



A Publication  
of Reliable Methods  
for the Preparation  
of Organic Compounds

## Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at [http://www.nap.edu/catalog.php?record\\_id=12654](http://www.nap.edu/catalog.php?record_id=12654)). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

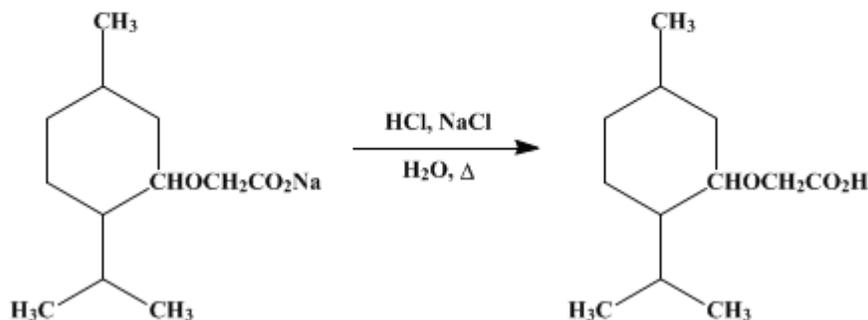
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*These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

*Organic Syntheses, Coll. Vol. 3, p.544 (1955); Vol. 23, p.52 (1943).*

## ***L*-MENTHOXYACETIC ACID**

**[Acetic acid, (menthyloxy)-, *L*-]**



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### **1. Procedure**

A 5-l. three-necked round-bottomed flask is fitted with a mechanical stirrer (Note 1) and a reflux condenser bearing a calcium chloride tube. A solution of 400 g. (2.56 moles) of *L*-menthol (crystals, m.p. 41–42°) in 1 l. of dry toluene (Note 2) is placed in the flask, and to it is added 70 g. (3.04 gram atoms) of clean sodium. The third neck of the flask is then tightly closed with a cork stopper, and the flask is heated in an oil bath until the toluene refluxes gently. As soon as the sodium has melted, stirring is begun and is maintained at such a rate that the sodium is broken into fine globules.

After the reaction mixture has been refluxed for 15 hours, the stirrer is stopped, the reaction mixture is allowed to cool, and the excess sodium (Note 3) is carefully removed. The apparatus is then assembled as before (Note 1), but with a 1-l. separatory funnel fitted into the third neck of the flask (Note 4). The temperature of the oil bath is raised to 85–90°, and with continued stirring, a solution of 95 g. (1.01 moles) of monochloroacetic acid (Note 5) in 800 ml. of warm dry toluene is added from the separatory funnel at such a rate that refluxing is not too vigorous. A heavy precipitate of sodium chloroacetate forms immediately. After all the chloroacetic acid has been added, the mixture is refluxed and stirred for 48 hours. During this period, the stirring must be as thorough as possible; it is necessary to add 1–1.5 l. of dry toluene, and the stirrer must be stopped at frequent intervals while the solid material is removed from the side of the flask.

When the reaction is complete, the flask is removed from the oil bath and the cooled reaction mixture is transferred to a 5-l. separatory funnel and extracted with three 1-l. portions of water (Note 6). The water extract is carefully acidified with 20% hydrochloric acid, and the crude menthoxyacetic acid, which collects on top as a brown oil, is extracted with three 200-ml. portions of benzene. The benzene extracts are combined, and the solvent is removed by distillation on a steam cone. The residue is then fractionally distilled under reduced pressure. The fraction boiling below 100°/20 mm. is mainly water and toluene. The second fraction boiling at 100–115°/8–10 mm. is impure *L*-menthol and may be saved for redistillation (Note 6). The yield of *L*-menthoxyacetic acid, boiling at 134–137°/2 mm. (150–155°/4 mm.),  $[\alpha]_D^{25} -92.4^\circ$ , amounts to 166–180 g. (78–84%).

### **2. Notes**

1. The success of the reaction depends largely on the type of agitation used. A stainless-steel stirrer of the anchor type with a gas-tight rubber or metal-graphite bearing serves well because of its strength. It should be operated at high speed in the first part of the reaction in order to powder the [sodium](#); in the second stage vigorous stirring is not so essential, but the solid and liquid phases should be mixed efficiently.
2. The [toluene](#) may be dried by refluxing it over metallic [sodium](#) for several hours. It is distilled from the [sodium](#) into a receiver protected from the air by a calcium chloride tube.
3. The excess [sodium](#) should amount to about 11 g. If the [sodium](#) remains divided, it is removed by filtering the hot mixture through glass wool.
4. It is not advisable to leave the separatory funnel attached to the flask during the long period of stirring which follows, as the constant, heavy vibration tends to loosen the connection. As soon as it has been used, the funnel should be replaced by a tightly fitting cork stopper.
5. The commercial grade (m.p. 61–63°) of [monochloroacetic acid](#) should be ground and thoroughly dried over concentrated [sulfuric acid](#) in a vacuum desiccator for 2 days. The yield was lowered by about 10% when the [chloroacetic acid](#) was used without previous drying.
6. The [toluene](#) layer, containing the [menthol](#) formed in the reaction, is saved for the recovery of both the [toluene](#) and the [menthol](#), which are separated by distillation under atmospheric pressure. The *l*-[menthol](#) collected at 210–212° (cor.) amounts to 150–225 g.

### 3. Discussion

*l*-Menthoxycetic acid has been prepared only by the action of sodium menthoxide upon monochloroacetic acid.<sup>1</sup>

This preparation is referenced from:

- [Org. Syn. Coll. Vol. 3, 547](#)

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### References and Notes

1. Frankland and O'Sullivan, *J. Chem. Soc.*, **99**, 2325 (1911); Rule and Tod, *J. Chem. Soc.*, **1931**, 1929.

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### Appendix

#### Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

[sodium menthoxide](#)

[sulfuric acid](#) (7664-93-9)

[hydrochloric acid](#) (7647-01-0)

[Benzene](#) (71-43-2)

[chloroacetic acid](#),  
[monochloroacetic acid](#) (79-11-8)

[sodium chloroacetate](#) (3926-62-3)

[toluene](#) (108-88-3)

sodium (13966-32-0)

menthol,  
l-menthol (15356-60-2)

menthoxyacetic acid,  
l-MENTHOXYACETIC ACID,  
Acetic acid, (menthyloxy)-, l- (40248-63-3)