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.

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.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

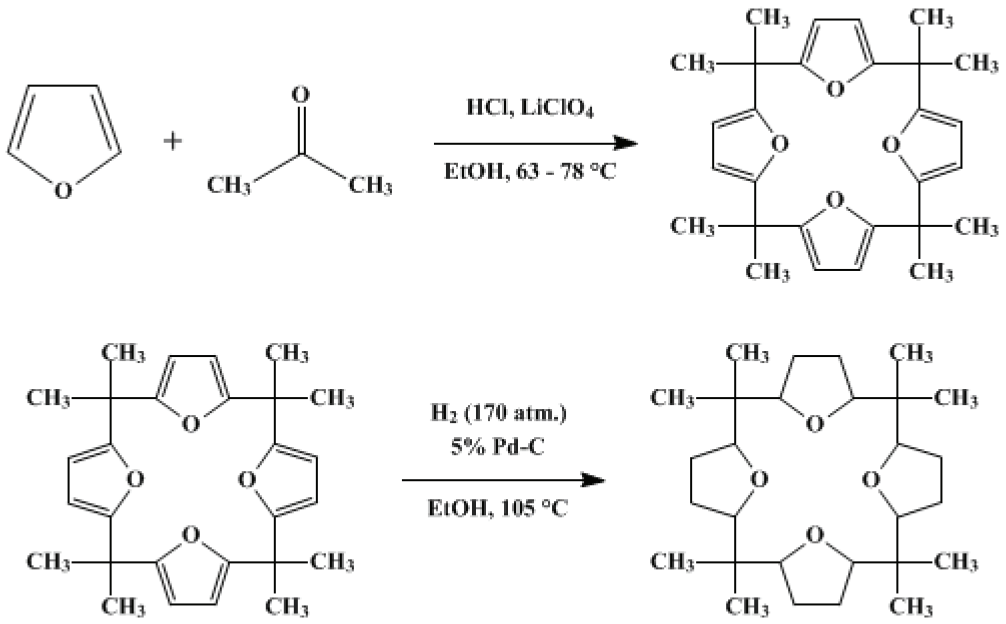
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.057.0074

Organic Syntheses, Coll. Vol. 6, p.856 (1988); Vol. 57, p.74 (1977).

2,2,7,7,12,12,17,17-OCTAMETHYL-21,22,23,24-TETRAOXAPERHYDROQUATERENE

[21,22,23,24-Tetraoxapentacyclo-[16.2.1.$1^{3,6}$.$1^{8,11}$.$1^{13,16}$]tetracosane, 2,2,7,7,12,12,17,17-octamethyl-]



Submitted by Maurice Chastrette[1], Francine Chastrette, and Jean Sabadie.
Checked by William V. Phillips, Herbert O. House, James C. Kauer, and William A. Sheppard.

1. Procedure

A. 2,2,7,7,12,12,17,17-*Octamethyl*-21,22,23,24-*tetraoxaquaterene.* A 1-liter, three-necked flask fitted with a mechanical stirrer, a dropping funnel, and a condenser is charged with 27.2 g. (0.400 mole) of freshly distilled furan (Note 1), 24 ml. of absolute ethanol, 57.3 g. (0.200 mole) of the lithium perchlorate–1,2-dimethoxyethane complex (Note 2), and 16 ml. of reagent grade concentrated hydrochloric acid. The resulting pale-yellow to pale-tan solution is stirred continuously and heated to 63° with an oil bath before 58.1 g. (0.80 mole) of acetone (Note 3) is added dropwise over 1 hour. During this addition the heat of reaction causes the solution to reflux, and some white solid begins to separate. After the addition is complete, stirring and heating are continued until refluxing ceases (about 30 minutes). The temperature of the bath is then raised to 78°, and the mixture is refluxed with stirring for an additional 30 minutes. The reaction mixture, a dark red-brown solution containing a pasty white precipitate, is cooled to room temperature with continuous stirring, and 25 ml. of water and 300 ml. of diethyl ether are added. The resulting mixture is stirred at room temperature for 1 hour, converting the precipitate into a finely divided white solid, and the mixture is filtered with suction, employing a medium-porosity, sintered-glass funnel. The residual crude product is washed thoroughly (Note 4) with portions of ether (total volume 100 ml.) followed by portions of 95% ethanol (total volume 50 ml.) and allowed to air-dry. The crude product (14.2–14.8 g.), m.p. 231–240°, is recrystallized from 140–150 ml. of reagent grade chloroform, yielding 7.3–7.4 g. of product as white needles, m.p. 241.5–243°. The mother liquors are concentrated to one-third their initial volume, separating 2.9–3.1 g. of a second crop of crystalline product, m.p. 240–242°, for a total yield of the tetraoxaquaterene of 10.2–10.5 g. (24–25%) (Note 5).

