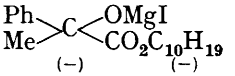
284. *An Investigation into the Mechanism of Asymmetric Synthesis with Reference to a New Type.*

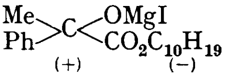
By J. Kenyon and S. M. Partridge.

(I) Most recorded examples of asymmetric synthesis where a compound of known constitution is used to impart a dissymmetric bias to a reaction depend for their success on the production of a mixture of diastereoisomerides in unequal amounts, an optically active product being obtained when the original centre of asymmetry is removed.

In order to account for an inequality in the amounts of the diastereoisomerides (I) and (II) obtained as intermediate products in the asymmetric synthesis of (—)-atrolactinic acid

(I.)


$$\begin{matrix}Ph\\Me\end{matrix}\!>\!\underset{(-)}{C}\!<\!\begin{matrix}OMgI\\CO_2\underset{(-)}{C_{10}H_{19}}\end{matrix}$$


(II.)

$$\begin{matrix}Me\\Ph\end{matrix}\!>\!\underset{(+)}{C}\!<\!\begin{matrix}OMgI\\CO_2\underset{(-)}{C_{10}H_{19}}\end{matrix}$$

from benzoylformic acid, McKenzie ("Ergebnisse der Enzymforschung," 1936, V, 58) suggests that the ethereal solution of (—)-menthyl benzoylformate used in the Grignard reaction contained a mixture of (A) and (B) in unequal amounts. Here it is assumed that

(A.) $Ph{\cdot}\underset{(-)}{CO}{\cdot}CO_2\underset{(-)}{C_{10}H_{19}}$ $\qquad$ $Ph{\cdot}\underset{(+)}{CO}{\cdot}CO_2\underset{(-)}{C_{10}H_{19}}$ (B.)

the ketonic double bond under the influence of "asymmetric induction" is capable of contributing to the optical rotatory power of the molecule, and further that, on addition of methylmagnesium iodide, (A) leads to (I) and (B) to (II), so (I) and (II) are also formed in unequal amounts. Clearly, in order to account for this inequality it is necessary to assume: (*a*) a constitutional difference in (A) and (B) and an excess of one over the other, or (*b*) that menthyl benzoylformate is homogeneous, but that collisions with the addendum likely to give rise to (I) are more favoured than those giving rise to (II). The following experiment was designed to test which of these two assumptions is the more probable.

It was found by Hills, Kenyon, and Phillips (this vol., p. 576) that (—)-$\alpha\gamma$-dimethylallyl alcohol (III) yields with phosphorus trichloride (+)-$\alpha\gamma$-dimethylallyl chloride, which on hydrolysis with a cold aqueous suspension of calcium carbonate gives a dextrorotatory form

$$\underset{(-)}{\overset{*}{\mathrm{C}}\mathrm{HMe(OH)}}{\cdot}\underset{(+)}{\mathrm{CH}\overset{*}{:}\mathrm{CHMe}} \longrightarrow \overset{*}{\mathrm{C}}\mathrm{HClMe}{\cdot}\mathrm{CH}\overset{*}{:}\mathrm{CHMe} \longrightarrow \mathrm{CHMe(OH)}{\cdot}\underset{(+)}{\mathrm{CH}\overset{*}{:}\mathrm{CHMe}}$$

(III.) (IV.) (V.)

of $\alpha\gamma$-dimethylallyl alcohol (V). Compound (III) on catalytic reduction yields optically pure (—)-methyl-*n*-propylcarbinol, whereas (V) yields the *dl*-carbinol. A possible explanation of these reactions is that during the hydrolysis of (IV) the optical activity due to the fixed centre of asymmetry is lost, whilst that due to induced dissymmetry in the double bond remains.

Thus a compound owing its optical activity solely to a centre of induced dissymmetry is available for a comparative study. The (—)-alcohol (III) readily combines with bromine to give (+)-*methyl-*$\alpha\beta$-*dibromo-*n-*propylcarbinol* (VI). This on oxidation with chromic anhydride in acetic acid solution yields (+)-*methyl* $\alpha\beta$-*dibromo-*n-*propyl ketone* (VII). On the other hand, the dextrorotatory alcohol (V), by similar treatment, yields a *dl*-dibromo-alcohol and subsequently *dl*-methyl $\alpha\beta$-dibromo-*n*-propyl ketone.

