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Absolute Configuration of β -Hydroxy- β -phenylpropionic acid*

K. Balenović, B. Urbas, and A. Deljac

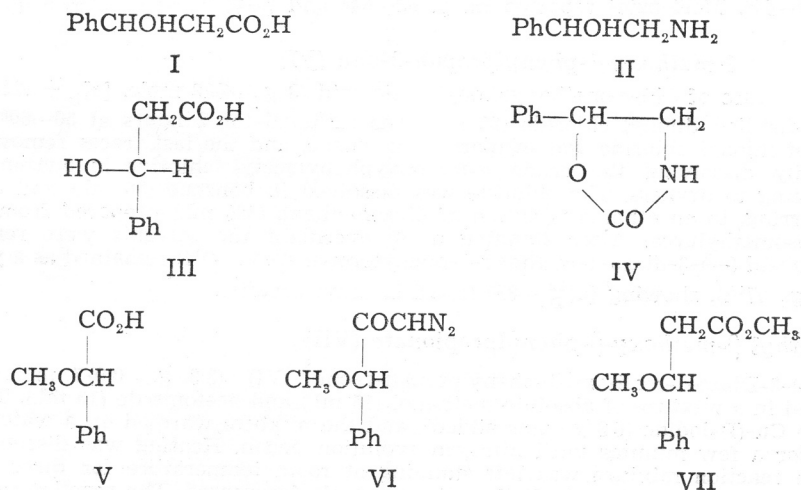
Chemical Laboratory, Faculty of Science, University of Zagreb,
Strossmayerov trg 14, Zagreb, Croatia, Yugoslavia

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(+)-Methyl β -methoxy- β -phenylpropionate (VIII) was prepared from (+)-mandelic acid and from (+)- β -hydroxy- β -phenylpropionic acid (I). In this way the configuration of I was correlated with that of mandelic acid.

Laevorotatory β -hydroxy- β -phenylpropionic acid (I) has been found in *Lobelia inflata* L. Degradation of *Lobelia* alkaloids and sedamine from *Sedum acre* L. also afforded optically active acids (I).** Knowledge of the absolute configuration of I is therefore important for the determination of the steric structure of these alkaloids.

Recently, Lukeš *et al.*¹ found that (+)- β -hydroxy- β -phenylethylamine (II) could be obtained from (+)- β -hydroxy- β -phenylpropionic acid as well as from (+)-mandelic acid. Mislow² had found earlier that (–)-mandelic acid belonged to the *D*-series of α -hydroxy acids; the dextrorotatory acid I has, therefore, the configuration III. This determination of the absolute configuration was repeated and confirmed³ by the preparation of the same (+)-5-phenyloxazolidone-(2) (IV) from the dextrorotatory acid I and from (+)-mandelic acid.



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** cf. e. g. lit. cit.³

In the present paper we wish to report another useful way for the correlation of the configurations of α - and β -hydroxy acids by the following series of stereospecific reactions [(+)-mandelic acid as model]: (+)-Mandelic acid was converted to (+)- α -methoxyphenylacetic acid (V) with methyl iodide and silver oxide⁴ and into the diazoketone VI in the usual way. Application of the Arndt-Eistert reaction to VI failed under normal conditions, but the homogeneous Wolff rearrangement⁵ afforded (+)-methyl β -methoxy- β -phenylpropionate (VII). We prepared the same compound from (+)- β -hydroxy- β -phenylpropionic acid with methyl iodide and silver oxide.

These results corroborate the earlier established configuration of (+)- β -hydroxy- β -phenylpropionic acid^{1,3}. Application of this series of reactions to the determination of the configuration of some other β -hydroxy acids has recently been described⁶.

EXPERIMENTAL

(+)- α -Methoxyphenylacetic acid (V)

(+)-Mandelic acid of 94% optical purity (5.3 g., 0.035 mole, $[\alpha]_D + 148^\circ$) was dissolved in benzene (30 ml.) and methyl iodide (20 g., 0.14 mole) and methylated according to McKenzie.⁴ To this solution silver oxide (20 g., 0.08 mole) was gradually added over a period of one hour, with stirring. The silver oxide was freshly prepared and washed successively with water, methanol and benzene. The reaction mixture was refluxed for 8 hours (bath temp. 50–55°), then cooled to room temperature, the silver iodide filtered off, washed with benzene (10 ml.) and the combined mother liquors evaporated *in vacuo* to dryness. The methyl α -methoxyphenylacetate thus obtained was a yellow oil (5.6 g., 90%). It was dissolved in methanol (50 ml.), and a solution of sodium hydroxide (2 g.) in water (3 ml.) added. After standing for 24 hours at room temperature (+)- α -methoxyphenyl acetic acid was isolated from the hydrolysate in the usual way (4.1 g., 71%). Recrystallization from benzene — petroleum ether gave colourless crystals with $[\alpha]_D^{23} + 122^\circ$ (c, 2.36 in ethanol), and m. p. 62–64°. McKenzie⁴ reported m. p. 63–64° and $[\alpha]_D^{12} + 150^\circ$ (c, 6.76 in ethanol).

