STUDIES IN ASYMMETRIC SYNTHESIS

(Abstract of thesis submitted by J.A. Reid for degree of Ph. D.)

It has been shown by McKenzie and his school that when optically active esters of α-keto-acids ($R.CO.CO_2R^*$) and a Grignard reagent ($R'MgX$) interact the diastereo-isomerides [$R.CR'(OMgX).CO_2R^*$] are produced in unequal amounts. The substituted glycollic acids, obtained by hydrolysis, were optically active, although not optically pure. The analogous reactions using optically active esters of γ-, δ-, ε- ..... keto-acids had virtually not been studied.

In the present investigation the interaction of (-)-menthyl esters of ω-acetyl fatty acids [$CH_3.CO.(CH_2)_n.CO_2C_{10}H_{19}$ (-)] and phenyl magnesium bromide has been studied with a view to obtaining asymmetric synthesis and to relating this to the length of the chain intervening between the carbonyl and carbomenthoxy groups.

The investigation has entailed the preparation of the above type of esters when n = 0, 2, 3, 4 and 8, and their treatment with phenyl magnesium bromide. The hydroxy-acids or (with n = 2 and 3) lactones, obtained after hydrolysis of the resulting esters, were optically

active, except in the case of n = 8. With n = 2 or 3, the degree of asymmetric synthesis was dependent on reaction conditions.

The addition of a Grignard reagent to a carbonyl group has previously been found to occur asymmetrically only when the carbonyl group is in a molecule containing a "fixed centre of asymmetry". It has now been found that an asymmetric reaction occurs when an optically active organo-metallic compound adds to a ketone. This type of reaction has been studied using (-)-menthyl bromoacetate, acetophenone and zinc. The β-hydroxy acid obtained on hydrolysis was optically active. The extent of the asymmetric synthesis was found to be remarkably constant, irrespective of a wide variation in reaction conditions.

Theories of asymmetric synthesis are discussed and a theory involving energy differences of two transition states is proposed as an explanation of the results obtained in this investigation.

(±)-γ-Hydroxy-γ-phenyl-n-valeric acid (n = 2) has been prepared and resolved.

14th February, 1950.

Joan Reid.

STUDIES IN ASYMMETRIC SYNTHESIS

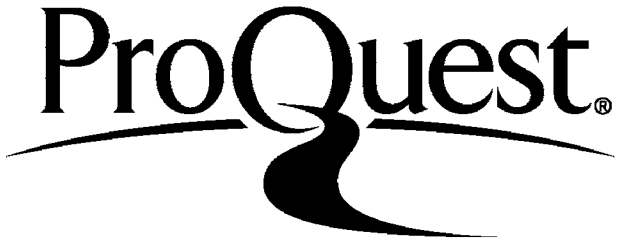
by

Joan A. Reid, B. Sc. (London)

Thesis submitted to the University of London for the Degree of Doctor of Philosophy

Chemistry Department
Bedford College for Women,
(University of London),
London,
N.W. 1.

February, 1950.



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ACKNOWLEDGEMENTS

I express my sincere thanks to Professor E.E. Turner, F.R.S., for his interest and advice in connection with this investigation.

I am indebted to Mr. F. Robinson for photographing the diagram of the Grignard reaction Apparatus.

The work was carried out during the tenure of an assistantship, which was made available to Professor Turner by the Department of Scientific and Industrial Research. I am grateful to them for permission to incorporate this work in a Ph. D. Thesis. Prior to holding the assistantship I received a training grant, from Hertfordshire County Council, which I gratefully acknowledge.

GENERAL NOTES

1. Analyses were carried out by Drs. Weiler and Strauss.
2. M.p.s. are uncorrected.
3. Solutions prepared for polarimetric use were ethanolic unless otherwise stated. If no concentration is mentioned measurements were made on the homogeneous undiluted liquid.
4. Rotations of solutions were measured in an all-glass water-jacketed tube at 25 $\pm$0·1°; the length being 2 dm. unless otherwise stated.
5. Rotations of homogeneous undiluted liquids were measured without temperature control and in an all-glass tube, the length being $\frac{1}{2}$ dm., unless otherwise stated.
6. Where relevant the errors, incurred during measurements of the rotatory power, are indicated. The error involved in determination of rotatory power of homogeneous liquids was $\pm$ 0.01°.

I. INTRODUCTION

Ia. Definition of asymmetric synthesis

The idea of asymmetric synthesis (as we understand it today) was first discussed by Fischer (1894). Having observed that, during the synthesis of manno-heptose from (+)-mannose, only one of the possible diastereoisomerides was formed, he suggested that an optically active glyceraldehyde should be formed by the fission of a manno-nonose, prepared by repeated cyanohydrin reactions on (+)-mannose and the subsequent products. The fission products should consist of the original mannose together with the optically active glyceraldehyde.

The first asymmetric synthesis actually put to the test of experiment was attempted by Fischer (1901) using the following series of reactions (similar to those suggested in his earlier publication):-

$$CHO.(\overset{*}{C}HOH)_4.CH_2.O.C_6H_4.CHO \longrightarrow CHO.(\overset{*}{C}HOH)_4.CH_2.O.C_6H_4.\overset{*}{C}H\begin{matrix}OH\\CN\end{matrix}$$

(not accomplished)

$$CHO.(\overset{*}{C}HOH)_4.CH_2OH \quad + \quad HO.C_6H_4.\overset{*}{C}H\begin{matrix}OH\\CN\end{matrix}$$

(where $\overset{*}{C}$ = asymmetric carbon atom).

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Marckwald (1904) claimed to have accomplished the first asymmetric synthesis after many other workers had failed. Marckwald carried out the decarboxylation of the half-brucine

salt of methylethylmalonic acid and obtained methylethylacetic (isovaleric) acid which contained a preponderance of the (-)-antipode. This led Marckwald to formulate the first precise definition of an asymmetric synthesis, viz., a synthesis which yields an optically active product from symmetrical substances with the aid of optically active substances as intermediates, but with no processes of fractionation involved. It is obvious that Fischer had this same concept of what constituted an asymmetric synthesis, since he classified only the hypothetical formation of the glyceraldehyde as an asymmetric synthesis and did not include the formation of the manno-heptose from (+)-mannose.

In the year in which Marckwald claimed the first asymmetric synthesis, McKenzie (1904) began an investigation into asymmetric syntheses using optically active esters of α-keto acids as starting materials. Products exhibiting optical activity were obtained both by reduction of such esters as (-)-menthyl pyruvate and subsequent hydrolysis, and by the Grignard reaction on similar esters. This work will be reviewed more fully later in this Section with special reference to the present investigation.

Ib. Total Asymmetric Synthesis

The type of asymmetric synthesis which has been described above is known as a partial asymmetric synthesis. van't Hoff had thought it possible that an optically active substance

might be formed from symmetrical compounds under the effect of an unsymmetrical physical force. This was not realized in the laboratory until Kuhn and co-workers (1929,1930) effected a photo-chemical decomposition by means of (+)- and (-)-circularly polarised light. An absolute asymmetric synthesis was claimed by Karagunis and Drikos (1933), who influenced the course of the reaction between chlorine and triaryl methyl by circularly polarised light; the degree of asymmetric synthesis was extremely small, as in other absolute asymmetric syntheses so far claimed.

Ic. Asymmetric syntheses involving Grignard Reagents

As will be discussed later, the primary interest in this investigation was the study of asymmetric syntheses resulting from the addition of an organo-metallic compound, such as a Grignard reagent, to a carbonyl group. Thus, it is necessary to review asymmetric syntheses, and relevant related observations, which have some bearing on this type of reaction.

First to be considered will be experiments carried out by McKenzie and co-workers using optically active esters of α-keto acids and Grignard reagents (see Table). The type of reaction involved is

$$R.CO.CO_2R^{\pm} + R'MgX \longrightarrow R.C(OH)R'.CO_2R^{\pm} \longrightarrow \underset{\text{(excess of one antipode)}}{R.C(OH)R'.CO_2H}$$

where $R^{\pm}$ is an optically active alcohol radical.

In the experiments outlined above, the glycollic acid

Interaction of α-keto esters and Grignard reagents (McKenzie et al)

Ester	R' (where R'MgX used)	Sign* of product	Reference
(-)-menthyl pyruvate	Me	None	McK. (1906)
	Et	+(salt)	McK. (1906)
	isobutyl	+(salt)	McK. and Wren (1906)
	Ph	+	McK. (1906)
	α-naphthyl	+(salt)	McK. and Wren (1906)
	p-tolyl	+	McK. and Christie (1935)
	p-anisyl	+	McK. and Ritchie (1932)
(-)-menthyl benzoylformate	Me	-	McK. (1904) and McK. (1906)
	Et	-	McK. (1904)
	isobutyl	-	McK. (1906)
	tert-butyl	-	McK. (1906)
	propyl	-	McK. (1906)
	Ph	None	McK. (1904)
	a-naphthyl	-	McK. (1906)
	p-tolyl	-	McK. and Christie (1935)
(-)-menthyl α-naphthoylformate	Me	-	McK. and Ritchie (1931a)
	Et	-	McK. and Ritchie (1931a)
	Ph	-	McK. and Ritchie (1931a)
(-)-menthyl p-anisoylformate	Me	-	McK. and Ritchie (1932)
(-)-menthyl p-toluylformate	Me	-	McK. and Christie (1935)
	Ph	+	McK. and Christie (1935)
(-)-bornyl pyruvate	Et	+	McK. and Wren (1906)
	isobutyl	+(salt)	McK. and Wren (1906)
	Ph	+(salt)	McK. and Wren (1906)
	α-naphthyl	-(salt)	McK. and Wren (1906)
	p-tolyl	None	McK. and Christie (1935)
(-)-bornyl benzoylformate	Me	-	McK. (1906)
	Et	-	McK. (1906)
	isobutyl	+(?)	cf. text
	α-naphthyl	+(salt)	McK. (1906a)
	p-tolyl	+	McK. and Christie (1935)

ctd.

ctd.

Ester	R' (where R'MgX used)	Sign* of product	Reference
(-)-bornyl α-naphthoylformate	Me	-	McK. and Ritchie (1931a)
(-)-bornyl p-toluylformate	Me	-	McK. and Christie (1935)
	Ph	-	McK. abd Christie (1935)
(+)-bornyl benzoylformate	Et	+/	(cf. text)
(-)-β-octyl pyruvate	Ph	+	McK. and Ritchie (1931b)
(-)-β-octyl benzoylformate	Me	-	McK. and Ritchie (1931b)
(+)-β-octyl pyruvate	α-naphthyl	-	McK. and Ritchie (1931b)
(+)-β-octyl benzoylformate	α-naphthyl	-	McK. and Ritchie (1931b)
(+)-amyl pyruvate	Et	+(Small)	McK. and Müller (1909)
	Ph	None	McK. and Müller (1909)
	α-naphthyl	None	McK. and Müller (1909)
(+)-amyl benzoylformate	Me	+	McK. and Müller (1909)
	Et	+	McK. and Müller (1909)
	α-naphthyl	+	McK. and Müller (1909)

Footnote * (± (salt) indicates sign of rotation of barium salt.
(± indicates sign of rotation of free acid.

(/ solution of acid +; but
(sign of α of solution of K salt varied with concentration.

obtained direct from the reaction mixture was far from optically pure. In most cases, on crystallisation, this product yielded a racemic glycollic acid. However, methylanisylglycollic acid, obtained by the action of MeMgI on (-)-menthyl anisoylformate or of anisyl MgBr on (-)-menthyl pyruvate, was obtained optically pure by subsequent repeated recrystallisation from benzene. Also, methyl p-tolylglycollic acid, prepared from (-)-menthyl p-toluylformate, was obtained in an almost optically pure state after repeated recrystallisation from benzene/light petroleum mixture.

From some of these experiments the glycol, obtained by the action of excess Grignard reagent, was isolated as a by-product.

$$R.CO.CO_2R^{\mp} + 3R'MgX \longrightarrow RR'C(OH).CR'R'(OH)$$

In one case, trimethylanisylethylene glycol was obtained from (-)-menthyl anisoylformate and MeMgI and was found to be laevorotatory.

With regard to the influence of conditions on the extent of asymmetric synthesis McKenzie (1906) remarks:

"The mode of formation of the Grignard reagent and the conditions under which its action on the ketonic ester is conducted doubtless in many cases influence the extent to which an asymmetric synthesis takes place. Whilst the activity of the mixture of unequal amounts of (d)- and (l)-phenylmethylglycollic acids does not very appreciably vary

with variation of the conditions under which the Grignard reagent is employed, the case is different when magnesium isobutyl iodide acts on (l)-menthyl benzoylformate, since, when the Grignard reagent is added in the proportion of $2\frac{1}{2}$ mols. of iodide to 1 mol. of ester, the extent of the asymmetric synthesis is much less marked than when the reagent is added in the proportion of $1\frac{1}{4}$ mols. of iodide to 1 mol. of ester."

McKenzie and Müller (1909) thought it might be possible to correlate degree of asymmetric synthesis with the magnitude of the optical rotatory power of the alcohol radical, but this was not confirmed by Ritchie (1933a) who commented as follows:-

"The extent of any asymmetric synthesis of this type appears to depend as much upon the conditions obtaining during the Grignard reaction as upon the rotatory power of the directing system; on repeating such a synthesis several times, the activity of the product has been found to vary markedly. The case recorded above is, however, the only one where there is the least doubt about the sign of the rotation - a rather puzzling result." Here Ritchie was referring to the synthesis involving isobutyl magnesium iodide upon (-)-bornylbenzoyl formate when McKenzie obtained a dextrorotatory and Ritchie a laevorotatory product.

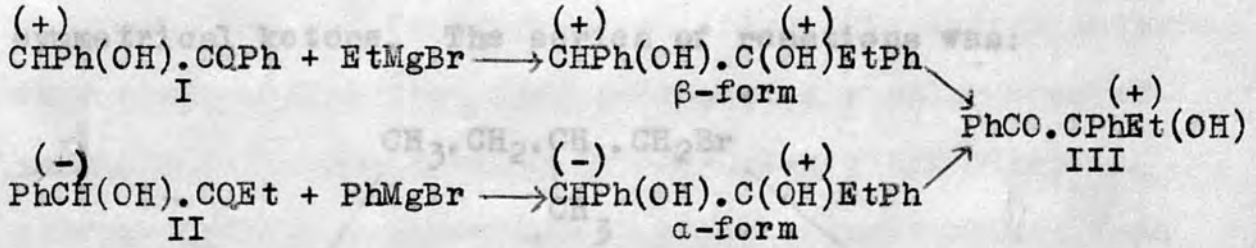
McKenzie (1906) also attempted a few asymmetric syntheses

Interaction of β- and γ- keto esters and Grignard reagents

(-)-menthyl ester of ------- acid	Grignard reagent	Conclusions
Acetoacetic	EtMgX	Reaction with enol form of ester only
Ethylacetoacetic	EtMgX	Some reaction (apart from that with enol) occurred. K salt solution from hydrolysis (after removal of menthol) almost inactive.
Diethylacetoacetic	EtMgX	K salt solution "practically inactive".
Diethylacetoacetic	PhMgX	K salt solution "practically inactive".
Laevulic	EtMgX α-naphthyl MgX	Solutions and products so coloured as not to permit of accurate investigation.
Laevulic	PhMgX	Aqueous solution of Ba salt of acid found to be "distinctly laevorotatory". Colour of solution evidently did not allow of quantitative investigation. "The action of PhMgBr yielded a slightly laevorotatory product, but its activity was presumably due to the formation of the asymmetric lactone." (Ritchie, 1933b).

using (-)-menthyl esters of β- and γ-keto acids in reactions analogous to the above (see Table).

Asymmetric syntheses have also been observed when an optically active acylcarbinol has been treated with a Grignard reagent and oxidation of the original asymmetric centre of the resulting glycol has been effected. Roger (1937, 1939) accomplished the asymmetric synthesis of (+)-ethyl benzoin (III) both from (+)-benzoin (I) and from (-)-phenyl propionyl carbinol (II).

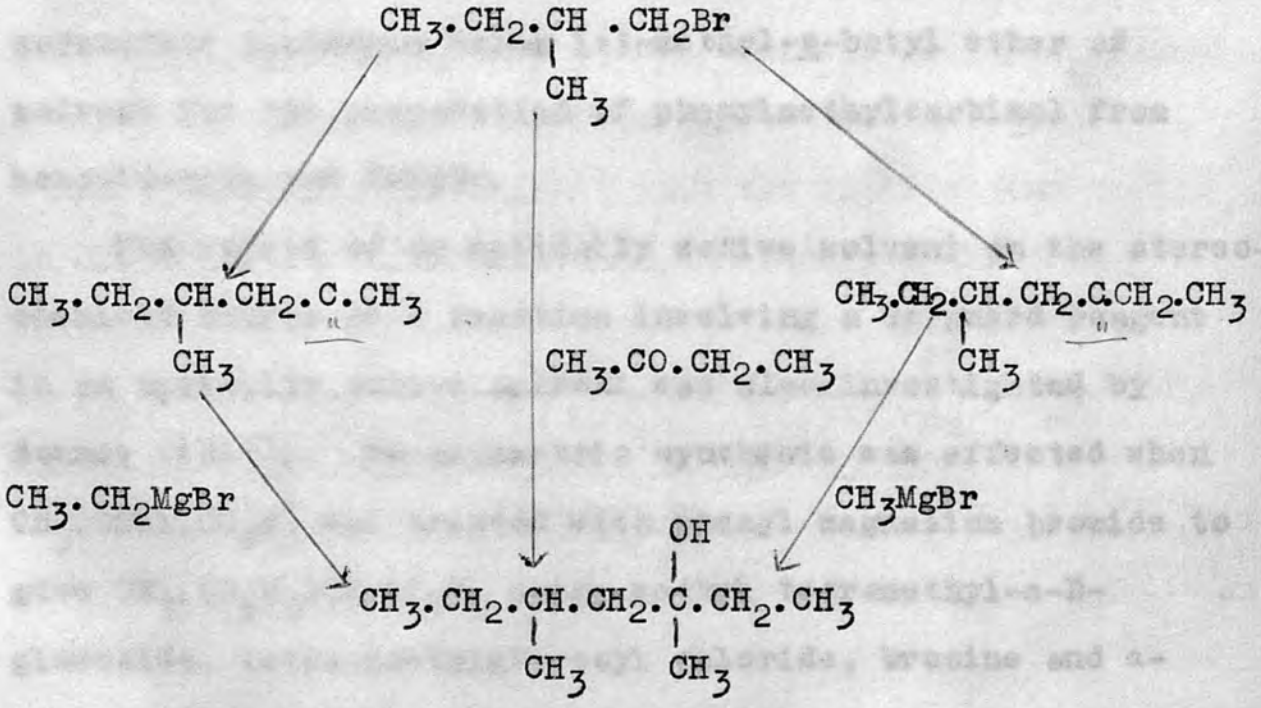


The above preparation of (+)-benzoin was termed a unilateral asymmetric synthesis by Roger since only one of the two possible forms was obtained.

As would be expected from this observation Tiffeneau and Levy (1927) had obtained different products by treating (±)-benzoin with ethyl magnesium bromide and (±)-phenyl-propionylcarbinol with phenyl magnesium bromide respectively, although in both cases the products were racemic compounds. Other observations analogous to the above have been recorded, only one of the two products that could be expected being formed, although preferential oxidation of the original optically active carbinol group has not always been

accomplished to give a new optically active carbinol.

Brokaw and Brode (1948) failed to effect an asymmetric synthesis by the interaction of either methyl- or ethyl-<u>active</u>-amyl ketone with ethyl or methyl magnesium bromide respectively. Nor was an asymmetric synthesis effected by the interaction of <u>active</u>-amyl magnesium bromide and methyl-ethyl ketone. This is the only reference which can be found to an attempted asymmetric synthesis involving an <u>additive</u> reaction between an optically active Grignard reagent and a symmetrical ketone. The series of reactions was:



The reactions discussed above (excluding the last example) have all involved addition of a Grignard reagent to a carbonyl group in a molecule which also contains an optically active centre. Attempts have also been made to

effect an asymmetric synthesis by treating an inactive carbonyl compound with a Grignard reagent in an optically active solvent.

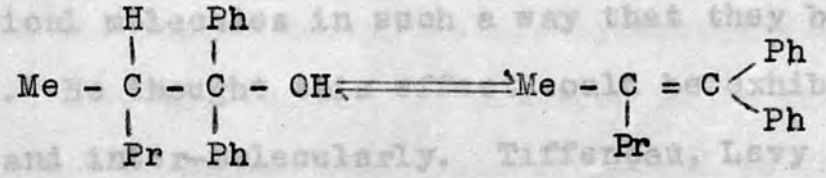
Betti and Lucchi (1940) claimed to have accomplished this type of asymmetric synthesis by treating benzaldehyde with methyl magnesium iodide in benzene and an optically active solvent such as dimethylbornylamine. Since then, this work has been criticised adversely by Tarbell and Paulson (1942), who consider that the supposed asymmetric synthesis was due to impurities. Also, the latter authors were unsuccessful when they attempted a similar type of asymmetric synthesis using (+)-methyl-s-butyl ether as solvent for the preparation of phenylmethylcarbinol from benzaldehyde and MeMgBr.

The effect of an optically active solvent on the stereochemical course of a reaction involving a Grignard reagent in an optically active solvent was also investigated by Bonner (1947). No asymmetric synthesis was effected when $CH_3.CHCl.OC_2H_5$ was treated with phenyl magnesium bromide to give $CH_3.(C_6H_5)CH.OC_2H_5$ using methyl tetramethyl-α-D-glucoside, tetra-acetylglucosyl chloride, brucine and α-bromocamphor as optically active solvents.

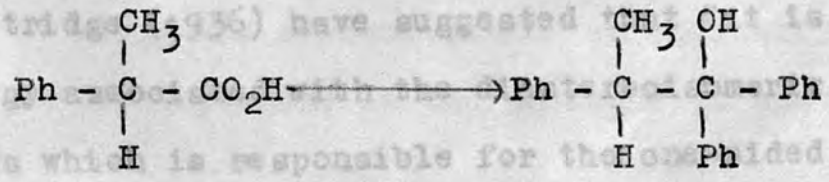
So far no mention has been made of asymmetric syntheses which have been effected by utilising the reducing properties of some Grignard reagents. Vavon, Rivière and

Angelo (1946) and Vavon and Angelo (1947) have effected a series of asymmetric reductions of ketones, containing no asymmetric carbon atom, with the aid of isobornyl magnesium bromide to give optically active carbinols. In this case the degree of asymmetric synthesis was dependent on the structure of the ketone.

In conclusion some other relevant observations may be mentioned. Bergmann and Hartrott (1935) attempted the preparation of optically active $CH_3.(CH_2)_2.\overset{*}{C}H(CH_3).C(OH)(Ph)_2$ from $CH_3.(CH_2)_2.\overset{*}{C}HCH_3.CO_2Et$ and PhMgBr but obtained only the inactive alcohol. They reject the idea that the ester undergoes enolisation before it reacts with the Grignard reagent or that the intermediate ketone formed enolises before further reaction, and suggest that the racemisation is due to the following equilibrium in the reaction mixture:



However, Campbell and Kenyon (1947) treated (+)-partially resolved hydratropic acid with PhMgBr and obtained an optically active glycol.



Further, to find if an equilibrium mixture was obtained, they

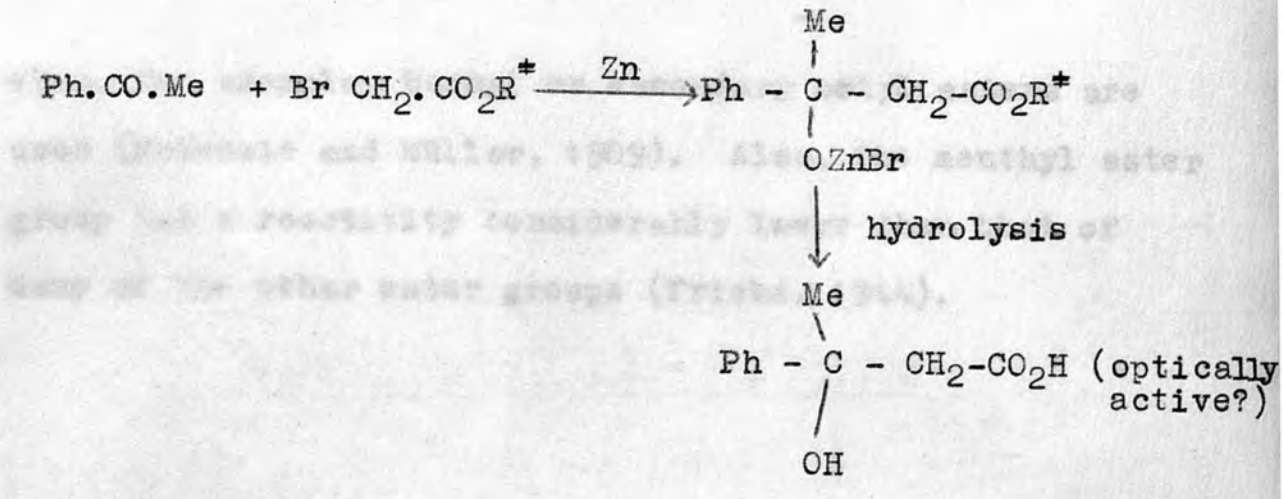
dissolved 1:1:2-triphenylpropylene in 4 mol. proportions of PhMgBr solution and after adding 1 mol. proportion of water heated the solution under reflux. Decomposition yielded the unchanged compound (4.5 g. from 5.0 g.), proving in this case that no equilibrium had been established.

Various suggestions have been advanced as to factors controlling asymmetric syntheses of the type involving the addition of a Grignard reagent to a carbonyl group, when the latter and an asymmetric centre are present in the same molecule. McKenzie and his colleagues were inclined to favour an explanation involving "induced asymmetry" in the carbonyl group undergoing reaction (cf. Ritchie, 1947). One of the more recent definitions of "asymmetric induction", advanced by Kortüm (1932), is: "The action of a force, arising in asymmetric molecules, which influences adjacent symmetrical molecules in such a way that they become asymmetric". He thought this effect could be exhibited both intra- and inter-molecularly. Tiffeneau, Levy and Ditz (1931, 1935) favour the explanation that one of the two bonds of the carbonyl group is attacked selectively when there is an optically active system elsewhere in the molecule. Kenyon and Partridge (1936) have suggested that "it is a difference in energy associated with the diastereoisomeric intermediate products which is responsible for the one-sided addition".

Various workers have suggested that the degree of

asymmetric synthesis will be controlled by the proximity of the asymmetric centre to the centre at which the reaction will take place (cf. Brokaw and Brode, 1948, and Tiffeneau, Levy and Ditz, 1931, 1935). However, there has been no systematic investigation into the effect on the degree of asymmetric synthesis of introducing a carbon chain of increasing length [$-(CH_2)_n-$] between the optically active centre and the reaction centre.

Also, it appeared from the above ideas on asymmetric synthesis that, if such syntheses (involving an α-keto ester and a Grignard reagent) were a result of asymmetric induction - which presumably must be an electronic mechanism - then the introduction of a methylene chain should decrease the extent of asymmetric synthesis. However, if asymmetric syntheses were due to energy differences at some stage, no such decrease in the degree of asymmetric synthesis would be expected. Moreover, further information as to the explanation of this type of asymmetric synthesis could be obtained by the study of the interaction of a Grignard reagent, containing an asymmetric centre, with a symmetrical ketone, with a view to obtaining an asymmetric synthesis. Thus, it was decided to study the interaction of an optically active bromoacetate and acetophenone in the presence of zinc, i.e.



Id. Present Investigation

Thus, the present investigation entailed the following steps:-

(1) preparation of (-)-menthyl esters of ω-acetyl fatty acids - $CH_3.CO.(CH_2)_n.CO_2R$;

(2) interaction of these esters with phenyl magnesium bromide, with subsequent hydrolysis and investigation of the resulting hydroxy-acid for optical activity;

(3) establishing whether the above type of asymmetric synthesis was dependent on reaction conditions;

(4) preparation of (-)-menthyl bromoacetate, and its treatment with acetophenone in the presence of zinc, with subsequent hydrolysis of the product. The hydroxy acid thus obtained would be examined for optical activity.

It will be seen from the above that it was decided to use the menthyl ester. It had been observed that asymmetric syntheses involving menthyl esters tend to be greater than

when, for example, bornyl or secondary octyl esters are used (McKenzie and Müller, 1909). Also, the menthyl ester group has a reactivity considerably lower than that of many of the other ester groups (Triebs, 1944).

PREPARATION OF (-)-MENTHYL ESTERS

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IIa. (-)-Menthyl pyruvate

Pyruvic acid was prepared according to the method in Organic Syntheses (Coll. Vol. I, p. 475) by the dry distillation of tartaric acid with potassium hydrogen sulphate. It was obtained in 39% yield, based on tartaric acid, and had b.p. 58°/7mm., which is in agreement with some of the published values, e.g. 58°/7 mm. (Henri and Fromageot, 1925), although there appear to be some discrepancies in the literature.

The (-)-menthyl ester was prepared by the Fischer-Speier method using 4 molecular proportions of menthol. Excess menthol was removed by steam distillation, and the low yield of menthyl pyruvate obtained (24% of crude, b.p. 128-130°/8 mm.) was attributed to the steam volatility of menthyl pyruvate which was suggested by the fact that, towards the end of the steam distillation, the distillate contained an oil which would not solidify. The physical constants obtained for pure (-)-menthyl pyruvate were, b.p. 132.5-133.5°/10 mm., $n_D^{16°}$ 1.4565, $\alpha_D^{15°}$ -46.64°, $\alpha_{5780}^{15°}$ -48.75°, $\alpha_{5461}^{15°}$ -55.74°. These values are comparable to those reported by McKenzie (1905), b.p. 131-132°/10 mm., and by Roger and Ritchie (1932), $\alpha_{5893}^{20°}$ - 46.54°, $\alpha_{5461}^{20°}$ -55.46° (l = 0.5 dm.); these authors prepared the ester by the same method.

IIb. (-)-Menthyl laevulate

(-)-Menthyl laevulate was prepared from laevulic acid by the Fischer-Speier method of esterification, excess menthol being finally removed by distillation in vacuo. (-)-Menthyl laevulate, b.p. 151°/2 mm. was obtained in 71% yield with the following physical constants:- $n_D^{20.5°}$ 1.4573, $d^{20.5°}$ 0.9765, $d^{25°}$ 0.971, $[\alpha]_D^{20.5°}$ -61.14°, $[\alpha]_{5780}^{20.5°}$ -63.62°, $[\alpha]_{5461}^{20.5°}$ -72.01°, $[\alpha]_{5780}^{25°}$ 63.49°, $[\alpha]_{5461}^{25°}$ 71.84°. McKenzie (1906), who prepared the ester by the same method, reported b.p. 169°/12 mm.; $d_4^{19.8°}$ 0.9773; $[\alpha]_D^{19.5°}$ -60.6° for this compound. The semi-carbazone crystallised from alcohol in prismatic needles, m.p. 156-156.5°.

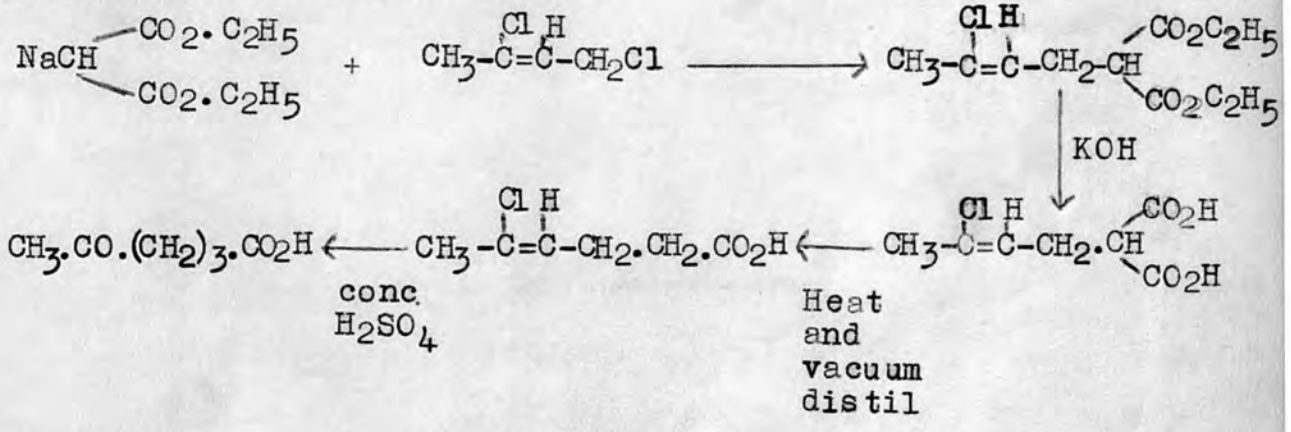
IIc. (-)-Menthyl ω-acetyl-n-butyrate [(-)-menthyl 4-keto-pentan-1-carboxylate]

In the earlier work, ring fission of 5- and 6-membered ring compounds by oxidation was often found to give acetyl-n-butyric acid (cf. Beilstein, III, 385). Vörlander (1897) effected hydrolytic fission of cyclohexan-1:3-dione by boiling with barium hydroxide solution and obtained this compound; cyclohexane-1:3-dione was prepared by reduction of resorcinol with sodium amalgam and water. The hydrolysis of acetyl substituted dicarboxylic acids and di-acetyl substituted acids has also been used for the preparation of acetylbutyric acid, e.g. (i) hydrolysis of α-acetyl-glutaric

acid prepared from acetoacetic ester and β-iodopropionate (Fittig and Wolff, 1883; Bentley and Perkin, 1896) or from methyl acrylate and acetoacetic ester (Albertson, 1948), (ii) hydrolysis of γγ'-diacetyl butyrate, and (iii) hydrolysis of α-carbethoxy-δ-ketocaproate prepared by the interaction of malonic ester and a Mannich base ($R_2N.CH_2.CH_2.CO.CH_3.HCl$) (Mannich and Fourneau, 1938, Harradence and Lions, 1939).

