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24. **Keizo Kitahonoki**: Diels-Alder Reaction. V.[1]
The Reaction of 2,5-Dialkylhydroquinones and Maleic Anhydride.

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Recently, Takeda and Kitahonoki[1] examined the reaction of maleic anhydride with hydroquinone homologs, such as toluhydroquinone, 2,5-dimethylhydroquinone, 2,6-dimethylhydroquinone, thymohydroquinone, and 2,3,5,6-tetramethylhydroquinone, and found that only 2,5-dimethylhydroquinone among these homologs could react with maleic anhydride to give the adduct (I) as in the case of hydroquinone itself.[2]

Since 2,5-dimethylhydroquinone, which gave the maleic anhydride adduct, is a 2,5-dialkylhydroquinone, such homologs seemed to be suitable for the reaction. However, thymohydroquinone did not give the desired adduct, although it is also 2,5-dialkylhydroquinone. In order to investigate the effect of alkyl groups on the reactivity of hydroquinone homologs, examination was made on the reaction of maleic anhydride with four 2,5-dialkylhydroquinones, i.e. 2-methyl-5-ethylhydroquinone (II), 2,5-diethylhydroquinone (III), 2-methyl-5-propylhydroquinone (IV),[3] and 2,5-dipropylhydroquinone (V).

The hydroquinone homologs (II), (III) and (V) were synthesized as shown in chart 1. (III), m.p. 176~178°, and (V), m.p. 148~149°, are new compounds. The intermediate compounds from *p*-diethylbenzene to (III) have been described in the literature,[4] but as the purity is questionable, pure samples of these substances were prepared and their physical constants determined.[5]

(II) and (III) reacted with maleic anhydride under the same reaction conditions as in the case of hydroquinone,[2] yielding adducts of m.p. 225~226° and m.p. 196~197.5°, respectively. On the other hand, (IV) and (V) did not give the maleic anhydride adduct. The above two adducts are apparently the desired adducts from their analytical data and infrared spectra. Since the structure of 2,5-dimethylhydroquinone-maleic anhydride adduct was proved[1] to be not (I') but (I), 2,5-diethylhydroquinone-maleic anhydride adduct should be represented by the formula (VIII). As for 2-methyl-5-ethylhydroquinone-maleic anhydride adduct, theoretically two isomeric adducts (VIIa) and (VIIb) can exist, provided that the addition of maleic anhydride occurs at the 2- and 5-positions of the hydroquinone homolog. It was not determined to which formula of these two the adduct corresponds. The crude adduct had an unsharp melting point even after several recrystallizations, so that another stereoisomeric adduct might be present in the mother liquor of recrystallizations, but no other adduct could be isolated because of the lack of material.

The melting point and yield of the maleic anhydride adducts of hydroquinone and its homologs, hitherto obtained, are shown in Table I.

The yield of 2,5-dimethylhydroquinone-maleic anhydride adduct (I) is somewhat better than that of the hydroquinone adduct, and the yields of the adducts (VII) and (VIII) are lower than that of the hydroquinone adduct. These results are quite similar to the fact that

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1) Part IV: K. Takeda, K. Kitahonoki: Ann., **606**, 153(1957).
2) K. Takeda, K. Kitahonoki, K. Igarashi: This Bulletin, **4**, 12(1956).
3) This compound was prepared by the catalytic reduction of 2-allyl-4-benzyloxy-5-methylphenol. Unpublished data.
4) A. Voswinkel: Ber., **22**, 315(1889).
5) On diazotization of 2,5-diethylaniline, 2,5-diethyl-4-nitrosophenol (VI) was obtained as a by-product.

