Synthesis of Methyl Substituted Chromanol. An Analogue of Vitamin K[1)]

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Methylation of 2,2-dimethyl-3,4-dihydro-2*H*-benzo[*h*]chromen-6-ol (**1**) is examined to yield 2,2,3-trimethyl-3,4-dihidro-2*H*-benzo[*h*]chromen-6-ol (**2**). The compound **2** is prepared by Mannich reaction followed by hydrogenative cleavage of the Mannich bases, which are obtained in the reaction with three kinds of amine. Chloromethylation of **1** quantitatively gave a dimer of naphthoquinone methide.

Vitamin K_1 and K_2 are widely distributed in natural products which are contributing in diverse biological processes such as blood clotting, electron transport and oxidative phosphorylation.[2)] Especially an association of vitamin K with the electron transport chain and a coupled phosphorylation in *Mycobacterium phlei* has been reported. The chromanol derivatives of vitamin K, to which noncyclized vitamin is enzymatically cyclized in bacterial system, is the acting vitamin of *M. phlei*.[3)]

We have recently reported the photochemical introduction of 2-alkenoyl group to 1,4-naphthoquinone and the facile preparation of 2,2-dimethyl-3,4-dihydro-2*H*-benzo[*h*]chromen-6-ol **1** ("benzochromanol") by the subsequent reactions (path a).[4)] Introduction of methyl group to the 5-position of **1** is of interest in view of the synthesis of a vitamin K methabolite in bacterial system.

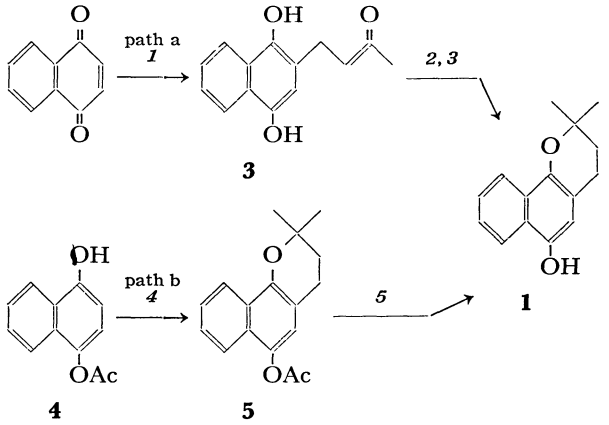
The ortho position of phenol in β- and γ-tocopherols has been methylated by Mannich condensation followed by the successive reduction.[5)] However, in the case of tocopherols high pressure and high temperature were needed in the step of reductive cleavage of the Mannich bases. Therefore, secondary amines liberated from Mannich beses at reduction process were found to induce destruction of tocopherols.

In this paper, we wish to report a successful methylation of benzochromanol **1** *via* the milder hydrogenative cleavage of the Mannich bases.

