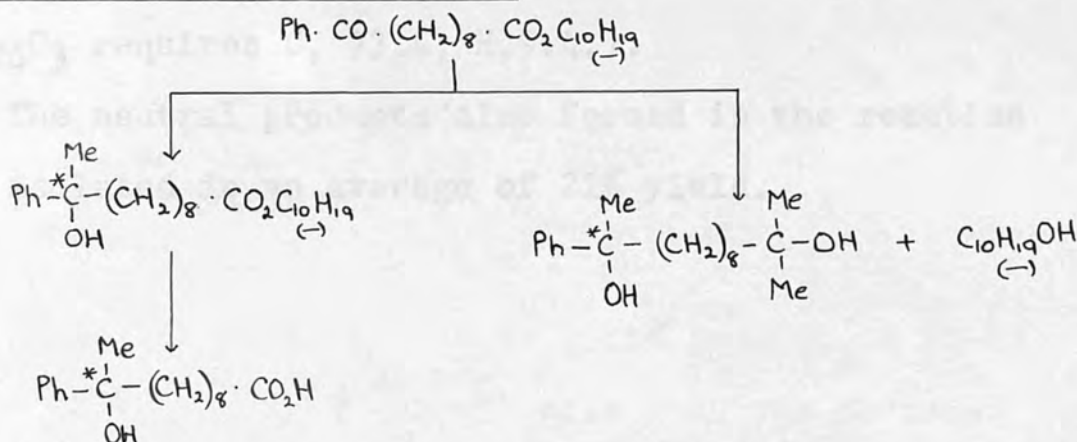
Using $1\frac{1}{4}$ mols. of the Grignard reagent a yield of about 70% of <u>θ</u>-hydroxy- <u>θ</u> -phenylundecenoic acid was obtained. In one experiment this product was found to have $\alpha_{5461}^{25} = - 0.02°$ in alcohol ($\underline{1} = 2$, $\underline{c} \doteq 12.65$) and a second experiment gave a product having $\alpha_{5461}^{25} = -0.01°$ in alcohol ($\underline{1} = 2$, $\underline{c} = 11.875$). Both these rotations are too low to be considered a significant indication of asymmetric synthesis, and no further experiments were performed under these conditions. The reaction of 2 mols. of methyl magnesium bromide with the ester was carried out under the conditions shown previously to give the

maximum asymmetric synthesis (Sections IIIb and IIIc).
Three reactions were performed and an average yield of
59% of $\underline{\theta}$-hydroxy-$\underline{\theta}$-phenylundecenoic acid was obtained
in an optically inactive condition. This acid, m.p. 60°,
was found to crystallise from a mixture of benzene and
light petroleum, b.p. 60° - 80°. (Found. C, 73.5, H,9.0.
$C_{17}H_{26}O_3$ requires C, 73.4, H,9.4.).

The neutral products also formed in the reaction
were isolated in an average of 21% yield.

Reaction between (-)-menthyl-ω-benzoylpelargonate

and ethylmagnesium bromide.

$$Ph. CO \cdot (CH_2)_8 \cdot CO_2 C_{10} H_{19} \atop (-)$$

EtMgBr + DECOMPOSITION

$$Ph - \overset{Et}{\underset{OH}{\overset{|}{C^*}}} - (CH_2)_8 \cdot CO_2 C_{10} H_{19} \atop (-)$$

$$Ph - \overset{Et}{\underset{OH}{\overset{|}{C^*}}} - (CH_2)_8 - \overset{Et}{\underset{Et}{\overset{|}{C}}} - OH + C_{10} H_{19} OH \atop (-)$$

HYDROLYSIS

$$Ph - \overset{Et}{\underset{OH}{\overset{|}{C^*}}} - (CH_2)_8 \cdot CO_2 H$$

Using 1.5 mols. of the Grignard reagent, a yield

of 83% of $\underline{\theta}$-hydroxy-$\underline{\theta}$-phenyllauric acid was obtained

as a yellow oil, having $\alpha_{5461}^{25} = -0.05°$ in alcohol

($\underline{l} = 2$, $\underline{c} = 14.475$).

The use of 2 mols. of ethyl magnesium bromide resulted

in a yield of 75% of acid having $\alpha_{5461}^{25} = -0.05°$ in

alcohol ($\underline{l} = 2$, $\underline{c} = 13.125$) which cannot be regarded as

affording proof of asymmetric synthesis.

S E C T I O N IV.   SUMMARY.

Part of McKenzie's work on the reaction between a
methyl Grignard reagent and (−)-menthyl benzoylformate has
been repeated under the conditions later used in other
Grignard reactions, and the results obtained have been
found to conform closely to his.

The homologous series of esters used in the present
work, Ph. CO. $(CH_2)_n.CO_2C_{10}H_{19}$, have not been previously
described, and the Grignard reactions between them and
methyl or ethyl magnesium bromide,

$$Ph \cdot CO \cdot (CH_2)_n \cdot CO_2C_{10}H_{19} \xrightarrow[+ \text{ DECOMPOSITION}]{RMgBr} Ph - \underset{OH}{\overset{R}{\underset{|}{\overset{|}{C}}}} - (CH_2)_n \cdot CO_2C_{10}H_{19} \longrightarrow Ph - \underset{OH}{\overset{R}{\underset{|}{\overset{|}{C}}}} - (CH_2)_n \cdot CO_2H$$
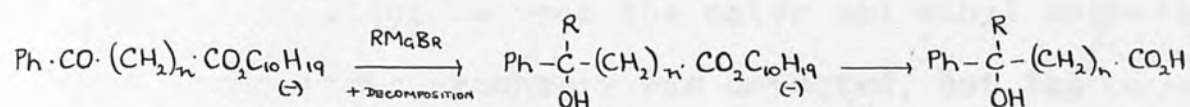
was proved to give an asymmetric synthesis when n was
2 or 3, but this could not be established when n was 4 or 8.

(−)-Menthyl-β-benzoylpropionate (n = 2) was obtained
as prisms from light petroleum, b.p. $60° - 80°$, m.p. $92°$,
$[\alpha]^{25}_{5461} = - 62.1°$ in chloroform ($\underline{l} = 2$, $\underline{c} = 1.715$).
The Grignard reaction between this ester and methyl magnesium
bromide yielded a slightly laevorotatory ɣ-hydroxy-ɣ-
phenylvaleric acid, which easily dehydrated to give a
dextrorotatory ɣ-methyl-ɣ-phenylbutyrolactone. The
ratio $\dfrac{[\alpha]_{LACTONE}}{[\alpha]_{ACID}}$ was found to be about - 10, and
therefore the lactone was usually isolated, as its higher

specific rotation afforded a more accurate means of deter-
mining the degree of asymmetric synthesis than did examination
of the acid itself. This degree of asymmetric synthesis was
found to vary only slightly with the conditions of reaction
(see Section IIIb), presumably because the reaction of the
ester with methyl and ethyl magnesium bromide was almost
instantaneous, even at 0°. The maximum specific rotation
of γ-methyl-γ-phenyl-γ-butyrolactone obtained was found
to be $[\alpha]_{5461}^{25} = + 10.5^{\circ}$, and since the specific rotation of
an optically pure lactone was found by another worker to
be $[\alpha]_{5461}^{25} = - 61.3^{\circ}$, about 15% asymmetric synthesis
took place.

In the reaction between the ester and ethyl magnesium
bromide, asymmetric synthesis was detected, but the
specific rotation of the product was low. A slightly
laevorotatory γ-hydroxy-γ-phenylhexanoic acid was obtained,
with a melting point of approximately 90°, the slightly active
acid having a higher melting point than the dl form. This
is some 13° lower than that reported by Trivedi and Nargund
(loc. cit. 102° - 103°), which was presumably for a dl
product. The laevorotatory acid dehydrated to give a
dextrorotatory lactone, the ratio $\dfrac{[\alpha]_{\text{LACTONE}}}{[\alpha]_{\text{ACID}}}$ being about -4.

$(\pm)$-Menthyl-γ-benzoylbutyrate (n = 3) was obtained
as colourless prisms from light petroleum b.p. 40°-60°,
having m.p. 19-19.5°, $[\alpha]_{5461}^{25} = -59.9^{\circ}$ in alcohol,

($\underline{l}$ = 2, $\underline{c}$ = 1.570).

Asymmetric synthesis was detected in the reaction between this ester and methyl magnesium bromide, but only proved after the acid had been converted into the corresponding lactone. This took place with ease, and the $\underline{\delta}$-methyl-$\underline{\delta}$-phenylvalerolactone so prepared was dextrorotatory. As in the previous reactions change in the conditions of the Grignard reaction were found to effect little change in the specific rotation of the end product. The maximum specific rotation recorded for the lactone was $[\alpha]_{5461}^{25}$ = + 2.9° ± 0.1°.

$\underline{\delta}$-Hydroxy-$\underline{\delta}$-phenylhexanoic acid, which has not been previously reported, was also prepared by a Grignard reaction between ethyl-$\underline{\gamma}$-benzoylbutyrate and methyl magnesium bromide, and was found to have m.p. 73° -74°, and crystallised in plates from alcohol.

The Grignard reaction between ($\underline{-}$)-menthyl-$\underline{\gamma}$-benzoyl-butyrate and ethyl magnesium bromide afforded no evidence of an asymmetric synthesis.

($\underline{-}$)-Menthyl-$\underline{\delta}$-benzoylvalerate (n = 4) was crystallised from ether, and was found to have m.p. 50° and $[\alpha]_{5461}^{25}$ = -59.5° in alcohol ($\underline{l}$ = 2, $\underline{c}$ = 1.650). No asymmetric synthesis could be proved in the reaction between this ester and methyl or ethyl magnesium bromide. This might not be due

to the absence of any such asymmetric synthesis because
it is possible that the specific rotation of the hydroxy-
acid formed is so low that a slight asymmetric synthesis
might be impossible to detect.

The same is true of Grignard reactions on (−)-menthyl-
-ω-benzoylpelargonate. This ester was found to crystallise
from alcohol in needles, m.p. $37^\circ - 38^\circ$, $\left[\alpha\right]^{25}_{5461} = -51.00^\circ$
in alcohol ($l = 2$, $c = 2.255$). It should be noted that
the ε- and θ-hydroxy-acids formed from the two last named
esters would not be expected to form lactones.

Therefore, as predicted, the Grignard reaction between
$Ph.Co.(CH_2)_n.Co_2C_{10}H_{19}$ ($n = 2$ or 3) and methyl or ethyl
magnesium bromide gives laevorotatory hydroxy-acids (with
corresponding dextrorotatory lactones) but no detectable
asymmetric synthesis when the methylene chain is lengthened
($n = 4$ or 8). The complementary reactions:

$$Me.CO.(CH_2)_n.CO_2C_{10}H_{19} \xrightarrow[+\ \text{DISCOMPOSITION}]{PhMgBr} Me-\overset{Ph}{\underset{OH}{\overset{*}{C}}}-(CH_2)_n.CO_2C_{10}H_{19} \longrightarrow Me-\overset{Ph}{\underset{OH}{\overset{*}{C}}}-(CH_2)_n.CO_2H$$
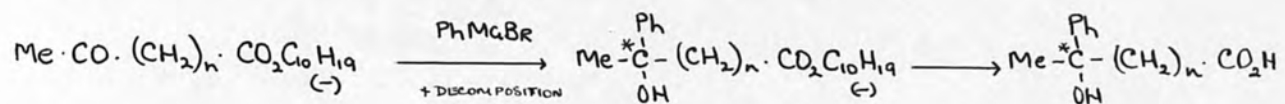
were performed by another worker, and were found to give,
as expected, dextrorotatory acids, with corresponding
laevorotatory lactones. The degree of asymmetric synthesis
in these reactions is lower than in those studied by the
author.

These results conform to the mechanism of asymmetric
synthesis put forward in Section I, and the course of an

asymmetric reaction of this type is seen to be influenced
by a number of factors, and not by any single force of
"asymmetric induction" as originally postulated by McKenzie.

SECTION V   EXPERIMENTAL

a)   General.

b)   (-)-Menthyl benzoylformate.

c)   (-)-Menthyl-β-benzoylpropionate.

d)   (-)-Menthyl-γ-benzoylbutyrate.

e)   (-)-Menthyl-δ-benzoylvalerate.

f)   (-)-Menthyl-ω-benzoylpelargonate.

SECTION Va.

General method of preparation of (-)-menthyl esters.

(-)-Menthyl esters were prepared by the Fischer-Speier method, 3 to 4 mols. of (-)-menthol and 1 mol. of acid being heated together on a water bath for 8 to 9 hours, dry HCl being passed through the mixture for about ten minutes every two hours. The reaction mixture was kept overnight, and then dissolved in ether. The solution was washed with 10% aqueous Na_2CO_3 (to remove HCl and unchanged acid. If much unchanged acid was present, 5% aqueous NaOH was also used). The solution was then washed with water and the ether was evaporated. The product was steam distilled to remove menthol, and the crude ester was purified, either by crystallisation or distillation, until its melting point, specific rotation and rotation dispersion for mercury, green (λ = 5461 Å) and yellow (λ = 5780 Å) lines were constant. The rotations were determined in absolute alcoholic solution (unless otherwise stated) at 25° in a 2 dcm.. tube.

General method of procedure in Grignard reactions.

The Grignard reagent was prepared in the (standard joint) apparatus shown in Fig. I. The apparatus was dried in the oven at 130° overnight, and set up while hot, the mouth of the funnel B and condenser C being protected with $CaCl_2$/soda lime tubes. The stem of the dropping funnel A in which the reagent was prepared was plugged with glass wool and a cork D was inserted into the bottom of the stem to ensure that the glass wool remained dry during the preparation. The magnesium used was dried in the oven at 130°, methyl bromide was dried over calcium chloride in the refrigerator and the ether was dried over sodium wire.

CaCl₂

SODA LIME

B

C

A

GLASS WOOL

FIG. I

D
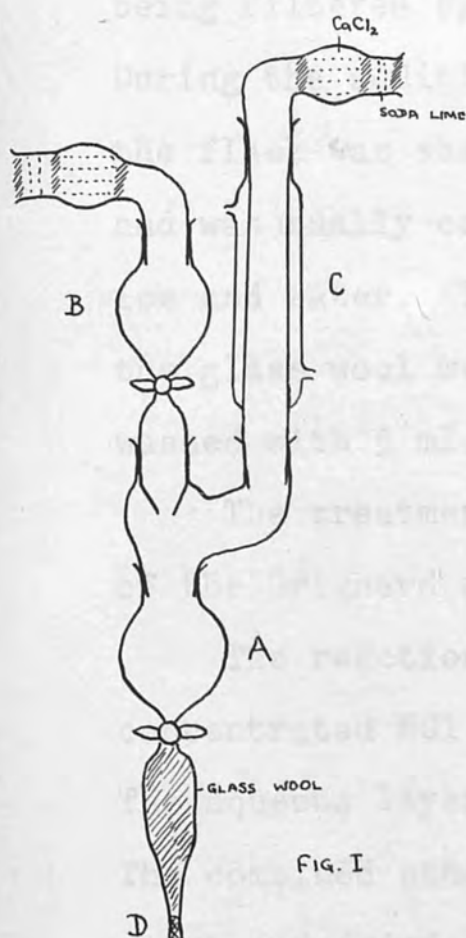
After the reagent had been prepared, the funnel A was disconnected, the mouth was fitted with a calcium chloride tube, and the cork D was removed. The apparatus was then set up as in Figure II.

