

CXXVII.—*Studies in Asymmetric Synthesis. I. Reduction of Menthyl Benzoylformate. II. Action of Magnesium Alkyl Haloids on Menthyl Benzoylformate.*

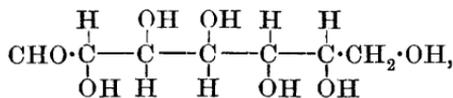
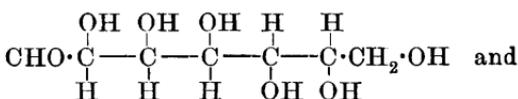
By ALEXANDER MCKENZIE.

It is well known that various optically active substances, of which *d*-glucose, *d*-fructose, *d*-tartaric acid, and *l*-malic acid are common types, occur in nature as products of plant or animal metabolism. They do not, however, occur as a mixture of two enantiomorphous forms in unequal amounts, but in the pure enantiomorphous form; thus *l*-glucose is not found in nature associated with *d*-glucose, nor is *l*-fructose found associated with *d*-fructose. With reference to the mode of formation of such compounds, it is improbable that their optical activity is due to the initial synthesis of the inactive form and its subsequent resolution by an asymmetric agent, with the total destruction of the one enantiomorphous form and the survival of the other. The conception of asymmetric synthesis, on the other hand, first introduced by Emil Fischer, and based by him on experiments with substances of definite constitution, meets with most favour. In the case, for instance, of the synthesis of *d*-glucose in the leaves of plants, it is assumed that the chlorophyll, which is presumably optically active, exerts a directive influence on the condensation of carbon dioxide or formaldehyde of such a kind that the sugar formed is also active (*Ber.*, 1894, 27, 3231); the chlorophyll and sugar may possibly form an additive compound, which is disrupted with the regeneration of the original chlorophyll complexes and the elimination of an optically active sugar. In support

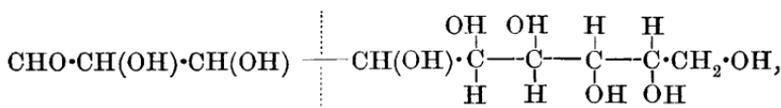
of this view, Fischer cites experimental evidence from the syntheses he accomplished by aid of the cyanohydrin reaction. In the formation of gluco-octonic acids, the yield of the α - is much greater than that of the β -acid ; a similar result is obtained in the synthesis of rhamnohexonic acid ; with mannoheptonic acid, the yield of the α -acid is as much as 87 per cent. of the theory, whilst no trace of the β -isomeride was detected (*Ber.*, 1889, 22, 370 ; *Annalen*, 1892, 270, 68). To make the idea clearer, the following instance is quoted by Fischer and Slimmer (*Sitzungsber. K. Akad. Wiss. Berlin*, 1902, 28, 597). Mannose with

the configuration
$$\text{CHO} \cdot \begin{array}{c} \text{OH} \\ | \\ \text{C} \\ | \\ \text{H} \end{array} - \begin{array}{c} \text{OH} \\ | \\ \text{C} \\ | \\ \text{H} \end{array} - \begin{array}{c} \text{H} \\ | \\ \text{C} \\ | \\ \text{OH} \end{array} - \begin{array}{c} \text{H} \\ | \\ \text{C} \\ | \\ \text{OH} \end{array} \cdot \text{CH}_2 \cdot \text{OH}$$
 might be expected

to yield, by the cyanohydrin reaction, the two isomeric mannoheptoses,



but, as a matter of fact, only one of them is formed. From this heptose again, by the further application of the cyanohydrin reaction, only one of the two possible octoses has been isolated, and this octose was also found to yield only one nonose. If now the molecule of mannononose, synthesised in the manner just indicated, be represented as follows :



and if it could possibly be degraded at the point indicated by the dotted line, it might be expected that the original active mannose would be regenerated and an active glyceric aldehyde formed.

All attempts to realise an asymmetric synthesis on the lines indicated by Fischer have, however, been hitherto unsuccessful. Thus, although helicin forms a crystalline cyanohydrin which has all the appearance of a uniform substance, it was not found possible to prepare from it salicylaldehydecyanohydrin owing to the ease with which the latter is hydrolysed (E. Fischer, *Ber.*, 1901, 34, 629). Cohen and Whiteley (*Trans.*, 1901, 79, 1305) studied the dibromo-derivatives of amyl and menthyl cinnamates and the reduction of the menthyl esters of mesaconic, α -methylcinnamic, and pyruvic acids, whilst Kipping (*Proc.*, 1900, 16, 226) examined the reduction of the bornyl esters of

pyruvic, lævulinic, and benzoylformic acids and the reduction of the quinine salts of pyruvic and lævulinic acids. Fischer and Slimmer (*Sitzungsber. K. Akad. Wiss. Berlin*, 1902, 28, 597; *Ber.*, 1903, 36, 2575) studied the formation of *o*-hydroxymandelic acid and of *o*-hydroxyphenylethylcarbinol from tetra-acetylhelicin.

