Synthesis of Racemic Menthol

WALLACE R. BRODE AND ROBERT W. VAN DOLAH[1]

The Ohio State University, Columbus, Ohio

A new method for the production of racemic menthol is described. The process is based on the discovery that a different mixture of isomeric menthols, richer in the desired *dl*-menthol, is obtained by copper chromite- rather than nickel-catalyzed hydrogenation of thymol. An attempt is made to rationalize this observation by a hypothesis for stereochemical inductance of configuration, which is aided circumstantially by evidence obtained in the copper chromite reduction of *o*- and *m*-cresols.

WITH the elimination of the major natural sources of menthol due to the onset of World War II, a considerable amount of interest arose in synthetic menthol. Many processes have been developed for the synthesis of menthol from thymol or *m*-cresol, but in general the resulting products have been of poor quality because of the presence of the isomeric menthols, different in configuration from the natural product (*21*). Menthol identical to the natural product has been synthesized from citronellal (*8*), but the supply of the latter became equally critical. Recently a process was published by which a pure racemic menthol was obtained in good yield through fractional distillation of the menthones obtained from thymol, followed by a second fractional distillation, after further reduction, to separate menthol from neomenthol (*2*).

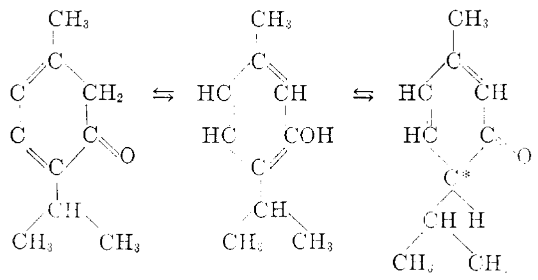
The problem of synthesizing racemic menthol from nonasymmetric starting materials is made difficult by the existence of four racemic modifications. The configurations shown in Figure 1 are generally assigned to these modifications, despite a recent publication in which the methyl and isopropyl groups in natural menthol were indicated as being *cis* forms (*9*). For many purposes the presence of the isomeric menthols in the synthetic product is of little importance, since it has been shown that the isomers differ but little in toxicity or in pharmacological properties (*3, 11, 16, 19*). They are, however, characterized by different, and, in the case of the stereoisomers other than *dl*-menthol, unpleasant tastes and odors (*9*). *dl*-Menthol of good quality is virtually indistinguishable from the natural product. The presence of relatively small amounts of the isomeric forms is distinguishable by the musty odor imparted to the product. In recognition of the similarities between racemic and natural *l*-menthol, the British (*4*), German (*18*), and recently, United States Pharmacopoeias (*20*) have given the former official status.

A mixture of inactive menthols is easily obtainable through the catalytic hydrogenation of thymol, which in turn is available through the condensation of *m*-cresol with isopropylene, isopropyl chloride, or other related compounds. The mixture of stereoisomers as usually obtained is difficultly separable into its components, although the patent literature gives methods for the isolation of *dl*-menthol by such procedures as fractional distillation or crystallization, or recrystallization of ester derivatives. It was felt that a possible solution to the problem lay in changing the proportions of isomeric menthols obtained on catalytic hydrogenation of thymol to a mixture richer in *dl*-menthol, since the more common techniques of separation and purification may often be successfully accomplished if the crude material is sufficiently rich in the desired isomer. Since the catalyst in general use for such hydrogenations is nickel in various forms, it was desirable to attempt the reduction of thymol with a different catalyst, one which was thought to effect hydrogenation through a different mechanism. Such a catalyst is copper chromite.

