Isomerization and Racemization of Menthols

Part II. Isomerization and Racemization with Hydrogenation Catalysts and Sodium Mentholates*

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The isomerization and racemization of menthol isomers have been investigated with copper chromite and Raney nickel catalyst or sodium mentholates. The equilibrium concentration has been found to correspond to 55~56% of menthol with the catalytic isomerization, whereas to 74~75% of menthol with sodium mentholates. From these data, the free energy difference between equatorial and axial group in menthols is calculated to be about 0.5~0.6 Kcal./mole for hydroxyl and 1.4~1.5 Kcal./mole for methyl at 200°C.

Isomerization and racemization of alcohols have been reported by some investigators.^{1,2)} For example, Eliel et al.³⁾ carried out the epimerization of many cyclohexanols and Takeshita et al.⁴⁾ epimerized borneols with copper chromite, aluminum isopropoxide and sodium ethoxide.

Especially, the epimerization of cyclohexanols has been studied in details according to the conformational analysis with regard to stereochemical behavior.^{3,5)}

The isomerization of isomeric menthols to (–)-menthol and the racemization of (+)-menthol series (IS) to (±)-menthol have been the important subjects in the industrial production of (–)-menthol as mentioned in the previous report.¹²⁾

In 1958, Hueckel and Cheema⁶⁾ reported that isomeric menthols had been isomerized with sodium in decalin at 230~240°C to give

the menthol mixture. The composition of menthols, however, was inaccurate because an excellent method for determination of menthol isomers had not been known in these days. In 1960, the same author⁷⁾ isomerized the hydrogenation product of thymol, i.e., optically inactive menthol mixture with Raney nickel in methanol at 200~250°C and obtained an equilibrium mixture which was composed of 57.1% menthol (I), 29.3% neomenthol (II) and 13.6% isomenthol (III) by gas chromatography. Recently Hueckel et al.⁸⁾ have studied the isomerization of menthol isomers with alcoholate in paraffin or decalin in the presence or absence of fluorenone. They have concluded that the composition of equilibrium with alcoholate at 200~230°C was 72% (I), 15% (II) and 13% (III).

On the other hand Booth⁹⁾ and Bottems¹⁰⁾ have reported the racemization of menthol by heating optically active menthol with nickel, cobalt, copper chromite or other

* Part I. This Journal, 27, 433 (1963).

1) W. Hueckel et al., *Chem. Ber.*, 77, 220 (1944).

2) W. E. Doering et al., *J. Am. Chem. Soc.*, 71, 838 (1949).

3) E. L. Eliel et al., *ibid.*, 79, 5986, 5992, 5995 (1957).

4) T. Takeshita and M. Kitajima, *Bull. Chem. Soc. Japan*, 79, 1468, 1472, 1476 (1958).

5) E. L. Eliel et al., *J. Am. Chem. Soc.*, 82, 1367 (1960).

6) W. Hueckel und C. Z. K. Cheema, *Chem. Ber.*, 91, 311 (1958).

7) W. Hueckel et al., *Ann.*, 637, 1 (1960).

8) W. Hueckel und E. Jordan, *Arch. Pharm.*, 66, 563 (1961).

9) A. B. Booth, U. S. 2,843,636 (1958); C. A., 53, 3271b (1959).

10) R. R. Bottems, U. S. 2,871,272 (1958).

hydrogenation catalysts.

Independently of other workers⁶⁻¹⁰⁾ we have carried out the isomerization of isomeric menthols and presented a part of the results in 1957 and 1960.¹¹⁾

This paper describes the isomerization of the isomeric menthols by heating them in the presence of hydrogenation catalysts and hydrogen in autoclave or by means of sodium mentholate. Especially, from the view of industrial production menthol was isomerized without solvents and the menthol composition accurately determined by gas chromatography.