This compound has also been prepared through the interaction of glutaric anhydride and methyl magnesium bromide in equimolecular proportions (Komppa and Rohrmann, 1934) as well as by the hydrolysis of 1:6-dimethyl-6-hydroxypiperid-2-one which is obtained by the interaction of glutarmethylimide and methyl magnesium bromide (Lŭkes and Gorocholinsky, 1936).

In 1942 a method was patented for the preparation of acetylbutyric acid by the interaction of ketene and vinyl methyl ketone (Hopff and Rapp, 1942). Tatevosyan, Melikyan and Tuteryan (1946) prepared acetylbutyric acid by the following series of reactions:-



The method chosen was based on the hydrolytic fission of cyclohexane-1:3-dione since it is now available commercially, and since the hydrolysis, with either barium hydroxide or potassium hydroxide, is readily accomplished and the ketoacid obtained in good yield. Hydrolysis with barium hydroxide solution gave a yield rather lower than that with potassium hydroxide. ω-Acetyl-n-butyric acid mono-hydrate crystallised from water in prisms, m.p. 37-37.5°. This m.p. is comparable with those recorded by other workers; e.g., 37° (Lipp, 1896); 36° (Vörlander, 1897; Haworth and Perkin, 1908; Mannich, 1938); 37-38° (Tatevosyan et al., 1946). The semi-carbazone, which crystallised in prisms from water, had m.p. 172.5-173.5° (dec.). M.p. 173-174° has been recorded by Mannich (1938) and by Bentley and Perkin (1896), 175° by Kötz, Blendermann, Mähnert and Rosenbusch (1913) whereas Tatevosyan (1946) reports m.p. 168-169°. It has been observed by Komppa and Rohrmann (1934) that the m.p. increased on drying at 110°, from 168° to 204° (with sintering at 180°).

(-)-Menthyl-ω-acetyl-n-butyrate was prepared from ~~prepared from~~ anhydrous acetylbutyric acid (the monohydrate being dehydrated by heating under reduced pressure) by the Fischer-Speier method. Excess menthol was removed by steam distillation and pure (-)-menthyl acetylbutyrate, b.p. 154.5-155.5°/3 mm., was obtained in 45% yield.

(-)-Menthyl ω -acetyl-n-butyrate had the following physical constants:- $n_D^{20.5^\circ}$, 1.4588; d^{25°, 0.973; $[\alpha]_{5780}^{25^\circ}$ -68.02°; $[\alpha]_{5461}^{25^\circ}$ -70.17°. The semicarbazone crystallised from aqueous alcohol in plates, m.p. 125-125.5°.

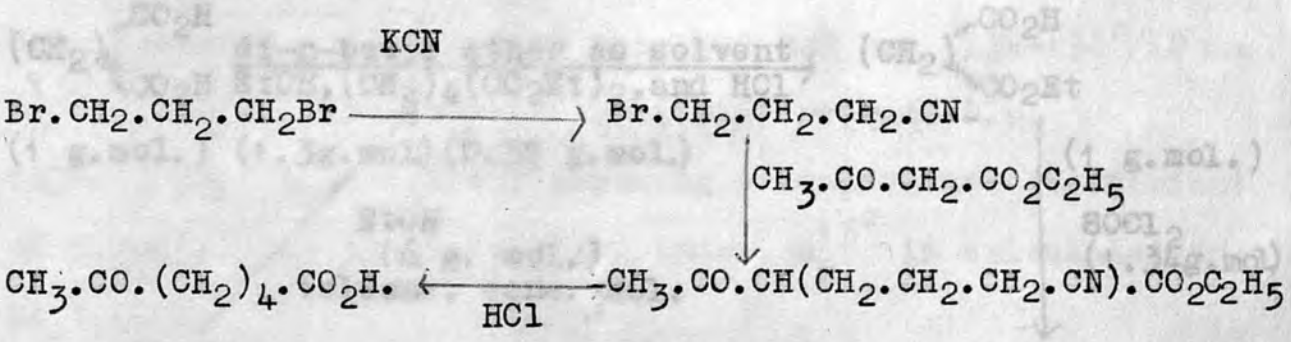
IId. (-)-Menthyl ω-acetyl-n-valerate [(-)-menthyl 5-keto-hexan-1-carboxylate]

Previous methods of preparation of acetylvaleric acid have included the oxidation of 1-methylcyclohexene-1 with potassium permanganate (Wallach, 1903, 1908) and of 1-methylcyclohexanone-2 with chromic and sulphuric acids (Wallach, 1903) and with oxygen in the presence of light (Ciamician and Silber, 1913).

Subsequent to the completion of the present series of experiments with acetylvaleric acid, the results of a detailed investigation of the preparation of this acid, by oxidation of 1-methylcyclohexanone-2, were published by Ruzicka, Seidel, Schinz and Pfeiffner (1948). Oxidation of the latter compound with chromic acid in acetic acid gave the keto-acid in good yield. Naves (1948) has recently reported that the crude keto-acid (no m.p. given) was obtained in good yield by oxidation of 1-methylcyclohexene. Milas, MacDonald and Black (1948) have described the oxidation of 2-methyl-1-ethynyl-cyclohexene to give acetylvaleric acid.

Hydrolysis of diethyl-α-acetyladipate, prepared by the interaction of sodioacetic ester and γ-chlorobutyric acid (Fichter and Gully, 1897) yields acetylvaleric acid, as does

the hydrolysis, with alcoholic potassium hydroxide, of ethyl α: δ-diacetylvalerate. The latter compound had been isolated by Perkin (1890) during the investigation of the product of interaction of acetoacetic ester and ethylenedibromide. Derick and Hess (1918) criticised the purity of the products obtained by earlier workers, and described the preparation of acetylvaleric acid by the acid hydrolysis of ethyl δ-cyano-α-acetylvalerate:-

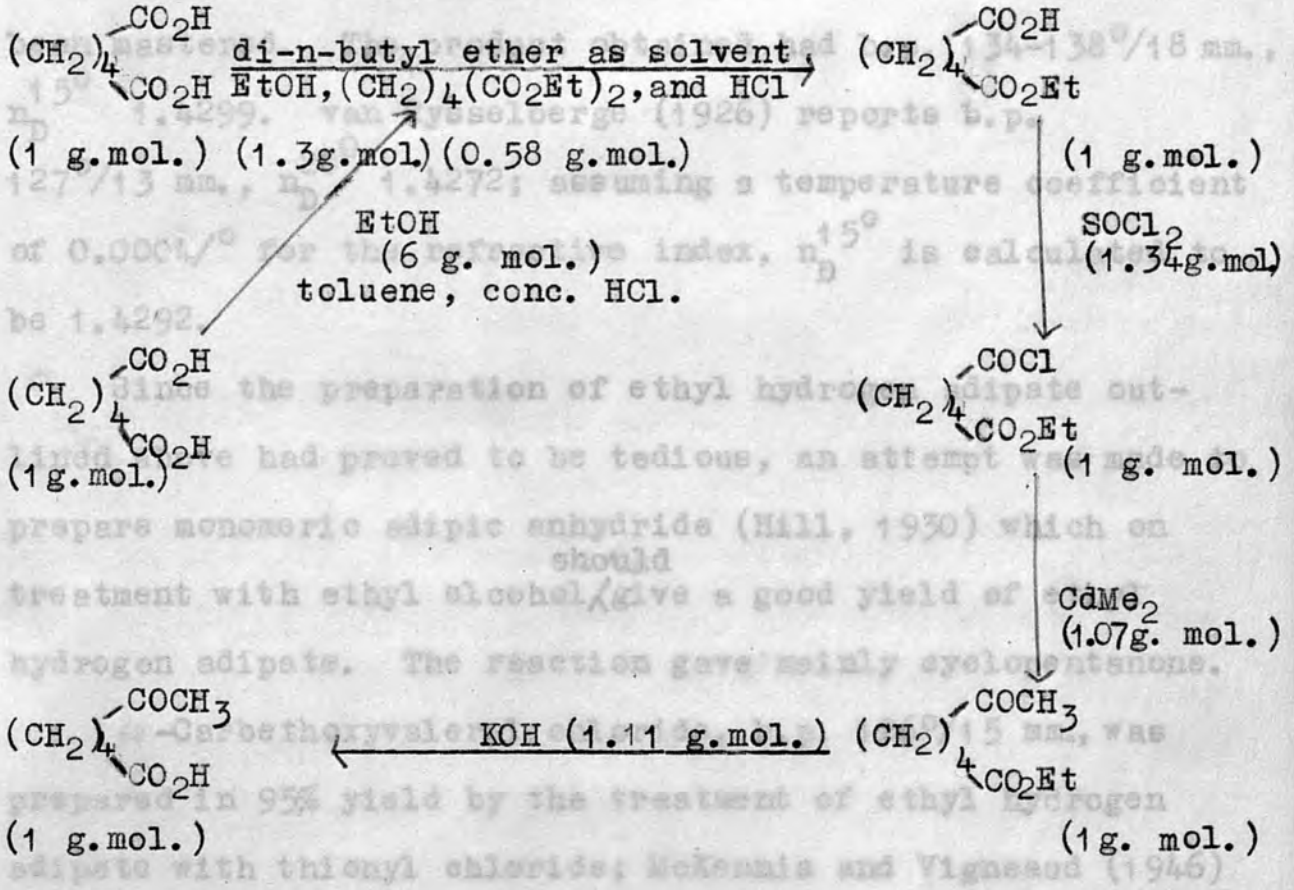


This method was also employed by Lease and McElvain (1933). Müller and Krauss (1932) prepared acetylvaleric acid by hydrolysis of the product of interaction of malonic ester and ω-carbethoxyvaleryl chloride. The latter compound has also been used as a starting material by Blaise and Koehler (1910), who treated it with dimethyl zinc.

Although Polgar and Robinson (1945) obtained excellent yields using the method of Blaise and Koehler (1910), Cason (1947) considers that dimethyl cadmium is to be preferred to dimethyl zinc, the former compound giving, in general, more reproducible results than the latter. Acetylvaleric acid

was therefore prepared in the present investigation by the method of Cason. Dimethyl cadmium has the further advantage of being less dangerous than dimethyl zinc, and it was anticipated that the preparation of ω-carbethoxyvaleryl chloride from adipic acid - which is readily available - would afford no difficulty.

Thus ω-acetyl-n-valeric acid was prepared by the following series of reactions:-



Ethyl hydrogen adipate was prepared essentially according to the method given for ethyl hydrogen sebacate in Organic Syntheses, Vol. IX, p. 45, i.e. by heating a mixture of adipic acid, diethyl adipate, ethyl alcohol and concentrated

hydrochloric acid with di-n-butyl ether as solvent. The diethyl adipate used in the above preparation was prepared in 94% yield according to Organic Syntheses, Coll. Vol. II, p. 264, i.e. by repeated distillation of toluene from an ethanolic solution of adipic acid. Ethyl hydrogen adipate, sufficiently pure for conversion to the acid chloride, was obtained in 56% yield in the last two experiments (total of 5 carried out) when the technique for the distillation had been mastered. The product obtained had b.p. 134-138°/18 mm., $n_D^{15^\circ}$ 1.4299. van Rysselberge (1926) reports b.p. 127°/13 mm., $n_D^{20^\circ}$ 1.4272; assuming a temperature coefficient of 0.0004/° for the refractive index, $n_D^{15^\circ}$ is calculated to be 1.4292.

Since the preparation of ethyl hydrogen adipate outlined above had proved to be tedious, an attempt was made to prepare monomeric adipic anhydride (Hill, 1930) which on treatment with ethyl alcohol should give a good yield of ethyl hydrogen adipate. The reaction gave mainly cyclopentanone.

ω-Carbethoxyvaleryl chloride, b.p. 126°/15 mm., was prepared in 95% yield by the treatment of ethyl hydrogen adipate with thionyl chloride; McKennis and Vigneaud (1946) report b.p. 127°/15 mm.

Ethyl ω-acetylvalerate, b.p. 104°/3 mm.-108°/4 mm., was prepared by the treatment of ω-carbethoxyvaleryl chloride with dimethyl cadmium in 66% yield. Redistillation

of this product gave a liquid, b.p. 114°/11 mm. (90% recovery); McKennis and Vigneaud (1946) report b.p. 120-123°/13 mm.

δ-Acetyl-n-valeric acid was prepared from its ethyl ester by hydrolysing with 10% potassium hydroxide solution; 52% yield was obtained (average of 2 experiments). δ-Acetyl-n-valeric acid crystallised in plates from ether/light petroleum (b.p. 40-60°) mixture, m.p. 34-35°; Derick and Hess (1918) reported m.p. 36.5°. The semicarbazone was prepared and found to have m.p. 144° after crystallisation from alcohol. Blaise and Koehler (1910) reported m.p. 144° and Ciamician and Silba (1913) m.p. 147°.

(-)-Menthyl δ-acetyl-n-valerate was prepared by the Fischer-Speier esterification method using 4 g. mols. (-)-menthol to 1 g. mol. acetylvaleric acid, after preliminary experiments had shown this method to yield better results than that involving repeated distillation of toluene from the acetylvaleric acid-menthol mixture. Two experiments gave an average yield of 71% of crude (-)-menthyl acetylvalerate. The product (obtained by four distillations of the crude product), b.p. 173-174°/3 mm., had $n_D^{20.5°}$ 1.4600, $d^{25°}$ 0.9605, $[\alpha]^{25°}_{5780}$ -58.74°, $[\alpha]^{25°}_{5461}$ -66.50°, and in chloroform $[\alpha]^{19°}_{5780}$ -63.2° ± 0.2°. $[\alpha]^{19°}_{5461}$ -72.2° ± 0.2° (c, = 1.5). The semicarbazone of (-)-menthyl δ-acetyl-n-valerate crystallised in plates, m.p. 105-106°, from aqueous

alcohol.

IIe. (-)-Menthyl ω-acetylpelargonate [(-)-menthyl 9-keto-decan-1-carboxylate]

ω-Acetylpelargonic acid was first prepared by Welander (1895) by the hydration of 2-decyne-10-carboxylic acid (CH_3-C≡CH-$(CH_2)_7$-CO_2H) with moderately concentrated sulphuric acid. It was shown by Myddleton and Barrett (1927) that he had actually obtained a mixture of the 2- and 3-keto-decane-10-carboxylic acids. Sherrill and Smith (1937) effected this hydration with mercuric acetate. Employing this reagent Myddleton and Barrett (1927) had effected the hydration of 1-decyne-carboxylic acid, to give only 2-keto-decane-10-carboxylic acid (acetylpelargonic acid). This keto-acid has also been prepared by the oxidation of undecane-2:11-diol (Chuit, Boelsing, Hausser and Malet, 1926) and by treating the ω-carbethoxynonoyl-chloride with dimethyl zinc (Ruzicka and Stoll, 1927) or dimethyl cadmium (Cason and Prout ,1944).

In the present investigation acetylpelargonic acid was prepared essentially according to the method of Myddleton and Barrett (1927), i.e. by the following series of reactions:-

$$CH_2.CH.(CH_2)_8.CO_2H \xrightarrow{Br_2} CH_2Br.CHBr.(CH_2)_8.CO_2H \xrightarrow{\text{alc.KOH}} CH{\equiv}C.(CH_2)_8.CO_2H \longrightarrow CH_3.CO.(CH_2)_8.CO_2H$$

Treatment of 1-decene-10-carboxylic acid with bromine in light petroleum gave 1:2-dibromo-decane-10-carboxylic acid, m.p. 35.5.36.5°, in 50% yield, and a further 27% of product m.p. 31.5°, whereas Myddleton and Barrett obtained a product of m.p. 38.5° in 79% yield. The 1-decene-10-carboxylic acid used by Myddleton and Barrett was somewhat purer (m.p. 24.5°) than that used in this investigation (m.p. 21°). 1-Decyne-10-carboxylic acid, m.p. 39.7-40°, was prepared from the dibromo compound by boiling with alcoholic potassium hydroxide solution according to Krafft (1896), who recorded m.p. 42.7-42.9°. The hydration of the crude acetylenic acid was then accomplished by heating a solution in acetic acid with mercuric acetate. The mercury salt complex - $(CH_3.CO_2Hg)_3C.CO.(CH_2)_8CO_2Hg/2$ - was decomposed with hydrochloric acid. Some of the mercury salts could be removed from this reaction mixture by filtration, but an ethereal extract of the filtrate still contained some mercury salts which were best removed by precipitation as the sulphide (cf. Sherrill and Smith, 1937). Concentration of this ethereal solution to dryness, and crystallisation of the product from light petroleum (b.p. 60-80°), gave acetylpelargonic acid of m.p. 37-38° in 78% yield. Further purification of this product was effected via its bisulphite derivative, which was prepared by shaking a benzene solution of the keto-acid with a saturated solution of sodium

bisulphite (cf. Abraham, Mowat and Smith, 1937). The product from this purification procedure was crystallised from light petroleum (b.p. 40-60°), giving small needles, m.p. 58.2-58.8°. Myddleton and Barrett (1927) record m.p. 59.5°, Chuit et al. (1926) m.p. 59-59.6° and Sherrill and Smith (1937) 58-59°. The semicarbazone had m.p. 135.5-136.5°; Myddleton and Barrett (1927) record m.p. 136.5°.

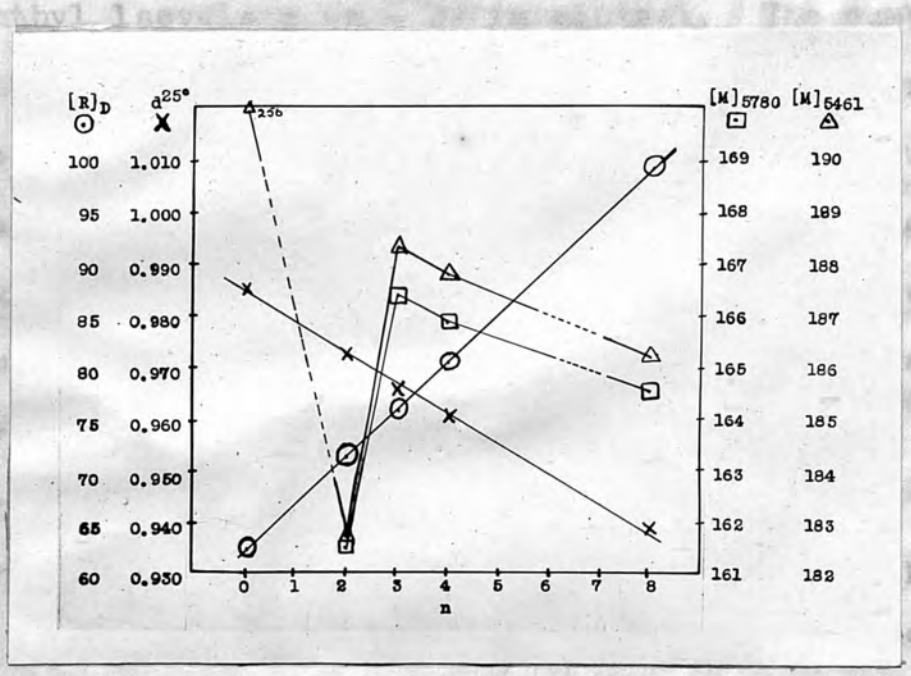
(-)-Menthyl ω-acetylpelargonate was prepared by the Fischer-Speier method in 75% yield with b.p. 209-210°/3 mm. This compound had the following physical constants: $n_D^{20.5^\circ}$ 1.4619, d^{25° 0.939, $[\alpha]_{5780}^{25^\circ}$ -48.59, $[\alpha]_{5461}^{25^\circ}$ -55.02°. The semicarbazone m.p. 100.5-101°, crystallised from aqueous alcohol in rectangular plates.

IIf. Note on physical properties of (-)-menthyl ω-acetyl fatty acid esters in relation to structure

The physical properties of the (-)-menthyl esters of ω-acetyl fatty acids ($CH_3.CO.(CH_2)_n.CO_2$(-)-menthyl) are tabulated below (see also graph).

n	Mol.wt.	d^{25°	$n_D^{25^\circ}$	$-[\alpha]_{5780}^{25^\circ}$ ±0.02°	$-[\alpha]_{5461}^{25^\circ}$ ± 0.02°
0	226.3	0.985 (20°)*	1.4539 (10°)⊖	-	113.1⊖
1	- solid				
2	254.4	0.973	1.4573	63.48	71.84
3	268.4	0.965(5)	1.4588	62.02	70.17
4	282.4	0.960(5)	1.4600	58.74	66.50
8	338.5	0.939	1.4619	48.59	55.02

* McKenzie (1905). ⊖ Roger and Ritchie (1932).



It will be seen that the molecular refractions (calculated from the expression $\left(\frac{n^2 - 1}{n^2 + 2}\ \frac{M}{d}\right)$ do lie on a straight line when plotted against n; the slope corresponds to a value of 4.64 for the refractivity of the $-CH_2-$ group. This is in agreement with the value (4.62) published by Eisenlohr (cf. Glasstone, 1940). Within the range studied, there appeared to be an inverse linear relationship between the density and the value of n.

The molecular rotation of (-)-menthyl pyruvate is considerably larger than that of the higher homologues, which might be expected in view of the proximity of the carbonyl and carbomenthoxy groups. The molecular refraction of (-)-menthyl laevulate (n = 2) is minimal. The number of compounds examined was not sufficiently great to enable any conclusions to be drawn as to the relationship between [M] and n over the whole series; all values for [M] might lie on a curve when plotted against n, or exaltations or depressions might be observed at regular intervals such as when (n + x) is a multiple of 5 and x is a constant.

IIg. (-)-Menthyl bromoacetate

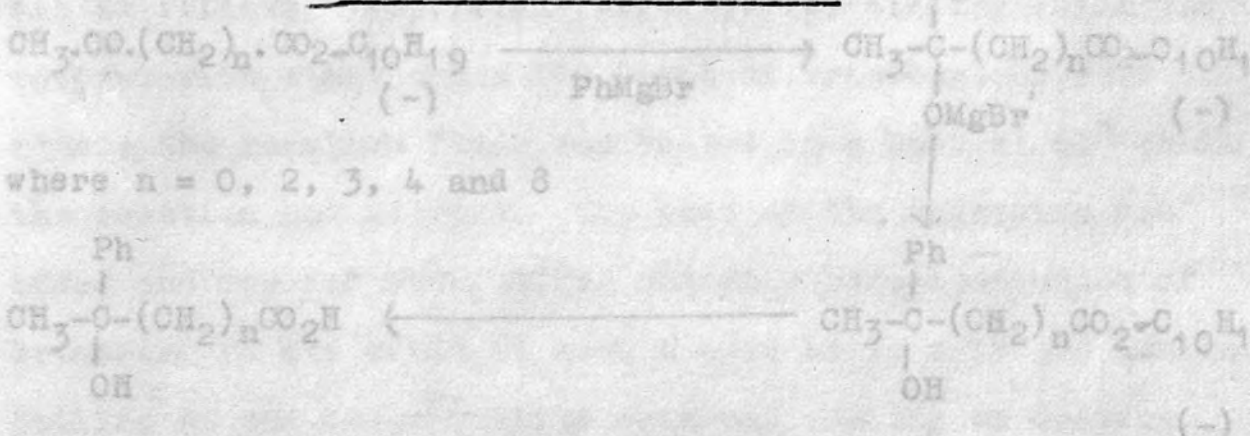
(-)-Menthyl bromoacetate has previously been prepared by the treatment of bromoacetyl bromide with menthol, either in chloroform solution (Cohen, 1911), or with no diluent (Smiles, 1905; Christopher and Hilditch, 1912). Smiles' (1905) attempt to prepare this ester from bromoacetic acid and menthol in the presence of sulphuric acid gave an ester of low specific rotation. In the present investigation (-)-menthyl bromoacetate was prepared by treating bromoacetyl chloride with menthol (no diluent), and also by heating bromoacetic acid and menthol at 100° in the presence of gaseous HBr. Bromoacetyl chloride, b.p. 121-125°, was prepared from bromoacetic acid and thionyl chloride, in 78% yield; in one experiment redistillation of this

product gave a liquid, b.p. 125.5-127°. Published values include:- 127° (de Wilde, 1864), 133-135° (Meyer, 1901), and 127-127.5° (Aschan, 1913).

Crude (-)-menthyl bromoacetate was obtained with b.p. 136°/8 mm. in 82% yield from the acid chloride, and with b.p. 108-116°/2-3 mm. in 55% yield from the free acid. Boiling points previously recorded include, 146-147°/12 mm. (Cohen, 1911), 141-145°/12 mm. (Smiles, 1905) and 177-178°/40 mm. (Christopher and Hilditch, 1912). The distillates solidified and the crude ester was found to crystallise from light petroleum (b.p. 40-60°) as needles, m.p. 18.5-19.5°. The product obtained from the acid chloride had $[\alpha]^{25°}_{5780}$ -68.9° ± 0.2°, $[\alpha]^{25°}_{5461}$ -78.1° ± 0.2° (c, 2.5 in chloroform), and that prepared from the free acid had $[\alpha]^{25°}_{5780}$ -68.3° ± 0.2°, $[\alpha]^{25°}_{5461}$ -77.4° ± 0.2° (c, 2.5 in chloroform). The former product had $[\alpha]^{21°}_{D}$ -67.9° ± 0.8° (l = 0.5 dm.). This value should be compared with that reported by Christopher and Hilditch (1912) for a 2.5% solution in chloroform - $[\alpha]^{20°}_{D}$ -63.20°.

III.

INTERACTION OF PHENYL MAGNESIUM BROMIDE AND (-)-MENTHYL ω-ACETYL FATTY ACID ESTERS



it was essential to develop a reproducible method for the preparation of phenyl magnesium bromide, and to determine the amount of diphenyl formed under these conditions so that this loss of bromobenzene during the preparation of the Grignard reagent could be allowed for.

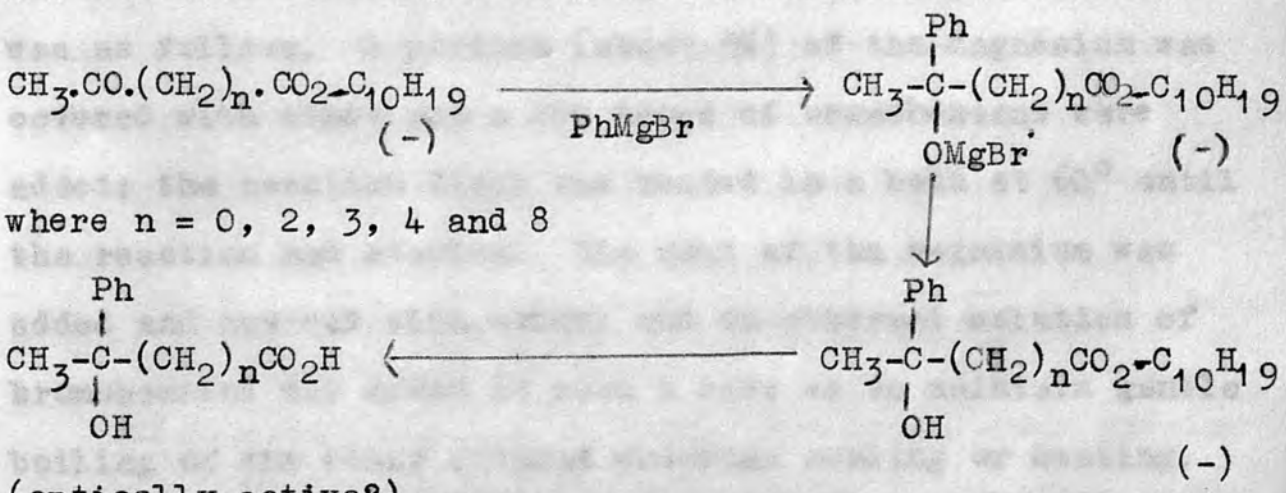
This Section includes descriptions of the method of estimation of diphenyl and of the basic conditions used for studying the above type of asymmetric synthesis, together with the experimental results obtained during the investigation.

(+) Unless otherwise stated optical observations were made on ethanolic solutions.

III.[+] INTERACTION OF PHENYL MAGNESIUM BROMIDE AND (-)-MENTHYL ω-ACETYL FATTY ACID ESTERS

IIIa. Introduction

Before studying the asymmetric syntheses resulting from the reaction between phenyl magnesium bromide and (-)-menthyl ω-acetyl fatty acid esters, i.e.



it was essential to develop a reproducible method for the preparation of phenyl magnesium bromide, and to determine the amount of diphenyl formed under these conditions so that this loss of bromobenzene during the preparation of the Grignard reagent could be allowed for.

This Section includes descriptions of the method of estimation of diphenyl and of the basic conditions used for studying the above type of asymmetric synthesis, together with the experimental results obtained during the investigation.

(+) Unless otherwise stated optical observations were made on ethanolic solutions.

IIIb. Preparation of phenyl magnesium bromide

Phenyl magnesium bromide was prepared in an atmosphere of nitrogen, using 3 molecular proportions of magnesium turnings to 1 of bromobenzene (to reduce the amount of diphenyl formed). The method finally evolved for the preparation of an ethereal solution of phenyl magnesium bromide was as follows. A portion (about 5%) of the magnesium was covered with ether and a few drops of bromobenzene were added; the reaction flask was heated in a bath at 60° until the reaction had started. The rest of the magnesium was added and covered with ether, and an ethereal solution of bromobenzene was added at such a rate as to maintain gentle boiling of the ether without external cooling or heating. When all the bromobenzene had been added the reaction mixture was heated in a bath at 60° for 30 mins. The supernatant was siphoned into a dropping funnel in an atmosphere of nitrogen, ready for addition to an ethereal solution of the (-)-menthyl ester.

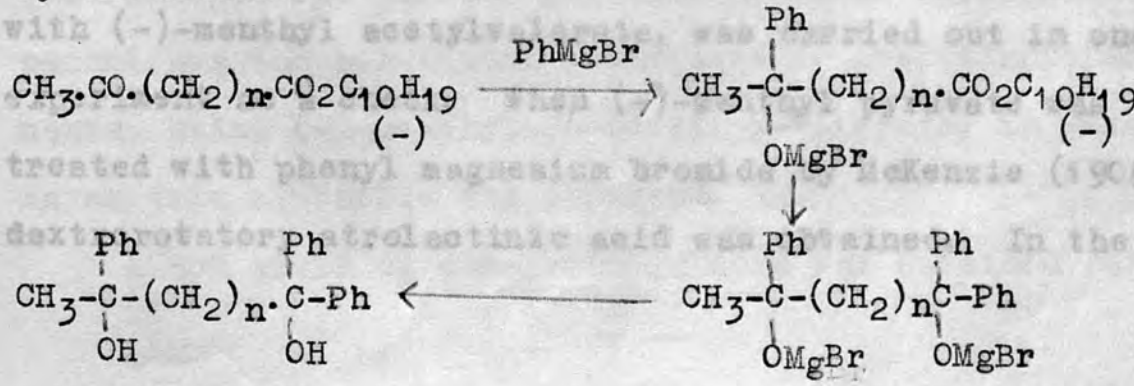
IIIc. Method of estimation of diphenyl

A phenyl magnesium bromide solution, prepared according to the above conditions, was separated from excess magnesium by siphoning and was poured on to ice. The mixture was acidified with 5N-sulphuric acid and the ether separated from the aqueous layer which was then extracted with ether. The ether extract, combined with the first ether solution,

was washed with water and sodium carbonate solution, and dried over sodium sulphate. The residue remaining after distillation of the ether was heated on a boiling water bath at a pressure of about 20 mm. to remove traces of benzene. From the weight of the residue (assuming it to be diphenyl) the amount of bromobenzene converted into diphenyl could be calculated. It was assumed that the rest of the bromobenzene was converted into the Grignard reagent. In the method of preparation outlined above, 95% of the bromobenzene was converted into the Grignard reagent.

IIId. Conditions employed for the Grignard reaction, and isolation of the products

An ethereal solution of PhMgBr was added under varying conditions to an ethereal solution of the (-)-menthyl ester. The reaction mixture was kept under varying conditions and then decomposed with ice and sulphuric acid. Concentration of the ether extract of this mixture gave an oil consisting of the (-)-menthyl ester of the hydroxy acid, neutral products and any unchanged (-)-menthyl keto ester, presumably regenerated from the product obtained by reaction of the enol form of the keto ester. A neutral product could be formed by the reaction



The oil described above was hydrolysed by boiling with aqueous 2·5N-alcoholic potassium hydroxide solution. The alcohol was distilled from the resulting solution, which was then thoroughly ether-extracted to remove menthol and neutral products. (In some cases this extract was steam distilled to remove menthol and the residue (neutral products) examined polarimetrically). The resulting alkaline solution was acidified with 5N-sulphuric acid and the hydroxy acid extracted with ether. Polarimetric and chemical examination was carried out on an ethanolic solution of the hydroxy acid, obtained after distillation of the ether, or on the corresponding lactone.