Fischer has afforded further evidence of the preferential formation of one isomeride before another under asymmetric influence in his recent syntheses of polypeptides (*Ber.*, 1904, 37, 2486). For example, *i*- α -bromoisocapronyl chloride, $C_4H_9 \cdot \overset{*}{C}HBr \cdot COCl$, which contains one asymmetric carbon atom, combines with *l*-tyrosine,



which also contains one asymmetric carbon atom, to form α -bromoisocapronyl-*l*-tyrosine, $C_4H_9 \cdot \overset{*}{C}HBr \cdot CO \cdot NH \cdot \overset{*}{C}H(CH_2 \cdot C_6H_4 \cdot OH) \cdot CO_2H$, containing two asymmetric carbon atoms. Now it might be expected that two stereoisomerides of the latter type should be formed, but the product obtained by Fischer behaved like a uniform substance, although, as he points out, it may nevertheless be a mixture of the two modifications should they form mixed crystals with one another (compare E. Fischer and Suzuki, *Ber.*, 1904, 37, 2843).

The first asymmetric synthesis has lately been effected by Marckwald (*Ber.*, 1904, 37, 349), who based his experiments on a conception different from that which guided previous investigators. Whilst two series of hydrogen sulphites, represented by $M \cdot SO_2 \cdot OH$ and $H \cdot SO_2 \cdot OM$, respectively, are theoretically possible, it is found that from such unsymmetrical dibasic acids only one hydrogen salt with one and the same base can be isolated. Methylene malonic acid, $CM_eEt(CO_2H)_2$, does not contain an asymmetric carbon atom, but when one of the replaceable hydrogen atoms is substituted by a metal, the carbon atom becomes asymmetric and two enantiomorphous salts are possible,

namely, $Me \cdot \overset{\overset{CO_2M}{|}}{C} \cdot Et$ and $Et \cdot \overset{\overset{CO_2M}{|}}{C} \cdot Me$. When a solution of methylethyl-

malonic acid, which has been half neutralised by an inactive base like potassium hydroxide, is evaporated, an inactive product (either the *dl*-mixture or the *r*-salt) separates, since the solubility of the two types under consideration is the same. On the other hand, when an active base is employed, the two salts are no longer mirror-images and, on evaporation of the solution, only one salt separates with re-establishment of equilibrium between the two salts in solution. Marckwald accordingly obtained the brucine hydrogen salt of methylethylmalonic acid, which, when heated at 170°, lost carbon dioxide and was converted into the brucine salt of methylethylacetic acid. The acid,

obtained after removal of the brucine from the latter salt, was a mixture of *dl*- and *l*-methylethylacetic acids, containing 10 per cent. of the latter.

Cohen and Patterson (*Ber.*, 1904, **37**, 1012) do not consider this synthesis of active valeric acid to be an asymmetric one, since a solution of methylethylmalonic acid is regarded by them as containing

the enantiomorphous ions, $\text{Me} \cdot \overset{\text{CO}_2'}{\underset{\text{CO}_2\text{H}}{\text{C}}} \cdot \text{Et}$ and $\text{Et} \cdot \overset{\text{CO}_2'}{\underset{\text{CO}_2\text{H}}{\text{C}}} \cdot \text{Me}$, that is, the

acid in solution already contains an asymmetric carbon atom before the active brucine enters into reaction with it. In reply to their criticism, Marckwald (*Ber.*, 1904, **37**, 1368), after giving a precise definition of an asymmetric synthesis as follows, "Asymmetrische Synthesen sind solche, welche aus symmetrisch constituirten Verbindungen unter intermediärer Benutzung optisch-activen Stoffe, aber unter Vermeidung jedes analytischen Vorganges, optisch-active Substanzen erzeugen," points out that the brucine hydrogen salt of methylethylmalonic acid is formed in quantitative yield, that no analytical separation is necessary, and that the salt may be produced in non-ionising solvents, such as ether or chloroform.

