Total Syntheses of Tanshinone-I, Tanshinone-II and Cryptotanshinone[*1,2]

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Total syntheses of tanshinone-II (II) and cryptotanshinone (III) from 3-methylbenzofuran-4, 7-quinone (X) and 6,6-dimethyl-1-vinylcyclohexene (IX), and of tanshinone-I (I) from quinone X and *o*-methylstyrene (XVIII) are described. Preliminary accounts for the Diels-Alder reaction of methoxybenzoquinone revealed that the effect of substituents for orientation phenomena can be considered to be of electronic nature.

Tanshinone-I (I),[1] tanshinone-II (II)[2] and cryptotanshinone (III)[3]–pigments isolated from the root of *Salvia miltiorrhiza* Bunge[4]–were found to posess the unique chromophore consisting of an orthoquinone and a furan ring. Recent investigations on minor components established the structures of tanshinone-IIB (IV),[5] hydroxytanshinone-II (V)[6] and methyl tanshinonate (VI)[6] having the same framework.

Fig. 1

I

II R=Me
IV R=CH₂OH
VI R=COOMe

III

V
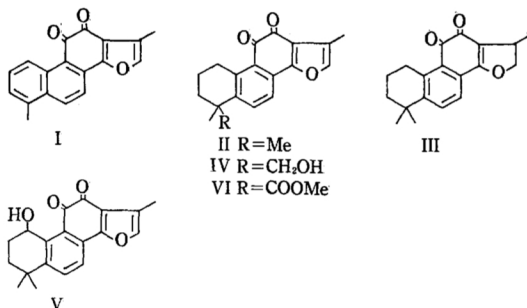
Synthetic approaches to these unique pigments have been reported by three groups,[5, 7–9] of which

two[5,9] succeeded in syntheses of tanshinones. In the early approaches,[7,8] A/B/C rings were built up by the Diels-Alder reaction of benzoquinone with suitable dienes, followed by attempted introduction of an alkyl side chain to make a furan ring. However, the alkylations resulted in an unsuitable position[7] or in an unseparable mixture.[8]

Recently these weakness were overcome by using the 1,3-dimethoxyphenanthrene derivative[9] or the 3-hydroxy-1,4-phenanthrenequinone derivatives[5] as an intermediate, where the introduction of an alkyl side chain could be controlled to occur at a suitable position (C_2).

Utilization of the Diels-Alder reaction to build the framework would be preferable for two reasons; firstly, this method will establish the general route to all tanshinones by using an appropriate quinone or diene, and secondly, some information can be obtained for the orientation in the Diels-Alder reaction, on which little is known especially in the case of substituted benzoquinones (*vide infra*).

In the purification of cryptotanshinone (III),

*1 Presented at the 21st Annual Meeting of the Chemical Society of Japan, Osaka, April, 1968; H. Kakisawa and Y. Inouye, *Chem. Commun.*, **1968**, 1327.

*2 Taken in part from the thesis of Y. Inouye, Tohoku University, 1968.

1) F. von Wessely and S. Wang, *Ber.*, **73**, 19 (1940).

2) a) Y. Okumura, H. Kakisawa, M. Kato and Y. Hirata, This Bulletin, **34**, 895 (1961). b) K. Takiura and K. Koizumi, *Chem. & Pharm. Bull.*, **10**, 112 (1962).

3) K. Takiura, *J. Pharm. Soc. Japan*, **61**, 482 (1941).

4) M. Nakao and T. Fukushima, *ibid.*, **54**, 154 (1934).

5) A. C. Baillie and R. H. Thomson, *J. Chem. Soc., C*, **1968**, 48.

6) H. Kakisawa, T. Hayashi, I. Okazaki and M. Ohashi, *Tetrahedron Letters*, **1968**, 3231.

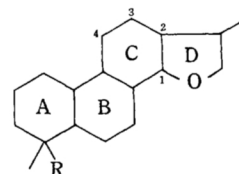7) T. J. King and G. Read, *J. Chem. Soc.*, **1961**, 5090.

8) H. Kakisawa and M. Ikeda, *Nippon Kagaku Zasshi (J. Chem. Soc. Japan, Pure Chem. Sect.)*, **88**, 476 (1967).