The 100 ml. flask E contained 5g.
of ester dissolved in 20 ml. of ether
and the Grignard reagent was
allowed to drip slowly into the flask,
being filtered by the glass wool.
During the addition of the reagent,
the flask was shaken continually
and was usually cooled in a bath of
ice and water. The funnel A and
the glass wool were finally
washed with 5 ml. of ether.
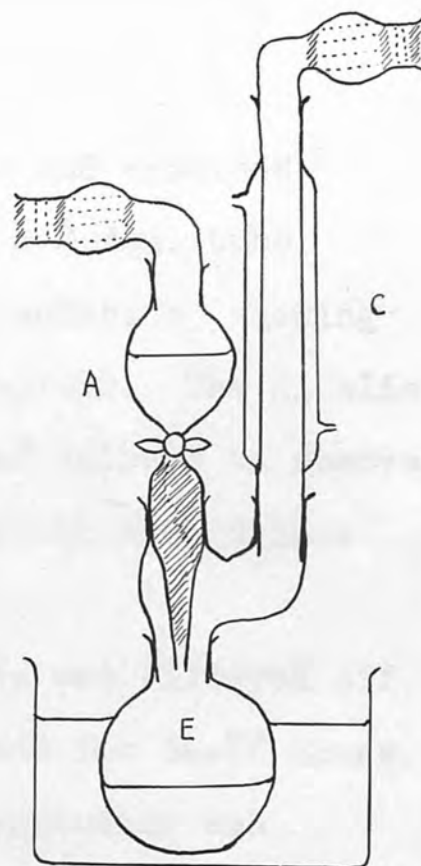
FIG Ⅱ.

The treatment of the reaction mixture after addition
of the Grignard reagent was varied in different experiments.

The reaction product was decomposed with ice and
concentrated HCl and the ethereal layer was separated.
The aqueous layer was extracted with 3 x 10 ml. of ether.
The combined ethereal extracts were washed with 10 ml. of
water and dried over anhydrous sodium sulphate. The
ethereal solution was distilled from a weighed flask and
the product was dried in vacuo for about half an hour.
The flask and contents were weighed and the ester was
hydrolysed by boiling with aqueous alcoholic potash ($1\frac{1}{4}$ mols.)

After hydrolysis the alcohol was distilled off from
a water bath and the remaining mixture of menthol, neutral
products and alkaline solution was extracted with 4 x 10 ml.
portions and 1 x 20 ml. portion of ether. The 20 ml.

portion was dried over sodium sulphate and examined
polarimetrically with sodium light in a 2 dcm. tube.
No rotation was ever observed in this solution, showing
that the extraction of menthol was complete. The alkaline
solution was heated on a water bath and stirred to remove
ether, and was cooled before acidification with dilute
(25%) sulphuric acid.

If a solid acid was obtained, this was filtered off
and dried in vacuo over calcium chloride for 14-18 hours.
If an oil was obtained, the acidified solution was
extracted with 5 x 10 ml. of ether. The combined ethereal
extracts were washed with 10 ml. of water and were dried
over sodium sulphate. The ether was distilled off and
the product was dried in vacuo over $CaCl_2$/wax.

It was found that the last traces of ether and
water were difficult to remove from the end products,
and from the hydroxy-(-)-menthyl esters obtained from the
reactions, as they were thick viscous liquids. All
products had therefore to be warmed repeatedly to facili-
tate the removal of solvents.

To isolate the dialcohols formed in some cases by
reaction of the Grignard reagent with the ester group
and the carbonyl group, the ethereal extract after
hydrolysis was evaporated and steam distilled to remove
menthol. The dialcohol was extracted from the distilling

flask with ether, and the ethereal extracts were dried and evaporated. The residue was dried _in vacuo_ and weighed. The dialcohol was not examined polarimetrically because steam distillation would not remove the last traces of (−)-menthol from the mixture, and the rotation due to this impurity would mask any optical activity present in the dialcohol.

The rotations of end products were determined at 25° in absolute alcoholic solution in a 2 dcm. tube using the mercury green ($\lambda = 5461$ Å) and yellow ($\lambda = 5780$ Å) lines. In a few cases, sodium ($\lambda = 5893$ Å) light was used.

S E C T I O N   Vb.

Benzoylformic acid (McKenzie J. 1904, 1247, modified by
Turner and Jamison (private communication)).

An alkaline solution of potassium permanganate
(32 g. of KMnO4 and 8.5g of NaOH in 200 ml. of water) was
heated to 70° and slowly added, with vigorous shaking, to
a mixture of acetophenone (12.g.) in 200 ml. of water. The
manganese dioxide was filtered off, and the filtrate was
kept and combined with four similar solutions prepared in
the same way. The combined solutions were evaporated to
200 ml. and then acidified with 25% sulphuric acid. The
benzoic acid precipitated was filtered off, and the
filtrate was basified with 30% aqueous caustic soda.
Any unchanged acetophenone was extracted with ether, and
the aqueous solution was then acidified with concentrated
HCl and extracted five times with ether.

The entire experiment up to this stage was repeated,
and the combined ethereal extracts of benzoylformic acid
were dried over anhydrous sodium sulphate. The ether was
evaporated, the residue was solidified by cooling, and
was then ground with carbon disulphide to remove benzoic
acid. The crude benzoylformic acid was crystallised from
benzene. Yield 50g. (30%).

(-)-Menthylbenzoylformate.

18 g. of benzoylformic acid were esterified with
(-)-menthol according to the general method (Section Va)

and the ester was crystallised from alcohol. After four
recrystallisations the ester had m.p. 73° and $[\alpha]^{25}_{5461} = -52.3°$
in absolute alcohol ($\underline{l} = 2$, $\underline{c} = 2.380$), fifteen minutes
after wetting the solid.

Turner and Jamison (J. 1941, 538) give $[\alpha]^{18.8}_{5461} = -51.6°$
in 99% alcohol ($\underline{l} = 2$, $\underline{c} = 3.5175$) three minutes after
wetting the solid.

Yield 27g. (79%)

Reaction between (-)-menthylbenzoylformate and

methylmagnesiumbromide, using $1\frac{1}{4}$ mols. of Grignard reagent.

Experiment 1.

The Grignard reagent prepared from 0.525g. of

magnesium, methyl bromide and 20 ml. of ether was added

over 10 minutes, with shaking, to a solution cooled in

ice, of 5g. of (-)-menthylbenzoylformate in 20 ml. of

ether. The mixture was boiled under reflux for one hour

and left to cool for half an hour before decomposition with

15 g. of ice and 35 ml. of dilute (25%) hydrochloric acid.

The product was isolated as described in Section Va.

5.20 G. (98%) were obtained, and were hydrolysed by

boiling under reflux with 12 ml. of 10% aqueous KOH and

25 ml. of alcohol for three hours. The alcohol was

removed and menthol extracted as described in Section Va,

and the alkaline solution was stirred with two successive

portions of 0.10 g. of charcoal. The volume of solution

was found to be 34 ml. which in a 2 dcm. tube gave

$$\alpha_D^{18} = -1.08°.$$

The solution was acidified and the acid isolated as

described in Section Va. 1.435 g. (53 %) of acid having

$$[\alpha]_{5461}^{25} = -9.2° \text{ in alcohol } (\underline{1} = 2, \underline{c} = 7.175) \text{ and}$$

$$[\alpha]_{5780}^{25} = -8.1° \text{ were obtained.}$$

The acid, crystallised from light petroleum,
b.p. 60°- 80° had m.p. 81° - 82° and $[\alpha]_D^{15} = -10.4°$
in alcohol ($\underline{l} = 2$, $\underline{c} = 1.58$).

Experiment 2.

In a second experiment the Grignard reagent
($1\frac{1}{4}$ mols.) was added to the ester solution over a
period of 7 minutes. The mixture was boiled under
reflux for half an hour before decomposition. 5.16 G.
(97%) of ester were obtained and after hydrolysis 2.48 g.
(97%) of α-phenyl glycollic acid were isolated having
$[\alpha]_{5461}^{25} = -9.3°$ in alcohol ($\underline{l} = 2$, $\underline{c} = 12.40$)
$[\alpha]_{5780}^{25} = -8.1°$.

S E C T I O N   Vc.

β-Benzoyl propionic acid (Organic Syntheses, II, 81).

Succinic anhydride (68g., 0.68g. mol) and thiophen-free, sodium-dried benzene (350 g.) were placed in a 2l. flask fitted with a reflux condenser and stirrer. Aluminium chloride (200 g. 1.5g. mol) was added in one portion, and the mixture was boiled under reflux in an oil bath, with stirring, for $\frac{3}{4}$ hour. The flask was then surrounded with ice-water, and 300 ml. of ice cold water were added through a dropping funnel, with stirring. 100 ml. of concentrated HCl were also added, and the mixture was steam-distilled to remove benzene. The mixture was then cooled and the β-benzoyl propionic acid, which had separated as an oil, solidified to a light brown solid. This was filtered off, washed with a mixture of 50 ml. of concentrated HCl and 150 ml. of water and then with 200 ml. of water. The crude acid was dissolved in a sodium carbonate solution (75 g. of anhydrous sodium carbonate in 500 ml. of water) by boiling for 15 minutes. The solution was filtered, and the $Al(OH)_3$ precipitate was washed with 100 ml. of hot water. The filtrate was stirred with 4g. of charcoal for 10 minutes and filtered.

The filtrate was cooled to 50° and was carefully acidified with 130 ml. of concentrated HCl. The β-benzoylpropionic acid was filtered off and crystallised from a mixture of benzene and light petroleum (b.p. 60° - 80°).

Yield 115g. (96%) m.p. 116°.

A semicarbazone was prepared and crystallised from aqueous alcohol, but it was found to decompose before melting.

A 2:4-dinitrophenyl-hydrazone, m.p. 135-137° was obtained.

(-)-Menthyl-β-benzoyl propionate.

The preparation was carried out according to the general method (Section Va) and the ester was crystallised from light petroleum (b.p. 60° - 80°). After four crystallisations the ester had m.p. 92°, and

$$\left[\alpha\right]^{25}_{5461} = - 62.1° \text{ in chloroform.}$$

$$\left[\alpha\right]^{25}_{5780} = - 54.8° \quad (\underline{1} = 2, \underline{c} = 1.715).$$

$$\frac{\left[\alpha\right]_{5461}}{\left[\alpha\right]_{5780}} = 1.133.$$

The specific rotation of this ester was determined in chloroform owing to its low solubility in alcohol.

Analysis: Found. C, 75.8 . H, 8.9.

$C_{20}H_{28}O_3$ requires C, 75.9 . H, 8.9. %

Reaction between (-)-menthyl-β-benzoylpropionate and methylmagnesiumbromide.

I. Using 1.25 mols. of Grignard reagent.

Experiment 3.   The Grignard reagent prepared from 0.480g. of magnesium, methyl bromide and 20 ml. of ether was added, with shaking, over 10 minutes, to a solution, cooled in ice, of 5g. of (-)-menthyl-β-benzoyl propionate in 20 mls. of ether. The mixture was boiled under reflux for 1½ hours and allowed to cool for 10 minutes before decomposition with 20 g. of ice and 2 ml. of concentrated HCl. The reaction product was isolated as described in Section Va and was found to smell of menthol.

Yield 4.995g. (95%)

The product was hydrolysed by boiling with 11 ml. of 10% aqueous KOH (1¼ mols.) and 15 ml. of alcohol for 2¼ hrs, and keeping for 16 hours. The acid was isolated as described in Section Va.

2.55 g. of a yellow solid were obtained, having $[\alpha]_{5461}^{25} = +1.1°$ in alcohol (l = 2, c = 11.95).

Crystallised from a mixture of benzene and light petroleum b.p. 60° - 80°, 0.975g. of optically inactive white crystals m.p. 116° were obtained, identified as β-benzoylpropionic acid by a mixed melting point with an authentic specimen.

The mother liquor was evaporated and 0.93 g. of a yellow viscous liquid were obtained, having $[\alpha]_{5461}^{15.5} = +3.5°$ in alcohol ($\underline{l} = 2$, $\underline{c} = 4.65$).

The alcoholic solution was evaporated on a water bath and the residue was dissolved in 10% aqueous KOH. The solution was slowly acidified with 25% sulphuric acid and a creamy white solid was obtained m.p. 98° - 100°. The yield was too small for further investigation, but was later identified as impure δ-hydroxy- γ -phenyl- n -valeric acid, $Ph-\overset{*}{\underset{\underset{OH}{|}}{\overset{\overset{Me}{|}}{C}}}-(CH_2)_2 \cdot CO_2H$.

Reactions using 1.5, 1.8 and 2.0 mols. of methyl-magnesium bromide were then carried out, details of which are given in Tables I and II.

Experiment 4.   After removal of the β-benzoyl propionic acid by crystallisation, the mother liquor was evaporated: the yellow viscous product (1.18g) gave

$$[\alpha]_{5461}^{25} = +5.0° \text{ IN ALCOHOL}$$
$$[\alpha]_{5780}^{25} = +4.5° \quad [\underline{l} = 2, \underline{c} = 5.90].$$

The alcoholic solution was evaporated, the residue was dissolved in 10% aqueous NaOH and the alkaline solution was acidified with 25% H_2SO_4. The acid precipitated (0.823 g.) was filtered off and dried $\underline{\text{in vacuo}}$ over $CaCl_2$ for 18 hours. The acid had m.p. 96 - 98°, and $[\alpha]_{5461}^{25} = -0.07°$ in alcohol ($\underline{l} = 2$, $\underline{c} = 4.115$).

The alcoholic solution was evaporated with a drop of dilute HCl to facilitate the change from acid to lactone. 0.75 G. of lactone were obtained, having $[\alpha]_{5461}^{25} = + 6.0°$ in alcohol ($\underline{l} = 2$, $\underline{c} = 3.75$).

Experiment 5. The end product (1.44g.) gave in alcohol ($\underline{l} = 2$, $\underline{c} = 7.20$), but as β-benzoylpropionic acid (0.12g) was isolated from the end product, no further investigation was carried out.

Experiment 6. The end product (1.59g.) gave $[\alpha]_{5461}^{25} = + 4.3°$ in alcohol ($\underline{l} = 2$, $\underline{c} = 7.95$).

γ-Hydroxy-γ-phenyl-n-valeric acid (1.545g) was isolated as described in experiment 3, and was found to have m.p. 100° - 102°, $[\alpha]_{5461}^{25} = - 0.13°$ in alcohol. $[\alpha]_{5780}^{25} = - 0.11°$

($\underline{l} = 2$, $\underline{c} = 7.725$).

