

335. *Partial Asymmetric Synthesis of β -Hydroxy-acids. Part II.*¹
Reaction of Aldehydes with Optically Active Halogeno-acetates.

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Reaction of benzaldehyde with (–)-menthyl bromoacetate in a Reformatsky reaction gives, after hydrolysis of the resulting ester, lævoro-rotatory β -hydroxy- β -phenylpropionic acid; the acid obtained with (–)-bornyl or with (–)- α -fenchyl bromoacetate is dextrorotatory. Slight asymmetric synthesis occurs on reaction of benzaldehyde with (+)-1-methylheptyl bromoacetate, the hydroxy-acid isolated being lævorotatory. These results are compared with those obtained from similar experiments¹ in which acetophenone was used in place of benzaldehyde.

Interaction of certain n-aliphatic aldehydes and (–)-menthyl bromoacetate gives ultimately hydroxy-acids which have slight optical activity or which are optically inactive.

Lævorotatory β -cyclohexyl- β -hydroxypropionic acid is ultimately obtained on reaction of cyclohexanecarboxaldehyde with (–)-menthyl bromoacetate.

THE occurrence of partial asymmetric synthesis in reactions such as the Reformatsky reaction, in which a new centre of asymmetry is formed when an organometallic compound containing a "fixed centre of asymmetry" adds to a carbonyl group, has hitherto been studied only with ketones.¹⁻³ This type of reaction has now been studied with aldehydes, certain of which have the advantage that they lead to β -hydroxy-acids of known configuration.

The condensation of acetophenone with optically active esters of monohalogenoacetic acids was studied earlier in some detail.¹ Similar experiments have now been carried out with benzaldehyde in place of acetophenone, with a view to ascertain how far the degree of asymmetric synthesis is affected by substituting a hydrogen atom for the methyl group, and whether variation of the dissymmetric group has the same effect in the two series of reactions on the sign and degree of optical rotation of the resulting β -hydroxy-acid. Interaction of benzaldehyde and (–)-menthyl bromoacetate in benzene solution in the presence of zinc wool ("classical Reformatsky conditions") gave a product which, on complete hydrolysis, yielded β -hydroxy- β -phenylpropionic acid with $[\alpha] -2.76^\circ$. Varying the volume of benzene did not affect the specific rotation of the product. From an earlier value⁴ for the optically pure hydroxy-acid it may be calculated that the product from such a Reformatsky reaction is about 15% optically pure.

It was shown in the analogous partial asymmetric synthesis of β -hydroxy- β -phenylbutyric acid that apparent asymmetric synthesis did not arise as a result of side reactions occurring during the alkaline hydrolysis of the mixture of diastereoisomeric esters;¹ thus, it seems unlikely that such side reactions would be of importance in the asymmetric

¹ Part I, Palmer and Reid, *J.*, 1960, 931.

² Reid and Turner, *J.*, 1949, 3365.

³ Sisido, Kumazawa, and Nozaki, *J. Amer. Chem. Soc.*, 1960, **82**, 125.

⁴ Kenyon, Phillips, and Shutt, *J.*, 1935, 1663.

synthesis of β -hydroxy- β -phenylpropionic acid. That this is so is supported by the fact that the hydrolysis of (–)-menthyl (–)- β -hydroxy- β -phenylpropionate gave the acid in good yield, and with a high degree of optical activity. This ester was obtained by repeated recrystallisation, to constant specific rotation, of a mixture of the diastereoisomeric (–)-menthyl β -hydroxy- β -phenylpropionates, prepared by catalytic hydrogenation of (–)-menthyl benzoylacetate. The specific rotation of the hydroxy-acid obtained by hydrolysis of this ester, under conditions similar to those used for the Reformatsky reaction products, was raised only slightly (from -17.6° to -18.4°) by recrystallisation from water, and then agreed with that determined by Kenyon *et al.*⁴ Unfortunately, the diastereoisomeric ester of the (+)-hydroxy-acid could not be obtained optically pure owing to its high solubility in diverse organic solvents.