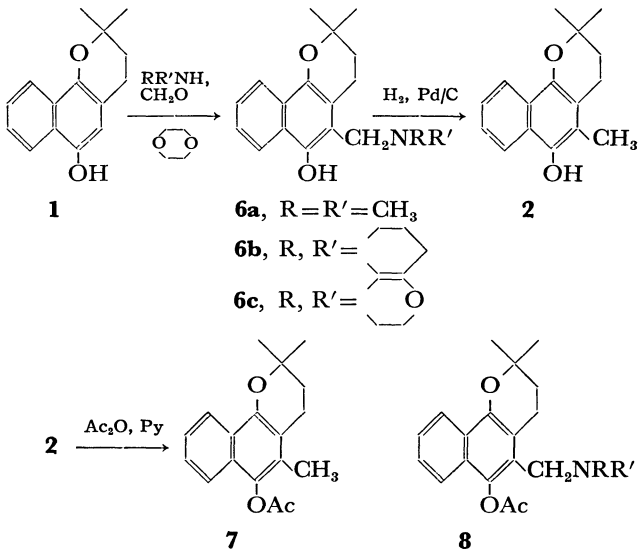
Result and Discussion

Chromanol **1** was prepared by the following two routes (paths a[4)] and b). With use of three kinds of secondary amine; dimethylamine, piperidine, and morpholine, Mannich beses **6a**—**c** were prepared in yields of 75, 81, and 84%, respectively. 5-Dimethylaminomethyl derivative **6a** shows chracteristic ^{1}H-NMR signals due to amino benzylic protons at δ 3.70, and IR absorption due to hydrogen bonded hydroxyl group at the region of 3000—2500 cm^{-1}. The corresponding spectra were observed similarly in other Mannich bases, **6b** and **6c**.

Three Mannich bases **6a**—**c** were catalytically hydrogenated in ethanol similar to that of benzylic amine.[6)] Hydrogenation of these bases at atmospheric pressure and ambident temperature in the presence of 5% Pd–C resulted, however, recovery of the starting chromanol **6** without any hydrogenated products after four days. On the other hand, catalytic hydrogenation under a medium pressure (H_2, 5 kg/cm^2) applying an elevated temperature (80 °C) proceeded smoothly, and after 1 h the reaction was completed to give 2,2,5-trimethyl-3,4-dihydro-2*H*-benzo[*h*]chromen-6-ol **2** in a good yield. (Table 1) Since the obtained chromanol **2** was difficult to purify for its air sensibility, the hydrogenated solution was concentrated directly *in vacuo* and treated with Ac_2O–pyridine solution to give its acetate **7**.



1. $h\nu$, $(CH_3)_2C{=}CHCHO$, C_6H_6
2. HCl, $SnCl_2$, dioxane
3. $LiAlH_4$, $AlCl_3$, ether
4. $(CH_3)_2C{=}CHCH_2Br$, $ZnCl_2$, $CHCl_3$
5. $LiAlH_4$, ether



Scheme 1.

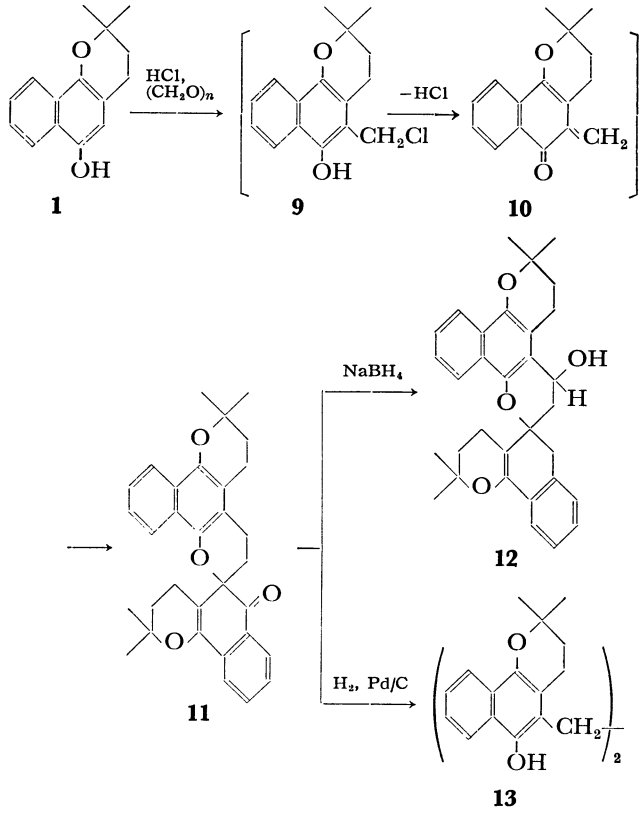
Chloromethylation is another useful procedure to introduce a methyl group to phenolic compounds. We tried the procedure to **1** passing dry hydrogen chloride in an ethereal solution of an excess amount of para-

TABLE 1. CATALYTIC REDUCTION OF MANNICH BASES **6a**—**c** AND ACETYLATION

6	R, R′	7 Yield,[a] %
a	CH_3, CH_3	68
b		83
c		81

a) Isolated yield after purification.

formaldehyde at 0—5 °C. After 2 h a product was isolated in a yield of 78%. The structure was assigned to dimer **11** on the basis of the following spectral and chemical evidences.



