



A Publication  
of Reliable Methods  
for the Preparation  
of Organic Compounds

## Working with Hazardous Chemicals

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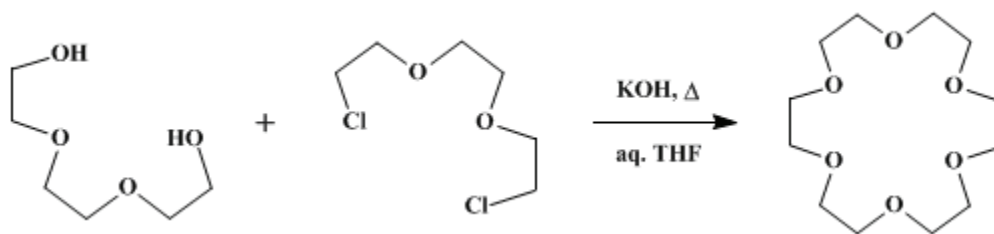
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*These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

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## 18-CROWN-6

### [1,4,7,10,13,16-Hexaoxacycloöctadecane]



Submitted by George W. Gokel<sup>1</sup>, Donald J. Cram<sup>2</sup>, Charles L. Liotta<sup>3</sup>, Henry P. Harris<sup>3</sup>, and Fred L. Cook<sup>3</sup>.

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### 1. Procedure

*Caution! Crown ethers may be toxic.<sup>4</sup> Due care should be exercised in the preparation and handling of 18-crown-6. An explosion has been reported during the thermal decomposition of the crude 18-crown-6-potassium salt complex; see (Note 8).*

A 3-l., three-necked flask equipped with a mechanical stirrer, a reflux condenser, and an addition funnel is charged with 112.5 g. (100.0 ml., 0.7492 mole) of triethylene glycol and 600 ml. of tetrahydrofuran (Note 1). Stirring is begun and a 60% potassium hydroxide solution, prepared by dissolving 109 g. (1.65 moles) of 85% potassium hydroxide in 70 ml. water, is added (Note 2). The solution warms slightly. After about 15 minutes of vigorous stirring (the solution begins to develop color and gradually becomes rust brown; (Note 3)), a solution of 140.3 g. (0.7503 mole) of 1,2-bis(2-chloroethoxy)ethane (Note 4) in 100 ml. of tetrahydrofuran is added in a stream. After the addition is complete, the solution is heated at reflux and stirred vigorously for 18–24 hours. The solution is allowed to cool and the bulk of the tetrahydrofuran is evaporated under reduced pressure (Note 5). The resulting thick, brown slurry is diluted with 500 ml. of dichloromethane and filtered through a glass frit. The salts removed by filtration are washed with more dichloromethane to remove absorbed crown and the combined organic solution is dried over anhydrous magnesium sulfate (Note 6), filtered, evaporated to minimum volume (aspirator vacuum), and distilled under high vacuum using a simple distillation head. The distillation should be carried out at the lowest possible pressure; a typical fraction contains 76–87 g. (38–44%) of crude 18-crown-6 and is collected over 100–167° (0.2 mm.) (Note 7),(Note 8),(Note 9).

To 50 g. of the crude 18-crown-6 in a 250-ml. Erlenmeyer flask is added 100 ml. of acetonitrile. A magnetic stirring bar is added, and the flask is equipped with a calcium chloride drying tube. The resulting slurry is heated on a hot plate to effect solution. The solution is stirred vigorously as it is allowed to cool to ambient temperature; fine white crystals of crown-acetonitrile complex are deposited. The flask is allowed to stand in a freezer for 24–48 hours and is finally cooled in a –30° bath to precipitate as much of the complex as possible. The solid is collected by rapid filtration (Note 10) and washed once with a small amount of cold acetonitrile. The hygroscopic crystals are transferred to a 200-ml., round-bottomed flask equipped with a magnetic stirring bar and a vacuum takeoff. The acetonitrile is removed from the complex under high vacuum (0.1–0.5 mm.), with gentle heating (~35°), over 2–3 hours. The pure colorless crown (28–33 g., 56–66%) (Note 11) crystallizes on standing, m.p. 38–39.5° (Note 12).