$$\overset{*}{\mathrm{C}}\mathrm{HMe(OH)}{\cdot}\mathrm{CH{:}}\overset{*}{\mathrm{C}}\mathrm{HMe} \longrightarrow \overset{*}{\mathrm{C}}\mathrm{HMe(OH)}{\cdot}\overset{*}{\mathrm{C}}\mathrm{HBr}{\cdot}\overset{*}{\mathrm{C}}\mathrm{HBrMe} \longrightarrow \mathrm{COMe}{\cdot}\overset{*}{\mathrm{C}}\mathrm{HBr}{\cdot}\overset{*}{\mathrm{C}}\mathrm{HBrMe}$$

(III.) (VI.) (VII.)

$$\text{(V.)}\qquad \mathrm{CHMe(OH)}{\cdot}\underset{(+)}{\mathrm{CH}\overset{*}{:}\mathrm{CHMe}} \longrightarrow \underset{\text{(inactive)}}{\mathrm{CHMe(OH)}{\cdot}\mathrm{CHBr}{\cdot}\mathrm{CHBrMe}} \qquad \text{(VIII.)}$$

It appears to follow, therefore, that induced dissymmetry of a double bond as indicated by its contribution to the optical rotatory power of a compound is incapable of effecting an asymmetric synthesis, and that, as in mechanism (*b*), it is a difference in energy associated with the diastereoisomeric intermediate products which is responsible for the one-sided addition.

(II) In order to make a further investigation into the course of the reaction described in Section I, a similarly constituted unsaturated alcohol, (+)-γ-phenyl-α-methylallyl alcohol (IX) (Kenyon, Partridge, and Phillips, this vol., p. 85), was chosen as being likely to afford crystalline dibromo-derivatives. This alcohol combines readily and completely with bromine at 18° to give a mixture of two methyl-$\alpha\beta$-dibromo-β-phenylethylcarbinols (X) which, without crystallisation or other form of separation, is smoothly oxidised to (—)-methyl $\alpha\beta$-dibromo-β-phenylethyl ketone (XI). By fractional crystallisation, (X) can be separated into a (+)- and a (—)-isomeride, m. p. 112—113° (fine hairy needles from light petroleum) and 87—88° (large glassy prisms from light petroleum) respectively. The rotatory powers are given in Table II. Oxidation of the alcohol of higher m. p. yields a (+)-ketone, and that of the other alcohol a (—)-ketone, both of m. p. 127°. Since the rotatory powers of these two ketones (Table II), although of opposite sign, are of equal magnitude, it is very probable that they are optically pure substances, and thus it is possible to calculate the degree of effectiveness of the asymmetric synthesis.

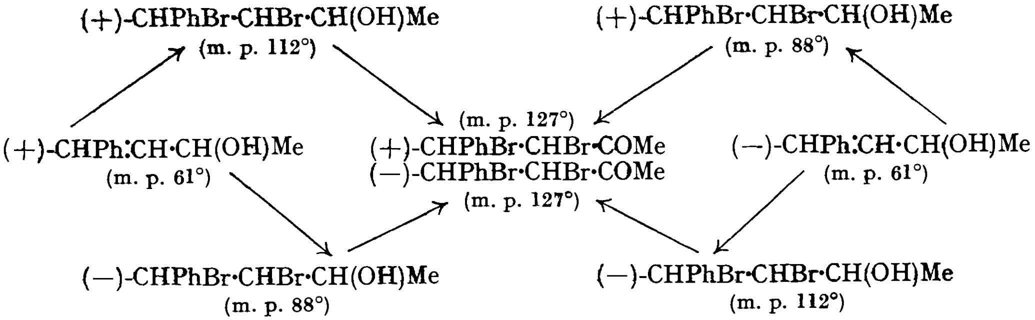
$$\underset{+45{\cdot}7^\circ}{\mathrm{CHMe(OH)}{\cdot}\mathrm{CH{:}CHPh}} \longrightarrow \underset{[M]_{5461}\text{ in }\mathrm{CHCl_3}}{\mathrm{CHMe(OH)}{\cdot}\mathrm{CHBr}{\cdot}\mathrm{CHBrPh}} \longrightarrow \underset{-31{\cdot}1^\circ}{\mathrm{COMe}{\cdot}\mathrm{CHBr}{\cdot}\mathrm{CHBrPh}}$$

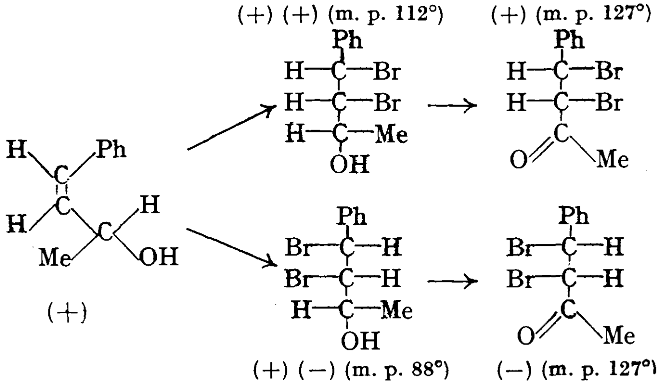
(IX.) (X.) (XI.)

