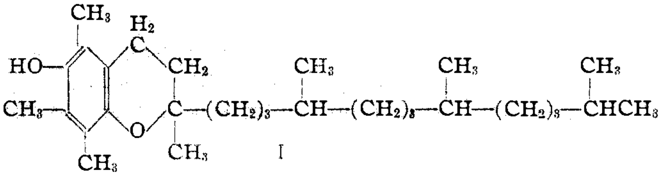
[Contribution from Research Laboratories, Merck & Co., Inc.]

Studies on Vitamin E. Ethers of Durohydroquinone

By E. Fernholz[1] and Jacob Finkelstein

Ethers of durohydroquinone have attained significance to those conducting research on vitamin E since the discovery[2] that α-tocopherol gives this phenol in a high yield on thermal decomposition. In a recent publication[3] the reasons which led to the abandonment of the original idea that α-tocopherol might be a monoether of durohydroquinone were summarized. Experimental evidence was cited to prove that α-tocopherol is a derivative of 6-hydroxychromane of the probable structure I.



I

Our interest in the preparation of monoethers of durohydroquinone did not cease, at the end of last year, after we had convincing evidence that α-tocopherol was a chromane derivative of durene. This was due to the discovery by H. M. Evans and G. A. Emerson of the University of California that certain of these ethers showed definite vitamin E-like activity.[4]

The absorption spectra and reducing properties of the primary and secondary ethers, the preparations of which are described below, previously have been reported briefly.[3] With the exception of the monocetyl ether, all mono- and diethers were formed simultaneously by adding an equivalent amount of alcoholic potassium hydroxide to a gently refluxing alcoholic solution of durohydroquinone and the halide. The two ethers were separated by distillation or by taking advantage of their difference in solubility in alcohol. To prepare the monocetyl ether, the diether was refluxed with one mole of aluminum chloride in benzene. When two moles of aluminum chloride were used with the diether the cleavage was complete. The properties of our mono- and dicetyl ethers are in good agreement with the properties of those prepared by John,[5] who used a method similar to that first mentioned. These ethers were also prepared by Bergel, *et. al.*,[6] by a slightly different method, but the melting points and analyses indicated that they were not quite pure.

In order to synthesize 2-methyl-*n*-octadecyl alcohol, an intermediate for one of the ethers, we first prepared ethylmethylcetyl malonate. Partial hydrolysis and decarboxylation of this gave ethyl α-methylstearate. This ester was reduced to the corresponding alcohol by hydrogen under high pressure in the presence of copper chromite catalyst.[7]

Although the preparation of the primary and secondary ethers did not prove to be difficult, the preparation of tertiary ethers of durohydroquinone failed completely as might have been expected.

Experimental

Mono-*s*-butyl Ether of Durohydroquinone.—To a gently boiling alcoholic solution of 8.6 g. of durohydroquinone and 20.2 g. of *s*-butyl iodide in an atmosphere of hydrogen, 111 cc. of 0.9 normal alcoholic potassium hydroxide was added in small drops over a period of fifteen minutes. After several hours of refluxing, the solution was cooled, diluted with an equal volume of water and extracted with ether. After it had been dried and concentrated, the oil was distilled.

After a forerun, consisting mainly of duroquinone, the monoether distilled at air-bath temperature of 145 to 150° at 0.05 mm. It was recrystallized from petroleum ether and obtained in the form of small needles; m. p. 85–86°; yield 0.5 g. This compound reduced silver nitrate slowly.

Anal. Calcd. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.57; H, 10.20.

The acetyl derivative was prepared by refluxing with excess acetic anhydride for twenty-four hours. The compound was obtained as long needles from alcohol; m. p. 62–63°.

Anal. Calcd. for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found C, 72.88; H, 9.13.

Ethers of Durohydroquinone and Dodecyl Iodide.—As described above, 20 g. of dodecyl iodide, 8.3 g. of durohydroquinone in 50 cc. of alcoholic potassium hydroxide were interacted and worked up.

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[1] Present address: E. R. Squibb & Sons, New Brunswick, N. J.

[2] E. Fernholz, This Journal, **59**, 1154 (1937).

[3] E. Fernholz, *ibid.*, **60**, 700 (1938).

[4] H. M. Evans, G. A. Emerson and O. H. Emerson, *Science*, **88**, 38 (1938).