### 2. Notes

1. The tetrahydrofuran may be used directly without drying or purification.
2. The potassium hydroxide may be added to the water in one portion, but the resulting base solution

- should be allowed to cool to nearly room temperature before adding to the reaction mixture. If the [potassium hydroxide](#) solution is cooled much below ambient temperature, the [potassium hydroxide](#) begins to separate; hot [potassium hydroxide](#) solution could cause the [tetrahydrofuran](#) solution to boil.
3. The rate of darkening is related to the temperature of the solution and, if warm [potassium hydroxide](#) solution is used, the color will develop somewhat more rapidly. Differences in the rate of darkening do not appear to affect the yield or purity of product.
  4. [1,2-Bis\(2-chloroethoxy\)ethane](#) is available from Eastman Organic Chemicals.
  5. As much water as possible should be removed during evaporation so that the salts will filter more readily and the solution can be dried more easily.
  6. Drying agents containing complexable cations, such as  $K^+$  or  $Na^+$ , should be avoided.
  7. There is generally a forerun (room temperature to *ca.* 100°) the size of which varies according to the vigor of the previous evaporation steps (see (Note 5)).
  8. In a large batch preparation of [18-crown-6](#) an explosion has been reported as a result of difficulties occurring during this distillation step.<sup>5</sup> In this instance the head temperature rose to near 200°. When the system was vented to the atmosphere at this temperature an explosion occurred, apparently the result of autoignition of [1,4-dioxane](#) vapors. [Dioxane](#) is reported to undergo autoignition in air at temperatures in excess of 180°. It is recommended that the head and pot be allowed to cool and then be vented with a [nitrogen](#) atmosphere.
  9. The material obtained in the distillation cut contains both alcoholic and vinylic impurities. The crown may be purified by a second, more careful distillation followed by recrystallization, sublimation or by chromatography in addition to the method described here (see Discussion).
  10. The filtration should be conducted in a dry-box or by using an inverted funnel-nitrogen flow, whichever is more convenient.
  11. The yield of pure crown depends somewhat on the purity of the crude material used. Additional crown may be obtained by combining mother liquors and repeating the distillation and complex formation process.
  12. The <sup>1</sup>H NMR spectrum (CCl<sub>4</sub>) exhibits a singlet at  $\delta$  3.56.

### 3. Discussion

The compound known as [18-crown-6](#) is one of the simplest and most useful of the macrocyclic polyethers. Its synthesis in low yield was first reported by Pedersen.<sup>5</sup> Greene<sup>6</sup> and Dale and Kristiansen<sup>7</sup> have reported syntheses of the title compound from [triethylene glycol](#) and [triethylene glycol di-\*p\*-toluenesulfonate](#). Both of these procedures use strong base and anhydrous conditions and achieve purification by more or less classical methods. The combination of distillation and formation of the [acetonitrile](#) complex affords crown of high purity without lengthy chromatography or sublimation.<sup>8,9</sup>

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### References and Notes

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  4. C. J. Pedersen, *J. Am. Chem. Soc.*, **89**, 7017 (1967).
  5. P.E. Stott, *Chem. Eng. News*, **54** (37), 5 (1976).
  6. R. N. Greene, *Tetrahedron Lett.*, 1793 (1972).
  7. J. A. Dale and P. O. Kristiansen, *Acta Chem. Scand.*, **26**, 1471 (1972).
  8. G. W. Gokel, D. J. Cram, C. L. Liotta, H. P. Harris, and F. L. Cook, *J. Org. Chem.*, **39**, 2445 (1974).
  9. Acknowledgment is made to E. P. Kyba (University of Texas) for noting that this crown can be distilled and to E. R. Wonchoba (Du Pont Co.) for helpful comments.
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### Appendix

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

acetonitrile (75-05-8)

nitrogen (7727-37-9)

potassium hydroxide (1310-58-3)

dichloromethane (75-09-2)

magnesium sulfate (7487-88-9)

dioxane (5703-46-8)

Tetrahydrofuran (109-99-9)

triethylene glycol (112-27-6)

1,4-dioxane (123-91-1)

18-Crown-6,  
1,4,7,10,13,16-Hexaoxacyclooctadecane (17455-13-9)

18-crown-6-potassium

1,2-bis(2-chloroethoxy)ethane (112-26-5)

triethylene glycol di-p-toluenesulfonate (19249-03-7)