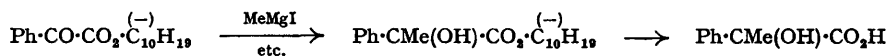


710. *Partial Asymmetric Synthesis with Keto-esters. Part II.**

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Interaction of methylmagnesium bromide with (–)-menthyl β-benzoyl-propionate and γ-benzoyl-*n*-butyrate is accompanied by partial asymmetric synthesis.

It was shown by McKenzie (*J.*, 1904, 85, 1249) that interaction of methylmagnesium iodide and (–)-menthyl benzoylformate was accompanied by partial asymmetric synthesis, the atrolactic acid obtained after removal of the fixed centre of asymmetry, *i.e.*, the (–)-menthyl group, being lævorotatory :



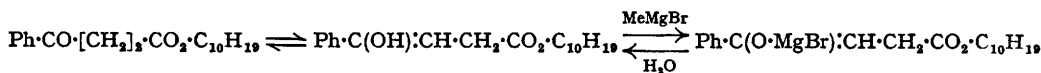
The present communication describes the analogous sets of reactions starting with methylmagnesium bromide and a series of (–)-menthyl esters, $\text{Ph}\cdot\text{CO}\cdot[\text{CH}_2]_n\cdot\text{CO}_2\cdot\overset{(-)}{\text{C}}_{10}\text{H}_{19}$ ($n = 0, 2, 3, 4$, and 8). The hydroxy-acids ultimately isolated were examined optically, either as such or as the lactones, if the latter were obtainable. All operations were carried out on a quantitative basis and were designed to ensure minimal loss of hydroxy-acid at any manipulative stage. The Grignard reactions were all performed in nitrogen, in the same all-glass apparatus, so as to secure reproducibility of results.

In order to link the present work with that of McKenzie (*loc. cit.*), we first treated (–)-menthyl benzoylformate with 1.25 molecular proportions of methylmagnesium bromide. Under our conditions, the atrolactic acid obtained (in 97% yield) had a specific rotation of $[\alpha]_{5780}^{25} -8.5^\circ$ in absolute ethyl alcohol, whereas McKenzie, using one molecular proportion of methylmagnesium iodide, obtained an acid having $[\alpha]_{\text{D}}^{18} -8.3^\circ$. Evidently the change from

* Part I, preceding paper.

methylmagnesium iodide to the bromide and the slightly different experimental conditions had very little effect on the extent of asymmetric synthesis.

In the reactions starting with (–)-menthyl β-benzoylpropionate and methylmagnesium bromide, a preponderance of (–)-γ-hydroxy-γ-phenyl-*n*-valeric acid has been found to be produced; the corresponding lactone was dextrorotatory. When 1·25 molecular proportions of Grignard reagent to one of menthyl benzoylpropionate were used, the final acid contained considerable quantities of β-benzoylpropionic acid, either owing to incomplete reaction or to reaction of the enolic form of the ester :



By using two molecular proportions of Grignard reagent this was almost entirely suppressed, but a small amount of the glycol, $\text{Ph}\cdot\text{CMe}(\text{OH})\cdot[\text{CH}_2]_2\cdot\text{CMe}_2\cdot\text{OH}$, was produced as a result of reaction at the carbomethyloxy-group. For optical examination the final hydroxy-acid was converted into its lactone. The degree of asymmetric synthesis was found to be dependent only to a slight extent on the conditions under which the initial Grignard reactions were carried out. A short boiling of the reaction mixture after addition was complete gave a lactone with a slightly higher rotation ($[\alpha]_{\text{D}}^{25} + 10\cdot2^\circ$) than that ($+9\cdot3^\circ$) of the product of a reaction mixture which had never been heated above 0° .

Fractional acidification of an aqueous alkaline solution of partially active γ-hydroxy-γ-phenylvaleric acid effected some resolution. Thus on acidification to pH 5, acid was precipitated with $[\alpha]_{\text{D}}^{25} - 4\cdot42^\circ$, giving a lactone with $[\alpha]_{\text{D}}^{25} + 46\cdot8^\circ$. Further acidification caused precipitation of acid with $[\alpha]_{\text{D}}^{25} + 2\cdot56^\circ$ (compare Part I, preceding paper).