9) a) M. Tateishi and H. Kakisawa, The 11th Symposium on the Chemistry of Natural Products (Oct. 10, 1967) held at Kyoto. The Abstracts, p. 166; b) H. Kakisawa, M. Tateishi and T. Kusumi, *Tetrahedron Letters*, **1968**, 3783.

Takiura[10] found that it readily dissolved in alcoholic potassium hydroxide to give a yellow enolic compound, and that the latter was reconverted into cryptotanshinone on heating with an equal amount of ethanol and concentrated sulfuric acid. From the structure of cryptotanshinone, and the ready hydrolysis of alkoxyquinone with alkali to hydroxyquinone, these phenomena can be explained as III ⇌VII. Possibility of conversion of isomer VIII


III ⇌   VII   VIII
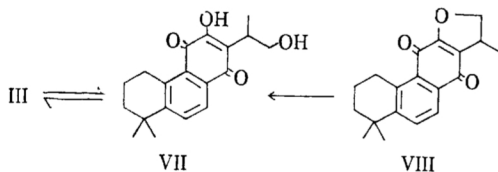
of cryptotanshinone (III) into cryptotanshinone through the same enolic intermediate VII prompted us to prepare isomer VIII by the Diels-Alder reaction between 6,6-dimethyl-1-vinylcyclohexene(IX)[8] and 3-methylbenzofuran-4,7-quinone (X) followed by catalytic hydrogenation of adduct XI. The unknown quinone X can be derived from 3-methyl-4-benzofuranol (XII)[11] by mild oxidation.

Before proceeding to the actual synthesis, we must briefly refer to the orientation in the Diels-Alder adduct. Although no reliable theory[12-15] has yet been given for the orientation in the adducts, the most conventional interpretation is to assume the biradical intermediates[*3] of which the main product may be anticipated by considering the radical stability.

The Diels-Alder reactions of substituted benzoquinones were mostly investigated by Ansell and co-workers.[16] They found that the dienophilic activity of the ethene linkage of benzoquinones

depends on whether its electron-density is greater or less than that of the other: i. e., the lower the electrondensity the greater the reactivity of the ethene linkage. For example, the reaction occurs at unsubstituted ethene linkage of methoxybenzoquinone and at a substituted one of methoxycarbonylbenzoquinone. Although Ansell's works did not concern the orientation and only few examples were found for the Diels-Alder reaction between unsymmetrical benzoquinones and dienes, the effect of substituents may be considered[*4] from two points of view: the radical stability in assumed biradical intermediates and the steric factor in the transition state.

Two possible structures XIIIa and XIIIb can be derived for the radical stability. XIIIa is stabilized more by the C_4-ketone which may have a large +M effect in comparison with the C_1-ketone.[17] Thus, the "radical stability" requires the reaction to proceed as XIIIa→XIVa. For the steric factor in the transition state,[*5] XVa would be energetically

XIIIa   XIVa   XIVb   XIIIb
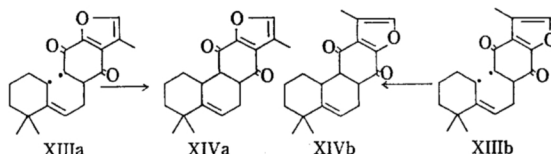
more stable than XVb because in VXb the steric repulsion between the geminal dimethyl group of the diene and the methyl group on the furan ring would become significant. Thus, the reaction was anticipated to proceed in the favorable direction.
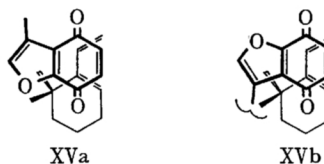

XVa   XVb

Fig. 2.   Possible transition states.

Syntheses of Tanshinone-II and Cryptotanshinone.   The oxidation of 3-methyl-4-benzofuranol (XII)[11] with Fremy's salt[18] gave 3-methyl-benzofuran-4,7-quinone (X) in almost quantitative yield. The p-quinone structure is based on physical properties: IR spectrum shows carbonyl absorptions at 1663 and 1655 cm^{-1}; UV maxima appear at 217, 248, 292 and 394 mμ;[19] and NMR spectrum

10)   K. Takiura, *J. Pharm. Soc. Japan*, **61**, 475 (1941).

11)   W. B. Whalley, *J. Chem. Soc.*, **1951**, 3229.

12)   J. Sauer, *Angew. Chem. Int. Edit.*, **6**, 16 (1967).