[5] W. John, E. Dietzel and Ph. Günther, *Z. physiol. Chem.*, **252**, 208 (1938).

[6] F. Bergel, A. R. Todd and T. S. Work, *J. Chem. Soc.*, 257 (1938).

[7] Adkins and Folkers, This Journal, **53**, 1095 (1931); **54**, 1145 (1932).

The monoether distilled at an air-bath temperature of 160° at 0.05 mm., and recrystallized from alcohol; m. p. 96–97°; yield 5 g.

Anal. Calcd. for $C_{22}H_{38}O_2$: C, 78.99; H, 11.45. Found: C, 79.30; H, 11.25.

The residue from the above distillation, which contained the diether, was dissolved in chloroform and filtered through charcoal. Upon evaporation of the solvent a white crystalline substance was obtained which was further purified by recrystallization from alcohol; m. p. 79–80°; yield 3.5 g.

Anal. Calcd. for $C_{34}H_{62}O_2$: C, 81.21; H, 12.43. Found: C, 81.13; H, 12.39.

Ethers of Durohydroquinone and Cetyl Iodide.[5,6]—As described above, 6.6 g. of durohydroquinone, 14 g. of cetyl iodide in 100 cc. of amyl alcohol and 200 cc. of 2 normal solution of potassium hydroxide in amyl alcohol were interacted. After refluxing several hours and as a crystalline substance formed, the mixture was diluted with water and ether and filtered. The undissolved crystals were purified by first crystallizing from chloroform-alcohol mixture and then from butanol and obtained as white leaflets. The crystals do not reduce silver nitrate, as the product is the diether; m. p. 88–89°.

Anal. Calcd. for $C_{42}H_{78}O_2$: C, 82.02; H, 12.78. Found: C, 82.06; H, 12.76.

The mono-ether was obtained from the diether, as follows.

To 3.6 g. of dicetyl ether of durohydroquinone in 50 cc. of benzene, 0.9 g. of aluminum chloride (1.1 mol) was added and the mixture refluxed for eight hours. It was washed successively with dilute hydrochloric acid, dilute sodium hydroxide, water and then concentrated until crystals appeared. It was now diluted with alcohol and filtered. After dissolving the precipitate in ether, the solution was washed with Claisen solution (equal parts of 50% potassium hydroxide solution in water and methanol), dried and distilled. After a forerun of duroquinone and some halide, the monoether distilled at air-bath temperature at about 190° at 0.05 mm. After recrystallizing from alcohol, it melted at 99–100.5° and reduced silver nitrate; yield 0.4 g.

Anal. Calcd. for $C_{26}H_{46}O_2$: C, 79.94; H, 11.87. Found: C, 79.98; H, 11.74.

When the above procedure was repeated using 2.7 g. of dicetyl ether and 1.35 g. of aluminum chloride in 50 cc. of benzene, the cleavage was so complete that no monoether was isolated.

Ethers of Durohydroquinone and Octadecyl Iodide.—In the usual way, 8.3 g. of durohydroquinone, 24 g. of octadecyl iodide in 50 cc. of alcohol and 50 cc. of normal alcoholic potassium hydroxide were interacted. After three hours, the mixture was cooled and the crystals which separated were filtered. The product was recrystallized from a hot mixture of alcohol and benzene to give the pure diether; m. p. 95–97°.

Anal. Calcd. for $C_{46}H_{86}O_2$: C, 82.32; H, 12.91. Found; C, 82.49, 82.25; H, 12.92, 12.84.

The mother liquor was concentrated to dryness and the residue dissolved in ether. This solution was washed with Claisen solution, dried and concentrated. The monoether distilled at 0.05 mm. with air-bath temperature at 170–190°. It was then recrystallized from alcohol and obtained as white leaflets. It reduces silver nitrate; m. p. 105.5°.

Anal. Calcd. for $C_{28}H_{50}O_2$: C, 80.32; H, 12.04. Found: C, 80.43, 80.16; H, 11.92, 12.18.