The alcoholic solution was evaporated, a drop of dilute HCl being added when evaporation was almost complete, and the product was dried *in vacuo*. 1.24 g. of lactone were obtained having $[\alpha]_{5461}^{25} = + 6.7°$ in alcohol ($\underline{l} = 2$, $\underline{c} = 6.20$).

TABLE I.

Expt. No.	No. of mols. of MeMgBr.	Condition of reaction.	Yield of product in g.
4	1.5	Grignard reagent added over 15 minutes, with cooling in ice. Mixture boiled under reflux for 1½ hours.	5.005
5	1.8	Grignard reagent added over 10 minutes, with cooling in ice. Mixture boiled under reflux for 1½ hours.	5.065
6	2.0	Grignard reagent added over 10 minutes, with cooling in ice. Mixture boiled under reflux for 1½ hours, and kept at room temperature for 1 hour.	4.925

TABLE II.

Expt. No.	Yield of final product in g.	Yield of β-benzoyl propionic acid in g.
4	1.945	0.625
5	1.94	0.12
6	1.59	0.0

II. Using 2 mols. of Grignard reagent.

The Grignard reagent was prepared from 0.768g. of magnesium, methyl bromide and 25 ml. of ether. The conditions of reaction and yields obtained are given in table III.

T A B L E   III.

Expt. No.	Conditions of reaction.	Yield of product(g.)
7	Grignard reagent added over 10	5.23.
8	minutes, with cooling in ice.	5.20(5)
9	boiled under reflux for 1½	5.13
10	hours.	5.20
11	Grignard reagent added over 10 minutes, with cooling in ice.	5.18
12	Mixture boiled under reflux for ½ hour.	5.15
13	Grignard reagent added over 15 minutes with cooling in ice. Mixture boiled under reflux for ½ hour.	5.19(5)
14	Grignard reagent added in one portion. Mixture kept at room temperature for 5 minutes, and boiled under reflux for ½ hour.	5.19

T A B L E   III.   (contd.)

Expt. No.	Conditions of reaction.	Yield of product (g).
15.	Grignard reagent added over 15 minutes, with cooling in ice: mixture kept for 15 minutes at room temperature, then boiled under reflux for $1\frac{1}{2}$ hours.	5.20(5)
16.	Grignard reagent added over 10 minutes, with cooling in ice ; mixture boiled under reflux for $\frac{1}{2}$ hour.	5.19
17.	Grignard reagent added over 10 minutes, with cooling in ice : mixture kept for 3 hours in ice.	5.22
18.	Grignard reagent added over 10 minutes, with cooling in ice.	5.25(5)
19.		5.06
20.	Mixture kept at room temperature for 16 hours.	5.25
21.	Grignard reagent added over 10 minutes, with cooling in ice.	5.23
22.	Mixture kept for $\frac{1}{2}$ hour. Boiled under reflux for $1\frac{1}{2}$ hours.	5.25(5)

Isolation of end products.

The hydrolysis of the ester obtained in experiments 7 to 22 was carried out by boiling under reflux for three hours with 11 ml. of 10% aqueous KOH and 15 ml. of alcohol. γ-Hydroxy- γ-phenyl- n-valeric acid on its lactone, was then isolated as described in Section Va.

In isolating the acid, acidification had to be carried out very slowly in order to obtain it in a crystalline state. If acidification was too rapid, a gummy solid was obtained. The acid was found to be slightly soluble in water, and if the solution was made only just acid to Congo Red some product could be isolated from the mother liquor after filtration, by extraction with ether. The acid was dried in vacuo over $CaCl_2$ for about 15 hours.

To isolate the lactone the acidified solution was extracted with 4 x 15 ml. of ether. The combined extracts were washed with 10 ml. of water and dried over anhydrous sodium sulphate. The ether was evaporated on a water bath, finishing the removal in presence of a drop of dilute HCl. Details of these experiments are given in tables IV to VII.

TABLE IV.   Yields and specific rotations of lactones.

Expt. No.	Yield of lactone in g.	Lactone $[\alpha]^{25}_{5461}$	Lactone $\dfrac{[\alpha]_{5461}}{[\alpha]_{5780}}$	c.
9	1.34	+10.0°	1.13	6.70
11	1.29(5)	+10.5°	1.13	6.47(5)
10	1.30	+9.9°	1.13	6.50
13	1.30	+10.1°	1.14	6.50
14	1.275	+10.5°	1.12	6.37(5)

TABLE V.   Yields and specific rotations of lactones.

Expt. No.	Yield of lactone in g.	Lactone $[\alpha]^{25}_{5461}$	Lactone $\dfrac{[\alpha]_{5461}}{[\alpha]_{5780}}$	c.
17	1.34	+9.5°	1.13	6.70
18	1.23	+9.0°	1.12	6.15
19	1.33	+9.5°	1.12	6.65
22	1.32(5)	+9.2°	1.12	6.62(5)
21	1.30	+9.5°	1.13	6.50

TABLE VI. Yields and rotations of acid.

Expt. No.	pH of mother liquor (approx)	Yield of acid in g.	Yield of product from mother liq. in g.	α^{25}_{5461} of acid (l = 2)	c of acid
7	3	1.324	0.0	$-0.14°$	6.62
8	5	1.100	0.28	$-0.13°$	5.50
15	5	1.068	Not recovered.	$-0.15°$	5.34

TABLE VII. Yields and specific rotations of lactones prepared from acids.

Expt. No.	Yield of lactone in g.	Lactone $[\alpha]^{25}_{5461}$	Lactone $\dfrac{[\alpha]_{5461}}{[\alpha]_{6780}}$	c.
7	1.19	$+10.5°$	1.08	5.95
8	0.96	$+10.8°$	1.14	4.80
15	0.89	$+14.5°$	1.13	4.45

CHART I   EXPERIMENT 23.

100 ML. OF
SOLUTION

① ② ③

LACTONE
1.85G.
$[\alpha]^{25}_{5461} = +8.48°$

ACID
1.65G. m.p. 100°–102°
$[\alpha]^{25}_{5461} = -1.30°$

ACID
3.41G. m.p. 99°–101°
$[\alpha]^{25}_{5461} = -1.26°$

LACTONE
1.66G
$[\alpha]^{25}_{5461} = +9.00°$

LACTONE
1.24G
$[\alpha]^{25}_{5461} = +12.20°$

LACTONE
1.11G
$[\alpha]^{25}_{5461} = +12.70°$

ALKALINE
SOLUTION

ACID
1.30G. m.p. 109°
$[\alpha]^{25}_{5461} = -4.42°$

ACID
1.25G. m.p. 102°–103°
$[\alpha]^{25}_{5461} = +2.56°$

IMPURE
β - BENZOYLPROPIONIC
ACID

LACTONE
0.795G.
$[\alpha]^{25}_{5461} = +46.8°$

LACTONE
1.06G.
$[\alpha]^{25}_{5461} = -22.20°$

ALKALINE
SOLUTION

ACID
0.23G. m.p. 110°
$[\alpha]^{25}_{5461} = +4.15°$

ACID
0.16G. m.p. 109.5°–110°

ACID
(RECRYSTALLISED)
m.p. 114.5 – 115°

Larger scale reaction between (-)-Menthyl- β-benzoylpropionate
and methylmagnesium bromide (2 mols.) (Experiment 23).

The Grignard reagent prepared from 3.84 g. of
magnesium, methyl bromide and 120 ml. of ether was added,
over 20 minutes, with shaking to a solution, cooled in ice,
of 25 g. of (-)-menthyl- β-benzoylpropionate in 100 ml. of
ether. The mixture was boiled under reflux for half an
hour before decomposition with 100 g. of ice and 15 ml. of
concentrated HCl. The ester (26.10g.) was isolated as
described in Section Va, and hydrolysed by boiling under
reflux with 44.5 ml. of 10% aqueous KOH (1¼ mols.) and
70 ml. of alcohol for 2½ hours and keeping overnight.

The menthol was extracted with ether, and the
alkaline solution made up to 100 ml. Portions were
treated as follows: (see also Chart I)
(1)   25 Ml. were acidified with 25% H_2SO_4 and extracted
with ether. The ethereal solution was dried and evaporated
with one drop of dilute HCl. 1.85 g. of product were
obtained having $[\alpha]_{5461}^{25} = + 8.4°$ in alcohol ($\underline{1} = 2$, $\underline{c} = 9.25$).
The alcoholic solution was evaporated on a water bath and
the product was dried $\underline{in\ vacuo}$ over P_2O_5 for 40 hours. The
lactone (1.66g.) had $[\alpha]_{5461}^{25} = + 9.0°$ in alcohol ($\underline{1} = 2$, $\underline{c} = 8.30$).
(2)   25 Ml. of solution were acidified with dilute H_2SO_4 and
the acid was filtered off and dried over $CaCl_2$ for 17 hours.

The acid (1.65g.) had m.p. $100^{\circ} - 102^{\circ}$, and $[\alpha]^{25}_{5461} = -1.30^{\circ}$ in alcohol ($\underline{1} = 2$, $\underline{c} = 8.105$).

The alcoholic solution was evaporated, 10 ml. of 10% aqueous KOH and 5 ml. of water being added during the evaporation. The alkaline solution was kept for 48 hours at room temperature with a little charcoal. The solution was filtered and made up to 20 ml. at 25°c.

The alkaline solution was then acidified and extracted with ether. The ethereal solution was dried and evaporated with a drop of dilute HCl. The lactone (1.24 g.) had

$$[\alpha]^{25}_{5461} = +12.20^{\circ} \text{ IN ALCOHOL}$$

$$[\alpha]^{25}_{5780} = +10.16^{\circ} \quad [\underline{l} = 2, \underline{c} = 6.20]$$

$$\frac{[\alpha]^{5461}_{LACTONE}}{[\alpha]^{5461}_{ACID}} = -9.42$$

(3) 50 Ml. were slowly acidified and the acid was filtered off and dried as in (2). The acid (3.41g.) was found to have m.p. $99^{\circ} - 101^{\circ}$ and $[\alpha]^{25}_{5461} = -1.26^{\circ}$ in alcohol ($\underline{1} = 2$, $\underline{c} = 7.55$).

The alcoholic solution was evaporated with a drop of dilute HCl and the lactone (1.110g.) was found to have

$$[\alpha]^{25}_{5461} = +12.70^{\circ} \text{ IN ALCOHOL}$$

$$[\alpha]^{25}_{5780} = +10.91^{\circ} \quad [\underline{l} = 2, \underline{c} = 5.55]$$

$$\frac{[\alpha]^{5461}_{LACTONE}}{[\alpha]^{5461}_{ACID}} = -10.08$$

A portion of the acid was crystallised from carbon tetrachloride. Needles, m.p. 106° - 107° were obtained. Recrystallised from carbon tetrachloride the acid had m.p. 106.5°.

The products from (1), (2) and (3) were combined and dissolved in 10% aqueous KOH, and the solution was stirred with a little charcoal. The filtered solution was acidified slowly with 25% H_2SO_4 until the solution was acid to litmus but not to methyl orange (pH about 5 - 6). The acid (1.30g.) was dried in vacuo over $CaCl_2$ for 14 hours and was found to have m.p. 109°, $[\alpha]_{5461}^{25} = -4.42°$ in alcohol ($\underline{1} = 2$, $\underline{c} = 6.44$).

The mother liquor was made/acid to methyl orange and the acid obtained (1.25g.) had m.p. 102°-103°, $[\alpha]_{5461}^{25} = + 2.56°$ in alcohol, ($\underline{1} = 2$, $\underline{c} = 5.86$).

The mother liquor on standing deposited a few crystals m.p. 116°, identified as β-benzoylpropionic acid, which probably contaminated the second crop.

The alcoholic solution of the first crop, on evaporation and drying in vacuo, gave a lactone (0.795g) having

$$[\alpha]_{5461}^{25} = +46.8° \text{ in ALCOHOL } [\underline{\ell} = 2 , \underline{c} = 3.475]$$

$$\frac{[\alpha]_{5461}^{LACTONE}}{[\alpha]_{5441}^{ACID}} = -10.5$$

The second crop gave a lactone (1.06g) having $[\alpha]_{5461}^{25} = -22.2°$ in alcohol ($\underline{1} = 2$, $\underline{c} = 5.30$) which gives $\dfrac{[\alpha]_{5461}^{LACTONE}}{[\alpha]_{5461}^{ACID}} = -9.1.$

This is low, probably owing to contamination with β-benzoylpropionic acid.

The alcoholic solution of the second crop was evaporated on a water bath with 10% aqueous KOH to obtain an aqueous solution of the potassium salt of the acid in excess potassium hydroxide. The solution was slightly laevorotatory.

The solution was acidified to pH 6, and the slight precipitate was filtered off. Most of the colour in the solution was absorbed onto this precipitate, so that the main precipitate was only slightly coloured. The mother liquor was acidified to pH 4.5-5, and the acid was filtered off and dried over $CaCl_2$. 0.23g. of acid, m.p. 110°, $[\alpha]_{5461}^{25} = + 4.15°$ in alcohol ($\underline{l} = 2$, $\underline{c} = 0.985$) were obtained.

The mother liquor, acidified to pH 3-3.5 gave an acid (0.16g) m.p. 109.5 - 110°. Recrystallised from benzene, the acid had m.p. 114.5 - 115°.

A second large scale experiment (24), using 20 g. of (-)-menthyl-β-benzoylpropionate was carried out in a similar manner to the first.

20.84 G. of "ester" were obtained, and the alkaline solution after hydrolysis and removal of menthol was made up to 100 ml. as before.

(1) 25 Ml. were acidified, extracted with ether and the ether extract was evaporated with a drop of dilute HCl. 1.295g of lactone were obtained having $[\alpha]_{5461}^{25} = + 9.1^\circ$ in alcohol## ($\underline{l} = 2$, $\underline{c} = 6.475$).

(2) 75 Ml. were acidified and extracted with ether. The ethereal solution was evaporated and the product (3.80g.) was dissolved in 10% aqueous KOH. An attempt was then made to obtain a pure specimen of the dextro-and laevo-forms of the acid by partial precipitation, extending the technique used in the previous experiment. Unfortunately the yield of acid decreased so rapidly using this method that although a small quantity of dextrorotatory acid of 80% purity was obtained, the pure form was not isolated.

