702. *Partial Asymmetric Synthesis in a Reformatsky Reaction.*

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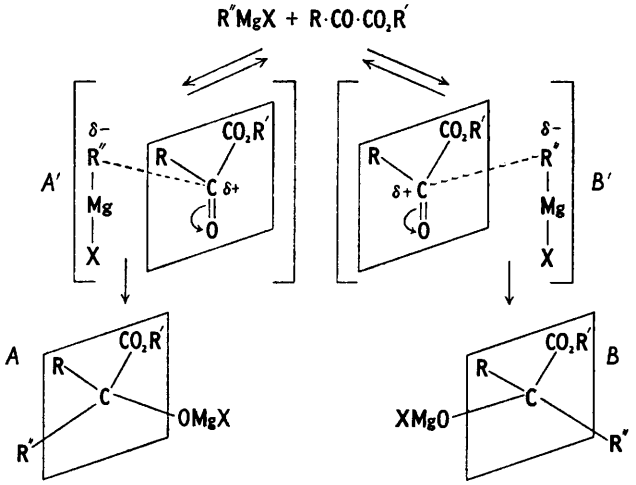
When acetophenone, (−)-menthyl bromoacetate, and zinc interact in benzene solution, a partial "asymmetric reaction" takes place, as is shown by the fact that the (−)-menthyl β-hydroxy-β-phenylbutyrate formed after acidification is hydrolysed to a (+)-rotatory β-hydroxy-β-phenylbutyric acid. Partial asymmetric synthesis can therefore occur during the addition of a dissymmetric reagent to a carbonyl group present in a molecule containing no "fixed centre of asymmetry."

The classical researches of McKenzie and his school (*J.*, 1904, **85**, 1249, etc.; *Ergeb. Enzymforsch.*, 1936, **5**, 49) showed that when a Grignard reagent, R″MgX, reacted with an α-keto-ester, R·CO·CO_2R′, where R′ is "optically active," there took place what was later termed an "asymmetric reaction" (Harris and Turner, *Quarterly Reviews*, 1948, **1**, 299), that is, the two diastereoisomerides *A* and *B* were formed in unequal amounts:

Replacement in the parent hydroxy-ester of the active group R′ by hydrogen gave unequal quantities of the free (+)- and (−)-hydroxy-acids, so that the whole process was an "asymmetric synthesis" in the original definition of the term. McKenzie was inclined to favour an explanation involving "induced asymmetry" in the carbonyl group undergoing reaction. Kenyon and Partridge (*J.*, 1936, 1313) took the view that collisions between molecules of the Grignard reagent and molecules of the keto-ester which led to one diastereoisomeric intermediate (*e.g.* *A*) were more likely to occur than those leading to the other, adding that "it is a difference in energy associated with the diastereoisomeric intermediate products which is responsible for the one-sided addition." Other considerations are, however, probably involved.

In the reaction between the Grignard reagent and the keto-ester, the two diastereoisomerides are admittedly formed in unequal quantities. Since, however, they are not interconvertible, mechanistic differentiation must be sought at the stage of the two corresponding transition states, from which they are formed irreversibly. The two transition states, *A′* and *B′*, (1) must have different energies, since they are of the nature of diastereoisomerides, and (2) are formed *reversibly* from the reactants. We thus have a mechanism whereby the route with the lower activation energy can be followed preferentially and an "asymmetric reaction" is possible. The process can be represented



The " equilibrium " between the two transition states bears a formal resemblance to that between two diastereoisomerides undergoing first-order asymmetric transformation.

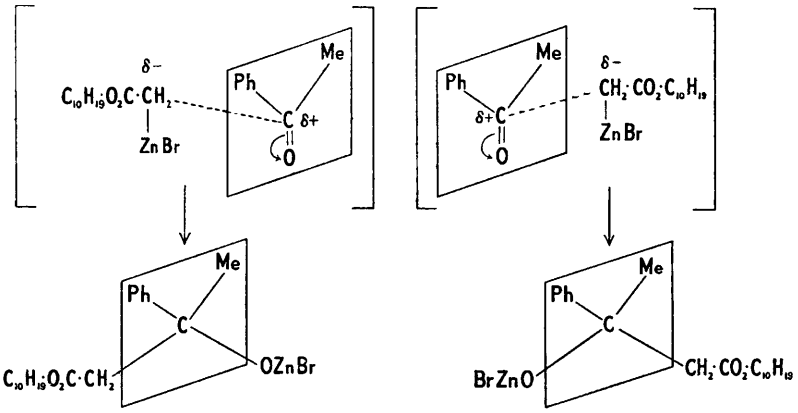
So far, an asymmetric reaction of the general type under discussion (*i.e.*, the addition of an organometallic compound to a carbonyl group) has only been observed when the " fixed centre of asymmetry " is in one of the groups attached to the carbonyl group, but two diastereoisomeric states corresponding to *A'* and *B'* could be predicted if there were an " optically active " group in the organometallic reactant and none in the carbonyl compound, provided the final stage in the synthesis leads to a new and formally asymmetric carbon atom. Such an " asymmetric reaction " could not be explained on the grounds of induced asymmetry in the carbonyl group.