In a similar way, the (—)-form of (IX) afforded a (—)-methyl-$\alpha\beta$-dibromo-β-phenylethylcarbinol of m. p. 112—113°, which proved to be the optical enantiomorph of the less soluble dibromo-alcohol mentioned above, and on oxidation it was converted into optically pure (—)-methyl $\alpha\beta$-dibromo-β-phenylethyl ketone.

These reactions are illustrated in different ways by Table I.

TABLE I.





Each of the optically active dibromo-alcohols, since it contains three asymmetric centres, is theoretically capable of existing in four isomeric forms the mixture of which on oxidation should give rise to two isomeric dibromo-ketones. The dibromo-ketone, however, was homogeneous and obtained in good yield, showing that only two of the four possible isomeric dibromo-alcohols were present in the mixture. This is in harmony with the fact that γ-phenyl-α-methylallyl alcohol behaves like a single geometrical isomeride and not as a mixture of *cis*- and *trans*-forms (Kenyon, Partridge, and Phillips, *loc. cit.*).

TABLE II.

Specific Rotatory Powers of Methyl-αβ-dibromo-β-phenylethylcarbinols and of the derived Ketones.

	Substance.	M. p.	*c.**	$[\alpha]_{5893}$.	$[\alpha]_{5790}$.	$[\alpha]_{5461}$.	$[\alpha]_{4358}$.
(1)	(+)-CHPh:CH·CH(OH)Me	61°	5·00	+ 24·7°	+ 26·5°	+ 30·9°	+ 60·7°
(2)	(+)-CHPhBr·CHBr·CH(OH)Me from (1)	112—113	1·473	+107·1	+115·9	+127·8	+261
(3)	(−)-CHPhBr·CHBr·CH(OH)Me from (1)	87—88	8·415	− 97·8	+115·3	−119·7	−224·4
(4)	(+)-CHPhBr·CHBr·COMe from (2)	127	3·70	+ 42·8	+ 46·1	+ 52·6	+ 84·4
(5)	(−)-CHPhBr·CHBr·COMe from (3)	127	3·025	− 40·7	− 45·3	− 51·7	− 80·7
(6)	(−)-CHPh:CH·CH(OH)Me	61	5·00	—	—	− 30·9	—
(7)	(−)-CHPhBr·CHBr·CH(OH)Me from (6)	112—113	1·535	−105·2	−109·4	−128·3	−248
(8)	(−)-CHPhBr·CHBr·COMe from (7)	127	3·545	− 43·4	− 47·9	− 52·5	− 87·8
(9)	(+)-CHPhBr·CHBr·CH(OH)Me from (6)	87—88	5·295	+ 98·9	+103·0	+120·0	+230
(10)	(+)-CHPhBr·CHBr·COMe from (9)	127	3·450	+ 40·0	+ 42·0	+ 47·8	+ 78·7

* The solvent was chloroform and $l = 2$ in every case.

The work of Soper and Smith (J., 1926, 1582) and of Eichelberger (*J. Amer. Chem. Soc.*, 1925, **47**, 1067) suggests that, in the addition of halogens at the ethylenic linkage, the attack is by the polarised molecule and not by either of its ions. The positive pole is assumed to enter before the negative pole, the latter, in ionising solvents, being liberated as an anion after addition of the former has taken place. It is probable that in a relatively non-polar solvent such as chloroform, the anion does not actually separate, with the result that *trans*-

TABLE III.