Details of this experiment are given in chart II.
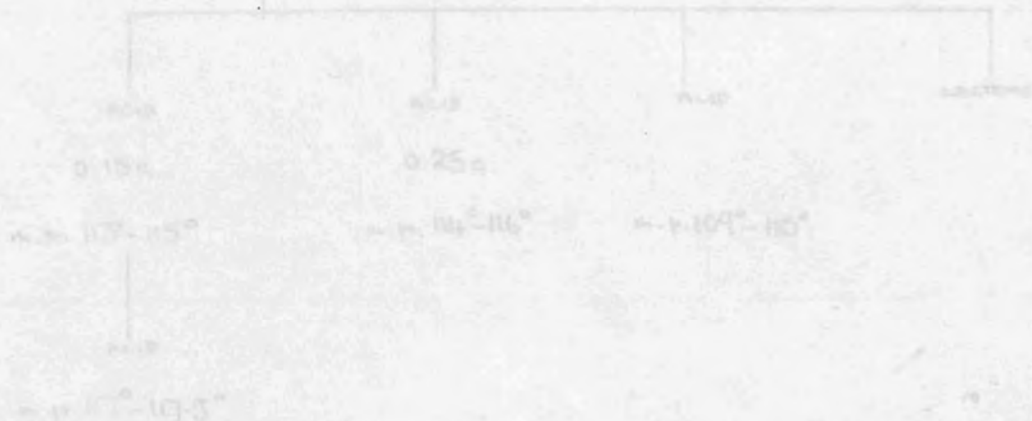
CHART II   EXPERIMENT 24

3.8 g. OF LACTONE

ALKALINE SOLUTION

ACID 1.93 g.
m.p. 109°-110°
$[\alpha]_{5461}^{25} = -2.0°$

ACID 0.84 g.
m.p. 98°-101°
$[\alpha]_{5461}^{25} = +0.62°$

LACTONE 0.61 g.
INACTIVE.

ACID 0.20 g.
m.p. 113.5-115°
$[\alpha]_{5461}^{25} = -5.0°$

ACID 1.38 g.
m.p. 105°-106.5°
$[\alpha]_{5461}^{25} = -1.56°$

LACTONE 0.05 g.

ACID 0.285 g.
m.p. 97°-102°
$[\alpha]_{5461}^{25} = +2.5°$

ACID 0.115 g.
m.p. 96°-100°

ACID 0.15 g.
m.p. 113°-115°

ACID 0.25 g.
m.p. 114°-116°

ACID
m.p. 109°-110°

LACTONE

ACID
m.p. 117°-117.5°

Reaction between (-)-menthyl- β -benzoylpropionate and
ethyl-magnesium bromide.

I.   Using 2 mols. of Grignard reagent.

The Grignard reagent prepared from 0.768 g. of
magnesium, 3.8g. of ethyl bromide and 25 ml. of ether
was added, with shaking, over 10 minutes, to a solution,
cooled in ice, of 5g. of (-)-menthyl- β -benzoylpropionate
in 20 ml. of ether. The mixture was boiled under reflux
for half an hour before decomposition with 20g. of ice
and 3 ml. of concentrated HCl. The product was isolated
as described in Section Va, and hydrolysed by boiling
under reflux with 11 ml. of 10% aqueous KOH and 15 ml. of
alcohol for three hours. The γ-hydroxy- γ -phenyl-n -
hexanoic acid or its lactone were then isolated as
previously described. Details of the yields obtained in
these experiments are given in table VIII.
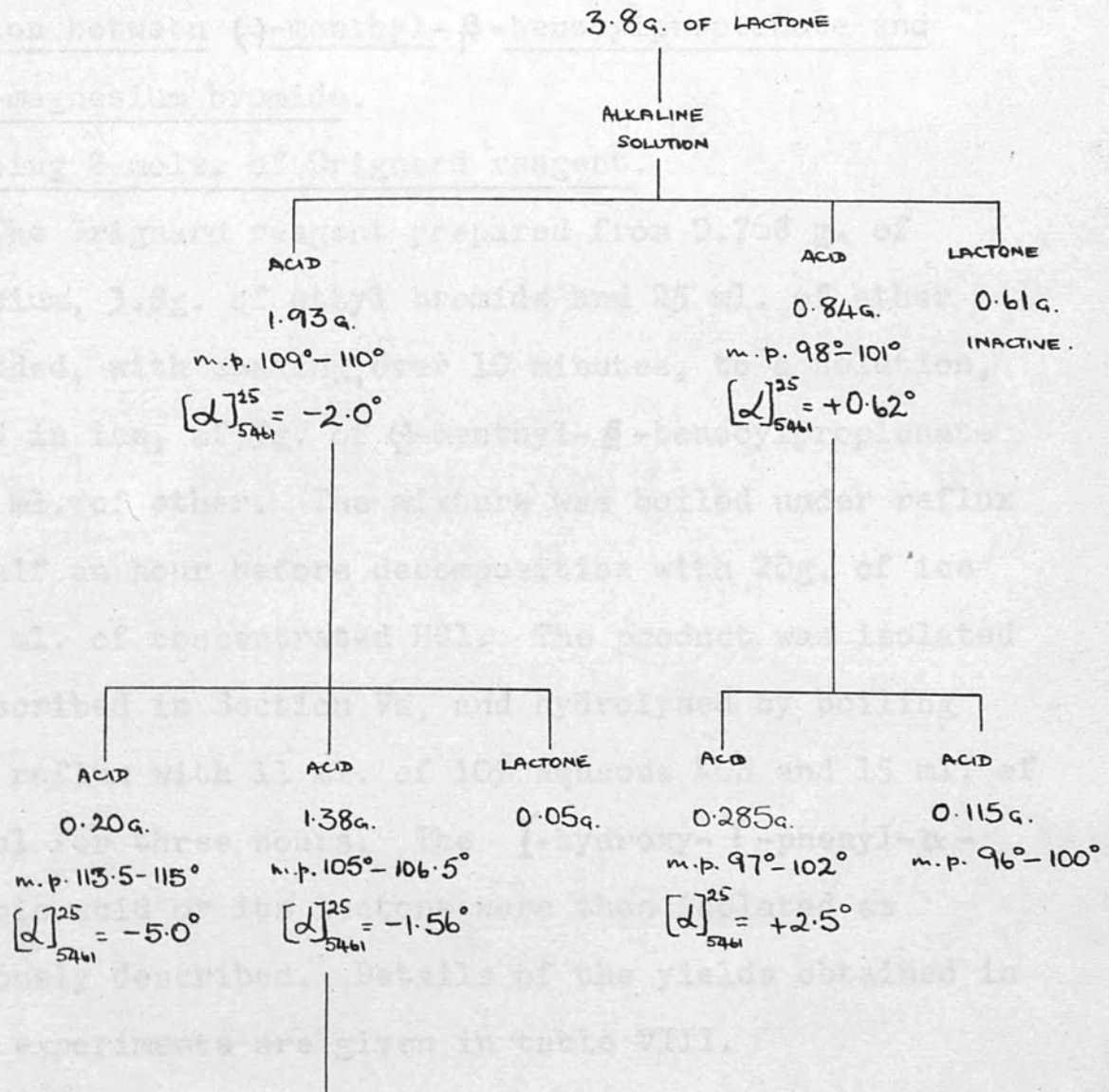
T A B L E   VIII.

Expt. No.	Yield of ester in g.	Yield of acid in g.	Yield of lactone in g.
25	5.23	-	1.55(5)
26	5.24	1.32	-
27	5.29	-	1.55
28	5.21	1.55	-

Experiment 25.   The ethereal solution of the end product
was evaporated with a drop of dilute HCl, and the residue
gave $[\alpha]_{5461}^{25} = + 3.40°$ in alcohol ($\underline{l} = 2$, $\underline{c} = 7.775$).

Experiment 27.   The end product was treated as in the
previous experiment and gave $[\alpha]_{5461}^{25} = +3.54°$ in alcohol
($\underline{l} = 2$, $\underline{c} = 7.75$). The alcoholic solution was evaporated
and the lactone was dried in vacuo. The lactone was found
to have $[\alpha]_{5461}^{25} = + 5.26°$ in alcohol ($\underline{l} = 2$, $\underline{c} = 5.325$),
showing that incomplete conversion into lactone occurs in
ethereal solution.

The alcoholic solution was again evaporated and the
residue was heated on a water bath with 10 ml. of 10%
aqueous NaOH. The solution was acidified and the acid
was dried in vacuo over $CaCl_2$ for 16 hours. The acid was
found to have m.p. 84-86°. (Compare Trivedi and Nargund,
J. Univ. Bombay, 10, Pt.3, 99-107, who give m.p. 102-3°).

Experiment 26.   The acid (1.32 g.) was dried in vacuo
for 16 hours over $CaCl_2$, and had m.p. 80° - 86°,
$\alpha_{5461}^{25} = -0.03°$ in alcohol, ($\underline{l} = 2$, $\underline{c} = 6.5725$). The
alcoholic solution was evaporated on a water bath and
dried in vacuo over $CaCl_2$ for one hour. The change from
acid to lactone appeared to take place easily in
alcoholic solution, and no mineral acid was needed.
The product (1.18g) had $[\alpha]_{5461}^{25} = +8.47°$ in alcohol
($\underline{l} = 2$, $\underline{c} = 5.9$).

Experiment 28.   The acid (1.55g.) im.p.84° was crystallised from carbon tetrachloride. Needles m.p.88-89° were obtained, and these, recrystallised from carbon tetrachloride had m.p. 89°. Analysis: Found.C,69.2, H,7.8, calculated for $C_{12}H_{16}O_3$, C,69.2, H,7.75.

It will be noted that the melting point of the acid is 13-14° below that reported by Trivedi and Nargund. Larger scale experiment (29) using 2 mols. of Grignard reagent, ethyl-magnesiumbromide.
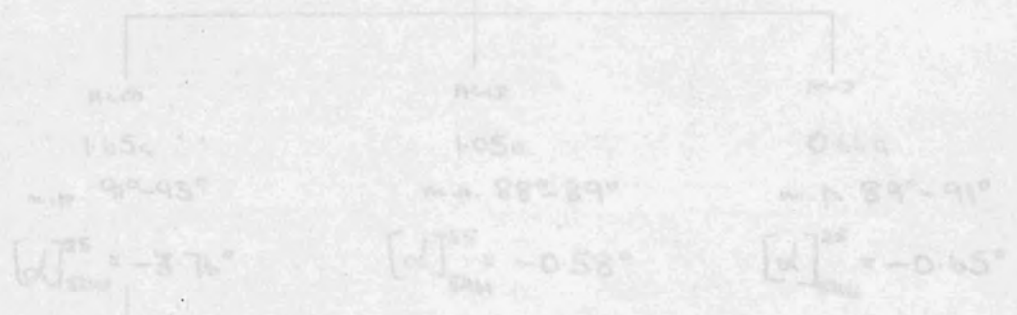
An experiment on a larger scale, using 25g. of (-)-menthyl-β-benzoylpropionate was carried out, in an attempt to separate the d- and l- forms of the acid, by fractional precipitation as may be done with the methyl analogue.

The Grignard reagent prepared from 3.84 g. of magnesium, 17.5g. of ethyl bromide and 200 ml. of ether was added over 10 minutes, with shaking, to a solution cooled in ice, of 25 g. of (-)-menthyl-β-benzoylpropionate in 100 ml. of ether. The reaction mixture was allowed to stand for 10 minutes and was then boiled under reflux for half an hour before decomposition with 100 g. of ice and 15 ml. of concentrated HCl. The product was isolated as described in Section Va, (yield 26.35g.) and was hydrolysed by boiling under reflux with 50 ml. of 10% aqueous KOH and 75 ml. of alcohol for three hours. The

menthol was extracted with ether and the alkaline solution
was acidified to pH6. It was found that colour was not
absorbed on the initial precipitate, as occurred with the
methyl analogue and this method of decolourising the
solution could not, therefore, be used. Details of this
precipitation are given in Chart III. The experiment
was abandoned because although the first crop of acid
precipitated had a higher specific rotation than subsequent
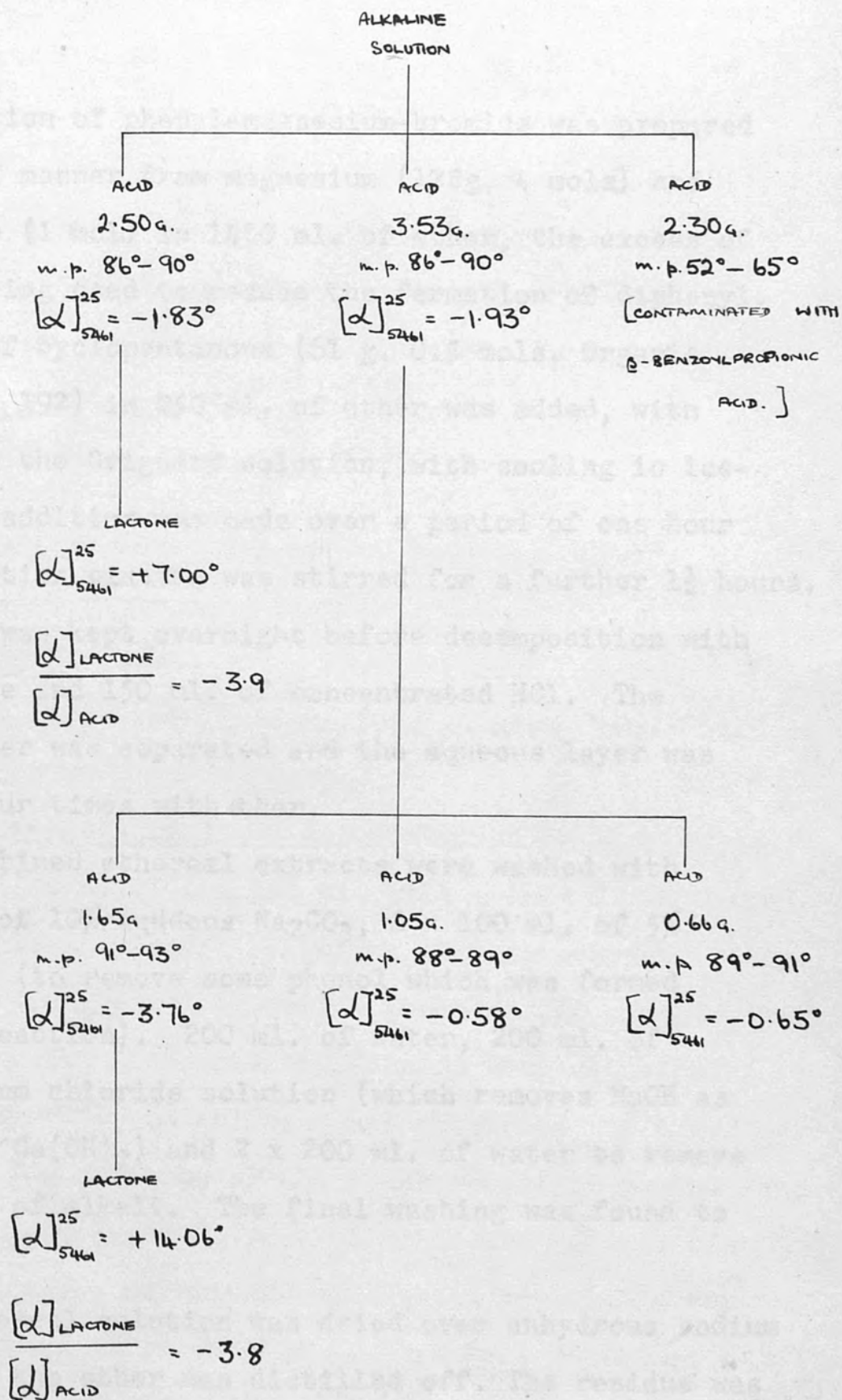crops, no real separation took place, as with the methyl
homologue.