THEORY OF COPPER CHROMITE REDUCTION

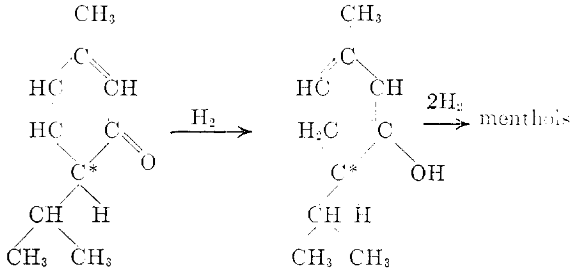
Musser and Adkins (*12*) first noted that copper chromite effects the reduction of β-naphthol and monohydroxy derivatives of biphenyl in the oxygenated rings, leaving the other rings unreduced. Moreover, under the same conditions of reduction they noted that the ethers of these phenolic compounds could not be hydrogenated. This observation, together with the knowledge that nickel catalysis would effect the reduction of phenols and their ethers with essentially equal ease, led the authors to postulate that the reduction of phenolic compounds by means of copper chromite proceeds through the tautomeric ketones. If this theory is applied to the reduction of thymol some interesting conclusions may be drawn.

In the reduction of thymol, formation of the tautomeric ketones may lead to a compound containing an asymmetric carbon atom, as indicated in Equation 1.



(1)

This asymmetric carbon atom (C*) may then have an inductive effect on the formation of succeeding asymmetric centers. This inductive effect is often seen in the synthesis of asymmetric compounds. In the case of the menthols it has been pointed out by Read (*14*) that the configuration of the carbon atom in question has a powerful inductive effect on the configuration of other asymmetric centers in the molecule. The hydrogenation may then proceed by 1:6 addition to yield an enol, which may be further reduced as such or may undergo ketonization to the beta unsaturated ketone before reduction to menthol. The course of this reaction is shown in Equation 2.



(2)

It is also possible that on ketonization the hydrogen migrates to carbon 2, in which case an asymmetric center is formed at carbon 1 (carbon with methyl attachment) in the first step of the hydrogenation. Here again the configuration of this carbon would be expected to influence the configuration of subsequent asymmetric centers, although the effect should not be so pronounced (*14*).

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[1] Present address, United States Naval Ordnance Test Station, Inyokern, Calif.

No menthone could be isolated from the reduction mixtures of thymol even when the reduction was stopped at 50% completion; nor could any partially unsaturated products be isolated from the reduction mixtures. The presence of varying quantities of menthones has been reported in most reduction mixtures following hydrogenation with a nickel catalyst. This discrepancy between the two results would in itself suggest different modes of reduction. The absence of menthone or menthene derivatives might indicate that the reduction proceeds by 1:4 addition to the enol rather than addition after ketonization.

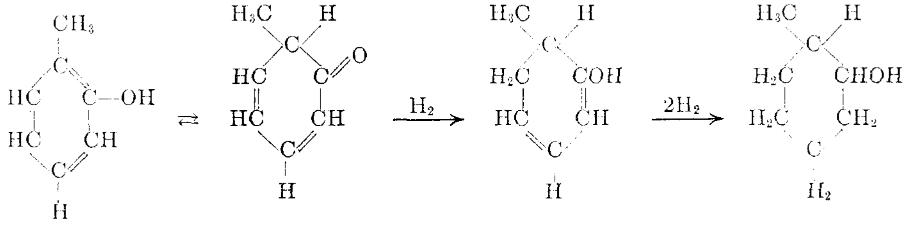
Assuming the inductive stepwise mechanism, an increased yield of one stereoisomer in the reduction mixture could be expected, although one could not forecast with certainty which isomer would predominate. It was found that, by copper chromite reduction, a yield of 81% *trans*-menthols (*dl*-menthol and *dl*-neomenthol) and 60 to 70% *dl*-menthol was obtained. In contrast to this a hydrogenation of thymol using nickel on kieselguhr (Universal Oil Products Company) gave only 56% *trans*-menthols and about 40% *dl*-menthol. The yield of *trans*-menthols is important in the purification, since *dl*-neomenthol may be readily separated from *dl*-menthol in the procedure to be described later. To test further this catalytic specificity of copper chromite catalyst, *o*- and *m*-cresols were reduced with copper chromite. These experiments were as follows:

