Studies on Menthol Derivatives

Part II. Application of NMR Spectroscopy for Configurational Analysis of (—)-Menthyl Carbinol and Related Compounds†

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In a previous paper,¹⁾ the authors have reported the synthesis of (—)-menthyl carbinol from (—)-menthol. This paper reports the stereochemical structure of (—)-menthyl carbinol particularly with respect to the C₃-position as elucidated by NMR spectral analyses. The configuration of (—)-menthyl carbinol-(1-(R)-methyl-3-(R)-hydroxymethyl-4-(S)-isopropylcyclohexane) was established in similar studies by using NMR spectra of menthols²⁾

and their derivatives.³⁾

Each isomer of menthols investigated exists in four preferred conformation^{4,5)} as shown in Table I.

These isomers of menthol and their deriva-

TABLE I.

Isomers	Conformations
(±)-Menthol	e-CH ₃ , e-OH, e-i-C ₃ H ₇
(±)-Isomenthol	a-CH ₃ , e-OH, e-i-C ₃ H ₇
(±)-Neomenthol	e-CH ₃ , a-OH, e-i-C ₃ H ₇
(±)-Neoisomenthol	e-CH ₃ , e-OH, a-i-C ₃ H ₇

tives can be classified into two series (e-series and a-series) according to the signal pattern and chemical shift of the methyl group in NMR spectra (Figs. 1, 2). The conformations of e-series all have equatorial substituents at the C₁-, C₃- and C₄-positions ((—)-menthol and its derivatives). On the other hand, those of a-series have more than one axial substituent (Isomenthol, Neomenthol, Neoisomenthol and their derivatives). It was found that the signal patterns and chemical shifts of CH₃ and i-C₃H₇ in NMR spectra were clearly different between e- and a-series as shown in Figs. 1, 2. In a-series the hydrogen resonance absorption peaks of the methyl and isopropyl groups shifted to lower field than those of e-series.^{6~8)} The chemical

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FIG. 1. NMR Spectra of e-Series ((-)-menthol and its derivatives) and a-Series ((+)-neomenthol and its derivatives).

FIG. 2. NMR Spectra of (—)-Menthyl Carbinol (I), (+)-Neomenthyl Carbinol (II), (—)-3-*p*-Menthane Carboxylic Acid (III), (I)-Menthyl Chloride (IV), and (+)-Neomenthyl Chloride (V).

TABLE II.

e-Series	δ ppm (chemical shift of signal in the highest field)
(—)-Menthol	0.76
(—)-Menthyl acetate	0.73
(—)-Menthyl benzoate	0.76
(—)-Menthyl- <i>p</i> -nitrobenzoate	0.77
(—)-Menthyl chloride	0.73
(—)-Menthyl carbinol	0.73
(—)-3- <i>p</i> -Menthane carboxylic acid	0.76
a-Series	
(+)-Neomenthol	0.83
(+)-Neomenthyl acetate	0.82
(+)-Neomenthyl benzoate	0.82
(+)-Neomenthyl- <i>p</i> -nitrobenzoate	0.86
(+)-Neomenthyl chloride	0.84
(+)-Neomenthyl carbinol	0.83
(+)-Isomenthol	0.83
(+)-Isomenthyl- <i>p</i> -nitrobenzoate	0.85
(+)-Neoisomenthyl- <i>p</i> -nitrobenzoate	0.88
(—)-Neoisomenthyl-3,5-dinitrobenzoate	0.90

shifts of the methyl hydrogen resonance absorption peak in the highest field in each compound were presented in Table II.

The difference of this chemical shift was caused by diamagnetic anisotropy which depends on the orientation of the bond with respect to the applied magnetic field (shielding and deshielding effect).

The signal patterns and the chemical shifts of (—)-menthyl carbinol and its derivative (3-*p*-methane carboxylic acid) surely belong to e-series. On the other hand, those of (+)-neomenthyl carbinol(epimer) belong to a-series (Fig. 3). Consequently, it is evident that the former had an equatorial carbinol group at the C₃-position. These results support the configuration of (—)-methyl carbinol(1-(R)-methyl-3-(R)-hydroxymethyl-4-(S)-isopropyl-cyclohexane) which was assigned on the basis

FIG. 3. NMR Spectra of *cis-p*-Menthane Derivatives.

(+)-Isomenthol (I), (+)-Isomenthyl-*p*-nitrobenzoate (II), ($\pm$)-Isomenthyl-*p*-nitrobenzoate (III), (+)-Neoisomenthyl-*p*-nitrobenzoate (IV), (-)-Neoisomenthyl-3,5-dinitrobenzoate (V).

of chemical analyses in the previous report. For configurational analysis of other menthan compounds NMR spectroscopy is useful.

