

Studies on Camphor Series, VII. Catalytic Formation of Menthols and Menthones from l-Menthol.¹

By

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In the fifteenth article of the studies on catalytic action², the authors have noticed that menthone formed from l-menthol of the rotatory power $[\alpha]_D^{20} = -49.9^\circ$ by passing on the various reduced copper heated to a high temperature, yields menthone oxime which shows no definite optical rotatory power according to the catalyst of the different sources and to the reaction temperature :

Reduced copper prepared from	Reaction temperature	$[\alpha]_D$ of oxime
1. $\text{CuSO}_4 + \text{Excess alkali}$	200°	-15°
2. $\text{Cu}(\text{NO}_3)_2 + \text{Excess alkali}$	200°	-7°
3. " + NH_4OH	300°	-11°
4. " "	200°	-29°
5. " by ignition	300°	-20°
6. " "	200°	-31°

This observation not being satisfactorily explained by taking the consideration such as we described in the fifth article of this series, the partial transformation of l-menthone formed by the catalytic oxidation of l-menthol into d-isomenthone, has led to the supposition that some isomeric menthones, except d-isomenthone and l-menthone, should occur in the menthone fraction of the reaction product. Moreover, the fact that the isolation of an oxime of the melting point of 84° from the reaction product supports this conception, since it corresponds to that of r-menthone oxime or r-isomenthone oxime.

¹ The expenses of the research were shared from the Tōshōgū Three Centennial Commemorative Fund.

² These Memoirs.

200 grm. of l-menthol $[\alpha]_D = 49.9^\circ$, B. p. 211–212°, purified from commercial menthol (pharm. Jap.) by distillation, and confirmed not to contain any trace of d-neomenthol by determination of the melting point of the hydrogen phthlate, which has been isolated previously by Pickard and Littlebury from Japanese peppermint oil¹, were passed at 250–260° on reduced copper obtained by reduction at 200° from copper oxide prepared from copper nitrate and one mol of ammonia, and 179 grm. of the menthone-menthol fraction B. p. 200–220° were obtained by the fractional distillation of the reaction product.

The fraction without further distillation to avoid the racemisation of menthone by heat, was soon treated with hydroxylamine according to the direction of E. Beckmann² to separate the menthone part from the menthol.

The oxime thus obtained composed of solid and liquid forms which were separated mechanically and found to be composed, 33 per cent. of the former and 67 per cent. of the latter, of the rotatory power $[\alpha]_D = -10^\circ$ in an alcohol solution.

r-Menthone.

From the solid oxime, the pure menthone oxime of M. p. 84° by fractional crystallisation from alcohol was isolated. The yield was 35 per cent. (15 grm.) of the crude oxime. It shows no rotatory power in an alcohol solution, and by hydrolysis yield 70 per cent. of free menthone.

The free menthone thus obtained boiled at 206–207°, $n_D^{25} = 1.4430$; $d_4^{25} = 0.8912$, and gave the semicarbazone of M. p. 157°. For the confirmation of racemic menthone, 5 grm. of the menthone were reduced by means of metallic sodium in a medium of moist ether, following the directions given by Pickard and Littlebury³ and 4 grm. menthol of B. p. 209–212°; M. p. 33–34°, were obtained which gave the hydrogen phthlate M. p. 131° and the magnesium phthlate M. p. 120–122°.

l-Menthone, d-Isomenthone and r-Isomenthone.

According to the literature,⁴ d-isomenthone which should be formed by catalytic inversion of l-menthone, gives liquid oxime. Consequently

1 J. Chem. Soc., **101**, 109 (1912).

2 J. prak. Chem. (2), **55**, 17 (1897).

3 Loc. cit.

4 E. Beckmann: J. prak. Chem. (2), **55**, 14 (1897); Ber. D. Chem. Ges., **42**, 846 (1909); H. D. Gardner, W. H. Perkin jun. and H. Watson: J. Chem. Soc., **97**, 1760 (1910); O. Wallach: Lieb. Ann., **362**, 272 (1908); **397**, 218 (1913); R. S. Hughesdon, H. G. Smith and J. Read: J. Chem. Soc., **123**, 218 (1923).

the liquid oxime was converted into a semicarbazone, in order to isolate d-isomenthone in a pure state, which was then by repeated fractional crystallization in an alcohol solution divided into the following fractions, and the melting point and the rotatory power were determined of each fraction :

