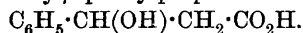


XIV.—*Experiments on the Walden Inversion. Part III.
Optically Active β -Hydroxy- β -phenylpropionic Acids
and the Corresponding β -Bromo- β -phenylpropionic
Acids.*

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THE effect, which in certain cases is associated with the electro-negative phenyl group, has been brought out clearly in previous work on the Walden inversion (McKenzie and Clough, *Trans.*, 1908, **93**, 811; 1909, **95**, 777). For example, *l*-phenylchloroacetic acid, $\text{C}_6\text{H}_5\cdot\text{CHCl}\cdot\text{CO}_2\text{H}$, is converted into a mixture of *r*- and *l*-mandelic acids when aqueous sodium hydroxide is used to displace the chlorine atom by the hydroxy-group; a mixture of *r*- and *d*-mandelic acids is, however, produced when silver carbonate is substituted for sodium hydroxide. This behaviour makes the problem of the Walden inversion more complicated than before, for this reason that, by analogy with previous work of Walden and others, it was to have been expected that sodium hydroxide should have caused the formation of a *dextro-rotatory* mandelic acid mixture from the *levorotatory* chloro-acid, and that silver carbonate should have caused the formation of a *laevo-rotatory* mandelic acid mixture. The contrast between the inter-conversion of the active lactic acids, $\text{CH}_3\cdot\text{CH}(\text{OH})\cdot\text{CO}_2\text{H}$, on the one hand, and the interconversion of the active mandelic acids, $\text{C}_6\text{H}_5\cdot\text{CH}(\text{OH})\cdot\text{CO}_2\text{H}$, on the other, by the Walden inversion, is very striking, and must be taken into account in any interpretation regarding the mechanism of the action which may be advanced.

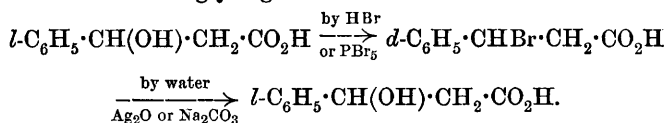
The present research is concerned with changes undergone by the optically active β -hydroxy- β -phenylpropionic acids,



One of the objects was to find out if any Walden inversion could be detected in the course of changes undergone by a compound where the carboxyl group is not attached directly to the asymmetric carbon atom. Meanwhile this problem has been investigated by E. Fischer and Scheibler (*Ber.*, 1909, **42**, 1219), who studied the displacement of the hydroxy-group in *l*- β -hydroxybutyric acid, $\text{CH}_3\cdot\text{CH}(\text{OH})\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$. By the action of phosphorus pentachloride, this acid was converted into *d*- β -chlorobutyric acid, from which the original *l*-hydroxy-acid was regenerated by displacing the chlorine by means of a number of different agents.

Bearing in mind the possibility of the phenyl group exerting an influence entirely different from that of the methyl group, we prepared the optically active β -hydroxy- β -phenylpropionic acids by the resolu-

tion of the inactive acid with morphine in aqueous solution. When the *l*-acid is acted on by hydrobromic acid, the resulting bromo-acid is dextrorotatory, and the change is accompanied by a certain amount of racemisation, which is less pronounced when the temperature at which the displacement occurs is kept low. The behaviour of the *d*-hydroxy-acid towards hydrobromic acid is, of course, similar. Phosphorus pentabromide also brings about a change of sign of rotation by its action on the active hydroxy-acids. When the bromine in the active bromo-acids is displaced by the hydroxy-group, either by means of silver oxide and water, or by sodium carbonate and water or by water alone, a change of sign of rotation again occurs. The parent acid is accordingly regenerated:



The displacement of the hydroxy-group in the active β -hydroxy- β -phenylpropionic acids by the bromine atom appears to be a normal action, since both phosphorus pentabromide and hydrobromic acid act in a similar manner, and since a change of sign also accompanies the action of hydrobromic acid on the methyl *d*-ester.

There is, therefore, no evidence of the occurrence of a Walden inversion in any of the changes studied.

EXPERIMENTAL.

Resolution of Inactive β -Hydroxy- β -phenylpropionic Acid.

Inactive β -hydroxy- β -phenylpropionic acid was prepared by the action of boiling water on inactive β -bromo- β -phenylpropionic acid, which is readily obtained from hydrobromic acid and cinnamic acid (Fittig and Binder, *Annalen*, 1879, 195, 131).

The resolution by means of morphine proceeds with exceptional ease. So far as we are able to judge, it is immaterial whether synthetic or storax cinnamic acid is used as the starting point for the preparation of the inactive acid.