CHART III   EXPERIMENT 29

ALKALINE
SOLUTION

ACID	ACID	ACID
2.50 g.	3.53 g.	2.30 g.
m.p. 86°-90°	m.p. 86°-90°	m.p. 52°-65°
$[\alpha]_{5461}^{25} = -1.83°$	$[\alpha]_{5461}^{25} = -1.93°$	[CONTAMINATED WITH β-BENZOYLPROPIONIC ACID.]

LACTONE

$[\alpha]_{5461}^{25} = +7.00°$

$\dfrac{[\alpha]_{LACTONE}}{[\alpha]_{ACID}} = -3.9$

ACID	ACID	ACID
1.65 g.	1.05 g.	0.66 g.
m.p. 91°-93°	m.p. 88°-89°	m.p. 89°-91°
$[\alpha]_{5461}^{25} = -3.76°$	$[\alpha]_{5461}^{25} = -0.58°$	$[\alpha]_{5461}^{25} = -0.65°$

LACTONE

$[\alpha]_{5461}^{25} = +14.06°$

$\dfrac{[\alpha]_{LACTONE}}{[\alpha]_{ACID}} = -3.8$

S E C T I O N   Vd.

Ph–⬠.
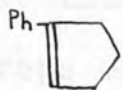
A solution of phenyl-magnesium-bromide was prepared in the usual manner from magnesium (128g., 4 mols.) and bromobenzene (1 mol.) in 1400 ml. of ether, the excess of magnesium being used to reduce the formation of diphenyl. A solution of cyclopentanone (61 g. 0.5 mols. Organic Syntheses I, 192) in 250 ml. of ether was added, with stirring, to the Grignard solution, with cooling in ice-water. The addition was made over a period of one hour and the reaction mixture was stirred for a further $1\frac{1}{2}$ hours. The mixture was kept overnight before decomposition with 1500g. of ice and 150 ml. of concentrated HCl. The ethereal layer was separated and the aqueous layer was extracted four times with ether.

The combined ethereal extracts were washed with 3 x 250 ml. of 10% aqueous Na_2CO_3, 2 x 100 ml. of 5% aqueous NaOH (to remove some phenol which was formed during the reaction). 200 ml. of water, 200 ml. of strong calcium chloride solution (which removes NaOH as precipitated $Ca(OH)_2$) and 2 x 200 ml. of water to remove final traces of alkali. The final washing was found to be neutral.

The ethereal solution was dried over anhydrous sodium sulphate and the ether was distilled off. The residue was

distilled in vacuo. As soon as distillation was started, drops of water formed in the flask, and water distilled over. The pressure was controlled at 30 mms. until this distillation ceased and was then decreased to about 4 mm.

The preparation was repeated several times and the dehydration of the 1-phenylcyclopentan-1-ol formed in the Grignard reaction occurred each time. Average yield, 75%. b.p. 84°/4 mm. m.p. 23°.

Bauer, (Comptes. Rend.156, 1685) gives b.p. 109°/9mm. m.p. 23°.

A picrate was prepared and found to have m.p. 63.5°.
Bauer (loc. cit) gives m.p. 64.5°.

γ-Benzoylbutyric acid.

(Compare Fieser and Szmuskovicz, J.Amer. Chem. Soc. 1948, 70, 3352).

1-Phenylcyclopent-1-ene (5g.) was dissolved in glacial acetic acid (200 ml.) in a 500 ml. bolt necked flask fitted with a mechanical stirrer. Powdered chromic anhydride (15g.) was added in small portions over a period of 40 minutes, with stirring. The flask was then surrounded with a bath of cold water (Ca.20°) and stirring was continued for a further 50 minutes. The contents of the flask were then poured into a separating funnel and 200 ml. of water and 200 ml. of ether were added. The mixture was shaken vigorously and left to separate. More water and ether were sometimes necessary to effect separation of the mixture into two layers.

The (lower) aqueous layer was run off and extracted with 4 x 100 ml. of ether. The combined ethereal extracts were washed with 3 x 100 ml. of water and 200 ml. of 5% aqueous NaOH, and these washings were discarded. (It was found that the chromic and acetic acids extracted from the reaction mixture with ether were not completely washed out with water, and it was only after these acids had been removed by washing with alkali that the bulk of the $\underline{Y}$-benzoylbutyric acid could be extracted). The ethereal layer was washed with 2 x 500 ml. of 10% NaOH, and these washings were acidified with concentrated HCl to recover traces of $\underline{Y}$-benzoylbutyric acid which was present.

The ethereal solution was then extracted with 2 x 50 ml. of 10% aqueous NaOH and 50 ml. of water. The combined extracts were slowly poured into concentrated HCl and the $\underline{Y}$-benzoylbutyric acid was filtered and dried _in vacuo_ over P_2O_5.

Yield 2.90g. (43%).

A few runs were carried out using 6g. of $\underline{1}$-phenylcyclopent-$\underline{1}$-ene but the large volumes of solution involved made them bulky to handle.

Recrystallised from hot water the acid had m.p. 126.5° - 127°. (See section IIc for details of melting points obtained by previous workers).

The semicarbazone of γ-benzoylbutyric acid was prepared and crystallised from aqueous alcohol m.p. 212°-213° Fieser (loc. cit.) gives 212°-213°.

Isolation and identification of 1-phenylcyclopent-1-en-3-one.

The ethereal solution after extraction of the γ-benzoylbutyric acid was dried over Na_2SO_4 and evaporated. The residue was dissolved in alcohol and a semicarbazone was prepared. Crystallised from aqueous acetic acid it darkened at 210°, melting at 223°-224°. Fieser (loc.cit) gives darkening at 210°, m.p. 226° - 227°.

(-)-Menthyl-γ-benzoylbutyrate.

The ester was prepared according to the general method (Section Va) and was solidified after steam distillation of the menthol, by cooling in ice. The crude ester was crystallised from light petroleum b.p. 40° - 60° cooled in a CO_2/EtoH bath. After four recrystallisations the ester had m.p. 18.5° - 19.0° and $[\alpha]_{5461}^{25} = -59.9^{\circ}$ in alcohol ($\underline{l} = 2$, $\underline{c} = 1.560$). $\dfrac{[\alpha]_{5461}}{[\alpha]_{5780}} = 1.135$. Average yield 73%.

Analysis: Found. C, 76.4, H, 9.6.

$C_{21}H_{30}O_3$ REQUIRES H, 76.4, H, 9.2.%

Reaction between (-)-menthyl- γ -benzoylbutyrate and
methylmagnesium bromide.

I. Using $1\frac{1}{4}$ mols of Grignard reagent.

The Grignard reagent was prepared from 0.464g. of
magnesium, methyl bromide and 20 ml. of dry ether.
Details of the conditions of reaction and the yield of
product obtained are given in Table IX.

T A B L E IX.

Expt. No.	Conditions of Grignard reaction.	Yield of product.	
30	Reagent added over 7 minutes with	4.91g.	93%
31	cooling in ice. Mixture boiled	5.09g.	97%
32	under reflux for half an hour.	5.095g.	97%
33	Reagent added over 7 minutes, the solution being boiled under reflux throughout. Mixture boiled for a further $\frac{1}{2}$ hour before decomposition.	4.94g.	94%
34	Grignard reagent added over 10 mins. with cooling in ice. The mixture was kept at 0° for a further three hours before decomposition.	5.10g.	97%

Hydrolysis of the product was effected by boiling under reflux with 10.5 ml. of 10% aqueous KoH and 16 ml. of alcohol for three hours. After extraction of the menthol (see Section Va) the alkaline solution was acidified with 25% sulphuric acid and extracted with ether. The ethereal solution was dried over anhydrous sodium sulphate and evaporated.

Experiment 30. 2.78G. (88%) of a yellow oil were obtained, having $\alpha_{5461}^{25} = 0.08^\circ$ in alcohol ($\underline{l} = 2$, $\underline{c} = 13.90$).

The $\underline{\delta}$-lactone of the acid was prepared by evaporating the alcoholic solution from the polarimetric determination on a water bath. The residue was dissolved in 20 ml. of sodium-dried benzene, and the solution was evaporated on a water bath. The removal of benzene was completed _in vacuo_. A yellow solid (2.40g, 83%) was obtained, having

$$[\alpha]_{5461}^{25} = + 3.08^\circ \text{ in alcohol, } (\underline{l} = 2, \underline{c} = 12.0).$$

$$\frac{[\alpha]_{5461}}{[\alpha]_{5780}} = 1.12$$

Experiment 31. The end product (2.78g. 88%) was found to have $\alpha_{5461}^{25} = 0.08^\circ$ in alcohol ($\underline{l} = 2$, $\underline{c} = 13.90$). The lactone was isolated as before, 2.41g. (84%) being obtained, having $[\alpha]_{5461}^{25} = + 2.90^\circ$ in alcohol ($\underline{l} = 2$, $\underline{c} = 12.05$). $\frac{[\alpha]_{5461}}{[\alpha]_{5780}} = 1.13$

Experiment 32.   The ethereal solution of the end product
was evaporated, and sodium dried benzene
was added to the residue.   This solution was evaporated in
an attempt to prepare the lactone, but the product, an oil,
was obviously a mixture of acid and lactone 2.59G. (ca.89%)
were obtained, having $[\alpha]_{5461}^{25} = +1.66°$ in alcohol ($\underline{l} = 2$,
$\underline{c} = 12.95$).

The alcoholic solution of this product was evaporated,
with sodium dried benzene, and the lactone obtained
(2.41g., 84%) had $[\alpha]_{5461}^{25} = +2.80°$ in alcohol,
($\underline{l} = 2$, $\underline{c} = 12.05$). The alcoholic solution from this
polarimetric determination was cooled in a bath of CO_2/EtoH:
the white crystalline plates obtained were found to have
m.p. 73° - 74°.   A mixed melting point with $\underline{\delta}$-hydroxy-
$\underline{\delta}$-phenylhexanoic acid was 52° - 56°, and the crystals
were therefore presumed to be those of the $\underline{\delta}$-lactone,
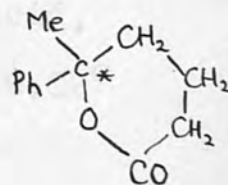
Experiment 33.   The end product was evaporated with
benzene and the residue was dissolved in
alcohol. The solution was cooled, and the first crop of
crystals (0.58g. m.p. 69°-71°) was found to be optically
inactive.

The second crop (0.83g., m.p. 65° - 67°) gave
$\alpha_{5461}^{25} = +0.05°$ in alcohol ($\underline{l} = 2$, $\underline{c} = 4.00$). The mother
liquor was evaporated, and the residue was found to have

$[\alpha]^{25}_{5461} = + 1.44°$ in alcohol ($\underline{1} = 2$, $\underline{c} = 4.50.$)

Experiment 34.   The end product was dissolved in sodium

dried benzene and the solution was

evaporated. 2.49G. (86%) of product (an oil) were obtained,

having $[\alpha]^{25}_{5461} = + 1.88°$ in alcohol ($\underline{1} = 2$, $\underline{c} = 12.45$).

The alcoholic solution was evaporated, and the residue was

evaporated with benzene. The lactone so obtained was

found to have $[\alpha]^{25}_{5461} = + 2.10°$ in alcohol ($\underline{1} = 2$, $\underline{c} = 11.25$),

and on repeating the evaporation of this product with

benzene, gave $[\alpha]^{25}_{5461} = + 2.10°$ in alcohol ($\underline{1} = 2$, $\underline{c} = 10.08$).

$$\frac{[\alpha]_{5461}}{[\alpha]_{5780}} = 1.135$$

The alcoholic solution was evaporated and the lactone was

dissolved in 10% aqueous NaOH. The alkaline solution was

acidified and 1.05g. of Y-hydroxy-Y-phenylhexanoic acid,

m.p. 77° - 79°, were obtained, having $\alpha^{25}_{5461} =$ $-0.02°$

in alcohol ($\underline{1} = 2$, $\underline{c} = 5.00$).

Details of these experiments are collected in

table X.

Experiment 35.   The end products from experiments 30,

31, 33 and 36 (see next section) were

combined and divided into three portions.

(1) 2.5G. of the combined products were found to have

$[\alpha]^{25}_{5461} = + 2.48°$ in alcohol ($\underline{1} = 2$, $\underline{c} = 12.50$). The

alcoholic solution was divided into two portions:

a) The alcohol was evaporated with a drop of dilute HCl. The product had $[\alpha]_{5461}^{25} = +0.57°$ in alcohol ($\underline{l} = 2$, $\underline{c} = 5.29$).

b) The alcoholic solution was evaporated, and the residue was evaporated with dry benzene. The residue, m.p. $55° - 62°$ gave $[\alpha]_{5461}^{25} = + 2.48°$ ($\underline{l} = 2$, $\underline{c} = 6.67$).

(2) 1.034 G. were dissolved in 10 ml. of 10% aqueous KoH by heating on a water bath for $1\frac{1}{2}$ hours. This solution was made up to 20 ml. at $25°$c, with water, and was found to have $\alpha_{5461}^{25} = + 0.02°$ ($\underline{l} = 2$).

The solution was acidified slowly and an acid (0.56g.) of m.p. $76° - 78°$ was obtained.

(3) Approximately 1.2 g. of product was dissolved in 10% aqueous KoH, and the solution was acidified slowly with 25% sulphuric acid. 1.14G. of acid, m.p. $76°-78°$ were precipitated, which, combined with the acid from (2) gave $\alpha_{5461}^{25} = -0.01°$ in alcohol ($\underline{l} = 2$, $\underline{c} = 8.435$).

Details of the yields of end products obtained, and of the specific rotations found in experiments, are collected in Table X. Yields can only be approximately calculated, as a mixture of acid and lactone was often present.

T A B L E   X.

Expt. No.	Approximate yield of end product.	Specific rotation of pure lactone isolated, $[\alpha]^{25}_{5461}$
30	88%	+ 3.0°
31	88%	+ 2.9°
32	89%	+ 2.8°
33	88%	Not isolated.
34	86%	+ 2.1°

II.   Using 2 mols. of Grignard reagent.

Experiment 36.   The reagent prepared from 0.742g. of magnesium, methyl bromide and 25 ml. of ether was added, with shaking, over 10 minutes, to a solution, cooled in ice, of 5g. of (−)-Menthyl-γ - benzoylbutyrate in 20 ml. of ether.   The mixture was boiled under reflux for half an hour and the product was decomposed with 20 g. of ice and 3 ml. of concentrated HCl. The product was isolated as previously described, (5.18g.98%) and smelt strongly of menthol.   Hydrolysis was effected with 10.5 ml. of 10% aqueous KoH and 16 ml. of alcohol, by boiling under reflux for three hours.   The end product was isolated as described in Section Va.   2.18 G. (69%) were obtained, having $\alpha_{5461}^{25} = +0.06°$ in alcohol ($\underline{1} = 2$, $\underline{c} = 10.40$).