Addition of zinc bromide to the Reformatsky reaction mixture had little effect upon either the degree of asymmetric synthesis or the yield of the hydroxy-acid. This is in contrast to the marked lowering of the yield of β -hydroxy- β -phenylbutyric acid in the analogous reaction with acetophenone, an effect which was presumably due to enolisation of the ketone. (The decreased yield was not due to the formation of 2,3-diphenylbutane-2,3-diol, since no diol could be isolated, and since acetophenone was recovered in good yield from a solution of acetophenone in benzene which had been heated with zinc-zinc bromide, and subsequently treated with dilute sulphuric acid.⁵)

The replacement of benzene by ether as solvent led to a marked increase in the degree of asymmetric synthesis (to 25%). With ether as solvent, zinc activated by being heated with iodine had to be used; however, it had been shown in the work with acetophenone that the use of activated zinc in "classical Reformatsky reactions" did not affect the degree of asymmetric synthesis. By the use of activated zinc it was possible to carry out a "2-stage reaction," that is, the bromo-ester was caused to react with the zinc metal, and the aldehyde was then added to the solution of the organometallic intermediate. The hydroxy-acid finally obtained from such experiments, metallic zinc being absent in the second stage, had similar specific rotation to that obtained in the presence of metallic zinc. The use of di-*n*-propylzinc as "condensing agent," in place of metallic zinc, caused a further increase in the degree of asymmetric synthesis (to 30%). The use of (–)-menthyl iodoacetate in place of the bromoacetate led to no marked change in the degree of asymmetric synthesis of β -hydroxy- β -phenylpropionic acid, or in the yield.

Under "classical Reformatsky conditions" the use of (–)-bornyl or (–)- α -fenchyl bromoacetate in place of the (–)-menthyl ester gave the same degree of asymmetric synthesis, and the (+)-1-methylheptyl bromoacetate caused slight asymmetric synthesis (the β -hydroxy- β -phenylpropionic acid had $\alpha -0.06^\circ$).

Quantitatively there are marked differences between these results and those obtained from analogous experiments with acetophenone in place of benzaldehyde. Thus, with (–)-menthyl bromoacetate although the degree of asymmetric synthesis from acetophenone was always greater than when from benzaldehyde, the use of "condensing agents" other than zinc caused with the latter a greater increase in asymmetric synthesis relative to that obtained under "classical Reformatsky conditions;" for example, with di-*n*-propylzinc as condensing agent a 100% increase was obtained in benzaldehyde experiments and only 50% in acetophenone experiments. Whereas the degree of asymmetric synthesis was greatly reduced with acetophenone under "classical Reformatsky conditions," when the (–)-menthyl ester was replaced by the (–)-bornyl or the (–)- α -fenchyl ester, this was not the case with benzaldehyde. Indeed, with the (–)- α -fenchyl ester the degree of asymmetric synthesis from benzaldehyde was about double that from acetophenone. In contrast to the present results, no asymmetric synthesis was observed on the interaction of (+)-1-methylheptyl bromoacetate and acetophenone even when di-*n*-propylcadmium, which with the (–)-menthyl ester had led to increased asymmetric synthesis, was used as the "condensing agent."

⁵ Palmer, unpublished observation.

The β -hydroxy- β -phenylpropionic acid obtained from the interaction of either (–)-menthyl or (+)-1-methylheptyl bromoacetate and benzaldehyde was lævorotatory, whereas (–)-bornyl or (–)- α -fenchyl bromoacetate led to a dextrorotatory product. In the analogous experiments with acetophenone, the (–)-bornyl or the (–)- α -fenchyl ester likewise led to β -hydroxy- β -phenylbutyric acid opposite in sign of rotation to that obtained with the (–)-menthyl ester.