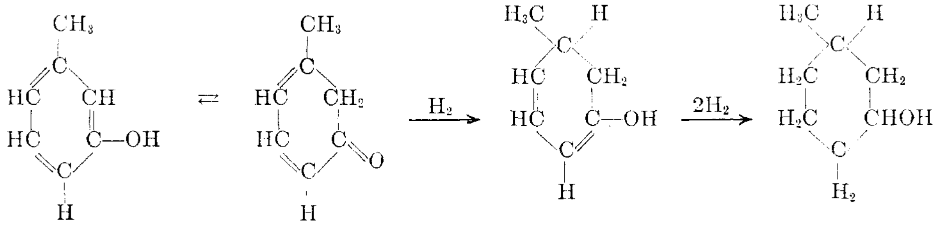
The cresols used were Coleman and Bell pure grade. Before reduction they were distilled under reduced pressure in an atmosphere of nitrogen and yielded water-white products. The cresols were hydrogenated with 10% of their weight of copper chromite catalyst at pressure of 500 to 2600 pounds per square inch for 3 hours at temperatures of 250° to 300° C. The hydrogenated products were filtered from the catalyst and distilled through a column of twelve plates efficiency to remove the toluene and unreduced cresol. The results were as follows: 2-methylcyclohexanol, yield 86.5%, n_D^{20} 1.4611; 3-methylcyclohexanol, yield 86.4%, n_D^{20} 1.4573.

The refractive indices of the *cis* and *trans* isomers of 2- and 3-methylcyclohexanols as published by Skita and Faust (*17*) and of the products resulting from the above reductions are shown in the following table:

	2-Methyl-cyclohexanol	3-Methyl-cyclohexanol
cis	1.4640	1.4572
trans	1.4611	1.4550
By copper chromite reduction	1.4611	1.4573

The results indicate essentially quantitative yields of *trans*-2-methylcyclohexanol and *cis*-3-methylcyclohexanol. Figure 2 gives an interesting comparison between the configurations of the methylcyclohexanols obtained by copper chromite reduction with that of *dl*-menthol.


(3)


(4)

REDUCTION OF CRESOLS

The reduction of *o*- and *m*-cresols through a similar inductive mechanism as postulated for the reduction of thymol is shown in Equations 3 and 4.

In Equation 3 an asymmetric center may be formed on carbon 2 through ketonization which could then allow for the induction of configuration of carbon 1. In the reduction of *m*-cresol the primary ketonization does not form an asymmetric center. Further reduction of the tautomer, however, does form an asymmetric carbon atom, which can then exert an influence on the configuration of the second asymmetric center. Although only one possibility of reduction is shown in these equations, if the ketonization and subsequent stepwise reduction mechanism is followed, an asymmetric center is formed at some time in the reaction which may then influence the formation of subsequent asymmetric centers.

REGENERATION OF CATALYST

The copper chromite used in carrying out the reductions reported here was prepared by a procedure given by Lazier (*10*). As has been previously described in the literature, different preparations of the catalyst tended to have different activities. These differences in activity are partially accounted for by a lack of uniformity in the preparation of different batches. Calingaert and Edgar described a process whereby a uniform and active copper chromite catalyst can be prepared on a semiplant scale (*5*).

It was of interest to see whether the efficiency of a particular sample of copper chromite decreased with continued use in successive hydrogenations. Copper chromite has a tendency to be reduced, under the conditions of hydrogenation, to an inactive red substance containing copper in the cuprous state. This reduction may possibly be catalyzed by water, usually present in the reduction of thymol through hydrogenolysis of the menthol to menthane. This tendency is, to a certain extent, circumvented by the incorporation of small amounts of barium or other alkaline earth oxides in the catalyst (*6*). In these reductions it was found that the catalyst, under the conditions employed, became less efficient with continued use and after two or three runs had a copper red color. In handling the used catalyst it was noted that the material tended to turn slowly black or dark green on the outside and to evolve a noticeable amount of heat. This led to the development of a method for the regeneration of used copper chromite catalyst.

