[Chem. Pharm. Bull. 16(2) 378—380 (1968)]

UDC 547.565.2.07

A New Synthesis of Trimethylhydroquinone

Hirotaka Otomasu

Hoshi College of Pharmacy[1]

(Received October 6, 1967)

Trimethylhydroquinone (TMH) is an important component for the synthesis of tocopherol (vitamin E) and various methods on synthesizing TMH have been reported. Excepting the methods which start from trimethylbenzenes, the nuclear methylation was ordinary employed with phenols, such as hydroquinones[2,3] or xylenols[4,5] by Mannich method. The author investigated the nuclear methylation of nitroxylenols by chloromethylation and established a new method for the practical synthesis of TMH as shown in Chart 1.

The starting material, 2,5-dimethyl-4-nitrophenol (I) was easily obtained in good yield by the nitric acid oxidation of nitroso compound which prepared from *p*-xylenol with nitrous acid.[6]

Chloromethylation of I by using methylal or formaldehyde with hydrogen chloride generally produced II and 1,3-benzodioxane compound (III) at the yield of 70% and 10%, respectively. In this case, the reaction was carried out under the sulfuric acid condition, in the absence of hydrogen chloride, only product (III) was obtained in nearly theoretical yield. Both II and III were reduced to 2,3,6-trimethyl-4-aminophenol (IV) by using metals,

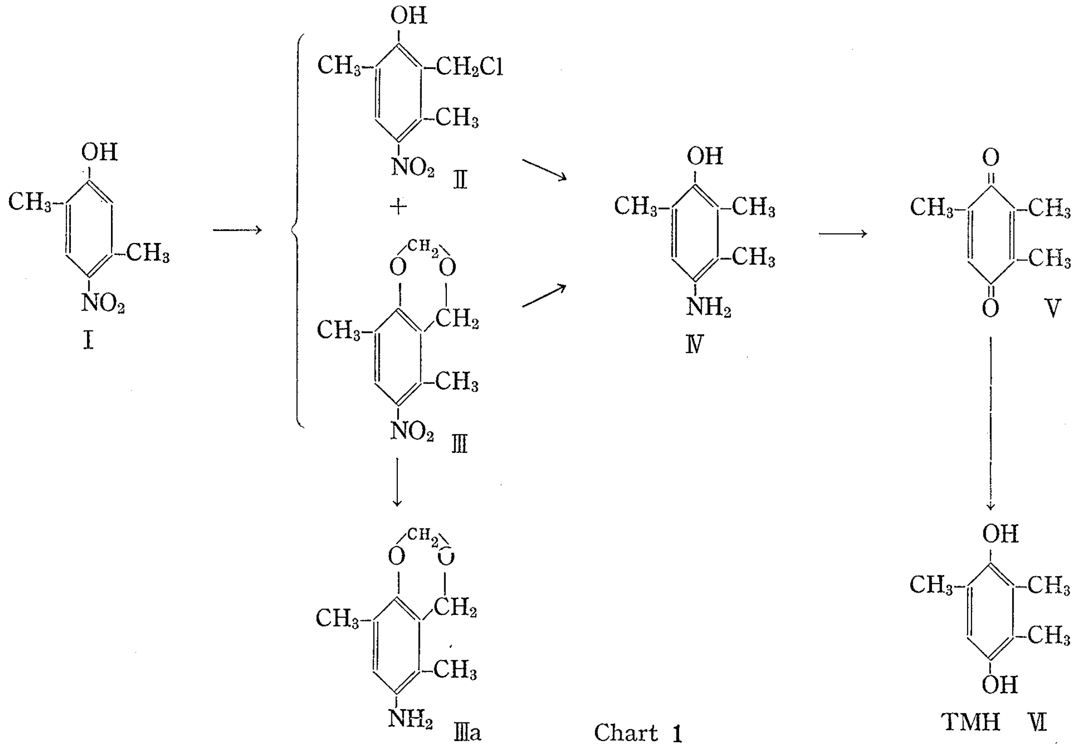

Chart 1

---

[1] Location: *4-41, 2-Chome, Ebara, Shinagawa-ku, Tokyo.*

[2] W.J. Burke, J.A. Warburton, J.L. Bishop, and J.L. Bilis, *J. Org. Chem.*, **26**, 4669 (1961).

