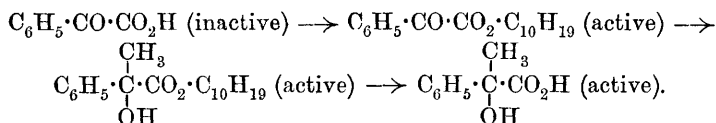


XLI.—*Studies in Asymmetric Synthesis. IV. The Application of Grignard's Reaction for Asymmetric Syntheses.*

By ALEXANDER MCKENZIE.

It has been shown in a former paper (Trans., 1904, 85, 1249) that, when *l*-menthyl benzoylformate is acted on by magnesium methyl iodide, the experimental conditions may be so chosen that the attack of the Grignard reagent takes place exclusively at the carbonyl grouping of the ketonic ester, whilst the carboxyaryl grouping is not attacked. When the product of this action is decomposed by ice and mineral acid, a mixture of unequal amounts of *l*-menthyl *d*-phenyl methylglycollate and *l*-menthyl *l*-phenylmethylglycollate is produced, and, when this mixture is saponified by an excess of alkali and the resulting menthol completely removed, the potassium salt formed is

lævorotatory, as also is the acid obtained from it. The asymmetric synthesis of an optically active phenylmethylglycollic acid (atrolactic acid) was therefore accomplished in accordance with the scheme:



An active phenylethylglycollic acid can be synthesised in an analogous manner.

The only other examples of the genesis of optically active compounds by asymmetric synthesis are the formation of a lævorotatory valeric acid from methylethylmalonic acid by the agency of brucine (Marckwald, *Ber.*, 1904, **37**, 349) and the formation of a lævorotatory lactic acid by the reduction of *l*-menthyl pyruvate (McKenzie, *Trans.*, 1905, **87**, 1373).\*

It was accordingly of interest to extend the application of Grignard's reaction for the purpose of obtaining other cases of asymmetric synthesis, and the present paper contains a description of the results so far attained in this direction.

The action of magnesium propyl iodide, magnesium *isobutyl* iodide, magnesium *tert.*-butyl iodide, and magnesium  $\alpha$ -naphthyl bromide respectively on *l*-menthyl benzoylformate was investigated. In each case, the asymmetric synthesis of a substituted glycollic acid was effected. The influence of the increase of weight of the hydrocarbon group introduced into the molecule of *l*-menthyl benzoylformate appears to be to diminish the value for the specific rotation of the mixture of unequal amounts of the *d*- and *l*-acids obtained; for example, the mixture of *d*- and *l*-phenylmethylglycollic acids resulting from the action of magnesium methyl iodide on *l*-menthyl benzoylformate is very much more lævorotatory than either the mixture of phenyl-*tert.*-butylglycollic acids resulting from the action of magnesium *tert.*-butyl iodide or the mixture of phenyl- $\alpha$ -naphthylglycollic acids resulting from the action of magnesium  $\alpha$ -naphthyl bromide. It is not, however, permissible to conclude from this result that the ratio of *l*- to *d*-acid produced in the latter cases is less than in the former, since neither of those substituted glycollic acids has yet been prepared in the pure optically active form, and it is accordingly impossible to state whether *l*-phenylmethylglycollic acid is a more active substance than *l*-phenyl-*tert.*-butylglycollic acid or *l*-phenyl- $\alpha$ -naphthylglycollic acid. Again, the mode of formation of the Grignard reagent and the conditions under

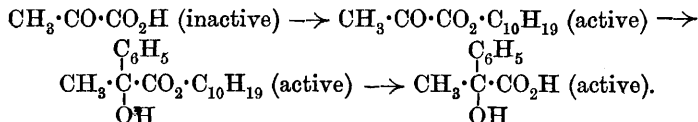
\* No asymmetric synthesis of a sulphur compound is recorded by Smiles in his paper entitled "An Asymmetric Synthesis of Quadrivalent Sulphur" (*Trans.* 1905, **87**, 450).

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 obtained from *l*-menthyl benzoylformate does not vary appreciably 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. Besides, in the preparation of magnesium *isobutyl* iodide, it was found that the reaction was always incomplete when equimolecular weights of magnesium and iodide interacted in presence of anhydrous ether, a certain amount of metal remaining undissolved. In the experiments quoted in this paper, accordingly, where magnesium *isobutyl* iodide was added in the proportion of  $1\frac{1}{4}$  mols. to 1 mol. of ester, the action on the ketonic ester was probably incomplete, so that one might expect to get very varying results with each individual experiment. It is likely that the formation of magnesium *isobutyl* iodide is accompanied by side reactions such as Tschelinzeff (*J. Russ. Phys. Chem. Soc.*, 1904, **36**, 549) has described as happening during the formation of magnesium *isopropyl* iodide in ethereal solution. In the latter case, 2 mols. of the iodide are requisite for the solution of 1 mol. of magnesium and, in addition to the normal formation of the organo-magnesium compound, both propane and propylene are produced, thus:  $2\text{CHMe}_2\text{I} + \text{Mg} = \text{CH}_2\text{Me}_2 + \text{CH}_2\text{:CHMe} + \text{MgI}_2$ ; as much as 41 per cent. of the iodide is used for this reaction and 1.47 per cent. of it undergoes the change represented by  $2\text{CHMe}_2\text{I} + \text{Mg} = 2\text{CH}_2\text{:CHMe} + \text{H}_2 + \text{MgI}_2$ .

In an asymmetric synthesis, an optically active substance is generated, without any analytical separation, from a non-asymmetric one, in which a carbon atom becomes asymmetric under the influence of an optically active asymmetric grouping, which is introduced and then eliminated. The question as to whether the extent of a synthesis of this kind, as measured by the optical activity of the resulting product, depends on the numerical value of the optical activity of the active group introduced and then eliminated was tested by acting on *l*-bornyl benzoylformate with magnesium alkyl (or aryl) halides. *l*-Borneol is not so strongly *l*ævorotatory as *l*-menthol, the specific rotations in ethyl-alcoholic solution being respectively  $-39.7^\circ$  and  $-49.4^\circ$  under similar conditions of temperature and concentration. It was thought likely that the influence of the *l*-bornyl group would be less marked than that of the *l*-menthyl group, and experiment showed this to be the case. When magnesium methyl iodide

