196. *Partial Asymmetric Synthesis of β-Hydroxy-acids. Part I. β-Hydroxy-β-phenylbutyric Acid.*

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Reaction of either (—)-bornyl or (—)-α-fenchyl bromoacetate with acetophenone in the presence of zinc is accompanied by partial asymmetric synthesis, as is shown by hydrolysis of the resulting ester to lævorotatory β-hydroxy-β-phenylbutyric acid. Hitherto, the asymmetric synthesis of this hydroxy-acid has been accomplished by using (—)-menthyl bromoacetate,[1] and now the effect of variations in reaction conditions, such as change of solvent or addition of metallic halides, has been studied.

Asymmetric synthesis also occurs in the absence of zinc metal; thus, an organozinc derivative of the bromo-ester may be prepared by treating it with zinc in the absence of acetophenone which is subsequently added, or the metallic zinc may be replaced by di-n-propyl-zinc or -cadmium.

(—)-Menthyl (+)-β-hydroxy-β-phenylbutyrate has been obtained optically pure. The hydrolysis of this ester, or of mixtures of it with the diastereoisomeric ester of the (—)-β-hydroxy-acid, gives the acid in 90% yield, that from the (—)-methyl (+)-hydroxy-ester being optically pure.

Reaction of acetophenone and (—)-menthyl bromoacetate in benzene solution in the presence of zinc (Reformatsky reaction), followed by complete hydrolysis of the β-hydroxy-ester obtained, has been shown to give a preponderance of the (+)-β-hydroxy-β-phenylbutyric acid over the (—)-antipode.[1]

It is commonly accepted [2] that in the Reformatsky reaction an organozinc intermediate, analogous to a Grignard reagent, is first formed, and this subsequently reacts with a carbonyl compound. Thus, it seems that a " partial asymmetric reaction " may occur during addition of an organometallic compound to a carbonyl group, when it is the organometallic compound which contains a " fixed centre of asymmetry." Before this observation, the only successful examples of an asymmetric reaction occurring during the addition of an organometallic compound to a carbonyl group had been when the " fixed centre of asymmetry " was in one of the groups attached to the carbonyl group. The latter type of asymmetric reaction has been extensively studied,[3] and accordingly we have now studied in more detail the occurrence of partial asymmetric synthesis in the Reformatsky reaction, and in related reactions, with a view to elucidating the steric course of addition of an optically active organometallic compound to a carbonyl group.

The asymmetric synthesis occurring during the interaction of acetophenone, (—)-menthyl bromoacetate, and zinc in boiling benzene, as shown by complete hydrolysis of the resulting (—)-menthyl β-hydroxy-β-phenylbutyrate with aqueous-alcoholic potassium hydroxide to give the hydroxy-acid of about 30% optical purity,[4] was characterised by the remarkable reproducibility of the degree of asymmetric synthesis, irrespective of variations in the reaction conditions. Variations in, for example, the concentrations of the reactants,

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[1] Reid and Turner, *J.*, 1949, 3365.

[2] Cf. Siegel and Keckeis, *Monatsh.*, 1953, **84**, 910.

[3] Klyne, " Progress in Stereochemistry," Butterworths, London, 1954, Vol. I, p. 198.

[4] Reid and Turner, *J.*, 1950, 3694.

the duration of heating of the Reformatsky reaction mixture, and the zinc–ester–acetophenone ratios had little effect upon the specific rotation of the β-hydroxy-acid obtained. This is in marked contrast to the non-reproducibility of the degree of asymmetric synthesis occurring when an optically active keto-ester reacts with a Grignard reagent (McKenzie type of asymmetric synthesis).[5] It seemed possible that the reproducibility in the Reformatsky reaction might in fact be due to either the Reformatsky reaction's being reversible,[6] or to side-reactions' occurring during the alkaline hydrolysis of the diastereoisomeric β-hydroxy-esters.

If the Reformatsky reaction were reversible under the conditions used, a first-order asymmetric transformation [7] could occur, and it would be difficult to ascertain whether the initial addition led to two diastereoisomeric β-hydroxy-esters in unequal amounts, or whether the two hydroxy-esters were formed in equal amounts and subsequent first-order asymmetric transformation gave an apparent asymmetric synthesis. Hauser and Puterbaugh [6] have shown that, since the Reformatsky reaction is reversible, only a 1% yield of ethyl β-hydroxy-β-phenylbutyrate is obtained when zinc, acetophenone, and ethyl bromoacetate are heated together in boiling benzene–toluene (1 : 1) for 29 hours, as compared with 60% when the reaction is carried out in benzene and heating is continued for only 75 minutes.

