



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). 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.

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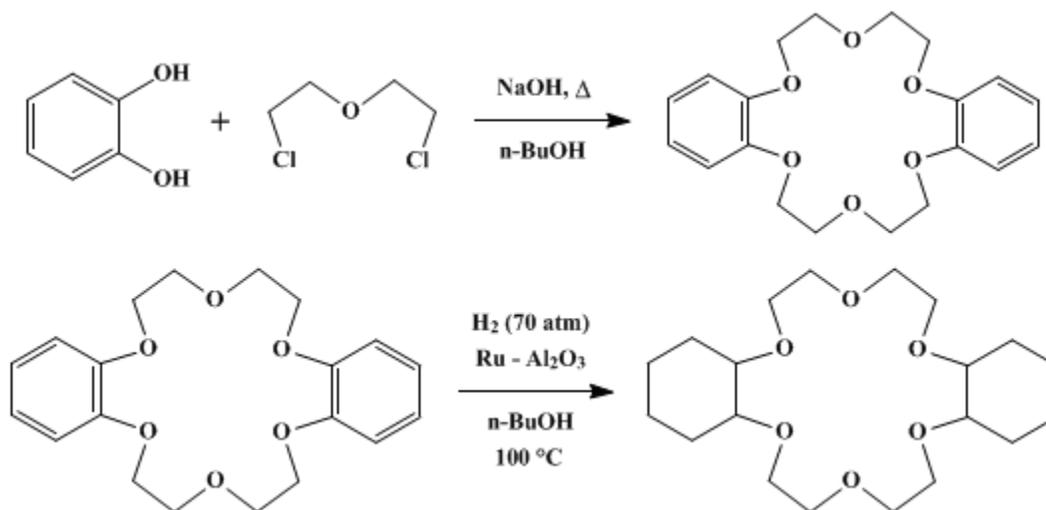
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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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MACROCYCLIC POLYETHERS: DIBENZO-18-CROWN-6 POLYETHER AND DICYCLOHEXYL-18-CROWN-6 POLYETHER

[Dibenzo *[b,k]* [1,4,7,10,13,16] hexaoxacycloöctadecin, 6,7,9,10,17,18,20,21-octahydro- and dibenzo *[b,k]* [1,4,7,10,13,16] hexaoxacycloöctadecin, eicosahydro-]



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1. Procedure

Caution! The subsequently described macrocyclic polyethers are toxic (Note 1) and should be handled with care.

Benzene has been identified as a carcinogen. OSHA has issued emergency standards on its use. All procedures involving benzene should be carried out in a well-ventilated hood, and glove protection is required.

A. *Dibenzo-18-crown-6 polyether.* A dry, 5-l., three-necked flask is fitted with a reflux condenser, a 500-ml., pressure-equalizing dropping funnel, a thermometer, and a mechanical stirrer. An inlet tube at the top of the reflux condenser is used to maintain a static nitrogen atmosphere in the reaction vessel throughout the reaction. The flask is charged with 330 g. (3.00 moles) of catechol (Note 2) and 2 l. of commercial *n*-butanol before stirring is started, and 122 g. (3.05 moles) of sodium hydroxide pellets are added. The mixture is heated rapidly to reflux (about 115°), and a solution of 222 g. (1.55 moles) of bis(2-chloroethyl) ether (Note 3) in 150 ml. of *n*-butanol is added, dropwise with continuous stirring and heating, over a 2-hour period. After the resulting mixture has been refluxed with stirring for an additional hour, it is cooled to 90° and an additional 122 g. (3.05 moles) of sodium hydroxide pellets are added. The mixture is refluxed, with stirring, for 30 minutes, and a solution of 222 g. (1.55 moles) of bis(2-chloroethyl) ether (Note 3) in 150 ml. of *n*-butanol is added, dropwise with stirring and heating, over a period of 2 hours. The final reaction mixture is refluxed, with stirring, for 16 hours (Note 4), then acidified by the dropwise addition of 21 ml. of concentrated hydrochloric acid. The reflux condenser is replaced with a distillation head and approximately 700 ml. of *n*-butanol is distilled from the mixture. As the distillation is continued, water is added to the flask from the dropping funnel at a sufficient rate to maintain a constant volume in the reaction flask. This distillation is continued until the temperature of the distilling vapor exceeds 99° (Note 5), and the resulting slurry is cooled to $30-40^\circ$, diluted with 500

