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Studies on the Syntheses of Tetracycline Derivatives. II.[1] Thermolytic Cycloaddition of *o*-Quinodimethanes with Tetrahydronaphthoquinone and Naphthoquinone

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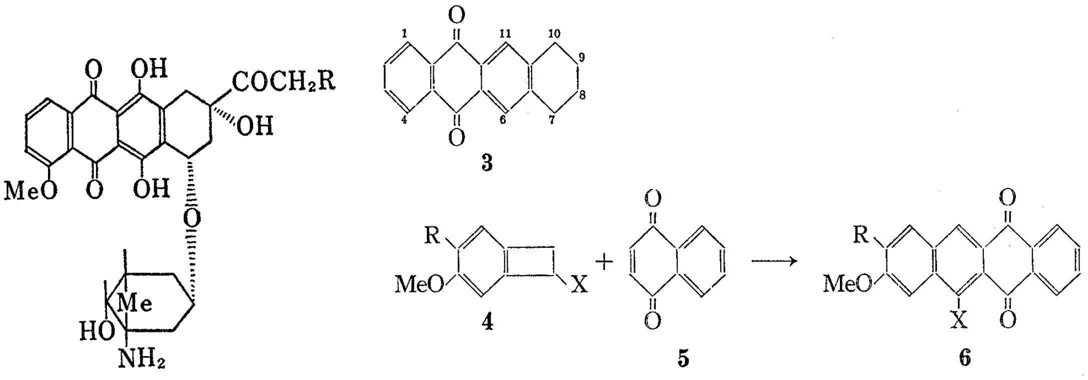
Tetrahydronaphthoquinone (**8**) and naphthoquinone reacted with the *o*-quinodimethanes, generated *in situ* from the benzocyclobutenes (**7**) and (**14**), to give the naphthacene-5,12-quinone derivatives (**9**, **15** and **25**).

Keywords——tetracycline compounds; *o*-quinodimethane; tetrahydronaphthoquinone; naphthoquinone; thermolytic cycloaddition

Recently many antibiotics with a linear tetracyclic skeleton have been isolated from different kinds of bacterial culture.[3] Especially adriamycin (1)[4] and daunomycin (2)[5] have shown a very high activity against tumors[6] and have been used successfully as a curative means for acute lymphomas.

The lack of an efficient biosynthetic progress, produced only by fermentation today, has prompted us to investigate the chemical synthesis to alleviate the scarcity of these



3

4

5

6

1: R=OH, Adriamycin
1: R=H, Daunomycin

a : R=OMe, X=CN
b : R=H, X=CN
c : R=OMe,X=H

Chart 1

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1) Part I: T. Kametani, T. Takahashi, M. Kajiwara, Y. Hirai, C. Ohtsuka, F. Satoh, and K. Fukumoto, *Chem. Pharm. Bull.* (Tokyo), **22**, 2159 (1974).

2) Location: *Aobayama, Sendai 980, Japan.*

3) J. Cook and W. Garruthers, "Progress in Organic Chemistry," Vol. 7, Bufferworths and Co. Ltd., London, 1968, p. 1—34.

4) F. Arcamone, G. Franceschi, S. Penco, and A. Selva, *Tetrahedron Lett.* **1969**, 1007; *Chem. and Eng. News*, April 12, p. 18 (1976).

5) F. Arcamone, G. Franceschi, P. Orezzi, G. Cassinelli, W. Barbiere, and R. Mondelli, *J. Am. Chem. Soc.*, **86**, 5334 (1964).

6) G. Rosen, N. Wollen, C. Tan, S.J. Wu, S.I. Hajdu, W. Cham, G.G. D'Angio, and M.L. Murphy, *Cancer*, 33, 384 (1974); J.F. Halazun, H.R. Wagner, J.F. Gaeta, and L.F. Sinks, *ibid.*, 33, 545 (1974).

drugs.[7,8,9] We have investigated a short and effective synthesis of tetracycline-type compounds[1] and here we wish to report a synthesis of tetracyclines such as tetrahydronaphthacenequinones (**3**), which are common for adriamycin and daunomycin, as potential intermediates for the total synthesis of adriamycin and daunomycin.