[3] K. Sato and S. Abe, *J. Org. Chem.*, **28**, 1928 (1963).

[4] W.T. Caldwell and T.R. Thompson, *J. Am. Chem. Soc.*, **61**, 765 (1939).

[5] E. Yamato and S. Ohshiro, Japan. Patent 5617 (1965).

[6] R. Oliveri, *Gazz. Chim. Ital*, **12**, 161 (1882).

zinc or tin with hydrochloric acid. In the case of using tin with hydrochloric acid, IV was obtained as stable stannichloride complex. IV was also obtained as that of hydrochloride by the catalytic reduction of II in acetic acid, in the presence of platinum oxide under the atmospheric pressure and room temperature. But by the same reduction condition, III was not reduced to IV and the amino compound (IIIa) which was only the nitro group reduced compound was obtained.

A more practical synthesis of IV is the reduction of III by the high pressure hydrogenation under 100 atm. at 270° in the presence of copper chromium oxide catalyst.

2,3,6-Trimethyl-4-aminophenol (IV), recrystallized as colorless needles, is very unstable and darkened on exposing to air for several hours. Therefore, it is convenient for the prepararion of trimethylquinone (V) that the reaction mixture was succesively carried out the next oxidation process without isolating IV.

Next, the ordinary methods were applied to the reaction procedures from IV to VI. IV was oxidized to trimethylquinone (V) with ferric chloride and V was reduced to TMH (VI) with sodium hydrosulfite as usual manner.

By the present synthesis through the route of III, the total yield of TMH is 60 to 70% based on the crude starting material (I).

Experimental

Preparation of 2,5-Dimethyl-4-nitrophenol (I)——Goldschmidt, *et al.*[7] obtained I by the oxidation of 4-nitroso-*p*-xylenol with potassium ferricyanide. I was prepared by the following modification of the literature procedure.[6,7] To a solution of 10 g of *p*-xylenol, 5 g of NaOH and 15 g of $NaNO_2$ in 450 ml of water was added 100 ml of 10% H_2SO_4 with vigorous stirring under cooling below 8° during half an hour. The reaction product separated was collected and suspended in 250 ml of water. To this suspension was added 140 ml of dil. HNO_3 (HNO_3 d. 1.38 3 part and H_2O 1 part) constantly with vigorous stirring at 28—30° for about 2 hr. The reaction mixture was kept standing over night at room temperature, whereupon, 12 g of curde product (I) of mp 94—110° (pure product, mp 122°[7]) was obtained. This was used the reaction without purification.

Chloromethylation of I: Formation of 2-Hydroxy-5-nitro-3,6-dimethylbenzylchloride (II) and 6-Nitro-5,8-dimethyl-1,3-benzodioxane (III)——According to the procedure of Organic Syntheses,[8] a mixture of 60 g of I, 75 g of methylal, 650 ml of conc. HCl and 5 ml of conc. H_2SO_4 was stirred while the temperature maintained at 70±2° for 4 hr. During this time HCl gas was passed into the reaction mixture. After colling, the solid product was collected, washed with water and dried at room temperature. The whole product was dissolved in 40 ml of MeOH and separated the insoluble product, which, on recrystallized from MeOH to give nearly colorless needles of III, mp 118°. Yield, 6.7 g of 9%. *Anal.* Calcd for $C_{10}H_{11}O_4N$: C, 57.41; H, 5.30; N, 6.70. Found: C, 57.20; H, 5.35; N, 6.47.