The lactone was prepared as previously described and had $[\alpha]_{5461}^{25} = + 2.40°$ in alcohol ($\underline{1} = 2$, $\underline{c} = 9.15$).

$$\frac{[\alpha]_{5461}}{[\alpha]_{5780}} = 1.13$$

The alcoholic solution was evaporated and the residue was evaporated with benzene.   The lactone gave $[\alpha]_{5461}^{25} = + 2.40°$ ($\underline{1} = 2$, $\underline{c} = 8.85$) in alcohol, showing that conversion from acid into lactone had been completed at the first attempt. The ethereal extract after hydrolysis, in this experiment, was evaporated, and the residue steam distilled to remove

menthol. 0.36G. of neutral product (probably the dialcohol

$$Ph-\underset{\underset{OH}{|}}{\overset{\overset{Me}{|}}{C}}-(CH_2)_3-\underset{\underset{Me}{|}}{\overset{\overset{Me}{|}}{C}}-OH$$
were isolated as described in
Section Va.

Experiment 37.   In a second experiment performed under
similar conditions, 5.21 g. of ester
were obtained and after hydrolysis, the acid isolated was
evaporated with dry benzene four times. The product (1.92g)
was not solid, and had $[\alpha]_{5461}^{25} = + 1.51°$ in alcohol
($\underline{l} = 2$, $\underline{c} = 9.60$). The alcoholic solution was evaporated
and the residue again evaporated three times with benzene.
1.71 G. of lactone having $[\alpha]_{5461}^{25} = + 2.2°$ in alcohol
($\underline{l} = 2$, $\underline{c} = 8.55$) were obtained. On evaporation of this
solution and treatment of the residue with benzene the
lactone was found to have $[\alpha]_{5461}^{25} = + 2.2°$ in alcohol
($\underline{l} = 2$, $\underline{c} = 7.80$).

$$\frac{[\alpha]_{5461}}{[\alpha]_{5780}} = 1.13$$

The alcoholic solution was evaporated to 10 ml. and
was cooled in a CO_2/EtOH baths. The crystals, m.p. 70°-71°
obtained were dried $\underline{in\ vacuo}$ over $CaCl_2$/wax for 16 hours.
Analysis. Found. C, 75.5. H, 7.3.

$\quad\quad$ $C_{12}H_{14}O_2$ requires C, 75.8. H, 7.4.

Details of these two experiments are collected in Table XI.

T A B L E XI.

Expt. No.	Yield of dialcohol.	Yield of end product.	Specific rotation of pure lactone. $[\alpha]_{5461}^{25}$
36	11%	69%	2.40°
37	not isolated	67%	2.20°

Reaction between (-)-menthyl-γ-benzoylbutyrate and
ethyl magnesium bromide.

I. Using 1.5 mols. of Grignard reagent.

Experiment 38.   The reagent prepared from 0.557 g. of

magnesium, 2.5 g. of ethyl bromide and
25 ml. of ether was added, over 10 minutes, with shaking,
to a solution, cooled in ice, of 5g. of (-)-menthyl-γ-
benzoylbutyrate in 20 ml. of ether. The mixture was
boiled under reflux for half an hour before decomposition
with 15 g. of ice and 2.5 ml. of concentrated HCl. The

ester $Ph - \overset{Et}{\underset{OH}{\overset{*}{C}}} - (CH_2)_3 \cdot CO_2 \underset{(-)}{C_{10}H_{19}}$,   (5.16g.) was isolated

as previously described and hydrolysed by boiling under
reflux with 10.5 ml. of 10% aqueous KoH and 15 ml. of
alcohol for three hours.

The end product was isolated as usual and was converted
into the lactone by evaporation with benzene. 2.65G. (86%)
of an optically inactive oil were obtained. After repeated
evaporation with benzene, no optical activity could be
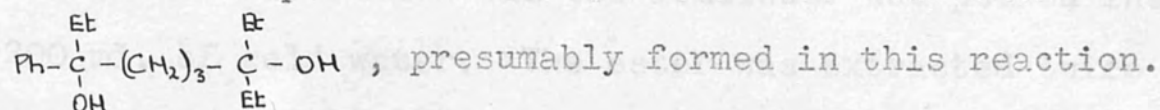detected in the product.

II. Using 2 mols. of Grignard reagent.

Experiment 39.   The Grignard reagent was prepared from

0.742g. of magnesium, 3.3g. of ethyl
bromide, and 25 ml. of ether. The reaction was carried
out under the same conditions as in I, and 5.15g. of
"ester" were isolated. The hydrolysis was carried out

Ethyl-γ-benzoylbutyrate.

as in the previous experiment and 2.55 g. (82.5%) of end
product were isolated. Since this product was found to
be optically inactive, the reaction was not further
investigated.

No attempt was made to isolate the dialcohol

$$Ph-\underset{\underset{OH}{|}}{\overset{\overset{Et}{|}}{C}}-(CH_2)_3-\underset{\underset{Et}{|}}{\overset{\overset{Et}{|}}{C}}-OH$$, presumably formed in this reaction.

Ethyl-γ-benzoylbutyrate.

γ-Benzoylbutyric acid (25 g.), concentrated sulphuric
acid (2.5 ml.) and absolute ethyl alcohol (25 g., 30 ml.)
were boiled together under reflux for three hours and
the mixture was kept overnight. The alcohol was distilled
off from a water bath and the remainder was poured into
200 ml. of cold water. The ester was extracted twice with
ether and the combined extracts were washed with 10% aqueous
Na_2CO_3 and water. The ethereal solution was dried over
anhydrous sodium sulphate and the ether was distilled off.
The crude ester was distilled in vacuo. Yield 23g. (80%).
b.p. 153°/5 mm. to 169°/7 mm. m.p. 26°.

dl-δ-hydroxy-δ-phenylhexanoic acid (1).

The Grignard reagent (1.5 mols.) prepared from 3.7g.
of magnesium, 17g. of methylbromide and 110 ml. of dry
ether was added, with stirring, over half an hour, to
a solution of 22g. (1 mol.) of ethyl-γ-benzoylbutyrate
in 100 ml. of ether. The reaction flask was cooled in ice,
and the mixture was stirred for a further ½ hour after
the addition of Grignard reagent was complete. The mixture
was then boiled under reflux for 15 minutes before
decomposition with 100 g. of ice and 20 ml. of concentrated

HCl. 40G. of ammonium chloride were added to facilitate

the decomposition of the Grignard complex.

The ethereal layer was separated and the aqueous

layer was extracted four times with ether. The combined.

ethereal extracts were washed with 10% aqueous Na_2CO_3

(some extraction took place here, and the sodium

carbonate solution was acidified with HCl and extracted

with ether). The ethereal solution was then washed with

water and dried over anhydrous sodium sulphate. The

ethereal solution was evaporated, and the residue (20g.)

was hydrolysed by boiling with 70 ml. of 10% aqueous

KoH and 40 ml. of alcohol for three hours. The alcohol

was evaporated off on a water bath and the alkaline

solution was extracted with ether to remove any neutral

products. The alkaline solution was slowly acidified with

25% sulphuric acid and the oil which precipitated and

solidified on standing was crystallised from benzene. Care

was taken to keep the temperature of the benzene solution

below 40° to avoid lactone formation. The crystalline

acid was dried in vacuo (yield 11g., 53%) and had m.p.

73°- 74°.

Analysis. Found: C, 68.8, H,7.4.

$C_{12}H_{16}O_3$ requires C, 69.2, H,7.7.

Ethyl- γ -acetylbutyrate.

γ-Acetylbutyric acid (50g) (available in the laboratory), ethyl alcohol (100 ml.) and concentrated sulphuric acid (10 ml.) were boiled together under reflux for 5 hours and the mixture was kept overnight. The alcohol was distilled off from a water bath and the residue was poured into 500 ml. of water. The ester separated as an oil which was extracted with ether. The ethereal solution was washed with 5% aqueous sodium carbonate to remove unchanged acid and dried over anhydrous sodium sulphate. The ethereal solution was evaporated and the crude ester distilled in vacuo.

Yield 45 g. (76%) b.p. $154^\circ - 5/98$ mm.

$$n_{18} = 1.4262.$$

dl- δ-hydroxy- δ-phenylhexanoic acid (2).

The procedure adopted was similar to that used
in the preparation of the acid from ethyl- γ-benzoyl-
butyrate. A solution of phenylmagnesium bromide prepared
from magnesium (28g.) bromobenzene (56g.) and dry ether
(200 ml.) was added, over one hour, with stirring to a
solution of ethyl- γ-acetylbutyrate (45g.) in 150 ml. of
ether, the reaction flask being cooled in ice. Stirring
was continued for a further hour and the mixture was then
decomposed with 300 g. of ice and 50 ml. of concentrated
HCl. The ethereal layer was separated and the aqueous
layer was extracted with ether. The ethereal solution was
washed with water and dried over sodium sulphate. The
crude ester (53g.) was hydrolysed by boiling under reflux
for three hours with 160 ml. of 10% aqueous KOH and 80 ml.
of alcohol. Much neutral product was obtained, this being
a liquid smelling of bromobenzene, suggesting that the
initial formation of the Grignard reagent had not been
complete. The neutral product was extracted with ether
and the alkaline solution was acidified with 25% sulphuric
acid. The crude acid was crystallised from a mixture of
benzene and light petroleum (b.p. 60° - 80°) Yield 20g. (30%)

m.p. 73° - 74°.

Attempted resolution of δ-hydroxy-δ-phenylhexanoic acid, using (-)-brucine.

Preliminary experiments.

1. 0.1g. of acid (1 mol.) and 0.224 g. of brucine $4H_2O$ (1 mol.) were warmed together in a solvent and left to crystallise.

	Solvent.	Result.
(i)	3 ml. of ethyl alcohol	No separation.
(ii)	2.5 ml. of acetone.	Some separation of "soft" crystals.
(iii)	9 ml. of water.	No separation.
(iv)	6 ml. of water.	No separation.
(v)	4 ml. of water.	Clusters of needles separated.
(vi)	8 ml. of methyl alcohol.	No separation.

Examination of (v).

0.12 g. of crystals m.p. 105° - 108° were obtained, having $[\alpha]_{5461}^{25}$ = -49.6° in chloroform,(l = 2, c = 0.5650).

1G. of acid and 2.24g. of (-)-brucine·$4H_2O$ were heated to boiling point in 40 ml. of water. The solution was filtered and kept at room temperature for 22 hours. 0.82 g. of needles, m.p. 105° - 109° were obtained, having $[\alpha]_{5461}^{25}$ = -42.3° in chloroform,(l = 2, c = 1.360).

The mother liquor was concentrated on a water bath under reduced pressure, and kept for a further 24 hours.

0.235 G. of crystals m.p. $106^\circ - 108^\circ$ were obtained, having $[\alpha]_{5461}^{25} = -45.2^\circ$ in chloroform, ($\underline{l} = 2$, $\underline{c} = 0.985$).

The mother liquor was evaporated to dryness on a water bath and an oil, setting to a glass was obtained. On heating this with 10 ml. of water, a solution was first obtained, which became cloudy on further heating. On cooling a clear solution was again formed, and crystals were then deposited.

CHART Ⅳ

ACID (8 G.) + BRUCINE (17·92 G.)

11·65 G.
m.p. 106°–108°
$[\alpha]^{25}_{5461} = -48\cdot2°$

1·84 G.
m.p. 105°–108°
$[\alpha]^{25}_{5461} = -50\cdot2°$

MIXED CRYSTALS.

8·37 G
m.p. 106°–108°
$[\alpha]^{25}_{5461} = -46\cdot8°$

5·93 G
m.p. 107°–110°
$[\alpha]^{25}_{5461} = -43\cdot4°$

1·08 G.
m.p. 106°–108°
$[\alpha]^{25}_{5461} = -46\cdot5°$

4·25 G
m.p. 108°–110°
$[\alpha]^{25}_{5461} = -43\cdot2°$

0·925 G.
m.p. 105°–108°
$[\alpha]^{25}_{5461} = -47\cdot2°$

[CONTAMINATED WITH BRUCINE.]