In the present communication, evidence is submitted to indicate the accomplishment of a successful asymmetric synthesis on the lines laid down by Fischer.

The preparation of *l*-menthyl *dl*-mandelate from *r*-mandelic acid and *l*-menthol by the hydrogen chloride method was described in a previous paper (McKenzie, *Trans.*, 1904, **85**, 378). When this ester is hydrolysed by an excess of alcoholic potassium hydroxide, it yields, of course, *r*-mandelic acid. When it is hydrolysed, however, by an amount of potassium hydroxide insufficient for complete hydrolysis, an optically active mandelic acid is invariably obtained from the potassium salt so formed; when the mixture of esters still remaining after this partial hydrolysis is then completely hydrolysed, the mandelic acid obtained is either optically active or inactive according to the conditions under which this final hydrolysis is conducted. The presence of a considerable excess of alkali is found to favour the formation of an inactive acid. Accordingly, in the complete hydrolysis by potassium hydroxide of a mixture of *l*-menthyl *d*-mandelate and *l*-menthyl *l*-mandelate containing an excess of either of these esters, racemisation phenomena come into play, since the acid obtained is not always optically active.

Now the asymmetric synthesis of mandelic acid might be attempted by reducing menthyl benzoylformate, $\text{PhCO} \cdot \text{CO}_2 \cdot \text{C}_{10}\text{H}_{19}$, to menthyl mandelate, $\text{PhCH}(\text{OH}) \cdot \overset{*}{\text{C}} \cdot \text{CO}_2 \cdot \text{C}_{10}\text{H}_{19}$, hydrolysing the latter and then removing the *l*-menthol. When this experiment was performed, the mandelic

acid obtained was inactive, as was fully expected from the racemisation phenomena described in the paper just referred to. But it does not at all follow from this result that equal amounts of *l*-menthyl *d*-mandelate and *l*-menthyl *l*-mandelate were present in the product obtained by the reduction of menthyl benzoylformate, since, had unequal amounts been present, the mandelic acid obtained might still have been inactive owing to the racemising effect of the alkali during hydrolysis of the esters. In order, therefore, to have some idea of the relative amounts of the two esters produced in the reaction in question, these esters themselves were prepared from *d*- and *l*-mandelic acids respectively. *l*-Menthyl *d*-mandelate melts at 99—100° and has $[\alpha]_D^{10^\circ} - 7.6^\circ$ ($c = 3.5956$) in ethyl-alcoholic solution, whilst *l*-menthyl *l*-mandelate melts at 81—82° and has $[\alpha]_D^{17^\circ} - 138.6^\circ$ ($c = 4.3732$) in ethyl-alcoholic solution. *l*-Menthyl *dl*-mandelate, prepared from *r*-mandelic acid (*loc. cit.*), melts at 85—86° and has $[\alpha]_D^{18^\circ} - 74.2^\circ$ in ethyl-alcoholic solution, a value sufficiently close to that calculated from the figures for the esters of the active acids, namely, -73.1° . The product, obtained by the reduction of menthyl benzoylformate, gave in one experiment $[\alpha]_D^{18^\circ} - 76.9^\circ$ ($c = 6.174$), and in another $[\alpha]_D^{20^\circ} - 77.6^\circ$ ($c = 2.558$), results which indicated that a slight excess of *l*-menthyl *l*-mandelate was present.

Distinct evidence of asymmetric synthesis was, however, afforded when the Grignard reaction was applied to menthyl benzoylformate. Grignard has shown (*Compt. rend.*, 1902, 135, 627; *Ann. Chim. Phys.*, 1902, [vii], 27, 548) that when a magnesium alkyl bromide, $MgR'Br$, for example, acts on a compound of the type $RCO \cdot CO_2Et$, the first phase of the reaction consists in the formation of the compound $CRR'(O \cdot MgBr) \cdot CO_2Et$, which, when acted on by water, forms $CRR'(OH) \cdot CO_2Et$, an ester of a hydroxy-acid; in the second phase, the reaction proceeds further to give $CRR'(O \cdot MgBr) \cdot C(O \cdot MgBr)R'R'$, which, when acted on by water, gives $CRR'(OH) \cdot C(OH)R'R'$, a ditertiary glycol. The experimental conditions may, however, be so chosen that the reaction is restricted to the first phase, the carbonyl grouping in esters of ketonic acids being much more reactive towards Grignard's reagent than the carboxyalkyl grouping.

