

*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.

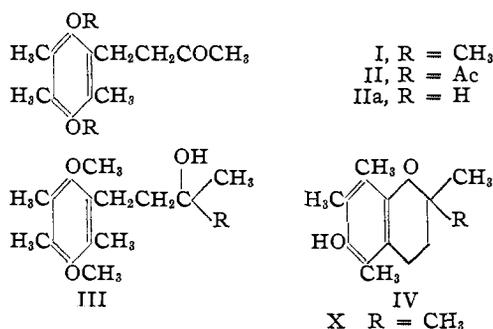
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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

## The Chemistry of Vitamin E. XXI.<sup>1</sup> Dealkylation of Hydroquinone Ethers Related to the Tocopherols

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In a previous paper<sup>2</sup> 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.



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  $\beta$ -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<sup>2</sup> 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  $\beta$ -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<sup>3</sup> appeared, in which was described the synthesis of ketone I starting with 3,4,6-trimethyl-2,5-dimethoxybenzaldehyde.<sup>4</sup> 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<sub>3</sub>), 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<sup>5</sup> 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<sub>3</sub> and C<sub>12</sub>H<sub>25</sub>, were obtained.

It has now been found that the carbinol ether III (R = CH<sub>3</sub>) can be cleaved by heating it at an elevated temperature with excess Grignard reagent.<sup>6</sup> Although the reaction does not pro-

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

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

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

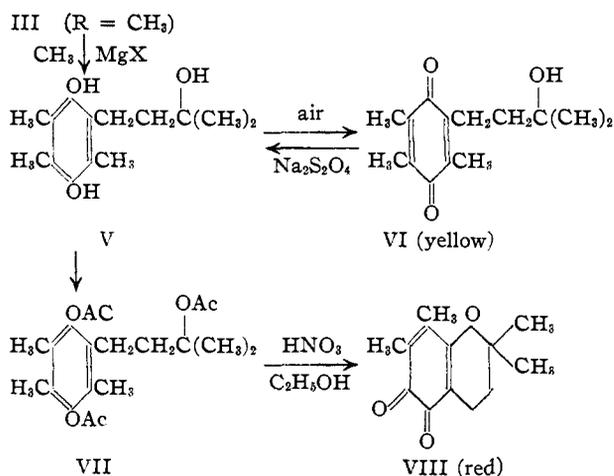
(6) For other examples of ether cleavage by Grignard reagents see (a) Wessely and Prillinger, *Ber.*, **72**, 633 (1939); (b) Lüttringhaus and co-workers, *ibid.*, **71**, 1673 (1938); (c) Späth, *Monatsh.*, **35**, 319 (1914).

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

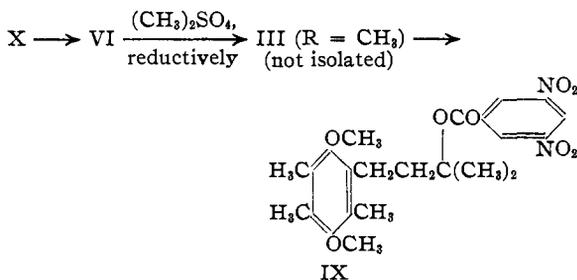
(2) Paper VIII, *J. Org. Chem.*, **4**, 323 (1939).

ceed to completion, it nevertheless affords another method of cleaving the methoxyl groups without affecting the rest of the molecule. Because of the incomplete reaction, it was not possible to isolate the products in a pure state, but sufficient evidence was available to follow the course of the reaction fairly accurately. The demethylation product appears to be the corresponding hydroquinone, V, since the ethereal solution, when shaken in air, turns to the yellow color of the quinone VI, and this color change can be reversed by shaking with sodium hydrosulfite. Neither of these substances could be isolated, since the presence of unchanged III in the reaction product prevents them from crystallizing. The reaction product was reductively acetylated, in the hope that the triacetate VII could be separated, but this likewise could not be crystallized. The product was therefore treated with nitric acid in ethanol<sup>7</sup>; the red color of the ortho quinone VIII<sup>8</sup> at once appeared. Since the carbinol ether III does not give the Furter and Meyer reaction, production of the very characteristic red color by nitric acid-ethanol after the carbinol III had been heated with the Grignard reagent indicated quite clearly that considerable demethylation had occurred.



The structure of the carbinol ether III (R = CH<sub>3</sub>) was proved by converting it to a 3,5-dinitrobenzoate (IX), m. p. 147-148°. The same dinitrobenzoate was obtained from 2,2,5,7,8-tetramethyl-6-hydroxychroman (X) by oxidation, followed by reductive methylation of the quinone VI to the carbinol ether III (R = CH<sub>3</sub>) and treat-

ment of the latter with 3,5-dinitrobenzoyl chloride.