( $1\frac{1}{4}$  mols.) acted on *l*-bornyl benzoylformate (1 mol.) under the conditions described in the experimental portion of this paper, the mixture of atrolactic acids obtained had  $[\alpha]_D^{15.5^\circ} - 1.9^\circ$  ( $c=7.57$ ) in ethyl-alcoholic solution, a value considerably less than that obtained from *l*-menthyl benzoylformate under similar conditions, namely,  $[\alpha]_D^{18^\circ} - 9.5^\circ$  ( $c=9.0704$ ). The interaction of magnesium ethyl iodide and *l*-bornyl benzoylformate also gave a levorotatory mixture of phenyl-ethylglycollic acids, having  $[\alpha]_D^{17^\circ} - 4.2^\circ$  ( $c=17.052$ ) in ethyl-alcoholic solution, but, as the specific rotation had not been determined with the product obtained from *l*-menthyl benzoylformate (Trans., 1904, 85, 1249), the results are not comparable. A striking observation as to the effect of the bornyl as contrasted with the menthyl group was made with the products resulting from the action of magnesium isobutyl iodide and magnesium  $\alpha$ -naphthyl bromide respectively on *l*-bornyl benzoylformate. A dextrorotatory acid mixture was obtained in both cases, whereas the corresponding acid mixtures obtained from *l*-menthyl benzoylformate were levorotatory.

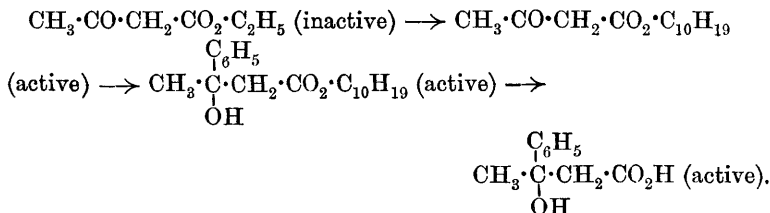
The asymmetric synthesis of phenylmethylglycollic acid can be accomplished not only by the action of magnesium methyl iodide on *l*-menthyl benzoylformate, but also by the action of magnesium phenyl bromide on *l*-menthyl pyruvate, thus:



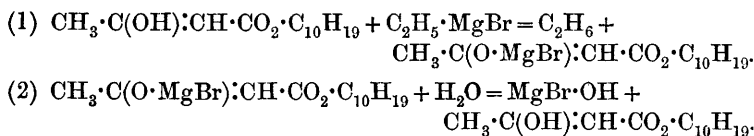
Whilst the first method, however, gives an asymmetric synthesis of the *l*-acid, the latter gives an asymmetric synthesis of the *d*-acid, the acid mixture obtained having  $[\alpha]_D^{16^\circ} + 5.5^\circ$  ( $c=14.7$ ) in ethereal solution. The mixture of *d*- and *l*-phenylethylglycollic acids obtained from the interaction of magnesium ethyl bromide and *l*-menthyl pyruvate was also dextrorotatory, although the rotation was not nearly so pronounced as with the mixture of phenylmethylglycollic acids referred to.

The application of Grignard's reaction to menthyl esters of the acetoacetic ester type was also studied. Grignard, who examined the action of magnesium methyl iodide on ethyl acetoacetate, found that the latter compound acts in this case in accordance with its enolic structure (*Compt. rend.*, 1902, 134, 849; *Ann. Chim. Phys.*, 1902, [vii], 27, 548). Now, since ethyl acetoacetate is generally regarded as consisting at the ordinary temperature of an alleotropic mixture of the ketonic and enolic forms, and since Lapworth and Hann (*Trans.*, 1902, 81, 1499) conclude that *l*-menthyl acetoacetate, which can readily be obtained as a crystalline solid by heating ethyl aceto-

acetate with *l*-menthol, probably possesses the ketonic structure, it appeared possible that the latter compound might lend itself for purposes of asymmetric synthesis. If it reacted with magnesium phenyl bromide, for instance, in the ketonic form, then the following changes might be effected:



It was found, however, that *l*-menthyl acetoacetate reacts in accordance with its enolic structure. When the product of its action with magnesium ethyl bromide was decomposed by ice and mineral acid, the original ester was regenerated. The following equations may accordingly be taken as representing the action:



This result was not altogether unexpected, since it has been found that substances which in solution form an allelotropic mixture, such as amides, thioamides, &c., act in accordance with their hydroxylic structure (Tschugaeff, *Ber.*, 1902, 35, 3912. Compare also Béis, *Compt. rend.*, 1903, 137, 575).

Grignard (*loc. cit.*) has further shown that the products of the action of magnesium methyl iodide on ethyl ethylacetoacetate are the unchanged ester and the ester  $\text{OH} \cdot \text{CMe}_2 \cdot \text{CHEt} \cdot \text{CO}_2\text{Et}$ , the latter on hydrolysis yielding  $\beta$ -hydroxy- $\beta$ -methyl- $\alpha$ -ethylbutyric acid,

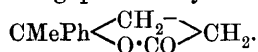


When the action of magnesium methyl iodide on ethyl ethylacetoacetate was conducted at a higher temperature than in the case just quoted, the unchanged ester and the glycol,  $\text{OH} \cdot \text{CMe}_2 \cdot \text{CHEt} \cdot \text{CMe}_2 \cdot \text{OH}$ , were formed. Those results showed that ethyl ethylacetoacetate reacted both in its ketonic and enolic forms.

By the action of magnesium ethyl bromide on *l*-menthyl ethylacetoacetate, which is easily prepared by heating ethyl ethylacetoacetate with *l*-menthol, the formation of an optically active  $\beta$ -hydroxy- $\alpha$ - $\beta$ -diethylbutyric acid was not observed, although there was evidence that a mixture of unequal amounts of menthyl esters had actually been produced.

When *l*-menthyl diethylacetoacetate was acted on by magnesium ethyl bromide or by magnesium phenyl bromide, no evidence of an asymmetric synthesis was obtained, although in this case, where the ester contains no hydroxyl group, the reaction must have taken place at the ketonic group. Disruption of the molecule apparently took place most probably during the saponification by alkali (compare Grignard, *loc. cit.*).