Methyl *n*-Heptadecyl Ketone.—This compound was prepared from barium stearate and barium acetate by the method of Morgan and Holmes.[8]

Methyl-*n*-heptadecylcarbinol.—A solution of 29 g. of the above ketone in 500 cc. of glacial acetic acid was hydrogenated at room temperature and atmospheric pressure using Adams platinum catalyst. The required amount of hydrogen was absorbed in twenty-five minutes and the solution was filtered. Upon the addition of water to the filtrate, a precipitate was obtained which was dissolved in ether and washed with dilute caustic and water. After drying, the ether was distilled and the remaining liquid was treated with excess alcoholic potash to saponify any ester that might have formed. The product was extracted with ether, dried and the oil obtained on concentration was treated with 21 g. of *p*-nitrobenzoyl chloride in pyridine. After recrystallization from petroleum ether, the derivative melted at 95.5°; yield 40 g.

Anal. Calcd. for $C_{26}H_{43}O_4N$: C, 72.02; H, 10.00. Found: C, 72.22, 72.14; H, 9.87, 9.64.

A solution of 38 g. of the above *p*-nitrobenzoate in 90 cc. of alcohol containing 4.5 g. of potassium hydroxide was refluxed for one hour. After diluting with water, extracting with ether and concentrating, a crystalline compound was obtained. After recrystallizing it from petroleum ether the m. p. was 48–49°; yield 17 g.

Anal. Calcd. for $C_{19}H_{41}O$: C, 79.93; H, 14.47. Found: C, 80.11; H, 14.30.

***n*-Nonadecyl Bromide-2.**—A stream of hydrogen bromide was passed into 15 g. of the above alcohol, heated in an oil-bath at 110–120° until the reaction was completed. The product was cooled, dissolved in chloroform, washed with concentrated sulfuric acid, water and then dried over calcium chloride. The chloroform was evaporated under reduced pressure and the oil which remained distilled at an air-bath temperature of 170° at 0.05 mm. The distillate was slightly yellow and turned darker on standing; yield 13 g.

Anal. Calcd. for $C_{19}H_{39}Br$: Br, 23.00. Found: Br, 23.65.

Ethers of Durohydroquinone and *n*-Nonadecyl Bromide-2.—In the usual way, 5.7 g. of durohydroquinone, 11 g. of *n*-nonadecyl bromide-2 in 50 cc. of alcohol and 37 cc. of 0.9 normal alcoholic potassium hydroxide were interacted. When the reaction mixture was neutral, it was diluted with water and extracted with a large volume of ether. After drying and concentrating, a crystalline product was obtained. Upon distillation at 0.05 mm. and air-bath temperature of 180–200°, the monoether was obtained. It was recrystallized from alcohol; m. p. 94–95°; yield 5 g. This compound reduced silver nitrate solution.

Anal. Calcd. for $C_{29}H_{42}O_2$: C, 80.49; H, 12.12. Found: C, 80.21; H, 11.93.

To obtain the diether, the residue in the flask was dissolved in chloroform and treated with charcoal. The

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(8) Morgan and Holmes, *J. Soc. Chem. Ind.*, 108 T (1925).

solvent was evaporated and the product recrystallized from alcohol–benzene mixture; yield 3.5 g., m. p. 75–76°.

Anal. Calcd. for $C_{48}H_{90}O_2$: C, 82.45; H, 12.97. Found: C, 82.20; H, 13.00.

Ethyl Methyl Cetyl Malonate.—To a solution of 5.2 g. of sodium in 100 cc. of absolute alcohol, 40 g. of ethyl methylmalonate was added. Then, 77 g. of cetyl iodide was added and the mixture refluxed until neutral. The alcohol was distilled *in vacuo* and the residue extracted with ether. The oil obtained after concentration was fractionated at reduced pressure: at 1 mm., b. p. 185–190°; yield 63 g.

Anal. Calcd. for $C_{24}H_{48}O_4$: C, 71.95; H, 12.07. Found: C, 72.47; H, 11.82.

Ethyl α-Methylstearate.—A mixture of 30 g. of the above malonate and 4.6 g. of potassium hydroxide in 52 cc. of alcohol was refluxed for sixteen hours. The solution was diluted with water and alcoholic potassium hydroxide and extracted with ether. The aqueous solution was acidified to congo with concentrated hydrochloric acid and the oil separated. After drying, the oil was heated at 180° until no more carbon dioxide was evolved. After cooling, it was taken up with ether and washed with dilute sodium carbonate and water and distilled, after drying: at 1 mm., b. p. 161–163°; yield 20 g.