ml. of **acetone**, stirred to coagulate the precipitate, and filtered with suction. The residual crude product is stirred with 2 l. of water, filtered with suction, stirred with 1 l. of **acetone**, and again filtered with suction. The residual product is washed with an additional 500 ml. of **acetone** and dried with suction, yielding 221–260 g. (39–48%) of tan, fibrous crystals, m.p. 161–162°, which are sufficiently pure for use in the next step. Dibenzo-18-crown-6 polyether may be recrystallized from **benzene**, giving white, fibrous needles, m.p. 162.5–163.5° (**Note 6**).

B. *Dicyclohexyl-18-crown-6 polyether*. A 1-l., stainless-steel autoclave is charged with a mixture of 125 g. (0.347 mole) of dibenzo-18-crown-6 polyether, 500 ml. of redistilled *n*-butanol (**Note 7**), and 12.5 g. of 5% ruthenium-on-alumina catalyst (**Note 8**). After the autoclave has been closed, it is flushed with **nitrogen** and filled with **hydrogen**. The mixture is hydrogenated at 100° and a **hydrogen** pressure of about 70 atm. (1000 p.s.i.) until the theoretical amount of **hydrogen** (2.08 moles) has been absorbed. The autoclave is cooled to room temperature and vented, and the reaction mixture is filtered to remove the catalyst (**Note 9**). The filtrate is concentrated at 90–100° with a rotary evaporator (**Note 10**), and the residual crude product solidifies on standing (**Note 11**). To remove hydroxylic impurities, a solution of the crude product (about 130 g.) in 400 ml. of *n*-heptane is filtered through a 7-cm. by 20-cm. column of acid-washed alumina (80–100 mesh, activity I–II), and the column is eluted with additional *n*-heptane until the eluate exhibits hydroxyl absorption in the 3300–3400 cm⁻¹ region of the IR. The solvent is removed from the combined eluates with a rotary evaporator, leaving 75–89 g. (58–69%) of mixture of diastereoisomeric dicyclohexyl-18-crown-6 polyethers as white prisms, melting within the range 38–54° (**Note 12**), which may be used to prepare complexes with various metal salts (**Note 13**) and (**Note 14**).

2. Notes

1. Dicyclohexyl-18-crown-6 polyether possesses unusual physiological properties which require care in its handling.² It is likely that other cyclic polyethers with similar complexing power are also toxic, and should be handled with equal care.

a. *Oral toxicity*. The approximate lethal dose of the dicyclohexyl-18-crown-6 polyether for ingestion by rats was 300 mg./kg. In a 10-day subacute oral test, the compound did not exhibit any cumulative oral toxicity when administered to male rats at a dose level of 60 mg./kg./day. It should be noted that dosage at the approximate lethal dose level caused death in 11 minutes, but that a dose of 200 mg./kg. was not lethal in 14 days.

b. *Eye irritation*. This dicyclohexyl polyether produced some generalized corneal injury, some iritic injury, and conjunctivitis when introduced as a 10% solution in **propylene glycol**. Although tests are not complete, there may be permanent injury to the eye even if the eye is washed after exposure.

c. *Skin absorption*. Dicyclohexyl-18-crown-6 polyether is very readily absorbed through the skin of test animals. It caused fatality when absorbed at the level of 130 mg./kg.

d. *Skin irritation*. Primary skin irritation tests run on this polyether indicate the material should be considered a very irritating substance.

2. **Catechol** of satisfactory purity may be purchased from Eastman Organic Chemicals or from Aldrich Chemical Company, Inc.

3. **Bis(2-chloroethyl) ether** may be obtained from Eastman Organic Chemicals. The checkers redistilled this material (b.p. 175–177°) before use.