It was found that if the catalyst, after washing with a solvent such as acetone, is dried and placed in an oven at 100° to 120° C., a decidedly exothermic reaction follows. If too high a temperature was used, the reaction was accompanied by a bright glowing of the catalyst mass, which left a grayish-green material found to be less active. Advantageously the spent catalyst is spread out in a thin layer, and the oven supplied with air when large quantities are to be treated. This gives a product of improved appearance and avoids the production of too much heat by the exothermic reaction. The catalyst thus regenerated is then ready for use without further treatment. Such a catalyst was found to have an equal or possibly greater activity than had the fresh catalyst and was more active than catalysts used for successive hydrogenation without such treatment. One sample of copper chromite was used for five successive reductions of thymol with a regeneration following the third run. By this regeneration the catalyst cost in a process which requires the use of large quantities of catalyst is measurably decreased. Since this work was completed, this method has been independently noted and described by Dunbar and Arnold (*7*).

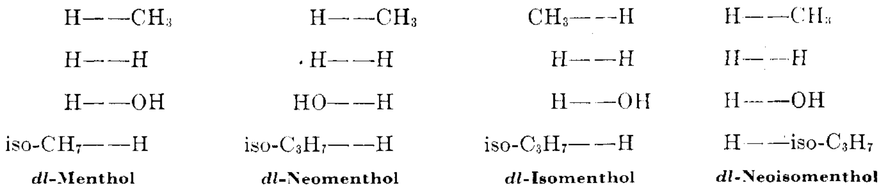


Figure 1. Configurations Assigned to Four Racemic Modifications of Menthol

HYDROGENATION OF THYMOL WITH COPPER CHROMITE

The reduction of thymol with copper chromite is not so efficient as when nickel is used for the catalysis. However, when a catalyst of sufficient activity is used and efficient mixing of the hydrogen with the thymol is accomplished, the reduction may be carried out within a reasonable length of time. The results of a number of reductions of thymol are listed in Table I.

A typical reduction, as carried out in the laboratory, is as follows:

> The equipment used consisted of a rocking steel autoclave of 3100-cc. capacity (American Instrument Company) which was supplied with a potentiometric thermoregulator (Brown Instrument Company). Hydrogen was supplied to the autoclave at the pressures obtainable from the cylinder. Seven hundred and fifty grams of thymol (U.S.P. quality) and 75 grams of copper chromite catalyst were placed in the autoclave, and air was removed by displacement with hydrogen; then the temperature was raised to 200° C. Hydrogenation was carried on at pressures varying from 800 to 1400 pounds per square inch until the reduction, as indicated by the uptake of hydrogen, was fairly complete. The crude reduction mixture was filtered from the catalyst by means of a basket centrifuge. The product gave the following values: freezing point 9° C., n_D^{20} 1.4460, methane 2%, thymol 0.8%, yield of mixed isomeric menthols (by difference) 97%.

The per cent menthane given here and in the table includes the water formed in the reaction and was determined by distillation through a short column. The amount of menthane formed is, to a considerable extent, dependent upon the temperature of the reaction (Table I). In the reduction carried out at 300° C., 50% of the reaction mixture consisted of menthane while some thymol still remained unreduced. This would indicate that the hydrogenolysis of menthol to menthane runs concurrently with the reduction of thymol to menthol. It was also found that, if the reaction were allowed to continue at 200° after a theoretical conversion to menthol, as determined from the hydrogen uptake, a considerable amount of menthane was produced. It is difficult to correlate the production of menthane with variation in the catalyst used, although there are some indications that a more active catalyst produces less menthane. Adkins *et al.* (*1*) studied the effects on the ratio of alcohol to hydrocarbon resulting from copper chromite reduction of esters produced by modifications of the catalyst, but could obtain little or no correlation.

