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# A Convenient Preparation of Pure Menthol and Menthone Isomers

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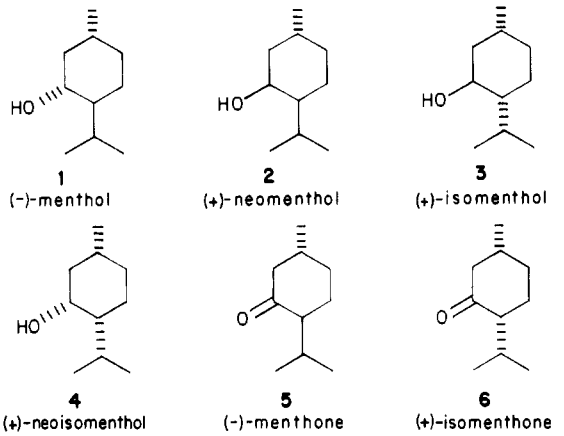
Menthol isomers can be easily prepared in gram quantities and in a high state of purity by utilizing simple and inexpensive chemical procedures and preparative-scale high-performance liquid chromatography (prep-HPLC). Chemically pure (−)-menthol (1) was oxidized with Jones reagent in ether. The resulting (−)-menthone (5), freed of (+)-isomenthone (6) by prep-HPLC, was reduced with $LiAl(OCH_3)_3H$ to give predominantly (+)-neomenthol (2), which was freed from 1 by prep-HPLC. Epimerization of 5 with acid or base produces an equilibrium mixture of 69% 5 and 31% 6. Isolation of 6 by prep-HPLC, subsequent reduction with $Li/NH_3/t$-BuOH or $LiAlH_4$, and purification by prep-HPLC give (+)-isomenthol (3) and (+)-neoisomenthol (4), respectively. Physical properties, GC, HPLC, and optical rotation indicated that these materials are free of related compounds.

There are four geometric isomers of (−)-menthol (1) that occur in nature. They are, in addition to 1, (+)-neomenthol (2), (+)-isomenthol (3), and (+)-neoisomenthol (4). Closely related to these are the ketones (+)-menthone (5) and (+)-isomenthone (6). Compounds 1–6 are components of peppermint and other essential oils (Guenther, 1949; Lawrence, 1980).




Pure 1 is readily available, and considerable research effort by many groups has been expended toward optimizing its production from natural (Guenther, 1949) and synthetic sources (Solodar, 1976).

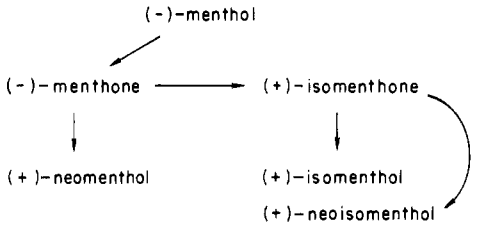
Many synthetic methods have been devised over the years to obtain the other isomers, but all are complicated by the simultaneous formation of one or more of the other isomers. This requires time-consuming and tedious separation techniques (e.g., derivatization, fractional crystallization, preparative gas chromatography, and spinning-band distillation).

Commerical samples of these compounds, particularly 2, are often contaminated by the other isomers. Since physical, chemical, and sensory properties can differ widely with minor differences in molecular structure, it was necessary to have isomerically pure samples of 1–4 and 5–6 in order to fully differentiate their characteristics.

The intent of this paper is to present for the first time a simple procedure to obtain these pure menthol and menthone isomers by combining their chemical interconvertability with separation techniques developed in our previous work with analytical (Haut and Core, 1981) and preparative high-performance liquid chromatography (prep-HPLC) (Haut and Core, 1982).

## METHODOLOGY

Readily available 1 was used as the starting point in the scheme




(−)-Menthol (1), purified by HPLC, was oxidized to (−)-menthone (5). The ketone 5 was then epimerized by acid or base to produce the equilibrium mixture containing 31% (+)-isomenthone (6). Pure samples of 5 or 6 tend to reequilibrate slowly on standing at room temperature. Storage in the cold is recommended to retard this process.

The complete separation of these ketones is a crucial step. Prior to HPLC (Bergman and Hall, 1979; Bergman, 1979), this separation was not a simple or efficient task and, as a result, may have led to some isomeric cross contamination in later synthetic manipulations. Reduction of either purified ketone with a suitable reagent followed by HPLC purification leads to the various isomers.

The synthesis of pure 1 or 3 by the dissolving metal reduction of 5 or 6 has already been described in the literature (Solodar, 1976).

Neoisomenthol (4) was produced by $LiAlH_4$ reduction of 6. The byproduct, compound 3 (2%), was easily removed by HPLC.