Reaction of (–)-menthyl bromoacetate with certain n-aliphatic aldehydes under "classical Reformatsky conditions" yielded ultimately hydroxy-acids with little or no optical activity. The highest observed optical rotations (-0.05° in chloroform) were for 3-hydroxynonanoic and 3-hydroxydecanoic acid. In view of the low rotations these results must be treated with reserve; however, it is of interest that the 3-hydroxy-nonanoic⁶ and decanoic⁷ acids which are lævorotatory in chloroform are (*R*)-3-hydroxyalkanoic acids (I; R' = Alk), as is the 3-hydroxypentanoic acid⁸ which is lævorotatory in ethanol.

Further, (–)- β -hydroxy- β -phenylpropionic acid, which is the (*S*)-form,⁹ has also the configuration depicted in (I; R' = Ph). Thus, in all of these cases, the (–)-menthyl group causes a preponderance of that isomer which has the configuration shown in (I) to be formed.

Consequently, it is possible that the stereochemical course of addition to the carbonyl group may be correlated with the configuration of the dissymmetric group. However, since the (–)-bornyl ester leads to a hydroxy-acid with the opposite sign of rotation to that obtained from the (–)-menthyl ester, this cannot be a simple relation as is found in the addition of a Grignard reagent to an optically active ester of an α -keto-acid ($\text{CH}_3\cdot\text{CO}\cdot\text{CO}_2\cdot\text{CR}^1\text{R}^2\text{R}^3$). In the latter case the preferred course of addition may be correlated with the configuration of the group $-\text{CR}^1\text{R}^2\text{R}^3$ in terms of the relative steric effects of the three R-groups; thus, the (–)-menthyl group and the (–)-bornyl group direct addition to the carbonyl group in the same direction.¹⁰ The steric course of this type of addition may be considered as being determined by the relative availability of the two sides of the carbonyl group to attack by the "symmetrical" Grignard reagent, attack being preferred on that side of it which is least shielded by the "optically active group" when the ester has the most reactive conformation (cf. ref. 11). In the Grignard reaction the interaction of a "symmetrical" group with the optically active group is important, yet in the Reformatsky reaction, when the "optically active group" is in the organometallic reactant, steric interaction of *two* groups (those attached to the carbonyl group) with the optically active group will be of importance in determining the steric course of addition. The effect of change of dissymmetric group on the degree of asymmetric synthesis in reactions with benzaldehyde has indeed been shown to be different from that in reactions with acetophenone.

It seems, then, that in such reactions account must be taken of the relative steric effects of the groups attached to the carbonyl group considered in relation to the structure of the optically active group. Moreover, with esters of alcohols which have more than one asymmetric centre the configuration of the asymmetric centres other than that directly attached to the bromoacetoxy-group would appear to be of importance.

Although marked asymmetric synthesis has been observed only when a phenyl group is attached to the carbonyl group it is unlikely that an aryl group is essential, since β -cyclohexyl- β -hydroxypropionic acid of high specific rotation (-1.21°) was obtained on interaction of cyclohexanecarboxaldehyde and (–)-menthyl bromoacetate under "classical Reformatsky conditions," with subsequent hydrolysis of the product. However, until

⁶ Serck-Hanssen, *Chem. and Ind.*, 1958, 1554.

⁷ Serck-Hanssen and Stenhagen, *Acta Chem. Scand.*, 1955, 9, 866.

⁸ Serck-Hanssen, *Arkiv Kemi*, 1956, 10, 135.

⁹ Lukeš, Bláha, and Kovár, *Chem. and Ind.*, 1958, 527; Balenović, Urbas, and Deljac, *Croat. Chem. Acta*, 1959, 31, 153; Schöpf and Wüst, *Annalen*, 1959, 626, 150.

¹⁰ Prelog *et al.*, *Helv. Chim. Acta*, 1953, 36, 308, 320.

¹¹ Cornforth, Cornforth, and Mathew, *J.*, 1959, 112.

this hydroxy-acid has been resolved it is not possible to calculate the actual extent of asymmetric synthesis.

Factors similar to those described above were considered to be of importance by Sisido *et al.*³ in the asymmetric synthesis occurring in the condensation of the acetates of (–)-menthol and (+)-borneol with substituted benzo- and naphtho-phenones under the action of diethylaminomagnesium bromide.