We have accordingly examined the interaction of acetophenone with (−)-menthyl bromoacetate in benzene solution in the presence of zinc (Reformatsky reaction). Hydrolysis of the total (−)-menthyl β-hydroxy-β-phenylbutyrate formed gave a (+)-rotatory specimen of β-hydroxy-β-phenylbutyric acid. The experimental reproducibility of the result is shown by the following table, which gives the results of representative experiments.

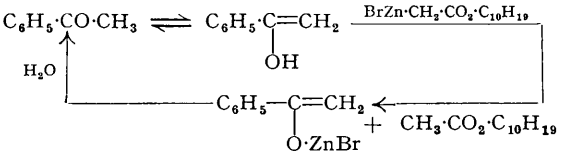
Ester, g. (g.-mol.).	Ketone, g. (g.-mol.).	Zinc, g. (g.-mol.).	Benzene, ml.	Reaction conditions.	Yield of acid, g. (%).	$[\alpha]^{25}_{6780}$ * ±0·05°.	$[\alpha]^{25}_{5461}$	Concn. (in EtOH).
5·87	2·40	1·39	30	Reactants mixed at once.	2·35	2·57°	2·89°	11·75
(0·0212)	(0·02)	(0·0212)		Boiled for 4½ hours.	(65)			
5·54	2·88	1·31	15	Reactants mixed at once.	1·80	2·31	2·57	9·00
(0·02)	(0·024)	(0·02)		Boiled for 3½ hours.	(50)			
5·54	2·40	1·96	15	Ester added during 3 hours.	1·975	2·43	2·70	9·88
(0·02)	(0·02)	(0·03)		Boiled for 4 hours.	(55)			
5·54	2·40	1·96	30	Ester added during 1 hour.	2·025	2·40	2·73	10·13
(0·02)	(0·02)	(0·03)		Boiled for 9½ hours.	(56)			
5·54	2·40	1·96	10	Mixed at once.	2·07	2·47	2·73	10·35
(0·02)	(0·02)	(0·03)		Boiled for 10½ hours.	(58)			
30·47	13·2	10·8	60	*Large scale experiment.*	—	2·34	2·64	9·10
(0·11)	(0·11)	(0·165)		Ester added during 7½ hours.	(53)			
				Boiled for 4 hours.		3·01	3·38	22·05

* All rotations are positive.

The two transition states and the two antepenultimate products in this asymmetric synthesis may be expressed as below :



The somewhat low yield (50—65%) may be attributed (cf. Hussey and Newman, *J. Amer. Chem. Soc.*, 1948, **70**, 3024) to loss of material by the side-reaction :



Acetophenone and acetic acid were in fact identified in the reaction product. Details of the synthesis are given in the experimental section. Care was naturally taken that no hydroxy-acid

was lost during the process. It may be noted that no interconversion of (+)- and (−)-forms could have occurred at the hydrolysis stage, since the new asymmetric carbon atom is not in the α-position with respect to the ester grouping.

The degree of asymmetric reaction (*i.e.*, the specific rotation of the product) showed no appreciable dependence on reaction conditions, such as the rate of mixing or the volume of solvent.

The specific rotation in ethyl alcohol of the β-hydroxy-β-phenylbutyric acid obtained was only slightly increased by crystallisation from light petroleum :

	$[\alpha]^{25}_{5780}$.	$[\alpha]^{25}_{5461}$.	*c*.
Crude acid	+2·67°	+3·02°	15·13
	+2·34	+2·64	9·10
Crystallised acid (m. p. 69—71°, indef.)	+2·79	+3·15	14·35
	+2·44	+2·73	7·74

As is seen from these figures, the specific rotation varies appreciably with concentration.