13)   A. Wassermann, "Diels-Alder Reactions–Organic Background and Physico-chemical Aspects," Elsevier Publishing Co., Amsteldm, London, New York (1965).

14)   M. Imoto and N. Tokura, "Fuka Hanno," Tokyo Kagaku Dojin, Tokyo (1967).

15)   J. Feuer, W. C. Herndon and L. H. Hall, *Tetrahedron*, **24**, 2575 (1968).

*3   It is known[12] that the Diels-Alder reactions of 1- and 2-substituted butadienes with acrylates proceed mainly as shown, regardless of the electronic nature of the substituents in the diene.
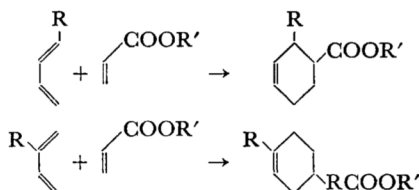
16)   M. F. Ansell, B. W. Nash and D. A. Wilson, *J. Chem. Soc.*, **1963**, 3012, and references cited therein.

*4   Details of these points will be reported elsewhere.

17)   M. J. S. Dewar, "The Electronic Theory of Organic Chemistry," Chapt. XII, Oxford Univ., Press., England (1949).

*5   We might say that the reaction proceeds through the "endo" transition state. See Ref. 16.

18)   H.-J. Teuber and N. Gotz, *Chem. Ber.*, **87**, 1236 (1954).

19)   C. J. P. Spruit, *Rec. Trav. Chim.*, **81**, 810 (1962), reported the longest wavelength absorption of benzofuran-4,7-quinone to be at 380 mμ.
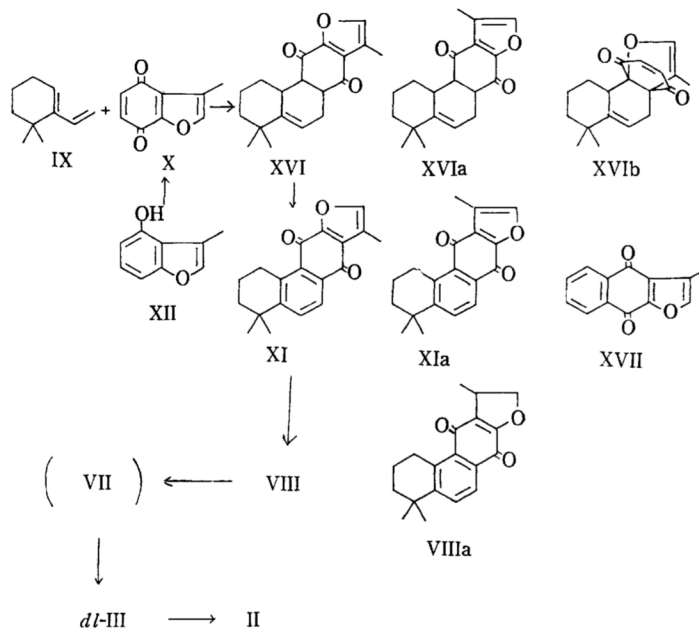
exhibits a doublet due to C_3–CH_3 at 2.30 ppm and a quartet due to C_2–H at 7.40 ppm with a coupling constant of 0.8 cps, and a two proton singlet at 6.62 ppm arising from the two hydrogen atoms on the quinone ring.

The Diels-Alder reaction between 3-methylbenzofuran-4,7-quinone (X) and 6,6-dimethyl-1-vinylcyclohexene (IX)[8] was conducted in ethanol at room temperature.[8] Only one adduct separated in crystalline form in high yield based on the quinone reacted and no other products were characterized. The adduct, mp 160—161°C, shows IR absorptions at 1695 and 1680 cm^{-1}. The molecular ion peak at m/e 298 in the mass spectrum and elementary analysis fitted the formula of 1 : 1 adduct, which was further confirmed by NMR spectrum; a singlet due to the geminal methyl group at 1.04 ppm and a slightly splitted signal due to the methyl group on the furan ring at 2.26 ppm. Moreover, the fact that only two vinyl protons appear at 5.40 and 7.45 ppm, and that the UV maxima at 214, 244 and 303 mμ differ makedly from the O=C–CH=C–O chromophore[16] enable us to reject the structure XVIb. The choice between the remaining two possibilities, XVI and XVIa, was not achieved at this stage.