A slight asymmetric synthesis was detected when magnesium phenyl bromide acted on *l*-menthyl lavulate, the *l*ævorotation observed being presumably due to the formation of the asymmetric lactone,



#### EXPERIMENTAL.

The asymmetric synthesis of *l*-phenylmethylglycollic acid (atrolactic acid), recorded in a former paper (*loc. cit.*), can also be accomplished when a large excess of alkali is used for the saponification of the mixture of unequal amounts of *l*-menthyl *l*-phenylmethylglycollate and *l*-menthyl *d*-phenylmethylglycollate resulting from the action of magnesium methyl iodide on *l*-menthyl benzoylformate. In other words, the alkali did not exert a racemising influence such as the author has already observed in the saponification of unequal amounts of *l*-menthyl *d*- and *l*-mandelates. It is necessary, however, to ensure the complete saponification of the ester mixture resulting from the Grignard reaction in question in order to prove that the rotations observed were actually due to an asymmetric synthesis and not to a resolution of a partially racemic ester by the fractional hydrolysis method, first used by Marekwald and McKenzie. Thus, if it were the case that the product of the action is *l*-menthyl *dl*-phenylmethylglycollate and not a mixture of unequal amounts of the *d*- and *l*-isomerides, saponification by an insufficiency of potassium hydroxide would yield an optically active potassium salt (compare McKenzie and Thompson, *Trans.*, 1905, 87, 1004). In the experiments formerly quoted, due regard was paid to this consideration, precautions being taken that the ester mixture was completely saponified; the following may, however, be submitted as corroborative evidence. The action of magnesium methyl iodide (1 mol.) on 5 grams of *l*-menthyl benzoylformate (1 mol.) was conducted as in the case of the second experiment formerly described (*Trans.*, 1904, 85, 1260), and the ester mixture was boiled for one and a half hours under a reflux condenser with 50 c.c. of alcoholic potassium hydroxide containing 3.1 grams of alkali. After sixteen hours, the mixture was again boiled for one hour and the alcohol and menthol entirely removed. The aqueous solution of potassium salt (20 c.c.) obtained was *l*ævorotatory, 14 c.c.

in a 1-dcm. tube giving  $\alpha_D - 1.50^\circ$ , whilst the resulting acid (2.1 grams) in ethyl-alcoholic solution gave  $l=2$ ,  $c=13.266$ ,  $\alpha_D - 2.25^\circ$ ,  $[\alpha]_D - 8.5^\circ$ . Although the saponification was in this case conducted with a large excess of alkali, the rotation of the acid was practically the same as in the previous case, when the specific rotation of the acid was  $-8.3^\circ$ .

Whilst the mixture of phenylmethylglycolates is readily saponified by alcoholic potassium hydroxide, the saponification is slow when aqueous baryta is used. A solution of magnesium methyl iodide ( $1\frac{1}{4}$  mols.) in 25 c.c. of ether was added within a minute to 5 grams (1 mol.) of *l*-menthyl benzoylformate dissolved in 25 c.c. of ether, and, when the vigorous action had subsided, the product was boiled for a quarter of an hour. The ester mixture obtained after the addition of ice and hydrochloric acid was freed from ether and then heated on the water-bath for twenty-four hours with a solution of 10 grams of barium hydroxide in 100 c.c. of water and the product distilled in a current of steam for several hours until all the menthol had been removed. The excess of barium hydroxide was separated by means of carbon dioxide and the aqueous solution of barium salt concentrated to 52 c.c., of which 28 c.c., when examined in a 4-dcm. tube, gave  $\alpha_D^{10} - 1.41^\circ$ . The concentration of the solution ( $c=3.634$ ) was estimated by evaporating 10 c.c. to dryness and then drying the residue at  $140^\circ$ ; whence  $[\alpha]_D^{10} - 9.7^\circ$ .

0.3634 gave 0.1802  $\text{BaSO}_4$ .  $\text{Ba}=29.2$ .

$\text{C}_{18}\text{H}_{18}\text{O}_6\text{Ba}$  requires  $\text{Ba}=29.4$  per cent.

#### *Action of Magnesium Propyl Iodide on l-Menthyl Benzoylformate.*

When a large excess of magnesium propyl iodide was added to a solution of 2.8 grams of ester in 15 c.c. of ether, the substituted glycollic acid obtained was found to contain some benzoylformic acid in admixture with it. The acid was levorotatory, 1 gram dissolved in 14 c.c. of ethyl alcohol giving  $\alpha_D - 0.28^\circ$  ( $l=2$ ).

#### *Action of Magnesium isoButyl Iodide on l-Menthyl Benzoylformate.*

A solution of magnesium ( $1\frac{1}{4}$  mols.) in isobutyl iodide ( $1\frac{1}{4}$  mols.) and 30 c.c. of ether was added by means of the siphon apparatus previously described (*loc. cit.*) within an interval of forty minutes to a solution of 5 grams of ester (1 mol.) in 20 c.c. of ether. The action was accompanied by the separation of iodine, the tint of which disappeared as the addition of the magnesium compound proceeded. After twelve hours, the product was decomposed by the successive addition of crushed ice and dilute sulphuric acid and the ethereal solution decolorised by

sulphurous acid. The product obtained after removal of the ether was then saponified by a solution of 5 grams of potassium hydroxide in a mixture of 50 c.c. of ethyl alcohol and 20 c.c. of water. After the solution had remained for five days at the ordinary temperature, it was boiled for two hours, the ethyl alcohol was removed by evaporation, water was added, and the precipitated menthol drained off. The aqueous solution of potassium salt, from which the menthol was entirely removed, was decolorised by charcoal, acidified by sulphuric acid, and extracted with ether. A deliquescent acid was obtained, which proved to be levorotatory, its rotation in ethyl alcohol being  $l = 2$ ,  $c = 12.1$ ,  $\alpha_D^{14} - 4.09^\circ$ ,  $[\alpha]_D^{14} - 16.9^\circ$ . The concentration was determined by withdrawing an aliquot portion, evaporating off the solvent, and weighing the residue, dried at  $100^\circ$ . An analysis of the silver salt of this acid showed that it contained some benzoylformic acid, since the percentage of silver was 35.8, whereas  $C_{12}H_{15}O_3Ag$  requires  $Ag = 34.3$  per cent.

The acid resulting from other experiments on the action of magnesium *isobutyl iodide* on *l*-menthyl benzoylformate had not such a marked rotation as in the instance quoted. The experimental conditions were, however, purposely varied in each case and the solutions submitted to polarimetric examination had, in each separate experiment, to be heated under varying conditions with charcoal in order to obtain results on which reliance could be placed. The experiment just quoted was repeated with the following modifications.

The Grignard reagent ( $1\frac{1}{4}$  mols.) was added within an interval of thirty minutes to an ethereal solution of 5 grams of the ester (1 mol.) and the product boiled for one hour. The ester mixture was saponified by boiling with a solution of 4.3 grams of potassium hydroxide in 50 c.c. of ethyl alcohol. The acid obtained was crystallised from water; the small crop which separated was inactive, whilst the filtrate (28 c.c.) gave only  $\alpha_D - 0.40^\circ$  ( $l = 4$ ).