IIIe. Outline of Grignard reactions studied

In the preliminary investigation, experiments on the reaction between (-)-menthyl acetyl-n-valerate and phenyl magnesium bromide, using various ester/Grignard reagent ratios, did not lead to an observable asymmetric synthesis, the 5-hydroxy-5-phenyl-hexan-1-carboxylic acid (CH_3-$\overset{Ph}{\underset{OH}{C}}$-$(CH_2)_4$-$CO_2H$) exhibiting no optical activity. Treatment of (-)-menthyl pyruvate with phenyl magnesium bromide, under conditions similar to those used in the experiments with (-)-menthyl acetylvalerate, was carried out in one experiment as a check. When (-)-menthyl pyruvate was treated with phenyl magnesium bromide by McKenzie (1906), a dextrorotatory atrolactinic acid was obtained. In the

present case the atrolactinic acid ($CH_3-\overset{\overset{Ph}{|}}{\underset{\underset{OH}{|}}{C}}-CO_2H$) was likewise dextrorotatory, although not optically pure, indicating that the general experimental technique was satisfactory. In view of this result, one further experiment, on a larger scale, was carried out using (-)-menthyl acetylvalerate.

The reaction most extensively studied was that between (-)-menthyl laevulate and phenyl magnesium bromide. Study of this reaction was complicated by the fact that γ-hydroxy acids are relatively unstable in solution, conversion into the lactones taking place.

A few experiments were carried out using (-)-menthyl ω-acetyl-n-butyrate; again the relative ease of ring closure of the δ-hydroxy acid to give the lactone made difficult the study of the reaction products.

A single experiment with (-)-menthyl-ω-acetyl-pelargonate was also carried out.

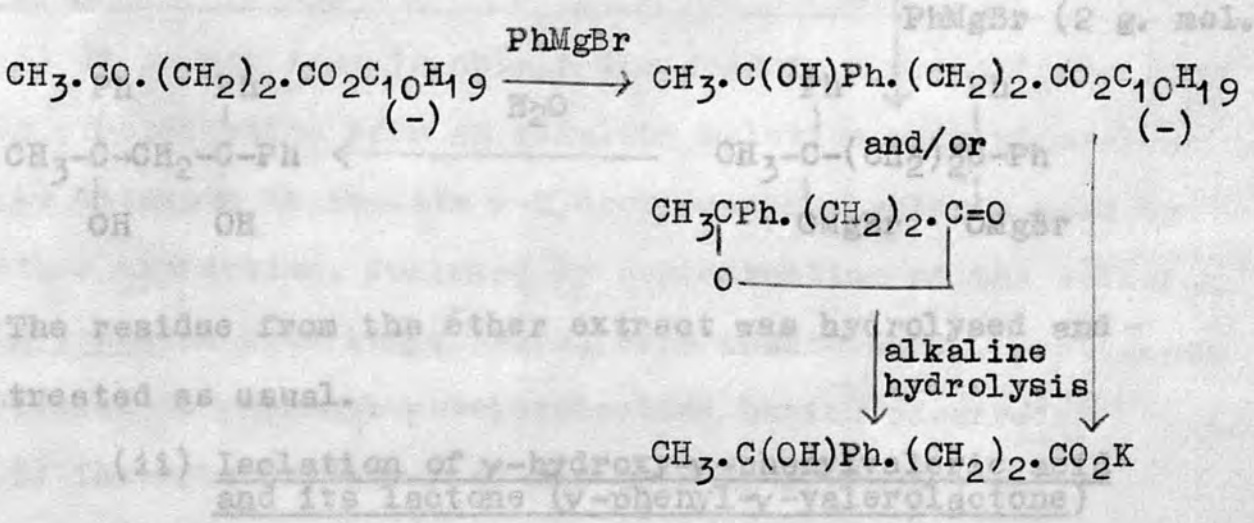
IIIf. Interaction of (-)-menthyl pyruvate and phenyl magnesium bromide

In the case of menthyl pyruvate, as has been mentioned previously, no attempt was made to study the degree of asymmetric synthesis in relation to reaction conditions; the reaction was carried out as a check on experimental techniques and conditions subsequent to preliminary experiments, using (-)-menthyl-ω-acetyl-n-valerate, in which no asymmetric synthesis was observed.

A 50% yield of atrolactinic acid was obtained using

0.02 g. mol. of menthyl pyruvate and 0.025 g. mol. of phenyl magnesium bromide. An aqueous solution of atrolactinic acid had $[\alpha]_D$ +7.8°, $[\alpha]_{5780}$ +8.2°, $[\alpha]_{5461}$ +9.5° (c, 6.15); and an alcoholic solution had $[\alpha]_D^{16°}$ +6.7°, $[\alpha]_{5780}$ +6.8°, $[\alpha]_{5461}$ +8.1° (c, 3.075).

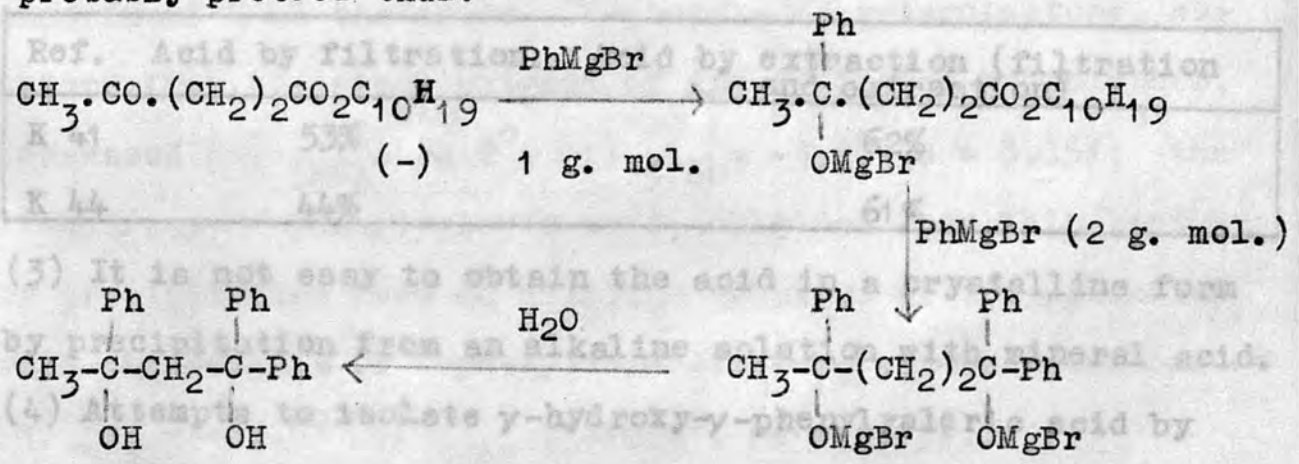
IIIg. Interaction of (-)-menthyl laevulate and phenyl magnesium bromide



(i) Reaction Conditions

An ethereal solution of phenyl magnesium bromide (containing 0.025 g. mol. phenyl magnesium bromide in preliminary experiments) was added under varying conditions to an ethereal solution of (-)-menthyl laevulate (0.02 g. mol. in preliminary experiments). The reaction mixture was kept under varying conditions and then decomposed with ice and sulphuric acid. Concentration of the ether extract of this solution gave an oil, smelling strongly of menthol, which presumably was a mixture of the unchanged (-)-menthyl laevulate, γ-hydroxy-γ-phenylvaleric ester and its lactone,

menthol and by-products (including neutral products formed by interaction of the Grignard reagent and the ester group). Reaction of the Grignard reagent with the ester group would probably proceed thus:-



The residue from the ether extract was hydrolysed and treated as usual.

(ii) Isolation of γ-hydroxy-γ-phenylvaleric acid and its lactone (γ-phenyl-γ-valerolactone)

Owing to the difficulty of isolating pure γ-hydroxy acids, it was not easy to obtain a product that could be used for comparative purposes. Thus, one of the first aims was to obtain a method for isolation of acid or lactone that was easily reproducible.

Isolation of the γ-hydroxy-γ-phenylvaleric acid, either by filtration or by ether extraction of the acidified hydrolysate, was considered impracticable for the following reasons:-

(1) Degree of precipitation would depend on concentrations, particularly of hydrogen ions, which would be hard to

reproduce.

(2) Filtration of the acid would have to be followed by ether extraction of the mother liquor to avoid loss of yield.

Ref.	Acid by filtration.	Acid by extraction (filtration and extraction)
K 41	53%	62%
K 44	44%	61%

(3) It is not easy to obtain the acid in a crystalline form by precipitation from an alkaline solution with mineral acid.

(4) Attempts to isolate γ-hydroxy-γ-phenylvaleric acid by ether extraction, followed by concentration of the solution in vacuo at room temperature, were unsuccessful, partial conversion to γ-phenyl-γ-valerolactone having occurred.

(5) The rotatory power of the acid is extremely small compared with that of the γ-phenyl-γ-valerolactone, and is incidentally, of opposite sign.

Ref.	$\alpha^{\text{Acid}}_{5461}$ (concn.)	$\alpha^{\text{Acid + Lactone}^{\oplus}}_{5461}$ (concn.)
K 43	+0.02 (5.65)	-0.76 (8.25)
K 44	+0.04 (4.28)	-0.34 (5.60)

(⊕) This product was obtained by extraction of the acid (after precipitation from the alkaline solution) with ether; the ether was distilled using a boiling water bath and partial conversion of the acid to lactone occurred. The figures are of little value quantitatively since the $\frac{\text{acid}}{\text{lactone}}$ ratio is unknown.

(6) Precipitation of the acid from an alkaline solution by acidification with mineral acid appears to effect a preferential separation of the antipode present in excess. In experiment K 46 the crude γ-phenyl-γ- valerolactone, obtained from the ether extract of the acidified hydrolysate, possessed $[\alpha]_{5461} = -4.2^{\circ}$, $[\alpha]_{5780} = -3.2^{\circ}$ (c = 8.15); the γ-hydroxy-γ-phenylvaleric acid, obtained from this lactone by precipitation from an alkaline solution of its potassium salt (hydrolysis of γ-phenylvalerolactone), gave a lactone of $[\alpha]_{5461} = -12.5^{\circ}$ $[\alpha]_{5780} = -10.9^{\circ}$. (c = 2.25).

(iii) Conversion of γ-hydroxy-γ -phenylvaleric acid into its lactone

Since isolation followed by polarimetric examination of the acid was rejected for reasons presented above, a reproducible method for conversion of γ-hydroxy-γ -phenylvaleric acid into its lactone was necessary. The first method to be considered was conversion by acid catalysis. In three experiments attempts to convert the acid into lactone by treating with aqueous alcoholic sulphuric acid led to complete racemisation. The product obtained after "ring closure" by this method was examined only polarimetrically, and not chemically. Although it seemed possible that racemisation might be minimised or eliminated by effecting the ring closure with more dilute acid, it was considered that the risk of partial racemisation was such

that further experiments with an acid catalyst were not justified.

It has been mentioned that partial lactonisation occurred on distilling the ethereal solution from a boiling water bath. Attempts were now made to dehydrate the γ-hydroxy-γ-phenylvaleric acid by repeatedly distilling benzene from it. In one experiment the ethereal extract of the acid was divided into two portions which were separately concentrated and distilled with benzene. Although conditions of distillation were not identical the specific rotations of the two products were in agreement.

(iv) Reconversion of γ-phenyl-γ-valerolactone into the acid

For polarimetric observations an absolute alcoholic solution of the lactone was prepared. The lactone could be recovered by distillation of the alcohol, and, in some cases, the γ-hydroxy-γ-phenylvaleric acid could be obtained as white crystals by dissolving the lactone in warm acqueous-potassium hydroxide-solution and precipitating the acid with a mineral acid. In experiment K 43 an acid with m.p. 100-100.5° was obtained; other melting points obtained were 97.5-98° (K 41), 103° (K 44). These specimens were of differing degrees of optical purity, and their melting points should be compared with those of the racemic γ-hydroxy-γ-phenylvaleric acid, m.p. 106° (Trivedi and Nargund, 1941), 104-106° (Johnson, Petersen and Schneider,

1947) and 105·5-106° (present investigation).

In one experiment (K 47) attempts to precipitate the acid gave only a dark brown oil. In another case (K 50) acidification of the alkaline solution to pH 5.0 (Universal Indicator papers) gave a brown oil. This oil was removed, and further acidification yielded the acid as yellowish needles. It is of interest that in the former of these experiments the phenyl magnesium bromide was added to the (-)-menthyl laevulinate whilst the reaction mixture was being heated in a bath at 60° and in the latter experiment addition at 0° was followed after ¼ hour by heating at 60°.

(v) Relationship between reaction conditions and yield

As has been mentioned above, in the preliminary experiments the acid was precipitated and ether extracted. The ether extract was concentrated on a boiling water bath; thus partial conversion into lactone occurred. In calculating the yield from these experiments it is arbitrarily assumed that the mixture obtained consisted of 50% lactone and 50% hydroxy acid. In the later experiments the "pure" lactone was isolated. Hence the yields obtained in the earlier experiments have been converted to the equivalent yield of lactone.

If the Grignard reagent is added to the ester solution over ¾ hour with ice cooling, the reaction is apparently complete after the mixture has been kept for ¼ hour at 0°

followed by 1 hour at room temperature.

Ref.	Hrs. at room temp.	Yield
K 44	1	61%
K 45	15½	57%

The following conditions apparently decrease the yield of lactone, relative to that obtained by mixing the reagents with ice-cooling and completing the reaction by keeping the mixture at room temperature:-

(1) Completion of the reaction by heating the mixture in a bath at 60° (cf. Table below , experiments K 46 and K 50; K 44 and K 45).

(2) Mixing of the reagents at 60° followed by completion of reaction at 60°. (Cf. Table, experiments K 47 and K 44, K 45).

When the whole reaction is accomplished at 60° the yield is lower than when mixing is in ice and the reaction completed by heating at 60°. (Cf. Table, experiments K 47 and K 46, K 50).

Ref.	Addition conditions.	Conditions for completion of reaction	Yield of lactone; calc.
K 44	¾ hr. at 0°	¼ hr. at 0° followed by 1 hr. at room temperature	61%
K 45	¾ hr. at 0°	¼ hr. at 0° followed by 15½ hrs. at room temperature	57%
K 46	¾ hr. at 0°	½ hr. at 60°/bath	44%
K 50	¾ hr. at 0°	¼ hr. at 0° followed by ½ hr. at 60°(bath), then by 15 hrs. at room temperature	47%
K 47	½ hr. at 60° (bath)	½ hr. at 60° (bath)	30%

Insufficient evidence was available, from these early experiments, to draw any conclusions as to the relationship between either the yield or the experimental conditions and the degree of asymmetric synthesis.

Once conditions had been perfected for the reproducible isolation of γ-phenyl-γ-valerolactone a series of preliminary experiments (0.02 g. mol. (-)-menthyl laevulate) was carried out to obtain indications of any effect of conditions on the degree of asymmetric synthesis. In these experiments the lactone was obtained by three benzene distillations from the hydroxy acid, which had been separated by ether extraction after precipitation from the alkaline solution. It was found that the yield was not affected by heating the reaction mixture in a bath at 60° as long as the reaction is first "complete".

Ref.	Addition conditions	Conditions for completion of reaction	Yield of lactone
K 56	½ hr. at 0°	½ hr. at 0° followed by 1 ¼ hr. at room temperature	53%
K 57	½ hr. at 0°	½ hr. at 0° followed by 15 hr. at room temperature and ½ hr. at 60° (bath)	53%
K 58	½ hr. at 60° (bath)	½ hr. at 60° (bath)	35%

Confirmation was obtained for the suggestion, derived from the earlier experiments, that the yield is lowered if the reaction is accomplished at 60° as distinct from 0° (compare K 58 with K 57 and 56). The yield seems to

decrease with increase of the mixing time, until a minimum yield is obtained which is not affected by further increase of the time over which the phenyl magnesium bromide solution is added to the solution of (-)-menthyl laevulate.

Ref.	Addition conditions	Conditions for completion of reaction	Yield of lactone
K 59	5 mins. at 0°	55 mins. at 0°, 1 hr. at room temperature	63%
K 56	½ hr. at 0°	½ hr. at 0°, 1¼ hr. at room temperature	53%
K 60	2¼ hr. at 0°	¼ hr. at 0°, 1 hr. at room temperature	50%

(vi) Relationship between reaction conditions and degree of asymmetric synthesis (i.e. specific rotation of product)

From the experiments carried out in this series (see above) it is apparent that the degree of asymmetric synthesis depends, in some way, on the conditions employed for the reaction. With the limited data so far obtained from these experiments it is impossible to state fully the relationship between these two factors.

It appears that if other reaction conditions are similar the degree of asymmetric synthesis is dependent (to a certain extent) on the mixing time (cf. experiments K 59, K 56 and K 60). There was an apparent lack of variation in the degree of asymmetric synthesis with variation of the temperature at which the reaction was carried out, at least under the particular reaction conditions employed (K 58 and K 61).

Relationship between specific rotation of lactone and rotation conditions

Ref.	Mixing conditions	Conditions for completion of reaction	$[\alpha]_{5780}$ (concn.) lactone
K 59	5 mins at 0°	55 mins at 0°, 1 hr. at room temperature	-3.0(11.03)
K 56	¼ hr. at 0°	½ hr. at 0°, 1¼ hrs. at room temperature	-4.0(7.83)
K 57	½ hr. at 0°	½ hr. at 0°, 15 hrs. at room temperature, ½ hr. at 60° (bath)	-4.0(3.85)
K 58	½ hr. at 60° (bath)	½ hr. at 60° (bath)	-4.2(5.75)
K 61	25 mins at 0°	½ hr. at 60° (bath)	-4.3(5.05)
K 60	2¼ hrs. at 0°	¼ hr. at 0°, 1 hr. at room temperature	-4.8(8.85)

In all the experiments described above (-)-menthyl laevulate was treated with phenyl magnesium bromide (1.25 molecular proportions). Experiments carried out using 2.25 and 4.0 molecular proportions of phenyl magnesium bromide gave γ-phenyl-γ-valerolactone in 26% and 12% yield respectively, of specific rotation $[\alpha]_{5780}$ -2.2° (c, 4.55) and $[\alpha]_{5780}$ -3.1° (c, 1.625) respectively.

(vii) Further observations, from large scale experiments, on the relationship between reaction conditions and results

The tentative suggestions enumerated above, as to the relationships existing between experimental conditions, yields and degrees of asymmetric synthesis, had to be

verified. It seemed that more useful information would be obtained by carrying out reactions on a larger scale (0.1 g. mol. or 0.8 g. mol. of ester instead of 0.02 g. mol.) and investigating the reaction products more fully.

The apparatus and conditions were essentially the same as those used for the preliminary experiments, but the ester solution was stirred during the addition of the Grignard solution. Of the seven large scale experiments, four were carried out under similar conditions with variation only in the time taken for addition of the phenyl magnesium bromide to the solution of ester at 0°. In these experiments stirring was discontinued when addition was complete, and the reaction mixture was kept at 0° overnight.

Ref.	Addition time	Yield⊕	$[\alpha]^{25}_{5780}$	(concn)
K 63	1 min.	61%	-3.0	(15.00)
K 64	1 hr.	44%	-5.5	(15.12)
K 68	2¾ hr.	46%	-5.3	(10.23)
K 65	3 hr. 50 mins.	39%	-5.1	(8.57)

(⊕) The yield is calculated as if the product consisted entirely of the lactone; for a discussion on the constitution of the product see later in this section.

Comparable results from preliminary experiments are tabulated below:-

Ref.	Mixing conditions	Conditions for completion of reaction	Yield of lactone	$[\alpha]_{5780}$ (concn) lactone
K 59	5 mins at 0°	55 mins at 0°, 1 hr. at room temperature	63%	−3.0(11.03)
K 56	½ hr. at 0°	½ hr. at 0°, 1¼ hrs. at room temperature	53%	−4.0(7.83)
K 57	½ hr. at 0°	½ hr. at 0°, 15 hrs. at room temperature, ½ hr. at 60° (bath)	53%	−4.0(3.85)
K 60	2¼ hrs. at 0°	¼ hr. at 0°, 1 hr. at room temperature	50%	−4.8(8.85)

Mixing of the reactants at 0° over a short period of time, and then allowing to stand, gave results in good agreement with those of preliminary experiments (cf. K 59), *viz.* a good yield (*ca.* 60%) and a low specific rotation ($[\alpha]_{5780}$ −3.0°). The three experiments carried out with a mixing time of 1 hour, 2 hours 45 mins. and 3 hours 50 mins. respectively, gave a product (for composition see later this section) in rather lower yield, and with a somewhat higher specific rotation, than would have been expected from preliminary results.

Since the conditions of these large scale experiments were essentially similar to those of the small scale experiments, apart from the use of stirring in place of hand shaking. It appeared probable that it was this change

in procedure that led to unexpected results. Confirmation of this point was afforded by the results obtained on continuing stirring after the mixing of the reactants.

Ref.	Addition time	Treatment before decomposition	Yield of lactone	$[\alpha]_{5780}$ (conc)
K 63	1 min. at 0°	Kept overnight at 0°	61%	-3.0 (15.00)
K 64	1 hr. at 0°	Kept overnight at 0°	44%	-5.5 (15.12)
K 69	30 mins. at 0°	Stirred at 0° for 1 hr. and kept at 0° overnight	50%	-6.1 (13.37)
K 104	30 mins. at 0°	- " -	47%	-6.6 (10.06)

A product was obtained with a specific rotation higher than would have been expected if the degree of asymmetric synthesis were directly related to the time of addition, or if it tended to a maximum after a certain addition time. Further, repetition of this experiment gave a product with a slightly higher specific rotation; if stirring were such a critical factor in determining the degree of asymmetric synthesis obtained, this difficulty in repeating results would be explained. In fact it appears that duration of stirring and rate of stirring are as important in determining the degree of asymmetric synthesis as is the length of the addition period.

In one experiment the reactants were mixed at -30° to -40°, and the mixture was stirred below -20° for 30 mins. and then kept overnight at 0°. This experiment also gave a product with a high rotation ($[\alpha]_{5780}$ -7°; yield 46%).

It became apparent from these experiments (as further discussed below) that further elucidation of the effect of reaction conditions on degree of asymmetric synthesis was outside the scope of this investigation, and an additional complication was that the lactone finally isolated was found to contain traces of an acid which could not be ring closed to a neutral product and thus was not γ-hydroxy-γ-phenylvaleric acid. The occurrence of this "free acid" was established by examination of the products obtained in the large scale experiments. In these experiments, as in the small scale experiments, the alkaline solution from the hydrolysis was freed from menthol and then acidified. The organic acid (thought to be only γ-hydroxy-γ-phenylvaleric acid) was isolated ~~by~~ employing ether extraction. Ring closure to obtain the lactone was effected by repeated distillation of benzene from the hydroxy acid; results obtained using pure γ-hydroxy-γ-phenylvaleric acid showed this method to be satisfactory. Titration gave a rough indication of the purity of the γ-phenyl-γ-valerolactone so obtained. In general, samples (2 ml.) of the ethanol solution of the lactone (1 - 3 g. in 20 ml.), prepared for polarimetric observation, were diluted with water and rapidly titrated

with 0.1 N-sodium hydroxide solution (to phenol phthalein). Excess sodium hydroxide solution was then added, and the solution boiled in order to open the ring; the final excess of sodium hydroxide was determined by back titration of the hot solution with standard acid. Results obtained are recorded below:

Ref.	Addition period	Further stirring period(0°)	Conc. of mixture g/20ml.	Approx. % free acid in mixture+	% lactone in mixture*
K63	1 min.	-	3.001	4%	96%
K64	1 hour	-	3.024	18%	83%
	after retreating with benzene		1.143	18%	86%
K68	2 3/4 hour	-	2.045	20%	78%
	after treatment with sodium carbonate		0.840	3%	95%
K65	3 hr. 50 min.	-	1.713	25%	80%
K69	30 min.	1 hour	2.673	14%	83%
	after treatment with sodium carbonate		1.680	2%	97%
-	different specimen after treatment with sodium carbonate		2.565	1%	95%
K104	30 min.	1 hour	2.012	13%	85%
	after treatment with sodium carbonate		1.038	2%	96%

+ $\frac{\text{(NaOH to neutralise acid) x 100}}{\text{total NaOH}}$; this ratio is a guide to % of acid in the mixture assuming the M.Wts. of the acid and lactone are approximately the same.

* $\frac{\text{(Equivs. of NaOH neutralised on boiling) x M.Wt. of lactone x 100}}{\text{wt. of crude mixture taken}}$

These results suggest that some acidic compound(s) or derivative(s), other than (-)-menthyl-γ-hydroxy-γ-phenylvalerate, was formed during the Grignard reaction. This "free acid" could be removed from the lactone by washing an ethereal solution of the "lactone + acid" with sodium carbonate solution (cf. preceding Table); the γ-phenyl-γ-valerolactone thus obtained was analytically pure and also gave analytically pure γ-hydroxy-γ-phenylvaleric acid on alkaline hydrolysis. Reconversion into the lactone gave a product with a negligible acid titration (< 0.20 ml., irrespective of the weight of material taken); a titration of this order would thus appear to be a blank for this method (see also Section IIIh). A small amount of the lactone (ca. 4 ml.) was distilled; the distillate, b.p. 134-139°/7 mm., had $n_D^{25^\circ}$ 1.5282 [Trivedi and Nargund (1941) record b.p. 145-147°/5 mm. and $n_D^{32.5^\circ}$ 1.5273; Grignard (1902) 168-170°/17 mm., $n_D^{17.4^\circ}$ 1.5300, and Johnson, Petersen and Schneider (1947) b.p. 140-145°/5 mm. and $n_D^{20^\circ}$ 1.5315].

By ether extraction of the acidified sodium carbonate extracts a small amount of dark brown viscous oil was obtained - about 20% of what could be expected from titration figures; it was not possible to decolourise this product (e.g. by charcoal). It will be remembered that, during the earlier work, gradual acidification of an alkaline solution of γ-hydroxy-γ-phenylvaleric acid sometimes led to the separation of a dark brown oil before the hydroxy

acid had separated. It is of interest that the washing with carbonate removed almost all the colour from the lactone. The result obtained from K64, viz. that re-treatment with benzene did not decrease the amount of "acid" in the "lactone + acid", proves that the acid was not γ-hydroxy-γ-phenyl-valeric acid. The dark brown oil obtained from the lactone was not appreciably soluble in water, which would suggest that it was not laevulic acid. The oil was partially soluble in light petroleum (b.p. 40-60°) and in carbon tetrachloride. Its partial solubility in these solvents suggested that it was not homogeneous. As far as could be judged, a carbon tetrachloride "solution" decolourised bromine. Attempts to prepare a 2:4-dinitrophenylhydrazone failed. In one experiment the "free acid" was examined polarimetrically, and was found to have a specific rotation ($[\alpha]^{25^\circ}_{5780}$) of ca. -7°.

The titration experiments indicated that the purity of the "crude lactone" was usually greater than 80%, and comparison of the specific rotation of the "crude lactone" (lactone + acid) with that of the lactone after sodium carbonate treatment shows that the difference in values is not marked.

Crude lactone ("lactone + acid")				Lactone after Na_2CO_3 treatment		
$[\alpha]_{5780}$	$[\alpha]_{5461}$	concn.	% lactone (approx.)	$[\alpha]_{5780}$	$[\alpha]_{5461}$	concn.
-5.3	-6.0	10.2	78	-5.7	-6.7	4.2
-6.1	*	13.4	83	-6.4	-7.2	8.4
-6.6	-7.5	10.1	85	-6.8	-7.7	10.1
* not observable - solution too coloured						

It is thus considered permissible to base general conclusions, on the effect of conditions on degree of asymmetric synthesis, on comparisons of the specific rotations of the "crude lactones" obtained in different experiments.

It was thought that the "free acid" might have been formed during the Grignard reaction. Attempts were made to isolate any acidic products that might be formed during this reaction, by washing the ethereal extract of the decomposed reaction mixture repeatedly with sodium carbonate solution. In most cases a small amount of dark brown oil was isolated by acidification of this solution; but, even after eight washings with sodium carbonate solution, coloured material - presumably acidic - was being extracted from the ethereal solution. From the experiment conducted at -30° to -40°, a semi-solid product was obtained (0.21 g. from a 0.1 molar experiment), which gave white plates on crystallisation from light petroleum (b.p. $40-60^{\circ}$). These plates, m.p. $70-74^{\circ}$, decolourised bromine. There was insufficient of the material to purify for analysis.

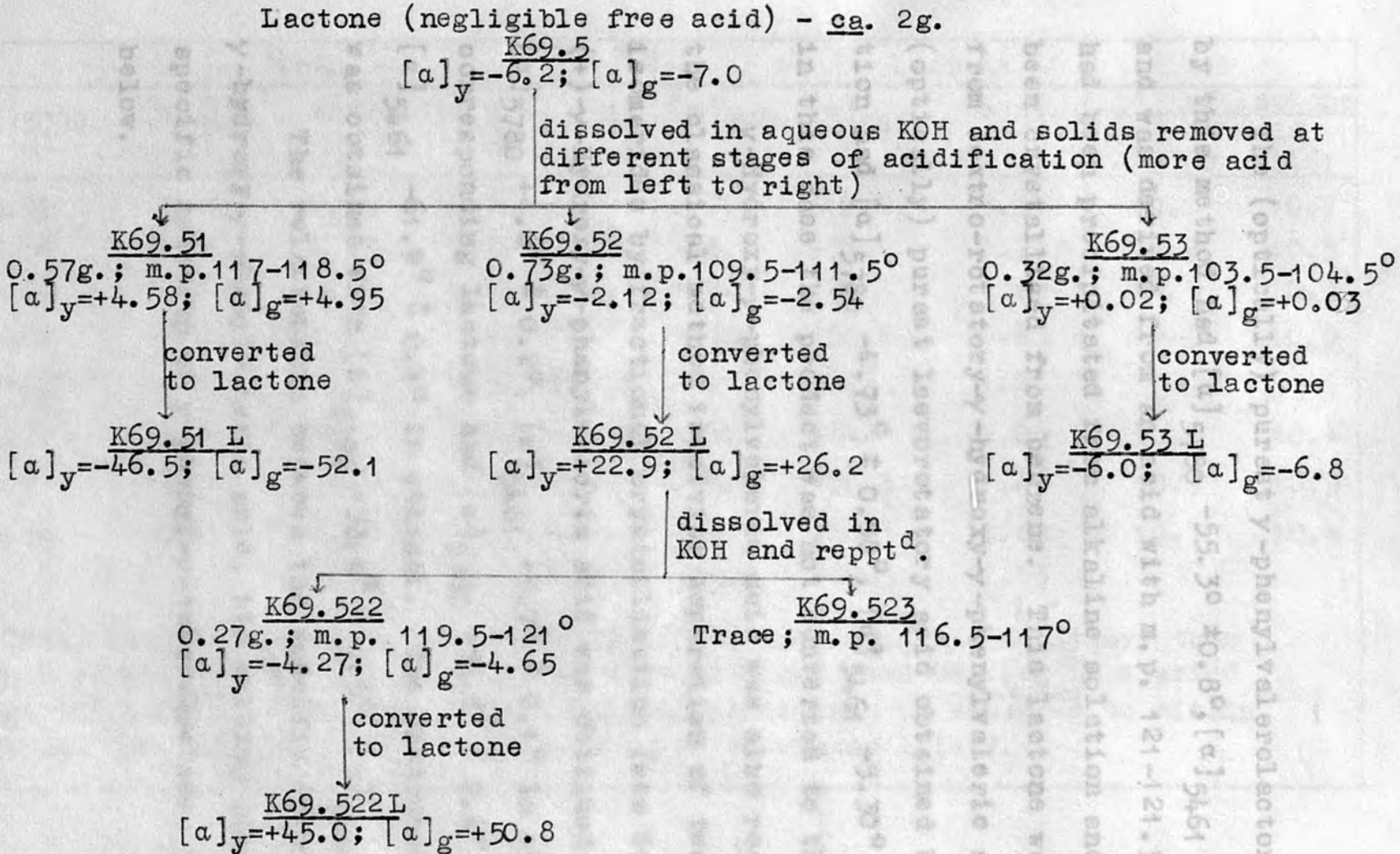
It was likely that γ-phenyl-γ-valerolactone would have been the precursor of any 4-phenyl-3-pentenoic acid present in the "free acid" (see Section V). Attempts were made to extract γ-phenyl-γ-valerolactone from the ether extract of the decomposed Grignard reaction mixture by shaking with strong potassium hydroxide solution. These were unsuccessful;

but a small amount of acid was isolated which appeared similar to that isolated with sodium carbonate solution although it was not examined for identification.

(viii) Optical examination of γ-hydroxy-γ-phenyl-valeric acid precipitated from alkaline solution

It was observed during early experiments that a lactone derived from an acid which had been reprecipitated from an aqueous solution had, in general, a specific rotation higher than the lactone of the original acid.