The adduct XVI (or XVIa) was converted by air oxidation[20] into a naphtho[2,3-b]furan-4,9-quinone derivative XI (or XIa), mp 214—215°C, the IR absorption (1660 cm^{-1}) and UV maxima (252 sh, 255, 305 and 360 mμ) of which were very similar to those of 3-methylnaphtho[2,3-b]furan-4,9-quinone (XVII).[21] An AB type quartet due to C_6

and C_7 protons appears in NMR spectrum at 7.68 and 8.00 ppm with a coupling constant of 10 cps.

The furan ring in XI (or XIa) was subjected to catalytic reduction with palladium on carbon in ethanol[2a] to afford a naphthoquinone derivative VIII (or VIIIa). The selective hydrogenation of the furan ring was confirmed by NMR spectrum of the product. Thus, a secondary methyl signal is present as a doublet at 1.40 ppm.

The naphthoquinone derivative VIII (or VIIIa) was hydrolyzed with alcoholic potassium hydroxide to give an enolic compound VII (or corresponding isomer), which was treated without purification with concentrated sulfuric acid in ethanol.[10] A red crystalline oil obtained was purified by column chromatography on silicic acid. The orange crystals(64%), mp 174—175°C, showed an identical IR spectrum with that of cryptotanshinone (III).

When cryptotanshinone (III) was treated with dichlorodicyanobenzoquinone (DDQ), tanshinone-II (II) was obtained exclusively in 70% yield. The synthetic II melted at 210—211°C alone or mixed with natural tanshinone-II (II), and showed identical IR spectrum with that of the latter.

Synthesis of Tanshinone-I. 3-Methylbenzofuran-4,7-quinone(X) and o-methylstyrene(XVIII)[22] were heated without solvent at 100°C[23,24] for 10 hr. The resulting dark red mass was chromatographed on a column of alumina. At least five colored materials were recognized on thin layer chromatography, but only one orange pigment could be isolated in crystalline form in 25% yield.

20) C. F. H. Allen and A. Bell, "Organic Syntheses," Coll. Vol. III, p. 310 (1955).

21) H. Kakisawa, M. Tateishi, in preparation.

22) Y. Hirshberg, *J. Am. Chem. Soc.*, **71**, 3241 (1949).

23) C. de Corral, *Chem. Abstr.*, **52**, 7257b (1958).

24) M. Lora-Tamayo, *Tetrahedron*, **4**, 17 (1958).

Although this product gave only a single spot chromatographically, recrystallization from benzene gave a pure adduct of mp 219—220°C and unpurified mixtures. The former shows a molecular peak at m/e 276 in the mass spectrum, which together with elementary analyses leads to a formula $C_{18}H_{12}O_3$. The NMR spectrum (Fig. 3a) of the adduct shows an aromatic methyl signal at 2.66 ppm, a methyl signal on the furan ring at 2.34 ppm, and six aromatic protons at 7.0 to 9.6 ppm, which indicates that the 1 : 1 adduct had undergone facile dehydrogenation[24] to give the phenanthrene quinone XIX (or XIXa).