When menthyl benzoylformate, $PhCO \cdot CO_2 \cdot C_{10}H_{19}$, is acted on by magnesium methyl iodide and the magnesium additive compound then decomposed by water and dilute acid, a new asymmetric carbon atom is produced. When the resulting compound, $C^*MePh(OH) \cdot CO_2 \cdot C_{10}H_{19}$, is hydrolysed, no racemising effects are observed in this case, since an optically active salt is present in solution after the complete removal of the *l*-menthol, and this salt yields an optically active phenylmethylglycollic acid, $C^*MePh(OH) \cdot CO_2H$. Magnesium ethyl bromide behaves similarly.

A confirmation of the fact that the activity observed with these substituted glycollic acids was actually due to their asymmetric synthesis was afforded by the formation of benzilic acid, $\text{CPh}_2(\text{OH})\cdot\text{CO}_2\text{H}$, from menthyl benzoylformate and magnesium phenyl bromide. In this case, an additional phenyl group was introduced into the molecule of menthyl benzoylformate, but a new asymmetric carbon atom was not produced, and the result was that the potassium salt, obtained after removal of the menthol, was inactive, as was also the corresponding acid.

EXPERIMENTAL.

Menthyl benzoylformate is conveniently prepared as follows.

Benzoylformic acid, obtained by the oxidation of acetophenone by alkaline potassium permanganate, was heated on a boiling water-bath with three times its weight of *l*-menthol for 9—10 hours, a current of dry hydrogen chloride being passed into the mixture at intervals of three hours. The ethereal solution of the product was then washed, first with water and afterwards with dilute sodium carbonate solution, after which the ether was expelled and the residue submitted to steam distillation until the menthol had nearly all been removed. The oil remaining after this treatment soon solidified and was then crystallised from ethyl alcohol, in which it is moderately soluble and from which it separates in glassy needles melting at 73—74°.

0.1982 gave 0.1538 H_2O and 0.5434 CO_2 . $\text{H} = 8.6$; $\text{C} = 74.8$.

$\text{C}_{18}\text{H}_{24}\text{O}_3$ requires $\text{H} = 8.3$; $\text{C} = 75.0$ per cent.

The specific rotation of the ester was determined in ethyl-alcoholic solution:

$$l = 2, c = 4.7832, \alpha_D^{20} - 4.25^\circ, [\alpha]_D^{20} - 44.4^\circ.$$

l-Menthyl *d*-mandelate was prepared from *d*-mandelic acid, obtained by the resolution of the *r*-acid by cinchonine, the method used being similar to that just described for menthyl benzoylformate. Steam distillation may also in this case be used for separating the menthol, since the ester undergoes no appreciable hydrolysis when boiled with water. *l*-Menthyl *d*-mandelate separates from ethyl alcohol in rectangular plates and melts at 99—100°.

0.2028 gave 0.1648 H_2O and 0.5500 CO_2 . $\text{H} = 9.0$; $\text{C} = 74.0$.

$\text{C}_{18}\text{H}_{20}\text{O}_3$ requires $\text{H} = 9.0$; $\text{C} = 74.4$ per cent.

The specific rotation was determined in ethyl-alcoholic solution:

$$l = 2, c = 3.5956, \alpha_D^{10} - 0.55^\circ, [\alpha]_D^{10} - 7.6^\circ.$$

l-Menthyl *l*-mandelate, prepared from *l*-mandelic acid, obtained from

amygdalin, separates from ethyl alcohol in long, glassy needles and melts at 81—82°. It was analysed by hydrolysis with standard alcoholic potassium hydroxide :

0.3226 required 0.0622 potassium hydroxide for complete hydrolysis, the theoretical amount being 0.0623.

The specific rotation was determined in ethyl-alcoholic solution :

$$l = 2, c = 4.3732, \alpha_D^{17^\circ} - 12.12^\circ, [\alpha]_D^{17^\circ} - 138.6^\circ.$$

Its *benzoyl* derivative, prepared by the Schotten-Baumann method, separates from ethyl alcohol in glassy, rectangular plates and melts at 54—55°. Its specific rotation in ethyl alcohol was determined :

$$l = 2, c = 4.2888, \alpha_D^{16^\circ} - 10.28^\circ, [\alpha]_D^{16^\circ} - 119.8^\circ.$$

When equal weights of *l*-menthyl *d*-mandelate and *l*-menthyl *l*-mandelate were dissolved in ethyl alcohol and mixed, and the alcohol then evaporated off, the product obtained was identical in appearance and properties with the partially racemic *l*-menthyl *dl*-mandelate previously described (*loc. cit.*). It melted at 86—86.5° and had the following rotation in ethyl-alcoholic solution :

$$l = 2, c = 3.1632, \alpha_D^{21^\circ} - 4.66^\circ, [\alpha]_D^{21^\circ} - 73.6^\circ.$$