In the present work with (—)-menthyl bromoacetate it has been shown that heating the benzene reaction mixture for 20 hours or for 1 hour gives the same degree of asymmetric synthesis and the same yield. Reaction in toluene gave the β-hydroxy-acid with about one-third of the previous optical purity but had little effect on the yield. Thus reversibility is of little importance in determining the degree of asymmetric synthesis, at least when benzene is the solvent. This conclusion is supported by the fact that (—)-menthyl (+)-β-hydroxy-β-phenylbutyrate could be recovered in quantitative yield, and with unchanged specific rotation, after it had been heated in ether with methylmagnesium bromide.

Moreover, it has now been shown that apparent asymmetric synthesis does not arise as a result of side reactions occurring during the alkaline hydrolysis of the β-hydroxy-ester; of these side reactions alkali-catalysed cleavage of the αβ-bond,[8] $R'R''C(OH){\cdot}CH_2{\cdot}CO_2R \longrightarrow R'R''CO + CH_3{\cdot}CO_2R$, appeared the most likely, and it would probably occur at different rates with the two diastereoisomers. So attempts were made to remove the (—)-menthyl group by reducing the ester with lithium aluminium hydride instead of by alkaline hydrolysis. Although the hydride reduction of ethyl (±)-β-hydroxy-β-phenylbutyrate to (±)-3-phenylbutane-1,3-diol was satisfactory, that of the (—)-menthyl ester did not proceed to completion under the conditions we used and, moreover, the last traces of (—)-menthol could not readily be removed from the diol. It is of interest that the diol obtained from an ester of the dextrorotatory hydroxy-acid was lævorotatory, whereas L-β-hydroxybutyric acid and L-butane-1,3-diol are dextrorotatory.[9]

Consequently the two pure diastereoisomeric (—)-menthyl β-hydroxy-β-phenylbutyrates were required for a study of the effects of alkali on them. In preliminary experiments attempts to esterify the racemic hydroxy-acid by using an ion-exchange resin, " Zeo Karb 225-H," as catalyst,[10] gave only β-methylcinnamic acid. Accordingly, a Reformatsky reaction was carried out in order to obtain a mixture of the two diastereoisomeric esters, from which the ester of the (+)-hydroxy-acid could be isolated in an optically pure condition by fractional crystallisation; however, the ester of the (—)-hydroxy-acid was not obtained optically pure (see below). The (—)-menthyl (—)-β-hydroxy-β-phenylbutyrate could be separated only if the mixture of diastereoisomerides,

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[5] Ritchie, " Asymmetric Synthesis and Asymmetric Induction," Oxford University Press, 1933, p. 110; Reid and Turner, *J.*, 1951, 3219.

[6] Hauser and Puterbaugh, *J. Amer. Chem. Soc.*, 1953, **75**, 4756.

[7] Turner and Harris, *Quart. Rev.*, 1947, **1**, 299.

[8] Ivanov, *Bull. Soc. chim. France*, 1933, **53**, 321.

[9] Lemieux and Giguere, *Canad. J. Chem.*, 1951, **29**, 678.

[10] Sussman, *Ind. Eng. Chem.*, 1946, **38**, 1228.

obtained from the Reformatsky reaction, was not allowed to solidify completely, but the first crop of crystals was removed; then the ester of the (—)-hydroxy-acid could be obtained by recrystallisation of the solidified residual oil. Hydrolysis of the separated (—)-menthyl β-hydroxy-β-phenylbutyrates, and of mixtures thereof, in all cases gave the hydroxy-acid in about 90% yield, only very small amounts of acetophenone being isolated (as the 2,4-dinitrophenylhydrazone) from the hydrolysates. There was a linear relation between the corresponding values for the specific rotations of mixtures of the diastereoisomeric esters and those of the β-hydroxy-acids derived therefrom, thus:

[α] of ester in C_6H_6	−31·3°	−38·5°	−47·2°	−56·3°	−61·2°	−69·0°
[α] of acid in EtOH	+8·92°	+5·94°	+1·0°	−2·59°	−5·12°	−7·40°

These results show conclusively that an asymmetric synthesis of the order of 30% could not occur as a result of preferential decomposition of one of the diastereoisomerides under the action of alkali. Incidentally, it may be calculated that the specific rotation of (—)-menthyl (—)-β-hydroxy-β-phenylbutyrate is about —71°, and the optically impure ester referred to above would be about 95% pure. Thus, the specific rotation (—45·3°) of the mixture of diastereoisomeric esters isolated from the Reformatsky reaction mixture corresponded to about 30% asymmetric synthesis, a result in good agreement with that originally calculated from the specific rotation of the β-hydroxy-acid obtained.