In another experiment, the Grignard reagent ( $1\frac{1}{4}$  mols.) was added to an ethereal solution of the ester (5 grams, 1 mol.) within forty-five minutes and the solution then allowed to remain at the ordinary temperature for eighteen hours. The ester mixture, obtained as usual, was dissolved in a solution of 5.2 grams of potassium hydroxide in 50 c.c. of ethyl alcohol and after twelve hours was boiled for one hour; 2 grams of acid were obtained which, when made up to 14 c.c. with ethyl alcohol, gave  $l = 2$ ,  $\alpha_D^{11} - 1.42^\circ$ , and  $[\alpha]_D^{11} - 5^\circ$ .

When the action was conducted with a larger excess of the Grignard reagent, the asymmetric synthesis was less marked. A solution of magnesium *isobutyl iodide* ( $2\frac{1}{2}$  mols.) in 20 c.c. of ether was added within one minute to a solution of 5 grams of ester (1 mol.) in 32 c.c. of ether; the product of the vigorous action was then boiled for half



an hour. The saponification of the ester mixture was conducted by dissolving it in a solution of 4.6 grams of potassium hydroxide in 50 c.c. of ether, and, after twelve hours, boiling the mixture for one and a half hours: 2.1 grams of acid were obtained, which, when made to 14 c.c. with ethyl alcohol, gave only  $l = 2$ ,  $\alpha_D - 0.35^\circ$ .

*Action of Magnesium tert.-Butyl Iodide on l-Menthyl Benzoylformate.*

Magnesium (0.53 gram,  $1\frac{1}{2}$  mols.) was added to a mixture of *tert.*-butyl iodide (4 grams,  $1\frac{1}{2}$  mols.) and 20 c.c. of ether. The action began at the ordinary temperature, but, after heating for four and a half hours, it was found that 0.16 gram of metal was not dissolved. The solution was quickly added to a solution of 4 grams of ester in 20 c.c. of ether. After twenty-four hours, the product was heated for a quarter of an hour and manipulated in the usual manner, the saponification of the ester mixture having been conducted by boiling for forty-five minutes with a solution of 3.3 grams of potassium hydroxide in 25 c.c. of ethyl alcohol. Only 0.85 gram of acid was obtained and this, when dissolved in ethyl alcohol and then examined in a 2-dcm. tube (14 c.c.), gave  $\alpha_D - 0.07^\circ$ , a reading which, although feeble, was quite distinct with the polarimeter used.

In a second experiment, where  $2\frac{1}{2}$  mols. of the Grignard reagent were used, 0.93 gram of acid was obtained from 4 grams of ester and this, when dissolved in ethyl alcohol as before, gave  $\alpha_D^{16^\circ} - 0.09^\circ$ .

*Action of Magnesium  $\alpha$ -Naphthyl Bromide on l-Menthyl Benzoylformate.*

A solution of magnesium  $\alpha$ -naphthyl bromide ( $2\frac{1}{2}$  mols.) in 25 c.c. of ether was gradually added to a solution of 5 grams of *l*-menthyl benzoylformate (1 mol.) in 25 c.c. of ether. At first a red coloration was imparted to the solution, but this disappeared as the addition of the Grignard reagent proceeded. The action was moderated in such a manner that the ether was gently boiling during the addition. After two days at the ordinary temperature, the product was decomposed first by crushed ice and then by dilute sulphuric acid, the ether was removed from the ethereal solution, and the residual oil submitted to distillation in steam until all the naphthalene had been separated. The remaining oil was then extracted with ether, the ether expelled, and the saponification conducted by boiling for two hours with an alcoholic solution of potassium hydroxide (5 grams). The alcohol was expelled, water added, and the precipitated menthol drained off. After the aqueous solution of potassium salt had been completely freed from menthol and after attempts to decolorise it had been unsuccessful, the addition of dilute sulphuric acid brought down a voluminous precipitate of the substituted glycollic acid, which was quantitatively extracted with ether. The

acid, which is sparingly soluble in water, was finally decolorised with difficulty by heating with charcoal its solution in a mixture of ethyl alcohol and water.

A mixture of *i*- and *l*-acids (3.3 grams) was withdrawn, whilst the filtrate, when evaporated to dryness and then dissolved in acetone (0.17 gram of acid in 14 c.c. of solution), gave  $\alpha_D - 0.25^\circ$  ( $l = 2$ ). The whole of the acid obtained was then converted into barium salt, which was crystallised from water, in which it is sparingly soluble. The crop which separated gave, on analysis, Ba = 19.2, whereas  $C_{36}H_{26}O_6Ba$  requires Ba = 19.7 per cent.; the filtrate (14 c.c.) gave  $\alpha_D^{19} - 0.35^\circ$  ( $l = 2$ ).

A second experiment was more successful. The saponification of the product obtained after the removal of the naphthalene was conducted by boiling with a solution of 5.2 grams of potassium hydroxide in 50 c.c. of ethyl alcohol for one and a half hours. The barium salt obtained was crystallised from water. *Barium phenyl- $\alpha$ -naphthylglycollate* separates from a mixture of ethyl alcohol and water in glassy prisms.

0.3748 (dried at  $130-140^\circ$ ) gave 0.1244  $BaSO_4$ .

Ba = 19.54;  $C_{36}H_{26}O_6Ba$  requires Ba = 19.87 per cent.

The filtrate (28 c.c.) gave  $l = 4$ ,  $c = 1.022$ ,  $\alpha_D - 0.45^\circ$ ,  $[\alpha]_D - 11.0^\circ$ .

#### *Action of Magnesium Methyl Iodide on l-Bornyl Benzoylformate.*

*l-Bornyl benzoylformate* was conveniently prepared as follows. Benzoylformic acid was heated on a boiling water-bath for ten hours with three times its weight of *l*-borneol, a current of dry hydrogen chloride having been passed at intervals into the mixture. The ethereal solution of the product was washed successively with water and dilute sodium carbonate, the ether removed, and the product distilled in a current of steam until the borneol was practically all removed. The residue, which solidified on cooling, was purified by crystallisation from ethyl alcohol, from which it separates in colourless, glassy prisms with pyramidal ends; it melts at  $42-43^\circ$ .

0.1897 gave 0.5252  $CO_2$  and 0.1326  $H_2O$ . C = 75.5; H = 7.8.