2·92 G.
m.p. 108°–110°
$[\alpha]^{25}_{5461} = -43\cdot1°$
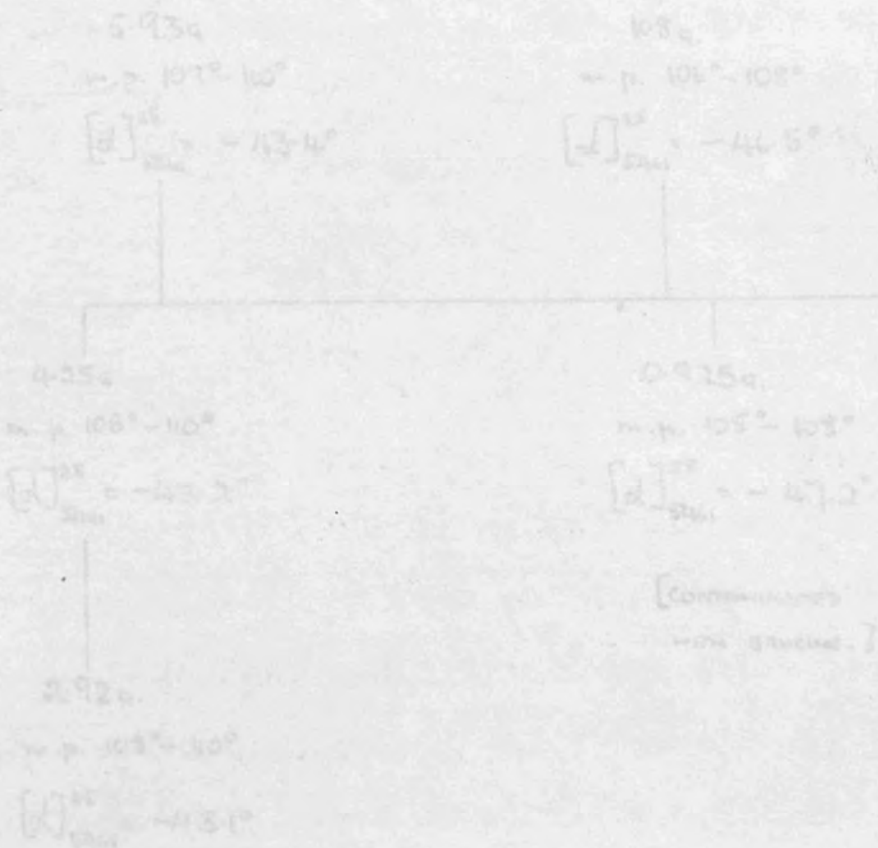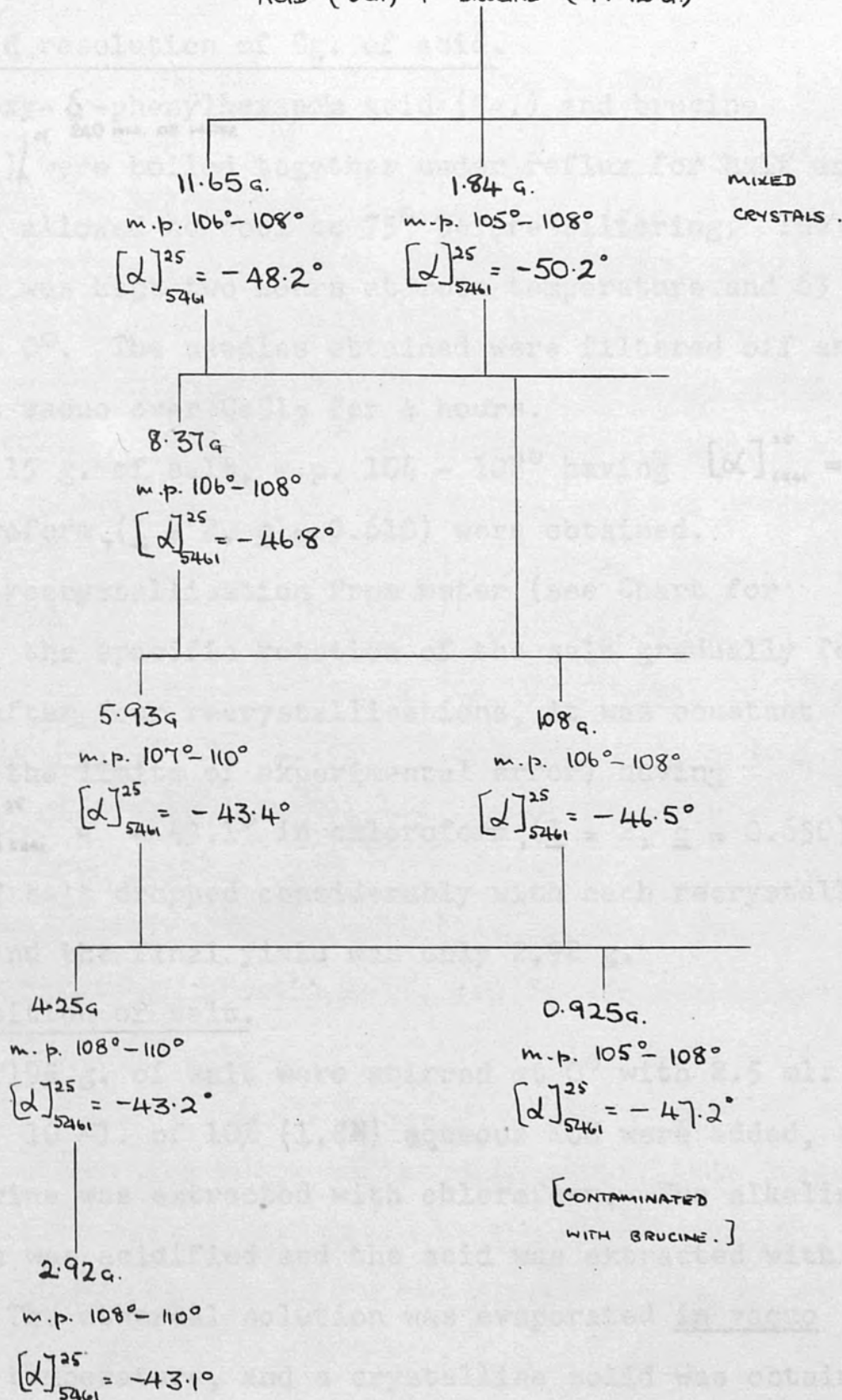
Attempted resolution of 8g. of acid.

δ-Hydroxy-δ-phenylhexanoic acid (8g.) and brucine
(17.92g.) IN 240 MLS. OF WATER were boiled together under reflux for half an
hour and allowed to cool to 75° before filtering. The
solution was kept two hours at room temperature and 63
hours at 0°. The needles obtained were filtered off and
dried in vacuo over $CaCl_2$ for 4 hours.

11.15 g. of salt, m.p. 104 - 108° having $[\alpha]_{5461}^{25} = -48.2°$
in chloroform,($\underline{1} = 2$, $\underline{c} = 0.610$) were obtained.

On recrystallisation from water (see Chart for
details) the specific rotation of the salt gradually fell
until, after four recrystallisations, it was constant
(within the limits of experimental error) having

$[\alpha]_{5461}^{25} = -43.1°$ in chloroform,($\underline{1} = 2$, $\underline{c} = 0.650$). The
yield of salt dropped considerably with each recrystallis-
ation, and the final yield was only 2.92 g.

Decomposition of salt.

2.7195 g. of salt were stirred at 0° with 2.5 ml. of
5N HCl. 10 Ml. of 10% (1.8N) aqueous KoH were added, and
the brucine was extracted with chloroform. The alkaline
solution was acidified and the acid was extracted with
ether. The ethereal solution was evaporated in vacuo
at room temperature, and a crystalline solid was obtained.
On further drying in vacuo, however, the product became
liquid, showing that conversion into lactone was t aking

place. Complete conversion into lactone was therefore effected by boiling the product in benzene solution on a water bath, finishing the removal of benzene *in vacuo*. The product (0.782g.) had $[\alpha]_{5461}^{25} = + 13.45^{\circ}$ in chloroform,($\underline{l} = 2$, $\underline{c} = 3.910$). The chloroform solution was evaporated, and the residue was evaporated with benzene as before. The residue, after drying *in vacuo* had $[\alpha]_{5461}^{25} = + 15.44^{\circ}$ in chloroform,($\underline{l} = 2$, $\underline{c} = 3.841$).

The solution was again evaporated, and the product evaporated with benzene. After drying, the lactone (0.758g) had $[\alpha]_{5461}^{25} = + 15.64^{\circ}$ in chloroform,($\underline{l} = 2$, $\underline{c} = 3.790$). On repeating the evaporation again, the product (0.739g.) had $[\alpha]_{5461}^{25} = + 15.67^{\circ}$ in chloroform,($\underline{l} = 2$, $\underline{c} = 3.695$) showing that complete conversion into lactone had probably taken place.

On evaporation of the mother liquor from the first crystallisation of brucine salt, brucine separated with the salt deposited, and, on further evaporation, rods were noticed among the crystals, in addition to the clusters of needles which characterised the first crops.

Since no stable salt could be isolated from the mother liquor, the resolution was not continued.

SECTION Ve.

δ-Benzoylvaleric acid.   (Hill. J. Amer. Chem. Soc. 1932,
4106).   Acetic anhydride (400 ml.) and adipic acid (146g.)
were boiled together under reflux for 6 hours. The acetic
acid and acetic anhydride were distilled in vacuo, and the
residue was dissolved in 400 ml. of warm benzene. Powdered
aluminium chloride (300g.) was mixed with sodium-dried
benzene (1600 ml.) in a 4l. flask fitted with reflux
condenser, stirrer and dropping funnel. The anhydride
solution was added over a period of one hour, with stirring,
and the mixture was boiled under reflux for two hours.
The product was poured into cracked ice (2 Kg.) and
concentrated HCl (300 ml.). The benzene layer was
separated and the δ-benzoylvaleric acid was extracted
with 1l. of N. NaOH solution. The alkaline solution was
cooled and acidified with 60% H_2SO_4. The precipitate
was filtered, dried and crystallised from a mixture of
benzene and light petroleum, b.p. 60° - 80°. Yield 25 g.
(24%). m.p. 76°.

The yield was increased to 39% when the reaction was
performed on a half-molar scale. A semicarbazone was
prepared and crystallised from aqueous alcohol m.p. 188°.
von Auwers and Trepmann. Ber., 48,1217. give m.p. 187°
Bauer. Ann.Chim. Phys. (IX) I, 394,gives m.p. 183.
Mlle. Grateau. Comptes rend. 1930, 949,gives m.p. 183°.

(-)-Menthyl-δ-benzoyl-n-valerate.

The preparation was carried out according to the general method (Section Va) and the ester was crystallised from ether cooled in a CO_2/EtOH bath. After four crystallisations the ester had m.p. 50°, and

$$\left[\alpha\right]_{5461}^{25} = -59.5^\circ \text{ in alcohol } (\underline{l} = 2, \underline{c} = 1.650).$$

$$\left[\alpha\right]_{5780}^{25} = -52.6^\circ$$

$$\frac{\left[\alpha\right]_{5461}}{\left[\alpha\right]_{5780}} = 1.130$$

Analysis: Found, C, 76.6, H, 9.3,

$C_{22}H_{32}O_3$ requires C, 76.7, H, 9.4. %

Reaction between (-)-menthyl- δ-benzoylvalerate and
methylmagnesium bromide.

I. Using 1¼ mols. of Grignard reagent.

Experiment 40.   The Grignard reagent prepared from 0.430g.

of magnesium, methyl bromide and 20 ml.
of ether was added over 10 minutes, with shaking, to a
solution, cooled in ice, of 5g. of (-)-menthyl- δ-benzoyl-
valerate in 20 ml. of ether. The mixture was boiled under
reflux for half an hour before decomposition with 30 g. of
ice and 2 ml. of concentrated HCl.

The product was isolated as described in Section Va.
4.91 G. of a yellow oil were obtained, and its hydrolysis
was effected by boiling under reflux for three hours with
10 ml. of 10% KoH and 15 ml. of alcohol. The acid
(3.08g, 97%) was isolated as an oil by the method described
in Section Va . It was examined polarimetrically in
alcoholic solution and found to be optically inactive.

Experiment 41.   In a second experiment, performed under
the same conditions, 5.2g. of (-)-menthyl-
ε-hydroxy- ε -phenyl heptanoate were obtained, giving,
after hydrolysis, 3.1g. (97%) of a yellow oily acid, which
was optically inactive.

II. Using 2 mols. of Grignard reagent.

Experiment 42.   The Grignard reagent prepared from 0.70 g.
of magnesium, methyl bromide and 25 ml. of
ether was added, over 10 minutes, with cooling in ice, to a
solution of 5g. of (±)-menthyl- δ -benzoylvalerate in 20 ml.
of ether. The mixture was boiled under reflux for half an
hour, before decomposition with 20 g. of ice and 3 ml. of
concentrated HCl. The product was isolated as usual
(5.15g.) and was hydrolysed by boiling under reflux for
three hours with 10 ml. of 10% aqueous KOH and 15 ml. of
alcohol. The acid was isolated as described in Section Va.
2.20 G. (69%) of a yellow oil were obtained, having

$\alpha_{5461}^{25} = +0.08^{\circ}$ in alcohol ($\underline{1} = 2$, $\underline{c} = 11.0$).

Experiment 43.   In a second experiment the Grignard
reagent (2 mols.) was added to the ester
solution over 5 minutes, and the reaction mixture was
boiled under reflux for half an hour before decomposition
and isolation of the product. 5.25 G. of product were
obtained, giving, after hydrolysis, 2.30 g. (72%) of an
optically inactive acid. 0.535 G. (16%) of the dialcohol

$$Ph - \underset{OH}{\overset{Me}{\underset{|}{\overset{|}{C}}}} - (CH_2)_4 - \underset{Me}{\overset{Me}{\underset{|}{\overset{|}{C}}}} - OH$$

were isolated from the

ethereal extract after hydrolysis, as described in Section Va.

III Using 4 mols, of Grignard reagent.

Experiment 44.   The Grignard reagent prepared from 1.41g.

of magnesium, methyl bromide and 40 ml. of
ether was added over 15 minutes, with shaking, to a
solution, cooled in ice, of 5g. of (±)-menthyl-δ-benzoyl-
valerate in 20 ml. of ether. The mixture was boiled under
reflux for half an hour before decomposition with 20g. of
ice and 25 ml. of dilute (25%) hydrochloric acid. The
reaction product was isolated as previously described.
5.445 G. of a yellow oil was obtained, smelling strongly
of menthol. This was hydrolysed by boiling under reflux
with 10 ml. of 10% aqueous KoH and 15 ml. of alcohol for
three hours. The acid was isolated in the usual manner.
1.375 G. were obtained, and this product was found to be
optically inactive in alcoholic solution.

Reaction between (-)-menthyl-δ-benzoylvalerate and
ethyl magnesium bromide.

I. Using 1¼ mols. of Grignard reagent.

Experiment 45.   The Grignard reagent prepared from

0.43 g. of magnesium, 2g. of ethyl
bromide and 20 ml. of ether was added, with shaking,
over 10 minutes, to a solution, cooled in ice, of 5g. of
(±)-menthyl-δ-benzoylvalerate in 20 ml. of ether. The
mixture was boiled under reflux for two hours before
decomposition with 15 g. of ice and 25 ml. of dilute (25%)

HCl. The reaction product was isolated as described in Section Va, (Yield 5.16g) and was hydrolysed by boiling under reflux for three hours with 10 ml. of 10% aqueous KoH and 15 ml. of alcohol. The acid was isolated as usual (2.91 g, 90%) and was found to be optically inactive.

II. Using 2 mols of Grignard reagent.

Experiment 46. The Grignard reagent prepared from 0.706g. of magnesium, 3.25 g. of ethyl bromide and 25 ml. of ether was added, over 10 minutes, to a solution, cooled in ice of 5g. of ($\pm$)-menthyl-δ-benzoylvalerate in 20 ml. of ether. The reaction mixture was boiled under reflux for half an hour before decomposition with 20 g. of ice and 3 ml. of concentrated HCl. The product was isolated as previously described and smelt slightly of menthol. 5.29 G. were obtained, and hydrolysis was carried out with 10 ml. of 10% aqueous KoH and 15 ml. of alcohol by boiling for three hours. The acid was isolated as before.

2.57 G. (79%) of acid were obtained, having $\alpha_{5461}^{25} = - 0.03°$ in alcohol ($\underline{l}$ = 2, $\underline{c}$ = 12.85).

The dialcohol was not isolated in this experiment, and since no appreciable evidence of asymmetric synthesis was obtained using this ester, no further investigation of this reaction was carried out.

Details of the Grignard reactions carried out on ($\pm$)-menthyl-δ-benzoylvalerate are collected in Table XII.

T A B L E   XII.

Expt. No.	Grignard reagent	Yield of product in g.	Yield of acid in g.	in %
40	1¼ mols.	4.91	3.08	97
41	MeMgBr.	5.20	3.10	98
42	2 mols.	5.15	2.20	69
43	MeMgBr	5.25	2.30	72
44	4 mols. MeMgBr	5.44(5)	1.375	43
45	1¼ mols. EtMgBr	5.16	2.91	90
46	2 mols. EtMgBr.	5.29	2.57	79

S E C T I O N   Vf.

<u>ω-Benzoyl-pelargonic acid</u>.(Hill,J. Amer. Chem. Soc. 1930, 4105)

Sebacic acid (101 g.) and acetic anhydride (300 ml.) were boiled together under reflux for 5 hours. The mixture was allowed to cool to 75° and was distilled <u>in vacuo</u> from an oil bath, the temperature being slowly raised to 125°. The residue was dissolved in 250 ml. of warm benzene.