Previously, we have reported a synthesis of tetracycline-type compounds (**6**) by an intermolecular cycloaddition reaction of the *o*-quinodimethane, generated *in situ* by a heating of the benzocyclobutene (**4**), to the naphthacenequinone (**5**).[1] As a continuation of our study on the synthesis of tetracycline-type compounds by cycloaddition, we have investigated the following reactions aimed at a synthesis of a potential precursor to adriamycin. Firstly, we examined the synthesis of 6,9,11-trioxygenated tetracycline-type compounds, which was the similar one to the key intermediate[9] in a total synthesis of adriamycin by Kende, as a model experiment. Heating a mixture of 1-cyano-6-methoxybenzocyclobutene (7)[10] and 6-ethoxy-4a,5,8,8a-tetrahydro-1,4-naphthoquinone (**8**)[11] at 150—160° for 75 min gave the tetracycline-type compound (**9**), mp 215—219°, whose structure, $C_{20}H_{19}NO_4$, was easily determined by infrared (IR) [$\nu_{\max}^{\text{Nujol}}$ cm^{-1}: 2250 (CN), 1720 (CO)], and mass (MS) spectra [*m/e*: 337 (M)$^+$], and nuclear magnetic resonance (NMR) spectrum supported the above structure, and in this reaction, the dihydronaphthalene (**10**) and the *β*-tetralone derivative (**11**) are obtained as by-products which are formed by an isomerization of the starting naphthoquinone (**8**). In this reaction, it would be possible that **9B** as the position isomer of **9A** exists. Therefore we tried a separation of isomers by thin layer chromatography, silica gel column chromatography, gas chromatography and high pressure liquid chromatography, and also repeated recrystallization but all the attempts were unsuccessful, the result of which shows our product to be a single compound. Thus, this suggests that this reaction proceeds regiospecifically, and this phenomenon has been supported by sharp melting point and NMR spectrum revealing a single peak of methoxy group. However, we could not determine the position of the methoxy group of this product.

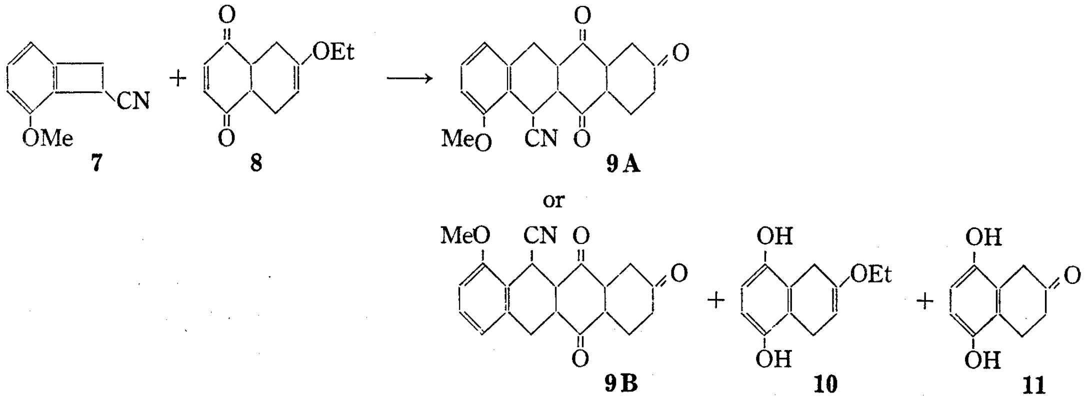

Chart 2

On this finding in a model experiment, we have secondly investigated a synthesis of 4-methoxylated tetracyclines, which are a common structure to the above natural compounds. The starting materials, 6-methoxylated benzocyclobutenes (**13** and **14**), which are key compounds in the synthesis of 4-methoxytetracyclines, are prepared from 3-bromo-6-methoxybenzocyclobuten-1-one (**12**)[12] as follows.