Powdered morphine (61 grams) was added to a solution of 36 grams of the hydroxy-acid in 750 c.c. of boiling water. Crystallisation began after the solution was allowed to cool at the ordinary temperature for one hour; the solution was then stirred occasionally, and left overnight at the ordinary temperature. About half of the total morphine salt separated. The crystals, which melted and decomposed at about 206°, were suspended in 50 c.c. of water and the morphine precipitated by means of a slight excess of ammonia. The addition of an excess of hydrochloric acid to the filtrate, from which the morphine

had been separated, caused the gradual separation, in the form of needles, of the *l*-acid, which is sparingly soluble in water. The acid was drained off and, after crystallisation from 300 c.c. of benzene, was pure. The yield amounted to 9 grams. Its melting point and its specific rotation did not alter after it had been recrystallised several times from benzene.

l- β -Hydroxy- β -phenylpropionic acid, $\text{C}_6\text{H}_5\cdot\text{CH}(\text{OH})\cdot\text{CH}_2\cdot\text{CO}_2\text{H}$, is sparingly soluble in water and in benzene. It separates in colourless needles and melts at $115\text{--}116^\circ$:

0.1925 gave 0.4579 CO_2 and 0.1032 H_2O . $\text{C} = 64.9$; $\text{H} = 6.0$.

$\text{C}_9\text{H}_{10}\text{O}_3$ requires $\text{C} = 65.0$; $\text{H} = 6.1$ per cent.

Its rotation was determined in ethyl-alcoholic solution:

$$l = 2, c = 5.153, \alpha_D^{20} - 1.95^\circ, [\alpha]_D^{20} - 18.9^\circ.$$

In order to obtain the enantiomorphously related isomeride, the mother liquor, from which the morphine *l*-salt had been separated, was concentrated by evaporation to 150 c.c., when no separation of salt took place. The dextro-acid was then separated in the manner described above and crystallised from benzene. The yield amounted to 10 grams.

d- β -Hydroxy- β -phenylpropionic acid melts at $115\text{--}116^\circ$, and resembles its *l*-isomeride in other particulars:

0.194 gave 0.4638 CO_2 and 0.1051 H_2O . $\text{C} = 64.9$; $\text{H} = 6.0$.

$\text{C}_9\text{H}_{10}\text{O}_3$ requires $\text{C} = 65.0$; $\text{H} = 6.1$ per cent.

A determination of its specific rotation in ethyl-alcoholic solution gave a value in agreement with that of the *l*-acid:

$$l = 2, c = 5.194, \alpha_D^{18} + 1.99^\circ, [\alpha]_D^{18} + 19.2^\circ.$$

Although the inactive acid had not been resolved previously, the active acids have been obtained by Barkow (*Inaug. Diss.*, Strasburg, 1906), working in Erlenmeyer's laboratory, in the course of an investigation dealing with the α -halogen- β -hydroxy- β -phenylpropionic acids. Barkow found that when *d*- α -bromo- β -hydroxy- β -phenylpropionic acid, $\text{C}_6\text{H}_5\cdot\text{CH}(\text{OH})\cdot\text{CHBr}\cdot\text{CO}_2\text{H}$, was reduced by sodium amalgam, it was converted into *d*- β -hydroxy- β -phenylpropionic acid with $[\alpha]_D + 19^\circ$ in ethyl-alcoholic solution.

Action of Hydrobromic Acid on the Active β -Hydroxy- β -phenylpropionic Acids.

Attempts to resolve inactive β -bromo- β -phenylpropionic acid into its optically active isomerides were not promising. The bases employed caused some decomposition of the bromo-acid into styrene. The active bromo-acids were accordingly obtained from the corresponding

hydroxy-acids, but they underwent partial racemisation in the process of their formation by this method.

The *l*-hydroxy-acid (2.5 grams) was covered with aqueous hydrobromic acid, which had previously been saturated at 0°. The hydroxy-acid dissolved, and the bromo-acid separated. After one hour, water was added, the sparingly soluble acid drained off, washed with water, and dried over soda-lime under diminished pressure. The product had $[\alpha]_D + 16.8^\circ$ for $c = 2.029$ in ethyl-alcoholic solution. It was a mixture of the *r*- and *d*-bromo-acids, since its melting point was indefinite and its rotation changed on crystallisation. The effect of crystallising three times from carbon tetrachloride was to give an acid mixture, which contained more of the inactive form than before, the value for its rotation in ethyl-alcoholic solution being $[\alpha]_D + 8.5^\circ$ for $c = 2.05$.

If the fuming hydrobromic acid is shaken with the *l*-hydroxy-acid for a few minutes only at the laboratory temperature, the racemisation is less pronounced. In one experiment, for example, the crude bromo-acid, obtained from the *l*-hydroxy-acid, was crystallised once from carbon tetrachloride, and then gave $[\alpha]_D + 20.6^\circ$ for $c = 2.204$ in ethyl-alcoholic solution.

When the *d*-hydroxy-acid was shaken with aqueous hydrobromic acid, saturated at 0°, for two or three minutes at 0°, the crude bromo-acid which separated had $[\alpha]_D - 23.9^\circ$ for $c = 2.974$ in ethyl-alcoholic solution.