Specific Rotatory Powers of Methyl αβ-Dibromo-β-phenylethyl Ketones obtained by Oxidation of the Methyl-αβ-dibromo-β-phenylethylcarbinols prepared at Temperature t°.

t.	Medium.	$[\alpha]_{5893}$.	$[\alpha]_{5790}$.	$[\alpha]_{5461}$.	$[\alpha]_{4358}$.	In $CHCl_3$ (*l*, 2), *c*.	% of maximum rotatory power, $[\alpha]_{5461}$ ±52·6°.
−15°	$CHCl_3$	—	−20·0°	−21·6°	−34·1°	2·13	41·1 of (−)
− 6	,,	—	16·5	17·9	30·3	5·15	34·0 ,, (−)
+18	,,	—	9·2	10·15	19·6	2·70	19·4 ,, (−)
+60	,,	+ 1·7°	+ 1·84	+ 2·45	+ 4·75	3·27	4·7 ,, (+)
+75	CCl_4	—	—	+ 3·50	+ 7·50	0·96	6·7 ,, (+)

addition to the double bond is inhibited, and the number of diastereoisomerides formed is consequently reduced.

As the energy of activation of a reaction frequently varies with the temperature at which it takes place, some variation in the composition of the mixture of dibromo-alcohols was to be anticipated when the addition of bromine to the unsaturated alcohol was made at different temperatures in the same solvent. Experiment proved that an unexpectedly wide variation in the rotatory powers of the ketones obtained by oxidation of the mixtures of dibromo-alcohols produced at different temperatures (Table III) did actually occur, the (—)- or the (+)-ketone predominating according as the temperature was low or high.

The five values of $[\alpha]_{5461}$ given in Table III lie on a curve, but attempts to extend these measurements were not very successful; at lower temperatures the reaction was very sluggish, and at higher temperatures it did not proceed smoothly. McKenzie (*op. cit.*, p. 60) has been able to predict the sign of rotation of substituted glycollic acids formed by asymmetric synthesis from (—)-menthyl benzoylformate and from (—)-menthyl pyruvate. His prediction is based upon the sense of the contribution of the ketonic system to the total rotatory power of the ester in certain alcoholic solvents.

Clearly, in the above example no such prediction could be made, for the same initial material is able to give rise to either the dextro- or the lævo-rotatory dibromo-ketone according to the temperature of the reaction.

In order to show that the diastereoisomerides were not in a state of tautomeric equilibrium under the conditions of the reaction, a portion of the mixture prepared at a low temperature was heated under reflux in chloroform solution for 2 hours without any change in composition taking place.

EXPERIMENTAL.

(+)-*Methyl-αβ-dibromopropylcarbinol* (8·3 g.), prepared by addition of bromine (8 g.) in chloroform (20 c.c.) at room temperature to (—)-αγ-dimethylallyl alcohol ($\alpha^{14°}_{5461}$ — 1·40°; *l*, 2) (4·3 g.), has $n^{19°}_{D}$ 1·5336, b. p. 103°/13 mm., $\alpha^{16°}_{5893}$ + 2·04°, $\alpha^{16°}_{5790}$ + 2·15°, $\alpha^{16°}_{5461}$ + 2·46°, $\alpha^{16°}_{4358}$ + 4·90° (*l*, 0·5) (Found : Br, 64·9. $C_5H_{10}OBr_2$ requires Br, 65·0%). This (8·3 g.) on oxidation with chromic anhydride (2·5 g.) in glacial acetic acid (10 c.c.) at 60° gave (+)-*methyl αβ-dibromopropyl ketone* (4·5 g.), b. p. 90°/13 mm., $n^{16°}_{D}$ 1·5195, $\alpha^{16°}_{5893}$ + 3·06°, $\alpha^{16°}_{5790}$ + 3·34°, $\alpha^{16°}_{5461}$ + 3·85°, $\alpha^{16°}_{4358}$ + 8·25° (*l*, 0·25) (Found : C, 25·4; H, 3·6. $C_5H_8OBr_2$ requires C, 24·6; H, 3·3%). In a similar manner the dextrorotatory αγ-dimethylallyl alcohol ($\alpha^{17°}_{5461}$ + 0·38°; *l*, 0·5) obtained by hydrolysis of (+)-αγ-dimethylallyl chloride gave optically inactive methyl-αβ-dibromopropylcarbinol, b. p. 112°/20 mm., which (12·3 g.) on oxidation with chromic anhydride (3 g.) gave inactive methyl αβ-dibromopropyl ketone (10 g.), b. p. 90°/13 mm.

Addition of bromine (8 g.) in 50% chloroform solution to (+)-γ-phenyl-α-methylallyl alcohol (7·4 g) in chloroform (30 c.c.) at room temperature yielded a mixture of two isomeric methyl-αβ-dibromo-β-phenylethylcarbinols which, after removal of the chloroform, were obtained crystalline (Found : C, 39·1 : H, 4·2. $C_{10}H_{12}OBr_2$ requires C, 39·0; H, 3·9%).