EXPERIMENTAL

Rotations were measured at 25°, the length of the tube being 2 dm. Sodium light (D line) was used.

The optically active esters of the halogeno-acetic acids were prepared as described in Part I.¹

Reaction of Benzaldehyde with (–)-Menthyl Bromoacetate.—The procedures used for the “condensation” of the aldehyde with the ester, for the hydrolysis, and for the isolation of the resulting β -hydroxy-acid are essentially those described in Part I.¹ The results of representative experiments are given below. All “condensations” were carried out at least in duplicate.

(a) “*Classical Reformatsky conditions.*” A solution of (–)-menthyl bromoacetate (5.56 g., 0.02 mole) and benzaldehyde (2.13 g., 0.02 mole) in benzene (15 ml.) was heated under reflux, in the presence of zinc wool (1.34 g., 0.02 mole), for 4 hr. The mixture was poured on ice and 5*N*-sulphuric acid, and the aqueous layer was extracted with ether. The combined ethereal extracts, together with the benzene solution, were washed with water, and dried (Na₂SO₄). The oil remaining after removal of the solvent was boiled under reflux with aqueous-ethanolic potassium hydroxide for 4 hr. After addition of water the ethanol was distilled off under reduced pressure, and the aqueous residue was extracted with ether. The aqueous layer was acidified with 5*N*-sulphuric acid and extracted with ether; the combined ethereal extracts were washed with water and dried (Na₂SO₄). Removal of the ether under reduced pressure gave β -hydroxy- β -phenylpropionic acid (2.48 g., 74%), m. p. 87–90°, $[\alpha]$ –2.76° (*c* 10.66 in EtOH) (Found: C, 65.25; H, 6.05. Calc. for C₉H₁₀O₃: C, 65.05; H, 6.05%).

In a similar experiment when double the volume of benzene was used, the resulting β -hydroxy-acid (2.02 g., 61%) had $[\alpha]$ –2.90° (*c* 3.42 in EtOH).

When zinc bromide (6.66 g., 0.03 mole) was added to the benzene reaction mixture, the β -hydroxy- β -phenylpropionic acid (2.14 g., 64%) isolated had m. p. 93.5–94.5°, $[\alpha]$ –3.27° (*c* 10.65 in EtOH) (Found: C, 65.05; H, 6.15%).

(b) “*Two-stage reaction.*” To the solution obtained on interaction of (–)-menthyl bromoacetate (6.50 g., 0.024 mole) and “activated” zinc [prepared from zinc wool (2.7 g., 0.041 g.-atom)] suspended in ether (30 ml.) was added benzaldehyde (5.0 g., 0.047 mole). After the reaction mixture had been heated under reflux for 2 hr. it was worked up as described under (a). β -Hydroxy- β -phenylpropionic acid (1.70 g., 40%) thus obtained had $[\alpha]$ –4.39° (*c* 2.63 in EtOH) (Found: C, 64.7; H, 6.0%).

An experiment on the same scale in which an ethereal solution of the aldehyde and ester was heated in the presence of activated zinc furnished the hydroxy-acid (2.40 g., 63%) having $[\alpha]$ –4.80° (*c* 2.19 in EtOH) (Found: C, 64.75; H, 6.05%).

(c) “*With di-*n*-propylzinc as “condensing agent.”*” A solution of (–)-menthyl bromoacetate (2.8 g., 0.01 mole) and benzaldehyde (2.0 g., 0.02 mole) in benzene (10 ml.) was added to an ethereal solution of di-*n*-propylzinc [prepared from zinc bromide (1.97 g., 0.01 mole)] in ether (20 ml.). The mixture was heated under reflux for 6 hr. and worked up as described under (a). β -Hydroxy- β -phenylpropionic acid (0.9 g., 54%) thus obtained had m. p. 90–91°, $[\alpha]$ –5.65° (*c* 5.17 in EtOH) [Found: *M* (by titration), 164. Calc. for C₉H₁₀O₃: *M*, 166].