An interesting correlation was found between the amount of thymol placed in the autoclave and the length of time necessary for reduction. The greater the amount of thymol placed in the autoclave, the longer the time it took for reduction, other factors being equal. This was probably due to a lack of thoroughness in the mixing of the thymol with the hydrogen or to a lack of solubility of the hydrogen in the thymol. It was also noted that, if the autoclave had been used for a nickel reduction prior to its use for copper chromite reduction, there was a considerable induction period before hydrogenation began. This induction period could be circumvented by the rapid reduction of acetone with copper chromite in the autoclave prior to its use for thymol.

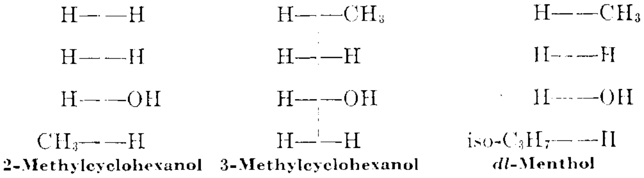


Figure 2. Configurations of Methylcyclohexanols and *dl*-Menthol

The table lists the freezing points and the refractive indices of the crude reduction mixtures. These are not of great significance, but illustrate some of the variations encountered when the conditions of hydrogenation are changed. Both properties are largely dependent on the amounts of thymol and menthane found in the mixture.

One of the greatest difficulties in completing this study was that of determining the stereoisomeric composition of the mixture. A method was developed whereby the amounts of *trans*-menthol, as compared to the *cis*-menthol, could be determined. This method consisted of oxidizing the menthols in a distilled sample to the corresponding menthones and determining the ratio of the two menthones by means of the refractive index. This method will be briefly described. The procedure for the oxidation of the mixture to menthone is modified after that of Sandborn (*15*).

> A stock solution of oxidant was prepared containing 134 grams of potassium dichromate dissolved in 111 grams of concentrated sulfuric acid and 670 cc. of distilled water; 76 cc. of this were sufficient for the oxidation of a 10-gram sample of menthol. The menthol was added to the oxidant and stirred vigorously until the maximum temperature was reached (around 49–50° C.). The reaction mixture was warmed gently until the black complex had decomposed completely, and then the mixture was steam-distilled. The steam distillate was extracted with ether, dried, then distilled, and the refractive index taken of the menthone mixture.

TABLE I. HYDROGENATIONS OF THYMOL

Run No.	Thymol, Grams	Catalyst, Grams	Temp., ° C.	Pressure, Lb./Sq. In.	Time, Hr.	n_D^{60}	F.P., ° C.	Thymol, %	Menthane, %	Menthols, %
1	1500	150	200–40	2820–780	23	1.4459	1	1.54	4	94
2	750	75	200	1400–800	13	1.4460	9	0.48	1–2	98
3	750	75[a]	200–40	1600–1000	10	1.4444	−3	0.92	16	83
4	750	75[b]	220	2880–1680	13	1.4554	−21	20.3	10	70
5	400	40[c]	220	3000–1400	6	1.4449	−7	1.58	10	88
6	400	40[d]	220	2900–1340	5	1.4448	−6	1.07	8	91
7	400	40	300	3000–1560	1	1.4394	−20	3.94	50	46
8	500	25[e]	220	2500–660	6	1.4455	1	0.2	4	96

[a] Second consecutive use.
[b] Third consecutive use.
[c] After regeneration.
[d] Second use after regeneration.
[e] From a more active preparation.

The steam distillation was used to eliminate the necessity of repeated washing of the ether extract with water or alkalies to remove residual acid. It was found by running a control on *l*-menthol that the steam distillation did not cause measurable inversion. Although this method is not very accurate, it gives a fair approximation of the ratio of isomers present in the mixture.