If an alkaline solution of the γ-hydroxy-γ-phenyl-valeric acid (containing an excess of one antipode) was partially acidified and the hydroxy-acid allowed to crystallise, the acid so obtained had a large excess of one of the antipodes (the one originally in small excess). If this crop was removed, further acidification of the mother liquor gave a product which had an excess of the other antipode. Thus, by repeated precipitation of the hydroxy-acid by acidification of an alkaline solution, it is possible to obtain products of a high enough degree of optical purity to permit complete purification to be achieved by recrystallisation from (say) benzene. Resolution can therefore be effected, and both antipodes obtained in a state of optical purity. Results obtained in one experiment are shown below.



Note: $[\alpha]_{5780}$ and $[\alpha]_{5461}$ are denoted by $[\alpha]_y$ and $[\alpha]_g$ respectively.

The (optically) purest γ-phenylvalerolactone obtained by this method had $[\alpha]_{5780}$ -55.3° ±0.8°, $[\alpha]_{5461}$ -62.5° ±0.8°, and was derived from an acid with m.p. 121-121.5°, which had been precipitated from alkaline solution and had not been crystallised from benzene. This lactone was obtained from dextro-rotatory-γ-hydroxy-γ-phenylvaleric acid. The (optically) purest laevorotatory acid obtained by precipitation had $[\alpha]_{5780}$ -4.73° ± 0.08°, $[\alpha]_{5461}$ -5.30° ± 0.08°; in this case the product was not converted to the lactone.

γ-Hydroxy-γ-phenylvaleric acid was also resolved by the classical method involving separation of two diastereoisomerides by fractional crystallisation (see Section VII). (+)-γ-Hydroxy-γ-phenylvaleric acid was obtained with $[\alpha]_{5780}$ +4.8° ± 0.2°, $[\alpha]_{5461}$ +5.7° ± 0.1° in ethanol; the corresponding lactone had $[\alpha]_{5780}$ -54.8° ± 0.4°, $[\alpha]_{5461}$ -61.9° ± 0.4° in ethanol. The dextrorotatory lactone was obtained with $[\alpha]_{5780}$ +53.9° ± 0.5°, $[\alpha]_{5461}$ +61.8° ± 0.5°.

The relationship between the specific rotation of γ-hydroxy-γ-phenylvaleric acid, its melting point, and the specific rotation of γ-phenyl-γ-valerolactone, is shown below.

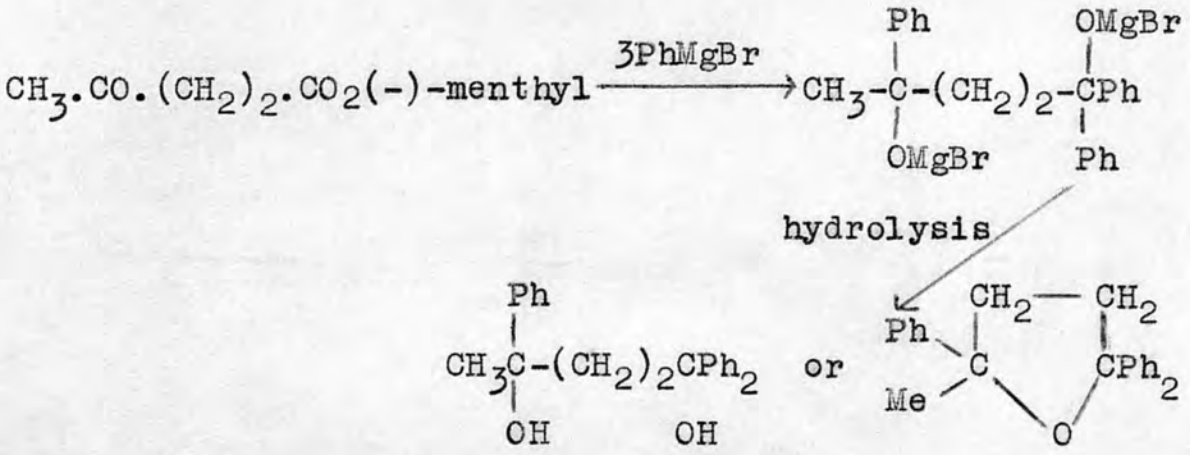
Ref.	Acid				Lactone			$\frac{[\alpha] \text{ of lactone}}{[\alpha] \text{ of acid}}$	
	$[\alpha]_{5780}$	$[\alpha]_{5461}$	conc.	m.p.+	$[\alpha]_{5780}$	$[\alpha]_{5461}$	conc.	λ=5780	5461
K 69.41	+0.87	+0.94	6.29	107.5-108°	-8.8	-10.2	3.34	10.1	10.7
K 69.51	+4.58	+4.95	2.73	117-118.5°	-46.5	-52.1	0.72	10.2	10.5
K 69.52	-2.12	-2.54	3.54	109.5-111.5°	+22.9	+26.2	2.16	10.8	10.3
K 69.522	-4.27	-4.65	1.29	119.5-121°	+45.0	+50.8	0.85	10.5	10.9
K 69.53	α=+0.02	α=+0.03	1.47	103.5-104.5°	-6.0	-6.8	1.24		
KR1.2	-4.73	-5.30	5.22	119.5-120.5°	+48.2	+54.9	2.06	10.2	10.4
KRre	+4.97	+5.64	2.22	119.5-120.5°	+54.4	+61.3	1.46	10.9	10.9
KRre	-4.94	-5.77	1.82	119.5-120.5°	+52.8	+60.3	1.13	10.7	10.4
KR1.31				121-121.5°	-55.3	-62.5	0.63		

+ The melting point obtained by slow heating of the specimen in a capillary tube from room temperature is not so sharp as that obtained when heating is started at about 10° below the melting point. Melting points can be repeated to within 1° although the hydroxy acid decomposes to give an opaque liquid.

It will be observed from the above that the specific rotation of the lactone is of the order of 10.5 times as great as that of the hydroxy-acid, and is of opposite sign.

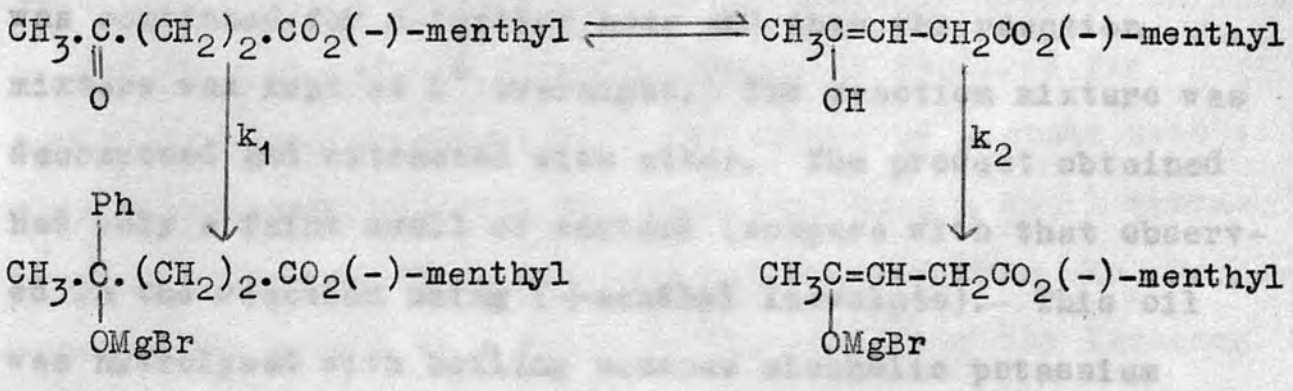
(ix) Neutral products obtained

So far no mention has been made of the neutral products obtained by the following reactions:-

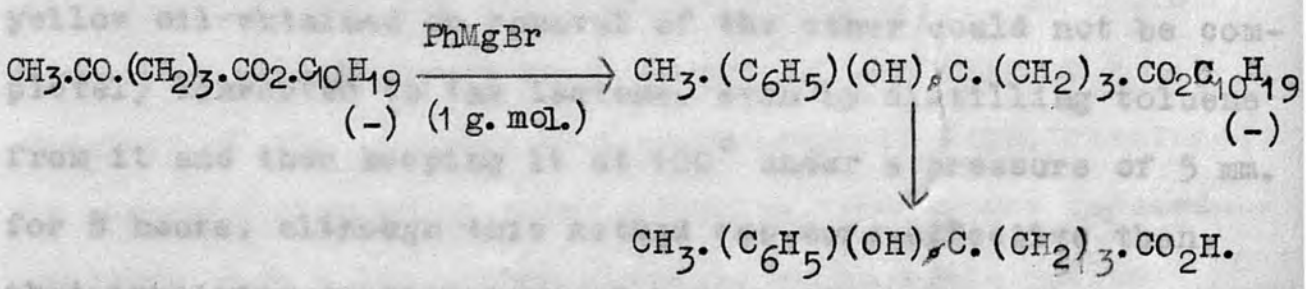


Grignard (1902) reported the isolation of the ring compound from the analogous reaction using the ethyl ester. In this investigation neutral by-products were isolated from the extract containing menthol, after removal of the latter by steam distillation. In the preliminary experiments small amounts of neutral products were isolated and were found to be optically inactive; the yield of neutral products in the larger scale experiments were of the same order. The amounts isolated were not enough to account for the low yields, and it must be assumed that the low yields were partly due to enolisation of the keto-ester. If this were the case, the decrease of yield with prolonged mixing time

might be due to the rate of reaction of the Grignard reagent with the enol (k_2) being greater than that with the keto (k_1). If so, the laevulic acid obtained after the hydrolysis would probably remain in the aqueous layer during ether extraction.



III h. Interaction of (-)-menthyl ω-acetyl-n-butyrate and phenyl magnesium bromide



One experiment was carried out using 0.08 g. mol. of (-)-menthyl ω-acetyl-n-butyrate and 0.1 g. mol. of phenyl magnesium bromide so as to have enough material for the study of the conversion of the 4-hydroxy-4-phenyl-pentan-1-carboxylic acid (δ-hydroxy-δ-phenylcaproic acid) to the corresponding lactone. Two smaller experiments (0.02 g. mol. of ester) were subsequently carried out to ascertain if the

degree of asymmetric synthesis were dependent on conditions used.

In the large scale experiment the phenyl magnesium bromide solution was added to the ethereal solution of the ester, with ice cooling and stirring, over ½ hour; stirring was continued for a further hour and then the reaction mixture was kept at 0° overnight. The reaction mixture was decomposed and extracted with ether. The product obtained had only a faint smell of menthol (compare with that observed in the reaction using (-)-menthyl laevulate). This oil was hydrolysed with boiling aqueous alcoholic potassium hydroxide solution. After removal of the menthol the solution was acidified and the product extracted with ether. The yellow oil obtained on removal of the ether could not be completely converted to the lactone, even by distilling toluene from it and then keeping it at 100° under a pressure of 5 mm. for 8 hours, although this method was more effective than that involving distillation of benzene from the oil and then keeping it at 100° at 5 mm. for 3 hours. The course of the ring closure was followed by titrating with 0.1 N-sodium hydroxide solution. Assuming δ-hydroxy-δ-phenylcaproic acid to have a very small rotation, compared with that of the corresponding lactone, no racemisation occurred even on distilling toluene from it. Eventually the lactone was obtained free from acid by washing an ethereal solution of

the mixture with sodium carbonate solution. A good analysis was obtained for the lactone prepared in this manner; it separated as rhomboid crystals from an ethanolic solution concentrated almost to dryness. By titration it showed a low free acid content, which was of the same order as the free acid content of γ-phenyl-γ-valerolactone treated in this manner (0,2 ml. of 0.1 N-sodium hydroxide required for neutralisation irrespective of the amount of lactone used); this observation supports the idea that such a small titration is a method error, and does not detract from the usefulness of the method as a guide to the purity of the lactones.

Ether extraction of the acidified sodium carbonate extracts gave a relatively low yield of acid, which was optically inactive and was not examined chemically. It could have been acetylbutyric acid, since the analysis of a specimen of the δ-hydroxy-δ-phenylcaproic acid, obtained by concentration of an ether solution at 0° under reduced pressure gave a low carbon content, which could not be attributed to partial lactonisation, since this would have given a product with a high carbon content. If the acid were in fact acetylbutyric acid, which is freely soluble in water, and is extracted with ether from an aqueous solution only with difficulty, a low yield of acid on extraction of an aqueous solution would be expected.

Since the conversion of the two isomeric δ-hydroxy-δ-phenylcaproic acids to the corresponding lactones will

proceed at the same rate, no attempt was made to obtain complete conversion in the case of the specimens to be used for optical observations. Partial conversion was effected by repeated distillation of benzene from the product and then keeping the product at 100° under a pressure of 5 mm. for three hours. An ethereal solution of the mixture thus obtained was washed with sodium carbonate solution followed by water, and dried over sodium sulphate. Removal of the ether gave a product suitable for optical investigation.

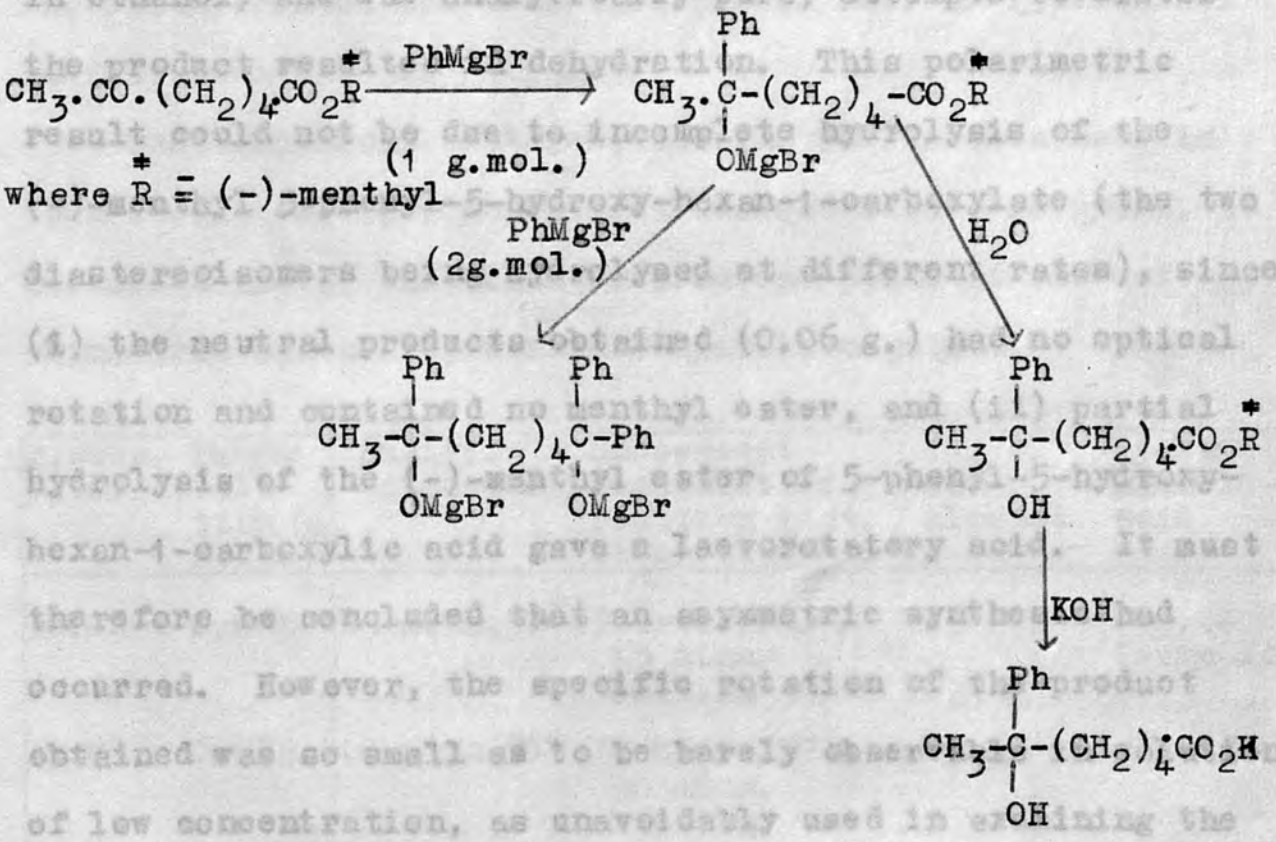
In the two small scale experiments, addition of the Grignard solution to the ester solution occupied 1 min. and ½ hour respectively, with shaking; the solutions were kept overnight at 0° before decomposition. The product obtained by the slow addition of the Grignard solution was more coloured than that from the fast addition experiment (as was the case in the experiments using (-)- menthyl laevulate) the colour was likewise removed when the lactone was washed with sodium carbonate solution.

g.mol. ester	g.mol. PhMgBr	Reaction conditions before keeping overnight (0°)	m.p. lactone	$[\alpha]_{5780}$	$[\alpha]_{5461}$	concn.
0.08	0.10	Addition with stirring over ½ hr. stirring continued further 1 hr.	62°	-0.22 ±0.04°	-0.24 ±0.04°	12.033
0.02	0.025	Addition with shaking over 1 min.	70-72°	-2.21 ±0.15	-2.52 ±0.15	5.626
0.02	0.025	Addition with shaking over 30 min.	68-71°	-1.32 ±0.08	-1.47 ±0.08	6.466

The yields, which were of the order of 60%, are of little value for comparative purpose since the exact composition of the product was not known.

The neutral product, freed from menthol by steam distillation, was not very soluble in alcohol. A solution of this product in ethanol-chloroform mixture was optically inactive, showing that complete hydrolysis of the ester had occurred.

IIIj. Interaction of (-)-menthyl-δ-acetyl-n-valerate and phenyl magnesium bromide



Three experiments were carried out using 0.025 g. mols of phenyl magnesium bromide to 0.02 g. mols of (-)-menthyl acetylvalerate. None of these experiments yielded 5-phenyl-5-hydroxy-hexan-1-carboxylic acid which exhibited an optical

rotation in ethanol solution (c, 9 to 18). In one of the experiments the crude 5-phenyl-5-hydroxy-hexan-1-carboxylic acid (yellow oil), titrated against NaOH, had a M.W. 219 (calc. for $C_{13}H_{18}O_3$, 222). Experiments using 0.045 g. mols and 0.06 g. mols of PhMgBr to 0.02 g. mols of (-)-menthyl acetylvalerate also yielded hydroxy acid which exhibited no optical activity. However, when an experiment was carried out using 22.26 g. (0.08 g. mol.) of (-)-menthyl-ω-acetyl-n-valerate, the product obtained had α_{5780} +0.09° (c, = 50 in ethanol) and was analytically pure; attempts to distil the product resulted in dehydration. This polarimetric result could not be due to incomplete hydrolysis of the (-)-menthyl 5-phenyl-5-hydroxy-hexan-1-carboxylate (the two diastereoisomers being hydrolysed at different rates), since (i) the neutral products obtained (0.06 g.) had no optical rotation and contained no menthyl ester, and (ii) partial hydrolysis of the (-)-menthyl ester of 5-phenyl-5-hydroxy-hexan-1-carboxylic acid gave a laevorotatory acid. It must therefore be concluded that an asymmetric synthesis had occurred. However, the specific rotation of the product obtained was so small as to be barely observable in solutions of low concentration, as unavoidably used in examining the products obtained in the small-scale experiments.

In the examination of the neutral products (including menthol and $CH_3.C(OH)Ph.(CH_2)_4.C(OH)Ph_2$) extracted by ether

from the hydrolysate, steam distillation was found to be the only satisfactory method for removing menthol; boiling with water for a prolonged period of time was unsatisfactory. After removal of the menthol by steam distillation, the product (assumed to be 1:6-dihydroxy-1:1:6-triphenylheptane, $H_3C-\overset{Ph}{\underset{OH}{C}}-(CH_2)_4-\overset{Ph}{\underset{OH}{C}}-Ph$), was removed by ether extraction, and in all cases was found to exhibit no pronounced optical activity (-0.05° observed in one case) even when 4 g. mols. of phenyl magnesium bromide had been used per g. mol. of (-)-menthyl acetylvalerate.

The conditions employed, and the yields obtained, in this series of experiments are recorded below, although, as discussed above, the results, from the point of view of asymmetric synthesis, were essentially negative.

g.mols. ester	PhMgBr solution (g. mols.)	Addition conditions	Subsequent treatment of reaction mixt. before decomp.	Wt. of di-alcohol	Wt. of hydroxy-acid
0.02	0.025	25 mins./17°	3 hrs./17°; 15 mins. boiling	-	1.9g. (43%) (some lost)
0.02	0.025	10 mins./30°	30 mins./17°; 90 mins. boiling	-	3.17g. (72%)
0.02	0.025	10 mins./60°	30 mins./17°; 90 mins. boiling	Trace	3.50 g. (80%)
0.02	0.045	10 mins./60°	90 mins./60°	1.5g. (21%)	2.54g. (58%)
0.015	0.06	10 mins./60°	3 hrs./60°	3.6g. (68%)	0.56g. (13%)
0.08	0.10	30 mins./0°/ stirring	60 mins./0 stood overnight	0.06g.	14.86g. (84%)

IIIk. Interaction of (-)-menthyl ω-acetylpelargonate and phenyl magnesium bromide

$$CH_3.CO.(CH_2)_8.CO_2C_{10}H_{19} \xrightarrow[(1\,g.mol.)]{PhMgBr} CH_3(C_6H_5)(OH)C.(CH_2)_8.CO_2C_{10}H_{19}$$
$$(-) \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad (-)$$

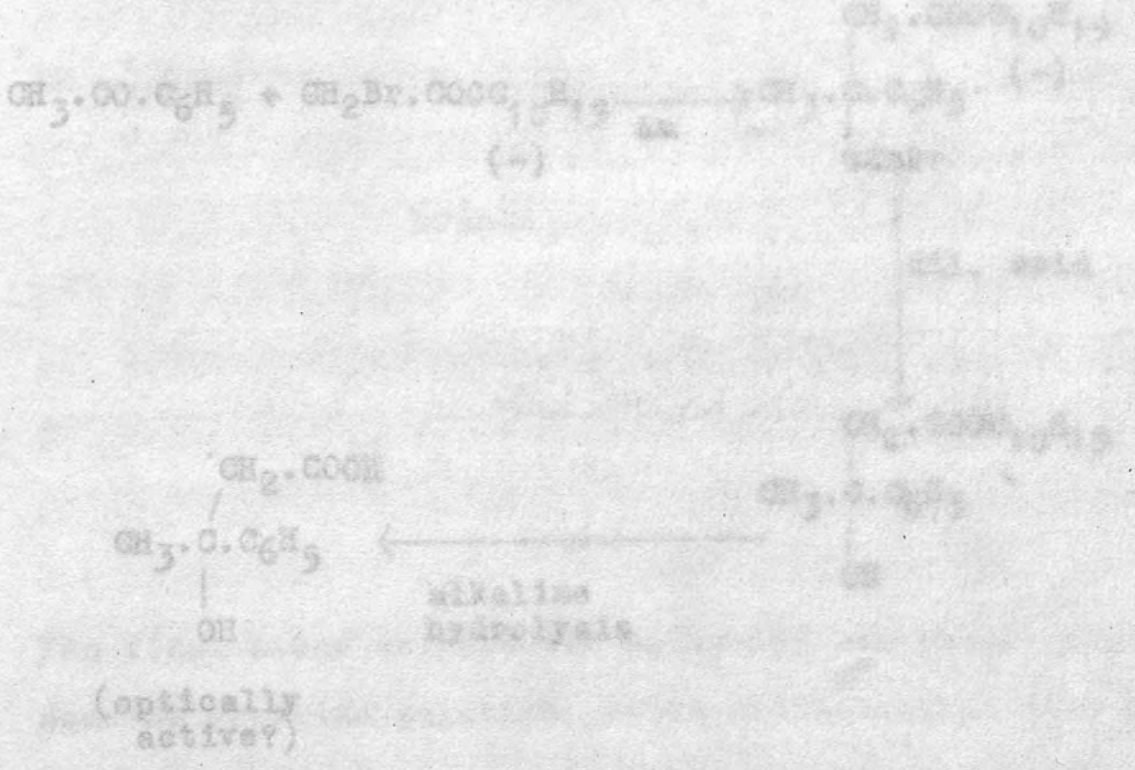
$$\downarrow$$

$$CH_3(C_6H_5)(OH)C.(CH_2)_8.CO_2H$$
$$\text{(optically active?)}$$

The one experiment carried out to study this reaction gave a product which exhibited no optical activity in ethanol solution (c. = 23.7). It is impossible to state the percentage yield of the 9-hydroxy-9-phenyl-decane-1-carboxylic acid since the product was not pure. On standing, crystals separated from the yellow oil obtained after hydrolysis, but there was not complete solidification, even on prolonged standing. The analysis gave a low carbon content, which suggests that the product was mixed with unchanged acetylpelargonic acid (presumably enol reaction had taken place). Since a negative result had been obtained from this experiment no further experiments were carried out.

IV.

INTERACTION OF ACETOPHENONE, (-)-MENTHYL BROMOACETATE AND ZINC

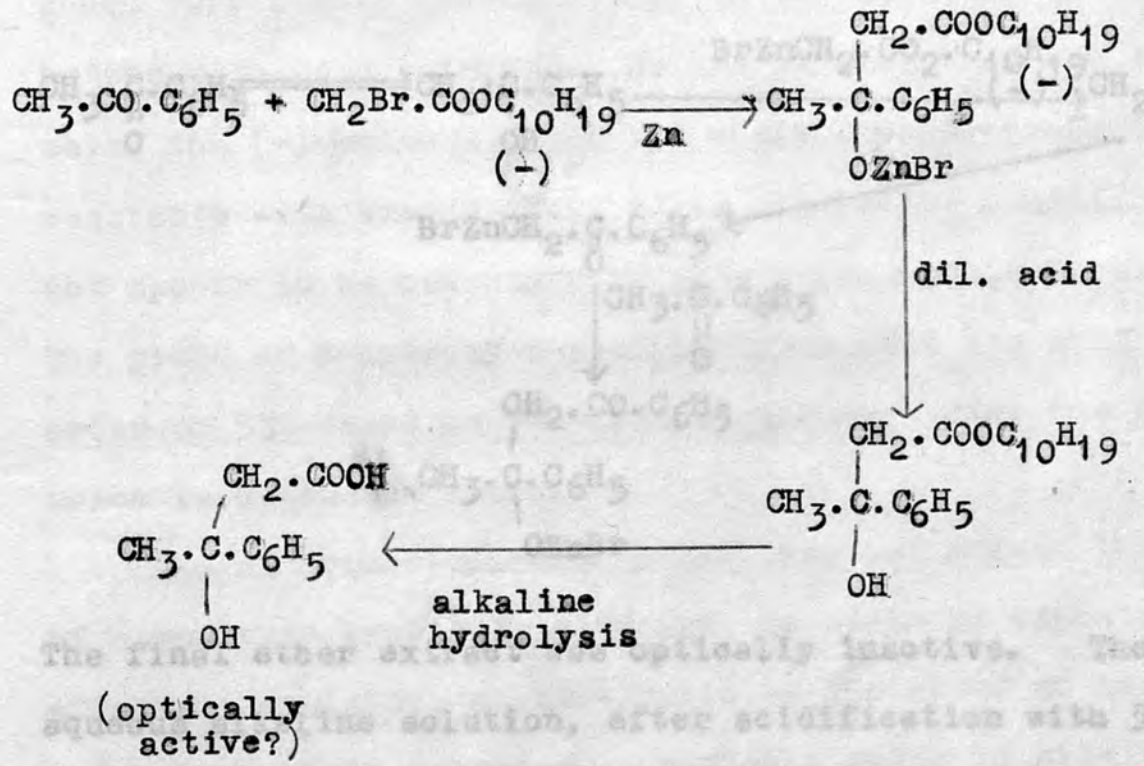


(optically active?)

(-)-Menthyl bromoacetate, zinc and acetophenone were allowed to react in benzene solution under varying conditions. Preliminary experiments were carried out on a [illegible] scale. The organometallic complex was decomposed with 5N-sulphuric acid and ice, and the aqueous solution extracted repeatedly with ether, the final aqueous layer having no optical activity. The reaction product, obtained

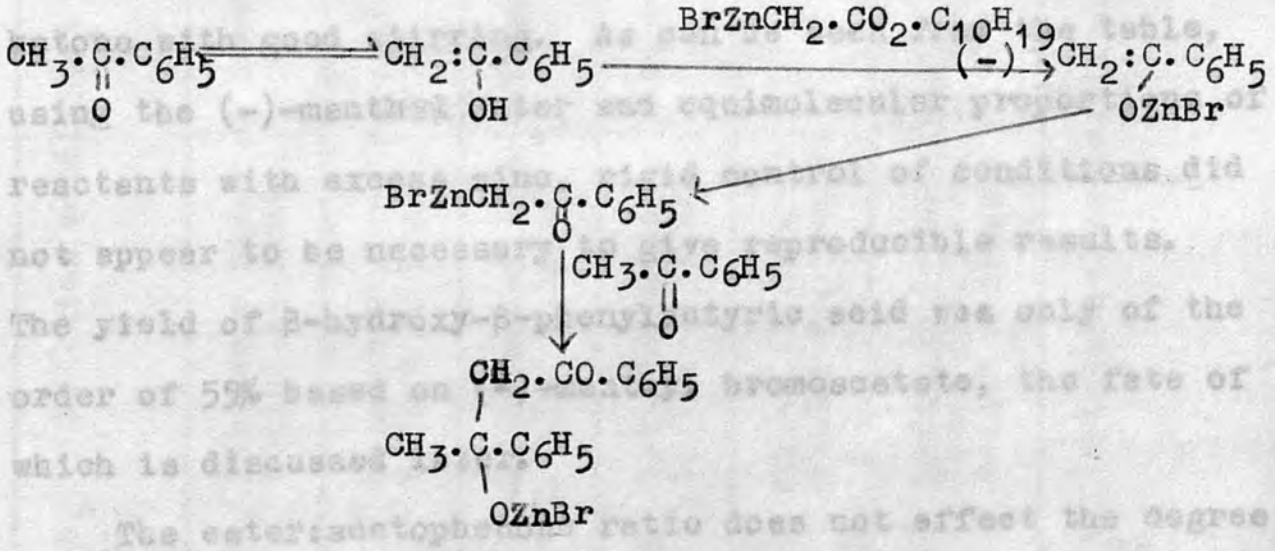
IV. INTERACTION OF ACETOPHENONE, (-)-MENTHYL BROMOACETATE AND ZINC

It was proposed to examine the β-hydroxy-β-phenylbutyric acid prepared by the interaction of acetophenone and (-)-menthyl bromoacetate in the presence of zinc (Reformatsky reaction) with subsequent hydrolysis, with a view to ascertaining whether any asymmetric synthesis had occurred.



(-)-Menthyl bromoacetate, zinc and acetophenone were allowed to react in benzene solution under varying conditions. Preliminary experiments were carried out on a 0.02 g. mol. scale. The organometallic complex was decomposed with 5N-sulphuric acid and ice, and the aqueous solution extracted repeatedly with ether, the final aqueous layer having no optical activity. The reaction product, obtained

by concentration of this ethereal extract, did not smell of menthol. Hydrolysis of this product was effected with 2.5N aqueous alcoholic KOH. The hydrolysate, from which the alcohol had been removed by distillation, was extracted repeatedly with ether to remove neutral products such as menthol, acetophenone and traces of neutral condensation products which might be formed by the following series of reactions:-



The final ether extract was optically inactive. The aqueous alkaline solution, after acidification with 5N-sulphuric acid, was ether extracted until the final aqueous layer was optically inactive. The ether extract was washed with water until free from inorganic acid, dried over sodium sulphate, and concentrated to dryness; the β-hydroxy-β-phenyl-butyric acid thus obtained was examined polarimetrically.

Initially, experiments were carried out employing an

excess of acetophenone relative to menthyl bromoacetate or vice versa, with zinc in equimolecular proportion to the amount of ester used. Finally, equimolecular proportions of acetophenone and (-)-menthyl bromoacetate were used in the presence of excess zinc (50% in excess of theory) according to Lipkin and Stewart (1939)+. Lipkin and Stewart claim to have perfected conditions for the Reformatsky reaction which will give reproducible results; the ester is added very slowly (10-12 hours) to the solution of the ketone with good stirring. As can be seen from the table, using the (-)-menthyl ester and equimolecular proportions of reactants with excess zinc, rigid control of conditions did not appear to be necessary to give reproducible results. The yield of β-hydroxy-β-phenylbutyric acid was only of the order of 55% based on (-)-menthyl bromoacetate, the fate of which is discussed later.

The ester:acetophenone ratio does not affect the degree of asymmetric synthesis although, as would be expected, it affects the yield; as this ratio is decreased so does the percentage yield decrease, presumably owing to side reactions of the ester such as coupling (see above). This ratio appeared to be the only factor that appreciably affected the yield, concentrations and time of reaction having no effect.

The degree of asymmetric synthesis, i.e. the specific rotation of the product (which was of the order of

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(+) In this paper it is stated that 234g. of ethyl bromoacetate was used. This appears to be a misprint for 334g., on which the yields are calculated and which is the correct molar quantity.