Interaction of (–)-menthyl β-benzoylpropionate and 2 molecular proportions of ethylmagnesium bromide, followed by the usual treatment of the reaction mixture, led to slightly lævorotatory 4-hydroxy-4-phenylhexanoic acid,* the lactone of which was dextrorotatory. The (±)-acid melted at 89° (Trivedi and Nargund, *J. Univ. Bombay*, 1941, 10, Part 3, p. 99, give $102\text{--}103^\circ$).

(–)-Menthyl γ-benzoyl-*n*-butyrate reacted almost quantitatively with methylmagnesium bromide (1·25 molecular proportions). The 5-hydroxy-5-phenylhexanoic acid finally isolated was feebly lævorotatory but gave a lactone with $[\alpha]_{\text{D}}^{25} + 2\cdot9^\circ \pm 0\cdot1^\circ$. Partial resolution of the acid could be effected by using the brucine salt, the highest rotation recorded of the derived lactone being $[\alpha]_{\text{D}}^{25} + 15\cdot7^\circ$ in chloroform.

No evidence of partial asymmetric synthesis was observed in the interaction of methyl- or ethylmagnesium bromide and (–)-menthyl δ-benzoyl-*n*-valerate. In view, however, of the low rotatory power of 4-hydroxy-4-phenylhexanoic acid, that of 6-hydroxy-6-phenylheptanoic acid may be assumed also to be slight and in the case of the second acid lactonisation could not be used to magnify the observable rotation.

(–)-Menthyl ω-benzoylpelargonate and methylmagnesium bromide led to 10-hydroxy-10-phenylundecanoic acid, which had no detectable optical activity.

EXPERIMENTAL.

General Method of Preparation of (–)-Menthyl Esters.—This was carried out essentially by McKenzie's method (*loc. cit.*). A mixture of the keto-acid (1 mol.) and 3–4 mols. of (–)-menthol was heated at 100° for about 9 hours, with occasional passage of hydrogen chloride. The reaction mixture was dissolved in ether, and the solution washed first with 10% aqueous sodium carbonate solution and then with water. The ethereal layer was evaporated and the residue freed from menthol by distillation in steam. The residual ester was crystallised or distilled until its specific rotation and rotatory dispersion ($\lambda_{5780} : \lambda_{5461}$) were constant. Unless otherwise stated, specific rotations were determined in absolute ethyl alcohol at 25° ($l = 2$).

General Procedure in Grignard Reactions.—The Grignard reagent was prepared in an all-glass apparatus previously dried at 130° and set up while still hot, with drying tubes (calcium chloride-soda-lime) in position. The magnesium used was dried at 130° and the methyl bromide over calcium chloride at 0° . The ether was dried over sodium wire. Air in the apparatus was replaced by nitrogen. After the Grignard reagent had been prepared, it was filtered through glass wool inside the apparatus and added drop by drop to a solution of 5 g. of keto-ester in 20 c.c. of ether with continuous shaking and (usually) ice-cooling. Conditions were varied from one series of experiments to another as regards the time allowed to elapse before the reaction product was treated with ice and hydrochloric acid. The ethereal layer was separated and the aqueous layer extracted thrice with 10 c.c. of ether. The total combined ethereal solution was washed with 10 c.c. of water and dried (Na_2SO_4). The ether was distilled off and the residue dried in a vacuum for 30 minutes. It was weighed and then hydrolysed

* Geneva nomenclature ($\text{CO}_2\text{H} = 1$).

with boiling aqueous alcoholic potassium hydroxide. The alcohol was distilled off and the remaining mixture of menthol, neutral products, and alkaline solution was extracted four times with 10 c.c. of ether and then once with 20 c.c. of ether. In all experiments the last extract was optically inactive, proving the absence of menthol. The alkaline solution was freed from ether by warming and then cooled and acidified with 25% sulphuric acid. If a solid acid was precipitated it was filtered off, washed, and dried in a vacuum over calcium chloride. If an oily acid was obtained, it was extracted with ether (5 × 10 c.c.), the (dried) ethereal solution being evaporated and the residue kept in a vacuum over calcium chloride and paraffin wax. It was usually necessary to warm the products several times and repeat the vacuum-drying in order to remove the last traces of water and ether.