B. 2,2,7,7,12,12,17,17-*Octamethyl*-21,22,23,24-*tetraoxaperhydroquaterene.* A 400-ml., stainless-steel, shaking autoclave is charged with 4.0 g. (0.0092 mole) of the tetraoxaquaterene from Part A, 200 ml. of ethanol, and 400 mg. of 5% palladium on charcoal (Note 6). The autoclave is filled with hydrogen at an initial pressure of 170 atm. and heated with shaking for 4 hours at 105°. The catalyst and a white solid are removed by filtration (Note 7), the solid is dissolved in 100 ml. of warm chloroform, the solution is filtered, the chloroform is evaporated, and the white solid obtained is dried under reduced pressure at 60° (Note 8), leaving the tetraoxaperhydroquaterene as a white solid, m.p. 204–209° (Note 9), in a yield of 2.85–2.97 g. (69–72%).

2. Notes

1. Furan, purchased from Aldrich Chemical Company, Inc., was distilled before use; b.p. 31–32°.

2. Anhydrous lithium perchlorate (60 g.), obtained from Ventron Corporation, was placed in a 500-ml. flask under dry nitrogen, and 85 ml. of anhydrous 1,2-dimethoxyethane was added. The resulting warm mixture was swirled and heated on the steam bath under dry nitrogen until all of the solid dissolved. The resulting solution was cooled and gradually crystallized to a solid mass. Additional 1,2-dimethoxyethane (155 ml.) was added, the mixture was stirred, and supernatant liquid was removed with a sintered-glass filter stick. The resulting solid was vacuum dried briefly in a vacuum dessicator (0.3 mm.) for 20 minutes then sealed under vacuum overnight. The resulting, solvated lithium perchlorate, $LiClO_4(C_4H_{10}O_2)_2$, 108 g, may be stored in a brown bottle under dry nitrogen until needed. When lithium perchlorate was initially dissolved in the entire 240 ml. of 1,2-dimethoxyethane and processed as above, the yield was considerably lower. The submitters report that if less lithium perchlorate is used in the preparation of the octamethyltetraoxaquaterene the yield of the product is lowered.

3. Reagent grade acetone was used. The submitters state that an excess of acetone is necessary. When a 1:1 mole ratio of acetone to furan was used, they obtained a 21% yield of crude product; when a 1:2 ratio of acetone to furan was employed, the yield of product was less then 5%.

4. The submitters report that if this material is not washed thoroughly to remove the soluble, low molecular weight, linear polymers present the crude product will melt and/or darken at much lower temperatures than 231–240°.

5. The product has the following spectral properties; ^1H NMR ($CDCl_3$), δ (multiplicity, number of protons, assignment): 1.48 (s, 24H, 8CH_3), 5.90 (s, 8H, 8CH); mass spectrum *m/e* (relative intensity): 432 (M^+, 40) 418 (34), 417 (100), 201 (28), 186 (31), 149 (55), 85 (46), 83 (67), 75 (21), 60 (21), 47 (20), 45 (24), 43 (53), and 41 (26).

6. Catalyst obtained from Engelhard Industries was used. The submitters used 200 mg. of Fluka 10% palladium on charcoal catalyst with 5 g. of starting material in 250 ml. of ethanol and obtained a total yield of 2.3 g. (46%), m.p. 208–211°.

7. The ethanolic filtrate can be concentrated to 10–15 ml. under reduced pressure to obtain 0.3 g. (7%) of crude product, m.p. 187–202°. Unchanged starting material, if present, is concentrated in this second fraction and may be detected by the furan resonance at δ 5.85 in the ^1H NMR spectrum or by a sharp IR absorption at 772 $cm.^{-1}$, not present in the product. Elemental analyses of these second crops suggested that other impurities were also present.

