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Synthesis of Trimethylhydroquinone from *p*-Xylene*[1]

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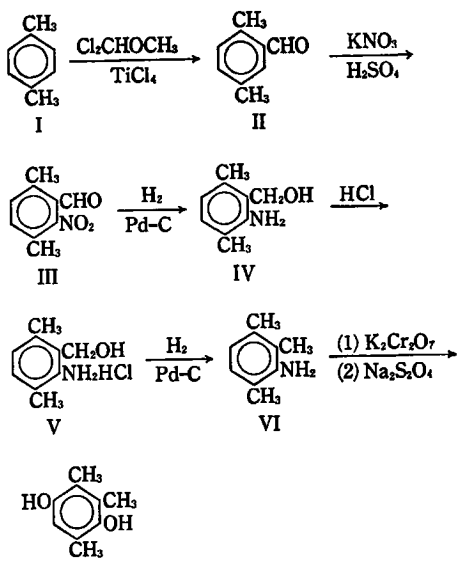
The synthesis of trimethylhydroquinone from *p*-xylene was carried out *via* two routes; one includes the formylation of *p*-xylene, followed by nitration, and the other, the chloromethylation of nitro-*p*-xylene. The oxidation of the trimethylanilines, VI and IX, prepared from 2, 5-dimethyl-6-nitrobenzaldehyde and 2, 5-dimethyl-3-chloromethylnitrobenzene and their subsequent reduction gave trimethylhydroquinone (TMH) in appreciable yields.

α-Tocopherol (vitamin E) may be obtained by the condensation of TMH with phytol[1] or its derivatives.[2] Earlier papers in this series have described how TMH has been synthesized from 2-methylhydroquinone, 3, 5-dimethylhydroquinone,[3] and pseudocumene.[4]

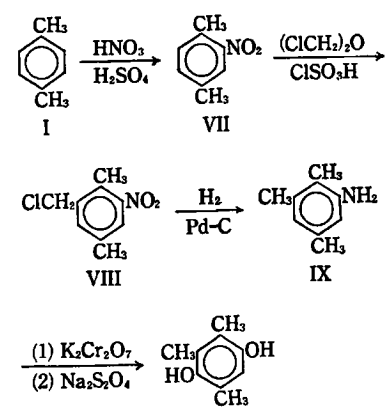
In this study the synthesis of TMH was carried out from *p*-xylene. No report could be found concerning such a synthesis of TMH from *p*-xylene. *p*-Xylene is now obtained readily through the petroleum chemical industry, so the synthesis of TMH from *p*-xylene may well prove of great interest. Two routes of synthesis are shown below.

The reaction of aromatic hydrocarbons with dichloromethyl methyl ether in the presence of a Lewis acid has been reported to give aromatic aldehydes.[5] The treatment of *p*-xylene with dichloromethyl methyl ether gave 2, 5-dimethylbenzaldehyde (II) in a 63% yield. The catalytic reduction of the 2, 5-dimethyl-6-nitrobenzaldehyde (III) prepared by the nitration[6] of II gave the methylolaniline IV, which was not reduced further even at a higher temperature. The attempted Clemmensen reduction of III or IV was also unsuccessful. The fact that the catalytic reduction of III can not provide VI is probably attributable

Route (1)



Route (2)



*1 Paper V of Studies of the Synthesis of Vitamin E.

1) P. Karrer, H. Salmon and H. Fritzshe, *Helv. Chim. Acta*, **21**, 309 (1938); Hoffmann-La Roche and Co., Swiss Pat. 212353 (1941); P. Karrer and O. Isler, U. S. Pat. 2411968 (1946); O. Ehrman, German Pat. 1015446 (1958).

2) Hoffman-La Roche and Co., Swiss Pat. 208446 (1940); P. Karrer and O. Isler, U. S. Pat. 2411969 (1946); P. Karrer, R. Esher, H. Fritzsche, K. Keller, B. Ringier and H. Salmon, *Helv. Chim. Acta*, **21**, 939 (1938); P. Karrer and H. Keller, *ibid.*, **21**, 1161 (1938); J. D. Surmatis and J. Weber, U. S. Pat. 2723278 (1955); J. D. Surmatis and J. Weber, Canadian Pat. 530254 (1956); L. I. Smith and H. E. Ungnale, U. S. Pat. 2421811 (1947); J. Weicht, *Chem. Listy*, **52**, 722 (1958); L. Blaha, J. Hodosova and J. Weicht, *Collection Czech Chem. Commun.*, **24**, 2023 (1959); L. Blaha and J. Weicht, Czech Pat. 88904 (1959).

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

4) K. Sato and Y. Fujima, *Yukigoseikagaku Kyokaishi (J. Synth. Org. Chem. Japan)*, **25**, 252 (1960).