In the first place, (–)-(I), (+)-(II), (+)-(III) and (±)-neoisomenthol (IV) were isomerized in the presence of copper chromite catalyst (10% weight) under the pressure of hydrogen and the results are summarized in Tables I, II and III. Although (–)-menthol has not been isomerized at a temperature below 100°C, it has been found that at 150°C the isomerization occurs and at a temperature above 200°C any isomeric menthols furnish an equilibrium mixture. The equilibrium concentration of three isomers, (I), (II) and (III) are to 55~56% (I), 30~31% (II) and 13~14% (III). These values are in good agreement with earlier values reported by Hueckel et al.⁷⁾ Although at a temperature above 230°C racemization occurs as shown in Table I and the quantity of hydrocarbons (mainly *cis*- and *trans-p*-menthane) as well as menthone and isomenthone produced by dehydrogenation or dehydration followed by hydrogenation of starting menthols, the equilibrium composition is always constant. In the absence of hydrogen no isomerization occurred as shown in Table I as previously reported.¹⁰⁾

Among the three isomeric menthols, neomenthol (II) was most easily isomerized and racemized to give the equilibrium mixture at a temperature above 200°C. At 150°C (+)-(II) afforded the mixture of isomeric menthols,

which gave a menthol, 62~63%, and showed optical rotation of α_D^{20} –19~–20°, but at 200°C the racemization already occurred (α_D^{20} –10~–12°). At a temperature above 230°C major parts of menthol were racemized and the more severe dehydration reaction occurred as shown in Table II.

In the case of (+)-isomenthol (III) the isomerization was somewhat difficult but also gave the same equilibrium concentration as (–)-(I) and (+)-(II) at 185~200°C as shown in Table III. Although at a temperature above 200°C racemization occurred, the amount of hydrocarbons by side reactions was very small in contrast with the case of (–)-(I) or (+)-(II). Moreover, (±)-neoisomenthol (IV) or the mixture composed of the equal amounts of (–)-(I), (+)-(II) and (+)-(III), was also isomerized under a hydrogen pressure of 35 kg/cm² at 200°C for 4.5 hours in the presence of copper chromite catalyst to afford the same equilibrium concentration mentioned above. The optical purity of isomerized menthol mixture from the optically active menthol mixture, however, was only 85.0% by the menthone enol acetate method.¹²⁾ It means that the partial racemization occurred at these conditions because the starting menthols were optically pure.

Concerning the isomerization, a copper chromite was most effective catalyst but Raney nickel was an inferior one.

Catalytic isomerization or racemization reaction was considerably inhibited by addition of ketones and in some cases even the lower alcohols such as methanol, ethanol and cyclohexanol as shown in Table IV (+)-Neomenthol which could be readily converted to the equilibrium mixture, was not smoothly isomerized in the presence of (–)-menthone, (+)-isomenthone or cyclohexanone (even 5% amount). On the other hand these reactions were not inhibited by hydrocarbons such as *n*-hexane, cyclohexane and methylcyclohexane.

11) The papers were presented at the 1st and 4th Annual Meeting of Chemistry of Perfume, Terpene and Essential Oil in Japan in Kinki and Hokkaido University, respectively.

12) T. Yoshida, A. Komatsu and M. Indo, This Journal 27, 433 (1963).

TABLE I. ISOMERIZATION AND RACEMIZATION OF (–)-MENTHOL (I) WITH COPPER CHROMITE CATALYST (10% weight)

Reaction			α_D^{20}	Composition of Products (%)				Composition of Menthols (%)		
Temp. °C	Time hr.	H ₂ -Press kg/cm ²		Hydrocarbons	Menth-one	Isomen-thone	Menthols	Neomen-thol	Menthol	Iso-menthol
100	4.5	35	C.*	0.0	0.0	0.0	100.0	0.0	100.0	0.0
150	4.5	35	–25.4	0.0	0.0	0.0	100.0	31.8	65.5	3.1
200**	2.0	15	C.*	0.0	1.6	trace	98.4	0.0	100.0	0.0
200	2.0	35	–17.4	1.0	0.0	0.0	99.0	31.0	56.2	12.8
230	4.5	15	–4.4	9.8	4.1	2.8	83.3	33.4	54.6	12.0
230	4.5	70	–12.6	4.0	0.0	0.0	96.0	30.7	55.1	14.2
250	4.5	15	–0.4	29.9	6.9	4.4	58.8	33.2	53.2	13.6
250	9.0	35	0.0	16.3	1.7	1.5	80.5	31.7	54.2	14.1
270	4.5	15	0.0	47.4	9.5	6.3	36.8	32.0	52.4	15.6

* Crystals.