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7) C.M. Wong, R. Schwenk, D. Popien, and T.L. Ho, *Can. J. Chem.*, **51**, 466 (1973).
8) A.S. Kende, J. Belletire, T.J. Benlley, E. Hume, and J. Airey, *J. Am. Chem. Soc.*, **97**, 4425 (1975).
9) A.S. Kende, Y.-G. Tsay, and J.E. Mills, *J. Am. Chem. Soc.*, **98**, 1967 (1976).
10) J.A. Skorcz and J.E. Robertson, *J. Med. Chem.*, **8**, 255 (1965).
11) T.R. Lewis, W.B. Dickinson, and S. Archer, *J. Am. Chem. Soc.*, **74**, 5321 (1952).
12) J.O. Amupitan and F. Stansfield, *J. C. S. Perkin I*, **1974**, 1949.

Hydrogenolysis of the 3-bromobenzocyclobuten-1-one (**12**) on 10% palladium-carbon in the presence of magnesium oxide in a current of hydrogen gave 6-methoxybenzocyclobuten-1-one (**13**) which was reduced with sodium borohydride in methanol at 0° to afford the corresponding benzocyclobuten-1-ol (**14**) in a moderate yield. A treatment of the benzocyclobuten-1-one (**13**) with the tetrahydronaphthoquinone (**8**) and naphthoquinone (**20**), described later, at 150—170° under several conditions gave no remarkable results. However, the similar reaction of the benzocyclobutenol (**14**) proceeds successfully as below. Heating a mixture of an equimolar amount of 6-methoxybenzocyclobutenol (**14**) and tetrahydronaphthoquinone (**8**) at 110—120° for 24 hr in a current of nitrogen gave the unexpected product, naphthacenequinone (**15A** or **15B**), mp 228—229°, whose structure [*m*/*e* 332 (M$^+$)] was determined by IR spectrum showing a quinone type carbonyl absorption at 1665 cm^{-1} and by NMR spectrum which revealed the presence of two deshielded protons at 8.71 and 9.23 ppm as singlets.[1]