Evaporation of the filtered solution under reduced pressure afforded chilled mass on cooling. Recrystallization from benzene gave pale yellow flat needles of II, mp 125°. Yield, 51 g or 67%. *Anal.* Calcd. for $C_9H_{10}O_3NCl$: C, 50.00; H, 4.62; N, 6.94. Found: C, 50.46; H, 4.80; N, 6.63.

In this reaction, corresponding formaldehyde was used instead of methylal, and the analogous results were obtained.

Preparation of III——A mixture of 10 g of I, 15 ml of formalin, 25 ml of water and 75 ml of conc. H_2SO_4 was kept standing at 30—40° for 20 hr with strring at times. The reaction mixture was diluted with water, the product was collected on a filter and washed with dil. ammonia until the filtrate decolorized. Recrystallization from MeOH gave III of mp 118°. Yield, 11.5 g or 92%.

2,3,6-Trimethyl-4-aminophenol (IV)——i) To a solution of 10 g of II in 30 ml of MeOH involves 30 g of tin trash was added 40 ml of conc. HCl in small portions under refluxing. After the completion of the reaciton, color of the solution turned faint brown-red, the mixture was decanted from tin refuse and concentrated to dryness. The residue was washed with small amount of cold water and purified with MeOH and water to white crystal powder of stannichloride complex. Yield, 16 g. *Anal.* Found: N, 3.40.

ii) A solution of 5 g of II in 30 ml of AcOH was shaken with PtO_2 in hydrogen stream under atmospheric pressure and room temperature. When the absorption of hydrogen ceased, 30 ml of water was added to the reaciton mixture to dissolve the deposited product and removed the catalyst by filtration. The filtrate was

---

7) H. Goldschmidt and H. Schmid, *Ber.*, **18**, 568 (1885).
8) Org. Synth., Coll. Vol. III, 468 (1955).

concentrated to dryness and the crude product obtained was recrystallized from MeOH–acetone to give colorless needles of mp >290°. *Anal.* Calcd. for $C_9H_{13}ON \cdot HCl$: C, 57.44; H, 7.44; N, 7.44. Found: C, 57.46; H, 7.43; N, 7.62.

6-Amino-5,8-dimethyl-1,3-benzodioxane (IIIa)——This was obtained by the catalytic reduction of III as for the manner of IV, II in dioxane solution. Colorless needles, mp 92—94° (ligroin). *Anal.* Calcd. for $C_{10}H_{13}O_2N$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.10;. H, 7.22; N, 7.59

Preparation of TMH (VI)——i) To a mixture of 10 g of III, 50 ml of benzene and 40 ml of conc. HCl was added 20 g of zinc powder in small portions with vigorous stirring, keeping its temperature at 60—70°. When the frothing ceased, HCl gas was passed into the reaction mixture to complete the reduction. The reduction mixture was filtered and separated from benzene. To the acidic layer was added 70 ml of 40% $FeCl_3$ solution and steam distilled. Then, the distillated mixture (about 400 ml) was added 20 g of sodium hydrosulfite powder with vigorous stirring at 40°. The colorless product that separated was recrystallized from $MeOH–H_2O$ to give mp 170°[9] which was identical with the authentic specimen of TMH. Yield, 5.2 g or 72% (Calcd. from III).

The same reaction was carried out with II, and TMH was obtained in 67% yield from II.

ii) A mixture of 10 g of III, 4 g of Na_2CO_3 and 200 ml of water was hydrogenolized in an autoclave in the presence of 6 g of copper chromium oxide under an initial hydrogen pressure of 100 atm. at 270° for 2 hr. After opening the autoclave, the catlyst was removed by filtration. The filtrate was acidified with conc. HCl and treated as above mentioned, whereupon 4.5 g of VI separated. Yield, 78% (Calcd. from III).

Acknowledgement The author is grateful to Mr. A. Katsushima, president of Masaru Pharm. Co., Ltd., for his kind encouragement and to Mr. N. Tani for his technical help.

---

9) R. Nietzki and J. Schneider, *Ber.*, 27, 1430 (1894).