Isomerically pure neomenthol (2) was the most difficult of these compounds to obtain because (a) reduction of 5

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**Table I. Product Ratios for Reduction of Menthone**

| reducing agent | % neomenthol | % menthol | % neoisomenthol |
|---|---|---|---|
| $LiAlH_4$ | 27 | 71 | 2 |
| $LiAl(OCH_3)_3H$ | 70 | 30 | 0 |
| $LiB(C_2H_5)_3H$ | 90 | 9 | 1 |
| $KB(s\text{-}C_4H_9)_3H$ | 85 | 0 | 15 |
| $KB(i\text{-}PrO)_3H$ | 77 | 29 | 4 |
| Literature Data | | | |
| $NaBH_4$[a] | 65 | 35 | |
| $Li/NH_3$[b] | 0 | 100 | 0 |
| $(i\text{-}C_3H_7O)_3Al$[c] | 70 | 30 | |
| $Na/aqueous\ NH_3$[a] | 10 | 90 | |
| Pt, Pd, Ru[b] | | mixtures | |

[a] Grubb and Read (1934). [b] Jacmann and Macbeth (1934). [c] Ueda et al. (1959); Ueda (1960).

by most reducing agents gave **1** as the primary product and (b) those reducing agents sufficiently stereoselective to produce predominantly **2** also caused some competitive epimerization of **5** to **6** and subsequent contamination by reduction of **6** to **4**. Most commercial samples of **2** are contaminated by **4**. The separation of **4** from **2** was difficult even with the HPLC method at hand.

Several reducing agents were studied. The results are shown in Table I. The reagent of choice was $LiAl(O\text{-}CH_3)_3H$ (Brown and Deck, 1965) because it combined a moderate level of stereoselectivity, a rapid and simple chemical procedure, and, most importantly, little or no generation of **4**. The utilization of several recycle passes on the prep-HPLC was sufficient to remove traces of **4**.

Analogous procedures to those above can be used with (+)-menthol to obtain the optical antipodes.

## EXPERIMENTAL SECTION

Analytical HPLC conditions have been discussed previously ($\mu$-Porasil, 3% ethyl acetate/isooctane, 3 mL/min) (Haut and Core, 1981). Preparative separations were accomplished with a Waters Associates Prep-500 liquid chromatograph by using one PrepPAK (5.7 × 30 cm) silica cartridge. Conditions varied with each separation and are noted within the text. All solvents used in chromatography were HPLC grade and when used for analytical HPLC were filtered (0.45 $\mu$m) prior to use.

Gas chromatography was performed on a Perkin-Elmer Sigma 1 chromatograph equipped with a Sigma 10 data station. Analysis was performed by using an adaption of the literature (Gillen and Scanlon, 1972; Thieme and Benecke, 1977): a 15 ft × $^1/_8$ in stainless steel column packed with 3% Carbowax-1500 Anachrome ABS (70–80 mesh). The temperature was programmed from 100 to 150 °C at 1 °C/min. To prevent column deterioration, the oven temperature was maintained at room temperature when not in use.

Optical rotations were obtained on a Perkin-Elmer 241 MC polarimeter by using a 1 cm × 10 cm cell maintained at 20.0 ± 0.2 °C and absolute ethanol (*c* 2).

Ethyl ether was from a freshly opened can (Mallinckrodt). All other chemicals were obtained from either Fisher Scientific or Aldrich Chemical Co.

**(−)-Menthol (1).** Commercial (−)-menthol (10 g) was recycled 3 times on the preparative chromatograph with 8% ethyl acetate/hexane. The leading and trailing edge of the peak was discarded on each pass. Collection of the main component and evaporation of the solvent gave 8 g of **1**, which was used without further purification in subsequent steps. A portion was distilled (102 °C/8 mmHg): $[\alpha]_D^{20}$ −50.1°; $[\alpha]_{546}^{20}$ −52.3°.

**(−)-Menthone (5).** Oxidation of **1** (78 g, 0.5 mol) with chromic acid (Brown et al., 1971), removal of residual **1** by prep-HPLC (15% ethyl acetate/hexane), and careful distillation 77–77.5 °C/13 mmHg) gave 70 g of pure **5**: $[\alpha]_D^{20}$ −26.1°; $[\alpha]_{546}^{20}$ −27.2°.

**(+)-Isomenthone (6).** Typically, 10 mL of 10% aqueous NaOH was added to a solution of 10 g of **5** dissolved in 100 mL of $CH_3OH$ under $N_2$. After being stirred for 1 h, the mixture was evaporated under reduced pressure to remove most of the $CH_3OH$. The residue was dissolved in ethyl ether, washed with water and brine, and dried with $MgSO_4$. Evaporation of the solvent gave a residue that contained about 69% **5** and 30% **6**. Separation of an 11-g sample of this equilibrated ketone mixture was accomplished by the HPLC method of Bergman (Bergman and Hall, 1979) on the Prep-500 using the shave and recycle technique. Most of this material was used in subsequent syntheses without further purification. A portion was vacuum distilled: bp 62–63.5 °C/9 mmHg; $[\alpha]_D^{20}$ +99.2°; $[\alpha]_{546}^{20}$ +104.4°. (Equilibration can also be achieved in methanol with a drop of concentrated HCl by stirring overnight at room temperature or 1 h at reflux.)