$C_{18}H_{22}O_3$  requires C = 75.5; H = 7.7 per cent.

A determination of its specific rotation in ethyl-alcoholic solution gave the result:  $l = 2$ ,  $c = 10.819$ ,  $\alpha_D^{20} - 5.76^\circ$ ,  $[\alpha]_D^{20} - 26.6^\circ$ .

The ester is readily soluble in hot ethyl alcohol and easily soluble in cold chloroform, acetone, benzene, carbon tetrachloride, or light petroleum.

When exposed to bright sunlight, the ester assumed an ochreous tint

in the course of two minutes, and after five minutes the tint had attained its maximum; when placed in the dark, the crystals again became colourless after a lapse of twelve hours. When the colourless crystals were exposed for five minutes to the light from an arc lamp, they also assumed an ochreous tint.

A solution of magnesium methyl iodide ( $1\frac{1}{4}$  mols.) in 20 c.c. of ether was quickly dropped by means of a siphon into a solution of 5 grams of ester (1 mol.) in 20 c.c. of ether cooled at  $0^{\circ}$ . The violent action was accompanied by the separation of iodine. After the product had been boiled for one and a quarter hours, ice and dilute acetic acid were successively added, and the ethereal solution, from which the acetic acid was removed, evaporated. Thirty c.c. of alcoholic potassium hydroxide (1 c.c. = 0.0565 gram of KOH) were added, and after eighteen hours the solution was boiled for one hour. The alcohol was evaporated, water added, and the precipitated borneol drained off. The filtrate, which was extracted with ether and then evaporated for several hours to ensure the complete removal of the borneol, was found to be levorotatory. After acidification by sulphuric acid and decolorisation by charcoal, the acid was extracted with ether; the ethereal solution, dried by sodium sulphate, yielded 2.12 grams of an acid crystallising in leaflets. This, when dried at  $100^{\circ}$ , gave the following rotation in ethyl-alcoholic solution:  $l=4$ ,  $c=7.57$ ,  $\alpha_D^{15.5^{\circ}} - 0.57^{\circ}$ ,  $[\alpha]_D^{15.5^{\circ}} - 1.9^{\circ}$ . After removal of the alcohol, the acid was dried at  $100^{\circ}$  and analysed by titration with standard sodium hydroxide:

1.5516 required 18.9 c.c. alkali (0.4964*N*) for neutralisation, the amount calculated for  $C_9H_{10}O_3$  being 18.8 c.c.

In a second experiment, where the addition of the Grignard reagent ( $1\frac{1}{4}$  mols.) to the ester (1 mol., 5 grams) was conducted within an interval of three-quarters of an hour instead of quickly, as in the experiment just described, and where the saponification of the resulting ester mixture was effected by a solution of 2.5 grams of potassium hydroxide in 30 c.c. of ethyl alcohol, the rotation of the acid obtained was practically the same as before, namely,  $l=2$ ,  $c=11.18$ ,  $\alpha_D - 0.36^{\circ}$ ,  $[\alpha]_D - 1.6^{\circ}$  (in ethyl-alcoholic solution). After the alcohol had been expelled from the latter solution and the residue crystallised from water, a crop of *i*-atrolactic acid was obtained, whilst the filtrate gave  $[\alpha]_D - 4.2^{\circ}$  ( $c=2.33$ ).

#### *Action of Magnesium Ethyl Iodide on l-Bornyl Benzoylformate.*

Magnesium ethyl iodide ( $1\frac{1}{4}$  mols.) in ethereal solution (30 c.c.) was added within half an hour to a solution of 12 grams (1 mol.) of *l*-bornyl benzoylformate in 30 c.c. of ether. After the mixture had

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been allowed to remain at the ordinary temperature for one hour, it was boiled for one hour and decomposed in the usual manner by ice and mineral acid. The ester mixture resulting from the ethereal extract was a yellow, viscid oil (13.25 grams), which was saponified by being heated for one hour with a solution of 2.95 grams of potassium hydroxide in 100 c.c. of ethyl alcohol. The alkaline aqueous solution, resulting after the removal of the ethyl alcohol and the borneol, was neutralised by hydrochloric acid, decolorised by charcoal, and concentrated to 25 c.c., of which 14 c.c., examined in a 2-dcm. tube, gave  $\alpha_D^{18} - 1.70^\circ$ . The phenylethylglycollic acid (4.3 grams) obtained by acidifying the potassium salt and then extracting with ether crystallised in long, fine needles which were dried at  $100^\circ$  and then polarimetrically examined in ethyl-alcoholic solution:  $l = 1$ ,  $c = 17.052$ ,  $\alpha_D^{17} - 0.72^\circ$ ,  $[\alpha]_D^{17} - 4.2^\circ$ .

After the expulsion of the alcohol, the residual acid was exactly neutralised by aqueous potassium hydroxide. The aqueous solution of potassium phenylethylglycollate thus obtained gave  $l = 1$ ,  $c = 27.71$ ,  $\alpha_D^{18} - 0.90^\circ$ ,  $[\alpha]_D^{18} - 3.2^\circ$ . The concentration was determined by evaporating off the water from an aliquot portion of the solution and drying the residue at  $140^\circ$  until constant in weight.

0.2266 (dried at  $140^\circ$ ) gave 0.0915  $K_2SO_4$ .  $K = 18.1$ .

$C_{10}H_{11}O_3K$  requires  $K = 17.9$  per cent.

*Action of Magnesium isoButyl Iodide on l-Bornyl Benzoylformate.*

A solution of magnesium ( $1\frac{1}{4}$  mols.) in *isobutyl iodide* ( $1\frac{1}{4}$  mols.) and 25 c.c. of ether was added within an interval of one hour to a solution of 10.8 grams of *l*-bornyl benzoylformate (1 mol.) in 25 c.c. of ether. After two days, the product was decomposed in the usual manner by ice and mineral acid and the ethereal solution washed with an aqueous solution of sodium hydrogen sulphite. The ester mixture remaining after the removal of the ether was submitted to distillation in steam, when no *isobutyl iodide* was detected in the distillate; it was then saponified by the addition of a solution of 8.2 grams of potassium hydroxide in a mixture of ethyl alcohol and water, the mixture having been allowed to remain at the ordinary temperature for two days, after which it was boiled for one and a half hours. The ethyl alcohol and borneol were removed as usual and the aqueous solution (50 c.c.), which was decolorised with some difficulty by animal charcoal, proved to be dextrorotatory, 28 c.c. of it in a 4-dcm. tube giving  $\alpha_D^{17} + 0.19^\circ$ . The potassium salt, when acidified and extracted with ether, yielded 3.6 grams of a crystalline acid, which in ethyl-alcoholic solution (14 c.c.) gave  $l = 2$ ,  $\alpha_D^{14} + 0.50^\circ$ . The ethyl alcohol was expelled and the residue crystallised from a mixture of benzene and light petroleum.