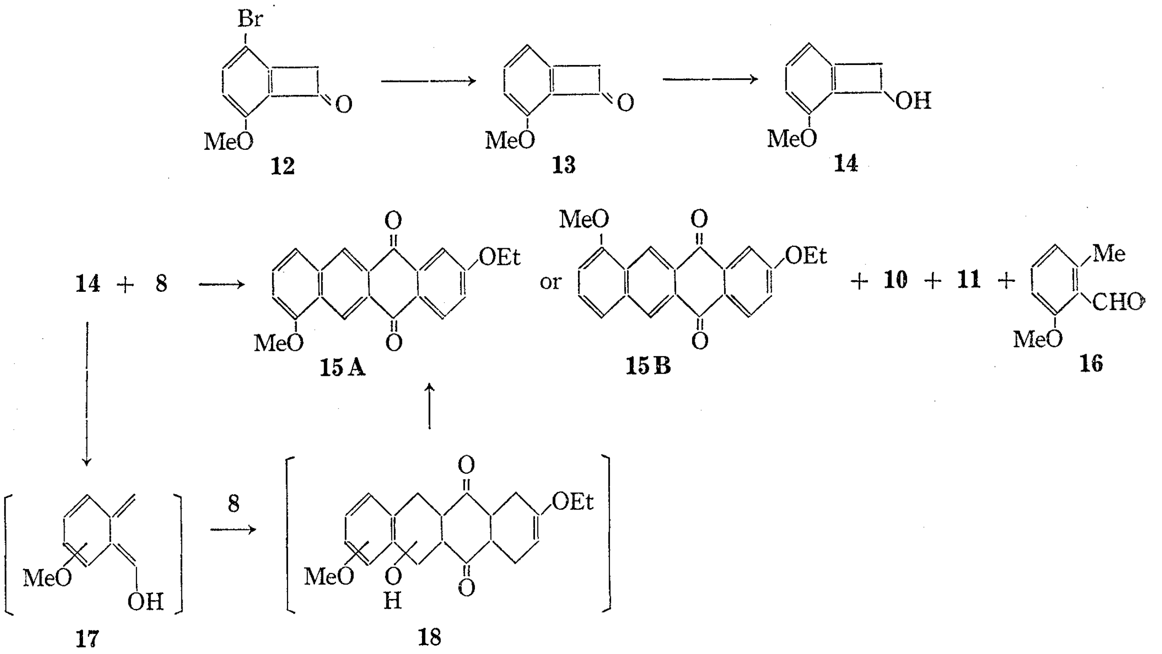

Chart 3

The formation of this compound (**15**) is due to a dehydration and dehydrogenation (aromatization) of the initially formed perhydrogenated one (**18**) derived by an intermolecular cycloaddition reaction of **8** with the *o*-quinodimethane (**17**) generated *in situ* by heating the benzocyclobutenol (**14**). In this reaction, the dihydronaphthalene (**10**) and the *β*-tetralone (**11**) are also formed in the same way as above.

Moreover, 2-methoxy-6-methylbenzaldehyde (**16**) was obtained as a by-product, which was formed by a [1.5]hydrogen sigmatropic reaction[13] of the *o*-quinodimethane (**17**). As shown in the above example, the tetrahydronaphthoquinone (**8**) has been transformed into the isomeric compounds (**10**) and (**11**), which were not a dienophile, under our reaction conditions. Therefore we supposed that the dihydronaphthoquinones (**19** and **21**), which could not be isomerized to nondienophiles, could react easily and smoothly with *o*-quinodimethane to give the expected linear tetracyclic compound in good yield. On this consideration we examined a preparation of **19** and **21**. Oxidation of the tetrahydronaphthoquinone (**8**) with oxygen in the presence of sodium hydroxide gave no expected 6,8-dihydro-1,4-naphthoquinone (**19**), and a conversion of the *β*-tetralone (**11**) into the quinone (**21**) by an oxidation with

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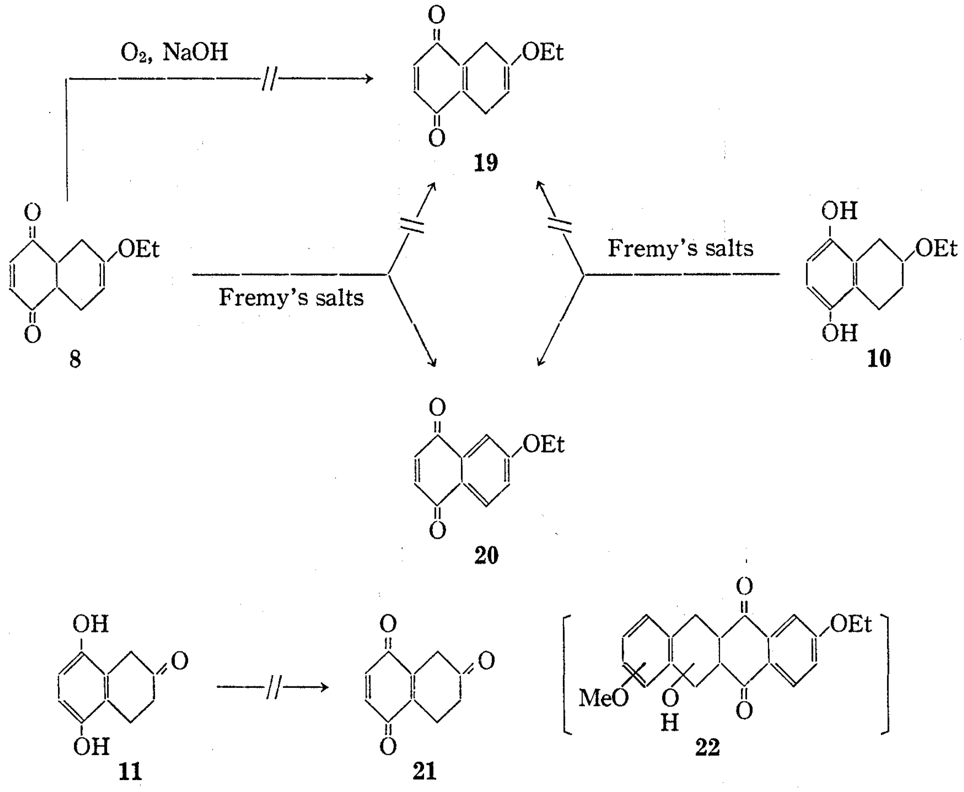
13) T. Kametani, M. Tsubuki, Y. Shiratori, Y. Kato, H. Nemoto, M. Ihara, K. Fukumoto, F. Satoh, and H. Inoue, *J. Org. Chem.*, 42, 2672 (1977).