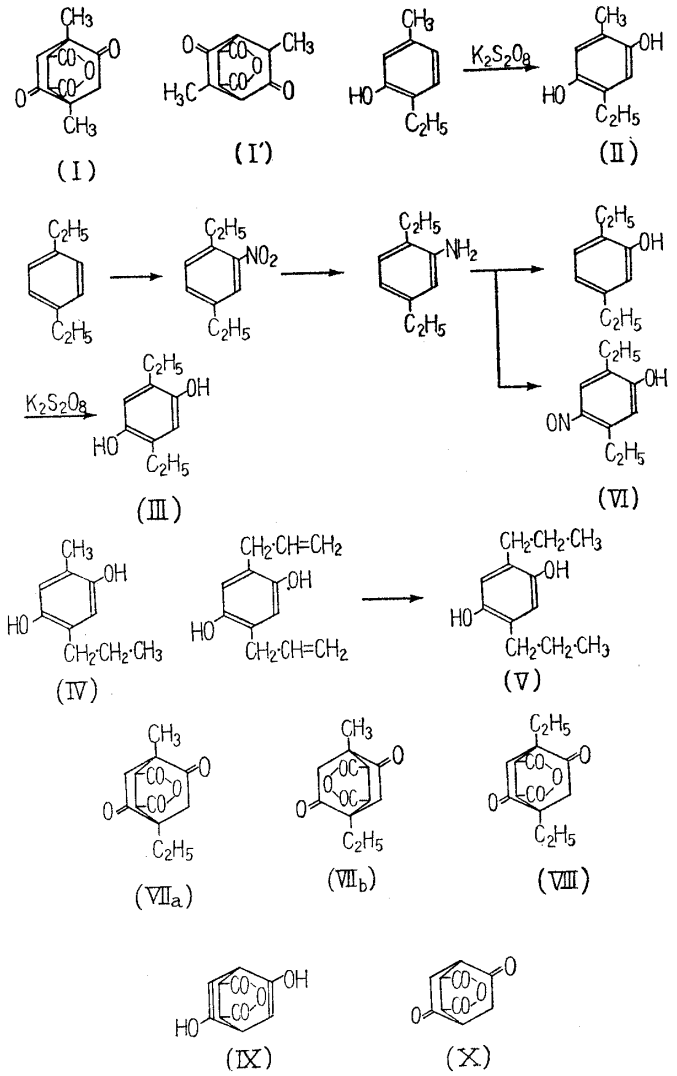

Chart 1.

TABLE I.

Hydroquinone homolog	Maleic anhydride adduct, m.p. (°C)	Yield,* (%)
Hydroquinone	251～253° (X)	10
2,5-Dimethylhydroquinone	235～236.5° (I)	20.8
2-Methyl-5-ethylhydroquinone	225～226° (VIIa) or (VIIb)	4.9
2,5-Diethylhydroquinone	196～197.5° (VIII)	5.4

* Theoretical yield, calculated for the hydroquinones.

methylnaphthalenes afford the maleic anhydride adduct in a better yield than naphthalene.[6] The data also agree with the fact that methyl groups in the 9- and 10-positions of anthracene facilitate the reaction with maleic anhydride[7] but ethyl groups in the same positions do not increase the reactivity so much.[8]

From these results and observations, the effect of alkyl groups in 2,5-dialkylhydroquinones on the reactivity may be considered as follows: The methyl groups of 2,5-di-

6) M. C. Kloetzel, R. P. Dayton, H. L. Herzog: J. Am. Chem. Soc., **72**, 273(1950); M. C. Kloetzel, H. L. Herzog: *Ibid.*, **72**, 1991(1950); J. Org. Chem., **15**, 370(1950); B. J. Abadir, J. W. Cook, D. T. Gibson: J. Chem. Soc., **1953**, 8.
7) W. E. Bachmann, M. C. Kloetzel: J. Am. Chem. Soc., **60**, 481(1938).
8) W. E. Bachmann, J. M. Chemerda: *Ibid.*, **60**, 1023(1938).

methylhydroquinone facilitate the reaction with maleic anhydride by their polar effect. The accelerating effect of the alkyl groups on the reactivity of 2-methyl-5-ethyl- and 2,5-diethyl-hydroquinone is smaller than the retarding effect by steric hindrance or other reasons. The retarding effect of alkyl groups is much larger than the accelerating effect in 2-methyl-5-isopropyl- and 2,5-dipropyl-hydroquinone; and in these cases the adduct is not obtained.

When phenols and maleic anhydride are fused together, a yellow to yellowish red color is produced, irrespective of whether diene syntheses can proceed or not. This step may be interpreted by electron-transfer from phenol as a diene to maleic anhydride as a dienophile, forming an ionic complex, which involves the flat dipolar aggregate.[9] The rearrangement of this complex to an adduct is a rate-determining step and the ease with which the rearrangement takes place differs greatly depending upon the kind of the phenols. It is reasonable to consider that the polar and steric effects of a substituent in phenols exert a great influence on the structure of the ionic complex formed and formation of an adduct. In some instances, no further reaction proceeds or only polymerisation occurs rapidly (e.g., in the case of resorcinol[1]) or gradually (e.g. in the case of toluhydroquinone).

Benzene and its homologs are known to form 1:1 associate of low stability with maleic anhydride,[10] but its rearrangement to the adduct is impossible. Ability of hydroquinone to form the maleic anhydride adduct is, therefore, attributed to the accelerating effect of hydroxyl groups and stabilization of the possible initial adduct (IX) by its conversion to the ketoform (X).