8. The solid tenaciously holds a small amount of chloroform which can be detected by ^1H NMR (δ 7.25). Vacuum drying overnight at 60° removes this impurity.

9. In one isolated case the checkers found that no hydrogen uptake occurred, and unreacted starting material was recovered. This erratic result may have resulted from accidental poisoning of the catalyst by contaminants present in the autoclave or associated valves and lines. If multiple runs are carried out, the products of each should be checked by IR or ^1H NMR spectroscopy before being combined. The ^1H NMR spectrum ($CDCl_3$) shows singlets at δ 0.74, 0.82, 0.93, and 1.04 (24H, 8CH_3) and multiplets at 1.2–1.9 (16H, 8CH_2), 1.9–2.8 (4H, 2CH_2), and 3.0–4.2 (8H, 4CH_2); IR (Nujol) $cm.^{-1}$ strong absorptions: 1078, 1039, medium: 999, 991, 552, 528, 520, and weaker: 1285, 1248, 1204, 977, 884, 840, 719, 659, 598, 560. The checkers concluded from examination of the spectra that a variable mixture of isomers is obtained from the hydrogenation.

3. Discussion

The unsaturated tetraoxaquaterene (accompanied by linear condensation products) was first synthesized in 18.5% yield by the acid-catalyzed condensation of furan with acetone in the absence of added lithium salts.[2] Other ketones also condensed with furan, giving analogous products in 6–12%

yield.[2,3,4] A corresponding macrocycle was also prepared in 9% yield from pyrrole and cyclohexanone.[4] The macrocyclic ether products have also been obtained by condensation of short, linear condensation products of 2, 3, or 4 furan rings with a carbonyl compound.[5]

The method described here gives higher yields of the macrocyclic tetraethers and allows the product from furan and cyclohexanone to be formed directly in 5–10% yield, whereas this product was previously obtained only by an indirect route. Lithium perchlorate undoubtedly accelerates the reaction; after short reaction times, the product was isolated in 20% yield when the salt was present and in only 5% yield when the salt was absent. The lithium cation presumably acts as a template which coordinates with the oxygen atoms of the furan units, favoring cyclization instead of linear polymerization.[6] The hydrogenated macrocycle has been shown to form complexes with lithium salts.[6,7]

References and Notes

1. Laboratoire de Chimie Organique Physique, Laboratoire de Chimie Organique II, Université Claude-Bernard Lyon I, 43, Boulevard du 11 Novembre 1918, F 69622 Villeurbanne Cedex, France.
2. R. G. Ackman, W. H. Brown, and G. F. Wright, *J. Org. Chem.*, **20**, 1147 (1955).
3. R. E. Beals and W. H. Brown, *J. Org. Chem.*, **21**, 447 (1956).
4. W. H. Brown, B. J. Hutchinson, and M. H. MacKinnon, *Can. J. Chem.*, **49**, 4017 (1971).
5. W. H. Brown and W. N. French, *Can. J. Chem.*, **36**, 537 (1958).
6. M. Chastrette and F. Chastrette, *J. Soc. Chem. Commun.*, 534 (1973).
7. Y. Kobuke, H. Hanje, K. Horiguchi, M. Asada, Y. Makayama, and J. Furukawa, *J. Am. Chem. Soc.*, **98**, 7414 (1976).

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

2,2,7,7,12,12,17,17-Octamethyl-21,22,23,24-tetraoxaperhydroquaterene

2,2,7,7,12,12,17,17-Octamethyl-21,22,23,24-tetraoxaquaterene

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

ether,
diethyl ether (60-29-7)

hydrogen (1333-74-0)

chloroform (67-66-3)

Cyclohexanone (108-94-1)

oxygen (7782-44-7)

nitrogen (7727-37-9)

acetone (67-64-1)

palladium (7440-05-3)

Furan (110-00-9)

Pyrrole (109-97-7)

1,2-dimethoxyethane (110-71-4)

lithium perchlorate (7791-03-9)

21,22,23,24-Tetraoxapentacyclo-[16.2.1.1^{3,6}.1^{8,11}.1^{13,16}]tetracosane, 2,2,7,7,12,12,17,17-octamethyl-