Studies on the Reduction of Terpenes with Sodium in Aqueous Ammonia

Part VIII. On the Reduction of (–)-Isomenthone*

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Received March 17, 1960

In the reduction of (–)-isomenthone with sodium in aqueous ammonia, it was found that the reduction product gives a mixture consisting of 75.5% of (–)-isomenthol (a,e,e), 9.5% of (+)-menthol (e,e,e) and 8.6% of (–)-neoisomenthol (a,a,e). From this fact, it might be concluded that this reduction is stereospecific for isomenthone and is mechanistically different from reduction with sodium and alcohol.

In the previous papers of this series, it has been shown that (–)-menthone is reduced quantitatively to (–)-menthol by treatment with sodium in aqueous ammonia¹⁾, and a small amount of the by-product (ca. 10%) has been presumed to be (+)-neomenthol. However, from the result of elution gas-chromatographic study by Tagaki²⁾, it was found that this by-product is not (+)-neomenthol but (+)-isomenthol, and therefore, the conclusion previously reported should be revised showing that (–)-menthone is reduced with sodium in aqueous ammonia to (–)-menthol (90%) and (+)-isomenthol (10%).

On the other hand, by application of this method of reduction, (+)-isomenthol has been obtained in a good yield from inverted menthone, namely a mixture of (–)-menthone and (+)-isomenthone³⁾. In this case, the (+)-isomenthol content in menthol mixture obtained from the reduction of inverted menthone was lower than the theoretical value which was expected from the (+)-isomenthone content in the original

inverted menthone. As an explanation for this fact, it seemed reasonable to assume that (+)-isomenthone is considerably inverted to (–)-menthone by alkali, while (–)-menthone is hardly inverted to (+)-isomenthone.

The present investigation was undertaken in order to clarify this mechanistic problem.

(–)-Isomenthone was reduced with sodium in aqueous ammonia, and the compositions of isomerides in the resulted product were investigated. The application of a combination of recrystallisation and absorption chromatography revealed that the reduction product of (–)-isomenthone consisted of 75.5% of (–)-isomenthol (a,e,e), 9.5% of (+)-menthol (e,e,e) and 8.6% of (–)-neoisomenthol (a,a,e). In this case no (–)-neomenthol was identified. The production of neoisomenthol may be related somewhat to the fact that isomenthone is reduced predominantly to neoisomenthol with lithium aluminum hydride²⁾.

The difference of isomenthol content from the theoretical value described above might be attributed to the production of neoisomenthol from isomenthone and also to the inversion of isomenthone to menthone.

It is interesting to note that the reduction of

* For Part VII see This Bulletin, **24**, 508 (1960).

1) H. Ueda, Y. Shibahara and S. Shimizu, This Bulletin, **23**, 376 (1959).

2) Y. Tagaki, private communication.

3) H. Ueda and S. Shimizu, This Bulletin, **23**, 380 (1959).

isomenthone with sodium in aqueous ammonia afforded isomenthol in predominance, while with sodium and alcohol, menthol predominated⁴.

EXPERIMENTAL

All melting and boiling points were uncorrected. Microanalyses were carried out by the Microanalytical Division, Prof. Mitsui's Laboratory, University of Kyoto. Infrared spectra were recorded with a Shimadzu spectrophotometer.

(-)-**Isomenthone** (-)-Isomenthone fraction (19.1 g), b.p. 66~68°/6 mm, d_4^{23} 0.8988, n_D^{23} 1.4532, $[\alpha]_D^{23}$ -73.9° (homog.), obtained from geranium oil (*Pelargonium graveolens*) by fractional distillation, was reduced with sodium in aqueous ammonia according to the procedure previously reported¹. The product (17.0 g), b.p. 73~75°/4.5 mm, was recrystallised from nitromethane to give pure (-)-isomenthol (8.1 g), m.p. 81.0~81.8°. The resulting (-)-isomenthol (7.00 g) was treated with Beckmann's chromic acid at 47° to give pure (-)-isomenthone (6.12 g, Yield 88.56%), b.p. 67.0°/6 mm, d_4^{17} 0.9039, n_D^{17} 1.4544, MR 46.24 (Calcd. 46.19), $[\alpha]_D^{17}$ -94.0° (homog.).

Reduction of (-)-Isomenthone (-)-Isomenthone (5.33 g) was reduced with sodium (4.0 g) in aqueous ammonia and benzene, according to the procedure previously described¹. The reaction temperature was maintained in the range of 0~3°. The product was treated with semicarbazide hydrochloride in the same way as previously reported³. The unreacted menthone was completely converted into semicarbazone (0.36 g) and removed by steam distillation. The fraction, from which the contaminated menthone was removed, was distilled to give a menthol mixture (4.77 g, Yield 88.44% based on (-)-isomenthone), b.p. 75~77°/5 mm, m.p. 55~65°, $[\alpha]_D^{17}$ -8.77° (c, 19.378 in ethanol).

Separation of Menthol Isomers Recrystallisation of the menthol mixture (4.72 g) from *n*-hexane gave (-)-isomenthol (3.21 g, Yield 68.07% from menthol mixture), m.p. 81.2~81.9°. It gave the corresponding 3,5-dinitrobenzoate as pale yellow needles, m.p. 146.5~147.0°. *Anal.* Found: C, 58.55; H, 6.52. Calcd. for $C_{17}H_{25}O_6N_2$: C, 58.27; H, 6.33%.