Scheme 2.

The ^{1}H-NMR spectrum of **11** exhibits three singlets at δ 1.32 (6H), 1.37 (3H), 1.38 (3H), representing four methyl groups and multiplets at δ 1.00—2.66, representing twelve methylene protons. The IR spectrum shows an absorption at 1695 cm^{-1} ($\nu_{C=O}$).[7] Mass spectrum and analytical result of **11** were also consistent with the structure of dimer **11**. Reduction of **11** by $NaBH_4$ gave an alcohol **12**. The ^{1}H-NMR of **12** exhibits two singlets at δ 3.62 (1H) and 5.15 (1H), representing a hydroxyl proton and a methine proton, respectively, and the IR spectrum shows an absorption at 3435 cm^{-1} (ν_{OH}). Dimer **11** absorbed equimolecular hydrogen under the conditions of catalytic hydrogenation[7] to give 2,2,2′,2′-tetramethyl-3,4,3′,4′-tetrahydro-5,5′-ethylenedi(2*H*-naphtho[1,2-*b*]pyran)-6,6′-diol (**13**), quantitatively. The ^{1}H-NMR of **13** shows a broad singlet due to phenolic OH at δ 6.32, and the IR spectrum, being compatible with the structure. Thus, the dimeric product **11** obtained by chloromethylation of **1** corresponds to the structure of naphthoquinone methide dimer. The dimer has been prepared independently by oxidizing **2** with potassium hexacyanoferrate(III).[7] Our reaction may be explained taking into consideration of that the 5-chloromethyl-2,2-dimethyl-3,4-dihydro-2*H*-benzo[*h*]chromen-6-ol (**9**) is formed initially and despite in a strong acidic conditions **9** was hydrolized to *o*-naphthoquinone methide **10**.[10] These evidences are also supported by the fact that α-methylenecyclanones and *o*-quinone methides easily dimerize to the corresponding dihydropyran derivatives.[11]

Experimental

All melting points are uncorrected. The elemental analyses were performed at the Microanalysis Center of Kyoto University. ^{1}H-NMR spectra were measured with a JEOL PS-100 with TMS as an internal standard, infrared spectra with a JASCO 402G or a IRA-1, mass spectra with a Hitachi M-52. Analytical gas chromatographs were obtained with a JEOL JGC-20K instrument with a flame ionization detecter using a column (5% SE-30 silicon rubber on 60—80 mesh Celite 545, 3 mm×1 m).

*2,2-Dimethyl-3,4-dihydro-2*H*-benzo*[h]*chromen-6-ol (**1**).* was prepared by the photochemical method (path a)[4] and a series of the following reactions (path b). 4-Hydroxy-1-naphthyl acetate **4** was prepared by the similar method to the literature.[8] **4**; Mp 130—131.5 °C. **4** (1.01 g, 5 mmol) and zinc chloride (0.1 g) were dissolved in chloroform (40 ml) under nitrogen. The solution was refluxed and the chloroform solution (5 ml) of 1-bromo-3-methyl-2-butene[9] (745 mg, 5 mmol) was slowly added, after refluxing for thirty minutes the solution was poured into ice water and was washed twice with 2 M hydrochloric acid and once with brine, and dried over Na_2SO_4. The mixture was purified with a use of Wakogel C-200 (30 g) eluted by 4.5% ether–hexane. 6-Acetoxy-2,2-dimethyl-3,4-dihydro-2*H*-benzo[*h*]chromen **5** was obtained (isolated yield; 60%. GLPC yield; 78%); Mp 66.9—67.1 °C. ^{1}H-NMR ($CDCl_3$): δ 1.36 (s, 6H, $2CH_3$), 1.77 (t, 2H, J=7 Hz, O–C–CH_2), 2.34 (s, 3H, $COCH_3$), 2.75 (t, 2H, J=7 Hz, Ar–CH_2), 6.87 (s, 1H, arom. H), 7.28—7.46 (m, 2H, arom. H), 7.57—7.73 (m, 1H, arom. H). IR: ν_{max}^{KBr} 2975 (vs), 1747 (vs), 1367 (vs), and 1189 cm^{-1} (vs).