The crop, which separated as glistening needles grouped in rosettes, melted at 119—120° after having first been dried at 100°, and was inactive. The filtrate contained 2.2 grams of acid and was dextro-rotatory; the silver salt was analysed.

0.4338 gave 0.1517 Ag.  $\text{Ag} = 34.2$ .

$\text{C}_{12}\text{H}_{15}\text{O}_3\text{Ag}$  requires  $\text{Ag} = 34.3$  per cent.

*Action of Magnesium  $\alpha$ -Naphthyl Bromide on l-Bornyl Benzoylformate.*

A solution of magnesium  $\alpha$ -naphthyl bromide ( $2\frac{1}{2}$  mols.) in 32 c.c. of ether was gradually added within an interval of forty minutes to a solution of 10 grams of *l*-bornyl benzoylformate (1 mol.) in 25 c.c. of ether. After twelve hours, the product was decomposed in the usual manner and the naphthalene removed from it by distillation in steam. The residue in the flask was a yellow, semi-solid mass and the supernatant aqueous solution was neutral. After it had been found that the saponification could not readily be effected by aqueous potassium hydroxide (9.6 grams), ethyl alcohol was added and the saponification completed by boiling for several hours. The ethyl alcohol and borneol were removed, but it was not found possible to decolorise the aqueous solution of potassium salt to an extent necessary for accurate polarimetric observations. The acid obtained by acidifying the potassium salt and extracting with ether was crystallised first from a mixture of ethyl alcohol and water and then from chloroform, after which treatment it was optically inactive. For analysis, the acid was dried at 100°.

0.1975 gave 0.5618  $\text{CO}_2$  and 0.0941  $\text{H}_2\text{O}$ .  $\text{C} = 77.6$ ;  $\text{H} = 5.3$ .

$\text{C}_{18}\text{H}_{14}\text{O}_3$  requires  $\text{C} = 77.7$ ;  $\text{H} = 5.1$  per cent.

*i*-Phenyl- $\alpha$ -naphthylglycollic acid, when dehydrated at 100°, melts at 143—144° to a green liquid; it is somewhat sparingly soluble in hot benzene, from which, on cooling, it separates in glassy prisms grouped in rosettes. It is practically insoluble in cold water and sparingly soluble in hot chloroform, from which it separates in needles; it dissolves with difficulty both in hot and cold light petroleum and in carbon tetrachloride; it is easily soluble in cold acetone or cold ethyl alcohol.

The mother liquors, from which the *i*-acid (4.2 grams) had been removed by filtration, and which contained the optically active product of the asymmetric synthesis, were evaporated, but the dark brown mass thus obtained, when boiled in various organic solvents with animal charcoal, could not be sufficiently decolorised. The following method, however, was successful. The acid was boiled with water, charcoal, and an excess of barium carbonate for several days. A considerable

amount of water was necessary to bring all the barium salt into solution. The aqueous solution (28 c.c.) which was filtered off from charcoal, barium carbonate, and some barium *r*-phenyl- $\alpha$ -naphthylglycollate gave the following rotation:  $l=4$ ,  $c=2.456$ ,  $\alpha_D^{15} + 0.96^\circ$ ,  $[\alpha]_D^{15} + 9.8^\circ$ .

The concentration of the salt was determined by withdrawing 10 c.c. of the solution, evaporating off the water, and drying the residue at  $130^\circ$  until constant in weight.

*Action of Magnesium Ethyl Bromide on l-Menthyl Pyruvate.*

The *l*-menthyl pyruvate used for this action was portion of the product employed for the asymmetric synthesis of *l*-lactic acid (Trans., 1905, 87, 1373); it had  $[\alpha]_D^{19.6} - 92.8^\circ$ . A solution of magnesium ethyl bromide ( $2\frac{1}{2}$  mols.) in 25 c.c. of ether was added within an interval of thirty minutes to a solution of 11 grams of *l*-menthyl pyruvate (1 mol.) in 25 c.c. of ether. The action, which was very vigorous, was accompanied in the initial stages by the separation of a white solid which gradually dissolved, whilst the solution assumed a green tint. After twelve hours, the product was decomposed as usual and the ester mixture obtained as a dark green oil, which became brown on the addition of a solution of 4.4 grams of potassium hydroxide in 40 c.c. of methyl alcohol, the solution having been boiled for one and a half hours. After removal of the methyl alcohol and menthol, the solution of potassium salt was decomposed by dilute sulphuric acid and extracted with ether. The resulting acid was converted into barium salt, the aqueous solution of which was decolorised by charcoal and a crop withdrawn, whilst the filtrate (18 c.c.) gave  $l=1$ ,  $c=15.8$ ,  $\alpha_D + 0.20^\circ$ . The acid obtained from this solution of barium salt gradually crystallised in the form of silky needles, and a portion, when sublimed, had the properties of *i*-methylethylglycollic acid already described by E. Frankland and Duppa (*Annalen*, 1865, 135, 37); it melted at  $67^\circ$ .

*Action of Magnesium Phenyl Bromide on l-Menthyl Pyruvate.*

A solution of magnesium phenyl bromide ( $1\frac{1}{4}$  mols.) in 30 c.c. of ether was added within an interval of thirty minutes to a solution of 18 grams of *l*-menthyl pyruvate (1 mol.) in 50 c.c. of ether. After eighteen hours, the product was decomposed as usual and the ester mixture saponified by being boiled for one hour with a solution of 6.2 grams of potassium hydroxide in 100 c.c. of ethyl alcohol. Attempts to decolorise the aqueous solution of potassium salt, which had been freed from menthol, were unsuccessful. The free acid, however, was decolorised by boiling its aqueous solution with charcoal. A crop of

an optically inactive acid was removed, which analysis and melting point determinations showed to be *i*-atrolactic acid. The filtrate (30 c.c.) proved to be dextrorotatory, 28 c.c. in a 4-dcm. tube giving  $\alpha_D + 2.14^\circ$ . The concentration of the solution, as determined by titrating an aliquot portion of it with standard alkali, was  $c = 2.9784$ , whence  $[\alpha]_D + 18.0^\circ$ .