On the other hand, the experimental results show that among the polyhydric phenols so far investigated, only hydroquinone and some 2,5-dialkylhydroquinones are able to give the maleic anhydride adduct. As already described, alkyl groups of 2,5-dialkylhydroquinones exert a great effect on the reactivity. The effects, especially the steric hindrance by larger alkyl groups, may be expected from the assumption of an ionic complex.

From these facts for the diene synthesis of phenols, it seems necessary for a compound to have a nearly symmetrical structure about the center of the benzene ring.

The author expresses his gratitude to Dr. K. Takeda, Director of this Laboratory, for his unfailing guidance throughout the course of this work. Also thanks are due to Mrs. A. Irie for the preparation of 2-methyl-5-ethylhydroquinone and 2,5-diethylhydroquinone. Ultraviolet and infrared spectra were measured by Mr. T. Kubota and Mr. Y. Matsui, and microanalyses were carried out by the members of Analysis Room of this Laboratory, to all of whom the author is indebted.

Experimental[11]

2-Methyl-5-ethylhydroquinone (II)—To a stirred solution of 2-ethyl-5-methylphenol[12] (5 g.) in 5% NaOH (150 cc.), $K_2S_2O_8$ (15 g.) was added in small portions under cooling below 10° over a period of 3 hrs. The solution was stirred for a further 2 hrs. and allowed to stand overnight. After acidification with 10% HCl to pH 1.8, the solution was extracted 3 times with ether to remove the starting material (2.46 g.). Conc. HCl (13 cc.) was added to the aqueous solution and it was heated on a boiling water-bath for 2 hrs. After cooling, the solution was extracted 3 times with ether. The ether solution was dried over Na_2SO_4 and evaporated to give brown crystals (1.85 g.). After filtration through alumina in benzene-ether solution, the crystals were recrystallized from ether-benzene to give plates, m.p. 164~165°. UV $\lambda_{max}^{95\%\ EtOH}$ 293 mμ ($\log\varepsilon$ 3.59). *Anal.* Calcd. for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 71.32; H, 8.10.

1-Nitro-2,5-diethylbenzene—*p*-Diethylbenzene (10 g.) was dropped into a vigorously stirred mixture of conc. H_2SO_4 (d=1.84, 10.8 cc.) and AcOH (6 cc.) at -10° during 15 mins. A mixture (cooled to 0° to 5°) of conc. H_2SO_4 (d=1.84, 10.8 cc.) and conc. HNO_3 (d=1.38, 5.5 cc.) was added dropwise to the emulsified mixture at -10° to -15° over a period of 2 hrs. After the addition was completed, stirring was con-

9) R. B. Woodward: J. Am. Chem. Soc., **64**, 3058(1942); R. B. Woodward, H. Baer: *Ibid.*, **66**, 645 (1944).
10) L. J. Andrews. R. M. Keefer: *Ibid.*, **75**, 3776(1953).
11) Melting points determined in capillary tubes and boiling points are uncorrected. Infrared spectra were measured with a Perkin-Elmer Single-beam Infrared Spectrophotometer, Model 12C, and ultraviolet spectra were taken with a Beckman Spectrophotometer, Model DU.
12) K. Auwers, H. Bundesmann, F. Wieners: Ann., **447**, 162(1926).

tinued for another hour. The mixture was then poured into ice-water (50 g.) and extracted 3 times with petr. ether. The petr. ether solution was washed with 5% Na_2CO_3 and water, dried over Na_2SO_4, and evaporated to give a yellow oil (12.6 g.), which was distilled to afford a pale yellow oil (7.7 g.), b.p_3 110~111.5°, n_D^{21} 1.5225. UV $\lambda_{max}^{95\%\ EtOH}$: 262 mμ (log ε 3.64). *Anal.* Calcd. for $C_{10}H_{13}O_2N$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.28; H, 7.58; N, 7.70.

When the nitration was carried out using fuming HNO_3 according to Voswinkel,[4] 4-ethylacetophenone was obtained in 50% yield and it was difficult to remove this by-product by fractional distillation. It was separated and identified as its 2,4-dinitrophenylhydrazone. Red prisms (from benzene), m.p. 202~203.5°. *Anal.* Calcd. for $C_{16}H_{16}O_4N_4$: C, 58.53; H, 4.91; N, 17.07. Found: C, 58.49; H, 4.93; N, 16.90.