Fremy's salt also resulted in failure. However, a treatment of **8** with Fremy's salt at room temperature afforded, in good yield, the unexpected naphthoquinone (**20**), which was further dehydrogenated from **19**. This compound (**20**) was also obtained by an oxidation of the dihydronaphthalene (**10**) with Fremy's salt. The structure of **20** was determined by NMR spectral analysis which showed three aromatic protons as a characteristic ABX pattern.

The reaction of the benzocyclobutenol (**14**) with the naphthoquinone (**20**), thus obtained, in a boiling toluene proceeded smoothly to give, in 62% yield, the tetracycline-type compound **15** *via* a dehydration and an aromatization of the linear tetracyclic compound (**22**) formed initially in addition to a trace of 2-methoxy-6-methylbenzaldehyde (**16**).



14 + **20** ⟶ **15A,B** + **16**

Chart 4

Finally, we examined a synthesis of 6,11-dihydroxy-1-methoxy-8-oxonaphthacene-5,12-quinone (**27**), which has been correlated with adriamycinone by Kende,[9] by our cycloaddition method. A synthesis of the requisite starting material (**24**) was planned by a Fremy's salt oxidation of the ketal derivative (**23**), derived from 1,4-dihydroxy-6-tetralone (**11**).

However, a ketalization of **11** with ethylene glycol in refluxing acetonitrile in the presence of a catalytic amount of *p*-toluenesulfomic acid gave no normal product **23** but, surprisingly, the key intermediate tetrahydronaphthoquinone (**24**) [IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1655, MS *m/e* 220 (M$^+$)] in one-step, which would be formed by an air oxidation of **23**. A cycloaddition reaction was carried out by heating a mixture of an equimolar amount of the benzocyclobutenol (**14**) and the naphthoquinone derivative (**24**) in dry toluene at 110—120° for 3 days in a current of nitrogen to give the expected linear tetracyclic compound (**25A** or **25B**), in 20% yield, by accompanying a dehydration and an aromatization of the firstly formed product (**26**). The structure of our product was determined by IR [$\nu_{max}^{CHCl_3}$ cm^{-1}: 1660], UV [λ_{max}^{EtOH} nm: 430 and 276] and NMR spectra [($CDCl_3$) δ: 8.10 (12-H) and 8.90 (5-H)]. In order to convert this compound (**25**) into Kende's intermediate (**27**) to adriamycin, **25** was treated with singlet oxygen generated by a photolysis in a current of oxygen in the presence of rose bengal under several conditions but the starting material was recovered.