**(+)-Isomenthol (3).** This compound was readily prepared stereospecifically by the dissolving metal reduction ($Li/NH_3$) of **6** according to the method of Solodar (1976). Purification of **3** was accomplished in the same manner as that of menthol. Kugelrohr distillation gave pure **3**: $[\alpha]_D^{20}$ +25.3°; $[\alpha]_{546}^{20}$ +26.2°.

**(+)-Neoisomenthol (4).** To a stirred slurry of $LiAlH_4$ (3.94 g, 0.104 mol) in anhydrous ethyl ether (200 mL) under $N_2$ was slowly added a solution of **6** (8.0 g, 52 mmol) in 125 mL of anhydrous ether. After being stirred at room temperature for 15 min the reaction mixture was quenched with 4 mL of water, 4 mL of 15% NaOH, and 12 mL of water (Steinhardt, 1967). The precipitate was vacuum filtered and washed with additional ether. The combined ether portions were evaporated under reduced pressure to give 6.3 g of a mixture containing 98% and 2% of **4** and **3**, respectively. Preparative chromatography using 8% ethyl acetate/hexane gave 6.2 g of **4** and 0.16 g of **3**. Vacuum distillation of the neoisomenthol fraction gave 4.2 g of pure **4**: bp 93–96 °C/16 mmHg; $[\alpha]_D^{20}$ +1.77°; $[\alpha]_{546}^{20}$ +1.85°.

**(+)-Neomenthol (2).** Typically, to a stirred slurry of 5.95 g (157 mmol) of $LiAlH_4$ in anhydrous ethyl ether under $N_2$ was slowly added dropwise 19.1 mL (471 mmol) of dry methanol. After the mixture was stirred for 15 min, a solution of 10 g (64 mmol) of **5** in 300 mL of ether was slowly added. When addition was complete, the mixture

**Table II. Menthol and Menthone Isomers**

| | $[\alpha]_D^{20}$ measured, deg | $[\alpha]_D$ literature,[a] deg | $[\alpha]_D$ literature,[b] deg |
|---|---|---|---|
| (−)-menthol | −50.1 | −49.2 (20 °C, *c* 2.5, EtOH) | −50.0 (20 °C, *c* 2, $CHCl_3$) |
| (+)-neomenthol | +20.1 | +19.6 (20 °C, EtOH) | +18.02 (10 °C, neat) |
| (+)-isomenthol | +25.3 | +25.5 (20 °C, *c* 4, EtOH) | +25.9 (20 °C, *c* 1.56, $CHCl_3$) |
| (+)-neoisomenthol | +1.77 | +2.2 (15 °C, *c* 2, EtOH) | +3.8 (18 °C, *c* 6, $CHCl_3$) |
| (−)-menthone | −26.1 | −24.8 (20 °C) | −24.8 (20 °C) |
| (+)-isomenthone | +99.2 | no data | +95 |

[a] Weast (1979). [b] "Dictionary of Organic Chemicals" (1982).

was stirred an additional hour. The hydride was quenched with water and 15% NaOH solution as above, and 1 g of anhydrous $MgSO_4$ was added. After the mixture was stirred about 15 min, the precipitate was filtered and washed with ether. The combined ether fractions were evaporated under reduced pressure to give 6 g of crude product containing 1% of residual **5**, 69% of **2**, 30% of **1** and only a trace of **4**. Following an initial prep-HPLC step at 8% ethyl acetate/hexane to remove **5** and **1**, similar fractions from several runs containing **2** were combined, evaporated (7.3 g), and preparatively chromatographed with 3% ethyl acetate/hexane. Three recycles, shaving, and discarding of the major peak's leading edge gave a final cut containing 3.5 g of isomerically pure (+)-neomenthol. Like samples of pure **2** from several runs were combined (8 g) and distilled to give 4.1 g of pure **2**: bp 41–43 °C/5 mmHg; $[\alpha]_D^{20}$ +20.1°; $[\alpha]_{546}^{20}$ +20.9°.

## RESULTS AND DISCUSSION

All samples are shown to be 99.8% free of impurities by NMR (Senda and Imaizumi, 1975; Bohlmann et al., 1975), GC, and HPLC. High purity is further indicated by a comparison of the respective rotation values to literature values as shown in Table II. On the basis of the synthetic derivation, each compound would be expected to inherit some quantity of a characteristic alternate isomer and thus exhibit a distinct shift in the value of the rotation. Although the differences found are relatively small, in all cases the values are consistently shifted in a direction that would reflect a lower level of contamination originating from a simultaneously synthesized isomer. This trend tends to diminish the possible presence of a systematic error in sample preparation and the instrument or a random experimental error in the observed values. For example, the value for our (+)-neoisomenthol is less positive, indicating less contamination by (+)-isomenthol. Likewise, the value for (−)-menthone is more negative than a typical literature value, indicating less (+)-isomenthone contamination (Bergman, 1979).

Preliminary sensory evaluation on these purified compounds indicates differences with their traditional, generally accepted flavor/odor attributes (Arctander, 1969; Fenaroli, 1975). If these evaluations are substantiated, it is probable that the accepted sensory characteristics of each individual menthol isomer reflect some influence from trace amounts of other isomers or related (e.g., peppermint oil) components and will need to be revised.

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