A second experiment was performed in order to confirm this dextrorotation. A solution of the Grignard reagent ( $1\frac{1}{4}$  mols.) in 25 c.c. of ether was added within an interval of thirty-five minutes to a solution of 10 grams of ester (1 mol.) in 25 c.c. of ether. The ester mixture, obtained as usual, was in this case saponified by dissolving it in 50 c.c. of ethyl alcohol, adding 3.6 grams of solid potassium hydroxide, and then allowing the mixture to remain overnight, and finally boiling for one hour after the addition of a few c.c. of water. The ethereal solution of the acid, decolorised in the manner indicated in the previous experiment, measured 24 c.c., of which 14 c.c. in a 2-dcm. tube gave  $\alpha_D^{16^\circ} + 1.6^\circ$ ; its concentration, as determined by titration against standard baryta, was  $c = 14.7$ , whence  $[\alpha]_D^{16^\circ} + 5.4^\circ$ . The whole of the acid obtained was converted into barium salt (50 c.c.), 28 c.c. of the aqueous solution giving  $\alpha_D^{13^\circ} + 1.89^\circ$  in a 4-dcm. tube. The concentration, as determined by withdrawing an aliquot portion and drying it at  $130^\circ$  until constant in weight, was  $c = 5.034$ , whence  $[\alpha]_D^{13^\circ} + 9.4^\circ$ .

The acid obtained by the action of magnesium methyl iodide ( $1\frac{1}{4}$  mols.) dissolved in 20 c.c. of ether on 5 grams of *l*-menthyl pyruvate (1 mol.) dissolved in 20 c.c. of ether was optically inactive, a result which was expected, as no asymmetric synthesis was possible under these conditions.

#### *Action of Magnesium Alkyl Halides on l-Menthyl Acetoacetate.*

*l*-Menthyl acetoacetate has already been described by Cohn (*Monatsh.*, 1900, 21, 200), Cohn and Tauss (*Ber.*, 1900, 33, 731), and Lapworth and Hann (*Trans.*, 1902, 81, 1499). The method of preparation described by those authors was slightly modified. A mixture of *l*-menthol ( $1\frac{1}{2}$  mols.) and ethyl acetoacetate (1 mol.) was heated in a paraffin-bath at  $140$ — $150^\circ$  for six hours. The bulk of residual menthol was then removed by distillation in steam, and the product remaining in the flask extracted with ether. The ethereal solution was dried, the ether removed, and the product fractionated under diminished pressure. *l*-Menthyl acetoacetate, obtained in this manner, boiled at  $146$ — $147^\circ$  under 9 mm. pressure (Cohn gives  $145^\circ$  under 9 mm. pressure), readily solidified, and had the following rotation in ethyl-alcoholic solution:  $l = 2$ ,  $c = 5.24$ ,  $\alpha_D^{20^\circ} - 7.35^\circ$ ,  $[\alpha]_D^{20^\circ} - 70.1^\circ$ .



Lapworth and Hann give  $[\alpha]_D - 68.5^\circ$  for  $c = 1.5$  (temperature not quoted). No multirotation in ethyl-alcoholic solution was observed.

A solution of magnesium phenyl bromide ( $1\frac{1}{4}$  mols.) in 20 c.c. of ether was gradually added to a solution of 10 grams of *l*-menthyl acetoacetate (1 mol.). The aqueous solution of potassium salt, obtained by the methods previously indicated, was decolorised and proved to be inactive.

A solution of magnesium ethyl bromide ( $1\frac{1}{4}$  mols.) in 33 c.c. of ether was gradually added within an interval of forty minutes to a solution of 8.7 grams of menthyl acetoacetate (1 mol.) in 21 c.c. of ether. The action was vigorous, the white precipitate at first formed gradually disappearing. After eighteen hours at the ordinary temperature, ice and dilute hydrochloric acid were successively added, the ethereal solution removed, and the aqueous solution extracted twice with ether. The ethereal extracts were united, washed once with a little water, and dried over anhydrous sodium sulphate. After the expulsion of the ether, an oil was obtained which quickly crystallised to a solid mass when nucleated with menthyl acetoacetate. A determination of the specific rotation of the product (7.6 grams) in ethyl-alcoholic solution proved it to be *l*-menthyl acetoacetate:  $l = 2$ ,  $c = 5.333$ ,  $\alpha_D^{20} - 7.46^\circ$ ,  $[\alpha]_D^{20} - 69.9^\circ$ .

*Action of Magnesium Ethyl Bromide on l-Menthyl Ethylacetoacetate.*

*l*-Menthyl ethylacetoacetate was prepared as follows: equimolecular weights of ethyl ethylacetoacetate and *l*-menthol were heated for five hours in an oil-bath at  $145-155^\circ$ . The bulk of the menthol was removed by distillation of the product in a current of steam, and the remaining aqueous liquid, which was neutral to litmus, extracted with ether together with the oil. The ethereal extract was dried by calcium chloride, the ether distilled off, and the residual menthol readily separated by fractionation under diminished pressure. *l*-Menthyl ethylacetoacetate was obtained as a colourless oil, which did not solidify when immersed for several hours in a freezing mixture; it boils at  $159-161^\circ$  under 9—10 mm. pressure.

0.3244 gave 0.8482  $\text{CO}_2$  and 0.3109  $\text{H}_2\text{O}$ .  $C = 71.3$ ;  $H = 10.7$ .

$\text{C}_{16}\text{H}_{28}\text{O}_3$  requires  $C = 71.6$ ;  $H = 10.5$  per cent.

The following polarimetric results were obtained:  $l = 0.5$ ,  $\alpha_D^{20} - 30.40^\circ$ ,  $d_{20}^{20}/4^\circ 0.9653$ ,  $[\alpha]_D^{20} - 63.0^\circ$ .

In ethyl-alcoholic solution:  $l = 2$ ,  $c = 4.442$ ,  $\alpha_D^{20} - 6.03^\circ$ ,  $[\alpha]_D^{20} - 67.9^\circ$ .

When a few drops of an anhydrous ethereal solution of ferric



chloride were added to a solution of the ester in anhydrous ether, a coloration was not observed until the mixture had remained for about an hour at the ordinary temperature; it then gradually intensified, but was never very marked. Under the same conditions, the ethyl ethylacetoacetate used in the preparation of the menthyl ester gave a pronounced violet coloration at once.