Attempts were also made to analyse the mixtures of the diastereoisomeric esters spectroscopically; however, the infrared and ultraviolet absorption spectra of the two esters showed no fundamental differences. In cyclohexane an absorption maximum occurs at 258 mμ, and in carbon tetrachloride there is strong absorption in the region 850—1750 cm.$^{-1}$; in these regions absorption would be due in part to the phenyl group and to the ester group. No absorption occurs in the region 3650—3590 cm.$^{-1}$ which is characteristic for the free hydroxyl group;[11] but there is strong absorption at 2801, 2871, and 3363 cm.$^{-1}$. These last frequencies come within the range characteristic of polymeric intermolecular hydrogen bonding associated with the hydroxyl group (3400—3200 cm.$^{-1}$), and of strong intramolecular hydrogen bonding associated with chelate compounds (3200—2500 cm.$^{-1}$). Thus, it appears that, in both diastereoisomerides, there is strong intramolecular hydrogen bonding between the β-OH group and the C=O of the ester group, the configuration at the β-carbon atom having no effect on this.

The lower degree of asymmetric synthesis in a Reformatsky reaction in toluene, apparently not attributable to reversibility of the reaction, could be due to a difference in the temperature coefficient for the formation of each of the two diastereoisomerides.[12] The use of boiling ether–benzene in place of benzene alone slightly increased the degree of asymmetric synthesis, and use of ether alone led to a slight further increase. Attempts to carry out reactions in benzene or in toluene below their boiling points were unsuccessful; accordingly it has not so far been possible to show whether the degree of asymmetric synthesis depends solely on the temperature or also on the solvent.

A Reformatsky reaction using ether alone as solvent could be accomplished only when activated zinc was used. The use of activated zinc also enabled a Reformatsky reaction to be effected under homogeneous conditions (cf. ref. 2). Thus, interaction of activated zinc and (—)-menthyl bromoacetate in ether gave an intermediate which, on treatment with acetophenone and subsequently with dilute acid, furnished the β-hydroxy-ester. Under these conditions (" two-stage " reaction) the specific rotation of the β-hydroxy-acid was more variable ([α] +3·01° to +3·78°) than in the " classical one-stage " Reformatsky reaction; however, the average specific rotation of the product was the same as that from a one-stage reaction in ether. Control experiments showed that the use of activated zinc in classical Reformatsky reactions with benzene as solvent did not affect the degree of

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[11] Bellamy, " The Infra-red Spectra of Complex Molecules," Methuen and Co. Ltd., London, 1954, p. 84.

[12] Kenyon and Partridge, *J.*, 1936, 1313; Balfe, Kenyon, and Waddan, *J.*, 1954, 1366.

asymmetric synthesis. It has been suggested by Arcus and Smyth [13] that a marked degree of asymmetric synthesis in the Reformatsky reaction might arise as result of reaction on the surface of the zinc metal. However, results from the above type of experiment show conclusively that this is not the case. It is of interest that the specific rotation of the products obtained from " two-stage " reactions were not so consistent as when the " classical " conditions were used; in fact the results were more reminiscent of those obtained in the McKenzie type of asymmetric synthesis, to which the reaction conditions more closely approximated.

The addition of 1½ molecular proportions of a halide of a Group II metal to the Reformatsky reaction mixture had little effect on the specific rotation of the β-hydroxy-acid (addition of magnesium bromide had the most marked effect, causing a decrease of [α] from +2·68° to +2·02°); however, the yield was markedly affected. Thus, with cadmium bromide, zinc bromide, and magnesium bromide, the yields were respectively 120%, 65%, and 40% of that obtained in the absence of these salts. Despite the lower yield obtained with the use of magnesium bromide, the conjoint use of magnesium metal (in place of zinc) and magnesium halide (iodide) gave the β-hydroxy-acid in the same yield, and of the same optical purity as that obtained from a " classical " Reformatsky reaction. Indeed, as was shown by using the ethyl ester in place of the (—)-menthyl ester, there was some reaction with magnesium iodide alone, although none occurred with magnesium alone.