4. A shorter period of refluxing may be sufficient.

5. The bulk of the material, a *n*-butanol–water azeotrope, distils at 92°.

6. The product has UV maxima (CH₃OH): 223 nm (ϵ 17,500) and 275 nm (ϵ 5500) with ¹H NMR peaks (CDCl₃), δ : 3.8–4.3 (m, 16H, 8CH₂O), 6.8–7.0 (m, 8H, aryl CH). The mass spectrum exhibits the following abundant peaks: *m/e* (rel. int.), 360 (M⁺, 29), 137 (29), 136 (74), 121 (100), 109 (23), 80 (31), 52 (21), 45 (27), and 43 (34).

7. It is advisable to use redistilled solvent to avoid the presence of catalyst poisons.

8. The 5% ruthenium-on-alumina catalyst is available from Engelhard Industries.

9. Since the catalyst, saturated with **hydrogen**, is pyrophoric, it should be kept wet with water after the filtration has been completed.

10. Since the product, a polyether, is apt to be oxidized by air, especially at elevated temperatures in the molten state, the product should be stored under a **nitrogen** atmosphere.

11. This residue is a mixture of stereoisomeric dicyclohexyl-18-crown-6 polyethers which may be contaminated with unchanged dibenzo-18-crown-6 polyether and alcohols, arising from hydrogenolysis

of the polyether ring. The submitter reports that this residue is sufficiently pure for many purposes such as the preparation of complexes with [potassium hydroxide](#) which are soluble in aromatic hydrocarbons.

12. The submitter reports that the two major diastereoisomers present, designated isomer A, m.p. 61–62° and isomer B, as one of two crystalline forms, m.p. 69–70° or m.p. 83–84°, may be separated by chromatography on alumina.³ An x-ray crystal structure determination for the complex of [barium thiocyanate](#) with isomer A of dicyclohexyl-18-crown-6 polyether has shown this polyether to have the *cis-syn-cis* stereochemistry.⁴ An x-ray crystal structure determination for the complex of [sodium bromide](#) with isomer B has shown this isomer to have the *cis-anti-cis* stereochemistry.⁵ The mixture of isomers A and B has negligible UV absorption (95% C₂H₅OH) and exhibits ¹H NMR (C₆D₆) multiplets at δ 0.9–2.2 (16H, aliphatic CH) and 3.3–4.0 (20H, OCH). The mass spectrum of the mixture exhibits the following relatively abundant peaks: *m/e* (rel. int.), 372 (M+, 2), 187 (35), 143 (100), 141 (47), 99 (92), 98 (46), 97 (41), 89 (66), 87 (41), 83 (45), 82 (55), 81 (99), 73 (77), 72 (46), 69 (58), 67 (42), 57 (50), 55 (58), 45 (77), 43 (61), and 41 (58). Although the IR (CCl₄) and ¹H NMR (C₆D₆, 100 MHz.) spectra of the pure isomers A and B differ slightly from one another, the checkers were unable to use these spectra to determine quantitatively the composition of mixtures of the two isomers. The most notable difference in these spectra is the shape of the ¹H NMR multiplet in the region 3.3–4.0 p.p.m.; this multiplet is considerably broader in isomer A than in isomer B allowing a qualitative estimate of the purity of each isomer.

13. The submitter prepared a [toluene](#) solution of the complex of [potassium hydroxide](#) with dicyclohexyl-18-crown-6 polyether by the following procedure. A mixture of 14.9 g. (0.0402 mole) of dicyclohexyl-18-crown-6 polyether (mixture of isomers) and 2.64 g. (0.0400 mole) of 85% [potassium hydroxide](#) was dissolved in 50 ml. of [methanol](#) with gentle warming on a steam bath. The solution was diluted with 100 ml. of [toluene](#) and then concentrated with a rotary evaporator to a volume of 50 ml. An additional 100 ml. of [toluene](#) was added, and the solution was again concentrated to a volume of 50 ml. This solution was diluted with [toluene](#) to a volume of 100 ml., 1 g. of decolorizing charcoal was added, and the mixture was allowed to stand overnight under a [nitrogen](#) atmosphere. After gravity filtration, a clear [toluene](#) solution of the complex was obtained. Titration with standard [hydrochloric acid](#) indicated the solution to be approximately 0.3 M in base. This solution, which must be protected from atmospheric moisture and [carbon dioxide](#), has been used for the saponification of sterically hindered esters.²