The ethereal solution (30 ml) of chromanol acetate derivative **5** (2.703 g, 0.01 mol) was treated with lithium aluminum hydride (0.35 g) in ether (30 ml). After usual work-up, the obtained benzochromanol **1** was used without further purification.

*5-Dimethylaminomethyl-2,2-dimethyl-3,4-dihydro-2*H*-benzo*[h]*-chromen-6-ol (**6a**).* The dioxane solution (25 ml) of benzochromanol **1** (228 mg, 0.01 mol) was cooled in ice water under N_2, and dimethylamine solution (3.7 ml, 40% in water) and formalin solution (2.5 ml, 37% in water) were added and the mixture was stirred for one hour at room temperature and then at gentle refluxing for 4 h. After evaporation of solvent, the residue was extracted with ether, and the ethereal solution was washed several times with brine, dried over Na_2SO_4, and concentrated *in vacuo*. To the residual oil a few ml of ethanol was added, then white crystals of **6a** were obtained (214 mg, 75%): Mp 110.5—113.0 °C (from hexane–ether). ^{1}H-NMR ($CDCl_3$): δ 1.38 (s, 6H, $2CH_3$), 1.88 (t, 2H, J=7 Hz, O–C–CH_2), 2.38 (s, 6H, $N(CH_3)_2$), 2.68 (t, 2H, J=7 Hz, Ar–CH_2–C), 3.70 (s, 2H, Ar–CH_2–N), 7.40 (m, 2H, arom. H), 8.14 (m, 2H, arom. H). IR: ν_{max}^{KBr} 2978(vs), 2830 (bs),

2780 (s), 1592 cm^{-1} (s). MS (20 eV); *m/e* 285 (M^+), 240 ($M^+-NH(CH_3)_2$). Found: C, 75.69; H, 8.26; N, 4.91%. Calcd for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12; N, 4.91%.

Crude Mannich base **6a** was acetylated with acetic anhydride and pyridine. 6-Acetoxy-5-dimethylaminomethyl-2,2-dimethyl-3,4-dihydro-2*H*-benzo[*h*]chromen **8a**: Mp ≈210 °C (dec) ^{1}H-NMR ($CDCl_3$): δ 1.42 (s, 6H, $2CH_3$), 1.88 (t, 2H, J=7 Hz, O-C-CH_2), 2.17 (s, 6H, $N(CH_3)_2$), 2.36 (s, 3H, $COCH_3$), 2.99 (t, 2H, J=7 Hz, Ar-CH_2-C), 3.31 (s, 2H, Ar-CH_2-N), 7.30—7.52 (m, 3H, arom. H), 8.04—8.20 (m, 1H, arom. H). IR: ν_{max}^{KBr} 2950 (s), 1765 (vs), 1370 (vs), 1208 (vs), 1183 cm^{-1} (s).