5) A. Rieche, H. Gross and E. Höft, *Chem. Ber.*, **93**, 88 (1960); H. Gross, A. Rieche and G. Mattley, *ibid.*, **96**, 308 (1963).

6) L. Gattermann, *Ann.*, **393**, 221 (1912).

to the poisonous effect of the resulting amino-group on the catalyst.[7] The methylolaniline IV was converted into the hydrochloride V. The catalytic reduction of V gave 2, 3, 6-trimethylaniline (VI) in a 33% yield. TMH was obtained in a 67% yield by the oxidation of VI, followed by reduction. Each step in Route (1) gives a comparatively good yield except the reduction. If the method for the conversion of III to VI can be improved, therefore, Route (1) may be useful for the synthesis of TMH. The reduction of aldehyde involving the nitro-group was hard in Route (1), so chloromethylation was carried out *via* Route (2).

The chloromethylation of nitrotoluenes with bis-(chloromethyl) ether in chlorosulfonic acid has been reported by Berezovskii[8] and other workers.[9,10] The chloromethylation of VII with bis(chloromethyl) ether afforded 2, 5-dimethyl-3-chloromethylnitrobenzene (VIII) in a 67% yield, along with a considerable amount of a by-product. As Table 1 shows, when the reaction temperature was 5—10°C and the reaction time was 64 hr, the chloromethyl compound, VIII, was obtained in a maximum yield. The material VII was recovered at a lower temperature in spite of the long reaction time. The chloromethylation of VII at a higher temperature yielded more of the by-product.

Table 1. The chloromethylation of nitro-*p*-xylene with bis(chloromethyl) ether in various conditions

No.	Reaction		Yield of product, %	
	Temp. °C	Time hr	A[1]	B[1]
1	0— 5	36	32.4[2]	—[3]
2	0— 5	72	50.0[2]	—[3]
3	5—10	64	67.0	—[3]
4	7—10	12	21.6[2]	—[3]
5	10—15	24	44.5	12
6	10—15	64	25.2	32
7	15—20	24	41.6	15
8	20—25	16	27.6	24

1) A=2, 5-dimethyl-3-chloromethylnitrobenzene (VIII); B=2,5-bis(chloromethyl)-3,6-dimethylnitrobenzene.
2) The material VII was recovered.
3) The yield was not measured.

The structure of VIII was identified on the basis of the infrared spectrum and confirmed by the retention time[11] of trimethylaniline, IX, in gas chromatography. The by-product was regarded as 2, 5-di(chloromethyl)-3, 6-dimethylnitrobenzene on the basis of the results of the elementary analysis and infrared spectroscopy, and by the fact that 2, 3, 5, 6-tetramethylaniline was obtained by the catalytic reduction.

The catalytic reduction of VIII gave 2, 3, 5-trimethylaniline (IX), which was then converted into TMH in a 44% yield.

Route (2) does not have the same difficulty in reduction as Route (1), as has fewer steps as well. TMH is obtained in a better yield from VI than from IX. Route (2), however, gives higher yields than Route (1) on the whole.

Experimental[12]

Materials. Dichloromethyl methyl ether was prepared from methyl formate by the procedure of Rieche.[5] The preparation of 2, 5-dimethyl-6-nitrobenzaldehyde-(III) followed the method of Gattermann.[6] Nitro-*p*-xylene was obtained by the nitration of *p*-xylene with mixed acid.[13] Bis(chloromethyl) ether was prepared by the procedure of Berezovskii.[8]

2, 5-Dimethylbenzaldehyde (II). Into a cold mixture of 106 g of *p*-xylene and 190 g of titanium tetrachloride, 57.5 g of dichloromethyl methyl ether was added, drop by drop, at 5—10°C, then the mixture was stirred for about 1 hr, poured into ice water, and extracted with benzene. After drying, the benzene was removed and the residue was distilled under reduced pressure. II was obtained in a yield of 42.2 g (63%), bp 99—100°C/16 mmHg; ν_{max}^{film} 1680 cm^{-1} (CHO). Its semicarbazone showed a melting point of 215°C.

Found: C, 62.80; H, 6.85%. Calcd for $C_{10}H_{13}N_3O_3$ of the semicarbazone: C, 62.81; 6.72%.