Interaction of (–)-Menthyl Benzoylformate and 1.25 Molecular Proportions of Methylmagnesium Bromide.—The Grignard reagent prepared from 0.525 g. of magnesium (ether, 20 c.c.) was added during 7 minutes, with shaking, to an ice-cooled solution of 5 g. of (–)-menthyl benzoylformate in 20 c.c. of ether. The mixture was then boiled under reflux for $\frac{1}{2}$ hour. When cold, it was treated with ice (15 g.) and 25% hydrochloric acid (35 c.c.). The atrolactic acid finally obtained (2.48 g., 97%) had $[\alpha]_{D}^{25} -8.5^{\circ}$, $[\alpha]_{D}^{25} -9.3^{\circ}$ (c, 12.40 in absolute ethyl alcohol). (–)-Menthyl β -benzoylpropionate, after being crystallised four times from light petroleum (b. p. 60–80°), had m. p. 92°, $[\alpha]_{D}^{25} -62.1^{\circ}$, $[\alpha]_{D}^{25} -54.8^{\circ}$ (c, 1.715 in chloroform) (Found: C, 75.8; H, 8.9. $C_{20}H_{28}O_3$ requires C, 75.9; H, 8.9%).

Interaction of (–)-Menthyl β -Benzoylpropionate with Methylmagnesium Bromide (\times Mols.).—(a) $\times = 1.25$. The Grignard reagent prepared from 0.480 g. of magnesium, methyl bromide, and ether (20 c.c.) was added with shaking, during 10 minutes, to an ice-cooled solution of 5 g. of (–)-menthyl β -benzoylpropionate in 20 c.c. of ether. The mixture was boiled under reflux for $1\frac{1}{2}$ hours, cooled, and treated with 20 g. of ice and 2 c.c. of concentrated hydrochloric acid. The γ -hydroxy- γ -phenylvaleric acid obtained had m. p. 96–98°, $[\alpha]_{D}^{25} -0.07^{\circ}$ (c, 4.115 in absolute alcohol). Evaporation of the rotation solution in presence of a drop of dilute hydrochloric acid gave the lactone with $[\alpha]_{D}^{25} +6.0^{\circ}$ (c, 3.75 in absolute alcohol). In a similar experiment the lactone had $[\alpha]_{D}^{25} +6.7^{\circ}$ ($l = 2$; c, 6.20 in absolute alcohol).

(b) $\times = 2$. Sixteen different experiments were carried out in which the time of addition of Grignard reagent was varied from 0 to 15 minutes and subsequent treatment, before treatment with ice and acid, was varied between keeping at 0° for 3 hours and boiling under reflux for $1\frac{1}{2}$ hours. The rotations of the lactones ultimately isolated varied from $[\alpha]_{D}^{25} +9.0^{\circ}$ to $+10.5^{\circ}$ (c, about 6.5 in absolute ethyl alcohol).