Crushed aluminium chloride (50 g.) and 750 ml. of dry benzene were placed in a 2l. flask fitted with stirrer, reflux condenser and dropping funnel. The solution of sebacic polyanhydride was added over a period of 1 hour, with stirring. The mixture was then heated on a water bath for 2 hours with stirring, before decomposition with 1 Kg. of cracked ice and 150 ml. of concentrated HCl. A large quantity of solid, identified as sebacic acid, separated out at this stage and was filtered off. The benzene layer was separated, washed with water and extracted with 750 ml. of 3% caustic soda solution. The alkaline solution was cooled in ice and acidified with 25% sulphuric acid. The precipitate was boiled with two successive portions of 200 ml. of water to remove sebacic acid and the crude <u>ω</u>-benzoylpelargonic acid was crystallised from aqueous alcohol. Yield 20 g. (15%)

<u>Diethyl sebacate</u>. (Organic Syntheses II, 277).

Sebacic acid (130 g.), ethyl alcohol (250 g.) and

concentrated sulphuric acid (25 ml.) were boiled under
reflux for seven hours and the mixture was kept overnight.
The alcohol was distilled off from a water bath and the
residue was poured into 500 ml. of water. 200 Ml. of
ether were added and the layers were separated. The
ethereal layer was washed with 10% aqueous Na_2CO_3 and
water, and dried over anhydrous sodium sulphate. The
ether was distilled off, and the residue was distilled
in vacuo.

Yield 150 g. (90%). b.p. 170° / 7mm.

Ethyl hydrogen sebacate.

Sebacic acid (115g.), diethyl sebacate (83g.),
concentrated HCl (14 ml.) and di-n-butyl ether (28 ml.)
were heated together under reflux in a metal bath at
160° - 170° until a homogeneous solution was obtained.
The bath was then allowed to cool to 120°-130° and
alcohol (34 ml.) was added through the condenser. The
mixture was boiled under reflux for two hours when a
further 11.5 ml. of ethyl alcohol was added and the
mixture was boiled for another two hours. The mixture
was allowed to cool to 75° and was distilled at 30 mm.
to remove alcohol, water and di-n-butyl ether, the
temperature of the bath being slowly raised to 125°. The
pressure was lowered to 6-7 mm. and the diethyl sebacate
and ethyl hydrogen sebacate were distilled. The distillation

proceeded more smoothly than in the analogous preparation
of ethyl hydrogen adipate.

Yield 75g. (65%) b.p. 186° / 6 mm.

Sebacic ethyl ester-chloride: $(CH_2)_8 \begin{smallmatrix} CO_2Et \\ COCl \end{smallmatrix}$

Ethyl hydrogen sebacate (68g.) and thionyl chloride
(68g.) were heated together on a water bath until the
evolution of hydrogen chloride ceased (about $1\frac{1}{2}$ hours.).
The excess thionyl chloride was distilled from a water
bath under reduced pressure, and the crude sebacic
ethyl-ester-chloride was distilled in vacuo.

Yield 65g. (89%) b.p. 165° / 10 mm.

Papa, Schwenk and Hankin, J.Amer. Chem. Soc. 1947, 3018.
give b.p. 145° / 5 mm.

Ruzicka and Stoll. Helv. Chim. Acta. 1927, 10, 693 give
b.p. 168° - 170°/18 mm.

Ethyl ω-benzoylpelargonate and ω-benzoylpelargonic acid,
Ph. CO. $(CH_2)_8$. CO_2H.

Crushed aluminium chloride (75 g.) and benzene (400 ml.)
were placed in a 2l. flask fitted with reflux condenser,
mechanical stirrer and dropping funnel. A solution of
sebacic ethyl ester-chloride (62g.) in 100 ml. of benzene
was slowly added, with stirring, over a period of $\frac{3}{4}$ hour.
Stirring was continued for two hours and the mixture was
kept at room temperature overnight. The solution was
then poured onto 400g. of cracked ice and 60 ml. of

concentrated HCl. The benzene layer was separated and
the aqueous layer was extracted three times with benzene.
The benzene extracts were washed with 5% aqueous NaOH to
remove any sebacic acid or unchanged ester-chloride, and
then with water. The benzene solution was dried over
sodium sulphate and the benzene was distilled off. The
crude ethyl-ω-benzoylpelargonate was hydrolysed with
200 ml. of 10% aqueous KoH and 100 ml. of alcohol by
boiling under reflux for three hours.

Yield (crude) 60g. (92%). The acid was recrystallised
from a mixture of benzene and light petroleum b.p.
60° - 80°. m.p. 83°.

A semicarbazone m.p. 153° was prepared.

ω-Benzoylpelargonic acid, using the method of Papa,
Schwenk and Hankin, J.Amer. Chem. Soc. 1947, 3018.

A solution of sebacic ethylester-chloride (29g.) in
benzene (50 ml.) was added to a mixture of crushed
aluminium chloride (37 g.) in benzene (200 ml.) as in
the previous experiment, and the mixture was boiled under
reflux for half an hour. The mixture was then decomposed
and extracted as before. The combined benzene extracts
were extracted with 5% aqueous NaOH and the alkaline
solution was acidified with 25% sulphuric acid. The
impure ω-benzoylpelargonic acid (30 g. 98%) was
recrystallised from benzene-petroleum b.p. 60° - 80°.

On evaporation of the benzene solution only a small residue was obtained, which remained insoluble in alcoholic caustic soda after boiling under reflux for six hours, and was presumably dibenzoyl octane.

(-)-Menthyl-ω-benzoylpelargonate (from acid obtained by Hill's method).

The ester was prepared according to the general method (Section Va) and after steam distillation, the crude ester, which would not solidify, was extracted with ether. The ethereal solution was dried and evaporated, and the residue was distilled in vacuo.

Some menthol distilled at first, and after this distillation had ceased, the condenser and receivers were changed.

Wt. of acid used.	Distillation.	Yield.	Specific rotation.
10g.	I. b.p. 240°-260° 18 mm. (Solid - sebacic acid)	0.69g.	
	II. b.p. 260°-265°/8mm (Solid and liquid).	6.27g.	
	III. b.p. 270°-275°/8mm. (Liquid, later solid-ifying). Crystallised from EtOH, had m.p. 35°.	1.55g.	$[\alpha]_{5461}^{25} = -51.7°$ in chloroform (l = 2, c =1.645).

Wt. of acid used	Distillation	Yield	Specific Rotation.
35g.	I. b.p. Up to 256°/4mm.		
	II. b.p. 256°-258°/4mm. 262°/5 mm. 2.66°/6 mm.	21g.	$[\alpha]_{5461}^{25} = -50.0°$, in chloroform. ($\underline{1} = 2$, $\underline{c} = 3.335$)

(-)-<u>Menthyl</u> ω-<u>benzoylpelargonate</u> from pure ω-benzoyl pelargonic acid.

The preparation was carried out according to the general method (Section Va).

	Wt. of acid used.	Yield (crude).	
a.	20 g.	24g.	79%
b.	65 g.	65g.	65%

In experiment **a** , the crude ester was distilled <u>in vacuo.</u> Fraction I. b.p. 238°/1.5mm - 253° /2mm.

II. b.p. 253-254° /2mm.

III. b.p. 254°-258° /2mm.

Fraction II redistilled: IV up to 250°/1.5 mm.

V 250°/1.5 mm.

Fractions III and V combined gave $[\alpha]_{5461}^{25} = -50.62°$ in chloroform ($\underline{1} = 2$, $\underline{c} = 2.123$), $[\alpha]_{5461}^{25} = -51.25°$ in alcohol ($\underline{1} = 2$, $\underline{c} = 1.975$).

Recrystallised from alcohol, the ester had m.p. 37° - 38°, and $[\alpha]_{5461}^{25} = -51.00°$ in alcohol ($\underline{1} = 2$, $\underline{c} = 2.255$).

$$\frac{[\alpha]_{5461}^{25}}{[\alpha]_{5780}^{25}} = 1.140.$$

Analysis. Found. C, 78.0, H, 10.4.

$C_{26}H_{40}O_3$ requires C, 78.0, H, 10.1.

In experiment b , the crude ester was crystallised from alcohol. After four recrystallisations the ester had m.p. 37-38° and $[\alpha]_{5461}^{25} = -51.05°$ in alcohol ($\underline{1} = 2$, $\underline{c} = 2.145$).

The menthol obtained from the steam distillation did not solidify, indicating that it was not pure. It seems probable that some $(\underline{-})$-menthyl-$\underline{\omega}$-benzoyl pelargonate steam distilled, and this may account for the low yield (65% crude) obtained.

Reaction between (-)-menthyl-ω-benzoylpelargonate
and methyl magnesium bromide.

I. Using 1¼ mols. of Grignard reagent.

Experiment 47.   The Grignard reagent prepared from
0.380g. of magnesium, methyl bromide
and 20 ml. of ether was added, with shaking, over seven
minutes, to a solution, cooled in ice, of 5g. of
(±)-menthyl-ω-benzoylpelargonate in 20 ml. of ether.
The mixture was boiled under reflux for half an hour
and was decomposed with 15 g. of ice and 2 ml. of
concentrated hydrochloric acid. The reaction product
(4.89 g., 94%) was isolated as described in Section Va
and hydrolysed by boiling under reflux for four hours
with 9 ml. of 10% aqueous KoH (1¼ mols) and 18.5 ml. of
alcohol. A longer reflux time was allowed as the
hydrolysis appeared to take place more slowly than with
the esters previously investigated.

The ω-hydroxy-ω-phenyl-n-undecenoic acid was isolated
as described in Section Va   , and was obtained as a
yellow oil. Yield 2.53g (73%).

$$\alpha_{5461}^{25} = -0.02^{\circ} \text{ in alcohol } (1 = 2, c = 12.65).$$

$$\alpha_{5780}^{25} = -0.02^{\circ}.$$

Experiment 48.   In a second experiment carried out

under the same conditions, 4.95g. (95%)

of hydroxy-ester was obtained, giving, after hydrolysis,

2.375 (70%) of ω-hydroxy-ω-phenyl ~~capric~~ hexanoic acid, having

α_{5461}^{25} = -0.01° in alcohol ($\underline{1}$ = 2, $\underline{c}$ = 11.875).

The combined alcoholic solutions of the acid

from these two experiments were evaporated, and a

small quantity of white solid was observed in the

residue. This was isolated and found to have m.p.

80° - 81°. A mixed melting point (80° - 82°) with an

authentic specimen identified it as ω-benzoylpelargonic

acid and reactions were therefore carried out using

2 mols. of Grignard reagent, to obtain complete reaction

at the carbonyl group.

II. Using 2 mols. of Grignard reagent.

The Grignard reagent prepared from 0.608 g. of

magnesium, methyl bromide and 25 ml. of ether was added,

with shaking, over 10 minutes, to a solution, cooled in

ice, of 5g. of ($\pm$)-menthyl-ω-benzoyl pelargonate in 20 ml.

of ether. The reaction mixture was boiled under reflux

for half an hour before decomposition with 20g. of ice

and 3 ml. of concentrated HCl. The reaction product was

isolated as described in Section Va , and was found to

smell strongly of menthol.

This product was hydrolysed by boiling under reflux for 3½ hours with 10 ml. of 10% aqueous KoH and 15 ml. of alcohol. The acid was isolated as previously described and was examined polarimetrically in alcoholic solution. Three reactions were carried out under these conditions, details of which are given in Table XIII. In each case the acid was found to be optically inactive.

TABLE   XIII.

Expt. No.	Wt. of product of Grignard reaction in g.	Wt. of ο-hydroxy-ο-phenyl-undecenoic acid in g.
49	5.06	2.05
50	5.06	2.04
51	5.04	2.02

The average yield of acid obtained (2.04 g.) was 59% of the theoretical yield.

The ethereal extracts after hydrolysis of menthol and neutral products of the above experiments were combined, and the dialcohol $Ph - \underset{\underset{OH}{|}}{\overset{\overset{Me}{|}}{C}} - (CH_2)_8 - \underset{\underset{Me}{|}}{\overset{\overset{Me}{|}}{C}} - OH$ was isolated as described in Section Va. 2.4 G. of product were obtained, which corresponds to an average yield of 21% in each reaction.

The alcoholic solutions of the acid from these experiments were combined and evaporated on a water bath.

The residue was dried <u>in vacuo</u>, and the ө-hydroxy-ө-
phenylundecenoic acid, which had hitherto been obtained
as a yellow oil, was finally crystallised from a mixture of
benzene and light petroleum b.p. $60^{\circ} - 80^{\circ}$. A white
crystalline solid, m.p. $61^{\circ} - 62^{\circ}$ was obtained.
Analysis: Found. C, 73.5, H, 9.0.

$C_{17}H_{26}O_3$ requires C, 73.4, H, 9.4. %

Reaction between (-)-menthyl-ω-benzoylpelargonate and
ethyl magnesium bromide.

I.   Using 1½ mols. of Grignard reagent.

Experiment 52. The Grignard reagent prepared from 0.456 g. of
                    magnesium, 2.1g of ethyl bromide and 20 ml.
of ether was added over 10 minutes, with shaking, to a
solution, cooled in ice, of 5g. of (-)-menthyl-ω-benzoyl
pelargonate in 20 ml. of ether. The mixture was kept at
room temperature for 15 hours before decomposition with
15 g. of ice and 2 ml. of concentrated HCl. The reaction
product was isolated as usual.

    The product (5.19 g., 96.5%) was hydrolysed by
boiling under reflux for 8 hours with 20 ml. of 10%
aqueous KoH and 25 ml. of alcohol. The longer reaction
time was allowed and the large excess of alcoholic potash
used because the hydrolysis appeared to take place slowly,
and it was essential that it should be completed.

    The ɵ-hydroxy-ɵ-phenyl-lauric acid was isolated in
the usual manner. 2.895 G. (83%) were obtained, having

$$\alpha_{5461}^{25} = -0.05° \text{ in alcohol,}$$

$$\alpha_{5780}^{25} = -0.04° \quad (\underline{1} = 2, \underline{c} = 14.475).$$

II.   Using 2 mols. of Grignard reagent.

Experiment 53.   The Grignard reagent prepared from 0.608 g.

of magnesium, 2.80 g. of ethyl bromide

and 25 ml. of ether was added, with shaking, over 10 minutes,

to a solution, cooled in ice, of 5 g. of (−)-menthyl-ω-

benzoylpelargonate in 20 ml. of ether.   The mixture was

boiled under reflux for half an hour before decomposition

with 20 g. of ice and 3 ml. of concentrated HCl.

The product was isolated as described in Section Ⅳₐand

smelt strongly of menthol.   5.35 G. were obtained, and

were hydrolysed by boiling under reflux with 6 ml. of

20% KoH and 10 ml. of alcohol for three hours.   The acid

was isolated in the usual manner.   2.625 G. (75%) were

obtained, having α_{5461}^{25} =   − 0.05° in alcohol

(l = 2, c = 13.125).

The dialcohol was not isolated from this experiment,

and the reaction was not further investigated.

Acknowledgments.