The NMR spectrum (Fig. 3b) of the original mixture is quite similar to that of the product of mp 219—220°C except broadening of all the signals and a new doublet at 9.43 ppm. This suggests the formation of both isomers XIX and XIXa. The ratio of XIX to XIXa was found to be ca. 1.4 calculated from the intensity of the signals 9.55 ppm (corresponds to XIX, vide infra) and 9.43 ppm (XIXa).
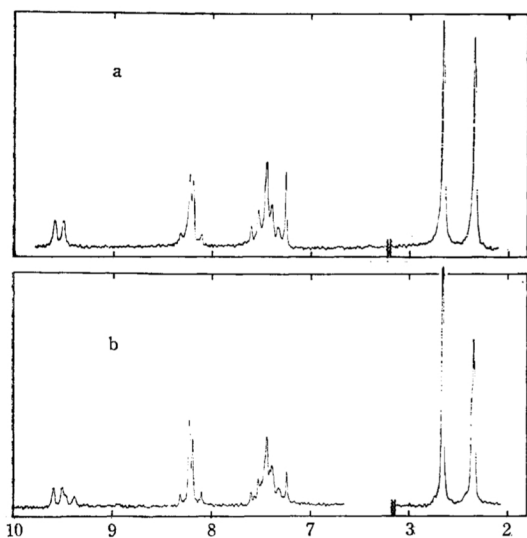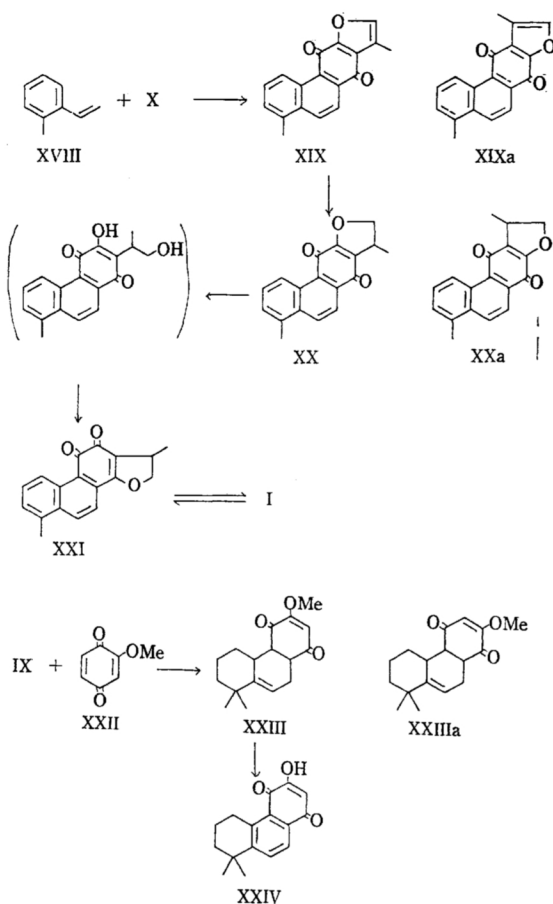

Fig. 3. NMR spectra (100 Mc[*6]) of adducts in CDCl₃.
  a XIX   b the original mixture

The furan ring of the adduct XIX (or XIXa) resisted catalytic flydrogenation under the conditions used for the naphthoquinone XI. However, it was reduced with platinum oxide in acetic acid to afford a dihydro compound XX (or XXa).

The dihydro compound XX (or XXa), without purification, was hydrolyzed with alcoholic potassium hydroxide to give an orange enol, which was

*6 We are deeply indebted to Dr. Y. Nakadaira for measurement of the 100 Mc NMR spectra (performed at Tohoku University).

heated with concentrated sulfuric acid in ethanol to afford known[5] dihydrotanshinone-I (XXI), mp 200—201°C in 35% yield from the adduct XIX. In the present work, the authentic dihydrotanshinone-I was prepared from tanshinone-I (I) by catalytic hydrogenation over platinum oxide in acetic acid and melted at 202°C. The UV and IR spectra of both dihydrotanshinone-I were identical and no depression of mixed melting point took place.

As in the case of cryptotanshinone (III), dihydrotanshinone-I(XXI) was dehydrogenated with DDQ to give tanshinone-I (I) in 50% yield. Synthetic tanshinone-I melted at 229—230°C alone or mixed with the natural specimen. They were identical.

Preliminary Account for Diels-Alder Reaction. The successful conversion of the Diels-Alder adduct to the natural tanshinones established the direction of the furan ring to be as in XVI, but not as in XVIa. Conversely, use of a natural product as a synthetic object clarifies the reaction mechanism to some extent, especially with respect to the stereochemical problem. The result prompted us to undertake a preliminary experiment to decide which factor, electronic or steric, would be predominant in the Diels-Alder reaction of benzoquinones. The diene IX and methoxybenzoquinone (XXII)

were allowed to react under the same conditions as used for the preparation of XVI. The structure of the adduct was confirmed to be XXIII, but not XXIIIa. Firstly, UV spectrum of the adduct fitted the chromophore O=C–C(OMe)=CH–C=O and only vinyl protons appeared at 5.4 and 6.03 ppm. Secondly, the dehydrodemethylation of the adduct with alkaline ethanol afforded a 2-hydroxy-naphthoquinone derivative, which was found to be identical with XXIV.[25]

This is consistent with the electronic effect, but it shows that the steric factor is not, at least, the main factor for the orientation phenomena in the Diels-Alder reaction.