EXPERIMENTAL

All melting and boiling points were uncorrected. NMR spectra were obtained with a Varian A-60A NMR spectrometer at the fixed frequency of 60 Mc. in carbon tetrachloride and benzene containing tetramethylsilane (TMS) as an internal reference.

(-)-Menthol and its derivatives. (-)-Menthol, mp 42.5~43.0°C, $[\alpha]_D^{20} - 50.0^\circ$ ($c=2.00$ in chloroform); (-)-Menthyl acetate, bp 83.0~84.0°C/5 mm, $d_4^{20} 0.929$, $[\alpha]_D^{20} - 73.32$ ($c=2.001$ in chloroform). (-)-Menthyl

benzoate, mp 54.5°C, $[\alpha]_D^{16} - 87.1^\circ$ ($c=1.97$ in methanol); (-)-Menthyl-*p*-nitrobenzoate, mp 62.0°C, $[\alpha]_D^{16} - 76.0$ ($c=1.82$ in methanol); (-)-Menthyl chloride, bp 78~80°C/12 mm, $n_D^{30} 1.4589$, $[\alpha]_D^{30} - 46.0$ (neat).

(+)-Neomenthol and its derivatives. (+)-Neomenthol, bp 83~84°C/14 mm, $[\alpha]_D^{10} + 18.02^\circ$ (neat); (+)-Neomenthyl acetate, bp 82~83°C/5 mm, $n_D^{23} 1.6515$, $[\alpha]_D^{23} + 22.44^\circ$ ($c=2.002$ in methanol); (+)-Neomenthyl benzoate, bp 148~149°C/5 mm, $[\alpha]_D^{20} + 103.4^\circ$ ($c=0.116$ in methanol); (+)-Neomenthyl-*p*-nitrobenzoate, mp 96~97°C, $[\alpha]_D^{10} + 18.1^\circ$ ($c=2.005$ in chloroform). (+)-Neomenthyl chloride, bp 58~65°C/9 mm, $[\alpha]_D^{20} + 54.5^\circ$ ($c=2.003$ in methanol).

(-)-Menthyl carbinol, (-)-3-*p*-menthane carboxylic acid,

and (+)-*neomenthyl carbinol*. (–)-Menthyl carbinol, bp 105~111°C/11 mm, n_D^{30} 1.4646, $[\alpha]_D^{30}$ –39.62° (neat); benzoate of (–)-menthyl carbinol, bp 168~169°C/5 mm, $[\alpha]_D^{20}$ –27.2° (c =0.624 in methanol).

p-Nitro benzoate of (–)-menthyl carbinol, mp 85~86°C, $[\alpha]_D^{20}$ –44.99° (c =13.56 in chloroform).

(–)-3-*p*-Menthane carboxylic acid, mp 66~67°C, $[\alpha]_D^{30}$ –60.00° (c =2.00 in methanol). (+)-Neomenthyl carbinol; Pure (+)-neomenthyl carbinol was obtained from the (+)-menthyl ester of (+)-3-*p*-menthane carboxylic acid by reduction. This ester was separated from a mixture of the methyl esters of (–)-3-*p*-menthane and (+)-3-*p*-menthane carboxylic acids by preparative gas-chromatography. bp 87~88°C/8 mm, $[\alpha]_D^{20}$ +10.5° (c =2.02 in chloroform), 5-Dinitrobenzoate; mp 97~99°C. *Anal.* Found: C, 59.55; H, 6.73. Calcd. for $C_{17}H_{20}O_6N_2$: C, 59.41; H, 6.64%. Preparative gas-chromatography was

carried out using a 8 mm×2.5 m column packed with polyethylene glycol 20 M in Toyo P-1. Column Temp. 105°C, Flow rate 60 ml/min.

cis-p-Menthane derivatives. (+)-Isomenthol, mp 82.5°C. $[\alpha]_D^{20}$ +25.9° (c =1.56 in chloroform).

(+)-Isomenthyl-*p*-nitrobenzoate, mp 54.0°C. $[\alpha]_D^{20}$ +24.9° (c =2.00 in chloroform). (+)-Neoisomenthyl-*p*-nitrobenzoate, mp 73°C. $[\alpha]_D^{15}$ +2.95° (c =2.002 in chloroform). (–)-Neoisomenthyl-3,5-dinitrobenzoate, mp 99.5°C. $[\alpha]_D^{15}$ –5.0° (c =1.98 in chloroform).

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