** Under nitrogen pressure.

TABLE II. ISOMERIZATION AND RACEMIZATION OF (+)-NEOMENTHOL (II) WITH COPPER CHROMITE CATALYST (10% weight)

Reaction			α_D^{20}	Composition of Products (%)				Composition of Menthols (%)		
Temp. °C	Time hr.	H ₂ -Press kg/cm ²		Hydrocarbons	Menth-one	Isomen-thone	Menthols	Neomen-thol	Menthol	Iso-menthol
100	4.5	35	+13.6	0.0	0.0	0.0	100.0	92.7	7.3	8.0
130	4.5	35	–12.2	0.0	0.0	0.0	100.0	47.5	52.5	trace
150	4.5	35	–20.8	0.0	0.0	0.0	100.0	30.9	63.6	5.5
200	4.5	15	–10.0	7.0	0.9	trace	92.1	31.0	55.6	13.4
200	9.0	35	–11.8	3.1	trace	trace	96.9	31.1	55.2	13.7
230	4.5	15	–0.2	20.7	2.8	1.3	75.2	29.5	55.9	14.6
230	4.5	70	–5.8	8.9	0.0	0.0	91.1	31.1	54.8	14.1
250	4.5	35	0.0	50.0	1.4	trace	48.6	32.3	53.1	14.6

TABLE III. ISOMERIZATION AND RACEMIZATION OF (+)-ISOMENTHOL (III) WITH COPPER CHROMITE CATALYST (10% weight)

Reaction			α_D^{20}	Composition of Products (%)				Composition of Menthols (%)		
Temp. °C	Time hr.	H ₂ -Press kg/cm ²		Hydrocarbons	Menth-one	Isomen-thone	Menthols	Neomen-thol	Menthol	Iso-menthol
150	3.0	10	C.*	0.0	0.0	0.0	100.0	15.4	27.2	57.4
170	3.0	10	–8.8	0.0	0.0	0.0	100.0	25.8	49.3	24.9
185	3.0	10	–14.4	0.0	1.6	trace	98.4	28.8	57.8	13.4
185	3.0	35	–14.4	trace	0.0	0.0	100.0	30.3	57.9	11.8
200	1.0	10	–12.8	0.0	1.7	1.1	97.2	30.4	55.8	13.8
230	3.0	10	–1.0	0.5	5.7	3.0	90.8	31.0	55.1	13.9
250	2.0	10	–0.2	4.9	8.6	6.2	80.3	32.0	54.4	13.6

* Crystals

TABLE IV. INHIBITION OF ISOMERIZATION OF MENTHOL ISOMERS WITH COPPER CHROMITE CATALYST (10% weight)*

Menthol Isomers	Additives	Amount %	α_D^{20}	Composition of Products (%)				
				Menthone	Isomenthone	Neomenthol	Menthol	Isomenthol
(-)-Menthol	None	0.0	-24.0	0.0	0.0	26.3	67.9	5.8
	(+)-Isomenthone	5.0	C. **	trace	trace	5.6	94.4	0.0
	(-)-Menthone	5.0	C. **	1.4	2.2	2.3	94.1	trace
(+) - Isomenthol	None	0.0	-14.4	1.6	trace	28.3	56.9	13.2
	(+)-Isomenthone	10.0	C. **	1.5	1.1	17.2	28.0	52.2
	(-)-Menthone	10.0	C. **	1.5	0.9	4.2	7.6	85.7
(+) - Neomenthol	None	0.0	-20.6	0.0	0.0	30.8	62.5	6.7
	(+)-Isomenthone	5.0	+15.2	0.8	0.8	90.6	7.8	0.0
	(-)-Menthone	5.0	+13.4	3.3	0.0	94.6	2.1	0.0
	Cyclohexanone	10.0	+14.4	0.0	0.0	94.7	5.3	0.0
	Cyclohexanol	10.0	+2.4	0.0	0.0	74.8	25.2	0.0
	Methanol	10.0	-3.2	0.0	0.0	62.9	34.5	2.6
	Ethanol	10.0	+13.4	0.7	0.0	90.5	8.8	trace
	n-Hexane	10.0	-20.8	0.0	0.0	33.0	62.0	5.0
	Cyclohexane	10.0	-16.8	0.0	0.0	41.2	56.0	2.8
	Methylcyclohexane	10.0	-16.8	0.0	0.0	40.8	55.7	3.5

* Hydrogen pressure, 10kg/cm²; Reaction time and temperature, 2 hrs. and 150°C in the case of (-)-menthol and (+)-neomenthol, 3 hrs. and 185°C in the case of (+)-isomenthol