From the results obtained by the author in connection with the fractional hydrolysis of *l*-menthyl *dl*-mandelate (*loc. cit.*), which in solution may be regarded as consisting of equal amounts of *l*-menthyl *d*-mandelate and *l*-menthyl *l*-mandelate, it had been concluded that unusual racemisation phenomena must occur during the hydrolysis of the latter esters by alkali. Further opportunity of studying this case has now been afforded by hydrolysing the individual esters, isolated as above described. After it had been observed that the resulting potassium salt was inactive when either of the esters was hydrolysed by boiling with a large excess of alcoholic potassium hydroxide, the hydrolyses were next conducted under such conditions as might be expected to yield a mandelic acid of the maximum activity. It was curious to find that in every case a partially racemised mandelic acid resulted.

l-Menthyl *l*-mandelate (1.5 grams) was dissolved in 30 c.c. of ethyl alcohol, and 4.2 c.c. of alcoholic potassium hydroxide (the calculated amount, 1 c.c. = 0.06935 KOH) added, the mixture being then heated in a reflux apparatus for two hours. The alcohol was then expelled, the residual oil treated with water, and the menthol removed. The neutral filtrate was acidified and extracted with ether. The mandelic acid obtained melted at 114—117° and

a determination of its specific rotation in aqueous solution gave the following result :

$$l=2, c=2.7208, \alpha_D - 1.56^\circ, [\alpha]_D - 28.7^\circ,$$

whereas *l*-mandelic acid melts at 133° and has $[\alpha]_D$ about -156° .

Very marked racemisation also took place when the hydrolysis was conducted at a temperature lower than in the preceding case: 1.3 grams of the ester were hydrolysed by 50 c.c. of alcoholic potassium hydroxide, containing the calculated amount of alkali, by being kept in a thermostat for 42 hours at 25° , after which time the hydrolysis was complete. The neutral solution was manipulated as before; the mandelic acid obtained had the following rotation in aqueous solution :

$$l=2, c=1.928, \alpha_D^{20^\circ} - 1.40^\circ, [\alpha]_D^{20^\circ} - 36.3^\circ.$$

When the hydrolysis is conducted with the calculated amount of aqueous sodium hydroxide of about *N*/30 strength, the action proceeds very slowly, even at the temperature of the boiling water-bath, and the racemisation is not nearly so pronounced: 0.908 gram of ester was taken, an amount which required for complete hydrolysis 94.4 c.c. of the aqueous sodium hydroxide used. Fifty c.c. of this solution were first added, and after two days at 25° the solution still had an alkaline reaction. The mixture was then heated on the boiling water-bath for 9 hours, when the solution was still slightly alkaline. After 12 hours at the ordinary temperature, 44 c.c. of the sodium hydroxide solution were further added and the heating continued for 14 hours, at the end of which time the solution was practically neutral. The acid recovered gave the following result :

$$l=2, c=0.9452, \alpha_D^{19^\circ} - 2.39^\circ, [\alpha]_D^{19^\circ} - 126.4^\circ.$$

Although *l*-menthyl *d*-mandelate and *l*-menthyl *l*-mandelate are hydrolysed at different rates, the acids obtained when the esters are separately hydrolysed under exactly the same conditions by slightly more than the calculated amount of alcoholic potassium hydroxide possess the same numerical value: 1.9216 grams of each ester were dissolved in 25 c.c. ethyl alcohol and 30 c.c. of alcoholic potassium hydroxide (1 c.c. = 0.01386 gram KOH) were added, the calculated amount being 26.8 c.c. After remaining at 25° for 27 hours, the acid was obtained in the usual manner from each solution. The dextro-rotatory acid had the following specific rotation :

$$l=2, c=3.2232, \alpha_D^{20.5^\circ} + 2.89^\circ, [\alpha]_D^{20.5^\circ} + 44.8^\circ,$$

whilst the lævorotatory acid had

$$l=2, c=3.3352, \alpha_D^{20.5^\circ} - 2.97^\circ, [\alpha]_D^{20.5^\circ} - 44.6^\circ$$

The extent to which racemisation took place is accordingly the same in both cases.

Reduction of Menthyl Benzoylformate.