14. The checkers prepared a crystalline complex of [potassium acetate](#) with isomer B of dicyclohexyl-18-crown-6 polyether by the following procedure. To a stirred solution of 15.0 g. (0.0404 mole) of dicyclohexyl-18-crown-6 polyether (mixture of isomers) in 50 ml. of [methanol](#) was added a solution of 5.88 g. (0.0600 mole) of anhydrous [potassium acetate](#) (dried at 100° under reduced pressure) in 35 ml. of [methanol](#). The resulting solution was concentrated with a rotary evaporator, and the residual white solid was extracted with 35 ml. of boiling [dichloromethane](#). The resulting mixture was filtered, and the filtrate was cooled in an acetone–dry-ice bath and slowly diluted with petroleum ether (b.p. 30–60°, approximately 200 ml. was required) to initiate crystallization. The resulting suspension of the crystalline complex was allowed to warm to room temperature and filtered with suction. Recrystallization of this complex from a [dichloromethane](#)–petroleum ether (b.p. 30–60°) mixture separated 4.21–4.35 g. (22–23%) of the complex of [potassium acetate](#) with isomer B of dicyclohexyl-18-crown-6 polyether as white needles, m.p. 165–250° (dec.). This complex has IR absorption (CH₂Cl₂) at 1570 and 1385 cm.⁻¹ (COO⁻) with ¹H NMR absorption (CDCl₃), δ 1.0–2.1 (m, 16H, aliphatic CH), 1.95 (s, 3H, CH₃CO), 3.3–4.0 (m, 20H, OCH). A 4.21-g. sample of this complex was partitioned between 75 ml. of water and three 25-ml. portions of [ether](#). The combined [ether](#) solutions were dried over anhydrous [magnesium sulfate](#) and concentrated under reduced pressure, yielding 1.82 g. of isomer B of dicyclohexyl-18-crown-6 polyether as white prisms, m.p. 68–69°.

3. Discussion

The preparation of dibenzo-18-crown-6 polyether directly from [catechol](#) and [bis\(2-chloroethyl\) ether](#) has been reported previously.² The present procedure is an improvement of this method. Although dibenzo-18-crown-6 polyether can be obtained in 80% yield from [bis-\[2-\(*o*-hydroxyphenoxy\)-ethyl\] ether](#) and [bis\(2-chloroethyl\) ether](#), the former intermediate has to be synthesized by a method involving several steps. One of the hydroxyl groups of [catechol](#) must be protected against alkali with [dihydropyran](#) or [chloromethylmethyl ether](#). The intermediate is treated with [bis\(2-chloroethyl\) ether](#) in the presence of alkali and, finally, converted into the desired intermediate by acid hydrolysis.² The yield

of bis[2-(*o*-hydroxyphenoxy)-ethyl] ether was less than 40% so that the overall yield of dibenzo-18-crown-6 polyether never approached 39–48%, the yield of the present, direct method.

Dibenzo-24-crown-8 and dibenzo-30-crown-10 polyethers can be prepared by this method with the substitution of the appropriate ω,ω' -dichloropolyether for bis(2-chloroethyl) ether. However, dibenzo-12-crown-4 and macrocyclic polyethers containing two or more benzo groups and an uneven number of oxygen atoms have to be prepared by the alternative method mentioned above, using the intermediate catechol monoethers. Macrocyclic polyethers containing one benzo group can be synthesized by the direct reaction between one molecule of catechol and one molecule of ω,ω' -dichloropolyethers in the presence of alkali. Certain substituted crown compounds can be obtained by using catechol derivatives, such as 4-(*tert*-butyl)-catechol and 4-chlorocatechol, which do not give side reactions in the presence of alkali.

