

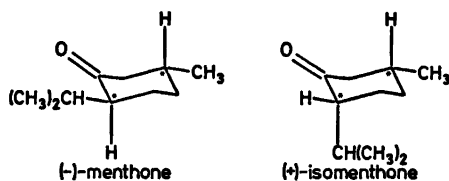
## Short Communications

## Small-scale Preparative Separation of (–)-Menthone and (+)-Isomenthone by High Performance Liquid Chromatography

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For some of our kinetic studies on the epimerization of (–)-menthone in methanol<sup>1</sup> we needed samples of optically pure (–)-menthone\* and (+)-isomenthone.\*



(–)-Menthone is easily obtained from (–)-menthol by oxidation with sodium dichromate.<sup>2</sup> The resulting (–)-menthone contains, however, some percentage of (+)-isomenthone probably formed by acid-catalyzed epimerization of (–)-menthone during the synthesis. To a large extent this can be circumvented by a somewhat modified procedure.<sup>3</sup>

(+)-Isomenthone is not easily obtained; Beckmann<sup>4</sup> synthesized "Rechtsmenthon" by acid-catalyzed epimerization of (–)-menthone. The product was, however, a mixture of (–)-menthone and (+)-isomenthone.<sup>5</sup>

Separation of the two epimers from the mixture can be achieved by formation of the corresponding oxime or semicarbazone. The menthones can then be regenerated by decomposing the oxime or semicarbazone with dilute sulfuric acid.<sup>6</sup> Another method for obtaining (+)-isomenthone is by catalytic hydrogenation of (–)-piperitone first suggested by Robinson

and Robinson<sup>7</sup> or by catalytic hydrogenation of (+)-isopulegon.<sup>8</sup> (+)-Isomenthone can also be obtained by sodium dichromate oxidation of (+)-isomenthol.<sup>5,8</sup> Naves<sup>9</sup> was able to isolate essentially optically pure (+)-isomenthone from *Micromeria abyssinica* (Hochst.) Benth.

All the methods mentioned are of rather limited practical use as they either require exclusive starting materials or are very laborious and there is always the problem of obtaining (+)-isomenthone completely free of (–)-menthone.

We have found that the separation of (–)-menthone and (+)-isomenthone can be made very conveniently on a small scale basis by using HPLC (High Performance Liquid Chromatography). On a column of silica gel with a mixture of hexane and ethyl acetate as the mobile phase (see Experimental) we have been able to obtain good base-line separation of the two epimers. (Fig. 1). A gas-chromatographic analysis also showed that the two fractions were pure.

The specific rotations of the two epimers at different wavelengths are given in Table 1. As can be seen the values reported in the present work are comparable with the highest reported values.

Due to the simplicity of the present method (HPLC) we would also like to recommend its application to other related problems of separation.



Fig. 1. Isocratic separation of the isomers menthone (1) and isomenthone (2) on  $\mu$ -Porasil. Flow rate 1 ml/min. Temp. ambient.

\* The systematic names for (–)-menthone and (+)-isomenthone according to Chemical Abstracts are (5*R*,2*S*)-*trans*-5-methyl-2-(1-methylethyl)cyclohexanone and (5*R*,2*R*)-*cis*-5-methyl-2-(1-methylethyl)cyclohexanone, respectively.

Table 1. Specific rotations of (-)-menthone and (+)-isomenthone separated by HPLC.

Wavelength (λ)/nm	[α] <sub>D</sub> <sup>20</sup> /° <sup>a</sup>	
	(-)-Menthone (neat)	(+)-Iso- menthone (neat)
589	-29.23 <sup>b</sup>	+96.32 <sup>c</sup>
578	-30.59	+101.7
546	-35.12	+120.2
436	-63.72	+265.2
365	-110.7	+662.3

<sup>a</sup> [α]<sub>D</sub><sup>20</sup> calculated from the observed rotation using  $d_{20} = 0.8946 \text{ g ml}^{-1}$  and  $d_{20} = 0.9000 \text{ g ml}^{-1}$  for (-)-menthone and (+)-isomenthone, respectively.<sup>6</sup>  
<sup>b</sup> Lit.: [α]<sub>589</sub><sup>20</sup> -29.9° (neat).<sup>3</sup> <sup>c</sup> Lit.: [α]<sub>589</sub><sup>20</sup> +95° (neat).<sup>6</sup>

**Experimental.** (-)-Menthone was synthesized from (-)-menthol (FLUKA AG, [α]<sub>D</sub><sup>20</sup> -58.0 ± 1, c 10, ethanol) according to Ref. 2. By a somewhat modified procedure to that given in Ref. 4 a mixture containing 54 % of (-)-menthone and 46 % of (+)-isomenthone was synthesized. This mixture was used for the separation experiments. The polarimetric measurements were made on a Perkin-Elmer Model 141 Polarimeter using a thermostated 10 mm cell.

A Waters Model 201 (Waters Ass., Milford, Mass. USA) liquid chromatograph equipped with a Valco injector (Model CV-6-UHPa-N60, 50 MPa) and with a Refractive Index Detector was used for the HPLC separations. A 30:1 v/v mixture of hexane (Fisher Sc. Comp., isomer mixture) and ethyl acetate (May & Baker Ltd.) was used as the mobile phase. The solvents (*pro analysi* quality) were degassed in an ultrasonic bath and used without further treatment. A stainless-steel column (30 cm × 4.6 mm I.D.) prepacked with μ-Porasil (Waters Ass.) was used for analytical separations. For the preparative scale separations a stainless-steel column (30 cm × 7.7 mm I.D.) packed with Partisil 10 (Whatman) was used. About 50 mg of the isomer mixture, dissolved in 50–100 μl of mobile phase solvent, was injected in each run.

Number of theoretical plates in the actual separations: analytical column 5600 T.P., preparative column: 3200 T.P.. *k'* values (for the analytical column) for the two compounds: 0.70 and 1.20, respectively.

A Perkin-Elmer Model 3920 or 900 equipped with a flame ionization detector was used for a further check of the purity of the two fractions. On a stainless steel column (2 m × 2.2 mm I.D.) packed with Fluorosilicone oil FS-1265 (QF 1), 1.5 % on Chromosorb W AW-DMCS

80–100 mesh, the retention time of (+)-isomenthone relative to (-)-menthone (1.00) was 1.13 at 70°C. No measurable quantity of one epimer in the other could be detected.

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