Two grams of menthyl benzoylformate were dissolved in 75 c.c. of ether containing a little water. After remaining for 24 hours in contact with an excess of aluminium amalgam, the mixture was filtered and the filtrate evaporated to dryness. The substance obtained in this manner had the asbestos-like appearance of *l*-menthyl *dl*-mandelate; it melted at 85—86° and was analysed by hydrolysis with standard alcoholic potassium hydroxide.

0.3905 required 0.0754 potassium hydroxide for complete hydrolysis, the theoretical amount being 0.0758.

A determination of its specific rotation in ethyl alcohol gave the following result:

$$l = 2, c = 6.174, \alpha_D^{18} - 9.49^\circ, [\alpha]_D^{18} - 76.9^\circ.$$

In a second experiment, where an ethyl-alcoholic solution of menthyl benzoylformate was left in contact with aluminium amalgam for several days, the product obtained melted at 83—85° and had the following rotation in ethyl-alcoholic solution:

$$l = 2, c = 2.558, \alpha_D^{20} - 3.97^\circ, [\alpha]_D^{20} - 77.6^\circ.$$

When the reduction products from these two experiments were respectively hydrolysed by heating with a slight excess of alcoholic potassium hydroxide, inactive mandelic acid, melting at 119°, was obtained from the potassium salt in each case.

When menthyl benzoylformate in ethyl-alcoholic solution was acted on by sodium amalgam and glacial acetic acid, a product was obtained which melted indistinctly at 65—78° and had $[\alpha]_D^{20} - 64.0^\circ$ ($c = 4.4172$) in ethyl-alcoholic solution. The reduction was probably incomplete, and some unchanged menthyl benzoylformate was probably present, although, when the product was crystallised twice from aqueous ethyl alcohol, the rotation was much the same as before, namely, $[\alpha]_D^{20} - 63.2^\circ$ ($c = 2.7428$). On hydrolysis, inactive mandelic acid was again produced.

Action of Magnesium Ethyl Bromide on Menthyl Benzoylformate.

Magnesium (0.61 gram = $1\frac{1}{2}$ mols.) was added to a mixture of 3 grams of ethyl bromide ($1\frac{1}{2}$ mols.) and 40 c.c. of ether with the usual precautions to ensure dryness. When the magnesium had almost all

dissolved, the solution was gradually added, within an interval of 7 minutes, to a solution of 5 grams of menthyl benzoylformate (1 mol.) in 40 c.c. of dry ether. The temperature of the mixture rose slightly, but the reaction was never a vigorous one. After half an hour at the temperature of the laboratory, the product was heated on the water-bath for two hours and then left overnight. After the addition first of water and then of dilute hydrochloric acid, the ethereal solution was separated and washed once with water. The ether was next expelled and a product obtained, which remained as a viscid oil after having been left for several days in a partial vacuum over sulphuric acid. The oil was dissolved in 45 c.c. of ethyl alcohol and 17 c.c. of alcoholic potassium hydroxide (1 c.c. = 0.0606 gram KOH) were added and the mixture boiled for 1 hour. After expulsion of the alcohol, water was added to the oil, and the menthol, which separated as a solid, drained off. The filtrate was then completely freed from menthol by evaporating to a small bulk and then extracting with ether (although the extraction with ether is really unnecessary). The aqueous solution of potassium salt was acidified and the acid extracted with ether. The acid, obtained after evaporation of the ether, was an oil, which, after remaining for a night in a vacuum over sulphuric acid, had begun to crystallise in tiny, rectangular plates grouped in rosettes. It was moderately soluble in water. When dissolved in ethyl alcohol and made up to 8 c.c., a volume sufficient to fill the 1 cm. tube employed, the acid was found to be distinctly laevorotatory, giving $\alpha_D^{19} - 1.03^\circ$. It formed a zinc salt which was laevorotatory, and which, when dried at $130-140^\circ$, gave, on analysis, 15.3 per cent. of zinc, whereas zinc phenylethylglycollate, $C_{20}H_{22}O_6Zn$, requires 15.4 per cent.

In a second experiment, the conditions were altered by using a larger excess of Grignard's reagent, to which the ethereal solution of the ester was added. Five grams of menthyl benzoylformate (1 mol.) dissolved in 40 c.c. of ether were added within an interval of 10 minutes to magnesium ethyl bromide (3 mols.) dissolved in 40 c.c. of ether. The action was moderated by immersion of the flask, containing the reaction mixture, in ice-cold water. After 12 hours at the temperature of the laboratory, the mixture was heated to gentle boiling for 2 hours and then cooled and decomposed carefully by water and dilute hydrochloric acid. The product obtained was hydrolysed as before. The aqueous solution of potassium salt, obtained after complete removal of the menthol formed from the hydrolysis, was decolorised by animal charcoal, and, when examined in a 2 cm. tube, gave $\alpha_D^{16} - 1^\circ$, whilst the zinc salt prepared from the acid was also distinctly laevorotatory.