Anal. Calcd. for $C_{21}H_{42}O_2$: C, 77.24; H, 12.96. Found: C, 77.56; H, 12.70.

2-Methyl-*n*-octadecyl Alcohol.—An alcoholic solution of 14 g. of the above ester, in the presence of 1 g. of copper chromite, was heated at 250° under 2000 lb. (133 atm.) pressure of hydrogen for eight hours. After cooling and filtering, the product was distilled. At air-bath temperature of 125–130° and 0.05 mm., the alcohol was obtained and upon cooling it solidified; m. p. 32–33°; yield 12 g.

Anal. Calcd. for $C_{19}H_{40}O$: C, 80.21; H, 14.17. Found: C, 80.25; H, 14.00.

2-Methyl-*n*-Octadecyl Iodide.—A mixture of 12 g. of the above alcohol, 6 g. of iodine and 1 g. of red phosphorus was heated at 170–180° for one hour. The product was dissolved in ether and washed with water, thiosulfate, water and then dried. On distilling at 0.05 mm. and air-bath temperature of 185°, a colorless liquid is obtained which soon turns pink; yield 14 g.

Anal. Calcd. for $C_{19}H_{39}I$: C, 57.86; H, 9.96. Found: C, 57.74; H, 10.04.

Ethers of Durohydroquinone and 2-Methyl-*n*-octadecyl Iodide.—In the usual way, 5.5 g. of durohydroquinone, 13 g. of the above iodide in alcohol and 28 cc. of 1.15 *n* alcoholic potassium hydroxide interacted. After several hours of refluxing, water was added and the precipitate dissolved in ether. The extract was washed with Claisen solution, water and then dried. On distillation at 0.05 mm., a forerun of a hydrocarbon and duroquinone was obtained and then at an air-bath temperature of 210–220°, the monoether distilled. After recrystallization from alcohol, it was obtained pure, m. p. 94–95°; yield 2 g. The reducing power of this ether was rather strong but not like that of α-tocopherol.

Anal. Calcd. for $C_{29}H_{52}O_2$: C, 80.49; H, 12.12. Found: C, 80.44; H, 11.91.

The residue was dissolved in chloroform and filtered through charcoal several times. The solvent was evaporated and the diether recrystallized from alcohol, m. p. 76–78°; yield 1 g.

Anal. Calcd. for $C_{48}H_{90}O_2$: C, 82.45; H, 12.97. Found: C, 82.34; H, 12.99.

We gratefully acknowledge our indebtedness to Messrs. D. F. Hayman and W. Reiss for the microanalyses.

Summary

Several mono- and diethers of durohydroquinone have been prepared.

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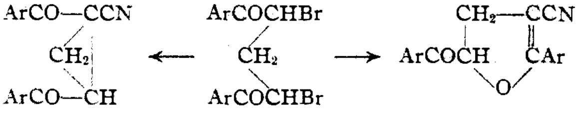
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

The Action of Sodium Cyanide on 1,3-Dibromo-1,3-dibenzoylpropane

BY REYNOLD C. FUSON, J. R. LITTLE AND GAIL MILLER

The successful closure of the cyclobutane ring by treatment of α,α'-dibromoadipic esters with sodium cyanide[1] could not be extended to 1,4-dibromo-1,4-diaroylbutanes. The latter underwent closure to cyanodihydro-1,4-pyrans, *i. e.*, to six-membered rings.[2] The present work grew out of an attempt to extend the method to the closure of a 1,3-dibromo-1,3-diaroylpropane (I). It was thought that this compound might yield a cyclopropane derivative (II) or a cyanodihydrofuran derivative (III) depending on whether the reaction resembled the cyclobutane or the dihydro-1,4-pyran closure.



II I III

In an effort to determine which of these two courses the reaction would follow, we have treated 1,3-dibromo-1,3-dibenzoylpropane (IV) with sodium cyanide. A rapid reaction took

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[1] Fuson and Kao, THIS JOURNAL, **51**, 1536 (1929); Fuson, Kreimeier and Nimmo, *ibid.*, **52**, 4074 (1930); Rydon, *J. Chem. Soc.*, 593 (1936).

[2] Fuson, Kuykendall and Wilhelm, THIS JOURNAL, **53**, 4187 (1931).