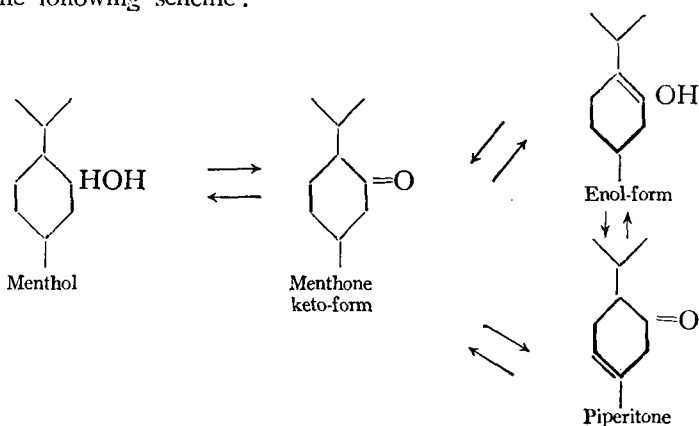
Fraction	M. p.	Yield	α_D	Remark
1.	111-120°	0.1 gm.	...	
2.	156-169°	0.2 „	+	d-Isomenthone
3.	176-195°	0.6 „	...	
4.	184°	13.0 „	-	l-Menthone
5.	212°	0.1 „	slightly positive	r-Isomenthone

The fourth fraction was confirmed to be composed of pure l-menthone by determination of the melting point of the mixture of the sample and pure l-menthone semicarbazone. The fifth fraction was assumed to be composed of r-isomenthone owing to its high melting point.¹

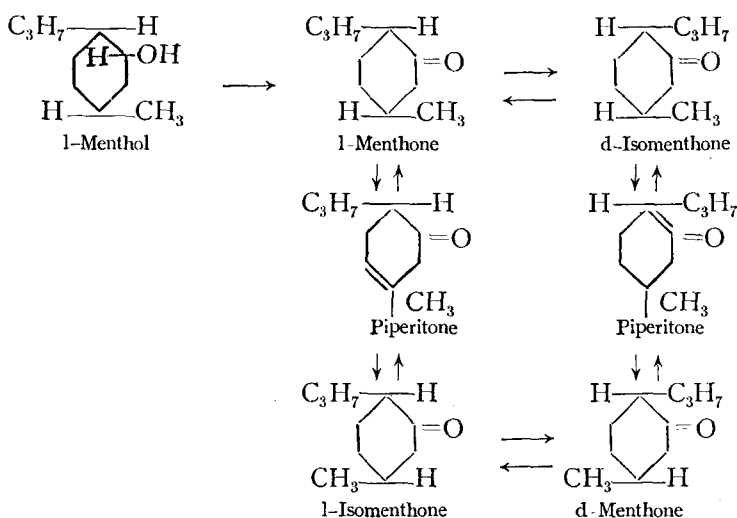
Thus it has been noted that r-menthone, l-menthone, r-isomenthone and d-isomenthone occur in the reaction product from menthol by the catalytic action of reduced copper at 250°, though some of them could not be isolated in a pure state.

How can we satisfactorily explain the mechanism of the formation of these isomeric menthones from l-menthol? l-Menthone formed by the catalytic oxidation of l-menthol suffers by the catalytic action of the catalyst or the heat and is caused to yield d-isomenthone but not other isomers.

The formation of racemic menthone and also isomenthones could not be perfectly illustrated, unless we admit the existence of piperitone in the course of the catalytic action of reduced copper on l-menthol, as will be seen in the following scheme :



¹ Wallach denotes 212°, Pickard 217° and Smith 219-220°, for the melting point of racemic isomenthone semicarbazone.



The assumption for the formation of the isomeric menthone seems much more than we refer to the fact that l-menthone when it comes into contact with reduced copper at 300° as we have noticed previously, was converted into thymol. Moreover, the facts which support the present conception mentioned above were that piperitone has been found in Japanese oil of peppermint¹ and other essential oils, which by catalytic reduction with hydrogen and nickel was actually reduced to menthone², and that recently Dr. T. Hiraizumi in our laboratory has isolated this compound by means of benzaldehyde from the reaction product of menthol by passing on reduced copper at 250° .