A second but tedious method (developed by The Wm. S. Merrell Company), consisting of the fractional crystallization of the acid phthalate esters, was used to evaluate the stereoisomeric mixture obtained on reduction of thymol. These were prepared by reacting 20 grams of menthol mixture with 22 grams of phthalic anhydride in pyridine for 3 hours. The esters were thrown out by adding the reaction mixture to dilute hydrochloric acid, and the stereoisomeric forms were isolated by recrystallization from petroleum ether. By this method only the neomenthol and menthol contents were usually determined, the *cis*-menthol content being determined by difference. It was found that a typical copper chromite reduction mixture contained 16% neomenthol and 61% menthol. The menthone oxidation method gives, for typical copper chromite reduction mixtures, 80% *trans*-menthols.

PURIFICATION OF CRUDE MIXTURE

Even with the increased amount of *dl*-menthol in the crude mixture, purification by such methods as distillation or recrystallization was still unsatisfactory. However, the mixture could be readily purified by means of esterification with phthalic anhydride as originally described by Pickard and Littlebury (*13*). The best conditions found for the purification are as follows:

> One hundred grams of crude menthol are mixed with an equal weight of phthalic anhydride and heated under a reflux condenser with stirring at 100–130° C. for 2 hours. At the conclusion of the esterification the melt is allowed to cool to 85–90° C., and 300 cc. of petroleum ether (boiling point 90–95° C.) are added and stirred thoroughly into the melt. When the mixture is allowed to cool, the ester slowly crystallizes out. To avoid the formation of a hard mass of solid in the bottom of the container, the mixture should be stirred gently until crystallization has well begun. This gives a readily filterable slurry. The ester is removed by filtration and washed with 200–300 cc. of the same solvent by resuspension of the solid, stirring, and subsequent filtration. It may then be further purified by recrystallizing from a minimum of hot petroleum ether and filtering hot to remove any difficultly soluble *dl*-neomenthyl acid phthalate. The ester thus obtained is saponified by refluxing 1 hour with 2.2 molar proportions of sodium hydroxide and then steam distilling. The menthol is separated from the aqueous layer and dried by distillation or treatment with a drying agent.

By this method 60% yields of menthol (freezing point 26–28° C.) were obtained, the product having an excellent odor and taste; this indicated the absence of appreciable amounts of the stereoisomeric menthols. The phthalic acid is recovered by acidifying the hot residue from the steam distillation and filtering hot to remove any unsaponified ester. On cooling, the acid crystallized out in a relatively pure condition. The isomeric esters may be obtained from the mother liquors by evaporation and, after saponification, may be isomerized by any of several well known methods. By adding this isomerized mixture to succeeding hydrogenation crudes, the over-all yield of *dl*-menthol may be increased.

ACKNOWLEDGMENT

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Based on a dissertation submitted by Robert W. Van Dolah to the faculty of The Ohio State University in partial fulfillment of the requirements for the degree of doctor of philosophy.

Storage of Commercial Dehydrated Alfalfa Meal

RALPH E. SILKER[1], W. G. SCHRENK, AND H. H. KING
Kansas Agricultural Experiment Station, Manhattan, Kans.

THIS storage study was undertaken in the hopes of finding a possible postwar means of utilizing the natural cooler storage which was developed as a wartime expedient. The effect of different types of bags for storage of dehydrated alfalfa meal was also a consideration.

The dehydrated alfalfa meal used in this study was placed in a blender and mixed thoroughly. The meal used in the first series was of relatively high carotene content and was placed in regular size plain burlap bags, small plain burlap bags, small waterproofed burlap bags, plain paper bags, and two types of paper bags containing special asphalt-laminated sheets. The regular burlap bags contained 100 pounds of meal, whereas all of the others held approximately 25 pounds. A lower carotene meal was chosen for the second series, but no paper bags were available for samples of this meal.

The plain burlap bags were sewed by hand, and all of the other bags were closed by use of a stapling machine. Precautions were taken to avoid trapping air above the meal in the stapled bags.

The various bags of meal in each series were placed in a single

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[1] Present address, The W. J. Small Company, Inc., Kansas City, Mo.