** Crystals

TABLE V. ISOMERIZATION AND RACEMIZATION OF MENTHOL ISOMERS WITH RANEY NICKEL (W-4) CATALYST (10% weight)

Menthol Isomers	Temp.* °C	α_D^{20}	Composition of Products (%)				Composition of Menthols (%)		
			Hydrocarbons	Menthone	Isomenthone	Menthols	Neomenthol	Menthol	Isomenthol
(-)-Menthol	180	-15.8	0.0	0.0	0.0	100.0	33.2	66.8	0.0
	200	-7.6	0.6	0.0	0.0	99.4	29.7	58.5	11.8
	230	0.0	5.8	2.3	1.5	90.4	31.5	55.4	13.1
(+) - Neomenthol	150	-18.4	0.0	0.0	0.0	100.0	40.0	60.0	0.0
	180	-18.6	0.0	0.0	0.0	100.0	30.8	61.1	8.1
	200	-9.0	0.0	1.3	0.0	98.7	30.4	57.8	11.8
	230	0.0	2.0	1.7	1.0	95.3	33.5	55.2	11.3
(+) - Isomenthol	180	-8.0	0.0	0.0	0.0	100.0	28.4	55.1	16.5
	200	-7.6	trace	trace	trace	100.0	27.7	55.5	16.8
	230	0.0	4.7	trace	trace	95.3	30.5	54.6	14.9

* Reaction time 3 hrs., hydrogen pressure 35 kg/cm²

It seems reasonable that at a catalyst surface π -electrons or lone-pair electrons belonging to these ketones or alcohols will fill the vacant d -orbitals of catalyst metals, namely active center, and act as a kind of catalyst poison.

The results by means of Raney nickel

catalyst are summarized in Table V. At 150~180°C (+)-(II) is isomerized to give a mixture, of which menthol (I) content is 60~61% and at 230°C it affords the same equilibrium mixture mentioned above, being completely racemized.

By this catalyst, (+)-(III) is similarly equi-

brated at 180~200°C but shows a tendency of racemization to some extent. At 230°C (+)-(III) as well as (-)-(I) are sufficiently racemized.

It was shown that Raney nickel catalyst has an excellent racemization ability and produces very small quantity of by-products such as *p*-menthanes.

The isomerization by means of sodium mentholate was also investigated. After (+)-(II) had been converted to sodium mentholate by adding sodium metal (0.8 mole equivalent), the mentholate mixture was heated at 190~210°C for 12 hours to afford an equilibrium mixture. The final composition was 8~9% (-)-menthone and (+)-isomenthone, 67~68% (-)-(I), 8~9% (+)-(II) and 15~16% (+)-(III). It is known that the equilibrium menthol mixture contains 74~75% of (-)-(I) which corresponds to much more (-)-(I) than by means of hydrogen catalysts.

Moreover, as a result of these experiments it became clear that all isomeric menthols of an equilibrium mixture with mentholates were optically pure, in other words no racemization reaction occurred and ketones such as menthone or isomenthone showed no inhibitory action.

Although (-)-(I), especially (+)-(III), was hardly isomerized with the corresponding sodium mentholate, these crystalline menthols, (I) and (III), were readily isomerized to give an equilibrium mixture in the presence of menthone or neomenthol (about 30~50% amount for them). Moreover, the menthol mixture composed of equal amounts of isomers afforded the same equilibrium mixture.

The mechanism of isomerization is not clear but the enolization of menthones formed through these conditions might be fairly important. Menthone and isomenthone are invariably formed in the equilibrium mixture with both hydrogen catalysts and mentholates.

In the case of catalytic isomerization the equilibrium concentration of the three isomers is 56% (I), 31% (II) and 13% (III) and cor-

responds to 64.4% (I) and 35.6% (II), giving an equilibrium constant (K) of 31/56 and a free energy difference ($\Delta F = -RT \ln K$) of 0.56 Kcal./mole at 200°C. Similarly, the above equilibrium data give a free energy difference between menthol and isomenthol of 1.4~1.5 Kcal./mole.