The identity of the dinitrobenzoates prepared by these two methods constitutes an additional proof of the structure of the chroman X, and it is also important as a model research for a direct structure proof of  $\alpha$ -tocopherol, since the corresponding dimethoxy-3,5-dinitrobenzoate from  $\alpha$ -tocopherol has already been prepared.<sup>9</sup>

Chromans such as IV and X have been prepared by the action of Grignard reagents upon hydrocoumarins, first by Robertson and his associates<sup>10</sup> and shortly thereafter in other laboratories.<sup>11,12</sup> Some doubt has been expressed, however, that the products of such reactions actually were chromans,<sup>13</sup> but the present results, together with those of John and his associates,<sup>3,5</sup> leave no doubt as to the course of these reactions; the products are certainly 2,2-dialkyl chromans.

### Experimental Part

**1 - (3,6 - Dimethoxy - 2,4,5 - trimethylphenyl) - 3 - methylbutanol-3 (III, R = CH<sub>3</sub>).**—A solution of the ketone I (0.85 g.) in ether (25 cc.) was added to a solution of methylmagnesium iodide prepared from methyl iodide (1.419 g.), magnesium (0.243 g.) and ether (25 cc.). After stirring for an hour, the mixture was poured onto ice and sulfuric acid (30%) and extracted with ether. The ether extracts were washed with bicarbonate (10%), then with water, and dried over sodium sulfate. Evaporation of the solvent left 800 mg. of III, a colorless oil. It was not analyzed.

**3,5-Dinitrobenzoate (IX).**—The carbinol III (800 mg.) and 3,5-dinitrobenzoyl chloride (900 mg.) were allowed to stand in pure pyridine (15 cc.) for twenty-four hours. The solution was poured into iced sulfuric acid (30%) and extracted with ether. The extract was washed with bicarbonate (10%), and then with water. The residue obtained on evaporation of the solvent was crystallized from alcohol. It then melted at 147-148°; after several crystallizations it formed light yellow crystals which melted at 148-148.5°.

- (9) John, Dietzel and Emte, *Z. physiol. Chem.*, **257**, 173 (1939).  
 (10) Bridge, Crocker, Cubin and Robertson, *J. Chem. Soc.*, 1533 (1937).  
 (11) Smith, Ungnade and Prichard, *J. Org. Chem.*, **4**, 358 (1939).  
 (12) John, Günther and Schmeil, *Ber.*, **71**, 2617 (1938).  
 (13) Private communication from Professor Robertson.

(7) Furter and Meyer, *Helv. Chim. Acta*, **22**, 240 (1939).

(8) Paper XVII in this series, *THIS JOURNAL*, **61**, 2424 (1939).

*Anal.* Calcd. for  $C_{23}H_{25}O_3N_2$ : C, 59.98; H, 6.10. Found: C, 59.78; H, 5.75.

**Oxidation of 2,2,5,7,8-Pentamethyl-6-hydroxychroman (X).**—A solution of the chroman (750 mg.) in methanol (30 cc.) was refluxed for an hour with silver acetate. The suspension was cooled and the sludge was removed and washed with a small amount of methanol. The combined filtrate and washings were diluted with water (100 cc.) and extracted with ether. The ether solution was washed with water and dried over calcium chloride. Evaporation of the solvent left the quinone VI (740 mg.) as a yellow oil. John, Dietzel and Emte<sup>9</sup> report that VI is a solid which melts at 62° but many preparations of VI in this Laboratory have given the substance only as an oil. This oil, when reductively acetylated, gave the known triacetate, m. p. 114–115°<sup>9,14</sup>; however, cleavage of the pure triacetate by methylmagnesium iodide according to the method of Doisy<sup>15</sup> followed by action of silver oxide upon the product also gave VI as an oil which could not be crystallized.

**Carbinol III.**—Reductive methylation of the quinone VI must be carried out with great care to avoid the destructive action of excess alkali upon the quinone. The general procedure of John, Dietzel and Emte<sup>9</sup> was used, modified so that there was never more than a momentary darkening of the reaction mixture due to free alkali. The above quinone (749 mg.) was taken up in methanol (15 cc.) and sodium hydrosulfite (700 mg.) was added. To this suspension sodium hydroxide (20%, 4 drops) was added, followed immediately by methyl sulfate (2 cc.). During the next forty-five minutes, base (12 cc.) and methyl sulfate (8 cc.) were added alternately and with intermittent refluxing, in such proportions that the solution never darkened. The final colorless solution was diluted with sodium hydroxide (3%, 100 cc.) and extracted with ether several times. The combined extracts were washed with dilute base, then with water, and dried over sodium sulfate. Removal of the solvent left a pale yellow oil (570 mg.).