Racemic β-hydroxy-β-phenylbutyric acid was synthesised by the Reformatsky reaction from acetophenone and ethyl bromoacetate. It melted at 71—72°. Arbusov (*J. pr. Chem.*, 1901, (ii), **64**, 553), who described it as being formed by the oxidation of phenylmethylallylcarbinol, recorded m. p. 50—53°.

Experimental.

M. p.s are uncorrected. Most analyses are by Drs. Weiler and Strauss. Rotations were measured in all-glass water-jacketed tubes at 25° ± 0·01°, the length being 2 dm. unless otherwise stated.

(−)-*Menthyl Bromoacetate.*—(*a*) A mixture of bromoacetic acid (70 g., 0·05 g.-mol.) and menthol (300 g., 1·93 g.-mols.) was heated in the presence of dry hydrogen bromide for 8 hours at 100°. An ethereal solution of the reaction mixture was washed with 10% sodium carbonate solution and then with water, and dried (Na_2SO_4). (−)-Menthyl bromoacetate, containing a trace of menthol, was obtained from this solution by distillation; it had b. p. 108—116°/2—3 mm. (yield, 76·2 g., 55%). After one crystallisation from light petroleum (b. p. 40—60°) (−)-menthyl bromoacetate was obtained as needles, m. p. 18·5—19·5°, $[\alpha]^{25}_{5780}$ −68·3° ±0·2°, $[\alpha]^{25}_{5461}$ −77·4° ±0·2° (*c*, 2·5 in chloroform) (Found : C, 52·6; H, 7·77; Br, 28·3. Calc. for $C_{12}H_{21}O_2Br$: C, 52·0; H, 7·65; Br, 28·8%). The ester has been described hitherto as a liquid.

(*b*) (Cf. Smiles, *J.*, 1905, **87**, 454.) A solution of bromoacetic acid (78 g., 0·56 g.-mol.) in thionyl chloride (55 ml.) was boiled under reflux for 2½ hours, the reaction mixture then being distilled through a packed column; the bromoacetyl chloride had b. p. 121—125° (yield, 69 g., 78%). Menthol (67 g., 0·43 g.-mol.) was added to bromoacetyl chloride (67 g., 0·425 g.-mol.) at room temperature with shaking. After 15 minutes the reaction mixture was slowly warmed to 100° and kept at that temperature for 20 minutes. (−)-Menthyl bromoacetate, b. p. 136°/8 mm. (yield, 96·5 g., 82%), was isolated as in (*a*); after one crystallisation it had $[\alpha]^{25}_{5780}$ −68·9° ±0·2°, $[\alpha]^{25}_{5461}$ −78·0° ±0·2°, $[\alpha]^{21}_{D}$ −67·9° ±0·8° (*c*, 2·5 in chloroform) (Found : C, 52·1; H, 7·88; Br, 29·0. Calc. for $C_{12}H_{21}O_2Br$: C, 52·0; H, 7·65; Br, 28·8%).

Partial Asymmetric Synthesis of β-Hydroxy-β-phenylbutyric Acid.—A solution of (−)-menthyl bromoacetate (30·47 g., 0·11 g.-mol.) in benzene (10 ml.) was added dropwise with mechanical stirring, during 7½ hours, to a boiling solution of acetophenone (13·2 g., 0·11 g.-mol.) in benzene (50 ml.; thiophen-free) in the presence of zinc needles (10·8 g., 0·165 g.-atom). Boiling and stirring were continued for a further 4 hours after addition was completed. The reaction mixture was kept overnight at room temperature, and finally the liquid was decanted from unreacted zinc (3·68 g., 0·0564 g.-atom) which was washed with ether and water. The combined liquids were treated with ice (25 g.) and 5N-sulphuric acid (100 ml.). The aqueous layer was extracted with ether (1 × 100, 2 × 50 ml.); the combined ether extracts and benzene solution were washed with water (3 × 25 ml.) and dried (Na_2SO_4). Concentration of this solution to dryness, finally under reduced pressure, gave 33·32 g. of a yellow oil which solidified when kept. This product had a bromine content of 1·71%, corresponding to 1·98 g. of unchanged (−)-menthyl bromoacetate. The product was hydrolysed in 2 portions, each using 15·15 g. of "ester" (corresponding to the product obtained from 0·05 g.-mol. of (−)-menthyl bromoacetate).