In a third experiment, where the same amounts of menthyl benzoylformate and magnesium ethyl bromide as in the second experiment

were used, the ethereal solution of the ester was added in one instalment to Grignard's reagent. After the vigorous action had subsided, the mixture was heated on the water-bath for $1\frac{1}{2}$ hours. The hydrolysis was conducted as previously described. The aqueous solution of potassium salt, obtained after removal of the menthol, was heated with animal charcoal and then gave $\alpha_D^{18} - 0.80^\circ$ ($l=2$); the alcoholic solution of the acid obtained from it gave $\alpha_D^{18} - 0.41^\circ$ ($l=0.5$). The silver salt of the acid was analysed:

0.4485 gave 0.1701 Ag. $Ag = 37.9$.

$C_{10}H_{11}O_3Ag$ requires $Ag = 37.6$ per cent.

Action of Magnesium Methyl Iodide on Menthyl Benzoylformate.

Magnesium (1.26 grams = 3 mols.) was added to a solution of 7.4 grams of methyl iodide (3 mols.) in 30 c.c. of anhydrous ether. When the magnesium had practically all dissolved, the solution was cooled in ice-cold water and a solution of 5 grams of menthyl benzoylformate (1 mol.) in 30 c.c. of ether added to it in one instalment. The solution instantly turned dark brown from the separation of iodine, but there was no ebullition until the flask was shaken, when the reaction proceeded with violence, the solution becoming almost colourless and a solid product separating. After the mixture had been boiled gently for $1\frac{1}{2}$ hours, ice was gradually added and then an excess of dilute hydrochloric acid. The ethereal layer was separated and the residue extracted with ether. The total ethereal solution was then agitated with a little dilute sulphurous acid to remove the free iodine present in small amount and then washed with water. The oil, obtained after removal of the ether, was then heated with 33 c.c. of ethyl alcohol and 17 c.c. of alcoholic potassium hydroxide (1 c.c. = 0.0606 gram KOH) for one hour, after which the ethyl alcohol was evaporated off and water added to the resulting oil. The solid menthol was next drained off and the alkaline filtrate heated on a boiling water-bath with animal charcoal for several hours, by which time all the menthol had been expelled. When the filtered solution was extracted with ether, 0.15 gram of a substance was obtained, melting indistinctly between 65° and 70° and yielding an optically inactive solution when dissolved in ethyl alcohol. This substance, which may possibly have been the ditertiary glycol, $CMePh(OH) \cdot CMe_2(OH)$, formed owing to the presence of the excess of Grignard's reagent in the initial action, was not further examined. The solution from which it had been removed was next neutralised by the addition of a few drops of dilute hydrochloric acid. The volume measured 16 c.c., and 14 c.c. of this, when examined in a 2 dm. tube, had the

rotation $\alpha_D^{17} - 4.16^\circ$; the solution, when extracted with ether six times, did not alter in rotation and the ethereal extract yielded the merest trace of a residue. In this way, it was conclusively proved that the activity observed could not have been due to the above-mentioned by-product.

When an excess of hydrochloric acid was added to the solution of potassium salt, a solid separated. This is in accordance with the properties of phenylmethylglycollic acid, which can be recrystallised from water (Fittig and Wurster, *Annalen*, 1879, 195, 153; Fittig and Kast, *Annalen*, 1880, 206, 24). The acid was quantitatively extracted with ether, and the liquid, which had been extracted, when tested in the polarimeter, was inactive. The acid, obtained after removal of the ether, was a white solid, which, when dried in a vacuum over sulphuric acid, softened at 84° and melted completely at 88° : 2.2676 grams were obtained, and a determination of its specific rotation in ethyl alcohol gave the following result:

$$l = 4, c = 9.0704, \alpha_D^{18} - 3.44^\circ, [\alpha]_D^{18} - 9.5^\circ.$$

The product seemed to be a mixture of *i*- and *l*-phenylmethylglycollic acids. The melting point of the former acid, $93-94^\circ$, is apparently lowered by the presence of the active isomeride, the amount of which present in the mixture cannot yet be determined as the optically active form has so far not been described. When the mixture was crystallised from light petroleum, the crop which separated melted at $90-91.5^\circ$ and had $[\alpha]_D - 11.6^\circ$ ($c = 2.669$) in ethyl-alcoholic solution.