Each menthol isomer should exist as the two conformational pairs in the stable and chair form as shown in Fig. 1. If the one of the two conformers, in which the most bulky isopropyl group occupies an equatorial (e) position, i.e., (Ia), (IIa) or (IIIa), is a preferred conformation as reported by Cole and Jefferies,¹³⁾ a free energy difference (0.5~0.6 or 1.4~1.5 Kcal./mole) between menthol (Ia) and neomenthol (IIa) or isomenthol (IIIa) would correspond to $e\text{-OH} \rightarrow a\text{-OH}$ or $e\text{-CH}_3 \rightarrow a\text{-CH}_3$. The ΔF between equatorial and axial hydroxyl is in fair agreement with earlier values of 0.8,¹⁴⁾ 0.9¹⁵⁾ and 0.5³⁾ Kcal./mole reported in cyclohexanols, and the ΔF between equatorial and axial methyl is in good agreement with the reported values of 1.49~1.61^{16,17)} in dimethylcyclohexanes; 1.5 ± 0.1 ¹⁾ and 1.8 Kcal./mole¹⁴⁾ in methylcyclohexanols.

Although the composition of neoisomenthol (IV) was not determined, ΔF between menthol (Ia) and neoisomenthol (IVa) is theoretically calculated as about 2.0 Kcal./mole ($e\text{-CH}_3$, $e\text{-OH} \rightarrow a\text{-CH}_3$, $a\text{-OH}$). Consequently, the theoretical equilibrium concentration of four menthol isomers should be 53.5% (I), 28.3% (II), 12.1% (III) and 6.1% (IV). The precise determination of (IV) under the best conditions of gas chromatography afforded the values of 51.9% (I), 30.9% (II), 12.5% (III) and 4.7% (IV) in an equilibrium mixture. These values are in good agreement with the calculated ones.

13) A. R. H. Cole and P. R. Jefferies, *J. Chem. Soc.*, 4391 (1956).

14) S. Winstein and N. J. Holness, *J. Am. Chem. Soc.*, 77, 5562 (1955).

15) S. J. Angyal and D. J. Mchugh, *Chem. & Ind.*, 1147 (1956).

16) J. E. Kilpatrick et al., *C. A.*, 42, 2504°C (1948).

17) B. J. Armitage et al., *Tetrahedron*, 20, 747 (1964).

Fig. 1. The Conformations of Isomeric Menthols.

a), b) R=H; c), d) R=Na

In the catalytic isomerization mentioned above the species equilibrated are the free alcohols, whereas in the isomerization with sodium mentholate the species equilibrated are alcoholates. The bulky alkoxide group will have a strong tendency to occupy the equatorial position so that the conformers are entirely in forms (Ic), (IIId), (IIIc) and (IVd) as suggested by Eliel et al.^{5,18)} Accordingly, the energy difference between their isomers should be equal to that of between equatorial and axial methyl or isopropyl group.

For the methyl group the free energy difference between *e*- and *a*-methyl at 200°C is 1.4~1.5 Kcal./mole as already mentioned above. The ΔF value for isopropyl group is reported previously as about 3.3 at 25~50°C¹⁴⁾ or 3.5 Kcal./mole at 100°C.¹⁹⁾ From these data, the equilibrium concentration of sodium mentholates is calculated to be about 79.2% (I), 0.6% (II), 17.8% (III) and 2.4% (IV). Although the calculated value is in fairly good agreement with the observed one (74~75% (I), 8~9% (II), 16~17% (III)), the agreement is not so good for neomenthol (II).

The discrepancy may possibly be due to

the presence of unreacted free neomenthol in the equilibrium mentholate mixture because the available amount of sodium had to be restricted to 0.8 equivalent for menthol in order to avoid the solidification of reaction mixture.

By precise gas chromatographic analysis it was possible to detect very small quantities (about 1%) of neoisomenthol in an equilibrium mixture with sodium mentholates. This value is also in excellent agreement with the calculated one.

SUMMARY

1) The catalytic isomerization and racemization of menthol isomers by means of copper chromite and Raney nickel catalyst were investigated.

2) Although Raney nickel catalyst was excellent in the racemization ability, copper chromite had to be better used as the isomerization catalyst.

3) In the case of catalytic isomerization and racemization the ketones, especially menthone and isomenthone, showed considerable inhibitory action.

4) The equilibrium concentration in the catalytic isomerization corresponded to 52~53% menthol, 30~31% neomenthol, 12~13%

18) E. L. Eliel, *Experientia*, **9**, 91 (1953).

19) D. S. Noyce and L. S. Dolby, *J. Org. Chem.*, **26**, 3619 (1961).

isomenthol and 4~5% neoisomenthol at 200°C.