2, 3, 6-Trimethylaniline (VI). In the presence of 5%-palladium-carbon, 10 g of III in methanol was reduced under a pressure of about 100 atm of hydrogen at room temperature in an autoclave. After opening the bomb, the catalyst was removed by filtration and the solvent distilled off. Recrystallization from benzene gave 7.3 g (98%) of IV, mp 106°C. IV in methanol was converted into its hydrochloride V, mp 251°C (dec.), by dry hydrogen chloride. The methanol was then removed, and the V was dried over sodium hydroxide. The hydrochloride, V, in methanol was reduced in the presence of 5%-palladium-carbon under a pressure of about 110 atm of hydrogen in an autoclave at 60°C. After opening the bomb, the catalyst was removed and the solvent distilled off. The residue was

7) E. B. Maxted, "The Poisoning of Metallic Catalysts" in "Advances in Catalysis and Related Subjects," Vol. III, Academic Press Inc., N. Y. (1951), p. 129; M. H. Dilike, D. D. Eley and E. B. Maxted, *Nature*, **161**, 804 (1948); E. B. Maxted, *J. Chem. Soc.*, **1949**, 1987.
8) V. M. Berezovskii, V. A. Kurdyukova and N. A. Preobrazhenskii, *Zhur. Obshchei. Khim.*, **21**, 1163 (1951); *ibid.*, **21**, 1269 (1951); *Chem. Abstr.*, **46**, 5006 (1952).
9) W. Polaczkowa and N. Porowska, *Roczniki Chem.*, **31**, 1207 (1957).
10) U. S. Pat. 2758137.
11) J. H. Jones, C. D. Ritchie and K. S. Heine, Jr., *J. Assoc. Offic. Agr. Chemists*, **41**, 749 (1958).
12) All melting points and boiling points are uncorrected. Infrared spectra were recorded on a Hitachi Model EPI-S2 spectrophotometer and gas chromatographic analyses were carried out on Shimadzu Model GC-IC chromatograph.
13) M. Ya. Kraft and A. M. Tsyganova, *Med. Prom. S. S. S. R.*, **14**, No. 10, 27—30 (1960).

treated with a 30% aqueous solution of potassium hydroxide, and extracted with ether. After drying, the ether was removed, distillation under a reduced pressure then gave 2.8 g (33%) of VI, bp 98—99°C/8 mmHg. The melting point of its acetyl derivative was 188—189°C (Lit.[14] mp 186°C).

Trimethylhydroquinone from VI. A solution of 36 g of sulfuric acid in 160 g of water was cooled to 5°C, and then 2 g of VI was added. The subsequent addition of 1.8 g of potassium bichromate to the solution took about 1 hr, after which the solution was stirred for 11 hr at 3—5°C. To the solution, 2.6 g of potassium bichromate was added again over a 1-hr period. After stirring for thirty minutes, the solution was extracted with ether and treated with a saturated solution of sodium hydrosulfite in water. After drying, the ether was removed. Recrystallization from water gave 1.5 g (67%) of TMH, mp 168—169°C.

2, 5-Dimethyl-3-chloromethylnitrobenzene (VIII). Into a mixture of 20 g of VII and 16 g of bis-(chloromethyl) ether, 24 g of chlorosulfonic acid were added, drop by drop, the temperature being 5—10°C. After having been stirred for 64 hr, the mixture was poured into ice water and extracted with ether, and the ethereal extract was dried over sodium sulfate. The ether was removed, and the distillation of the residue under reduced pressure gave 16.7 g (67%) of VIII, bp 112—113°C/2 mmHg, ν_{max}^{film} 1525, 1370 (NO_2), 840 (C–H) and 720 cm^{-1} (C–Cl).

Found: C, 54.40; H, 4.98%. Calcd for $C_9H_{10}ClNO_2$: C, 54.15; H, 5.05%.

2, 3, 5-Trimethylaniline (X). In the presence of 4 g of 5%-palladium-carbon and 25 g of triethylamine, VIII (39.2 g) in ethanol was reduced under a pressure of about 80 atm of hydrogen at room temperature. After opening the bomb, the catalyst was removed by filtration and the ethanol was distilled off. The residue was dissolved into water and extracted with ether. After drying with potassium hydroxide, the ether was removed. The distillation of the residue under a reduced pressure gave 21.4 g (84%) of IX, bp 110°C/9 mmHg, mp 35—37°C (Lit.[15] mp 36°C).

Trimethylhydroquinone from IX. The trimethylaniline, IX (2 g), was added into a mixture of concentrated sulfuric acid (16 g) and water (60 ml). The mixture was then cooled to 10—15°C, and potassium bichromate (2 g) was added to the mixture over a 1-hr period. After the mixture had been stirred for about 10 hr, potassium bichromate (3.3 g) was further added. Then the mixture was extracted with ether, and the extract was treated with a saturated solution of sodium hydrosulfite in water. After drying, the ether was removed. Recrystallization from water gave 1 g (44%) of TMH, mp 168—170°C.

14) F. Mayer, *Ber.*, **20**, 972 (1887).

15) F. M. Beringer and I. Ugelow, *J. Am. Chem. Soc.*, **75**, 2635 (1953).