An experiment was performed on 25 g. of keto-ester, using 2 mols. of methylmagnesium bromide. The reaction mixture was worked up in the usual way and the product of alkaline hydrolysis, after removal of menthol, was made up to 100 c.c. This solution was divided into three portions which were treated as follows: (1) 25 c.c. were acidified with sulphuric acid and extracted with ether. The lactone was prepared and was found to have $[\alpha]_{D}^{25} +9.0^{\circ}$ (c, 8.30 in alcohol). (2) 25 c.c. were acidified and the acid (1.65 g.; m. p. 100–102°) was filtered off and dried. It had $[\alpha]_{D}^{25} -1.30^{\circ}$ (c, 8.1 in alcohol). The lactone prepared from this acid had $[\alpha]_{D}^{25} +12.2^{\circ}$ (c, 6.2) suggesting that precipitation of the acid from its alkaline solution resulted in preferential precipitation of the optically active isomeride present in excess in the mixture. (3) 50 c.c. were acidified and the acid (3.41 g.; m. p. 99–101°) was filtered off and dried. The products from (1), (2), and (3) were combined and dissolved in 10% aqueous potassium hydroxide. By acidification of this solution to pH 5–6, 1.3 g. of acid, m. p. 109°, were obtained, having $[\alpha]_{D}^{25} -4.42^{\circ}$, giving a lactone with $[\alpha]_{D}^{25} +46.7^{\circ}$ (c, 3.475 in alcohol). The ratio $[\alpha]_{\text{lactone}} : [\alpha]_{\text{acid}} = -10.5$. Acidification of the mother-liquor to methyl-orange gave 1.25 g. of acid, m. p. 102–103°, having $[\alpha]_{D}^{25} +2.56^{\circ}$ (c, 5.86 in alcohol), giving a lactone with $[\alpha]_{D}^{25} -22.2^{\circ}$ (c, 5.3). This crop was slightly contaminated with β -benzoylpropionic acid, which accounts for the low ratio, $[\alpha]_{\text{lactone}} : [\alpha]_{\text{acid}}$ of -9.1 .

A second experiment on the same scale was performed, in an attempt to extend the above technique to effect a separation of the acid into its two optical isomerides, but although a laevorotatory acid of 90% optical purity was obtained, the pure form was not isolated.

Reaction between (–)-Menthyl β -Benzoylpropionate and Ethylmagnesium Bromide.—Four experiments were performed, using 5 g. of the keto-ester and 2 mols. of Grignard reagent. A slightly laevorotatory 4-hydroxy-4-phenylhexanoic acid was obtained, giving a lactone with $[\alpha]_{D}^{25} +8.47^{\circ}$ (c, 5.9 in alcohol). The acid, recrystallised from carbon tetrachloride, had m. p. 89° (cf. Trivedi and Nargund, *J. Univ. Bombay*, 10, Part 3, 99–107, who give m. p. 102–103°) (Found: C, 69.2; H, 7.8. Calc. for $C_{12}H_{16}O_3$: C, 69.2; H, 7.75%).

1-Phenylcyclopentene. A solution of cyclopentanone (61 g., 0.5 g.-mol.) in ether (250 c.c.) was added during 1 hour with stirring and ice-cooling to a Grignard reagent made from bromobenzene (1 g.-mol.) (1 l. of ether). Stirring was continued for a further $1\frac{1}{2}$ hours and the mixture kept overnight. It was decomposed in the standard way. The ethereal layer and subsequent ethereal extracts of the aqueous layer were washed with aqueous alkali and with water. The dried (Na_2SO_4) ethereal solution was distilled at atmospheric pressure and later at 30 mm. until no more water distilled. The pressure was then decreased to 4 mm., 1-phenylcyclopentene distilling 84° (m. p. 23°; yield 75%).

γ -Benzoylbutyric Acid.—A solution of 1-phenylcyclopentene (5 g.) in glacial acetic acid (200 c.c.) was stirred and powdered chromic anhydride (15 g.) added in small portions during 10 minutes. Thereafter stirring was continued for 50 minutes, and water and ether (200 c.c. each) were added. After vigorous shaking the mixture was kept until it separated into two layers, more water being added if necessary. The aqueous layer was extracted 4 times with 100 c.c. of ether, and the total ethereal solution extracted thrice with 100 c.c. of water and then with 200 c.c. of 5% aqueous sodium hydroxide. These extracts were discarded as containing mainly chromic and acetic acids. The ether was then extracted twice with 500 c.c. of 10% sodium hydroxide solution. This extract consisted

mainly of chromic and acetic acids, but was acidified with concentrated hydrochloric acid to recover the traces of γ -benzoylbutyric acid present. The bulk of the γ -benzoylbutyric acid was then extracted with 2×50 c.c. 10% aqueous sodium hydroxide and finally with 50 c.c. of water. These combined extracts were poured slowly into concentrated hydrochloric acid and the precipitated acid was filtered off and dried *in vacuo* (P_2O_5). Recrystallisation from water gave γ -benzoylbutyric acid, m. p. 126.5–127°. Fieser and Szmuszkowicz (*J. Amer. Chem. Soc.*, 1948, **70**, 3352), by chromic-acetic acid oxidation of 1-phenylcyclopentan-1-ol, obtained material of m. p. 126°.