2,5-Diethylaniline—The above 1-nitro-2,5-diethylbenzene was catalytically reduced with H_2 in MeOH over Pd-C to give an oil, b.p_2 93~94°, n_D^{21} 1.5423. UV $\lambda_{max}^{95\%\ EtOH}$ mμ (log ε): 235 (3.83), 287 (3.34). *Anal.* Calcd. for $C_{10}H_{15}N$: C, 80.48; H, 10.13; N, 9.39. Found: C, 80.79; H, 10.45; N, 9.74.

Acetate: Needles (from MeOH-Et_2O), m.p. 154~154.5°. *Anal.* Calcd. for $C_{12}H_{17}ON$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.34; H, 9.01; N, 7.37.

2,5-Diethylphenol—2,5-Diethylaniline (5 g.) was dissolved in warm dil. H_2SO_4 (18.8 cc., containing 3.1 cc. of conc. H_2SO_4) and the solution was cooled rapidly by the addition of ice (26.6 g.) to give a suspension of the sulfate. $NaNO_2$ solution (3 g. in 12 cc. of H_2O) was added dropwise with stirring at 0° until an excess of HNO_2 was realized (I-Zn-starch test paper). The cold diazonium solution was dropped into a boiling 10% H_2SO_4 (100 cc.) and the resulting phenol was steam distilled at the same time. Steam distillation was continued until all the phenol distilled.

The distillate was extracted with ether. The ether solution was shaken 3 times with 5% Na_2CO_3 and then 6 times with Claisen solution (50% KOH:MeOH=1:1). The Claisen extract was acidified with 10% HCl and extracted again with ether. The ether solution was dried over Na_2SO_4 and evaporated to give an oil (3.78 g.), which was chromatographed on alumina and distilled to colorless oil (2.82 g.), b.p_3 96~96.5°. *Anal.* Calcd. for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.48; H, 9.60.

Phenylurethane: Needles (from petr. ether), m.p. 92~92.5°. *Anal.* Calcd. for $C_{17}H_{19}O_2N$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.69; H, 7.21; N, 5.16.

The above 5% Na_2CO_3 washings of the ether extract of the steam-distillate were acidified with dil. HCl and extracted with ether. The ether solution was washed with water, dried over Na_2SO_4, and evaporated to give crystals (290 mg.), which were recrystallized from benzene to pale yellow crystals of (VI), m.p. 137~139° (decomp.). UV $\lambda_{max}^{95\%\ EtOH}$ mμ (log ε): 237 (3.44), 307 (4.32). *Anal.* Calcd. for $C_{10}H_{13}O_2N$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.05; H, 7.52; N, 7.77.

2,5-Diethylhydroquinone (III)—To a stirred solution of 2,5-diethylphenol (2.4 g.) in 5% NaOH (64 cc.), $K_2S_2O_8$ (5.6 g.) was added in small portions at 0° to 2° over a period of 3 hrs. and stirring was continued for a further 2 hrs. After being allowed to stand overnight excess of $K_2S_2O_8$ was destroyed with Na_2SO_3, and the solution was acidified with dil. HCl to pH 1~2 and washed with ether to remove unchanged material (1.38 g.). The aqueous layer was heated on a boiling water bath with conc. HCl (5 cc.) for 3 hrs. After cool, the solution was extracted 3 times with ether. The ether solution was washed with water, dried over Na_2SO_4, and evaporated to give brown crystals (1.3 g.), which were purified by filtration through alumina as ether-benzene solution and recrystallized from ether-benzene to colorless plates, m.p. 176~178° (in a sealed tube). UV $\lambda_{max}^{95\%\ EtOH}$ 293 mμ (log ε 3.63). *Anal.* Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.43; H, 8.49.

2,5-Dipropylhydroquinone (V)—2,5-Diallylhydroquinone[13] (2 g.) in MeOH (20 cc.) was catalytically reduced over Pd-C (0.2 g., Pd 10%). It smoothly absorbed a calculated amount of H_2. After removal of catalyst and evaporation, the residual crystals were recrystallized from benzene-ether to scales, m.p. 148~149°, which seemed to contain some benzene of crystallization and was dried at 100° *in vacuo* for 8 hrs. for an analytical sample. *Anal.* Calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.21; H, 9.39.