After accomplishment of the syntheses, compound XI (named isotanshinone-II), VIII (isocryptotanshinone) and XIX (isotanshinone-I) were isolated[26] as minor components from the same plant. Total syntheses of these minor pigments were achieved in the present work.

Experimental

All melting points were determined in a sealed tube and are uncorrected. IR spectra were recorded on a Hitachi EPI-2 spectrophotometer, UV spectra were measured on a Hitachi EPS-3T spectrophotometer, and NMR spectra were obtained on a Hitachi H-60 spectrometer. Mass spectra were performed at Meijo University on a Hitachi RMU-7 high resolution spectrometer operating at 70 eV (inlet: 200°C). Microanalyses were carried out at Tohoku University.

3-Methylbenzofuran-4,7-quinone (X). To an ice-cooled solution of 300 mg of 3-methyl-4-benzofuranol (XII)[11] in 20 ml of ethanol, was added 1.35 g of Fremy's salt[18] in 70 ml of water and 20 ml of M/6 KH_2PO_4. After stirring for 15 min, the mixture was left in an ice-box for one hour. The precipitates were collected and the filtrate was extracted with ether. The precipitates and the ether extract were combined and chromatographed on silicic acid (20 g). From benzene elute, 327 mg (100%) of quinone X was obtained.

Pure X (sublimation at ca. 140°C/55 mmHg), mp 129—131°C. IR (KBr): 1663, 1655, 860 cm⁻¹. UV (EtOH): 217 (log ε: 4.14), 248 (4.20), 292 (4.19), 394 mμ (3.31). NMR (CDCl₃): 2.30 (d, 3H, J=0.8 cps), 6.62 (s, 2H), 7.40 ppm (q, 1H, J=0.8).

Diels-Alder Reaction[8] between 3-Methylbenzo-furan-4,7-quinone (X) and 6,6-Dimethyl-1-vinylcyclohexene (IX). To a solution of 255 mg of quinone X in 2 ml of hot ethanol, 216 mg of diene IX[8] was added and the mixture was left for 15 hr at room temperature in the dark. The light yellow solution solidified immediately when the flask wall was scratched. The solids were collected on filter-paper to give slightly yellow needles XVI (198 mg), and the filtrate was chromatographed on silicic acid (10 g). The chloroform

elute (No. 1) gave 86 mg of crude adduct XVI, while the chloroform elute (No. 3) gave 75 mg of starting quinone X.

Pure XVI, mp 160—161°C (from methanol). IR (KBr): 1695, 1680 cm⁻¹. UV (EtOH): 214 (4.05), 244 (3.71), 303 mμ (3.90). NMR (CDCl₃): 1.04 (s, 6H), 2.26 (d, 3H, J=1), 5.40 (m, 1H), 7.45 ppm (q, 1H, J=1). Mass: m/e 298 (M⁺).

Found: C, 76.70; H, 7.65%. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43%.

Dehydrogenation[20] of Adduct XVI to Naphtho-[2,3-b]furan-4,9-quinone Derivative XI. Air was bubbled through the suspension of 72 mg of adduct XVI in 12 ml of ethanol containing 200 mg of potassium hydroxide for 20 hr (after 20 min, the initial green color turned yellow). The solids were collected, washed with water and then with ethanol, and dried over phosphorus pentoxide to give 59 mg of naphtho[2,3-b]furan-4,9-quinone XI. The filtrate and washing were extracted with ether, and the extract was chromatographed on silicic acid (5 g). From the benzene elute, 4 mg of XI was obtained. Purification was conducted by initial filtration through alumina column, followed by recrystallization from benzene/n-hexane

Pure XI, mp 214—215°C. IR (KBr): 1660 cm⁻¹. UV (EtOH): 252 sh (4.80), 255.5 (4.81), 270 sh (4.22), 305 (4.02), 360 mμ (4.08). NMR (CDCl₃): 1.33 (s, 6H), ca. 1.7 (m, 4H), 2.35 (d, 3H), 3.38 (t, 2H), 7.40 (m, 1H), 7.68 (d, 1H, J=8), 8.00 ppm (d, 1H, J=8). Mass: m/e 294 (M⁺).