(–)-Menthyl γ -benzoylbutyrate was caused to crystallise by cooling a solution in light petroleum (b. p. 40–60°) in solid carbon dioxide-alcohol. Four such processes gave a product, m. p. 18.5–19.0°, with $[\alpha]_{D}^{25} -59.9^\circ$, $[\alpha]_{D}^{25} -52.7^\circ$ (c, 1.560 in alcohol) (Found: C, 76.4; H, 9.6. $C_{21}H_{30}O_3$ requires C, 76.4; H, 9.2%).

Interaction of (–)-Menthyl γ -Benzoylbutyrate with Methylmagnesium Bromide.—(a) With 1.25 molecular proportions of Grignard reagent. Five separate experiments were made, the extreme variation in conditions being (1) to add the Grignard reagent to the ethereal ester solution at 0° and keep the mixture at 0° for a further 3 hours and (2) to add the Grignard reagent to the boiling ethereal ester solution and continue to boil it for a further $\frac{1}{2}$ hour. The reaction mixture was worked up as usual and the product hydrolysed with aqueous-alcoholic potassium hydroxide. Menthol was removed by ether-extraction and the alkaline solution then acidified and extracted with ether. The (dried) ethereal extract was evaporated. The acids obtained had a low rotation and were therefore converted into the lactone by evaporating a solution in alcohol-benzene or in benzene. The yield of 5-hydroxy-5-phenylhexanoic acid, m. p. ca. 76°, only varied from 86 to 89%, but the specific rotation of the corresponding lactone (m. p. ca. 73°) was $[\alpha]_{D}^{25} +2.1^\circ$ (c, 11.25) when the reaction was carried out entirely at 0°, and $[\alpha]_{D}^{25} +2.8^\circ$ to $+3.0^\circ$ (c, 12) when the reaction mixture was boiled under reflux.

(b) With 2 molecular proportions of Grignard reagent. The lactone isolated had, in one experiment, $[\alpha]_{D}^{25} +2.40^\circ$ (c, 8.85) and in a second $[\alpha]_{D}^{25} +2.20^\circ$ (c, 7.80) (yields, 69 and 67% respectively). A sample of the lactone obtained in these experiments crystallised in plates from alcohol, m. p. 70–71° (Found: C, 75.5; H, 7.3. $C_{12}H_{14}O_2$ requires C, 75.8; H, 7.4%).

Interaction of (–)-menthyl γ -benzoylbutyrate and ethylmagnesium bromide led to an oily lactone which was optically inactive.

(±)-5-Hydroxy-5-phenylhexanoic Acid.—(a) A Grignard reagent (1.5 mols.) prepared from methyl bromide (17 g.) was added with stirring to ethyl γ -benzoylbutyrate (22 g., 1 mol.) in ether. The reaction was completed by boiling and the mixture worked up normally. The crude hydroxy-ester obtained was hydrolysed with aqueous alcoholic alkali. The alkaline solution was freed from by-products by ether-extraction and acidified. The oil precipitated soon solidified and was crystallised from benzene below 40° to prevent lactonisation. The acid (11 g., 53%) had m. p. 73–74° (Found: C, 68.8; H, 7.4. $C_{12}H_{16}O_3$ requires C, 69.2; H, 7.7%).

(b) A Grignard reagent prepared from bromobenzene (56 g.) was added at 0° to an ethereal solution of ethyl γ -acetylbutyrate (45 g.). The pure acid finally obtained (20 g., 30%) had m. p. 73–74°.