Adding catalytic amounts of cobaltous chloride to the reaction mixture gave a small increase in yield of the β-hydroxy-acid, but did not affect its specific rotation. In view of this result, together with the lack of effect of iodine on the degree of asymmetric synthesis, it appears that asymmetric synthesis does not arise as the result of a radical mechanism. However, a fuller investigation into the effects of adding halides of Group II metals to the Reformatsky reaction mixture might well help in elucidating the mechanism of this reaction, about which little is known.

The use of iodoacetate in place of the bromoacetate had no effect on either the yield or the specific rotation of the hydroxy-acid. No reaction occurred with the chloroacetate, even when promoters such as cupric chloride [14] were added.

Asymmetric syntheses were also achieved by treatment of (—)-menthyl bromoacetate and acetophenone in benzene solution with ethereal di-n-propyl-cadmium [15] or -zinc. The former reagent led to an increase of 80% in the degree of asymmetric synthesis, whereas the latter gave a 30% increase, as compared with results from a " two-stage " reaction to which these conditions most closely approximated. It thus appears that the size of the organometallic group is of importance; however, these results will have to be considered in the light of results from experiments with reactants other than (—)-menthyl bromoacetate and acetophenone.

Experiments were also carried out using " classical " Reformatsky conditions, but with esters $Br{\cdot}CH_2{\cdot}CO_2R'$, other than the (—)-menthyl ester, in order to determine the effect of the group R′ on the degree of asymmetric synthesis. From (+)- or (—)-1-methylheptyl bromoacetate the racemic β-hydroxy-acid was obtained; this was the case even when di-n-propylcadmium was used as the " condensing agent." However, (+)-s-butyl bromoacetate gave a (+)-hydroxy-acid having [α] +0·43°; a similar result was obtained when di-n-propylzinc was used as " condensing agent." These last results should be treated with reserve in view of the solubility of butan-2-ol in water and the consequent difficulty of removing it from the aqueous hydrolysate. Both (—)-α-fenchyl and (—)-bornyl bromoacetate gave lævorotatory β-hydroxy-acid, the degree of asymmetric synthesis being respectively about ½ and ¼ of that from the (—)-menthyl ester. Thus, the (—)-bornyl ester gives the β-hydroxy-acid of opposite configuration to that obtained from the

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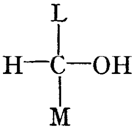
[13] Arcus and Smyth, *J.*, 1955, 34.
[14] Miller and Nord, *J. Org. Chem.*, 1951, **16**, 728.
[15] Cason and Fessenden, *ibid.*, 1957, **22**, 1326.

(—)-menthyl ester. This is in contradistinction to results obtained in McKenzie type asymmetric syntheses which have been summarised by Prelog[16] as follows: if the benzoylformate of an optically active alcohol is treated with methylmagnesium iodide, and the resulting ester is hydrolysed to atrolactic acid, then alcohols the absolute configuration of which may be represented as



$$\begin{array}{c} L \\ | \\ H\text{—}C\text{—}OH \\ | \\ M \end{array}$$

(where M and L represent medium and large substituents respectively) will give a lævorotatory specimen of atrolactic acid. Both (—)-menthol and (—)-borneol should, and do indeed, give lævorotatory specimens of atrolactic acid. Since, however, in the Reformatsky reaction, these two alcohols lead to products of opposite configuration, it appears that no simple relation exists between the configuration of the alcohol and that of the resulting acid. These results will be discussed in a future publication in conjunction with results obtained with carbonyl compounds other than acetophenone.

EXPERIMENTAL

Rotations were measured at 25°, the length of the tube being 1 dm. for undiluted liquids and 2 dm. for solutions. Sodium light (D line) was used.