Reaction of Benzaldehyde with Esters of Bromoacetic Acid other than the (–)-Menthyl Ester.—The following results were obtained from typical experiments carried out under “classical Reformatsky conditions:”

Ester	β -Hydroxy- β -phenylpropionic acid		
	Yield (%)	$[\alpha]$	<i>c</i> (in EtOH)
(+)-1-Methylheptyl	84	–0.36°	8.27
(–)-Bornyl	76	+2.89	10.80
(–)- α -Fenchyl	88	+3.00	8.34

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Reaction of Benzaldehyde with (-)-Menthyl Iodoacetate.—A suspension of zinc (1.25 g., 0.019 mole) in a solution of benzaldehyde (0.94 g., 0.009 mole) and (-)-menthyl iodoacetate (2.55 g., 0.008 mole) in benzene (10 ml.) was heated under reflux for 4 hr., and the mixture was worked up as described above. β -Hydroxy- β -phenylpropionic acid (1.07 g., 79%) was thereby obtained; it had $[\alpha] -3.52^\circ$ (*c* 10.01 in EtOH) (Found: C, 65.25; H, 6.1%).

(-)-Menthyl (-)- β -Hydroxy- β -phenylpropionate.—(-)-Menthyl benzoylacetate was obtained in 56% yield by heating together ethyl benzoylacetate¹² and (-)-menthol at 160° until no more ethanol distilled over, and then fractionally distilling the residue. One crystallisation of the fraction having b. p. 168–169°/0.4 mm. from light petroleum (b. p. 40–60°) gave the keto-ester, m. p. 43–43.5°; it had initial specific rotation $[\alpha] -52.4^\circ$, changing to -56.5° in 6 hr. (*c* 10.00 in EtOH) {lit.,¹³ m. p. 41°, $[\alpha]_D^{20} -56.41^\circ$ (initial value) and -56.89° (final value) (*c* 10 in EtOH)}. The keto-ester gave the semicarbazone, m. p. 167° (lit.,¹³ 163°) (leaflets from ethanol), and the 2,4-dinitrophenylhydrazone, m. p. 177–178° (orange needles from acetone-ethanol) (Found: C, 62.15; H, 6.3; N, 11.6. $C_{25}H_{30}N_4O_6$ requires C, 62.25; H, 6.25; N, 11.6%).

(-)-Menthyl benzoylacetate (7.28 g.) in ethanol was hydrogenated in the presence of W-4 Raney nickel (0.3 g.) at atmospheric pressure and room temperature with shaking for 1½ hr. The mixture was filtered, and the solvent evaporated; the residual mixture of the diastereoisomeric (-)-menthyl β -hydroxy- β -phenylpropionates (7.35 g.) had m. p. 31.5–34°, $[\alpha] -56.1^\circ$ (*c* 1.50 in EtOH). Four recrystallisations of the mixture (11.9 g.) from small volumes of light petroleum (b. p. 40–60°) gave (-)-menthyl (-)- β -hydroxy- β -phenylpropionate (0.89 g.) as needles, m. p. 60.5–61.5°, $[\alpha] -58.31^\circ$ (*c* 1.49 in EtOH) (Found: C, 74.95; H, 9.15. $C_{19}H_{28}O_3$ requires C, 74.95; H, 9.25%). A second crop from the first mother-liquor of the recrystallisations gave, after three further recrystallisations from light petroleum (b. p. 40–60°) at -20° , a small amount of solid, m. p. 31–32°, $[\alpha] -55.7^\circ$ (*c* 1.50 in EtOH).

Hydrolysis of the (-)-menthyl (-)- β -hydroxy- β -phenylpropionate (0.8 g.), under our usual conditions, furnished the *lavo*-hydroxy-acid (0.4 g., 90%), m. p. 115°, $[\alpha] -17.6^\circ$ (*c* 4.02 in EtOH); after being recrystallised from water the acid had m. p. 116°, $[\alpha] -18.4^\circ$ (*c* 1.96 in EtOH) {lit.,⁴ m. p. 115–116°, $[\alpha]^{17} -19.0^\circ$ (*c* 5.13 in EtOH)}.