A solution of magnesium ethyl bromide ( $1\frac{1}{2}$  mols.) in 20 c.c. of ether was added to a solution of 10 grams of the ester (1 mol.) in 20 c.c. of ether. No perceptible action took place until about two-thirds of the Grignard reagent had been added, when the ether boiled and continued to do so until the addition was complete. After remaining overnight, ice and mineral acid were added and the ethereal solution dried with sodium sulphate. The residue, after evaporation of the ether and drying over sulphuric acid in a partial vacuum, was polarimetrically examined in a 5 per cent. ethyl-alcoholic solution, when the value  $[\alpha]_D^{20} - 64.6^\circ$  was obtained. This result indicates that menthyl ethylacetoacetate had not acted towards the Grignard reagent exclusively in accordance with the structure



since the variation of the value  $-64.6^\circ$  from that of menthyl ethylacetoacetate itself is beyond the limit of experimental error.

The product (8.5 grams) was saponified by heating it with a solution of 2.2 grams of potassium hydroxide in 50 c.c. of ethyl alcohol for one and a half hours, and the solution of potassium salt, obtained in the usual manner, was practically inactive.

#### *Action of Magnesium Alkyl Halides on l-Menthyl Diethylacetoacetate.*

*l*-Menthyl diethylacetoacetate is not formed in any appreciable amount when ethyl diethylacetoacetate is heated with an excess of *l*-menthol even at  $190^\circ$ , nor can it be conveniently obtained from the latter substances by heating them in the presence of hydrogen chloride according to the method which Patterson and Dickinson (Trans., 1901, 79, 280) have successfully devised for the interconversion of methyl and ethyl tartrates. The following method was employed: a solution of sodium ethoxide, prepared from sodium ( $2\frac{1}{2}$  grams) and ethyl alcohol (35 grams), was added to a mixture of *l*-menthyl ethylacetoacetate (33 grams) and ethyl iodide (20 grams). After having been gently boiled for two hours, the liquid was neutral to litmus. The alcohol was expelled, water added to the residue, and the whole extracted with ether. The ethereal solution was dried with calcium chloride, the ether distilled off, and the resulting oil submitted to fractional distillation under diminished pressure.

*l*-Menthyl diethylacetoacetate,  $\text{CH}_3 \cdot \text{CO} \cdot \text{CEt}_2 \cdot \text{CO}_2 \cdot \text{C}_{10}\text{H}_{19}$ , was obtained

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as a colourless oil boiling at 180—182.5° under 13 mm. pressure, the yield being 15 grams.

0.1926 gave 0.5150 CO<sub>2</sub> and 0.1926 H<sub>2</sub>O. C = 72.9; H = 11.2.

C<sub>18</sub>H<sub>32</sub>O<sub>3</sub> requires C = 72.9; H = 10.9 per cent.

A determination of the specific rotation of the freshly-prepared ester gave the result:  $l = 0.5$ ,  $d_{20}^{20}/4^\circ$  0.9605,  $\alpha_D^{20} - 26.30^\circ$ ,  $[\alpha]_D^{30} - 54.8^\circ$ .

A solution of magnesium ethyl bromide ( $1\frac{1}{4}$  mols.) in 20 c.c. of ether was added within an interval of twenty minutes to a solution of 5.5 grams of *l*-menthyl diethylacetoacetate (1 mol.) in 20 c.c. of ether. A reaction, evidenced by the boiling of the ether, took place. The usual treatment was followed, but the potassium salt obtained proved to be practically inactive.

In a similar manner, when magnesium phenyl bromide was substituted for magnesium ethyl bromide, the generation of an additional asymmetric carbon atom was not accompanied by an asymmetric synthesis, since the aqueous solution of potassium salt, prepared in a manner analogous to that usually employed, was optically inactive.

*Action of Magnesium Alkyl Halides on l-Menthyl Lævulate.*

For the preparation of *l*-menthyl lævulate, a mixture of lævulic acid (50 grams) and *l*-menthol (160 grams) was heated for eighteen hours in an oil-bath at 95—105°, whilst a current of dry hydrogen chloride was passed occasionally through the liquid; the product was dissolved in about its own volume of ether, and the solution washed first with water and then with sodium hydrogen carbonate solution until it no longer gave an acid reaction. The ether was distilled off and the residual oil submitted to distillation in steam in order to remove the bulk of the menthol, after which process the ester was extracted with ether from the liquid in the distilling flask. The ethereal solution was dried over potassium carbonate, the ether expelled, and the residue fractionated under diminished pressure.

*l*-Menthyl lævulate, CH<sub>3</sub>·CO·CH<sub>2</sub>·CH<sub>2</sub>·CO<sub>2</sub>·C<sub>10</sub>H<sub>19</sub>, was obtained as a colourless oil which boiled at 169° under 12 mm. pressure, the yield being 80 grams.

0.1679 gave 0.4377 CO<sub>2</sub> and 0.1620 H<sub>2</sub>O. C = 71.1; H = 10.8.

C<sub>15</sub>H<sub>26</sub>O<sub>3</sub> requires C = 70.8; H = 10.3 per cent.

A determination of its specific rotation gave the following result:  $l = 0.5$ ,  $d_{20}^{19.8}/4^\circ$  0.9773,  $\alpha_D^{19.8} - 29.59^\circ$ ,  $[\alpha]_D^{19.8} - 60.6^\circ$ .

No asymmetric synthesis was detected when magnesium ethyl bromide interacted with *l*-menthyl lævulate, but the solution of potass-

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ium salt, obtained in the usual manner, was so highly coloured, as also was the acid (or lactone) derived from it, that much reliance could not be placed on this result. A similar difficulty was also encountered when magnesium  $\alpha$ -naphthyl bromide was substituted for magnesium ethyl bromide; attempts to decolorise the aqueous solution of potassium salt and of the free acid respectively failed to give solutions sufficiently colourless for accurate polarimetric observations, whilst even the barium salt was unsuitable, as it was found to be practically insoluble in water. On the other hand, a positive result was obtained when magnesium phenyl bromide was used. A solution of magnesium phenyl bromide ( $1\frac{1}{4}$  mols.) in 20 c.c. of ether was added within an interval of thirty minutes to a solution of 9.5 grams (1 mol.) of *l*-menthyl lævulate in 20 c.c. of ether. After twenty-four hours, the product was treated as usual, the saponification being conducted by boiling with a solution of 4 grams of potassium hydroxide in methyl alcohol. All attempts to decolorise the potassium salt and the free acid having failed, the latter was converted into barium salt, the aqueous solution of which was decolorised and found to be distinctly lævorotatory.

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