2,2-Dimethyl-5-piperidinomethyl-3,4-dihydro-2H-benzo[h]*chromen-6-ol (6b).* To a mixture of benzochromanol **1** (228 mg, 0.01 mol), piperidine (4 ml, 0.04 mol), and dioxane (30 ml), formalin solution (3 ml) was added at 10 °C, and allowed to react as described above. Colorless crystals **6b** (1.311 g, 81%) was obtained: Mp 133.5—134.2 °C (from aceton). ^{1}H-NMR ($CDCl_3$): δ 1.39 (s, 6H, $2CH_3$), 1.40—1.77 (m, 6H, $(CH_2)_3$), 1.86 (t, 2H, J=7 Hz, O-C-CH_2), 2.46—2.68 (m, 4H, $N(CH_2)_3$), 2.70 (t, 2H, Ar-CH_2-C), 3.76 (s, 2H, Ar-CH_2-N), 7.32—7.48 (m, 2H, arom. H), 8.08—8.24 (m, 2H, arom. H). IR: ν_{max}^{KBr} 2940 (vs), 2800 (s), 1593 (s), 1450 (vs), 1381 cm^{-1} (vs). MS (20 eV); *m/e* 325 (M^+). Found: C, 77.41; H, 8.30; N, 4.14%. Calcd for $C_{21}H_{27}NO_2$: C, 77.50; H, 8.36; N, 4.30%. **6b** was acetylated with acetic anhydride and pyridine. 6-Acetoxy-2,2-dimethyl-5-piperidinomethyl-3,4-dihydro-2*H*-benzo[*h*]chromen **8b**: Mp 155—157 °C (from acetone). ^{1}H-NMR ($CDCl_3$); δ 1.26—1.64 (m, 12H, $2CH_3$ and $(CH_2)_3$), 1.88 (t, 2H, J=7 Hz, O-C-CH_2), 2.22—2.44 (m, 7H, $COCH_3$ and $N(CH_2)_2$), 2.95 (t, 2H, J=7 Hz, Ar-CH_2-C), 3.36 (s, 2H, Ar-CH_2-N), 7.22—7.50 (m, 3H, arom. H), 7.94—8.16 (m, 1H, arom. H). IR: ν_{max}^{KBr} 2920 (vs), 1778 (vs), 1369 (vs), 1263 (vs), 1177 cm^{-1} (vs). MS (20 eV); *m/e* 367 (M^+). Found: C, 74.97; H, 8.13; N, 3.68%. Calcd for $C_{23}H_{29}NO_3$: C, 75.17; H, 7.95; N, 3.81%.

2,2-Dimethyl-5-morpholinomethyl-3,4-dihydro-2H-benzo[h]*chromen-6-ol (6c).* To a mixture of benzochromanol **1** (228 mg, 0.01 mol), morpholine (4 ml, 0.046 mol), and dioxane (20 ml), formalin solution (3 ml) was added at 10 °C. After 20 min at room temperature, white precipitate was observed in the reaction mixture. After the solution was stirred for 1 h at room temperature, it was refluxed for 3 h. After solvent was removed *in vacuo*, white crystals **6c** (2.74 g, 84%) were obtained in ethereal solution. **6c**: Mp 149—151 °C from acetone. ^{1}H-NMR ($CDCl_3$); δ 1.35 (s, 6H, $2CH_3$), 1.89 (t, 2H, J=7 Hz, O-C-CH_2), 2.57—2.90 (m, 6H, $N(CH_2)_2$ and Ar-CH_2-C), 3.68—3.84 (m, 6H, Ar-CH_2-N and CH_2-OCH_2), 7.28—7.43 (m, 2H, arom. H), 8.00—8.12 (m, 2H, arom. H). IR; ν_{max}^{KBr} 2960 (vs), 2895 (vs), 2830 (s), 1592 (vs), 1450 (vs), 1380 (vs), 1323 (vs), 1163 (vs), 1111 (vs), 976 cm^{-1} (s). MS (20 eV); *m/e* 327 (M^+), 240 ($M^+-HN\langle\rangle O$). Found: C, 73.21; H, 7.68; N, 4.22%. Calcd for $C_{20}H_{25}NO_3$: C, 73.36; H, 7.70; N, 4.28%.