(–)-3-Diazo-1-methoxy-1-phenylpropan-2-one (VI)

A mixture of (+)- α -methoxyphenylacetic acid (3 g., 0.018 mole, $[\alpha]_D + 122^\circ$) and freshly distilled thionyl chloride (20 ml.) was refluxed for 2 hours at 50–60°. The excess of thionyl chloride was evaporated *in vacuo*, and the last traces removed by repeatedly dissolving the crude α -methoxyphenylacetyl chloride in benzene and evaporating to dryness. The chloride was dissolved in benzene (50 ml.) and added, with stirring, to an ethereal solution of diazomethane (300 ml.) prepared from 35 g. of nitrosomethylurea. After standing at 0° overnight the solvents were removed *in vacuo* and (–)-3-diazo-1-methoxy-1-phenylpropan-2-one (VI) remained as a yellow oil (3.3 g., 97%), showing $[\alpha]_D^{22} - 83^\circ$ (c, 3.5 in ethyl acetate).

(+)-Methyl β -methoxy- β -phenylpropionate (VII)

(–)-3-Diazo-1-methoxy-1-phenylpropan-2-one (VI) (3.3 g., 0.017 mole) was dissolved in a mixture of absolute methanol (15 ml.) and acetonitrile (15 ml.). To this mixture Cu(I)-iodide (0.3 g.) was added⁵, and the mixture warmed on a water bath to 35° for a few minutes until nitrogen evolution began. Heating was discontinued and the reaction mixture was left standing at room temperature for three hours. After one hour of heating at 50° the nitrogen evolution ceased. The reaction mixture was filtered, poured into water (100 ml.), and extracted with benzene (3 × 50 ml.). The combined benzene layers were washed with water, dried (anhydrous Na₂SO₄) and evaporated *in vacuo*. The remaining greenish oily residue (3.1 g.) was dissolved in benzene and filtered through a column of neutral aluminium oxide (50 g., activity

III according to Brockmann). The first benzene filtrates (50 ml.) were evaporated to dryness and 2.28 g. (68%) of (+)-methyl β -methoxy- β -phenylpropionate (VII) were obtained showing the b. p. 50–60°/0.01 mm. and $[\alpha]_D^{21} + 40^\circ$ (c, 2.57 in benzene); colourless oily liquid.

Anal. 9.19 mg. subst.: 22.90 mg. CO₂, 5.87 mg. H₂O
 C₁₁H₁₄O₃ (194.22) calc'd.: C 68.03; H 7.26%
 found: C 68.00; H 7.15%

(+)-Methyl β -methoxy- β -phenylpropionate (VII)
 from (+)- β -hydroxy- β -phenylpropionic acid

The resolution of inactive β -hydroxy- β -phenylpropionic acid prepared according to E. Fischer *et al.*⁷ was accomplished with morphine according to McKenzie and Humphries⁸.

To a solution of (+)- β -hydroxy- β -phenylpropionic acid [0.6 g., 0.0036 mole, $[\alpha]_D^{20} + 19.5^\circ$ (ethanol), optical purity 100%] in benzene (15 ml.) and methyl iodide (2.5 g., 0.017 mole) silver oxide (2.7 g., 0.011 mole) was added and the reaction mixture refluxed for 8 hours. (+)-Methyl β -methoxy- β -phenylpropionate was isolated in the usual way, showing the b. p. 50–55°/0.007 mm. and $[\alpha]_D^{24} + 61.0^\circ$ (c, 2.935 in benzene).

Anal. 9.520 mg. subst.: 23.562 mg. CO₂, 6.028 mg. H₂O
 C₁₁H₁₄O₃ (194.22) calc'd.: C 68.03; H 7.26%
 found: C 67.54; H 7.09%

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IZVOD

Apsolutna konfiguracija β -hidroksi- β -fenilpropionske kiseline

K. Balenović, B. Urbas i A. Deljac

Opisana je priprava (+)-metil β -metoksi- β -fenil-propionata (VII) iz (+)-bade-move kiseline i iz (+)- β -hidroksi- β -fenilpropionske kiseline (I). Na taj način je određena konfiguracija spoja I.

KEMIJSKI ZAVOD
 PRIRODOSLOVNO-MATEMATIČKI FAKULTET
 ZAGREB

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