The solid residue (15 g.) was dissolved in glacial acetic acid (15 c.c.), and the solution at 60° mixed with chromic anhydride (3·0 g.) in portions.

Methyl αβ-dibromo-β-phenylethyl ketone separated on dilution with water, and crystallised from hot alcohol in glistening prismatic needles, m. p. 127°, $[\alpha]_{5461}$ — 10·15° (*l*, 2; *c*, 2·7 in chloroform) (Found : C, 39·4; H, 3·3; Br, 52·2. $C_{10}H_{10}OBr_2$ requires C, 39·2; H, 3·3; Br, 52·3%).

In a second experiment a mixture of dibromo-alcohols, prepared at — 15° (9·0 g.) (m. p. 65—70°), was recrystallised six times from hot light petroleum to constant m. p. (112—113°)

and rotatory power, $[\alpha]_{5893}$ + 107·1°, $[\alpha]_{5790}$ + 115·9^{c}, $[\alpha]_{5461}$ + 128·0°, $[\alpha]_{4358}$ + 261·0° (*l*, 2; *c*, 1·473 in chloroform). This homogeneous (+ +)-methyl-αβ-dibromo-β-phenylethylcarbinol (2·0 g.) on oxidation in acetic acid solution with chromic anhydride (1·0 g.) yielded (+)-methyl αβ-dibromo-β-phenylethyl ketone (1·75 g.) as prismatic needles, m. p. 127° (decomp.); $[\alpha]_{5893}$ + 42·8°, $[\alpha]_{5790}$ + 46·1°, $[\alpha]_{5461}$ + 52·6°, $[\alpha]_{4358}$ + 84·4° (*l*, 2·0; *c*, 3·70 in chloroform).

The light petroleum mother-liquors from the first three crystallisations of the mixed dibromo-alcohols, after standing for several days, deposited crystals of two distinct types : (i) fine hairy needles characteristic of the (+ +)-methyl-αβ-dibromo-β-phenylethylcarbinol described above, and (ii) large regular hexagonal prisms. The former were readily removed by pouring off the mother-liquor, leaving the latter behind; these had m. p. 87—88°, and $[\alpha]_{5893}$ − 97·8°, $[\alpha]_{5790}$ − 115·4°, $[\alpha]_{5461}$ − 119·7°, $[\alpha]_{4358}$ − 224·0° (*l*, 2·0; *c*, 8·42 in chloroform).

This homogeneous (+ −)-methyl-αβ-dibromo-β-phenylethylcarbinol (0·8 g.) on oxidation with chromic anhydride in acetic acid yielded (−)-methyl αβ-dibromo-β-phenylethyl ketone (0·7 g.), m. p. 127° (decomp.), $[\alpha]_{5893}$ − 40·7°, $[\alpha]_{5790}$ − 45·3^{c}, $[\alpha]_{5461}$ − 51·7°, $[\alpha]_{4358}$ − 80·7° (*l*, 2; *c*, 3·02 in chloroform). In a similar manner (−)-γ-phenyl-α-methylallyl alcohol yields the (− −)-carbinol, m. p. 112—113°, which on oxidation yields the (−)-ketone, m. p. 127°, and the (− +)-carbinol, m. p. 87—88°, which on oxidation yields the (+)-ketone, m. p. 127° (rotatory powers in Table II).

The m. p. of the methyl αβ-dibromo-β-phenylethyl ketones is very susceptible to the rate of heating—rapid heating gives values as high as 131°. For this reason a specimen of the *dl*-ketone, which melts at 127° with a normal rate of heating, was always used for comparison.

The addition of bromine (1 mol.) to *dl*-γ-phenyl-α-methylallyl alcohol gave a mixture of isomeric *dl*-dibromo-alcohols, m. p. 60—90°, which was much more difficult to separate by fractional crystallisation than mixtures of the corresponding optically active compounds. After seven recrystallisations from light petroleum (other solvents were tried), a fraction was obtained of m. p. 128—130°. A mixture of equal amounts of (+ +)- and (− −)-methyl-αβ-dibromo-β-phenylethylcarbinols had m. p. 134°, and this when mixed with the former product melted at 129—132°; hence it appears that the separation of the two isomeric racemic dibromo-alcohols has not been completely effected.

Thanks are due to the Government Grants Committee of the Royal Society and to Imperial Chemical Industries Ltd. for grants.

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[*Received, May 23rd*, 1936.]