5) The isomerization of menthols by means of sodium mentholates was also studied. It was shown that the equilibrium menthol mixture was composed of 74~75% menthol, 8~9% neomenthol, 16~17% isomenthol and trace of neoisomenthol without any racemization.

6) From these data a free energy difference between equatorial and axial hydroxyl (or methyl) in menthols is calculated to be 0.5~0.6 Kcal./mole for hydroxyl and 1.4~1.5 Kcal./mole for methyl at 200°C.

EXPERIMENTAL

Materials

(-)-**Menthol**. It was commercial preparation and showed the following constants; m.p. 41~42°C, $[\alpha]_D^{20} = -50.0$ ($c=10$, in ethanol).

(+)-**Neomenthol**. The crude neomenthol (500 g) containing about 78% of neomenthol, which was obtained as by-product in our company in the synthesis of (-)-menthol, acetic anhydride (500 g) and anhydrous sodium acetate (50 g) were refluxed for 16 hrs. at 140~150°C. After cooling, water (500 ml) was added and the mixture stirred for 1 hr. at 60°C in order to decompose excess of acetic anhydride. The oily layer was separated, washed with water thoroughly, dried and distilled through a 800×15mm column packed with Helipac at reflux ratio of 8:1 to give an oil, b.p. 75~77°C/2.5 mm. Yield 506 g. The oil was kept overnight at -10°C to afford 340 g of crystals. Recrystallization from *n*-hexane (70 ml) gave pure (+)-neomenthyl acetate (255 g), m.p. 35~36°C. The pure acetate in methanol (360 ml) was saponified with 50% aqueous sodium hydroxide (220 g) under reflux for 7~8 hrs. After methanol was recovered and water was added, the oily layer was extracted with ether, washed with water, dried and distilled through a Widmer column (15 cm) to give pure (+)-neomenthol (181 g), b.p. 64~66°C/2.5 mm, $n_D^{20}=1.4615$, $d_4^{20}=0.9002$, $\alpha_D^{20}=+16.8$ (homog.), *p*-nitrobenzoate, m.p. 95°C (Lit.²⁰ 95°C).

(+)-**Isomenthol**. The crude (+)-isomenthol (about 80% content, 690 g) (one of the by-products in menthol synthesis) was recrystallized from nitromethane (two-fold weight for isomenthol) several times to give pure (+)-isomenthol (343 g), m.p. 82~83°C (Lit.²⁰)

²⁰) J.L. Simonsen, "The Terpenes," Vol. 1, Cambridge at the University Press, 1947, p. 243.

82~83°C), $[\alpha]_D^{20}=+27.1$ ($c=10$, in ethanol), *p*-nitrobenzoate, m.p. 53~54°C (Lit.²⁰ 54°C).

(±)-**Neoisomenthol**. Thymol (20 g) in ethanol (40 ml) was hydrogenated in the presence of Raney nickel W-4 (about 3 g) at 150°C for 8 hrs. while the pressure of hydrogen kept constant at 20 kg/cm² in order to prevent the isomerization of neoisomenthol formed. The hydrogenated product was filtered and the solvent was recovered. The residual oil (20.5 g) was composed of menthone 2.6%, isomenthone 10.9%, neomenthol 4.3%, neoisomenthol 52.6%, menthol trace and isomenthol 19.6%. Then the oil (75 g) was fractionally distilled at reflux ratio of 40:1 through the same column packed with Helipac to give crude (±)-neoisomenthol (34.8 g), b.p. ~70°C/1~2 mm (menthone 2.3%, isomenthone 8.9%, neomenthol 21.4% neoisomenthol 67.4%). To this crude neoisomenthol (34 g) in pyridine (90 ml) 3,5-dinitrobenzoyl chloride (34 g) was added in a small portion with stirring below 30°C and the mixture was stirred for 4.5 hrs. at room temperature. Then the reaction mixture was poured into water, extracted with ether, washed with water, 10% sulfuric acid and water successively. The ether was distilled off and residual oil steam distilled to give the distillate and the residue (*p*-nitrobenzoates). The residue was dissolved in ether, washed with 5% sodium carbonate and then water, removal of ether gave crude ester (43.8 g). Since an attempt to purify this crude ester by recrystallization from methanol was unsuccessful, the impure crystals (35 g), m.p. 76~79°C (Lit.²⁰ 73°C), after once recrystallization, were hydrolyzed with methanolic potassium hydroxide to give impure (±)-neoisomenthol, b.p. 72~73°C/3.5 mm, $n_D^{20}=1.4661$, $d_4^{20}=0.9098$, $\alpha_D^{20}\pm 0.0$, which was composed of neomenthol 19.1%, neoisomenthol 78.5% and isomenthol 2.4%.