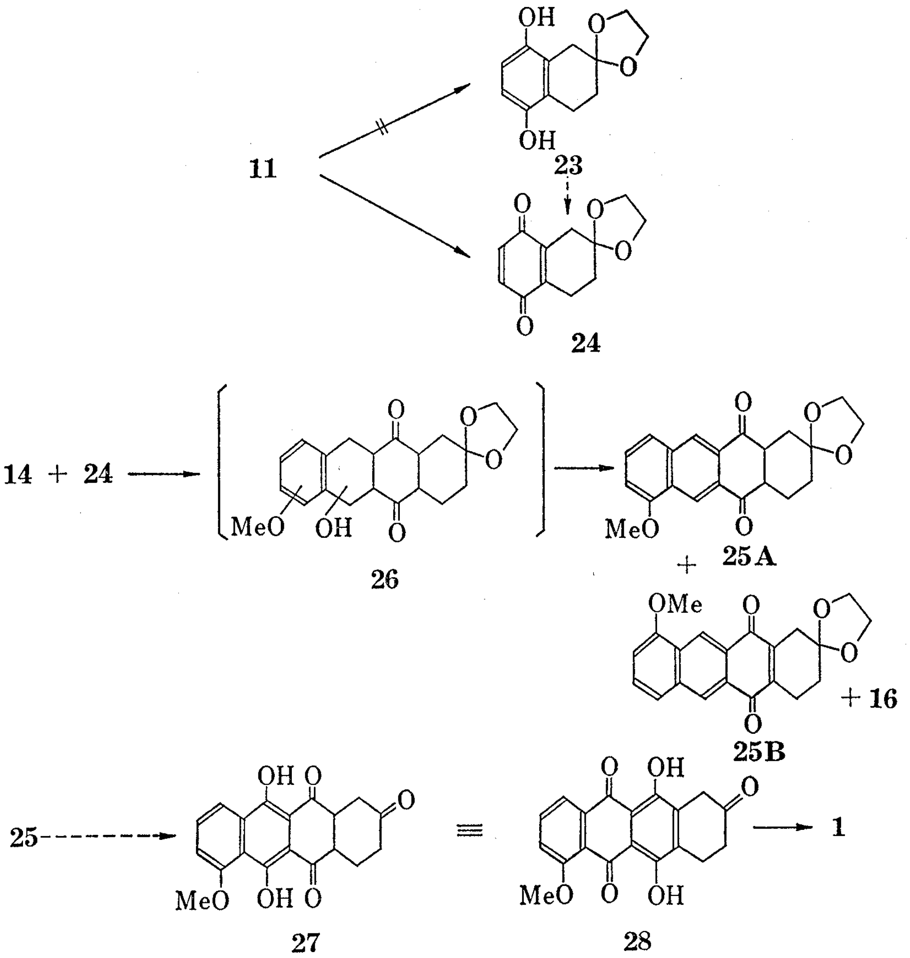


Chart 5

Thus, we synthesized a few naphthacenequinone derivatives through *o*-quinodimethane intermediates, and this reaction would provide a useful route for a synthesis of tetracycline and anthracycline compounds.

Experimental[14]

Reaction of Benzocyclobutene (7) and Tetrahydronaphthoquinone (8)——A mixture of 300 mg of 1-cyano-6-methoxybenzocyclobutene (7) and 364 mg of 6-ethoxy-4a,5,8,8a-tetrahydronaphthoquinone (8) was heated at 150—160° for 75 min in a current of N_2. After cooling, the reaction mixture was washed with ether and $CHCl_3$, and the residue was recrystallized from MeOH–benzene to give 80 mg of hydroquinone derivative (10) as colorless plates, mp 179—180°. *Anal.* Calcd. for $C_{12}H_{14}O_3$: C, 69.86; H, 6.84. Found: C, 69.55; H, 6.91. IR $\nu_{\max}^{\mathrm{Nujol}}$ cm^{-1}: 1680 (x=$C\langle^{OEt}$). NMR ($CDCl_3$–DMSO-d_6) δ: 1.33 (3H, t, $J=7$ Hz, $-CH_2C\underline{H}_3$), 3.33 (2H, s, $-C\underline{H}_2-C=$), 3.80 (2H, q, $J=7$ Hz, $-C\underline{H}_2CH_3$), 4.00—3.63 (2H, m, $-C\underline{H}_2-CH=$), 4.73 (1H, brs, $-C\underline{H}=C$) 6.50 (2H, s, ArH).

The above ethereal and $CHCl_3$ layers were mixed and evaporated to give a residue which was chromatographed on 20 g of silica gel using benzene as an eluant. Evaporation of the solvent afforded 40 mg of tetracycline-type compound (9) as a colorless powder, whose recrystallization from $CHCl_3$-hexane gave colorless crystals, mp 215—219°. *Anal.* Calcd. for $C_{20}H_{19}NO_4\cdot 0.25\ H_2O$: C, 70.26; H, 5.74; N, 4.01. Found:

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[14] All melting points are uncorrected and were measured with a Yanagimoto micro melting point apparatus (MS-S2). IR spectra were measured with a Hitachi 215 grating spectrophotometer, NMR spectra with a Hitachi H-60 and JEOL-JNM-PMX-100 spectrometer with Me_4Si as an internal standard, mass spectra with a Hitachi RMU-7 spectrometer, and UV spectra with a Hitachi 124 spectrophotometer.