Optically Active Esters of Halogeno-acetic Acids.—Esters of the α-chloro- and α-bromo-acid were prepared by adding the optically active alcohol (1 mol.) to the α-chloro-acyl chloride or the α-bromo-acyl bromide (1·15 mol.) at room temperature with shaking. The mixture was heated at 100° for 1 hr., then dissolved in ether. The solution was washed with 10% aqueous sodium carbonate and dried (Na_2SO_4). The ester was isolated and purified by fractional distillation, except for (—)-menthyl chloroacetate which was recrystallised from 96% ethanol.

(—)-Menthyl iodoacetate was prepared by heating a methanolic solution of (—)-menthyl chloroacetate with potassium iodide.

The physical constants obtained for those esters ($Hal{\cdot}CH_2{\cdot}CO_2R$), which have been reported previously, are recorded below:

R	Hal.	B. p./mm.	M. p.	α (Homogeneous)	[α] (*c*, solvent)	Ref.
(—)-Menthyl	Cl		38·5—39·5°		—80·0° (1·63, $CHCl_3$)	17
(—)-Menthyl	Br	74°/0·05	19·5—20·5	—74·85°		18, 1
(+)-1-Methylheptyl	Br	91/1·5		+13·05		19
(—)-1-Methylheptyl	Br	85/0·9		—12·25		19
(—)-Bornyl	Br	104/0·8		—40·44	—30·2 (7·46, EtOH)	20
(—)-Menthyl	I	117—120/0·9		—67·28		17

(—)-α-*Fenchyl bromoacetate* had b. p. 83°/0·2 mm., n_D^{25} 1·4887, d_4^{25} 1·2640, [α] —41·91° (Found: C, 52·75; H, 6·85. $C_{12}H_{19}O_2Br$ requires C, 52·4; H, 6·95%).

(+)-*s-Butyl bromoacetate*, prepared from (+)-butan-2-ol[21] of 95% optical purity, had b. p. 72·5°/14 mm., n_D^{25} 1·4465, d_4^{25} 1·3250, [α] +19·83° (Found: C, 37·0; H, 5·65. $C_6H_{11}O_2Br$ requires C, 36·95; H, 5·65%).

Reaction of Acetophenone with (—)-Menthyl Bromoacetate.—(a) *In presence of zinc metal: "classical Reformatsky conditions."* A solution of (—)-menthyl bromoacetate (6·31 g., 0·023 mole) and acetophenone (2·66 g., 0·022 mole) in benzene (30 ml.) was heated under reflux, in the presence of zinc wool (1·55 g., 0·024 g.-atom), for 4 hr. The liquid was decanted from unchanged zinc (0·06 g.) which was washed with ether and then with water. The combined liquids were mixed with ice (5 g.) and 5N-sulphuric acid (20 ml.), and the aqueous layer was extracted with ether (3 × 25 ml.). The combined ethereal extracts and the benzene solution

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[16] Prelog *et al.*, *Helv. Chim. Acta*, 1953, **36**, 308, 320.

[17] Cohen, *J.*, 1911, **99**, 1058.

[18] Smiles, *J.*, 1905, **87**, 450; Christopher and Hilditch, *J.*, 1912, **101**, 202.

[19] Rule and Mitchell, *J.*, 1926, 3202.

[20] Minguin and De Bollemont, *Compt. rend.*, 1902, **134**, 608.

[21] Pickard and Kenyon, *J.*, 1911, **99**, 45; Hauser and Kantor, *J. Amer. Chem. Soc.*, 1953, **75**, 1744.

were washed with water (3 × 25 ml.) and dried (Na_2SO_4). Removal of the solvent, finally under reduced pressure, gave an oil (6·8 g.) which slowly deposited crystals.

The product (" ester ") was hydrolysed by boiling 2·5N-potassium hydroxide (11 ml.) and 96% ethanol (25 ml.) for 4 hr. The mixture was diluted with water (20 ml.), and the alcohol removed under reduced pressure at 60°. The aqueous residue was extracted with ether (2 × 25 ml., 3 × 10 ml.) to remove neutral compounds, *e.g.*, (—)-menthol, then acidified with 5N-sulphuric acid. The β-hydroxy-β-phenylbutyric acid was extracted with ether (3 × 25 ml., 2 × 10 ml.), and the ethereal extracts were washed with water (3 × 10 ml.) and dried (Na_2SO_4). Removal of the ether gave β-hydroxy-β-phenylbutyric acid (2·56 g., 64%), m. p. 68—70°, [α] +2·62° (*c* 10·87 in EtOH) [Found: C, 66·3; H, 6·65%; *M* (by titration), 178. Calc. for $C_{10}H_{12}O_3$: C, 66·7; H, 6·7%; *M*, 180].