2-Methyl-5-ethylhydroquinone-Maleic Anhydride Adduct (VIIa) or (VIIb) (1-Methyl-4-ethyl-2,5-dioxobicyclo[2.2.2]octane-7,8-dicarboxylic Anhydride)—A mixture of 2-methyl-5-ethylhydroquinone (1.47 g.) and maleic anhydride (2.84 g.) was heated at 195~200° (bath temp.) in CO_2 atmosphere for 4 hrs. The brown reaction product was dissolved in ether (ca. 10 cc.) and allowed to stand to give plates (93 mg.), m.p. 203~211°. Four recrystallizations from acetone-ether gave prisms, m.p. 225~226°. IR λ_{max}^{Nujol} μ: 5.36, 5.61 (anhydride), 5.78 (carbonyl). *Anal.* Calcd. for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.41; H, 5.36.

2,5-Diethylhydroquinone-Maleic Anhydride Adduct (VIII) (1,4-Diethyl-2,5-dioxobicyclo[2.2.2]-octane-7,8-dicarboxylic Anhydride)—A mixture of 2,5-diethylhydroquinone (0.5 g.) and maleic anhydride (1.18 g.) was heated at 195~200° (bath temp.) in CO_2 atmosphere for 4.25 hrs. The brown reaction product was dissolved in ether (30 cc.) and an amorphous substance (10 mg.) precipitated, which was removed. When the ether solution was concentrated and allowed to stand, beautiful prismatic needles

13) L. F. Fieser, W. P. Campbell, E. M. Fry: J. Am. Chem. Soc., **61**, 2206(1939).

separated out gradually, which weighed 43 mg. and melted at 195~196°. Recrystallization from acetone-ether gave prisms, m.p. 196~197.5°. IR λ_{max}^{Nujol} μ: 5.36, 5.60 (anhydride), 5.79 (carbonyl). *Anal.* Calcd. for $C_{14}H_{16}O_5$: C, 63.32; H, 6.10. Found: C, 63.12; H, 6.20.

Summary

The reaction of 2,5-dialkylhydroquinones, 2-methyl-5-ethylhydroquinone (II), 2,5-diethylhydroquinone (III), 2-methyl-5-propylhydroquinone (IV), and 2,5-dipropylhydroquinone (V), with maleic anhydride was investigated. Of these hydroquinone homologs, (II) and (III) gave the maleic anhydride adducts, (VIIa) or (VIIb) and (VIII), respectively.

The effect of alkyl groups on the reactivity of the hydroquinone homologs is discussed.

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25. Komei Miyaki, Makoto Hayashi, and Tsutomu Unemoto: Degradation Pathway of Ethanolamine in *Proteus morganii.*

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Reports on the metabolism of ethanolamine in the past have been concentrated on oxidative deamination forming hydroxyacetaldehyde and ammonia in animals[1] or decomposition into ethylene glycol and ammonia by *Clostridium* genus in microörganisms.[2]

Recently, it has been found in this laboratory that the presence of ethanolamine ($10^{-3}M$) in a medium containing glucose and glutamate stimulated the growth of *Proteus morganii.*[3] It was also revealed that the cells and ethanolamine-adapted cells of this bacteria effected decomposition of ethanolamine into ammonia and acetaldehyde, irrespective of aerobic or anaerobic conditions, instead of oxidative deamination like ordinary monoamines and diamines. The acetaldehyde here formed then produces acetic acid and ethanol. Consequently, the presence of an enzyme that decomposes ethanolamine into ammonia and acetaldehyde was assumed and it was designated as ethanolamine dehydrase, in accordance with the example of serine.[4]

It is interesting that such a new pathway for decomposition of ethanolamine has been found only in *Pr. morganii.*

Experimental Method

Materials—Ethanolamine, N-methylethanolamine, N,N-dimethylethanolamine, choline chloride, phosphorylethanolamine (2-aminoethyl dihydrogen phosphate), and 2-hydroxypropylamine used in this work were all prepared in this laboratory. Other reagents used were commercial products.

Enzyme Preparation—Throughout all the experiments, the washed cells of *Pr. morganii* AS-21 (in the collection of the Institute of Food Microbiology, University of Chiba) cultured in a medium (pH 7.0) containing 0.5% yeast extract and 1% glucose at 30° for 16~18 hrs. was used as the enzyme preparation. Its suspension in a final concentration of 0.1~0.2 mg. Kjeldahl N/cc. was used. The enzymatic reaction seemed to proceed somewhat more actively under anaerobic than aerobic conditions. As will be described

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1) A. Weissbach, D. B. Sprinson: J. Biol. Chem., **203**, 1013(1953).
2) G. Cohen, B, Nisman, M. Raynaud: Compt. rend., **225**, 647(1947).
3) H. Momiyama: Nippon Eiseigaku Zasshi, **11**, 296(1957).
4) E. Chargaff, D. B. Sprinson: J.Biol. Chem., **151**, 273(1943).