Reaction of (-)-Menthyl Bromoacetate with Aliphatic Aldehydes.—Experiments analogous to those described above under (a) are recorded below:

β -Hydroxyvaleric acid (58% yield) was obtained as an oil having $\alpha -0.03^\circ$ (*c* 3.07 in H_2O) [Found: *M* (by titration), 116. Calc. for $C_5H_{10}O_3$: *M*, 118].

3-Hydroxyhexanoic acid (71% yield) was obtained as an oil having no observable optical rotation in chloroform solution (Found: *M*, 128. Calc. for $C_6H_{12}O_3$: *M*, 132).

3-Hydroxynonanoic acid (84% yield) was obtained as needles, m. p. 58–59° (lit.,¹⁴ m. p. 59° for the racemate), $\alpha -0.05^\circ$ (*c* 10.26 in $CHCl_3$) (Found: C, 61.9; H, 10.25. Calc. for $C_9H_{18}O_3$: C, 62.05; H, 10.4%).

3-Hydroxydecanoic acid (75% yield) was obtained as needles, m. p. 55° (lit.,¹⁴ 56.5° for the racemate), $\alpha -0.05^\circ$ (*c* 9.63 in $CHCl_3$) (Found: C, 63.9; H, 10.55%; *M*, 185. Calc. for $C_{10}H_{20}O_3$: C, 63.8; H, 10.7%; *M*, 188). Similar results were obtained if hydrolysis was effected by keeping the alkaline solution of the ester at room temperature for 5 hours.

None of the products described above decolorised bromine in either water or carbon tetrachloride.

Partial Asymmetric Synthesis of β -Cyclohexyl- β -hydroxypropionic Acid.—Cyclohexanecarboxaldehyde was prepared by the addition of an ethereal solution of *NN*-dimethylformamide (35 g., 0.48 mole) to the Grignard reagent prepared from cyclohexyl chloride (62.3 g., 0.53 mole). The mixture was kept for 3 hr. at room temperature, and then 3*N*-hydrochloric acid (100 ml.) was added to it. The aqueous layer was extracted with ether, and the combined ethereal solutions were washed with water and dried (Na_2SO_4). The ether was distilled off, and the residue was shaken with aqueous sodium hydrogen sulphite. Treatment of the resulting solid (34 g.) with 10% aqueous sodium carbonate gave cyclohexanecarboxaldehyde, b. p. 90°/93 mm., $n_D^{25} 1.4525$ (lit.,¹⁵ $n_D^{19} 1.4495$).

A solution of (-)-menthyl bromoacetate (2.76 g., 0.01 mole) and cyclohexanecarboxaldehyde (1.14 g., 0.01 mole) in benzene (10 ml.) was heated under reflux, in the presence of zinc wool

¹² McElvain and Weber, *Org. Synth.*, 1943, **23**, 35.

¹³ Rupe and Lenzinger, *Annalen*, 1912, **395**, 87.

¹⁴ Skogh, *Acta Chem. Scand.*, 1952, **6**, 809.

¹⁵ Wallach and Isaac, *Annalen*, 1906, **347**, 316.

(1.31 g., 0.02 g.-atom) for 4 hr. The mixture, when worked up as described under (a) (classical Reformatsky conditions), gave β -cyclohexyl- β -hydroxypropionic acid (1.19 g., 69%), m. p. 74—75°, $[\alpha] -1.21^\circ$ (*c* 5.70 in EtOH) (Found: C, 62.95; H, 9.42. $C_9H_{16}O_3$ requires C, 62.75; H, 9.35%).

We thank Imperial Chemical Industries Limited and the Central Research Funds Committee of the University of London for grants, also the London County Council and the Governing Body of the College for a Research Assistantship (to M. H. P.).

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[Received, November 21st, 1961.]
