[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

The Chemistry of Vitamin E. XX.[1] The Preparation of o-Xylohydroquinone

BY OLIVER H. EMERSON[2] AND LEE IRVIN SMITH

o-Xylenol is not available in quantity and is difficult to prepare. The preparation of *o*-xyloquinone and hydroquinone from it by the generally useful method previously described[3] is, therefore, impracticable. The present paper reports improvements in the previously described[4,5,6] synthesis of this quinone from *o*-xylene via the *o*-nitro compound and the amine. The yields obtained in the three steps are, respectively, 85, 75 and 33%, or an over-all yield of 21% of quinone from hydrocarbon. The corresponding over-all yield previously reported by this method is 12%.[4,5,6]

Procedure

3-Nitro-*o*-xylene.—*o*-Xylene (50 g.) is nitrated at −10 to 0° by stirring it vigorously and dropping into it slowly a mixture of sulfuric acid (100 g.) and nitric acid (50 g., d. 1.4). During the addition, the tip of the dropping funnel is shielded from spray by keeping it well up in the neck of the flask, out of the path of the droplets thrown by the stirrer. This prevents any contact of xylene with an excess of the nitrating mixture and thus avoids the formation of any dinitro compound.[5] The product is poured into water and washed with dilute sodium hydroxide. Any polynitro-*o*-xylene can be removed from the mono compound by steam distillation but is more efficiently eliminated by distillation in a vacuum from a Claisen flask, the fraction boiling at 115–130° at 15 mm. pressure being refractionated through a Fenske 1-meter column and the final fraction (61 g., 85.6%) boiling at 127–130° at 18 mm. pressure being taken as the pure 3-nitro compound. The residues, especially the first, should not be heated too strongly as they may decompose quite vigorously.[7]

3-Amino-*o*-xylene (II).—For the reduction of the nitro compound, the directions of Yokoyama[6] were followed, except that the amine finally was isolated as the sulfate, which is of advantage both for removal of small amounts of 4-amino-*o*-xylene whose sulfate is much more soluble, and in giving the amine in a good physical state for the subsequent oxidation. From 75 g. of the nitro compound there resulted about 60 g. of the amine. This was vigorously stirred into water (500 cc.) and sulfuric acid (30 g.) and the solution cooled overnight in a refrigerator. The amine sulfate weighed 62 g. (74%).[8]

o-Xyloquinone (III).—The oxidation was based on the procedure of Yokoyama[6] but it is preferable to use the dry, powdered amine sulfate and dilute sulfuric acid rather than the free amine which forms coarse lumps when added to the strong sulfuric acid as recommended by Yokoyama. Dry, well powdered 3-amino-*o*-xylene sulfate (31 g.) was added to a solution of sulfuric acid (95 cc., 175 g.) in water (680 cc.) and the solution was placed in a refrigerator (5–10°) until cold. A solution of sodium dichromate dihydrate (22.5 g.) in water (60 cc.) was also cooled to 5–10°. During the course of an afternoon the dichromate was added to the amine solution in 4 or 5 portions, with vigorous shaking. The solutions were returned to the refrigerator between the additions, and the final solution was kept at 5–10° overnight. During the next day, more dichromate (50 g.) in water (150 cc.) was added in portions as before, and then the reaction mixture was kept in the refrigerator for thirty-six hours longer. The reaction mixture was filtered using a *large* Buchner funnel, and the filtrate was thoroughly extracted with ether (three times, 250 cc. of ether each time). The precipitate was thoroughly triturated with methanol (about 75 cc.),[9] filtered, and washed two or three times with small amounts of methanol. Ether (500 cc.) was added to the methanol filtrate; any precipitate was removed and washed with a little ether. All of the ethereal solutions and extractions were combined and shaken with water (400 cc.). Any precipitate at this point was removed, washed with ether and the ether washing was combined with the main solution. The aqueous layer was separated, and thoroughly extracted with ether. The united ether solutions and extracts were washed with small amounts of water, and the ether was distilled off. Since *o*-xyloquinone is thermolabile, care must be taken to keep a fair amount of ether in the distilling flask. Finally water was added, and the removal of the ether was completed by heating to 40–45°.

Ordinary steam distillation of the quinone is accompanied by great loss, but steam distillation under 100 mm. pressure proceeds quite well. A 500-cc. Kjeldahl flask with a side arm (12 mm. dia.) attached high up formed a very satisfactory still, and an Allihn condenser provided adequate cooling. The distillate was extracted with ether, the ether was evaporated carefully and the residue crystallized from petroleum ether (b. p. 30–60°). The quinone is quite soluble in this solvent, even in the cold, necessitating concentration of the mother liquors for second and third crops; yield 8.3 g. (33%); m. p. 56–57°.[6,10]

(1) Paper XIX, THIS JOURNAL, **61**, 3079 (1939).

(2) Honorary Fellow of the Graduate School, University of Minnesota, Spring Quarter, 1938–1939.

(3) Paper VII on Vitamin E, *J. Org. Chem.*, **4**, 318 (1939).

(4) Noelting and Forel, *Ber.*, **18**, 2670 (1885).

(5) Crossley and Renouf, *J. Chem. Soc.*, **95**, 207 (1909).