In a similar experiment benzene–ether (10 ml.: 5 ml.) was used instead of benzene. The β-hydroxy-β-phenylbutyric acid (yield 64%) isolated had [α] +3·03° (*c* 7·33 in EtOH).

When the benzene was replaced by toluene (40 ml.) the resulting acid (yield 58%) had [α] +0·85° (*c* 10·36 in EtOH).

Results from typical experiments in which benzene was the solvent, but in which the duration of heating of the Reformatsky reaction mixture was varied are:

	β-Hydroxy-β-phenylbutyric acid		
Duration of heating	Yield (%)	[α]	*c* (in EtOH)
1 hour	64	+2·75°	11·03
10 hours	60	+2·57	10·83
20 hours	55	+2·32	10·55

Experiments, with benzene as solvent, were also performed in which various " potential catalysts " were added to the reaction mixture:

	β-Hydroxy-β-phenylbutyric acid		
Catalyst (mol. propn.)	Yield (%)	[α]	*c* (in EtOH)
$CoCl_2$ (0·05)	76	+2·67°	10·52
$MgBr_2$ (1·5)	26	+2·04	8·80
$ZnBr_2$ (1·5)	42	+2·20	7·63
$CdBr_2$ (1·5)	77	+2·63	10·07

(b) *In the absence of zinc metal: " 2-stage reaction."* Zinc (4·7 g., 0·072 g.-atom) was activated by heating it with a crystal of iodine at 1 mm. pressure until a white sublimate appeared on the walls of the flask, and then allowing the whole to cool *in vacuo*. (—)-Menthyl bromoacetate (10·2 g., 0·037 mole) was added to the activated zinc, suspended in ether (50 ml.), with vigorous stirring. A few drops of an ethereal solution of methylmagnesium iodide were added to the mixture, which was then heated under reflux for 90 mins., whilst stirring was continued. To the ethereal solution which had been decanted from zinc, acetophenone (5·0 g., 0·042 mole) was added, and the mixture was then heated under reflux for 2 hr., worked up as described under (a), and then hydrolysed. β-Hydroxy-β-phenylbutyric acid (2·33 g., 37%) was obtained as an oil which when kept gave a solid, m. p. 67—68°, [α] +3·01° (*c* 9·6 in EtOH) (Found: C, 66·65; H, 6·7. Calc. for $C_{10}H_{12}O_3$: C, 66·7; H, 6·7%).

(c) *With di-n-propylcadmium as " condensing agent."* Cadmium chloride (6·24 g., 0·034 mole) was added in one batch to the Grignard reagent prepared from n-propyl bromide (8·0 g., 0·065 mole), and the mixture heated under reflux for 90 min., after which it gave a negative Gilman test for a Grignard reagent. To this grey suspension was added a solution of (—)-menthyl bromoacetate (5·5 g., 0·02 mole) and acetophenone (2·4 g., 0·02 mole) in benzene (18 ml.). After the mixture had been heated for 6 hr. it was worked up essentially as described under (a) above, and hydrolysed. The resulting β-hydroxy-β-phenylbutyric acid (2·45 g., 68%) had m. p. 68°, [α] +5·42° (*c* 9·05 in EtOH) [Found: *M* (by titration), 176. Calc. for $C_{10}H_{12}O_3$: *M*, 180].

(d) *With di-n-propylzinc as " condensing agent."* A solution of di-n-propylzinc was prepared from zinc bromide (3·95 g., 0·018 mole), by a procedure similar to that used for the preparation of the cadmium analogue. To this ethereal solution were added (—)-menthyl bromoacetate (5·5 g., 0·02 mole) and acetophenone (2·5 g., 0·02 mole) in benzene (18 ml.). The mixture was heated for 6 hr. and worked up in the usual manner. β-Hydroxy-β-phenylbutyric acid (2·37 g., 66%) obtained had m. p. 70°, [α] +3·95° (*c* 7·60 in EtOH) (Found: *M*, 177. Calc. for $C_{10}H_{12}O_3$: *M*, 180).