In a second experiment, Grignard's reagent, prepared from 0.42 gram of magnesium (1 mol.) and 2.5 grams of methyl iodide (1 mol.) and 40 c.c. of ether, was added drop by drop to a solution of 5 grams of menthyl benzoylformate (1 mol.) in 20 c.c. of ether. As soon as the magnesium methyl iodide had been prepared, the flask containing it was quickly connected with the flask containing the ester by means of a doubly-bored stopper, through one hole of which passed a siphon provided with a stop-cock, whilst the other hole was fitted with a U-tube filled with solid potassium hydroxide. The flask containing the ester was in turn attached to a reflux condenser provided with a guard-tube of calcium chloride and soda-lime. By this arrangement, the addition of the magnesium methyl iodide could be conveniently regulated; it was added drop by drop within an interval of 45 minutes. The solution of the ester became dark brown as soon as the magnesium methyl iodide was added; this coloration persisted, and towards the end of the reaction a solid crystalline compound separated. The ether boiled gently towards the end of the reaction, which never at any time became vigorous. After

12 hours, ice and dilute hydrochloric acid were added successively, after which the ethereal layer was separated, washed with sulphurous acid and then with water. The ether was expelled, and the resulting oil boiled with 50 c.c. of ethyl alcohol and 17 c.c. of alcoholic potassium hydroxide (1 c.c. = 0.0606 gram KOH) for one hour. The menthol was removed, and the potassium salt remaining was extracted with ether, when it was found that in this case the ethereal solution left no residue. The solution was decolorised with animal charcoal and, when filtered and evaporated to 14 c.c., the bulk necessary to fill the 2-dcm. tube used, gave $\alpha_D^{20} - 4.51^\circ$. The acid, obtained as before, had $[\alpha]_D^{20} - 8.3^\circ$ ($c = 6.718$) in ethyl-alcoholic solution, this determination having been made with a specimen which had been fused by heating on a boiling water-bath and then dried in a vacuum over sulphuric acid.

0.1904 gave 0.1096 H₂O and 0.4536 CO₂. H = 6.4; C = 65.0.

C₉H₁₀O₃ requires H = 6.0; C = 65.1 per cent.

Action of Magnesium Phenyl Bromide on Menthyl Benzoylformate.

Magnesium (1.26 grams = 3 mols.) was added to a solution of 8.1 grams of bromobenzene (3 mols.) in 40 c.c. of ether. When the mixture was warmed, the action started, and when it was complete the solution was gradually added within an interval of 7 minutes to a solution of 5 grams of menthyl benzoylformate (1 mol.) in 40 c.c. of ether, the action being moderated by cooling in ice. After being boiled for two hours, the product was decomposed by ice and hydrochloric acid, the ester obtained hydrolysed as usual, and the menthol removed. The aqueous solution of potassium salt was concentrated by evaporation and a crop allowed to crystallise. After removal of this, the filtrate was heated with animal charcoal. When the latter was separated, the solution was examined in the polarimeter and proved to be inactive. When acidified by hydrochloric acid, a solid separated, which, when recrystallised from water, separated in needles, melted at 149—150°, and had the properties of benzoic acid. Its solution in concentrated sulphuric acid was carmine-red. Its silver salt was analysed:

0.5748 gave 0.1853 Ag. Ag = 32.2 per cent., being the amount calculated for C₁₄H₁₁O₃Ag.

The crop, which had been removed from the solution of potassium salt, proved to be potassium benzoate. Its aqueous solution was inactive, and, when acidified, yielded benzoic acid, which was identified by its melting point and its colour reaction with concentrated sulphuric acid.

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In a second experiment, a solution of 0.42 gram of magnesium (1 mol.) in 2.7 grams of bromobenzene (1 mol.) and 40 c.c. of ether was added drop by drop to a solution of 5 grams of menthyl benzoylformate (1 mol.) in 20 c.c. of ether. The operations were conducted so far as possible under the same conditions as those already described for the second experiment on the action of magnesium methyl iodide on menthyl benzoylformate. The aqueous solution of potassium salt, obtained after removal of the menthol, was quite inactive, and, when acidified, yielded benzilic acid.

The applicability of Grignard's reaction for the asymmetric syntheses of other acids from the menthyl and bornyl esters of ketonic acids is at present under investigation.

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