**3,5-Dinitrobenzoate, IX. A.**—The crude carbinol III (210 mg.) was added to approximately an equivalent amount of standardized methylmagnesium iodide in ether (50 cc.). The volume of methane collected indicated roughly 0.67 mole of active hydrogen per mole of carbinol, and showed that reductive methylation of VI had not involved the aliphatic hydroxyl group too greatly. To the resulting suspension of the bromomagnesium derivative of III there was added 3,5-dinitrobenzoyl chloride (520 mg.) and the mixture was allowed to stand at room temperature for two days. It was poured into cold sulfuric acid (30%, 150 g.) and extracted with ether. The ether extracts were washed with water, saturated bicarbonate, and again with water. Evaporation of the solvent left an oily residue (360 mg.) which was taken up in a little ether and cooled. The light yellow solid was removed and washed twice with small amounts of cold ethanol. It weighed 50 mg. After crystallization from ethanol, the substance melted at 145–146°. When mixed with a specimen of IX (m. p. 147.5–148°) prepared from the dimethoxy ketone I, the substance melted at 145–147°.

(14) In ref. 9, the m. p. is reported as 113°.

(15) Binkley, MacCorquodale, Cheney, Thayer, McKee and Doisy, *THIS JOURNAL*, **61**, 1295 (1939); see also Fieser, Campbell and Fry, *ibid.*, **61**, 2209 (1939).

**B.** The crude carbinol III (290 mg.) was dissolved in dry pyridine (5 cc.) and 3,5-dinitrobenzoyl chloride (550 mg.) was added. After standing at room temperature for four days, a small amount of white solid (m. p. 165–167°) was removed and the filtrate poured into cold sulfuric acid (30%, 150 g.). The product (300 mg.) was isolated and purified as described above. The solid weighed 100 mg. and melted at 143–144.5°. When mixed with the pure 3,5-dinitrobenzoate (m. p., 147.5–148°) the substance melted at 144–145.5°.

**Cleavage of the Ether Carbinol, III (R = CH<sub>3</sub>).**—The ketone I (1.43 g.) in ether (30 cc.) was added to a Grignard solution prepared from methyl iodide (4.06 g.), magnesium (0.69 g.) and ether (50 cc.). After refluxing for an hour, the ether was distilled off and the residue was heated at 180° for forty-five minutes. After cooling, ice and sulfuric acid (30%) were added and the mixture was extracted with ether. A few cc. of the ethereal solution (practically colorless), when shaken in air, turned bright yellow (quinone VI). The whole of the ethereal solution was shaken with aqueous sodium hydrosulfite, and the colorless ethereal solution which resulted (hydroquinone V) was evaporated. The residue, a yellow oil, could not be crystallized. It was acetylated by refluxing it for thirty minutes with acetic anhydride (12 cc.), zinc (1 g.) and fused sodium acetate (3 g.). The mixture was poured into water and extracted with ether. The ether solution was washed with water, then with dilute sodium hydroxide, followed by water again. The solution was dried and the solvent was evaporated. This residue, a viscous oil (acetate VII), likewise could not be crystallized.

The acetate was dissolved in absolute ethanol (500 cc.) and nitric acid (100 cc.) and the solution was warmed on the steam-bath for thirty minutes. The deep red color characteristic of the Furter and Meyer reaction appeared at once (quinone VIII). The red quinone was removed by ether extraction, but evaporation of the solvent left a deep red oil which also could not be made to crystallize.

## Summary

1. Carbinols such as III derived from 1-(3,6-dimethoxy-2,4,5-trimethylphenyl)-butanone-3 (I) by action of Grignard reagents, have been demethylated by heating with excess reagent.
2. The structure of the carbinol III (R = CH<sub>3</sub>) has been proved by converting it to the same 3,5-dinitrobenzoate as that obtained from 2,2,5,7,8-pentamethyl-6-hydroxychroman (X) by a series of reactions involving oxidation to a quinone, reductive methylation of the quinone and conversion of the dimethoxy compound to the 3,5-dinitrobenzoate.
3. These reactions also prove the structure of the chroman X and show definitely that when Grignard reagents react with dihydrocoumarins, the products are 2,2-dialkylchromans.