Found: C, 77.15; H, 6.14%. Calcd for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16%.

dl-Cryptotanshinone (III). The naphtho[2,3-b]-furan-4,9-quinone XI (50 mg) was hydrogenated in 25 ml of methanol over 50 mg of 10% palladium on carbon. The filtrate was evaporated and the residue was dissolved in 8 ml of ethanol. When 115 mg of potassium hydroxide was added, the solution turned dark red immediately. After standing overnight, 25 ml of water was added and the solution was made acidic with dilute sulfuric acid. The ether extract (yellow) was evaporated to dryness to give a light orange oil (45 mg), which was dissolved in 2 ml of ethanol. Concentrated sulfuric acid (2 ml) was added, when the solution turned red; the solution was heated in a boiling water-bath for a few minutes. Pouring into ice-water and extracting with ether afforded a red crystalline oil, which was purified by passing through a silicic acid column (5 g). dl-Cryptotanshinone (32 mg, 64%) was obtained in crystalline form.

dl-Cryptotanshinone (III), mp 174—175°C (from ether). IR (KBr): 1680, 1650, 1625 cm⁻¹. UV (EtOH): 219 (4.19), 264 (4.37), 272 (4.30), 290 sh (3.78), 358 (3.36), 450 mμ (3.37).

Tanshinone-II (II). Cryptotanshinone (III, 30 mg) and 35 mg of DDQ were refluxed in benzene for 1.5 hr under nitrogen atmosphere. The mixture (containing some precipitates) was purified through alumina (5 g), upon which 21 mg (70%) of tanshinone-II and 5 mg of starting crytotanshinone were obtained.

Pure tanshinone-II (from ethanol) melted at 210—211°C alone, or mixed with the natural specimen. IR (KBr): 1690, 1670, 1640 cm⁻¹.

Diels-Alder Reaction between 3-Methylbenzo-furan-4,7-quinone (X) and o-Methylstyrene (XVIII). The mixture of 80 mg of 3-methylbenzofuran-4,7-

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25) This compound was first prepared by Baillie and Thomson.[5] We prepared it by a different method. H. Kakisawa, M. Tateishi, to be published.

26) H. Kakisawa, T. Hayashi and T. Yamazaki, *Tetrahedron Letters*, **1969**, 301.

quinone (X) and an excess amount of *o*-methylstyrene (XVIII) in a test tube containing a pinch of hydroquinone was heated at 100—110°C[23,24] for 10 hr. The resulting dark red solid (at least five colored materials were recognized by thin layer chromatography) was dissolved in hot benzene and was chromatographed on alumina (10 g). From benzene elute, 36 mg of orange substances were isolated in a crystalline from. Recrystallization from benzene afforded a pure adduct XIX.

Pure XIX, mp 219—220°C. IR (KBr): 1665 sh, 1660 cm⁻¹. UV (EtOH): 212 (4.39), 234 (4.55), 283 sh (4.29), 292.5 (4.40), 347 (3.70), 455 br m*μ* (3.35). NMR (CDCl₃): 2.34 (s, 3H), 2.66 (s, 3H), 7.2—7.7 (m, 3H), 8.21 (AB quartet center, 2H, $J=9$), 9.55 ppm (d, 1H, $J=9$). Mass: *m/e* 276 (M⁺).

Found: C, 78.55; H, 4.75%. Calcd for $C_{18}H_{12}O_3$: C, 78.25; H, 4.38%.

The filtrate could not be purified, but the NMR spectrum of the original crystal (from ethanol) shows that it was composed of XIX and a very similar compound, probably XIXa (see Fig. 3).

Catalytic Reduction of the Adduct XIX. The adduct XIX (25 mg) was hydrogenated over platinum oxide (25 mg) in 20 m*l* of acetic acid. After absorption of 23 m*l* of hydrogen, the solvent was evaporated to give solids, which were stirred with DDQ (40 mg) in 2 m*l* of benzene for 1.5 hr. The mixture was filtered through alumina (10 g) with chloroform to afford 14 mg (56%) of XX, mp 175—177°C (from ethanol). IR (KBr): 1670 w, 1640 cm⁻¹.

Catalytic Reduction of Tanshinone-I (I). A) Tanshinone-I (I) was hardly reduced under the following conditions: 10% palladium on carbon in methanol, 10% palladium on carbon in ethyl acetate, and platinum oxide in ethyl acetate.