(*a*) The product (15·15 g.) was boiled under reflux with 2·5N-potassium hydroxide (25 ml.; 0·0625 g.-mol. of potassium hydroxide) and ethyl alcohol (50 ml.) for 4 hours. β-Hydroxy-β-phenylbutyric acid was isolated (as described below) as an oil (yield, 4·735 g.; 53%), which solidified on prolonged standing. This had $[\alpha]^{25}_{5780}$ +3·01° ±0·05°, $[\alpha]^{25}_{5461}$ +3·38° ±0·05° (*c*, 22·05 in alcohol); $[\alpha]^{25}_{5780}$ +2·34° ±0·05°, $[\alpha]^{25}_{5461}$ +2·64° ±0·05° (c, 9·1 in alcohol) (Found : *M* (by titration), 181. Calc. for $C_{10}H_{12}O_3$: *M*, 180).

(*b*) The condensation product (15·15 g.) was boiled under reflux with N-potassium hydroxide (62·5 ml., 0·0625 g.-mol. of potassium hydroxide) and ethyl alcohol (30 ml.) for 17 hours; at the end of the hydrolysis there were still two layers whereas in (*a*) a clear solution had been obtained. β-Hydroxy-β-phenylbutyric acid (yield, 4·365 g., 49%) was obtained as in (*a*), and had $[\alpha]^{25}_{5780}$ +2·73° ±0·05°, $[\alpha]^{25}_{5461}$ +3·06° ±0·05° (*c*, 15·75 in alcohol) (Found : C, 66·4; H, 7·04. Calc. for $C_{10}H_{12}O_3$: C, 66·7; H, 6·71).

Systematic Examination of the Products of Hydrolysis.—The product from 0·05 g.-mol. of (−)-menthyl bromoacetate was boiled with aqueous alcoholic potassium hydroxide (see above); finally the alcohol was removed by distillation, the residue then being extracted with ether (1 × 50, 5 × 25 ml.) to remove neutral compounds. The ethereal extract was concentrated to dryness, and the 9·73 g. of oil left were steam-distilled. A small amount (0·04 g.) of non-steam-volatile residue was extracted by means of ether, and gave, in alcohol (15 ml.), α^{25}_{5780} −0·07°, α^{25}_{5461} −0·08°. This oil was not soluble in alkali, nor was it hydrolysed further by boiling with alkali. The steam-volatile material was a mixture of menthol and acetophenone. From 4·87 g. of neutral products 2·1 g. of acetophenone 2 : 4-dinitrophenylhydrazone,

m. p. 239—240°, were obtained; crystallised from aqueous acetic acid, this had m. p. 242—243° (decomp.).

The aqueous alkaline solution (after removal of the neutral products as above) was acidified with 5N-sulphuric acid and the β-hydroxy-β-phenylbutyric acid extracted with ether (1 × 50, 3 × 20 ml.). The ethereal extract was washed with water (3 × 20 ml.), dried (Na_2SO_4), and concentrated to dryness, thereby giving the products described above. The acid aqueous layer (after extraction of β-hydroxy-β-phenylbutyric acid) was optically inactive. Steam-distillation gave acetic acid, requiring 11·8 ml. of N-KOH for neutralisation (to thymol-blue).

Preparation of (±)-*β-Hydroxy-β-phenylbutyric Acid.*—A solution of ethyl bromoacetate (3·34 g., 0·02 g.-mol.) and acetophenone (2·88 g., 0·024 g.-mol.) in benzene (15 ml.) was boiled under reflux in the presence of zinc (1·31 g., 0·02 g.-mol.) for 1½ hours. The condensation product (4·365 g.) obtained as in the above example, was hydrolysed by boiling under reflux with 2·5N-potassium hydroxide (10 ml.; 0·025 g.-mol. of potassium hydroxide) and ethyl alcohol (25 ml.). The product of hydrolysis was worked up as in the above experiment and β-hydroxy-β-phenylbutyric acid (yield, 2·355 g.; 65%) was obtained as an oil which solidified when kept. On crystallisation from light petroleum (b. p. 100—120°) needles were obtained, m. p. 71—72° (Found: C, 66·7; H, 6·85. Calc. for $C_{10}H_{12}O_3$: C, 66·7; H, 6·71%).

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