(6) Yokoyama, *Helv. Chim. Acta*, **12**, 771 (1929).

(7) The presence of small amounts of the 4-nitro isomer is of little consequence since the corresponding amine sulfate is much more soluble than the 3-amine sulfate (6 *vs.* 1.4% at 0°), Noelting and Pick, *Ber.*, **21**, 3153 (1888).

(8) Hydrochloric acid and tin or tin chloride should not be used for reduction of the nitro compound, because the product prepared in this way invariably contains considerable amounts of chloroxylidines which are very difficult to remove.

(9) A silver spatula or glass rod should be used at this point. Stainless steel appeared to catalyze the decomposition of the quinone to a red oil, while silver or glass had much less effect upon the quinone.

(10) Yokoyama, Ref. 6, reported 20% yield, m.p. 55°.

o-Xylohydroquinone.—The quinone (8.3 g.) was dissolved in acetic acid (50 cc.), water (25 cc.) was added, and the solution was refluxed with zinc (8.3 g., 20-mesh). The reduction proceeds rapidly and the solution is practically colorless in twenty minutes. Boiling water (50 cc.) is added to the hot solution, which is then immediately decanted from the zinc. The zinc is boiled with water (50 cc.) which is decanted into the main solution. On cooling, the solution deposits 7.90 g. (95%) of the hydroquinone, which melts at about 220° with complete decomposition.

Summary

1. This paper reports an improved preparation of *o*-xyloquinone and hydroquinone from *o*-xylene.

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The Chemistry of Vitamin E. XXI.[1] Dealkylation of Hydroquinone Ethers Related to the Tocopherols

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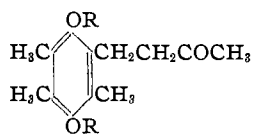
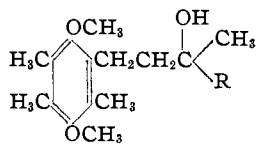
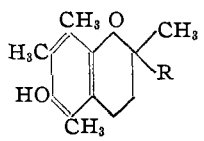
In a previous paper[2] a report has been made of the syntheses of certain compounds related to the tocopherols, using as starting materials 1-[3,6-dimethoxy-2,4,5-trimethylphenyl]-butanone-3 (I) and the closely related diacetate, II.



I, R = CH_3
II, R = Ac
IIa, R = H



III



IV
X R = CH_3

The substance I can be prepared readily from the dimethyl ether of pseudocumohydroquinone, via the chloromethyl derivative, which is used to alkylate acetoacetic ester. Hydrolysis of the substituted β-keto ester gives I, and the over-all yield in the synthesis is very good. The ketone I reacts well with Grignard reagents to give the carbinols III so that, by proper choice of Grignard reagent, a wide variety of these carbinols may be synthesized.

It was planned to convert the carbinols into the related chromans (IV) by demethylation followed by cyclization, but in the earlier work[2] no method could be found for cleaving the methoxyl groups without at the same time involving deep seated changes elsewhere in the molecule. While the acetate II underwent chloromethylation well, the chloromethyl derivative was difficult to handle and alkylation of acetoacetic ester with it gave only fair yields of the β-keto ester, from which, in turn, only a complicated mixture of products was obtained on hydrolysis. Thus, starting with either I or II, the synthesis of chromans IV appeared to involve such difficulties as to render the method of doubtful value.

While this work was in progress, a paper by John and Günther[3] appeared, in which was described the synthesis of ketone I starting with 3,4,6 - trimethyl - 2,5 - dimethoxybenzaldehyde.[4] The aldehyde was condensed with acetone to give 80% of the benzalacetone, which was then reduced to I. John and Günther found that I, when subjected to the action of hydrobromic acid, was simultaneously demethylated and reduced, giving the chroman IV (R = H). Addition of methylmagnesium iodide to I gave about 40% of III (R = CH_3), which was converted, by action of hydrobromic acid, into X. Addition of a dodecyl Grignard reagent was also carried out, although the results were not as satisfactory as those obtained using methylmagnesium iodide. Subsequently, John and Schmeil[5] by oxidation of the chroman IV (R = H) obtained the ketone IIa, and by addition of Grignard reagents to this ketone, the chromans IV, R = CH_3 and $C_{12}H_{25}$, were obtained.

It has now been found that the carbinol ether III (R = CH_3) can be cleaved by heating it at an elevated temperature with excess Grignard reagent.[6] Although the reaction does not pro-

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(1) Paper XX, THIS JOURNAL, **62**, 141 (1940).

(2) Paper VIII, *J. Org. Chem.*, **4**, 323 (1939).

(3) John and Günther, *Ber.*, **72**, 1649 (1939).

(4) Smith, THIS JOURNAL, **56**, 472 (1934).

(5) John and Schmeil, *Ber.*, **72**, 1653 (1939).

(6) For other examples of ether cleavage by Grignard reagents see (a) Wessely and Prillinger, *Ber.*, **72**, 633 (1939); (b) Lüttringhaus and co-workers, *ibid.*, **71**, 1673 (1938); (c) Späth, *Monatsh.*, **35**, 319 (1914).