B) Tanshinone-I (I, 205 mg) was dissolved in 50 m*l* of acetic acid and was hydrogenated over 200 mg of platinum oxide (110 m*l* of hydrogen absorbed during two hours). Removal of the solvent by evaporation gave a red oil, which was purified through chromatography on silicic acid (10 g). From the chloroform elute, 160 mg of dihydrotanshinone-I (XXI) was obtained.

Pure XXI, mp 202°C (from methanol). IR (KBr): 1680, 1650, 1622 cm⁻¹. UV (EtOH): 216 (4.30), 242 (4.40), 292 br (4.20), 335 (3.48), 414 m*μ* (3.61). NMR (CDCl₃): 1.40 (d, 3H, $J=7$), 2.64 (s, 3H), *ca.* 3.6 (m, 1H), 4.37 (dd, 1H, $J=9$ and 6), 4.94 (t, 1H, $J=9$). 7.30—7.80 (m, 3H), 8.18 (d, 1H, $J=8$), 9.20 ppm (d, 1H, $J=8$). Mass: *m/e* 278 (M⁺).

Found: C, 78.15; H, 5.34%. Calcd for $C_{18}H_{14}O_3$: C, 77.68; H, 5.07%.

Dihydrotanshinone-I (XXI) from Adduct XIX. The adduct (XIX, 40 mg) was hydrogenated over 40 mg of platinum oxide in 120 m*l* of acetic acid. After removal of the solvent, the residue was dissolved in 4 m*l* of ethanol, to which *ca.* 100 mg of potassium hydroxide was added and the mixture was left for several hours. The solution was diluted with water, acidified with 6N hydrochloric acid and was extracted with ether to give a yellow enol. The enol, without purification, was dissolved in a mixture of 2 m*l* of ethanol and 2 m*l* of concentrated sulfuric acid, heated in boiling water-bath for a few minutes, and was poured into ice-water. The ether extract was chromatographed on silicic acid (5 g). From the chloroform elute, 14 mg (35%) of dihydrotanshinone-I (XXI) was isolated.

Pure XXI, mp 200—201°C, alone or mixed with an authentic sample (from methanol).

Tanshinone-I (I). A mixture of dihydrotanshinone-I (XXI, 28 mg) and DDQ (35 mg) in benzene was refluxed for two hours under a nitrogen atmosphere. After removing the solvent by evaporation, the residue was dissolved in small amount of chloroform and filtered through alumina (5 g). The filtrate evaporated to give solids. Tanshinone-I (I) was isolated in 50% yield (14 mg) by chromatography on silicic acid (10 g) with benzene.

Pure tanshinone-I (I), mp 229—230°C, alone or mixed with the natural specimen (from ethanol). IR (KBr): 1665 br cm⁻¹.

Diels-Alder Reaction between Methoxybenzoquinone (XXII) and 6,6-Dimethyl-1-vinylcyclohexene (IX). To a solution of 338 mg of quinone XXII in 5 m*l* of hot ethanol, was added 0.5 g of diene IX and the mixture was allowed to stand overnight at room temperature. The crystals were collected and were recrystallized from methanol to give adduct XXIII (265 mg). From the filtrate, a further 44 mg of adduct XXIII was obtained by chromatography on silicic acid.

Pure XXIII, mp 151—154°C (from methanol). IR (KBr): 1690, 1670, 1603 cm⁻¹. UV (EtOH): 273 m*μ* (3.93). NMR (CDCl₃): 1.04 (s, 6H), 1.2—1.6 (6H), 3.80 (s, 3H), 5.4 (m, 1H), 6.03 (s, 1H). Mass: *m/e* 274 (M⁺).

Found: C, 74.42; H, 8.08%. Calcd for $C_{17}H_{22}O_3$: C, 74.10; H, 8.04%.

Conversion of Adduct XXIII to 2-Hydroxynaphthoquinone Derivative XXIV. Air was bubbled through the solution of 106 mg of the adduct XXIII and 90 mg of potassium hydroxide in 5 m*l* of ethanol for 2.5 hr. After acidification with dilute hydrochloric acid, the product was purified by chromatography on silicic acid. From chloroform elute, 27 mg of yellow crystals were obtained.

Pure XXIV (from *n*-hexane) melted at 161.5—163.5°C alone, or at 162.5—163.5°C when mixed with the authentic sample.[25] IR (KBr): 1645, 1570 cm⁻¹.