Obviously, therefore, the amount of racemisation could be lessened by maintaining the temperature low during the action of the hydrobromic acid. Forty c.c. of aqueous hydrobromic acid (saturated at 0°) were accordingly cooled to -10° , and 8.5 grams of the *l*-hydroxy-acid added. The rapid solution of the hydroxy-acid was succeeded by the separation of a voluminous crop of the bromo-acid. After five minutes, the crystals were separated, washed with a little water, and dried. The product melted indefinitely at $126-133^\circ$, and had $[\alpha]_D + 32.2^\circ$ for $c = 2.125$ in ethyl-alcoholic solution. It was crystallised from 65 c.c. of chloroform, and the crop which separated (6 grams) had $[\alpha]_D + 21^\circ$. From the mother liquor, two successive crops were withdrawn, the second of which (1.1 gram) had $[\alpha]_D + 58.3^\circ$ for $c = 1.03$ in ethyl-alcoholic solution, whilst the residual mother liquor yielded 2 grams of acid with $[\alpha]_D + 96.2^\circ$ for $c = 1.107$ in ethyl-alcoholic solution. An estimation of bromine in the latter acid indicated the presence of cinnamic acid together with the bromo-acid.

The pure active bromo-acids have accordingly a value for their specific rotation higher than 96.2° , and appear to be more readily soluble in most solvents than the inactive isomeride. Further attempts to isolate them were not made, since the points of interest,

from the point of view of this investigation, could be established by aid of the partly-racemised acids.

The *d*-hydroxy-acid gave similar results to the above when it was treated with fuming hydrobromic acid at -10° .

Action of Phosphorus Pentabromide on the l-Hydroxy-acid.

The *l*-acid was dissolved in a mixture of chloroform and ether and acted on with an excess of phosphorus pentabromide, the temperature being maintained low. The bromo-acid, obtained after decomposition of the acid bromide with water, gave $[\alpha]_D + 14.4^{\circ}$ for $c = 2.39$ in ethyl-alcoholic solution.

Thus phosphorus pentabromide behaves like hydrobromic acid in causing a change of sign of rotation when it acts on the active hydroxy-acid, As is usually the case when a phosphorus halide acts on an active hydroxy-acid, the formation of the halogen acid is accompanied by partial racemisation.

Formation of l-Bromo-ester from d-Hydroxy-ester.

d- β -Hydroxy- β -phenylpropionic acid was converted into its methyl ester by the Fischer-Speier method. This ester, which had $[\alpha]_D + 14.1^{\circ}$ for $c = 4.717$ in ethyl-alcoholic solution, was added to an excess of fuming hydrobromic acid at -10° , and, after shaking for five minutes, the bromo-ester was separated. It was laevorotatory, giving $[\alpha]_D - 28.5^{\circ}$ for $c = 6.654$ in ethyl-alcoholic solution.

The action of phosphorus pentabromide on the *d*-hydroxy-ester was also examined, the bromination being effected in dry chloroform and at a low temperature. The resulting bromo-ester was again laevorotatory, giving $[\alpha]_D - 4.6^{\circ}$ for $c = 3.03$ in ethyl-alcoholic solution.

Displacement of Bromine in the d-Bromo-acid by the Hydroxy-group.

A mixture of the dextro- and inactive bromo-acids (0.4 gram) with $[\alpha]_D + 58.3^{\circ}$ was added to water (10 c.c.), and, after five days at the ordinary temperature, the solution was heated for a few minutes until the odour of styrene had disappeared. The product was then evaporated to dryness at the ordinary temperature under diminished pressure. The residue gave the value $[\alpha]_D - 7.7^{\circ}$ for $c = 2.27$ in ethyl-alcoholic solution.

A mixture of the dextro- and inactive bromo-acids (0.7 gram) with $[\alpha]_D + 58.3^{\circ}$ was added to a solution of 0.4 gram of sodium carbonate in 10 c.c. of water. After five days, the small amount of styrene present was removed. On acidification with hydrochloric acid, there

was no appreciable separation of cinnamic acid. The hydroxy-acid was extracted with ether, and had the specific rotation $[\alpha]_D - 5.5^\circ$ for $c = 1.451$ in ethyl-alcoholic solution.

Silver oxide, obtained from 1 gram of silver nitrate, was added to the dextrorotatory bromo-acid (0.7 gram) with $[\alpha]_D + 96.2^\circ$ and 10 c.c. of water. After twenty-four hours, with occasional shaking, the product was treated with hydrochloric acid, filtered, and the filtrate extracted with ether. The resulting hydroxy-acid gave the value $[\alpha]_D - 13.7^\circ$ with $c = 1.17$ in ethyl-alcoholic solution.

In these cases, therefore, using either water alone, sodium carbonate and water, or silver oxide and water, the hydroxy-acid recovered is opposite in sign to that of the bromo-acid used, and of the same sign as the parent hydroxy-acid from which the bromo-acid was obtained.

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