6-Acetoxy-2,2-dimethyl-5-morpholinomethyl-3,4-dihydro-2*H*-benzo[*h*]chromen **8c**: Mp 151.5—153.0 °C (from acetone). ^{1}H-NMR ($CDCl_3$); δ 1.41 (s, 6H, $2CH_3$), 1.90 (t, 2H, J=7 Hz, O-C-CH_2), 2.36—2.50 (m, 7H, $COCH_3$ and CH_2N-CH_2), 2.98 (t, 2H, J=7 Hz, Ar-CH_2-C), 3.44—3.67 (m, 6H, Ar-CH_2-N and CH_2OCH_2), 7.36—7.60 (m, 3H, arom. H), 8.12—8.24 (m, 1H, arom. H). IR; ν_{max}^{KBr} 2930 (vs), 2865 (vs), 1770 (vs), 1450 (s), 1368 (vs), 1200 (vs), 1180 (vs), 1113 cm^{-1} (vs). MS (20 eV); *m/e* 369 (M^+). Found: C, 71.51; H, 7.44; N, 3.76%. Calcd for $C_{22}H_{27}NO_4$; C, 71.52; H, 7.39; N, 3.79%.

6-Acetoxy-2,2,5-trimethyl-3,4-dihydro-2H-benzo[h]*chromen (7) from 6a—c.* Aminomethylchromanol derivatives **6a—c** (1.7 mmol) were hydrogenated (5% Pd-C, 150 mg in 50 ml ethanol, H_2 5 kg/cm^2 at 80 °C for 2 h) to give **2**. **2**: ^{1}H-NMR ($CDCl_3$); δ 1.38 (s, 6H, $2CH_3$), 1.89 (t, 2H, J=7 Hz, O-C-CH_2), 2.27 (bs, 3H, Ar-CH_3), 2.60—3.00 (m, 2H, Ar-CH_2), 3.80 (bs, 1H, OH), 7.32—7.48 (m, 2H, arom. H), 7.88—8.24 (m, 2H, arom. H). IR; ν_{max}^{KBr} 3250 (vs), 2980 (s), 2920 (s), 1586 (s), 1396 (vs), 1323 (vs), 1161 (vs), 1019 cm^{-1} (vs). MS (20 eV); *m/e* 242 (M^+), 240 (M^+-H_2), 186 ($M^+-C_4H_8$).

Since **2** was very unstable in air, it was directly acetylated in acetic anhydride–pyridene to give **7** in each case of **6a**, **b**, and **c**. After usual work-up, **7** was obtained in the yield of 68, 83, and 81%, respectively (based on **6a**, **b**, and **c**). **7**; Mp 91.4—92.4 °C (from hexane). ^{1}H-NMR ($CDCl_3$) δ 1.39 (s, 6H, $2CH_3$), 1.87 (t, 2H, J=7 Hz, O-C-CH_2), 2.11 (s, 3H, Ar-CH_3), 2.36 (s, 3H, $COCH_3$), 2.71 (t, 2H, J=7 Hz, Ar-CH_2), 7.23—7.56 (m, 3H, arom. H), 8.00—8.14 (m, 1H, arom. H). IR; ν_{max}^{KBr} 2920 (s), 1754 (vs), 1362 (vs), 1206 (vs), 1162 cm^{-1} (vs). MS (20 eV); *m/e* 284 (M^+), 242. Found; C, 76.21; H, 7.04%. Calcd for $C_{18}H_{20}O_3$; C, 76.03; H, 7.09%.

Chloromethylation of 1. The ethereal solution (40 ml) of benzochromanol **1** (1 mmol) and paraformaldehyde (0.8 g) was chilled and dry hydrogen chloride was bubbled into the mixture for 2 h. The reaction mixture was poured into ice (20 g) and ethereal solution was separated, aqueous layer, was extracted with ether. The combined solution was washed with water and dried over Na_2SO_4. Products were separated by Wakogel C-200 column chromatography, dimer **11** was isolated (188 mg, 78%). **11**; Mp 177.5—178.0 °C (lit,[7] 160—161 °C). ^{1}H-NMR (CCl_4); δ 1.32 (s, 6H, $2CH_3$), 1.37 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.60—1.80 (m, 4H), 1.80—2.33 (m, 4H), 2.33—2.66 (m, 4H), 7.19 (m, 4H, arom. H), 7.43, 7.68 (each 1H, m, arom. H), 7.95 (m, 2H, arom. H). IR; ν_{max}^{KBr} 2980 (s), 2930 (s), 1695 (vs), 1658 (m), 1637 (w), 1595 (vs), 1385 (vs), 1162 cm^{-1} (vs). MS (20 eV); *m/e* 480 (M^+), 240 ($M^+/2$), 197 ($M^+/2-C_2H_3O$). Found; C, 79.95; H, 6.76%. Calcd for $C_{32}H_{32}O_4$; C, 79.97; H, 6.71%.