Ester g. (g.mol.)	Ketone g. (g.mol.)	Zinc g. (g.mol.)	C_6H_6 ml.	Reaction conditions	Hydroxy acid			
					Yield g. %	$[\alpha]_{5780}$ ± 0.05	$[\alpha]_{5461}$	c./EtOH
5.87 (0.0212)	2.40 (0.02)	1.39 (0.0212)	30	Reactants mixed at once. Boiled 4½ hours.	2.35 65%	2.57	2.89	11.75
5.54 (0.02)	2.88 (0.024)	1.31 (0.02)	15	Reactants mixed at once. Boiled 3½ hours.	1.80 50%	2.31	2.57	9.00
5.54 (0.02)	2.40 (0.02)	1.96 (0.03)	15	Ester added over 3 hours. Boiled 4 hours.	1.975 55%	2.43	2.70	9.88
5.54 (0.02)	2.40 (0.02)	1.96 (0.03)	30	Ester added over 1 hour. Boiled 9½ hours.	2.025 56%	2.40	2.73	10.13
5.54 (0.02)	2.40 (0.02)	1.96 (0.03)	10	Mixed at once. Boiled 10½ hours.	2.07 58%	2.47	2.73	10.35
30.47 (0.11)	13.2 (0.11)	10.8 (0.165)	60	Large scale experiment Ester added over 7½ hrs. Boiled 4 hours.	53%	2.34 3.10	2.64 3.38	9.1 22.55

All rotations are positive.

$[\alpha]_{5780}$ +2.4°; $[\alpha]_{5461}$ + 2.7° (c. ≈ 10 in ethanol)) showed no appreciable dependence on reaction conditions such as mixing time of the ester and ketone, period of heating, or the volume of solvent used. Any apparent variation of the specific rotation of the product can be attributed to the dependence of the specific rotation on the concentration of the solution: as the concentration is increased so does the specific rotation increase. This is shown from the following results:-

$[\alpha]_{5780}$ ±0.05°	$[\alpha]_{5461}$ ±0.05°	c.
+ 2.79	+3.15	14.35
+ 2.58	+2.87	9.83
+ 2.44	+2.73	7.74

The crude β-hydroxy-β-phenylbutyric acid, which gave a satisfactory analysis, could be crystallised from light petroleum (b.p. 100-120°). The crystallised material showed a slightly higher degree of optical activity than the crude:-

	$[\alpha]^{25°}_{5780}$ ±0.05°	$[\alpha]^{25°}_{5461}$ ±0.05°	c.
before	+2.67	+3.02	15.13
	+2.34	+2.64	9.10
after cryst.	+2.79	+3.15	14.35
	+2.44	+2.73	7.74

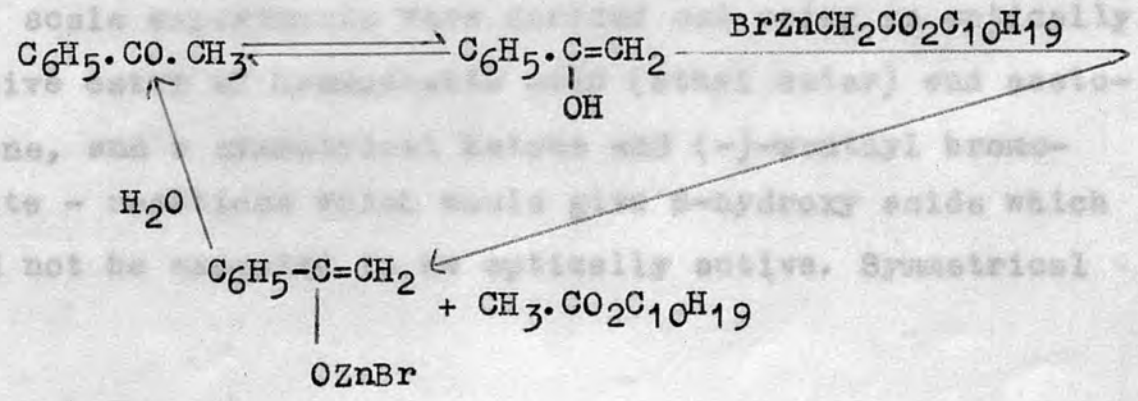
Concentration of the mother liquor yielded a product of low

specific rotation which decolourised aqueous potassium permanganate solution readily, whereas the crude product had not affected the permanganate solution.

One larger scale experiment (0.11 g.mol.) was carried out with a view to a more detailed investigation of the course of the reaction; the conditions were essentially those of Lipkin and Stewart (1939). β-Hydroxy-β-phenylbutyric acid was obtained in yield comparable to that obtained on the small scale and with the same specific rotation. It was possible to account for 83% of the (-)-menthyl bromoacetate used:-

β-Hydroxy-β-phenylbutyric acid (53% yield) would be formed from	16.0g	(-)-menthyl ester
Acetic acid (0.026 g. mol.) would be formed from	7.2g	"
Unchanged (-)-menthyl bromoacetate.	2.0g	"
Total accounted for	25.2g	
Ester used.....	30.47g	
% ester unaccounted for.....	17%	

The somewhat low yield may be attributed (compare Hussey and Newman, 1948,) to loss of material by the side-reaction:



This would account for the acetic acid, found to be present after hydrolysis. The (-)-menthyl bromoacetate unaccounted for could have been due to (i) mechanical losses, and (ii) formation of water soluble acids such as succinic acid, which would have resulted from two molecules of (-)-menthyl bromoacetate reacting together.

It was proved that the small amount of optically active neutral product that was isolated was not unhydrolysed ester. It is probable that it included neutral condensation products (see above).

Unreacted acetophenone was estimated as its 2:4-dinitrophenylhydrazone by the method of Iddles, Low, Rosen and Hart (1939). The figure obtained (29% unreacted) can only be considered as a minimum, since, prior to the estimation, loss of unreacted acetophenone might have occurred by volatilisation when the reaction mixture was subjected to (i) heating on a steam bath under reduced pressure to remove traces of benzene, and (ii) heating on a steam bath for a prolonged period to remove the alcohol from an aqueous alcoholic solution.

As checks on techniques and purity of starting materials, small scale experiments were carried out using an optically inactive ester of bromoacetic acid (ethyl ester) and acetophenone, and a symmetrical ketone and (-)-menthyl bromoacetate - reactions which would give β-hydroxy acids which would not be expected to be optically active. Symmetrical

ketones used included acetone, benzophenone and isobutyl ketone. The product obtained using acetone was too soluble to give a reliable check on conditions; the one obtained from benzophenone was not sufficiently soluble to make the conditions comparable with those of experiments using acetophenone. 2-Hydroxy-2-isobutyl-4-methyl-pentan-1-carboxylic acid was obtained as a yellow oil in 37% yield by the hydrolysis of the addition product of the Reformatsky reaction using di-isobutyl ketone and (-)-menthyl bromoacetate; no optical activity was exhibited in the crude product. It was not found possible to obtain this acid crystalline, and no attempt was made to distil it; but a satisfactory analysis was obtained for the "crude" product which did not decolourise acid potassium permanganate solution. Kon and May (1927) prepared the ethyl ester of 2-hydroxy-2-isobutyl-4-methyl-pentan-1-carboxylic acid from ethyl bromoacetate and di-isobutyl ketone in 35% yield; attempts to isolate and purify the free acid led to a mixture of unsaturated acids.

(±)-β-Hydroxy-β-phenylbutyric acid was obtained satisfactorily from ethyl bromoacetate and acetophenone as white needles, m.p. 71-72° [from light petroleum (b.p. 100-120°)]. The crude product, which exhibited no optical activity, was obtained in 65% yield, rather higher than the yield obtained from (-)-menthyl bromoacetate using the same conditions (50%). The racemic acid has previously been described only by Arbusov (1901). By oxidation of methyl-allyl-phenyl-carbinol

with 4% potassium permanganate solution and isolation of (±)-hydroxy-β-phenylbutyric acid through its silver salt, he obtained it as white needles, m.p. 50-53°; the silver content of the silver salt was estimated but no analysis of the free acid was carried out.

Attempts were also made to effect the reaction between acetophenone and (-)-menthyl bromoacetate in the presence of magnesium instead of zinc, but no reaction was observed.

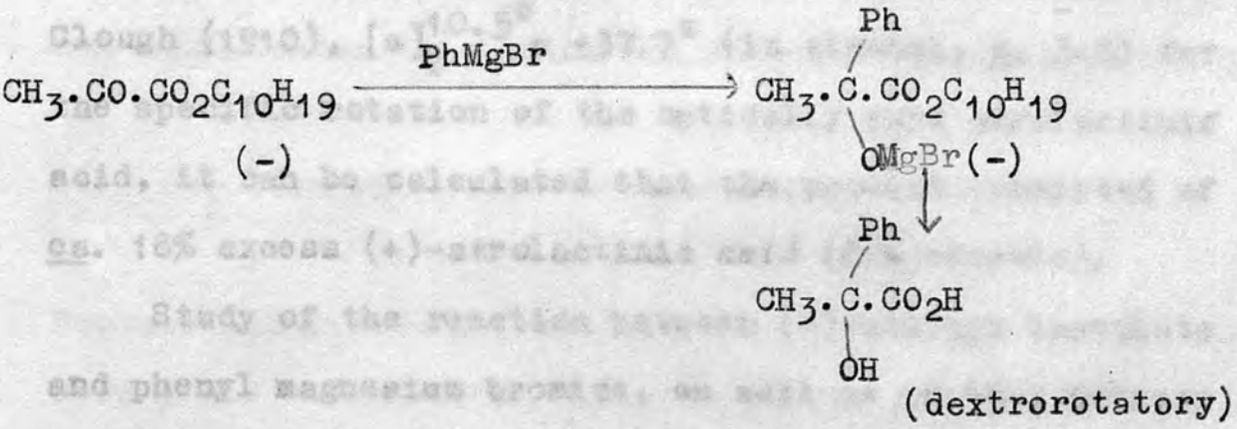
V.

CORRELATION OF RESULTS

V. CORRELATION OF RESULTS

The reaction studied, both chemically and polarimetrically, between (-)-menthyl esters of ω-acetyl fatty acids - $CH_3.CO.(CH_2)_n.CO_2$(-)-menthyl - and phenyl magnesium bromide was not likely to be complicated by reduction of the keto group, since phenyl magnesium bromide does not effect reduction of ketones.

McKenzie (1906) found that the reaction between (-)-menthyl pyruvate and phenyl magnesium bromide produced a dextrorotatory atrolactinic acid:-



Experiments (two) were carried out in which the Grignard reagent was added to the solution over 30 minutes, but further conditions are not specified; an aqueous solution of the atrolactinic acid obtained had $[\alpha]_D^{16^\circ} = +5.4^\circ$(c, 14.7). This rotation would be obtained with a product consisting of about 10% of (+)-atrolactinic acid and 90% of racemic acid. This calculation is based on the specific rotation of the pure acid obtained by McKenzie and Clough (1910), i.e. $[\alpha]_D^{14.5^\circ}$ $+51.1^\circ$ (c, 2.160 in water). From an aqueous

solution of the optically active atrolactinic acid the racemic acid crystallized preferentially, the mother liquor having enhanced optical activity.

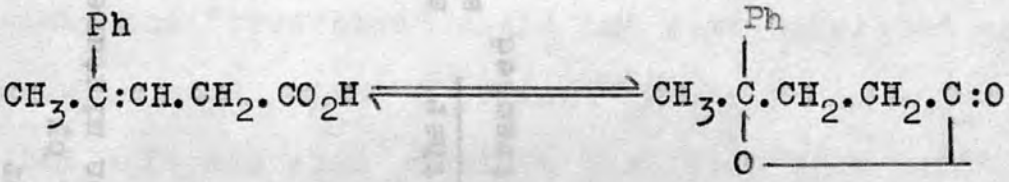
Experiments in this investigation, involving addition of phenyl magnesium bromide to (-)-menthyl pyruvate over 30 minutes with warming, did in fact yield a dextrorotatory atrolactinic acid, the specific rotation of the crude product being $[\alpha]_D^{20^\circ} = +7.9^\circ$ (c, 6.15 in water). An alcoholic solution of the crude atrolactinic acid had $[\alpha]_D^{18^\circ} = +6.7^\circ$ (c, 3.075); using the figures published by McKenzie and Clough (1910), $[\alpha]_D^{10.5^\circ} = +37.7^\circ$ (in alcohol; c, 3.5) for the specific rotation of the optically pure atrolactinic acid, it can be calculated that the product consisted of ca. 18% excess (+)-atrolactinic acid (82% racemic).

Study of the reaction between (-)-menthyl laevulate and phenyl magnesium bromide, as well as of that between (-)-menthyl ω-acetyl-n-butyrate and phenyl magnesium bromide (i.e. when n = 2 and 3), was complicated by the ease of conversion of γ- and δ-hydroxy acids into their corresponding lactones.

$$CH_3.\overset{\overset{Ph}{|}}{\underset{\underset{OH}{|}}{C}}.(CH_2)_n.CO_2H \longrightarrow CH_3.\overset{\overset{Ph}{|}}{\underset{O\text{———}}{C}}.(CH_2)_n.\underset{|}{C}{:}O \qquad (n = 2 \text{ or } 3)$$

γ-Hydroxy-γ-phenylvaleric acid (n = 2 in above formula) could be converted into γ-phenyl-γ-valerolactone, with no apparent racemisation, by repeated distillations of benzene from the compound. Partial conversion of δ-hydroxy-δ-

phenylcaproic acid (n = 3 in above formula) into the corresponding lactone could also be accomplished by similar treatment. An attempt to form γ-phenyl-γ-valerolactone by treating the hydroxy acid with dilute mineral acid caused racemisation to occur, presumably by a mechanism involving lacto-enoic tautomerism. Johnson, Petersen and Schneider (1947) point out that unsaturated acids and γ-lactones appear to be interconvertible via this type of equilibrium, although in the case of phenylvalerolactone, in their medium (2 vols. 48% HBr: 3 vols. acetic acid: 1 vol. H_2O), the equilibrium was far to the right, if it existed at all.



Boorman and Linstead (1933) observed that a γ-unsaturated acid could be converted into the corresponding lactone with sulphuric acid; but the reverse reaction (lactone to unsaturated acid) was never observed. This phenomenon was also observed in the case of δ-unsaturated acids and δ-lactones. In view of the difficulty of devising reproducible conditions for the quantitative isolation of γ-hydroxy-γ-phenylvaleric acid and δ-hydroxy-δ-phenylcaproic acid free from lactone, polarimetric measurements for comparative purposes were carried out on solutions of the lactones.

An extensive study was made of the reaction involving

(-)-menthyl laevulate. The course of the reaction is outlined schematically below (R^{*} = (-)-menthyl):

It was found by titration that the "crude lactone" (E) contained in most cases an appreciable amount of acidic material which could not be ring-closed to give a neutral product (lactone). Washing of an ethereal solution of the "crude lactone" with sodium carbonate solution gave analytically pure phenylvalerolactone (F).

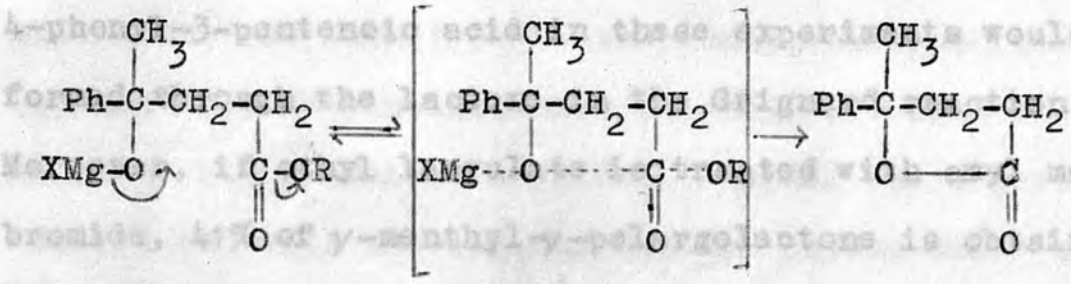
It might be suggested that the "free acid" (G) was laevulic acid. This, however, is unlikely since laevulic acid is extremely soluble in water, especially relative to its solubility in ether, and the ethereal extract of the acidified hydrolysate had been washed well with water. Certainly the "free acid" could not have consisted entirely of laevulic acid, since a product insoluble in water was isolated. It was also possible that the "free acid" could have contained an unsaturated acid (e.g. 4-phenyl-3-pentenoic acid), since the "crude lactone" (E) decolourised a carbon tetrachloride solution of bromine. 4-Phenyl-3-pentenoic acid could have been formed either during the course of the Grignard reaction (see below), or during the conversion of the γ-hydroxy-γ-phenylvaleric acid into its lactone after hydrolysis; the latter is unlikely, since it has been found possible to interconvert these two compounds without formation of any other acidic product.

It is significant that if methyl benzoylpropionate ($Ph.CO.(CH_2)_2.CO_2CH_3$) is treated with methyl magnesium

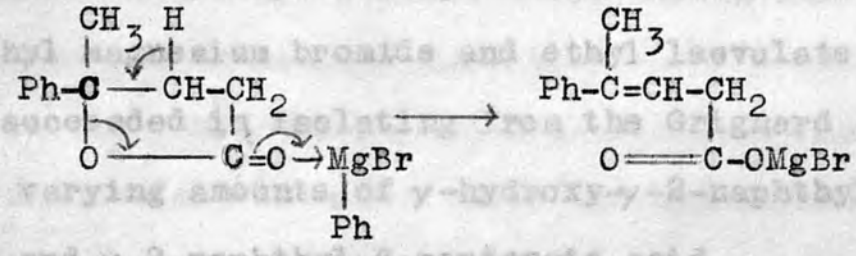
bromide (1.25 g. mol. to 1.0 of ester) under suitable conditions (slow mixing of the reactants at 0°, followed by heating at 55-60°), 4-phenyl-3-pentenoic acid ($Ph(CH_3)C:CH.CH_2.CO_2H$) is obtained in 75% yield (Kloetzel, 1940). In these experiments the Grignard reaction mixture was decomposed and the aqueous layer extracted with ether. The ethereal solution was repeatedly extracted with sodium bicarbonate solution, from which 4-phenyl-3-pentenoic acid was isolated. A similar result was obtained by Mayer and Stamm (1923) using the ethyl ester. It appears that this type of reaction may yield 4-phenyl-3-pentenoic acid or γ-phenyl-γ-hydroxy valeric acid (or its lactone); the latter was the main product isolated in the present investigation and in that of Trivedi and Nargund (1941). These authors found that treatment of ethyl benzoylpropionate with methyl magnesium bromide at 0° (1 g. mol.: 1 g. mol.), followed by keeping the reaction mixture at room temperature for a short period, gave γ-phenyl-γ-valerolactone in 40% yield (after hydrolysis and conversion of the hydroxy acid into the lactone).

From this published work it seems probable that, since 4-phenyl-3-pentenoic acid was isolated as such from the reaction mixture, with no intermediate steps involving hydrolysis, it might be formed via the lactone during the Grignard reaction. The formation of the lactone could

probably proceed as follows:-



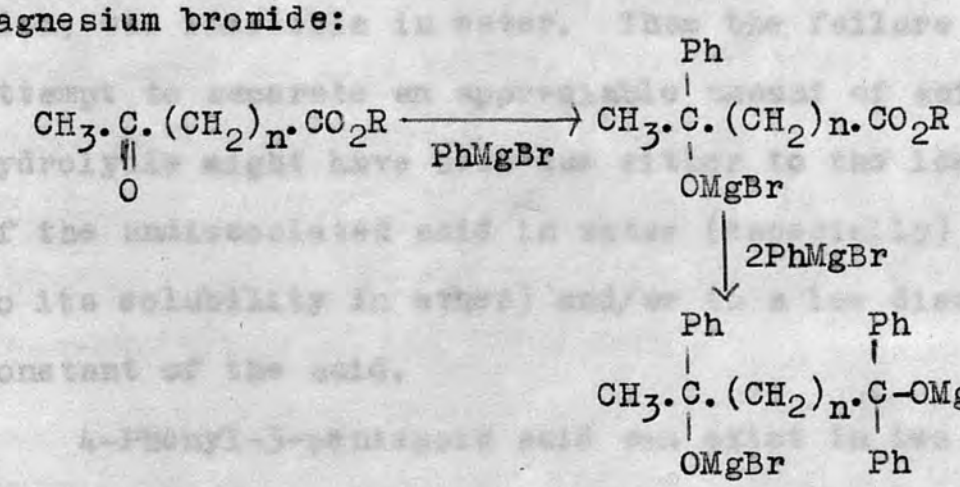
Further, the conversion of the lactone to the unsaturated acid could be represented as follows:-



This type of reaction would be facile in the case of the methyl ester since the reactivity of methyl esters is generally greater than that of the higher esters. The alternative is that the unsaturated acid would be formed by internal elimination involving the $\beta\gamma$ carbon atoms to give the unsaturated ester, which might be hydrolysed with ice-cold hydrochloric acid during decomposition of the Grignard reagent. This latter course seems the less likely of the two since it is improbable that a C-O bond of C-OMgX would be broken compared with the C-O bond of an ester group, fission of which would give the lactone as discussed above. Further, Campbell and Kenyon (1947) have shown that tertiary alcohols, or their bromomagnesium derivatives, do not undergo dehydration in the presence of

excess Grignard reagent. It thus appears likely that the 4-phenyl-3-pentenoic acid in these experiments would be formed through the lactone in the Grignard reaction mixture. Moreover, if ethyl laevulate is treated with amyl magnesium bromide, 41% of γ-menthyl-γ-pelargolactone is obtained direct from the Grignard reaction mixture by decomposition with water (Soloway and La Forge, 1947). Also, Robinson and Slater (1941), by varying the conditions under which 2-naphthyl magnesium bromide and ethyl laevulate interacted, succeeded in isolating from the Grignard reaction mixture varying amounts of γ-hydroxy-γ-2-naphthylvalerolactone and γ-2-naphthyl-β-pentenoic acid.

If the lactone were the precursor of the unsaturated acid in the experiments using (-)-menthyl laevulate, the "ester" (B) should have smelt strongly of menthol; this was the case. The strong smell of menthol could also have arisen by interaction of the ester group with the phenyl magnesium bromide:



However, at the analogous stage using (-)-menthyl

acetylbutyrate (n = 3), the smell of menthol was considerably less, and when (-)-menthyl acetylvalerate (n = 4) and (-)-menthyl acetylpelargonate (n = 8) were used there was no perceptible smell of menthol. In all the experiments carried out with the various menthyl esters under similar conditions, only very small yields of neutral products were obtained. Thus, it is more probable that in experiments with (-)-menthyl laevulate the strong smell of menthol was due to lactone formation.

When the γ-hydroxy-γ-phenylvaleric acid and other acidic product(s), obtained after the hydrolysis, were precipitated from an alkaline solution by acidification with mineral acid, it will be remembered that in some cases a brown oil separated first, before the separation of γ-hydroxy-γ-phenylvaleric acid, at a pH very little below 7. Also, the acid fraction (F), isolated as a syrup by washing the "crude lactone" with sodium carbonate solution, was insoluble in water. Thus the failure of the attempt to separate an appreciable amount of acid before hydrolysis might have been due either to the low solubility of the undissociated acid in water (especially) relative to its solubility in ether) and/or to a low dissociation constant of the acid.

4-Phenyl-3-pentenoic acid can exist in two geometrically isomeric forms, and it may be significant that when Michael

and Ross (1931) prepared it from ethyl malonate and α-phenyl propionaldehyde, they obtained it as a syrup which they could not induce to crystallise, although Kloetzel (1940) and Mayer and Stamm (1923) obtained it as a white crystalline solid.

The "free acid" fraction exhibited optical activity; hence it could not have been entirely, if at all, 4-phenyl-3-pentenoic acid. It is possible that some optically active acidic by-products might have been formed by reactions involving two molecules of (-)-menthyl laevulate, yielding compounds such as $CH_3.CO.\underset{\displaystyle CH_3}{\overset{\displaystyle CH_2.CO_2H}{\overset{|}{C}}}H.C(OH) . CH_2.CH_2.CO_2H$ and $CH_3.CO.\overset{\displaystyle CO.CH_3}{\overset{|}{C}}H.CH_2.CO_2H$, the carbonyl group(s) of which might then react with phenyl magnesium bromide. It is significant that Soloway and LaForge (1947) obtained only 41% of γ-methyl-γ-hydroxypelargonic acid on treating ethyl laevulate with amyl magnesium bromide, together with a large amount of high boiling fraction which they suggest might be a triketocapric acid such as $CH_3.CO.(CH_2)_2.CO.CH_2.CO.(CH_2)_2.CO_2H$. In the present investigation it was not possible to prepare a 2:4-dinitrophenylhydrazone of the "free acid".

Comparison of the specific rotations of the lactone before and after carbonate washing indicates that a large

proportion of the "free acid", which was demonstrated by titration, must have been an optically inactive acid. Thus, it appears that the "free acid" was, in fact, a mixture, a conclusion which is supported by solubility considerations. The mixture might have included 4-phenyl-3-pentenoic acid and compounds resulting from the interaction of two or more molecules of (-)-menthyl laevulate.

The degree of asymmetric synthesis obtained, i.e. the specific rotation of the lactone before any process of fractionation such as precipitation of the hydroxy-acid from an alkaline solution with mineral acid had been performed, was dependent on the conditions used for the Grignard reaction. The degree of asymmetric synthesis varied with the time of adding the phenyl magnesium bromide to the solution of (-)-menthyl laevulate, within certain limits. There was also some dependance on the conditions of mixing the reagents during addition and on whether stirring was continued after addition of the phenyl magnesium bromide was complete. γ-Phenyl-γ-valerolactone obtained by adding phenyl magnesium bromide to (-)-menthyl laevulate over a very short period of time had a specific rotation corresponding to a product consisting of 5.5% (-)-lactone and 94.5% of racemic lactone. When addition of the phenyl magnesium bromide to the ester was prolonged (from 1 to 4 hours) with no subsequent stirring of the reaction mixture,

the lactone contained 9.5-10% of (-)-lactone, the rest being racemic lactone. Mixing of the reactants over ½ hour followed by stirring for 1 hour gave products with specific rotations corresponding to 11-12% excess (-)-lactone. Preliminary experiments had shown that the product obtained by addition of the phenyl magnesium bromide to the ester over ½ hour with no subsequent stirring had an optical purity mid-way between that of the product obtained by mixing the reactants over a few minutes and that by mixing over 1 hour (say). Also comparison of results from preliminary experiments with those from the larger scale experiments indicates that stirring as opposed to hand shaking, whilst mixing the reactants, increases the degree of asymmetric synthesis.

The yield was considerably higher in the experiment where mixing of the reactants was over a very short period of time, and the percentage of "free acid" in the "crude lactone" from this experiment was considerably lower than in the other experiments, in which, as far as could be discerned, the yield and percentage of other acid(s) varied little with conditions. It would have been of interest to study the effect of mixing the reactants over a very short period of time and then stirring the reaction mixture.

The degree of asymmetric synthesis of δ-phenyl-δ-caprolactone, obtained by the interaction of phenyl

magnesium bromide and (-)-menthyl ω-acetyl-n-butyrate, was again found to be dependent on the conditions prevailing during the Grignard reaction. In this case conditions affecting the degree of asymmetric synthesis have the opposite effect to what they have in experiments involving (-)-menthyl laevulate. Work done by a colleague (Miss D.M. Bovey) indicates that the specific rotation of δ-phenyl-δ-caprolactone in ethanol at 25° is of the order of 15.5° for the mercury green line (5461A°). Thus, the lactone obtained from the experiment where the phenyl magnesium bromide was added to the ester over 1 min. with shaking consisted of about 16% (-)-lactone and 84% racemic. By addition over 30 mins. with no subsequent stirring, a product was obtained consisting of about 9.5% (-)-lactone. By addition over 30 mins. with subsequent stirring a product with only 1.5% excess (-)lactone was obtained.

Since the interaction of (-)-menthyl ω-acetyl-n-valerate and phenyl magnesium bromide with subsequent hydrolysis gave 5-hydroxy-5-phenyl-hexan-1-carboxylic acid, polarimetric study of this product was not complicated by ring closure to give a lactone. However, this has the disadvantage that any asymmetric synthesis that might occur would be harder to detect since ring formation (such as the conversion of a hydroxy-acid into its lactone), is, in general, accompanied by a numerical increase in optical rotatory

power (cf. Kauzmann, Walter and Eyring (1940)).

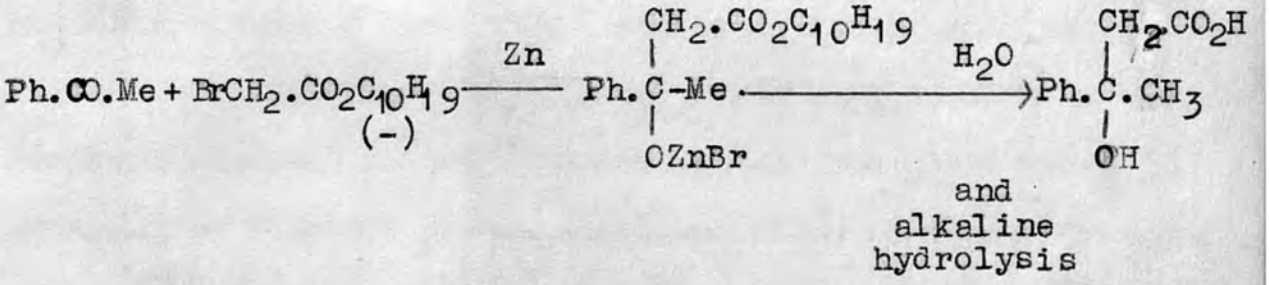
The 5-hydroxy-5-phenyl-hexan-1-carboxylic acid obtained from the preliminary experiments, using 1.25, 2.5 and 4 molecular proportions of phenyl magnesium bromide to 1 molecular proportion of (-)-menthyl ω-acetyl-n-valerate, had no observable optical rotatory power; but a larger scale experiment carried out under standardised conditions (mixing of reactants (1.25:1 ratio) over $\frac{1}{2}$ hour with stirring, followed by stirring for 1 hour at 0°) gave a product which had α_{5780} +0.09° (c, 50 in ethanol). There is no indication as to the degree of asymmetric synthesis that this represents since 5-hydroxy-5-phenyl-hexan-1-carboxylic acid has not been resolved.

The 9-hydroxy-9-phenyl-decan-1-carboxylic acid obtained by the interaction of (-)-menthyl acetylpelargonate and phenyl magnesium bromide, with subsequent hydrolysis, showed no optical rotatory power, but this might be due to the optically pure hydroxy acid having a low specific rotation.

The lactone prepared from γ-hydroxy-γ-phenylvaleric acid has opposite rotatory power to that of the acid. If one assumes that the δ-lactone has optical rotatory power in the opposite direction to that of the δ-hydroxy-δ-phenylcaproic acid, from which it is prepared, all the optically active hydroxy acids that were prepared by the

interaction of (-)-menthyl ω-acetyl fatty acid esters and phenyl magnesium bromide were dextrorotatory. Of the hydroxy-acids prepared only atrolactinic acid (n = 0) has previously been resolved. (±)-γ-Hydroxy-γ-phenylvaleric acid has been prepared by other workers but not resolved. No reference to δ-hydroxy- δ-phenylcaproic acid, 5-hydroxy-5-phenyl-hexan-1-carboxylic acid, or 9-hydroxy-9-phenyl-decan-1-carboxylic acid can be found in the literature.

An asymmetric synthesis was also accomplished through the interaction of (-)-menthyl bromoacetic ester, acetophenone and zinc (Reformatsky reaction) and subsequent hydrolysis. The series of reactions involved is indicated:-



The degree of asymmetric synthesis (i.e. the specific rotation of the β-hydroxy-β-phenyl-butyric acid obtained) was independent of the ester:acetophenone ratio and independent of the conditions used for the reaction (such as mixing time of the reactants and dilution). The apparent variation of the specific rotation of the product ($[\alpha]_{5780}$ 2.31 - 2.47; $[\alpha]_{5461}$ 2.57 - 2.89) could be correlated with the concentration of the solution used for the

specific rotation, an increase in concentration causing an increase in specific rotation. (±)-β-Hydroxy-β-phenyl-butyric acid has previously been prepared by Arbusov (1901) but has not been adequately described. In the present investigation the racemic acid was obtained with a melting point 20° higher than that recorded by Arbusov. So far the racemic acid has not been resolved.

VI.

DISCUSSION OF CONCLUSIONS IN RELATION TO THEORIES OF ASYMMETRIC SYNTHESIS

VI. DISCUSSION OF CONCLUSIONS IN RELATION TO THEORIES OF ASYMMETRIC SYNTHESIS

VIa. Previous work

This section will give a wider review of suggestions extended for explanation of the type of asymmetric syntheses involving the addition of a Grignard reagent to, either an optically active ester of an α-keto acid, or to an acyl carbinol. A brief outline of current ideas was given in Section I. The importance of the results obtained in this investigation with respect to such ideas, and how these results have extended our knowledge of this type of asymmetric synthesis, will then be discussed.

McKenzie and co-workers explained the asymmetric syntheses obtained in their earlier experiments using optically active esters of α-keto acids (see Section I) on the assumption that the addition of the Grignard reagent to the carbonyl group was subject to a "directing" influence exerted by the optically active alcohol radical; thus, after complete hydrolysis of the resulting glycollic ester an optically active glycollic acid was obtained. About 1930 it was suggested by McKenzie, Ritchie and co-workers that asymmetric induction might be an explanation for the mutarotation of the keto-esters in alcohol solutions. It was assumed that the carbonyl group existed as a labile centre of asymmetry and that there occurred in solution a

change of "equilibrium" e.g.