(-)-**Menthone** and (+)-**Isomenthone**. They were obtained by chromic acid oxidation of (-)-menthol or (+)-isomenthol in the usual way.²¹⁾

The other compounds in this experiment were purchased from commercial sources and used without further purification.

General Procedure for Catalytic Isomerization and Racemization

Menthol isomers (1.5~10.0 g) and commercial copper chromite catalyst (Nikko Co., Ltd., Tokyo, Japan) (10% weight for menthol isomers) or Raney nickel catalyst W-4 (stored in ethanol, 10% weight

21) Org. Synth., Coll., Vol. I, 340 (1961).

for menthols) was placed in an autoclave (100 ml) under hydrogen atmosphere (10~70 kg/cm²) and agitated electrically at a given temperature for several hours. In the case of Raney nickel catalyst, *n*-hexane (the same amount for menthols) was added as a solvent and the catalyst was sufficiently washed with the same solvent to remove ethanol previously. After the reaction, the catalyst was filtered off. The results are summarized in Tables I, II, III and V.

In the experiments of inhibitory action, (–)-menthone, (+)-isomenthone, cyclohexanone, *n*-hexane, cyclohexane, methylcyclohexane, cyclohexanol, methanol or ethanol in a given amount was added together with menthols and treated as described above. The results are shown in Table IV.

Isomerization of (+)-Neomenthol by Means of Sodium Mentholate

To (+)-neomenthol (20 g) heated at 120~130°C was portionwise added sodium metal (2.4 g, 0.8 mole equivalent) with vigorous stirring. After the addition the mixture was kept at this temperature for 2 hrs. until the major parts of sodium disappeared. Then the temperature was gradually raised to 190~210°C and the mixture was stirred for 12 hrs. at this temperature. After the temperature was kept below at 140~150°C, water (about 50 ml) was dropwise added. The mixture was refluxed for 30 min. and extracted with ether. The extract was washed with water, dried and evaporated to give an isomerized oil quantitatively. The oil was composed of menthone 4~6%, isomenthone 3~4%, menthol 67~68%, neomenthol 8~9% and isomenthol 15~16%.

Although (–)-menthol or (+)-isomenthol was treated similarly, the isomerization was very difficult or impossible owing to that the corresponding mentho-

lates have a strong tendency to solidify. Upon addition of 30~50% menthone or neomenthol the reaction smoothly proceeded.

The Determination of Optical Purity

Optical purity of menthol mixture was determined by the menthone enol acetate method reported in the preceding paper by the authors.¹²⁾

A) The optical purity of an equilibrium menthol mixture, which was obtained from optically pure (–)-menthol with copper chromite catalyst at 200°C for 3 hrs. under hydrogen pressure (35 kg/cm²), corresponded to 84.9%.

B) The racemization mixture which was obtained from optically pure (–)-menthol, (+)-neomenthol or (+)-isomenthol in *n*-hexane with Raney nickel W-4 under hydrogen pressure (35 kg/cm²) for 3 hrs. at 230°C, was completely optically inactive.

C) An equilibrium mixture by means of sodium mentholate from (+)-neomenthol (optical purity 96.2%) under the conditions mentioned above showed no racemization (optical purity 96.5%).

Gas Chromatography

The standard Kotaki Super Fractioner equipped with thermal conductivity detector was used. The samples were introduced through a 200×0.32 cm i.d. stainless steel column packed with 20 wt.% LAC-2-R446 (Cambridge Industries Co., Inc. Cambridge, Mass.) on celite 545 (50~80 mesh) at 140°C (or 120°C for the determination of neoisomenthol), 45 ml/min. of helium as carrier gas. The retention times for menthones and menthols at 140°C (or 120°C) were as follows: menthone 10.5 (13.9), isomenthone 12.0 (16.2), neomenthol 14.0 (19.8), neoisomenthol 16.2 (23.5), menthol 17.5 (25.6) and isomenthol 19.4 min. (28.4 min.).