Esterification of the material recovered from the mother liquors of the above-crystallisations of the menthol mixture gave crude 3,5-dinitrobenzoate (2.91

TABLE I. ABSORPTION CHROMATOGRAPHY OF ESTER-I (m.p. 127°)

Fraction No.	Eluted Solvent Total ml	Recovered Material	
		Weight mg	Melting point °C
1~9	90	0	—
10	100	0.6	153.5~154.0
11	110	1.6	153.5~154.0 (+)-Menthyl 3,5-
12	120	2.1	153.5~154.0 dinitrobenzoate
13	130	2.7	153.5~154.0
14	140	2.9	150.0~150.5
15	150	1.7	127~128
16	160	2.1	126~127
17	170	1.9	132~133 Mixture
18	180	1.0	137~138
19*	190	8.2	145.0~145.5 (-)-Isomenthyl
20*	200	2.8	145.0~145.5 3,5-
21~27*	270	0	— dinitrobenzoate
Total		27.6 mg	(Recovery 92%)

* Fractions 19~27 were eluted by 5% ether-*n*-hexane.

g, Yield 86.04% for theor.). Careful fractional recrystallisations of this ester from *n*-hexane gave the following fractions: (1) Ester-I, m.p. 127°, 1.20 g (Recovery 41.47% from crude ester); (2) Ester-II, m.p. 105~112°, 0.12 g (3.98%); (3) Ester-III, m.p. 87~89°, 1.12 g (38.60%); (4) Ester-IV, m.p. 54~62°, 0.21 g (7.32%); the experimental loss being 0.25 g (8.61%).

(1) Ester-I, m.p. 127°, $[\alpha]_D^{20}$ +19.68° (c, 11.028 in chloroform), was not altered on further recrystallisations. *Anal.* Found: C, 58.56; H, 6.37. Calcd. for $C_{17}H_{25}O_6N_2$: C, 58.27; H, 6.33%. From optical rotation, it probably consists of (±)-menthyl 3,5-dinitrobenzoate. In order to make a more detailed study of the composition, Ester-I (30.0 mg) was eluted by *n*-hexane on an alumina column (Brockmann Alumina, 9.0 g; Column diameter, 11 mm), and it gave two fractions, as shown in Table I. However, no other fraction was obtained. These fractions were identified by the mixed m.p. comparison with authentic samples.

From the result of chromatography, Ester-I seemed to be composed of approx. 45.7% of (+)-menthyl 3,5-dinitrobenzoate and 54.3% of (-)-isomenthyl 3,5-dinitrobenzoate. This proportion agreed well with values of 43.6% and 56.4%, calculated from the optical rotation of Ester-I.

(+)-Menthyl 3,5-dinitrobenzoate, m.p. 153°, used in the mixed m.p. method, was prepared from (-)-isomenthone by reduction with sodium and alcohol.

(2) Ester-II, m.p. 105~112°, probably consists of a mixture of Ester-I and Ester-III, but its composition

4) J. Read and A.M.R. Cook, *J. Chem. Soc.*, **1925**, 2782.

TABLE II. ABSORPTION CHROMATOGRAPHY OF ESTER-III (m.p. 87~89°)

Fraction No.	Eluted Solvent Total ml	Recovered Material	
		Weight mg	Melting point °C
1~11	110	0	—
12	120	1.1	153.0~153.5
13	130	2.4	153.0~153.5
14	140	2.7	130~131
15	150	3.3	88~90
16	160	2.4	87~89
17	170	2.1	91~93
18	180	2.1	91~94.5
19	190	1.9	91~94.5
20	200	1.9	91~93
21	210	1.5	91~93
22	220	1.3	91~92
23	230	1.0	91~92
24	240	0.9	90
25~29	290	0	—
Total		25.9 mg	(Recovery 86%)

was not determined.

(3) Ester-III, m.p. 87~89°, $[\alpha]_D^{20} +17.25^\circ$ (c, 10.726 in chloroform), could not be purified satisfactorily by recrystallisation. It probably consists of a mixture of 3,5-dinitrobenzoates of menthol isomers by elementary analysis. *Anal.* Found: C, 58.78; H, 6.42, Calcd. for $C_{17}H_{22}O_6N_2$: C, 58.27; H, 6.33%. Then, Ester-III (30.0 mg) was chromatographed on alumina, in the same way as described above, to give two fractions, m.p. 153.5° and m.p. 91~94.5°, as shown in Table II. The former fraction was identified to be (+)-menthyl 3,5-dinitrobenzoate by the mixed m.p. method. Crystallisation of the latter fraction (8.0 mg)

from methanol gave pale yellow needles (4.7 mg), m.p. 92~93.5°, mixed m.p. 96~98° with (–)-neoisomenthyl 3,5-dinitrobenzoate, m.p. 99.5~100°. The infrared spectrum of this substance (in nujol) agreed completely with that of (–)-neoisomenthyl 3,5-dinitrobenzoate.

This experimental result shows that Ester-III consists of approx. 30.1% of (+)-menthyl 3,5-dinitrobenzoate and 69.9% of (–)-neoisomenthyl 3,5-dinitrobenzoate. This proportion also agreed well with values of 30.1% and 69.9%, calculated from the optical rotation of Ester-III.

The authentic sample of (–)-neoisomenthyl 3,5-dinitrobenzoate, m.p. 99.5~100°, was prepared from (–)-isomenthone by reduction with lithium aluminum hydride.

(4) Ester-IV, m.p. 54~62°, was not further investigated because of the small quantity available.

Acknowledgements The author is indebted to Emeritus Prof. S. Takei, Prof. T. Mitsui, Prof. M. Nakajima, Dr. Y. Inouye and Mr. Y. Tagaki, University of Kyoto, for their kind advice and suggestions. He also wishes to express his sincere thanks to Prof. S. Shimizu, Shinshu University, for his kind guidance throughout this work, and to Mr. H. Okamura, Eikōdo and Co., for his generous gift of geranium oil. Thanks are also extended to Mr. K. Fujimoto, Miss. Y. Fukumoto for their assistance in carrying out this work.