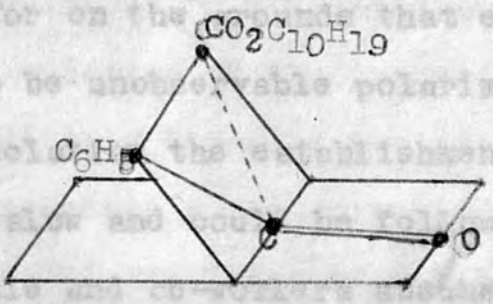
$$\underset{\text{Me.CO.CO}_2\text{(-)-menthyl}}{(-)\quad(-)} \;+\; \underset{\text{Me.CO.CO}_2\text{(-)-menthyl}}{(+)\quad(-)}$$

(equal amounts)

$$\underset{\text{Me.CO.CO}_2\text{(-)-menthyl}}{(-)\quad(-)} \;+\; \underset{\text{Me.CO.CO}_2\text{(-)-menthyl}}{(+)\quad(-)}$$

(unequal amounts)

It was suggested that the configuration of the carbonyl group was a non planar one such as:-



As a corollary to the above suggestion, the phenomenon of asymmetric synthesis was explained on the assumption that in the ethereal solution the two "diastereoisomerides" were present in unequal amounts (the carbonyl group assuming dissymmetric configuration under the influence of ~~the influence of~~ the optically active alcohol radical). On reacting with the Grignard reagent, the labile configurations of each "isomer" were fixed, thus forming two diastereoisomers in unequal amounts which yielded on hydrolysis an optically active glycollic acid.

In accordance with this tentative suggestion, experimental results suggested that, when the mutarotation of a ketoester in alcohol resulted in a numerical increase in the degree of rotation, the resulting glycollic acid would always have a rotation of the same sign as the parent ester. The above suggestion requires that an equilibrium between the two "diastereoisomers" be established in ether, and the lack of observed mutarotation in ether was accounted for on the grounds that equilibration was so rapid as to be unobservable polarimetrically, whereas in alcoholic solution the establishment of equilibrium was relatively slow and could be followed polarimetrically.

McKenzie and co-workers assume that rapid equilibrium occurs initially; it must, as Turner and Harris (1947) point out, be postulated that the rate of addition of the Grignard reagent to the carbonyl group is faster than the rate of equilibration (since it is unlikely that the rate of addition to diastereoisomerides would be the same).

Jamison and Turner (1941) and Turner and Harris (1947) prefer to regard the mutarotation of α-ketoesters in alcohol as a first order transformation between the diastereoisomeric hemiacetals, or as the slow formation of the hemiacetal. It has been shown by Glazer and Turner (1949) that the mutarotation was, in fact, due to slow hemiacetal formation. The lack of mutarotation in ether was taken to

disprove the existence of the hypothetical diastereo-isomerides.

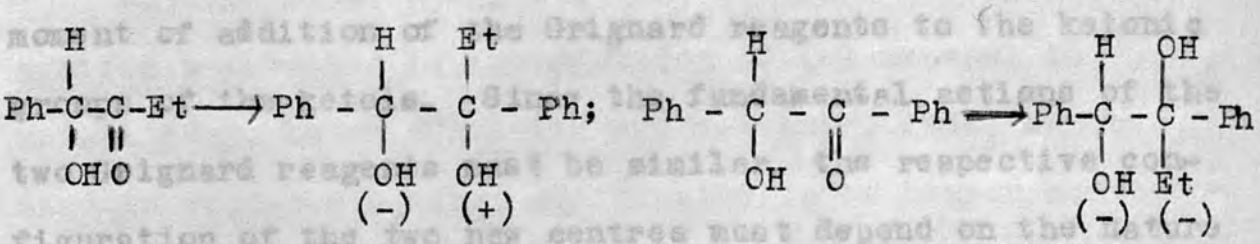
As has been shown in Section I, (-)-atrolactinic acid was prepared by the interaction of (-)-menthyl benzoyl-formate and methyl magnesium bromide, but (+)-atrolactinic acid by the interaction of (-)-menthyl pyruvate and phenyl magnesium bromide. On account of this, and of the apparent correlation between the change of direction of the rotation of α-ketoesters during mutarotation, and the algebraic sign of the rotation of the products obtained by asymmetric synthesis, Ritchie (1947) remarked:

"This suggests a mechanism in which the induced asymmetry of the two types of α-ketonic esters (opposite in sense perhaps owing to the very powerfully negative nature of the phenyl group as contrasted with the methyl group) is reflected by mutarotation in opposite sense, and also by the fixation by the Grignard reagent to give two oppositely rotating series of substituted glycollic acids."

Tiffeneau, Levy and Ditz (1931, 1935) have rejected the explanation of asymmetric synthesis proposed by McKenzie, Ritchie and co-workers in favour of the suggestion that the two bonds of the carbonyl group are attacked differentially when there is an optically active system elsewhere in the molecule. Like earlier investigators they had noted the unilateral attack of a Grignard reagent

on a carbonyl group which is adjacent to a dissymmetric carbon atom when one of the groups was either -OH or NH_2 (cf. work on benzoin). They also observed that, in the treatment of (+)-phenyl-α-campholenyl ketone (where the two groups are separated by a methylene group) with a Grignard reagent both of the antipodes are formed, one form preponderating. These workers suggest that, as the number of atoms introduced between the optically active group and the carbonyl group is increased, so will the extent of the asymmetric synthesis accomplished decrease. This suggestion is extended to apply to McKenzie's work and it is postulated that the degree of asymmetric synthesis may be low because of the introduction of the -COO-group. Ritchie (1947) considers that his hypothesis and Tiffeneau's are complementary rather than opposed.

Roger (1939) discussed the unilateral addition of a Grignard reagent to benzoin and phenyl propionyl carbinol where inversion of the order of introduction of two groups leads to inversion of configuration of the product, i.e.



He explains this type of "unilateral" asymmetric synthesis on the grounds that the carbonyl group assumes a

dissymmetric configuration, under the directing influence of the asymmetric group, which is fixed by the Grignard reagent. At the same time he suggests:

"Since the inducing centre is of the same sign in both cases, it might reasonably be expected that the direction of induction in the induced centres would be the same. Yet, when these two induced centres become fixed, they are of opposite sign, i.e. the same negative inducing centre has apparently caused a negative induction effect in one case and a positive effect in the other: this would appear to be illogical. The fact that the phenyl and the ethyl radical directly attached to the induced centres (the carbonyl groups) in the two ketols are very different in character may cause a relatively different arrangement in space of the two centres of induced asymmetry with regard to the centre of fixed asymmetry (the mandelyl complex in each case). From these considerations it would seem that the configurations of the new centres of asymmetry in the two forms of ethylhydrobenzoin are definitely fixed at the moment of addition of the Grignard reagents to the ketonic groups of the ketols. Since the fundamental actions of the two Grignard reagents must be similar, the respective configuration of the two new centres must depend on the nature or size of both the entrant radicals and also the alkyl or aryl radicals attached to the ketonic groups of the ketols.

No definite law can be formulated regarding this point..."

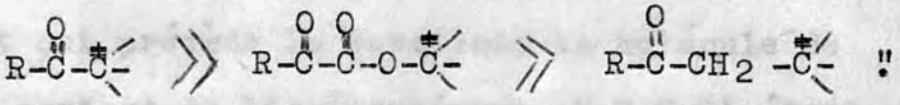
Partridge (1939) offers an explanation of the above results by assuming that addition to the double bond takes place by "the double bond opening in the same sense in each case", when "the difference of configuration between the ethyl benzoins produced by the two routes is a necessary consequence of the order in which the phenyl and ethyl groups have been introduced."

With respect to the asymmetric syntheses effected in the α-keto ester/Grignard reagent series, where diastereoisomerides of the type $R-\overset{R'}{\underset{OMgX}{C}}-CO_2R^*$ (R^* = optically active alcohol radical) are formed, Kenyon and Partridge (1936) took the view that collisions between Grignard reagent and keto-ester which led to one diastereoisomeric intermediate were more likely to occur than those leading to the other. They add that "it is a difference in energy associated with the diastereoisomeric intermediate products which is responsible for the one-sided reaction".

Ritchie (1947) suggests that the lack of asymmetric synthesis obtained by the addition of (-)-menthol to methyl ethyl keten (Christie and McKenzie, 1934) may be used in evidence against the hypothesis of Kenyon and Partridge. However, the two reactions are not strictly analogous.

Brokaw and Brode (1948) have investigated the "inductive

effect" of the active-amyl radical by studying the interaction of alkyl-active-amyl ketones with Grignard reagents, i.e. where the optically active centre and the unsaturated group are separated by a methylene group. No asymmetric synthesis was observed, and they comment on the lack of inductive effect:

"The lack of inductive effect noted herein was correlated with results of Roger and McKenzie to provide an interpretation of transmission or insulation of inductive power from directing centre to reaction centre. The following structures are listed in decreasing ability to transmit the influence:  "

These authors acknowledge that the compounds used in previous asymmetric syntheses involving Grignard reagents possess structures which permit of co-ordination of the Grignard reagent.

In connection with the work of Brokaw and Brode (1948), the lack of asymmetric synthesis observed might not have been due to the effect of the intervening methylene group between the carbonyl and optically active groups, but might be inherent in the low degree of asymmetric synthesis which, under any circumstances, might be associated with the group. It is interesting that investigation of the reaction between (-)-β-octyl α-keto esters and Grignard reagents (McKenzie and Ritchie, 1931) showed that only a very

low degree of asymmetric synthesis had occurred.

Tarbell and Paulson (1942), in discussing their lack of asymmetric synthesis using (+)-methyl-s-butyl ether as a solvent for the interaction of benzaldehyde and methyl magnesium bromide (see Section I), suggest that:

"... the organo magnesium compound is co-ordinated with two molecules of ether in such a way that the complex has a plane of symmetry".

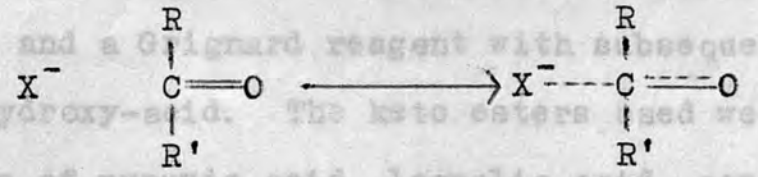
Vavon, Rivière and Angelo (1946) explain the asymmetric synthesis observed in the reduction of acetophenone with iso-bornyl magnesium chloride as follows:-

"à l'instant qui précède la reaction, la molécule de magnésien est au contact de l'acétophénone, H-C-MgCl étant voisin de l'une des deux valences C=O, valences qui sont symétriques par rapport au plan déterminé par les deux valences CH_3-C-C_6H_5. Cet ensemble, magnésien acétophénone, est différent et non symétrique de l'ensemble correspondant, où H-C-MgCl serait voisin de l'autre valence de C=O; il n'y a pas suite aucune raison pour qu'ils se forment avec la même facilité et évoluent avec la même vitesse. Or l'un, par rupture de l'une des valences C=O, conduit à l'isomère droit; l'autre, par rupture de l'autre valence, conduit à l'isomère gauche. Les deux isomères peuvent donc se former en quantités inégales."

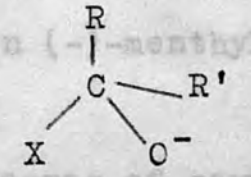
Turner and Harris (1947) have recently commented on

the type of asymmetric synthesis under discussion as follows:-

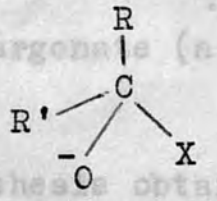
"In order that a fixed centre of asymmetry shall influence the steric course of an addition reaction at an unsaturated centre in the same molecule in an asymmetric synthesis, there must be some stage at which either stereoselective addition occurs as an irreversible process or first order asymmetric transformation takes place ..... some general lines of argument can be foreseen. Thus, in the addition of XY to a carbonyl group of a molecule already containing a fixed centre of asymmetry (in group R), the first stage may be regarded as the approach of X^- towards the positive end of the polarized carbonyl group:



The two tetrahedral arrangements represented by the plane diagrams



and



are possible before the addition of Y^+. If the energy changes concerned in the formation of these two structures are equal, there is no immediate asymmetric addition. If they are unequal (i.e. influenced by existing asymmetry), then we have <u>asymmetric addition</u>, which appears to take place

even in non-reversible asymmetric reactions of this type (e.g., Grignard reactions). On the other hand, addition which is known to be chemically reversible (e.g. when X^- is CN^-) could be accompanied by first order asymmetric transformation of the newly formed molecule at this stage, and it would be rash to say without further experiment, whether the new asymmetry is introduced during or after the first addition or at both stages."

VIb. Present investigation

Observations made during the present investigation, on asymmetric synthesis in relation to the structure of the compounds involved, are summarised below (cf. Section V).

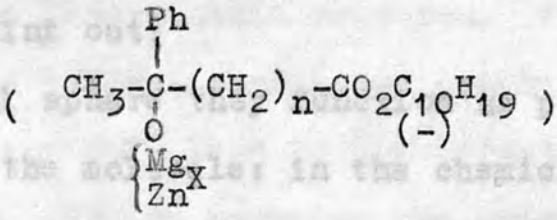
(1) Asymmetric syntheses have been observed in the interaction of optically active esters of α-, γ-, δ- and ε-keto acids and a Grignard reagent with subsequent hydrolysis to the hydroxy-acid. The keto esters used were the (-)-menthyl esters of pyruvic acid, laevulic acid, acetylbutyric acid and acetylvaleric acid. No asymmetric synthesis was observed when (-)-menthyl acetylpelargonate (a 9-keto ester) was used.

(2) The degree of asymmetric synthesis obtained using (-)-menthyl laevulate and (-)-menthyl acetylbutyrate was found to be dependent on the reaction conditions. Variation of conditions leading to an increase in the degree of asymmetric synthesis using (-)-menthyl laevulate, had the

opposite effect when (-)-menthyl acetylbutyrate was used.

(3) An asymmetric synthesis was accomplished by the interaction of (-)-menthyl bromoacetate, acetophenone and zinc, with subsequent hydrolysis of the product.

In these experiments the formation of unequal amounts of the two diastereoisomerides



at the initial stage (i.e. an asymmetric reaction) was proved by complete hydrolysis of the esters to give optically active hydroxy acids (i.e. an asymmetric synthesis).

Explanations of asymmetric synthesis hitherto advanced have had to accommodate asymmetric syntheses resulting from the addition of a Grignard reagent to a carbonyl group in a molecule which itself contains an asymmetric centre. Any theory of asymmetric synthesis must now accommodate the fact that an asymmetric synthesis can also be effected when the asymmetric centre is in the same molecule as the organometallic group and a symmetrical ketone is used.

In the light of current electronic theories of organic chemistry, the suggestion that a carbonyl group could assume a "dissymmetric" configuration, prior to the approach of the Grignard reagent, could not be accepted. It is now thought that the π electrons (of a chromophoric

group) moving in the unsymmetrical force field of an asymmetric centre give rise to an effect of optical activity; this phenomenon has been termed induced anisotropy by Balfe and Kenyon (1942). It is also known that it is the π molecular wave functions that are concerned in the addition reactions of the carbonyl group, as Turner and Harris (1947) point out:

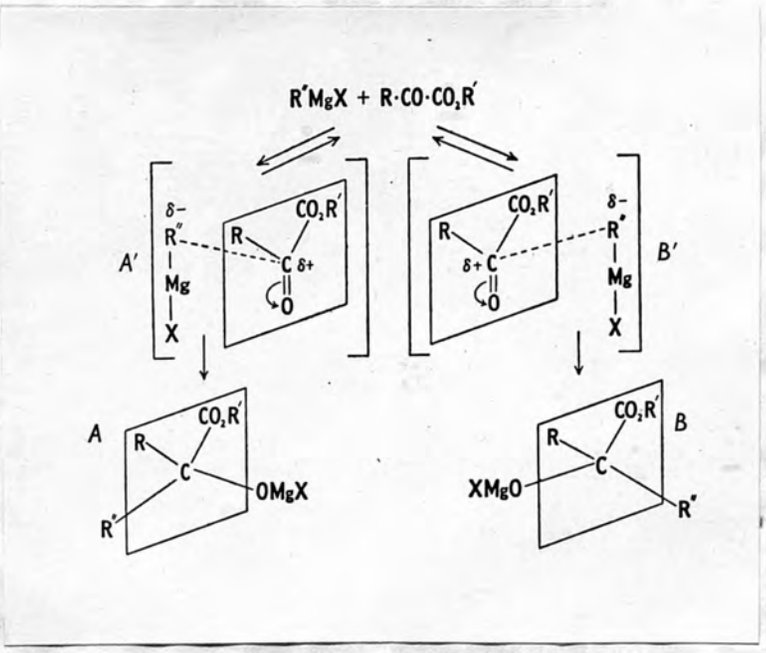
"In the optical sphere they function as part of the permanent state of the molecule; in the chemical sphere, for all we know to the contrary, they play their normal part in permitting electronic activation of the double bond prior to its two-stage saturation. It seems probable that, at any rate at the moment, only confusion will result from correlating the chemical reactivity ("asymmetric induction") of a carbonyl group with the rotatory dispersion effects ("induced asymmetry") associated with it. Until the two effects have been more closely investigated no useful conclusions can be drawn."

Apart from the above considerations, experimental results which have been obtained in this investigation cannot justify the idea of asymmetric induction, as it has been used to explain asymmetric synthesis. Presumably, in the case of the treatment of (-)-menthyl bromoacetate with acetophenone, the asymmetric synthesis observed would have to be explained on the basis of an intermolecular

inductive effect. If this were the case, it is extremely unlikely that such consistent results for the degree of asymmetric synthesis would have been obtained, irrespective of reaction conditions, especially concentrations of reactants.

The addition of an organometallic compound to a carbonyl group is an irreversible reaction. When one of these groups is in a molecule which has another centre of asymmetry, interaction will lead to the formation of diastereoisomerides. If, on removing the original centre of asymmetry, the compound is optically active, an asymmetric reaction will have occurred and the diastereoisomerides will have been present in unequal amounts. Since it is impossible for the diastereoisomerides to be interconvertoble and thus to be in equilibrium, i.e. no first order asymmetric transformation can take place, mechanistic differentiation must be sought at the stage of the two corresponding transition states from which the diastereoisomerides are formed irreversibly.

The interaction of an α-keto ester and a Grignard reagent can be represented as below (as can the analogous reactions involving other keto esters).

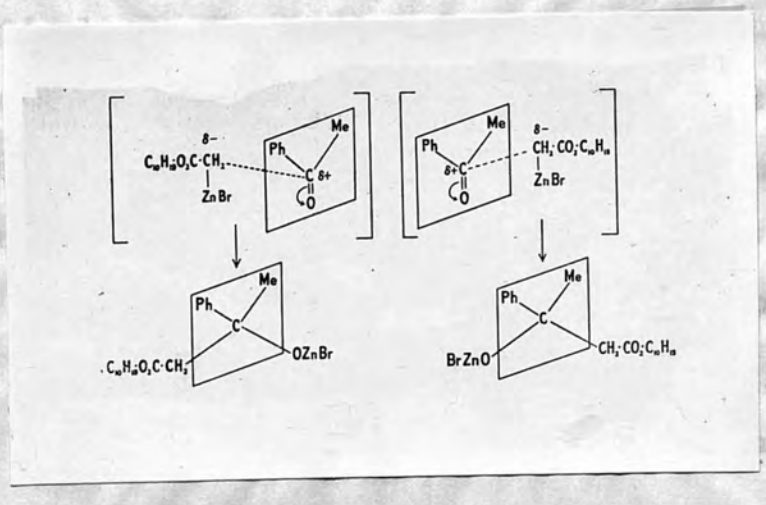


The two transition states, A' and B', (1) must have different energies, since they are of the nature of diastereoisomerides, and (2) are formed <u>reversibly</u> from the reactants. We thus have a mechanism whereby the route with the lower activation energy can be followed preferentially and an "asymmetric reaction" is possible. The "equilibrium" between the two transition states bears a formal resemblance to that between two diastereoisomerides undergoing first

order asymmetric transformation.

(Owing to steric effects it seems probable that the Grignard reagent will attack the ketone at an angle to the plane in which the two groups attached to the carbonyl groups lie).

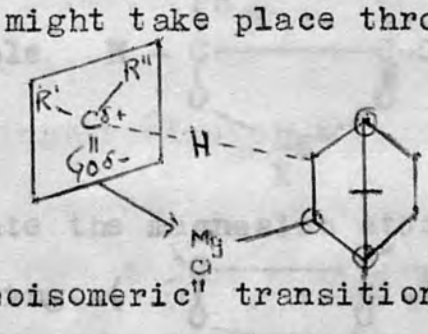
A similar state of affairs will exist when an optically active organometallic compound is used as opposed to an optically active ketone. In this case the two transition states and the resultant product can be expressed as:-



Since this type of reaction proceeds asymmetrically, the mechanism cannot be entirely through an intermediate cation $[R-\underset{OMgX}{\overset{+}{C}}-R']$; if it were, it is extremely unlikely that asymmetric addition would take place.

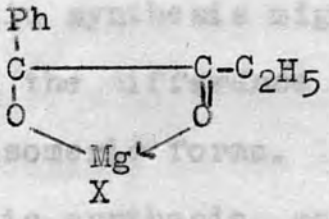
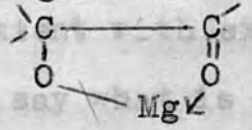
It has been suggested by various authors that such an asymmetric reaction might take place by the preferential opening of one of the bonds of the carbonyl group. This is still true, in a sense, and is compatible with the mechanism suggested above.

With reference to the asymmetric synthesis of secondary carbinols, accomplished by Vavon and co-workers (see Section I, and the first part of this Section) by reduction of symmetrical ketones with iso-bornyl magnesium chloride, it is difficult to say how this type of synthesis fits into the above theory until more is known of the mechanism of this type of reduction. It seems likely, however, that the reaction might take place through a transition state

such as 

, in which case "diastereoisomeric" transition states would exist and an argument similar to the above would be applicable. Vavon's explanation assumed that two "diastereoisomerides" are formed owing to the -Mg- being adjacent to one or other of the carbonyl bonds; the formation of the two diastereoisomerides would thus proceed at different rates, as would their

decomposition. Thus an asymmetric synthesis of the carbinol would be obtained. Presumably, a mechanism such as this would involve a π-complex with subsequent reaction such as that predicted for the trans addition of bromine to an ethylenic double bond. Whether such a complex would exist is difficult to say, in view of the fact that co-ordination of the oxygen atom on to magnesium is possible, owing to the lone pair of electrons.

The question of the asymmetric syntheses using benzoin or other acyl carbinols, where only <u>one</u> of the two possible diastereoisomerides was obtained (see Section I, and first part of this Section), must now be discussed. It seems unlikely that the difference of free energy of the two diastereoisomerides would be so large as to account for this. The alternative suggestion is that in this case the oxygen of the carbonyl is co-ordinated on to the magnesium, for example  . In order to accommodate the magnesium atom, it would not be possible for the ring  to be planar. It is likely that an ether molecule will also be co-ordinated on to the magnesium.

In published examples of such asymmetric reactions, one of the groups of the carbinol has been a large group

such as an aromatic radical. In the absence of steric hindrance, the magnesium atom could occupy either of two positions with reference to the other atoms in the ring. Thus, from steric considerations, it is probable that only one of these two configurations would be possible in this case. If so, attack of a molecule of Grignard reaction at the carbon of the carbonyl group would be hindered from one direction; thus only one of the two diastereoisomerides would be produced. This would be compatible with the finding that the configuration at the new asymmetric carbon atom depends on the order in which the two groups attached to this atom are introduced.

The experiments with Grignard reagents in the present investigation were carried out with a series of ω-acetyl fatty acid esters. One might expect that as the molecular weight of the reactants and products increased, so the degree of asymmetric synthesis might slowly decrease owing to the decrease of the difference in free energy between the two diastereoisomeric forms. In actual fact, the degree of asymmetric synthesis, using the same ester, varied to such a wide extent with experimental conditions that it is impossible to say what is the actual effect of structure on degree of asymmetric synthesis. If the asymmetric synthesis were due to some type of asymmetric induction, involving an electronic mechanism, it is highly improbable that the effect would be observed even with a compound

such as (-)-menthyl laevulate, where only two methylene groups intervene between the carbonyl group and the ester group. Another difficulty which arose in correlating structure and degree of asymmetric synthesis was that failure to observe asymmetric synthesis using the higher esters might have been due merely to the low specific rotation of the optically pure hydroxy acids, and not to a low or negligible degree of asymmetric synthesis. The optical rotatory power of hydroxy fatty acids of the general formula $CH_3-\overset{Ph}{\underset{OH}{C}}-(CH_2)_n-CO_2H$ would be expected to decrease as n is increased. When n = 2 or 3, the study of the optical rotatory power of the product was facilitated by the fact that γ- and δ-hydroxy acids are easily convertible to the corresponding lactones which, in general, have numerically a higher rotatory power than the hydroxy acids.

The variation of degree of asymmetric synthesis with conditions might possibly be due to secondary reactions taking place. This is especially true of the experiments involving (-)-menthyl laevulate, in which decomposition of the diastereoisomeric products of the Grignard reagent ($CH_3-\overset{Ph}{\underset{OMgX}{C}}-(CH_2)_2.CO_2R$) at different rates to give the lactone was a complicating factor. If no secondary reaction

were occurring, this decomposition would not have affected the ratio of the two hydroxy-acids finally obtained, since each of the lactones, as well as any unchanged ester, would be hydrolysed to give the corresponding hydroxy acid. But if the lactone underwent a secondary reaction, the ratio of the two stereoisomeric hydroxy acids formed on hydrolysis might be altered. A similar type of argument might also apply to a certain extent to the experiments with (-)-menthyl acetylbutyrate (n = 3). It would have been interesting to examine the reaction involving a compound such as the (-)-menthyl ester of a long chain fatty acid such as $CH_3.CO.(CH_2)_{14}.CO_2H$, where once again the resulting hydroxy acid can form a lactone.

The variation in degree of asymmetric synthesis might be, in part, due to the interaction of the Grignard reagent with the ester group to give a di-alcohol. This will involve the interaction of each of two diastereoisomerides with the Grignard reagent, reactions which will probably proceed at different rates. If this reaction proceeded to differing degrees, according to the conditions employed, it would, theoretically be possible to account for the variation in degree of asymmetric synthesis observed; but it must be noted that in many cases the yield of di-alcohol was extremely low and had no appreciable activity.

The lack of variation of asymmetric synthesis with

conditions in the case of the Reformatsky reaction might be associated with the fact that a clear reaction solution was obtained. In the case of the Grignard reaction, as soon as the Grignard reagent was added to the solution of the keto ester, the system became heterogeneous; it is significant that replacement of hand shaking by mechanical stirring had some effect on the reaction. The heterogeneity of the system might be partially or wholly the cause of the variability of asymmetric synthesis.

If the above hypothesis on the mechanism of asymmetric synthesis is correct, there will be no rule as to whether a reversal of the order of introduction of the groups of the new asymmetric centre will lead to products of opposite optical activity, since the transition states involved are different in the two cases. Moreover, there is no reason why the sign of the optical rotation of the resulting product should be the same if the same keto ester is treated with different Grignard reagents, as had been suggested in the theory of McKenzie and co-workers - sign of rotation is correlated with the numerical increase or decrease of the specific rotation of the ester in alcohol owing to mutarotation, Results of some experiments are not in accordance with this suggestion, e.g. the interaction of (-)-menthyl p-toluylformate and methyl magnesium bromide and phenyl magnesium bromide respectively, when products

of opposite optical rotatory power were obtained (McKenzie and Christie, 1935). If a menthyl ester is treated with various Grignard reagents, and if it is assumed that configuration and sign of rotation go hand in hand, it is probable that products of the same sign will be obtained, since the "diastereoisomeric" transition states with the same configuration must be the less or more stable in each case.

VII.

PREPARATION AND RESOLUTION OF (±)-γ-HYDROXY-γ-PHENYL-VALERIC ACID (3-HYDROXY-3-PHENYL-BUTAN-1-CARBOXYLIC ACID)

VIIa. Introduction

Investigation of the asymmetric syntheses of hydroxy-acids, from phenyl magnesium bromide and (-)-menthyl α-acetyl fatty acid esters, was that using (-)-menthyl laevulate. In order to determine the degree of asymmetric synthesis occurring in this reaction the racemic γ-hydroxy-γ-phenyl-valeric acid was prepared and resolved.

VIIb. Preparation of (±)-γ-hydroxy-γ-phenylvaleric acid

$$CH_3.CO.CH_2.CH_2.COOC_2H_5 \xrightarrow[\text{and subsequent hydrolysis}]{C_6H_5MgBr} CH_3\!\left(\begin{matrix} C_6H_5 \\ OH \end{matrix}\right)\!C.CH_2.CH_2.COOH$$

The interaction of phenyl magnesium bromide and ethyl laevulate (1.25 g. mol. : 1 g. mol.), with subsequent alkaline hydrolysis of the product, gave crude hydroxy-phenylvaleric acid which was immediately converted into γ-phenyl-γ-valerolactone by repeated distillations of benzene from the acid. The crude lactone was obtained in 47% yield as a dark brown oil. An ethereal solution of the lactone was washed repeatedly with sodium carbonate solution. The lactone obtained from the ethereal solution was dissolved in hot 2.5N-potassium hydroxide solution.

VII. PREPARATION AND RESOLUTION OF (±)-γ-HYDROXY-γ-PHENYL-VALERIC ACID (3-HYDROXY-3-PHENYL-BUTAN-1-CARBOXYLIC ACID)

VIIa. Introduction

The reaction studied most extensively during the investigation of the asymmetric syntheses of hydroxy-acids, from phenyl magnesium bromide and (-)-menthyl δ-acetyl fatty acid esters, was that using (-)-menthyl laevulate. In order to determine the degree of asymmetric synthesis occurring in this reaction the racemic γ-hydroxy-γ-phenyl-valeric acid was prepared and resolved.

VIIb. Preparation of (±)-γ-hydroxy-γ-phenylvaleric acid

$$CH_3.CO.CH_2.CH_2.COOC_2H_5 \xrightarrow[\text{and subsequent hydrolysis}]{C_6H_5MgBr} \begin{matrix} C_6H_5 \\ | \\ CH_3-C-OH \end{matrix} .CH_2.CH_2.COOH$$

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Acidification of this solution and crystallisation of the solid thus obtained from benzene gave γ-hydroxy-γ-phenylvaleric acid, m.p. 105.5-106°, in 27% yield. Trivedi and Nargund (1941) recorded m.p. 104-106° and Johnson, Petersen and Schneider (1947) m.p. 105.5-106°.

VIIc. Resolution - preliminary experiments

It was proposed to attempt the resolution of γ-hydroxy-γ-phenylvaleric acid by fractional crystallisation of the diastereoisomerides formed by combination of the acid with an optically active base. Preliminary experiments were carried out using equimolecular proportions of the acid and the base (strychnine or brucine) (0.1 g. of acid) and various solvents. Attempts to prepare the strychnine salt in ethanol and acetone led to the separation of strychnine; when chloroform and chloroform-light petroleum mixture were used no crystallisation occurred, but when water was used an oil separated which could not be induced to crystallise. The use of brucine as the base gave rather more promising results. A small amount of the salt separated from a somewhat concentrated solution in acetone, but there was no crystallisation from ethanol. A good yield of needles, m.p. 100-108° (decomp.) was obtained when water was used as the solvent; these crystals decomposed to give a white solid when treated with sodium carbonate and an opalescent "solution" when treated with hydrochloric acid, and it was

concluded from these observations that it was the salt that had separated.

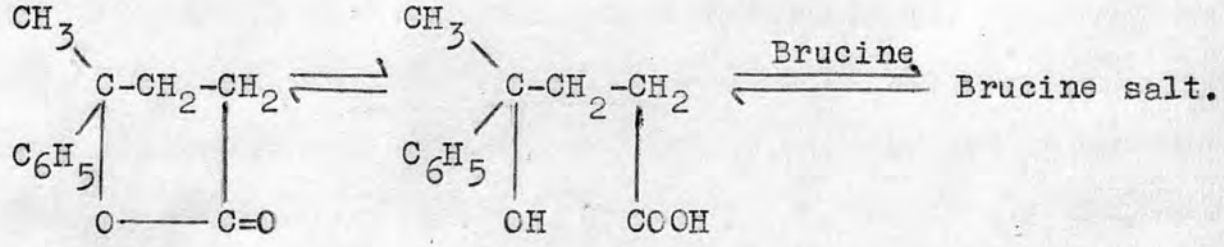
VIId. Conditions for isolation of γ-hydroxy-γ-phenylvaleric acid and γ-phenyl-γ-valerolactone from the brucine salt of the acid

The salt was suspended in excess sodium hydroxide solution and warmed. The brucine which had separated was extracted with chloroform. Traces of chloroform which had dissolved in the aqueous layer were expelled by warming and the acid was then precipitated from the alkaline solution with mineral acid. In general, the hydroxyphenylvaleric acid was extracted with ether, since the volume of the aqueous layer was large. The ether was expelled, and the residue either converted to the lactone (by benzene distillation, cf. Section III) or else dissolved in the minimum amount of 2.5N-potassium hydroxide solution and the hydroxy acid precipitated with acid. The solid was filtered off and washed thoroughly with water.