(e) *With magnesium iodide–magnesium as "condensing agent."* Iodine (7·62 g., 0·06 g.-atom) was added to a stirred suspension of magnesium (2·4 g., 0·10 g.-atom) in ether (40 ml.). To this suspension of magnesium in ethereal magnesium iodide were added acetophenone (3·6 g., 0·03 mole) and then (−)-menthyl bromoacetate (2·9 g., 0·01 mole) in benzene (10 ml.) with stirring. Ice (10 g.) and 5N-sulphuric acid were added to the cooled mixture after it had been heated under reflux for 4 hr. β-Hydroxy-β-phenylbutyric acid (1·2 g., 63%), which was obtained in the usual manner, had m. p. 60—64°, [α] +2·78° (*c* 6·77 in EtOH) (Found: *M*, 175).

Reaction of Acetophenone with Esters of Bromoacetic Acid other than (−)-*Menthyl Esters.*—Analogous experiments, under similar conditions, are recorded in the annexed Table. The bromo-esters $BrCH_2\cdot CO_2R'$ were optically active.

R′	Method	β-Hydroxy-β-phenylbutyric acid Yield (%)	[α]	*c* (in EtOH)
(+)-s-Butyl	(a) benzene as solvent (no catalyst)	82	+0·43°	10·68
(−)-1-Methylheptyl		80	0	10·14
(+)-1-Methylheptyl		76	0	9·99
(−)-Bornyl		79	−1·13	11·87
(−)-α-Fenchyl		56	−0·60	10·02
(−)-1-Methylheptyl	(c)	56	0	9·16
(+)-s-Butyl	(d)	77	+0·64	11·99

(±)-β-*Hydroxy*-β-*phenylbutyric Acid and the Ethyl Ester.*—Experiments were carried out similar to those described above but with ethyl bromoacetate in place of an optically active ester. Procedure (a) gave ethyl β-hydroxy-β-phenylbutyrate, b. p. 98—100°/1·2 mm. (lit.,[22] b. p. 146—148°/15 mm.), n_D^{25} 1·5027. This ester on hydrolysis gave the hydroxy-acid, m. p. 71—72° (lit.,[1] m. p. 71—72°) whose S-*benzylthiouronium salt* had m. p. 85—86° (Found: N, 8·0; S, 9·25. $C_{18}H_{22}O_3N_2S$ requires N, 8·1; S, 9·25%).

Procedure (c) gave the ethyl ester in 60% yield, procedure (d) in 61% yield, and procedure (e) in 43% yield.

Reaction of Acetophenone with (−)-*Menthyl Iodoacetate.*—A suspension of zinc (1·31 g.) in a solution of acetophenone (1·21 g.) and (−)-menthyl iodoacetate (3·23 g.) in benzene (10 ml.) was heated under reflux for 4 hr. The mixture was worked up and the β-hydroxy-β-phenylbutyric acid (1·12 g., 62%) isolated as described under (a); it had [α] +2·11° (*c* 10·98 in EtOH).

Separation of a Mixture of the Diastereoisomeric (−)-*Menthyl* β-*Hydroxy*-β-*phenylbutyrates.*—A mixture of the two diastereoisomeric esters (15·7 g.) was obtained, as an oil, from (−)-menthyl bromoacetate (13·5 g.) by using "classical" Reformatsky conditions (method a). This oil, which had [α] −45·3° (*c* 2·0 in benzene), gradually deposited crystals which were collected and washed with light petroleum (b. p. 40—60°) (10 ml.). This solid, which had m. p. 74·5—76°, [α] −38·3° (*c* 2·04 in benzene), after three recrystallisations from light petroleum (b. p. 40—60°), gave (−)-*menthyl* (+)-β-*hydroxy*-β-*phenylbutyrate* (5·22 g.) as needles, m. p. 80—80·5°, [α] −31·3° (*c* 2·02 in benzene) (Found: C, 75·85; H, 9·5. $C_{20}H_{30}O_3$ requires C, 75·45; H, 9·5%).

The oil, from which the solid had been removed, crystallised when kept; this solid had m. p. 46—51°, [α] −60·77° (*c* 2·01 in benzene). No apparent optical purification was effected by recrystallisation from aqueous ethanol; however, two further recrystallisations from small volumes of light petroleum (b. p. 40—60°) gave (−)-menthyl (−)-β-hydroxy-β-phenylbutyrate (0·55 g.) of about 95% optical purity; it had m. p. 60·5—61°, [α] −69·0° (*c* 2·00 in benzene) (Found: C, 75·55; H, 9·15. $C_{20}H_{30}O_3$ requires C, 75·45; H, 9·5%).