It is unusual to form a ring of eighteen atoms in a single operation by the reaction of catechol with bis(2-chloroethyl) ether. It seems possible that the ring-closure step is facilitated by the presence of sodium ion, which is solvated by the intermediate acyclic polyether. Some experiments appear to support this hypothesis. The yields of dibenzo-18-crown-6 polyether are higher when it is prepared with sodium or potassium hydroxide than when lithium or tetramethylammonium hydroxide is used; lithium and quaternary ammonium ions are not strongly complexed by the polyethers. Furthermore, the best ligands for alkali metal cations, polyethers containing rings of 15 to 24 atoms including 5 to 8 oxygen atoms, are formed in higher yields than smaller or larger rings, or rings of equal sizes with only 4 oxygen atoms.

The physical properties of many macrocyclic polyethers and their salt complexes have been already described.^{2,6-7} Dibenzo-18-crown-6 polyether is useful for the preparation of sharp-melting salt complexes. Dicyclohexyl-18-crown-6 polyether has the convenient property of solubilizing sodium and potassium salts in aprotic solvents, as exemplified by the formation of a toluene solution of the potassium hydroxide complex (Note 13). Crystals of potassium permanganate, potassium *tert*-butoxide, and potassium palladium(II) tetrachloride (PdCl₂ + KCl) are dissolved in liquid aromatic hydrocarbons merely by adding dicyclohexyl-18-crown-6 polyether.² The solubilizing power of the saturated macrocyclic polyethers permits ionic reactions to occur in aprotic media. It is expected that this property will find practical use in catalysis, enhancement of chemical reactivity, separation and recovery of salts, electrochemistry, and analytical chemistry. There are some limitations. Although salts with high lattice energy, such as fluorides, nitrates, sulfates, and carbonates, form complexes with macrocyclic polyethers in alcoholic solvents as readily as more polarizable (softer) salts, their complexes cannot be isolated in the solid state because one or the other uncomplexed component precipitates on concentrating the solutions. For the same reason, these salts cannot be rendered soluble in aprotic solvents by the polyethers.

References and Notes

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

petroleum ether

sodium or potassium hydroxide

decolorizing charcoal

Dibenzo-18-crown-6 polyether

DICYCLOHEXYL-18-CROWN-6 POLYETHER

ruthenium-on-alumina

dicyclohexyl-18-crown-6 polyethers

polyether

dibenzo-30-crown-10 polyether

ω,ω' -dichloropolyether

ω,ω' -dichloropolyethers

lithium or tetramethylammonium hydroxide

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

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

[methanol \(67-56-1\)](#)

[ether \(60-29-7\)](#)

[hydrogen \(1333-74-0\)](#)

[sodium hydroxide \(1310-73-2\)](#)

[potassium permanganate \(7722-64-7\)](#)

[sodium bromide \(7647-15-6\)](#)

[nitrogen \(7727-37-9\)](#)

[carbon dioxide \(124-38-9\)](#)

[n-butanol \(71-36-3\)](#)

[acetone \(67-64-1\)](#)

potassium hydroxide (1310-58-3)

toluene (108-88-3)

Catechol (120-80-9)

dichloromethane (75-09-2)

propylene glycol (57-55-6)

magnesium sulfate (7487-88-9)

potassium acetate (127-08-2)

n-heptane (142-82-5)

dihydropyran

bis(2-chloroethyl) ether,
chloromethylmethyl ether (111-44-4)

barium thiocyanate

Dibenzo-24-crown-8

dibenzo-12-crown-4

4-chlorocatechol (2138-22-9)

potassium palladium(II) tetrachloride

4-(tert-butyl)-catechol (98-29-3)

potassium tert-butoxide (865-47-4)

bis-[2-(o-hydroxyphenoxy)-ethyl] ether,
bis[2-(o-hydroxyphenoxy)-ethyl] ether

Dibenzo [b,k] [1,4,7,10,13,16] hexaoxacyclooctadecin, 6,7,9,10,17,18,20,21-octahydro- (14187-32-7)

dibenzo [b,k] [1,4,7,10,13,16] hexaoxacyclooctadecin, eicosahydro- (16069-36-6)