VIIe. Resolution using brucine in aqueous medium

From the above experiments it appeared that the crystallisation of the brucine salt of γ-hydroxy-γ-phenylvaleric acid from water might lead to resolution. The first attempt to crystallise the brucine salt from water led to the separation of brucine; in this experiment 4.85 g. (0.025 g. mol.) of hydroxy-phenylvaleric acid was used and 350 ml. of water. In a further experiment, using 0.0025 g. mol. of hydroxy-phenylvaleric acid and 10 ml. of water,

0.88 g. of salt (m.p. 105-106° (decomp.)) crystallised. This salt had $[\alpha]_{5780}$ -50.0°, $[\alpha]_{5461}$ -58.8° (c, 1.000 in chloroform) and on decomposition gave γ-phenyl-γ-valerolactone with $[\alpha]_{5780}$ -21.5°, $[\alpha]_{5461}$ -24.0° (c, 0.640 in ethanol). Since the optically pure γ-phenyl-valerolactone was expected to have $[\alpha]_{5780}$ ca. -50°, $[\alpha]_{5461}$ ca. -60° (cf. precipitation of hydroxy-phenylvaleric acid , Section III), it appeared that a fair degree of separation had been effected. Concentration of the aqueous mother liquor at atmospheric pressure caused a brown oil to separate, presumably phenylvalerolactone. It is probable that the following equilibrium exists in solution:-



Such an equilibrium would account for the separation of brucine in some cases.

In the next experiment more water was used in the hope of effecting a more complete separation. 4.85g. (0.025 g. mol.) of hydroxy-phenylvaleric acid was treated with brucine in 250 ml. of water. 5.49g. of salt separated with $[\alpha]_{5780}$ -53.0°, $[\alpha]_{5461}$ -63.0° (c, 1.000 in chloroform). Concentration of the mother liquor from which this crop was obtained gave brucine, and further concentration gave a

small amount of the salt. Three further crystallisations of the main crop gave a product of constant rotation - $[\alpha]_{5780}$ -66.6°, $[\alpha]_{5461}$ -77.8° (c, 1.000 in chloroform) -; but the phenylvalerolactone isolated from the salt had only $[\alpha]_{5780}$ -42.9° ± 0.4°, $[\alpha]_{5461}$ - 48.4° ± 0.4° (c, 0.640 in ethanol).

The main experiment, in which resolution was accomplished, was carried out using 9.7g. (0.05g. mol.) hydroxyphenylvaleric acid and water (200 ml.) This experiment is recorded in detail in Section VIII. The brucine salt of (+)-γ-hydroxy-γ-phenylvaleric acid, m.p. 107-108° (decomp.) separated from water with 2½ molecules of water of crystallisation as sheaves of needles; it had $[\alpha]_{5780}$ --64.9° ± 0.5°, $[\alpha]_{5461}$ -75.9° ± 0.5° (c, 0.995 in chloroform). (+)-γ-hydroxy-γ-phenylvaleric acid had m.p. 122-122.5°, $[\alpha]_{5780}$ +4.8° ± 0.2°, $[\alpha]_{5461}$ +5.7° ± 0.2° (c, 2.544 in ethanol). (-)-γ-Phenyl-γ-valerolactone had $[\alpha]_{5780}$ -54.8° ± 0.4°, $[\alpha]_{5461}$ -61.9° ± 0.4° (c, 1.214 in ethanol).

The brucine salt of (-)-γ-hydroxy-γ-phenylvaleric acid separated from water in plates; on recrystallisation from water it separated with brucine. Insufficient (-)-γ-hydroxy-γ-phenylvaleric acid, m.p. 121-122°, was obtained for an optical rotation determination but it was converted to (+)-γ-phenyl-γ-valerolactone, which had $[\alpha]_{5780}$ +53.9° ± 0.5°, $[\alpha]_{5461}$ + 61.8° ± 0.5° (c, 0.955 in ethanol).

VIII.

EXPERIMENTAL

VIIIa. Preparation of (-)-menthyl pyruvate

Pyruvic acid. - A mixture of tartaric acid (400 g.; 2.66 g. mol.) and potassium hydrogen sulphate (600g.; 4.42 g. mol.) was heated at 200-210° in a distillation apparatus until there was no further distillate. The 225 g. of pale yellow liquid obtained gave 90.5 g. (39%) of pyruvic acid, b.p. 58°/7 mm., after two further distillation

(-)-Menthyl pyruvate. - A mixture of pyruvic acid (44 g.; 0.5 g. mol.) and menthol (312 g.; 2 g. mol.) was heated at 100° for 7 hours whilst a stream of hydrogen chloride was bubbled through intermittently. After being kept overnight the mixture was shaken with ether and the ethereal solution washed with sodium carbonate solution (10%) and water. It was proposed to separate the menthol from the ester by steam distillation of the menthol. After the steam distillation had been proceeding for 8 hours an oil was observed to be distilling together with the menthol. The steam distillation was stopped and the residue in the distilling flask extracted with ether. The ethereal solution of menthyl pyruvate and menthol was dried over sodium sulphate and concentrated; 66 g. of oil was obtained which gave 26.5 g. (24%) of crude (-)-menthyl pyruvate, b.p. 128-130°/8 mm., on distillation in vacuum; a large amount of polymerised material remained undistilled. The product was

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distilled to constant rotation; two redistillations were required to give (-)-menthyl pyruvate of b.p. 132.5-133.5°/10 mm., $n_D^{16°}$ 1.4565, $\alpha_{5893}^{15°}$ -46.64°, $\alpha_{5780}^{15°}$ -48.75°, $\alpha_{5461}^{15°}$ -55.74°.

VIIIb. Preparation of (-)-menthyl laevulate

(-)-Menthyl laevulate. - A mixture of laevulic acid (116 g.; 1 g. mol.) and (-)-menthol (624 g.; 4 g. mol.) was heated at 100°C for 7 hours and hydrogen chloride bubbled through intermittently. The reaction mixture was then extracted with ether and the extract washed with sodium carbonate solution (10%) and water. After drying over sodium sulphate the ether was distilled from the solution and the residue [(-)-menthol and (-)-menthyl laevulate] distilled *in vacuo*. Two fractions of (-)-menthyl laevulate were collected having the same rotation; on redistillation of each the middle fractions had the same rotations as previously. (-)-Menthyl laevulate, b.p. 151°/2 mm., was obtained in 71% yield (180 g.) with $n_D^{20.5°}$ 1.4573, $d^{20.5°}$ 0.9765, $d^{25°}$ 0.971, $[\alpha]_D^{20.5°}$ -61.14°. $[\alpha]_{5780}^{20.5°}$ -63.62°, $[\alpha]_{5461}^{20.5°}$ - 72.01°, $[\alpha]_{5780}^{25°}$ -63.49°, $[\alpha]_{5461}^{25°}$ - 71.84°. Found: C,70.7; H,10.3%. Calc. for $C_{15}H_{26}O_3$: C, 70.8; H, 10.3%. The semicarbazone crystallised from ethanol in prismatic needles, m.p. 156-156.5°.

VIIIc. Preparation of (-)-menthyl ω-acetyl-n-butyrate

ω-Acetyl-n-butyric acid. - A solution of cyclohexane-1:3-dione (56g.; 0.5 g. mol.) in 4N-potassium hydroxide solution (500 ml.) was boiled under reflux for 12 hours. The cooled solution was acidified with conc. hydrochloric acid and ω-acetyl-n-butyric acid was extracted from the aqueous solution with ether using a continuous liquid-liquid extractor. Concentration of the ethereal extract gave a pale yellow oil which crystallised when stirred in the presence of a small amount of water (64 g. solid; 87% yield assuming it to be the mono-hydrate). ω-Acetyl-n-butyric acid monohydrate crystallised from water in prisms, m.p. 37-37.5°C. The semicarbazone crystallised from water in prisms, m.p. 172.5-173.5°. Anhydrous ω-acetyl-n-butyric acid was obtained by heating the monohydrate at 80° and 5 mm. until no water distilled, then the temperature was raised to 100° and the oil allowed to cool in vacuo; 40 g. of anhydrous acid was obtained from 46g. of monohydrate (theory, 40.5g.).

(-)-Menthyl ω-acetyl-n-butyrate. - ω-Acetyl-n-butyric acid (40 g.; 0.308 g. mol.) and (-)-menthol (190 g.; 1.22 g. mol.) were heated together at 100° for 10 hours whilst a stream of hydrogen chloride was passed through intermittently. The reaction mixture was diluted with ether; the solution was washed with sodium carbonate solution

and water and then concentrated. The oil obtained on concentrating this solution was steam distilled to removed the excess menthol from the ester. The non-steam volatile material was extracted with ether and distilled in vacuo. The distillate, b.p. 159.5-160.5°/5 mm., appeared to be homogeneous (all fractions had the same rotatory power) and on redistillation yielded 40 g. (45%) of (-)-menthyl ω-acetyl-n-butyrate, b.p. 154.5-155.5°/3 mm., which had $n_D^{20.5°}$ 1.4588, $d^{25°}$ 0.973, $[\alpha]^{25°}_{5780}$ -68.02°, $[\alpha]^{25°}_{5461}$ -70.17°. Found: C, 72.2; H, 10.8%. $C_{16}H_{28}O_3$ requires: C, 71.6; H, 10.5%. The semicarbazone crystallised from aqueous alcohol in plates, m.p. 125-125.5°.

VIIId. Preparation of (-)-menthyl ω-acetyl-n-valerate

Diethyl adipate.- A solution of adipic acid (438g.; 3 g. mol.) in ethanol (1080 ml.; 18 g. mol.) and toluene (540 ml.), together with concentrated sulphuric acid (2.5ml.) as catalyst, was heated in a distillation apparatus at 110-115°. Distillation was allowed to continue until the temperature of the distillate rose to 79°. After drying over potassium carbonate the distillate was returned to the reaction flask and distillation was allowed to continue until the temperature rose to 81°. The residue was distilled under reduced pressure. 574G. (94%) of diethyl adipate, b.p. 134-138°/18 mm., was collected; it had $n_D^{15°}$ 1.4299.

Ethyl hydrogen adipate. - A solution of adipic acid (292 g.; 2 g. mol.) and diethyl adipate (234 g.; 1.16 g. mol.) in di-n-butyl ether (100 ml.) and concentrated hydrochloric acid (60 ml.) was obtained by heating the mixture to 165°. When the solution had cooled to 125° ethanol (115 ml.; 1.95 g. mol.) was added and the solution then boiled under reflux for 2 hours when a further 40 ml. of ethanol (0.66 g. mol.) was added. After boiling for a further 2 hours the solution was distilled under reduced pressure, the following fractions being collected:-
I - dibutyl ether, water and ethanol; II - diethyl adipate (for use in future experiments) and, III - ethyl hydrogen adipate. 209G. of fraction III was collected with b.p. 124-150°/2 mm. Redistillation of this fraction gave 193 g. (56%) of ethyl hydrogen adipate, b.p. 118-131°/3 mm., which solidified at room temperature; this material, with m.p. 28-29°, was completely soluble in ether and in sodium carbonate solution.

ω-Carbethoxyvaleryl chloride. - A solution of ethyl hydrogen adipate (87 g.; 0.5 g. mol.) in thionyl chloride (50 ml.; 0.67 g. mol.) was boiled under reflux for 75 mins. The excess thionyl chloride was then removed by distilling under diminished pressure. Distillation of the residue gave 82 g. (91%) of ω-carbethoxy-n-valeryl chloride, b.p. 126°/15 mm. By Volhard titration the purity of the product was

estimated as 95% (supported by titration with alkali); redistillation (b.p. 134-136°/21 mm.) made little difference to the purity of the product.

Ethyl ω-acetyl-n-valerate. - Methyl magnesium bromide was prepared from magnesium (34.3 g.; 1.4 g. mol.) and methyl bromide (ca. 210 g. - excess) in ether (700 ml.). Cadmium chloride, which had been dried at 110°, (137.2 g.; 0.748 g. mol.) was added over 5 mins. to the ice-cold solution of methyl magnesium bromide and the reaction mixture was boiled under reflux for 30 mins. Ether (250 ml.) was distilled from the mixture and then benzene (thiophene free) (300 ml.) was added. 350 Ml. of distillate was collected (b.p. 56-70°) and a further 155 ml. of benzene added. 50 Ml. of distillate (b.p. 56-70°) was collected and finally benzene (55 ml.) added. The benzene was heated to boiling and then ω-carbethoxy-n-valeryl chloride (135.1 g.; 0.7 g. mol.) in benzene (200 ml.) was added over a few minutes; these operations were carried out with efficient stirring using a Hershberg stirrer. The reaction mixture was boiled for 30 mins. with stirring and for a further 45 mins. without. The reaction mixture was cooled and poured on to ice (1750 g.) and acidified with 5N-sulphuric acid. The benzene solution was separated from the aqueous layer which was extracted with benzene (3 times). The combined benzene solutions were washed (water, 10%-sodium carbonate solution,

water, saline, water) and dried over sodium sulphate. The benzene was distilled leaving 123 g. of crude ethyl - acetyl-n-valerate. Distillation gave 79.8 g. (66%) of product, b.p. 104°/ 3 mm. - 108°/4 mm. Redistillation of products of purity comparable to the above gave ω-acetyl-n-valerate of b.p. 114°/11 mm. (130 g. from 144g.).

ω-Acetyl-n-valeric acid.- Ethyl ω-acetyl-n-valerate (148 g.; 0.86 g. mol.) was boiled under reflux with 10%-sodium hydroxide solution (380 ml.; 0.95 g. mol. NaOH) for 1 hour. The cooled solution was extracted with ether and then neutralised with 3N-hydrochloric acid. This solution was concentrated and then acidified with concentrated hydrochloric acid and extracted with ether. The ether extract (dried over sodium sulphate) yielded 130 g. of crude acetylvaleric acid which on distillation gave 94g. (76%) of product, b.p. 131.5°-156°/2-3 mm., which solidified. Crystallisation from ether/light petroleum (b.p. 40-60°) gave plates of m.p. 34-35°. The semicarbazone, m.p. 144°, crystallised from ethanol.

(-)-Menthyl ω-acetyl-n-valerate. - Hydrogen chloride was bubbled intermittently through the molten mixture of ω-acetyl-n-valerate (72g.; 0.5 g. mol.) and (-)-menthol (312 g.; 2 g. mol.) at 100° for 7 hours. An ethereal solution of the mixture was washed with 10%-sodium carbonate solution and water; the residue obtained by concentration

of the solution was steam distilled. When all the menthol had distilled the non-steam volatile material was extracted with ether and the extract washed with 10%-sodium carbonate solution and water. The dried ethereal extract (sodium sulphate) was freed from solvent and the residual 132 g. of oil fractionally distilled *in vacuo*. After four distillations, (-)-menthyl ω-acetyl-n-valerate (b.p. 173-174°/3 mm., 186-187°/8 mm.) of constant rotation was obtained; $n_D^{20.5°}$ 1.4600, $d^{25°}$ 0.9605, $[\alpha]_{5780}^{25°}$ -58.74°, $[\alpha]_{5461}^{25°}$ -66.50°; in chloroform solution the specific rotation was $[\alpha]_{5780}^{19°}$ -63.2°; $[\alpha]_{5461}^{19°}$ -72.2° (*c.*, 1.5, *l* = 2 dm.). Found: C, 72.4%; H, 10.7%, $C_{17}H_{30}O_3$ requires: C, 72.3; H, 10.7%. The semicarbazone crystallised in plates from aqueous alcohol, m.p. 105-106°.

VIIIe. Preparation of (-)-menthyl ω-acetylpelargonate

1:2-Dibromodecane-10-carboxylic acid. - (The light petroleum used was treated with excess bromine and kept for 2 days; by this time the bromine was decolourised and hydrogen bromide was being evolved. More bromine was added and the solution was kept for a further day. The light petroleum was freed from excess bromine by shaking it with sodium bisulphite solution; it was then washed with water and dried over calcium chloride. After two distillations light petroleum (b.p. 65-75°) was obtained which was not lachrymatory).

Bromine (163 g.; 1.02 g. mol.) was added over 85 mins.

to a solution of 1:2-decene-10-carboxylic acid (184 g.; 1 g.mol.) in light petroleum (550 ml.), which was being cooled in ice/salt freezing mixture, with rapid stirring. Towards the end of the addition decolourisation of the bromine became very slow and 1:2-dibromo-decane-10-carboxylic acid began to separate. The temperature of the reaction mixture was allowed to increase to 6° over 1 hour before the solid was filtered off. The solid cake was triturated with light petroleum, and then dired in a vacuum over wax for 36 hours to remove last traces of bromine. 1:2-Dibromo-decane-10-carboxylic acid, m.p. 35.5-36.5° was obtained in 50% yield. A further 110 g. (32%) of product (m.p. 25-30°) was obtained by concentrating the petroleum ether mother liquor to dryness and treating the resulting oil with water. Recrystallisation of the product from light petroleum yielded 92 g. of 1:2-dibromo-decane-10-carboxylic acid of m.p. 31.5°.

1:2-Decyne-10-carboxylic acid.- 1:2-Dibromo-decane-10-carboxylic aicd (86 g.; 0.25 g. mol.) was allowed to stand with a solution of potassium hydroxide (86 g.; 1.54 g. mol.) in ethanol (650 ml.) and then boiled under reflux for 12 hours. The alcohol was distilled from the reaction mixture and the residue dissolved in water (300 ml.). The solution was acidified with conc. hydrochloric acid (100 ml.) with cooling and the mixture of organic acids was extracted

with ether. The ethereal solution was washed with water and dried over sodium sulphate. This extract was freed from solvent after the drying over sodium sulphate and the residue distilled until an oil which would not solidify started to distil (monobromo-undecene-carboxylic acid). Three fractions were collected:-

(i) b.p. 159-169°/6-7 mm.; 18.8 g.; m.p. 40.5-41.2°;
(ii) b.p. 169-174°/7-8 mm.; 9.95g.; m.p. 39-40°;
(iii) b.p. 170-173°/7-8 mm.; 4.03g.; m.p. 37-37.5°.

All three fractions gave faint positive bromide tests. The total weight of crude product, which was used for the preparation of the acetylpelargonic acid, was 32.8 g. (72% theory).

ω-Acetyl-pelargonic acid (9-keto-undecylic acid). - A hot solution of mercuric oxide (144 g.; 0.665 g. mol.) in acetic acid (900 ml.) was added to a hot solution of 1:2-decyne-10-carboxylic acid (36.9 g.; 0.203 g. mol.) in acetic acid (93 ml.). Initially a white precipitate appeared; this then dissolved giving an almost clear solution which was heated at 95-100° for 6 hours. Concentrated hydrochloric acid (300 ml.) was added to the mixture which, after heating at 80° for 15 mins., was kept overnight. The mixture was poured into water (ca. 1 l.) and filtered; the solid was washed with ether and the mother liquor ether extracted. Mercury salts were removed from the ethereal solution by precipitating as the sulphide with hydrogen

sulphide. Concentration of the ethereal solution, finally under reduced pressure, gave ca. 38 g. of product which almost all dissolved in 300 ml. of hot light petroleum (b.p. 60-80°). The hot solution was decanted from a small amount of insoluble dark brown oil. 31.5g. of acetylpelargonic acid, m.p. 57-58°, separated from the solution on cooling. A benzene (240 ml.) solution of this material was shaken for 10 hours with 630 ml. of saturated sodium bisulphite solution. The crystals which had separated were filtered off and washed with benzene. The bisulphite compound was decomposed by warming with 10%-hydrochloric acid and the acetylpelargonic acid extracted with ether. Concentration of the dried ethereal solution (sodium sulphate) gave 26.5 g. of oil (still warm) which on recrystallisation from light petroleum (b.p. 40-60°) gave 25 g. of ω-acetylpelargonic acid, m.p. 58.2-58.8° (needles) (62% yield).

(-)-Menthyl ω-acetylpelargonate. - Acetylpelargonic acid (42g.; 0.21 g. mol.) and menthol (131 g.; 0.84 g.mol.) were heated for 8 hours at 100° in the presence of gaseous hydrogen chloride (intermittent stream). An ethereal solution of the reaction mixture was washed with 10%-sodium carbonate solution and water. Menthol was removed from the residue obtained by concentration of the ethereal solution, by steam distillation. The non-steam volatile material (menthyl ester) was extracted with ether and the solution dried over sodium sulphate. The oil (62 g.),

obtained by concentration of the ethereal solution to dryness, was distilled in vacuo to constant rotation. 53 g. of (-)-menthyl ω-acetyl-pelargonate (75% yield) was obtained with b.p. 209-210°/3½-4 mm., $d^{18°}$ 0.944, $d^{25°}$ 0.939, $[\alpha]^{18°}_{5780}$ -48.67°, $[\alpha]^{18°}_{5461}$ -55.09°, $[\alpha]^{25°}_{5780}$ -48.59°, $[\alpha]^{25°}_{5461}$ -55.01°. Found: C, 74.4; H, 11.2%. $C_{21}H_{38}O_3$ requires: C, 74.5; H, 11.3%. The semicarbazone, m.p. 100.5-101° crystallised from aqueous ethanol in rectangular plates.

VIIIf. Preparation of (-)-menthyl bromoacetate

(-)-Menthyl bromoacetate. - (a) - A mixture of bromoacetic acid (70 g.; 0.05 g. mol.) and menthol (300 g.; 1.93 g. mol.) was heated in the presence of dry hydrogen bromide for 8 hours at 100°. An ethereal solution of the reaction mixture was washed with 10%-sodium carbonate solution and then with water, and then dried over sodium sulphate. (-)-Menthyl bromoacetate, containing a trace of menthol, was obtained from this solution by distillation, b.p. 108-116°/2-3 mm. (yield, 76.2 g.; 55%). After one crystallisation from light petroleum (b.p. 40-60°), (-)-menthyl bromoacetate was obtained as needles, m.p. 18.5-19.5°, $[\alpha]_{5780}$ -68.3 ± 0.2°, $[\alpha]_{5461}$ -77.4 ± 0.2° (c, 2.5 in chloroform). (Found: C, 52.6; H, 7.77; Br, 28.3%. Calc. for $C_{12}H_{21}O_2Br$: C, 52.0; H, 7.65; Br, 28.8%).

(b) - A solution of bromoacetic acid (78 g.; 0.56 g. mol.) in thionyl chloride (55 ml.) was boiled under reflux

for 2½ hours, the reaction mixture then being distilled through a packed column; the bromoacetyl chloride had b.p. 121-125° (yield, 69 g.; 78%). Menthol (67 g.; 0.43 g. mol.) was added to bromoacetyl chloride (67 g.; 0.425 g. mol.) at room temperature with shaking. After 15 minutes the reaction mixture was slowly warmed up to 100° and kept at that temperature for 20 minutes. (-)-Menthyl bromoacetate was isolated as in (a), b.p.136°/8 mm.(yield, 96.59.; 82%) after one crystallisation it had $[\alpha]_{5780}$ -68.9 ± 0.2°, $[\alpha]_{5461}$ -78.0 ± 0.2°, $[\alpha]_D^{21}$° -67.9± 0.8° (c, 2.5 in chloroform). (Found: C, 52.1; H, 7.88; Br, 29.0%. Calc. for $C_{12}H_{21}O_2Br$: C, 52.0; H, 7.65; Br. 28.8%).

VIIIg. Grignard reactions*

(i) Phenyl magnesium bromide solution (containing 0,125 g. mol. PhMgBr).

The following preparation was carried out in an atmosphere of nitrogen.

0.5 g. Magnesium was covered with ether, and bromobenzene (10 drops) was added; the reaction flask was heated in a bath at 60° until the reaction had started. The rest of the magnesium (total - 9.60 g.; 0.396 g. mol.) was added and covered with ether (90 ml.). The rest of the bromobenzene (total - 20.65 g.; 0.132 g. mol.) was added (in 45 ml. ether) at such a rate as to maintain gentle boiling

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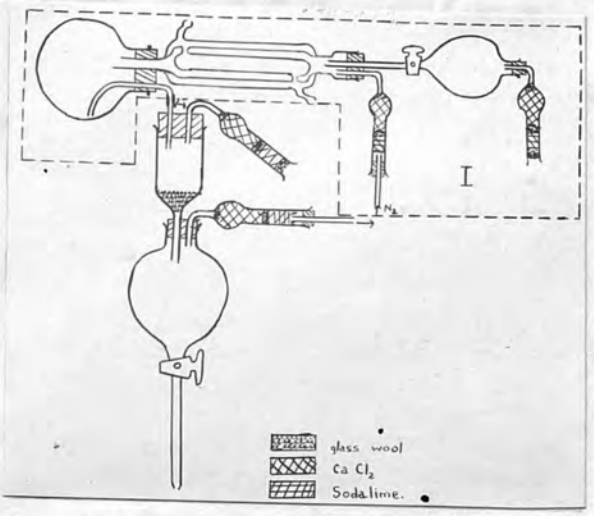
(*) The preparation of an ethereal solution of phenyl magnesium bromide and the subsequent addition to the ester were carried out in an atmosphere of nitrogen. Care was taken throughout to ensure that all operations were carried out as quantitatively as possible, all vessels being thoroughly washed with the appropriate solvent.

of the ether without external cooling or heating. After all the bromobenzene had been added the reaction mixture was heated in a bath at 60° for 30 minutes. The supernatant was siphoned into a dropping funnel in an atmosphere of nitrogen ready for addition to an ethereal solution of the (-)-menthyl ester using the apparatus shown in the diagram.



Apparatus for preparation of Grignard Reagent (I, with condenser upright, and N_2 inlet at A); apparatus for siphoning of Grignard reagent (complete apparatus - as in diagram).

Determination of amount of diphenyl formed. - The supernatant was siphoned from excess magnesium and poured on to ice. The mixture was acidified with 5N H_2SO_4 and the ether separated from the aqueous layer which was extracted twice with ether. The ether extract, after washing 3 times with water, 3 times with 10% sodium carbonate solution and twice with water, was dried over sodium

sulphate. The residue, from which the ether had been distilled, was heated on a boiling water bath under a pressure of about 20 mm. to remove traces of benzene. [From the weight of the residue (assuming it to be diphenyl) the amount of bromobenzene used for conversion into diphenyl could be calculated. It was assumed that the rest of the bromobenzene was converted into the Grignard reagent.] [redacted] 0.35 G. of diphenyl was obtained. This would correspond to 96.5% yield of phenyl magnesium bromide (based on bromobenzene). A repeat of the above experiment gave 93.5% yield.

(ii) Partial asymmetric synthesis of atrolactinic acid.- A solution of (-)-menthyl pyruvate (4.52g.; 0.02 g. mol.) in ether (20 ml.) was added to an ethereal solution of phenyl magnesium bromide (0.025 g. mol.), with ice-cooling and shaking, over 30 mins. The pale yellow solution was boiled under reflux for 2½ hours. The cooled solution was poured on to ice (20 g.) and treated with 5N-sulphuric acid (25ml.). The aqueous layer was extracted with ether (4 x 20 ml.), the final extract being optically inactive, and the combined ethereal solutions were washed with water (2 x 20 ml.), 10%-sodium carbonate solution (1 x 20 ml.) and again with water (1 x 20 ml.); all aqueous washings were optically inactive. Concentration of the dried ethereal solution

(sodium sulphate) to dryness gave 5.49 g. of pale yellow oil which was hydrolysed by boiling with 5N-potassium hydroxide solution (5 ml.) and ethanol (20 ml.) for 4 hours. Since there were two layers a further 5 ml. of sodium hydroxide, 5 ml. of ethanol and 10 ml. of water were added, when a clear solution was obtained, which was boiled under reflux for ½ hour. The ethanol was removed from the solution by distillation and the residue then extracted with ether (5 x 20 ml.). The last ether extract was optically inactive showing that all menthol had been removed (the ethereal extracts are referred to as "A"). The aqueous layer was acidified with 5N-sulphuric acid (it had α_D^{19} + 0.59°) and extracted with 20 ml. portions of ether. After the 5th extract the aqueous layer was optically inactive. The combined ethereal extracts were dried over sodium sulphate and concentrated to dryness. The residue was dried <u>in vacuo</u> over calcium chloride and paraffin wax and gave 1.23 g. (50%) of atrolactinic acid as a pale yellow solid, which had $[\alpha]_D^{20°}$ +7.8°, $[\alpha]_{5780}$ +8.2°, $[\alpha]_{5461}$ +9.5° (<u>c</u>, 6.15 in water) and $[\alpha]_D^{16°}$ +6.7°, $[\alpha]_{5780}$ +6.8°, $[\alpha]_{5461}$ +8.1° (<u>c</u>, 3.075 in ethanol).

Menthol and diphenyl were removed from the ethereal solution "A" by steam distillation; the non-steam volatile material (1-methyl-1:2:2-triphenyl glycol) was separated by ether extraction and was found to be optically inactive.

(iii) Partial asymmetric synthesis of γ-hydroxy-γ-phenyl-valeric acid and γ-phenyl-γ-valerolactone

Small scale preliminary experiment -

To a solution of (-)-menthyl laevulate (5.08g.; 0.02 g. mol.) in ether (20 ml.) was added an ethereal solution of phenyl magnesium bromide (0.025 g. mol.) with shaking and ice-cooling over 30 mins. The reaction mixture was kept at 0° for ½ hour and at room temperature for 1¼ hour, and then treated with ice (20 g.) and 5N-sulphuric acid (25 ml.). The aqueous layer was extracted with ether (4 x 20 ml.) and the combined ethereal solutions washed with water (3 x 20ml.), 10%-sodium carbonate solution (3 x 20 ml.) and water (2 x 20 ml.). The ether was distilled from the dried ethereal solution (sodium sulphate) and the residue (6.79 g.) hydrolysed by boiling under reflux with 2.5N-potassium hydroxide solution (10 ml.) and ethanol (20 ml.) for 4 hours. The alcohol was removed by distillation and the residue extracted with ether (6 x 20 ml.). (In some experiments this extract was examined for non-steam volatile compounds). The aqueous layer was acidified with 5N-sulphuric acid and extracted with ether (6 x 10 ml.). The combined ether extracts were washed with water and dried over sodium sulphate. The residue remaining after distillation of the ether had 3 portions of benzene distilled from it (10 ml. each); in the final distillation no water distilled with the benzene. The yellow oil was dried in vacuo over calcium

chloride and paraffin wax for 3 hours. γ-Phenyl-γ-valerolactone (1.89g.; 53%) was obtained; it had $[\alpha]_{5780}$ -4.0° (c, 7.825 in ethanol).

Large scale experiment -

An ethereal solution of (-)-menthyl laevulate (20.34 g.; 0.08 g. mol.) in ether (80 ml.) was cooled in ice; an ethereal solution of phenyl magnesium bromide (0.10 g. mol.) was added to it over 30 mins. with stirring. Stirring was continued at 0° for a further hour and then the reaction mixture was kept overnight at 0°. The reaction mixture was treated with ice (50 g.) and 5N-sulphuric acid (100 ml.) and the aqueous layer extracted with ether (4 x 50 ml.). The combined ethereal extracts were washed with water (3 x 50ml.), 10%-sodium carbonate solution (10 x 25 ml.) and water (3 x 25 ml.). The sodium carbonate washings removed much of the colour from the ethereal solution; but in the standard conditions it was washed only 3 times with carbonate solution. The ether was distilled from the dried ethereal solution (sodium sulphate) and the residue (27.8 g.), smelling strongly of menthol, which crystallised from the oil on standing, was hydrolysed by boiling under reflux with 2.5N-potassium hydroxide solution (40 ml.) and ethanol (80 ml.) for 4 hours. The alcohol was removed by distillation from a steam bath and the residue extracted with ether (2 x 75, 7 x 50 ml.) until all menthol and other neutral compounds had been removed (in some experiments this extract

was steam distilled and the non-steam volatile compounds examined). The alkaline aqueous layer was acidified with 5N-sulphuric acid and ether extracted. The ether extract was washed with water and dried over sodium sulphate. Ether was removed by distillation and the residue subjected to three benzene distillations (each with 75 ml. of benzene). Last traces of benzene were removed by heating the residue under reduced pressure at 100° for ½ hour and then keeping it <u>in vacuo</u> over paraffin wax for 3 hours. Crude γ-phenyl-γ-valerolactone (6.68 g.; 47%), with $[\alpha]_{5780}$ -6.6°, $[\alpha]_{5461}$ -7.5° (<u>c</u>, 10.060 in ethanol) was obtained. 2 Ml. of this ethanolic solution required 1.40 ml. 0.1N-sodium hydroxide solution for neutralisation in the cold; after opening of the lactone ring a further 9.70 ml. were required (corresponding to the lactone being 85% pure). An ethereal solution of the crude lactone was extracted repeatedly with sodium carbonate solution, which removed almost all the colour, and then dried over sodium sulphate. Removal of the ether from this solution by distillation gave γ-phenyl-γ-valerolactone, which, after drying over paraffin wax and calcium chloride <u>in vacuo</u>, had $[\alpha]_{5780}$ -6.82°, $[\alpha]_{5461}$ -7.71° ± 0.05° (<u>c</u>, 10.108 in ethanol). Found: C, 74.5, H, 7.2%. Calc. for $C_{11}H_{12}O_2$: C, 75.0; H, 6.9%. A small amount of this lactone was distilled and had b.p. 134-139°/7 mm., $n_D^{25°}$ 1.5282. Found: C, 75.6; H. 6.8%.