Hydrolysis of the Diastereoisomeric (−)-*Menthyl* β-*Hydroxy*-β-*phenylbutyrates.*—(−)-Menthyl (+)-β-hydroxy-β-phenylbutyrate (2·0 g., 0·006 mole) was heated under reflux with 2·5N-potassium hydroxide (3·1 ml.) and 96% ethanol (7 ml.) for 4 hr. The alcohol was then removed by distillation, and the aqueous residue was extracted with ether to remove neutral compounds, as described previously. Acidification of the alkaline solution and ether-extraction gave (+)-β-hydroxy-β-phenylbutyric acid (1·1 g., 90%), m. p. 82—83°, [α] +8·92° (*c* 1·76 in EtOH) {lit.,[4] m. p. 79—80°, $[\alpha]^{23}_{5780}$ −8·0°, $[\alpha]^{23}_{5461}$ −8·9° (*c* 1·75 in EtOH)} (Found: C, 66·75; H, 6·65. Calc. for $C_{10}H_{12}O_3$: C, 66·7; H, 6·7%).

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[22] Hauser and Lindsay, *J. Amer. Chem. Soc.*, 1955, **77**, 1050.

The ethereal solution, containing neutral compounds, was dried (Na_2SO_4) and evaporated to dryness. The residue, on treatment with 2,4-dinitrophenylhydrazine sulphate in methanol, gave only a trace of acetophenone 2,4-dinitrophenylhydrazone, m. p. 250° (Found: N, 18·15. Calc. for $C_{14}H_{12}O_4N_2$: N, 18·65%).

Hydrolyses of various mixtures of the two diastereoisomeric esters are summarised in the discussion section.

(±)-3-*Phenylbutane*-1,3-*diol.*—Ethyl β-hydroxy-β-phenylbutyrate (13·2 g., 0·063 mole) in ether (50 ml.) was added dropwise to a stirred suspension of lithium aluminium hydride (5·82 g., 0·153 mole) in ether (75 ml.), and the mixture was kept at room temperature for two days. Water (10 ml.) and 5N-sulphuric acid (75 ml.) were then added. The aqueous layer was extracted with ether, and the combined ethereal solutions were washed with water and dried (Na_2SO_4). Distillation of this solution gave (±)-3-phenylbutane-1,3-diol (5·47 g., 53%), b. p. 119·5°/0·75 mm., n_D^{25} 1·5355, m. p. 45—46° (it has been described as a liquid,[23] b. p. 134—136°/1 mm., 108—110°/0·5 mm., n_D^{26} 1·5320). In pyridine–benzene it gave the 1-p-*nitrobenzoate*, m. p. 91·5—92° (from aqueous methanol) (Found: C, 65·0; H, 5·55; N, 4·55. $C_{17}H_{17}O_5N$ requires C, 64·75; H, 5·55; N, 4·45%).

(−)-3-*Phenylbutane*-1,3-*diol.*—(−)-Menthyl (+)-β-hydroxy-β-phenylbutyrate (2·0 g., 0·006 mole) in ether (50 ml.) was added to lithium aluminium hydride (0·49 g., 0·013 mole) suspended in ether (75 ml.). The mixture was heated under reflux for 3 hr., then 2N-sulphuric acid was added. The aqueous layer was extracted with ether, and the combined ethereal solutions were washed with water and dried ($MgSO_4$). After removal of the ether, the residue was sublimed at 50—70°/0·2 mm. Fractional crystallisation of the residue (1·25 g.) from 1 : 1 benzene–light petroleum (b. p. 100—120°) gave (−)-3-*phenylbutane*-1,3-*diol*, m. p. 62·5°, [α] −56·82° (*c* 1·61 in benzene) (Found: C, 71·9; H, 8·55. $C_{10}H_{14}O_2$ requires C, 72·25; H, 8·5%). Unchanged (−)-menthyl β-hydroxy-β-phenylbutyrate (0·1 g.), m. p. 80—80·5°, was isolated from the aqueous methanolic mother-liquors.

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[23] Papa, Ginsberg, and Villani, *ibid.*, 1954, **76**, 4441; Price, Benton, and Schmidle, *ibid.*, 1949, **71**, 2860.