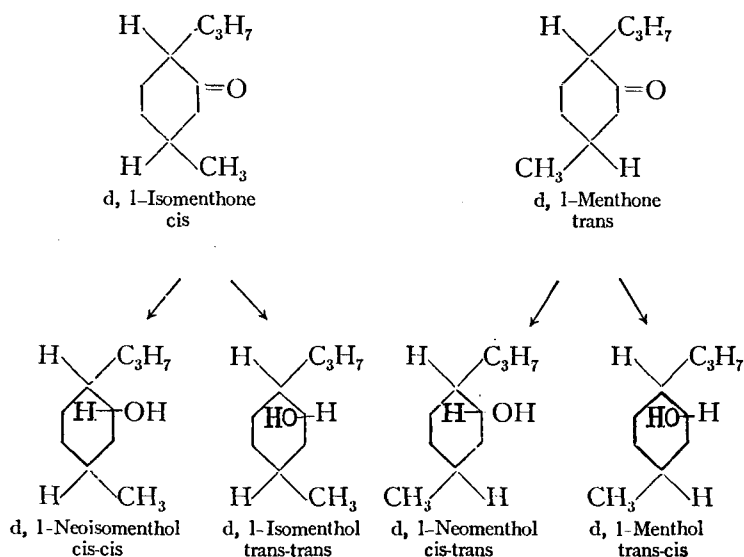
With respect to the spatial configuration of menthones, the authors are apt to denote the ordinary l-menthone in trans-type and the isomeric isomenthone in cis-type. One reason is that the atomic groups in optically active cyclic compounds occurring in nature were configurate, so far as we usually regarded, in the trans-form.

r-Menthol, d-Neomenthol and r-Neomenthol.

Menthol possesses three asymmetric carbon atoms, and therefore theoretically should be capable of existing in four spatial configurations, each of which would have two optical antipodes and one racemic one. The relationship between menthones and menthols with respect to the spatial configuration will be illustrated in the following diagram :

¹ Report of Schimmel & Co., Oct. 1910, 79; O. D. Robert: J. Chem. Soc., **107**, 1465 (1915).

² H. Smith and J. Read: J. Chem. Soc., **123**, 2916 (1923).



H. Smith and J. Read¹ have reported that *r*-isomenthone and menthol of M. p. 34-41° were obtained from *r*-piperitone by catalytic reduction with reduced nickel, and G. Vavon and A. Couderc² have obtained menthols by the catalytic action of reduced nickel and hydrogen on *l*-menthone, in which neomenthol was predominant. *r*-Menthol and *r*-neomenthol were isolated by Pickard from the reduction products of thymol by the aid of reduced nickel and hydrogen.

It is, therefore, highly probable from the above statements, that *r*-menthol, *r*-neomenthol and isomenthols would occur in the menthol fraction which should result by the catalytic reduction of *r*-menthone and *r*-menthone. To isolate these menthols, the following experiment was carried out on the menthol fraction.

The fraction, containing menthols which remained unaffected by the action of hydroxylamine, was soon transformed into hydrogen phthlate according to the directions of Pickard³. The acid esters (I) of menthols were divided by repeated fractional crystallization in acetic acid solution into six portions, and the melting point and the rotatory power of each fraction were determined. Purification of the fractions was further attempted by converting into their magnesium salt, following directions of Pickard, and then reconvertng into the free acid esters (II).

¹ Loc. cit.

² C. R., **179**, 405 (1924).

³ Loc. cit.

Hydrogen phthlate (I)		Mg. salt	Hydrogen phthalate (II)	
M. p.	$[\alpha]_D$	M. p.	M. p.	
1. 97-100°	—	{ 105-106° 110°	110-120°	
2. 108-109°	-55.1°	{ 118-120° 109-110° 103°	107-108°	
3. 124-125°	-9.6°		119-122°	by repeated { 105-106° crystallization { 130-132°
			133-135°	
4. 142°	—	68-110°	139-142°	
5. 162°	—	74-75°	145°	
6. 174°	+29°	79-80°	164-165°	
			174°	

Hydrogen phthlate			Free menthol		Remarks
M. p.	$[\alpha]_D$	Yield	M. p.	$[\alpha]_D$	
1. 110-120°	—	0.1 gm.	—	—	
2. 107-108°	-90.7°	0.9 "	} combined together	35.5-37°	-39.7° Mostly l-menthol.
3. 105-106°	-76.3°	1.5 "			
4. 130-132°	-7.4°	1.2 "			
5. 133-135°	-17.2°	0.2 "	32-33°	-4.3°	Racemic menthol.
6. 139-142°	+6.9°	0.2 "	—	—	
7. 145°	+24.7°	0.9 "	liquid	+9.4°	Racemic menthol and d-neomenthol.
8. 164-165°	+43.8°	0.4 "	—	—	
9. 174°	+29.1°	1.0 "	liquid	+7.3°	Racemic neomenthol and d-neomenthol.

The free menthol fractions obtained by hydrolysis from the corresponding hydrogen phthlates (II) were examined as to the melting point and rotatory power, by which to settle the configuration of the groups in the molecule.

From the data above mentioned, the authors have concluded that r-menthol, r-neomenthol and d-neomenthol, as we expected, should occur in the reaction product, though their identification of the isolated compounds was lacking, due to the small quantity of the material.

We can not, however, content merely to examine the menthones and menthols impure state as to the melting point and rotatory power, and further investigation of the isolation of these compounds is in progress in our laboratory and will be discussed again in another article.