Calc. for $C_{11}H_{12}O_2$: C, 75.0; H 6.9%. The main portion of this lactone was converted to γ-hydroxy-γ-phenylvaleric acid and then reconverted to the lactone by the above benzene treatment. γ-Phenylvalerolactone had $[\alpha]_{5780}$ -6.55°, $[\alpha]_{5461}$ -7.33° ± 0.1° (c, 5.190 in ethanol); 2 ml. required 0.14 ml. 0.1N-sodium hydroxide solution for neutralisation and a further 5.64 ml. after the lactone had been hydrolysed. This lactone was boiled with sodium hydroxide solution and then cooled. Slow acidification of this solution with 5N-sulphuric acid gave micro-crystals of γ-hydroxy-γ-phenylvaleric acid, with $[\alpha]_{5780}$ 0.60°, $[\alpha]_{5461}$ 0.73 ± 0.1° (c, 3.969 in ethanol). Found C, 67.8 ; H, 7.1%. Calc. for $C_{11}H_{14}O_3$; C, 68.0; H, 7.3%.

Precipitation of γ-hydroxy-γ-phenylvaleric acid, from an alkaline solution, with 5N-sulphuric acid

γ-Hydroxy-γ-phenylvaleric acid (ca. 8.1 g.) was dissolved in aqueous potassium hydroxide solution (60 ml. 1.05 N; 5N-sulphuric acid) and the solution acidified to pH 5.1-5.2; on standing crystallisation commenced. After 8 minutes the pH had risen to 5.8; crystals were separated by filtration (precipitate "a"). The mother liquor (100 ml.) was acidified to pH 4.8 and allowed to stand for 8 minutes, allowing gradual crystallisation of the acid (precipitate "b") and a rise in pH to 5.8. This procedure was repeated for precipitate "c", the final pH being 4.8. Precipitate "d" was obtained when the solution was acidified to pH 1 and kept for ½ hour before

filtration; slow crystallisation occurred.

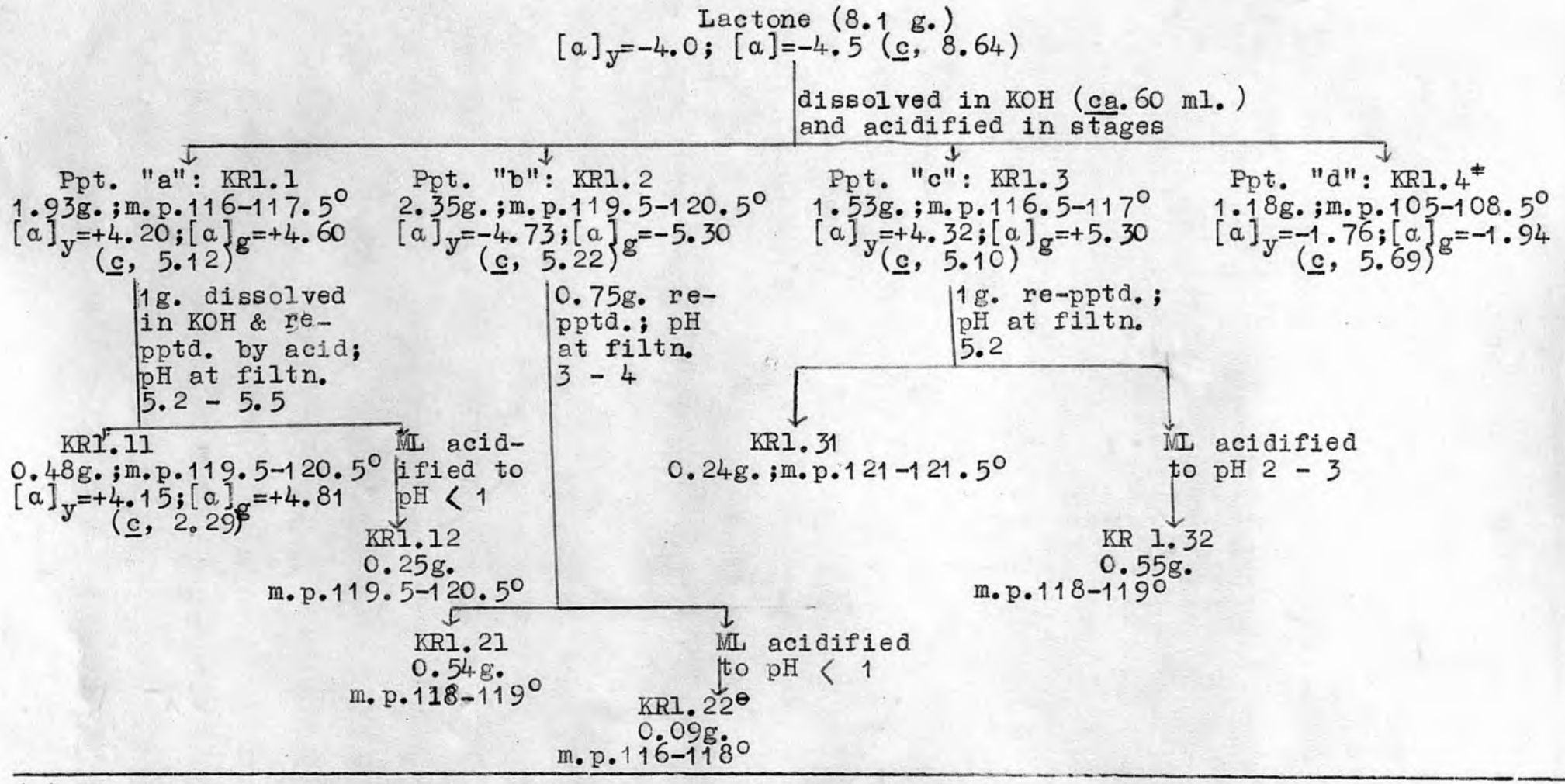
The complete separation is shown in the Table (p. 141) (in which $[\alpha]_{5780}$ and $[\alpha]_{5461}$ are denoted by $[\alpha]_y$ and $[\alpha]_g$ respectively).

(iv) Partial asymmetric synthesis of δ-phenyl- δ -caprolactone

(a) Large scale experiment

An ethereal solution of phenyl magnesium bromide (0.1 g. mol.) was added over $\frac{1}{2}$ hour to an ice-cooled solution of (-)-menthyl ω-acetylbutyrate (21.47g.; 0.08 g.mol.) in ether (80 ml.) with stirring. A thick oil had separated and stirring was continued for a further hour, at 0°. The reaction mixture kept at 0° overnight, and then treated with ice (50 g.) and 5N-sulphuric acid (100 ml.). The aqueous layer was extracted with ether (4 x 50 ml.). The combined ethereal solutions were washed with water (3 x 50ml.), 10%-sodium carbonate (3 x 25 ml.) and water (3 x 25 ml.) and then dried over sodium sulphate. Concentration of this solution to dryness left a yellow oil (26.3 g.) which smelt faintly of menthol. This oil was boiled under reflux with 2.5 N-potassium hydroxide solution (40 ml.) and ethanol (80 ml.) for 4 hours. The alcohol was removed from this clear solution by distillation from a steam-bath the residue then being extracted with ether (2 x 75 ml., 5 x 50 ml.) to remove neutral products. Steam distillation of the residue, obtained by concentrating this ethereal solution to dryness, left only a trace of yellow solid which was not

[For explanation of this tabel see pages 139 and 140]



(*) The aqueous mother liquor, after removal of KR1.4, was ether extracted. The lactone isolated from this extract weighed 0.902g. and had no definite rotation (α_y -0.01, α_g -0.02; c, 4.315).

(e) The aqueous mother liquor after filtration of KR1.21 was acidified to pH < 1, but no crystals separated during the first hour; it was kept overnight and the hydroxy acid crystallised in large needles.

steam volatile (neutral products formed by reaction of the ester group with the Grignard reagent). An ethanol/chloroform solution of this material was optically inactive; the solubility of the neutral compound was low in ethanol. The aqueous layer, after the ether extractions, was acidified with 5N-sulphuric acid and the δ-hydroxy-δ-phenylcaproic acid, which separated, was extracted with ether. The ethereal solution was dried over sodium sulphate and concentrated to dryness. Benzene (3 portions, 100 ml. each) was allowed to distil from the residue; finally, last traces of benzene were removed by heating under reduced pressure at 100°. 10.26G. of yellow oil was obtained, which, on standing, partially solidified. An ethanolic solution had α_{5780} -0.04°, α_{5461} - 0.05° (c, 15.455); when 2 ml. of this solution was diluted with water it needed 7.58 ml. of 0.1N-sodium hydroxide solution for neutralisation (phenolphthalein) and after hydrolysis of the lactone present required a further 7.71 ml. These figures correspond to about 47% lactone, calculated from the expression:-

$$\frac{\text{Vol. of N-NaOH needed to neutralise hydrolysed lactone}}{\text{Weight of material known to be present}} \times \frac{\text{M.W.}}{1000} \times 100.$$

Retreatment of this product with benzene, as above, followed by heating for 3 hours at 100°/5 mm. gave a product consisting of 78% lactone which had α_{5780} -0.06°, α_{5461} -0.06° (c, 13.238). This material then had toluene slowly distilled from it and was subsequently kept at 100°/ 5 mm. for

8 hours; slight darkening had occurred. The product thus obtained consisted of about 90% lactone and had α_{5780} -0.08° (c, 15.418) in ethanol solution.

An ethereal solution of the impure δ-phenyl-δ-caprolactone was washed with sodium carbonate solution and dried over sodium sulphate. Removal of the ether by distillation and drying in vacuo over calcium chloride and paraffin wax gave δ-phenyl-δ-caprolactone, m.p. 62°, an ethanolic solution of which had α_{5780} -0.05°, α_{5461} -0.06° (c, 12.033). Titration of 2 ml. of the solution used for optical observation with 0.1N-sodium hydroxide solution showed that 0.11 ml. was required for neutralisation, before hydrolysing the lactone to the hydroxy-acid, and then a further 12.34 ml. of alkali. Found: C, 75.2; H, 7.5%. $C_{12}H_{14}O_2$ requires: C, 75.8; H, 7.4%.

Acidification of the sodium carbonate extract, with subsequent ether extraction, gave a small amount of optically inactive material.

Small scale experiment

An ethereal solution of phenyl magnesium bromide (0.025 g. mol.) was added, with shaking, to a solution of (-)-menthyl acetylbutyrate which was cooled in ice-water, over ½ hour. The reaction mixture was kept at 0° overnight, and then decomposed with ice and sulphuric acid and subsequently worked up as in the previous example. By

concentration of the ether extract 6.84g. of oil was obtained which was hydrolysed and then treated so as to give an alkaline solution of δ-hydroxy-δ-phenylcaproic acid as described previously. This solution was acidified and ether extracted. The ether extract was washed with water, dried over sodium sulphate and then the ether removed by distillation. Three portions of benzene (50 ml. each) were distilled from the residue which was then kept at 100°/5 mm. for 5 hours, and finally weighed 2.71 g. An ethanolic solution had α_{5780} -0.27°, α_{5461} -0.29° (c,13.293); 2 ml. of this solution required 2.83 ml. 0.1N-sodium hydroxide solution for neutralisation (phenolphthalein) and a further 10.98 ml. after the lactone ring had been opened. An ethereal solution of the above material was extracted with sodium carbonate solution and δ-phenyl-δ-caprolactone obtained from the dried solution (sodium sulphate) by evaporation of the ether. The pale yellow oil, on cooling, gave a solid, m.p. 68-71° which had $[\alpha]_{5780}$ -1.32°, $[\alpha]_{5461}$ -1.47° ± 0.08° (c, 6.466 in ethanol); 2 ml. of this solution required 0.10 ml. alkali for neutralisation and a further 9.87 ml. after opening of the lactone ring.

(v) Interaction of (-)-menthyl ω-acetyl-n-valerate and phenyl magnesium bromide

Experiment (small scale) using 1.25 molecular proportions of Grignard reagent

An ethereal solution of phenyl magnesium bromide (0.025 g. mol.) was added to a solution of (-)-menthyl acetylvalerate (5.65g.; 0.02 g. mol.) in ether (20 ml.) over 10 mins. at room temperature; the temperature of the reaction mixture rose to 30°. The reaction mixture was kept at room temperature for 30 mins., and was then heated in a bath at 60° for 90 mins. The reaction mixture, from which had separated a sticky white solid, was treated with ice (50 g.) and 5N-sulphuric acid (25 ml.). The aqueous layer was extracted with ether (3 x 25 ml.) at the end of which it was optically inactive. The original ether layer and ether extracts were combined and washed with water, sodium carbonate solution and again with water. The aqueous washings had no optical activity. The dried ethereal solution (sodium sulphate) was concentrated to dryness, and the residue (7.43g.) was hydrolysed by boiling under reflux with 5N-sodium hydroxide solution (5 ml.) and ethanol (40 ml.) for 2¼ hours. Alcohol was removed by distillation from a steam-bath and a small amount of water was added to the residue which was then extracted with ether (4 x 15 ml.); the final ether extract had no optical activity (combined ether extracts referred to as "A"). The alkaline aqueous layer was

acidified with 5N-sulphuric acid; the oil which separated was extracted with ether (3 times); the aqueous layer was inactive. The ethereal extracts were combined, washed with water and dried over sodium sulphate. The ether was removed by distillation and the residue dried over calcium chloride and wax in vacuo. 3.17g. (72%), of a pale yellow oil was obtained which was optically inactive; M.W. (by titration): 219. $C_{13}H_{18}O_3$ has M.W. 222.

The combined ether extracts "A" were steam distilled, until free from menthol and diphenyl, and the non-steam volatile material was extracted with ether. Concentration of this dried ether extract gave a small amount of material which had, in ethanolic solution, α_D -0.05°.

Large scale experiment

An ethereal solution of phenyl magnesium bromide (0.10 g. mol.) was added to a solution of (-)-menthyl acetyl-valerate (22.6 g.; 0.08 g. mol.) in ether (80 ml.) over 30 mins. with ice-cooling and stirring. Stirring was continued with cooling for a further hour and the reaction mixture was kept overnight at 0°. The mixture was decomposed with ice (50 g.) and 5N-sulphuric acid (100 ml.). The aqueous layer was extracted with ether (4 x 50 ml.) and the combined ether extracts were washed with water (3 x 50 ml.), 10%-sodium carbonate solution (3 x 25 ml.) and water (3 x 25 ml.) and then dried over sodium sulphate. Concentration of this

solution to dryness gave a yellow oil (29.3 g.) which was hydrolysed by boiling under reflux with 2.5N-potassium hydroxide solution (40 ml.) and ethanol (80 ml.) for 4 hours. Ethanol was removed by distillation from a steam-bath and the residue was extracted with ether (2 x 75 ml., 5 x 50 ml.); no smell of menthol was perceptible when the last ether extract was concentrated. The ether extracts were steam distilled and 0.06g. of non-steam volatile material was isolated by ether extraction. This was optically inactive. The alkaline aqueous layer was acidified with 5N-sulphuric acid and then ether extracted. The ether extract was washed with water, dried over sodium sulphate and the ether expelled by heating on a steam-bath. 14.86G. (84%) of 5-hydroxy-5-phenyl-hexane-1-carboxylic acid was obtained as a yellow viscous oil which would not crystallise. Found: C, 70.3; H, 8.2%. $C_{13}H_{18}O_3$ requires: C, 70.2; H, 8.2%. It had α_{5780} +0.09° (c, 49.95 in ethanol). The yellow oil distilled at 160-192°/3 mm. and on redistillation a pale yellow liquid, b.p. 150-178/3 mm. was obtained. Found: C, 71.1; H 8.8%. A dehydration of product of 5-hydroxy-5-phenylhexan-1-carboxylic acid ($C_{13}H_{16}O_2$) would require: C, 76.4; H, 7.9%.

(vi) Interaction of (-)-menthyl ω-acetylpelargonate and phenyl magnesium bromide

An ethereal solution of phenyl magnesium bromide (0.1 g. mol.) was added over ½ hour to an ice-cooled solution of (-)-menthyl ω -acetylpelargonate (27.04g; 0.08 g. mol.) with stirring. A thick sticky oil separated which prevented efficient stirring, although attempts to continue stirring for a further hour were made. The reaction mixture was kept at 0° overnight, and then decomposed with ice (50 g.) and 5N-sulphuric acid (100 ml.). The aqueous layer was extracted with ether (4 x 50 ml.) and the combined ethereal solutions, after washing with water (3 x 50 ml.), 10%-sodium carbonate solution (3 x 25 ml.) and water (3 x 25 ml.), were dried over sodium sulphate. The solution was concentrated to dryness and the residue hydrolysed by boiling with 2.5N-potassium hydroxide solution (40 ml.) and ethanol (80 ml.) for 8 hours. The alcohol was removed by distillation from a steam bath and the residue was extracted with ether (2 x 75 ml., 6 x 50 ml.). The aqueous layer was acidified with 5N-sulphuric acid and the organic acids extracted with ether. The ethereal solution was washed with water (3 x 25 ml.) and after drying over sodium sulphate, concentrated to dryness to give 22.14 g. of impure 9-hydroxy-9-phenyl-decane-1-carboxylic acid as a yellow oil which partly solidified on prolonged standing. Found: C, 70.1; H, 9.9%. $C_{17}H_{26}O_3$ requires: C, 73.3;

H, 9.4%. An ethanolic solution (approx. 25%) exhibited no definite optical activity (α_{5780} and α_{5461} -0.01°), thus no attempt was made to purify the 9-hydroxy-9-phenyl-decane-1-carboxylic acid; unchanged acetylpelargonic acid would have accounted for the low carbon content.

VIIIh. Reformatsky reactions

(i) Partial asymmetric synthesis of β-hydroxy-β-phenyl-butyric acid

A solution of (-)-menthyl bromoacetate (30.47 g.; 0.11 g. mol.) in benzene (10 ml.) was added dropwise with mechanical stirring, over 7½ hrs., to a boiling solution of acetophenone (13.2 g.; 0.11 g. mol.) in benzene (50 ml.; thiophene free) in the presence of zinc needles (10.8 g.; 0.165 g. mol.). Boiling and stirring were continued for a further four hours after addition was complete. The reaction mixture was kept overnight at room temperature and finally the liquid was decanted from unreacted zinc (3.68g.; 0.0564 g. mol.) which was washed with ether and water. The combined liquids were treated with ice (25 g.) and 5N-sulphuric acid (100 ml.). The aqueous layer was extracted with ether (1 x 100, 2 x 50 ml.); the combined ether extracts and benzene solution were washed with water (3 x 25 ml.) and dried over sodium sulphate. Concentration of this solution to dryness, finally under reduced pressure, gave 33.32 g. of a yellow oil which solidified on standing. This product had a bromine content of 1.71%, corresponding to 1.98 g. of

unchanged (-)-menthyl bromoacetate. The product was hydrolysed in 2 portions, each using 15.15 g. of "ester" (corresponding to the product obtained from 0.05 g. mol. of (-)-menthyl bromoacetate).

(a) - The product (15.15 g.) was boiled under reflux with 2.5N-potassium hydroxide solution (25 ml.; 0.0625 g. mol. KOH) and ethyl alcohol (50 ml.) for 4 hours. β-Hydroxy-β-phenyl-butyric acid was isolated (as described below) as an oil (yield 4.735 g.; 53%), which solidified on prolonged standing, with $[\alpha]_{5780}$ + 3.01 ± 0.05°, $[\alpha]_{5461}$ +3.38 ± 0.05° (c, 22.05 in ethanol), and $[\alpha]_{5780}$ +2.34 ± 0.05°, $[\alpha]_{5461}$ +2.64 ± 0.05° (c, 9.1 in ethanol). Mol. weight found by titration: 181. Calc. for $C_{10}H_{12}O_3$: 180.

(b) - The condensation product (15.15 g.) was boiled under reflux with N-potassium hydroxide solution (62.5 ml.; 0.0625 g. mol. KOH) and ethyl alcohol (30 ml.) for 17 hours; at the end of the hydrolysis there were still two layers whereas in (a) a clear solution had been obtained. β-Hydroxy-β-phenylbutyric acid (4.365 g.; 49% yield) was obtained as in (a) with $[\alpha]_{5780}$ +2.73 ± 0.05°. $[\alpha]_{5461}$ +3.06 ± 0.05° (c, 15.75 in ethanol). Found: C, 66.4; H, 7.04%. $C_{10}H_{12}O_3$ requires: C, 66.7; H, 6.71%.

A systematic examination was made of the products of hydrolysis. The product from 0.05 g. mol. (-)-menthyl bromoacetate was boiled with aqueous alcoholic potassium

hydroxide (see above); finally the alcohol was removed by distillation, the residue then being extracted with ether (1 x 50, 5 x 25 ml.) to remove neutral compounds. The ethereal extract was concentrated to dryness and the 9.73 g. of oil left was steam distilled. A small amount (0.04g.) of non steam-volatile residue was extracted by means of ether and gave on dissolving in ethanol (15 ml.) $\alpha_{5780}^{25^\circ}$ - 0.07°, $\alpha_{5461}^{25^\circ}$ -0.08°. This oil was not soluble in alkali, nor was it hydrolysed further by boiling with alkali. The steam volatile material was a mixture of menthol and acetophenone. From 4.87 g. of neutral products 2.1 g. of the 2:4-dinitrophenylhydrazone of acetophenone was obtained, m.p. 239-240°; crystallised from aqueous acetic acid this had m.p. 242-3° (decomp.).

The aqueous alkaline solution (after removal of the neutral products as above) was acidified with 5N-sulphuric acid and the β-hydroxy-β-phenyl butyric acid extracted with ether (1 x 50, 3 x 20 ml.). The ether extracted was washed with water (3 x 20 ml.), dried over Na_2SO_4 and concentrated to dryness, thereby giving the products described above. The acid aqueous layer (after extraction of β-hydroxy-β-phenylbutyric acid) was optically inactive. Steam distillation gave acetic acid, requiring 11.8 ml. N KOH for neutralisation (to thymol blue);

(ii) Preparation of (±)-β-hydroxy-β-phenyl-butyric acid

A solution of ethyl bromo-acetate (3.34 g.; 0.02 g. mol.) and acetophenone (2.88 g.; 0.024 g. mol.) in benzene (15 ml.) was boiled under reflux in the presence of zinc (1.31 g.; 0.02 g. mol.) for 1½ hours. The condensation product (4.365 g.), obtained as in the above example, was hydrolysed by boiling under reflux with 2.5N-potassium hydroxide solution (10 ml.; 0.025 g. mol. KOH) and ethyl alcohol (25 ml.). The product of hydrolysis was worked up as in the above experiment and β-hydroxy-β-phenyl-butyric acid (yield 2.355 g.; 65%) was obtained as an oil which solidified on standing. On crystallisation from light petroleum (b.p. 100-120°) needles were obtained, m.p. 71-72°. Found: C, 66.7%; H, 6.85%. $C_{10}H_{12}O_3$ requires: C, 66.7%; H, 6.71%.

(iii) Preparation of 2-hydroxy-2-iso-butyl-4-methyl-hexanoic acid

A solution of (-)-menthyl bromoacetate (2.77 g.; 0.01 g. mol.) and di-iso-butyl ketone (1.70 g.; 0.012 g. mol.) in benzene (15 ml.) was boiled, in the presence of zinc (0.654 g.; 0.01 g. atoms), under reflux for 5 hours. The reaction mixture was worked up and hydrolysed as usual. 3.48 G. of condensation product was obtained which on hydrolysis gave a pale yellow oil (yield 0.75 g.; 37%) which did not decolourise acid potassium permanganate solution. (Found: C, 64.8; H, 10.8%. $C_{11}H_{22}O_3$ requires: C, 65.3, H, 11.0%).

VIIIj. (±)-γ-Hydroxy-γ-phenylvaleric acid

(i) Preparation

Ethyl laevulate. - A solution of laevulic acid (580g.; 5 g. mol.) in ethanol (1,150 ml.) and a saturated alcoholic solution of hydrogen chloride (60 ml.) was boiled under reflux for 24 hours. A small volume of ether was added and the ethereal solution was washed with 10%-sodium carbonate solution and water and finally dried over sodium sulphate and sodium carbonate. Distillation gave 586g. (81%) of ethyl laevulate, b.p. 98°/15 mm. Ruzicka (1917) records b.p. 95°/15 mm.

(±)-γ-Hydroxy-γ-phenylvaleric acid.- An ethereal solution of phenyl magnesium bromide (1.25 g. mol.) was added to ethyl laevulate (144 g.; 1.0 g. mol.) in ether (1000 ml.), with ice-cooling and stirring over 20 mins. Stirring was continued for a further 10 mins. with ice cooling, and the reaction mixture was then kept overnight at 0°. A hard solid mass had separated from the ether. The reaction mixture was treated with ice (500 g.) and 5N-sulphuric acid (1000 ml.). The aqueous layer was extracted with ether (4 x 500 ml.) and the combined ethereal solutions were washed with water (3 x 300 ml.), 10%-sodium carbonate solution (3 x 300 ml.) and water (3 x 300 ml.). Distillation of the ether from the dried solution (sodium sulphate) gave 180 g. of yellow oil which was hydrolysed by

boiling under reflux with ethanol (1000 ml.) and 2.5N-potassium hydroxide solution (500 ml.) for 5 hours. The dark brown solution was kept overnight and was extracted with ether. The aqueous layer was acidified with 5N-sulphuric acid and ether extracted. The ethereal solution was washed with water and dried over sodium sulphate. The ether was distilled and the residue, having had three portions of benzene (250 ml. each) distilled from it, was obtained as a dark brown oil (83 g.; 47%). Crude γ-phenyl-γ-valerolactone, obtained as above, was dissolved in ether and the solution was washed with 10%-sodium carbonate solution (6 x 50 ml.). The ether was distilled from the ethereal solution and the residue dissolved in hot 2.5N-potassium hydroxide solution. The solution was treated with charcoal, cooled and filtered. Slow acidification of the alkaline solution with 5N-sulphuric acid gave γ-hydroxy-γ-phenylvaleric acid as microcrystals (48g.; 27%). Crystallisation from benzene gave plates, m.p. 105.5-106°. Found: C, 68.2; H, 7.4%. Calc. for $C_{11}H_{14}O_3$: C, 68.0; H, 7.3%.

(ii) Resolution

γ-Hydroxy-γ-phenylvaleric acid (9.7 g.; 0.05 g. mol.) was dissolved in water (200 ml.) with the minimum amount of heating. Brucine (+ 4 H_2O) (23 g.; 0.05 g. mol.) was added in one batch with stirring and warming continued until solution was obtained. The solution was filtered

and allowed to cool. Rosettes of needles separated (13.47 g.) which had m.p. 105-110° (decomp.) and $[\alpha]_{5780}$ -49.6°, $[\alpha]_{5461}$ -58.2° (c, 0.998 in chloroform). (Mother liquor from this termed "Main aqueous mother-liquor"). After five crystallisations from water the brucine salt of (+)-γ-hydroxy-γ-phenylvaleric acid was obtained as sheaves of needles, m.p. 107-108° (decomp.) and $[\alpha]_{5780}$ -64.9° ± 0.5°, $[\alpha]_{5461}$ -75.9° ± 0.5° (c, 0.995 in chloroform). Found: C, 64.3; H, 7.3%. $C_{34}H_{40}O_7N_2$, $2\frac{1}{2}$ H_2O requires: C, 64.4; H 7.1%.

The salt was treated with warm excess sodium hydroxide solution and the brucine which had separated was extracted with chloroform (3 times). The alkaline solution, from which traces of dissolved chloroform had been expelled by warming was acidified with hydrochloric acid with ice-cooling and ether extracted. The ether extract was washed with water and dried over sodium sulphate. The ether was distilled and the residue dissolved in the minimum amount of hot 2.5N-potassium hydroxide solution. The solution was acidified with ice cooling and kept at 0° for ½ hour, and (+)-γ-hydroxy-γ-phenylvaleric acid filtered off and washed thoroughly with iced water. It had m.p. 122-122.5°, $[\alpha]_{5780}$ +4.8° ± 0.2°, $[\alpha]_{5461}$ 5.7° ± 0.2° (c, 2.544 in ethanol). Reprecipitation from alkaline solution with mineral acid did not affect the specific rotation. Re-crystallisation from benzene did not affect the rotation

and acid obtained from the mother liquor had the same rotation. The lactone was prepared by subsequent distillations of benzene from the acid (as described earlier) and, finally, the oil was heated at 100°. (-)-γ-Phenyl-γ-valerolactone was obtained with $[\alpha]_{5780}$ -54.8 ± 0.4°, $[\alpha]_{5461}$ -61.9° ± 0.4° (c, 1.214 in ethanol). Found: C, 67.9; H, 7.3%. Calc. for $C_{11}H_{14}O_3$: C, 68.0, H, 7.3%.

The "main aqueous mother liquor" was concentrated to 35 ml. Small amounts of solid, which had separated in the initial stages of the concentration, were removed by filtration. On cooling this solution, a mixture of needles and plates separated with $[\alpha]_{5780}$ -22.4°, $[\alpha]_{5461}$ -27.5° (c, 1.002 in chloroform). Recrystallisation of this material gave first a small amount of brucine and then a mixture of needles and plates which had α_{5780} +0.03°, α_{5461} -0.01° (c, 1.011 in chloroform).

γ-Hydroxy-γ-phenylvaleric acid was obtained from this material, as described above, and then reconverted to the brucine salt (since brucine had been separating during the crystallisation). The brucine salt thus obtained separated from water in plates, m.p. 95.5-98° (decomp.) and had $[\alpha]_{5780}$ +7.1° ± 0.1°. $[\alpha]_{5461}$ +6.5° ± 0.1° (c, 5.062 in chloroform). Recrystallisation of this salt gave a product with $[\alpha]_{5780}$ + 6.5° ± 0.1°, $[\alpha]_{5461}$ +5.8° ± 0.1° (c, 3.441 in chloroform) (it appeared from these figures that brucine was crystallising out as well as the salt). γ-Hydroxy-

γ-phenylvaleric acid was isolated both from the salt and the mother-liquor. Both crops were converted into the lactones which had $[\alpha]_{5780}$ +53.4°, $[\alpha]_{5461}$ +59.6° (c, 0.752 in ethanol) and $[\alpha]_{5780}$ +53.2°, and $[\alpha]_{5461}$ +59.9° (c, 0.854 in ethanol) respectively. These crops were combined and dissolved in hot potassium hydroxide solution. (-)-γ-hydroxy-γ-phenylvaleric acid was precipitated and filtered from this solution, as described before, and converted to (+)-γ-phenyl-γ-valerolactone. Reconversion of the lactone to the acid and the acid back to the lactone as previously caused no change in the specific rotation. (-)-γ-Hydroxy-γ-phenylvaleric acid, m.p. 121-122°, gave (+)-γ-phenyl-γ-valerolactone with $[\alpha]_{5780}$ +53.9° ± 0.5°, $[\alpha]_{5461}$ +61.8° ± 0.5° (c, 0.955 in ethanol). Found: C, 67.3; H, 7.1%. Calc. for $C_{11}H_{14}O_3$: C, 68.0; H, 7.3%.+

(+) Preparation of the solution of γ-phenyl-γ-valerolactone for optical measurements. Since only small amounts of the lactone were available the procedure used for the preparation of the solution was as follows. The lactone (dried at 100°, and allowed to cool in a vacuum desiccator) was dissolved in ethanol and transferred to a standard flask; the original flask was then dried under the conditions used previously and reweighed.

IX. SUMMARY

1. (-)-Menthyl esters of ω-acetyl fatty acids [$CH_3.CO.(CH_2)_n.CO_2.C_{10}H_{19}$] were prepared, with n = 0, 2, 3, 4 and 8.

2. These esters were treated with phenyl magnesium bromide. By hydrolysis of the resulting hydroxy-ester and examination of the product for optical activity, an asymmetric reaction was shown to occur when n = 0, 2, 3 or 4. When n = 0, 2 or 4 a dextro-rotatory hydroxy-acid was obtained and when n = 2 or 3 a laevo-rotatory lactone (corresponding to the hydroxy-acid) was obtained. No asymmetric synthesis was observed using (-)-menthyl ω-acetylpelargonate (n = 8).

3. The degree of asymmetric synthesis obtained using the esters with n = 2 or 3 varied with the experimental conditions employed. The reaction using (-)-menthyl laevulate (n = 2) was studied extensively. The yield, as well as the degree of asymmetric synthesis, was found to vary with reaction conditions. An attempt was made to ascertain the nature of the by-products from this reaction.

4. The product obtained from the reaction with n = 2 (γ-hydroxy-γ-phenyl-n-valeric acid) was separated into (+) and (-) isomers by controlled acidification of an alkaline solution with mineral acid. The products (acids and the corresponding lactones) were almost optically pure.

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as shown by comparison of their specific rotation with those of the optically pure specimens. The latter were obtained by resolution of (±)-γ-hydroxy-γ-phenyl-n-valeric acid.

5. (-)-Menthyl bromoacetate was prepared. An asymmetric reaction occurred when it was treated with acetophenone and zinc (Reformatsky reaction). The optical purity of the β-hydroxy-acid, obtained by hydrolysis of the hydroxy-ester, was found to be remarkably constant and independent of the conditions used for the reaction. Control experiments using the same ester and di-iso-butyl ketone, or the same ketone and ethyl bromoacetate respectively, gave products which, after hydrolysis did not exhibit optical activity.

6. Theories of asymmetric synthesis are discussed and an explanation of the results obtained in this investigation suggested.

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