Hydride Reduction of the Dimer (11). The ethanol solution (30 ml) of the dimer **11** (404 mg, 0.92 mmol) and $NaBH_4$ (40 mg) was stirred for 1 h at ambident temperature, and after the usual work-up, **12** was quantitatively obtained. **12**; Mp 169—170 °C (from ether-hexane). ^{1}H-NMR ($CDCl_3$); δ 1.26 (s, 3H, CH_3), 1.35 (s, 6H, $2CH_3$), 1.41 (s, 3H, CH_3), 2.47—2.77 (m, 12H, $6CH_2$), 3.62 (bs, 1H, OH), 5.15 (s, 1H, CH), 7.10—7.56 (m, 6H, arom. H), 7.96—8.12 (m, 2H, arom. H). IR; ν_{max}^{KBr} 3435 (vs), 2935 (vs), 1385 (vs), 1162 cm^{-1} (s). MS (20 eV); *m/e* 482 (M^+). Found: C, 79.64; H, 7.15%. Calcd for $C_{32}H_{34}O_4$; C, 79.64, H, 7.10%.

Catalytic Hydrogenation of the Dimer (11). The dimer **11** (201 mg, 0.42 mmol) was hydrogenated (5% Pd-C 60 mg in 50 ml ethanol, H_2, 4 kg/cm^2 at 50 °C for 4 h) quantitatively to give 2,2,2′2′-tetramethyl-3,4,3′,4′-tetrahydro-5,5′-ethylene-di(2*H*-naphtho[1,2-*b*]-pyran)-6,6′-diol **13**. **13**; Mp >270 °C (dec). ^{1}H-NMR ($CDCl_3$); δ 1.39 (s, 12H, $4CH_3$), 1.92 (t, 4H, J=7 Hz, 2O-C-CH_2), 2.68—3.12 (m, 8H, 4Ar-CH_2), 6.32 (bs, 2H, 2OH), 7.32—7.54 (m, 4H, arom. H), 7.92—8.34 m, 4H, arom. H). IR; ν_{max}^{KBr} 3450 (s), 2995 (s), 1660 (s), 1587 (vs), 1388 cm^{-1} (s). Found; C, 79.46; H, 7.16%. Calcd for $C_{32}H_{34}O_4$; C, 79.64; H, 7.10%.

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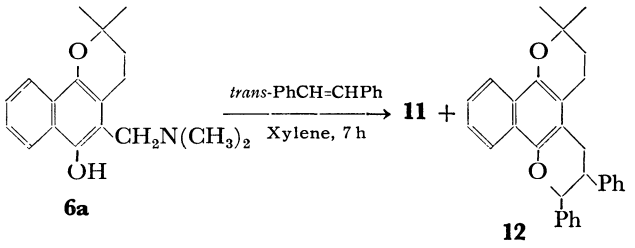
10) The xylene solution (50 ml) of **6a** (144 mg, 0.51 mmol) and *trans*-stilbene (450 mg, 2.5 mmol) was refluxed for 7 h. An adduct **12** (47 mg, 22%) of *o*-naphthoquinone methide with *trans*-stilbene accompanied with dimer **11** (50 mg, 21%) was obtained. This evidence also supports the generation of *o*-naphthoquinone methide **10** as an unstable intermediate in the course of preparation of the dimer.



6a **12**

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