Partial Optical Resolution of 5-Hydroxy-5-phenylhexanoic Acid.—Brucine formed a crystalline salt which was crystallised from water four times, the rotation falling from $[\alpha]_{D}^{25} -48.2^\circ$ to -43.1° in chloroform (c, 0.60), the m. p. rising from 106–108° to 108–110°. The salt was stirred at 0° with hydrochloric acid, and 10% aqueous sodium hydroxide added later. The brucine was extracted with chloroform, and the alkaline layer acidified; the acid was extracted with ether, which was then removed in a vacuum. Conversion into lactone was effected by boiling a benzene solution of the residue and subsequently removing the benzene in a vacuum. The lactone had $[\alpha]_{D}^{25} +15.67^\circ$ in chloroform (c, 3.695).

(–)-Menthyl δ -Benzoyl-n-valerate.—Prepared from the acid, obtained by Hill's method (*J. Amer. Chem. Soc.*, 1932, **54**, 4106), the ester crystallised from ether at the temperature of solid carbon dioxide-alcohol and had m. p. 50°, $[\alpha]_{D}^{25} -59.5^\circ$, $[\alpha]_{D}^{25} -52.6^\circ$ (c, 1.650 in absolute ethyl alcohol) (Found: C, 76.6; H, 9.3. $C_{22}H_{32}O_3$ requires C, 76.7; H, 9.4%).

Interaction of (–)-Menthyl δ -Benzoylvalerate with Methylmagnesium Bromide.—(a) With 1.25 mols. of Grignard reagent. The reaction was performed at 0°, followed by boiling for $\frac{1}{2}$ an hour. The 6-hydroxy-6-phenylheptanoic acid (yield, 97–98% in different experiments) formed by hydrolysis of the menthyl ester was optically inactive.

(b) With 2 mols. of Grignard reagent [otherwise, reaction conditions as in (a)]. The hydroxy-acid obtained (yield, 69–72% in different experiments) had $\alpha_{D}^{25} +0.08^\circ$ (c, 11.0 in ethyl alcohol).

(c) With 4 mols. of Grignard reagent [otherwise, reaction conditions as in (a)]. The hydroxy-acid obtained (yield, 43%) was optically inactive.

Interaction of (–)-Menthyl δ -Benzoylvalerate with Ethylmagnesium Bromide.—By use of 1.25 mols. of Grignard reagent an inactive hydroxy-acid was obtained. With 2 mols. of Grignard reagent an acid was obtained with $\alpha_{D}^{25} -0.03^\circ$ in alcohol (c, 12.85).

ω -Benzoylpelargonic Acid.—This was prepared by the Friedel-Crafts reaction between ω -carbethoxy-nononoyl chloride and benzene, in presence of aluminium chloride, followed by hydrolysis of the ethyl ω -benzoylpelargonate so obtained (see Papa, Schwenk, and Hankin, *J. Amer. Chem. Soc.*, 1947, **69**, 3018).

(–)-Menthyl ω -benzoylpelargonate (10-keto-10-phenyldecanoate) had b. p. 250°/1.5 mm. Crystallised from ethyl alcohol, it had m. p. 37–38°, $[\alpha]_{D}^{25} -51.05^\circ$ (c, 2.145 in absolute ethyl alcohol) (Found: C, 78.0; H, 10.4. $C_{26}H_{40}O_3$ requires C, 78.0; H, 10.1%).

Interaction of the Foregoing Menthyl Ester with Methylmagnesium Bromide.—This reaction gave a product from which only optically inactive 10-hydroxy-10-phenylundecanoic acid was obtained. Crystallised from light petroleum (b. p. 60—80°), it had m. p. 61—62° (Found: C, 73.5; H, 9.0. C₁₇H₂₆O₃ requires C, 73.4; H, 9.4%).

Interaction of Menthyl Benzoylpelargonate with Ethylmagnesium Bromide.—This gave rise to 11-hydroxy-11-phenyldodecanoic acid with a small but definite optical activity: $[\alpha]_{D}^{25} -0.05^{\circ}$ (c, 13—14 in alcohol).

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