C, 69.92; H, 5.64; N, 3.80. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 2250 (–C≡N), 1720 (>C=O), 1608. NMR ($CDCl_3$) δ: 3.63—2.23 (12H, m, aliphatic protons), 3.73 (3H, s, OCH_3), 4.36—4.03 (1H, m, 5-H), 7.43—6.70 (3H, m, Ar-H), MS *m/e*: 337 (M^+).

In the above chromatography, benzene–ether (5: 1) eluant gave 110 mg of the β-tetralone (**11**) as a brown powder, mp 183—186°, after recrystallization from MeOH. *Anal.* Calcd. for $C_{10}H_{10}O_3\cdot 0.33\ H_2O$: C, 62.06; H, 5.50. Found: C, 62.08; H, 5.26. IR $\nu_{\max}^{\mathrm{Nujol}}$ cm^{-1}: 1673 (>C=O), 1620. NMR ($CDCl_3$–DMSO-d_6) δ: 2.50 (2H, t, J=7 Hz, Ar–$CH_2\underline{CH_2}$CO–), 3.00 (2H, t, J=7 Hz, Ar–$\underline{CH_2}CH_2$CO–), 3.46 (2H, s, ArH), 8.10 (2H, brs, 2×OH, disappeared with D_2O). MS *m/e* 178 (M^+).

6-Methoxybenzocyclobuten-1-one (**13**)——A mixture of 300 mg of 3-bromo-6-methoxybenzocyclobutenone (**12**), 300 mg of magnesium oxide, 600 mg of 10% Pd–C and 20 ml of tetrahydrofuran (THF) is stirred under a current of H_2 at room temperature. After stirring for 24 hr, an undissolved material was filtered off, and the filtrate was evaporated to give a solid, to which 20 ml of water was added. The resulting mixture was extracted with ether. The extract was washed with water, dried over Na_2SO_4, and evaporated to yield a residue, which was subjected to sublimation at 70°/3 mmHg to give 200 mg of benzocyclobutenone (**13**) as colorless needles, mp 32—33°. *Anal.* Calcd. for $C_9H_8O_2$: C, 72.96; H, 5.44. Found: C, 73.01; H, 5.16. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1760 (>C=O), 1603, 1578. NMR (CCl_4) δ: 3.86 (2H, s, Ar$\underline{CH_2}$CO–), 4.04 (3H, s, OCH_3), 7.43—6.56 (3H, m, ArH).

6-Methoxybenzocyclobuten-1-ol (**14**)——To a mixture of 1 g of benzocyclobutenone (**13**) and 40 ml of MeOH, 700 mg of $NaBH_4$ was added in small portions with stirring at 0—5° during 30 min and the mixture was stirred for 30 min at room temperature. After the solvent had been evaporated at 30°, 20 ml of water was added and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4 and evaporated to give 300 mg of **14** as colorless plates, mp 65° (from petroleum ether). *Anal.* Calcd. for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 71.98; H, 6.64. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 3600 (OH), 1600, 1580. NMR (CCl_4) δ: 2.96 (1H, dd, J=2, 15 Hz, –CH_2–), 3.58 (1H, dd, J=4, 15 Hz, –CH_2–), 5.28 (1H, dd, J=2, 4 Hz, >C$\underline{H}$–OH), 7.33—6.50 (3H, m, ArH).

Reaction of Benzocyclobutenol (**14**) **and Tetrahydronaphthoquinone** (**8**)——A mixture of 308 mg of benzocyclobutenol (**14**) and 410 mg of tetrahydronaphthoquinone (**8**), and 10 ml of dry toluene was heated under a current of N_2 at 110—120° for 24 hr. After cooling, the reaction mixture was washed with ether and $CHCl_3$. The residue was recrystallized from MeOH–benzene to give 110 mg of **10** as colorless plates, mp 178—179°, which were identical with the authentic sample, prepared by the method mentioned above. The above washings are mixed and evaporated. The resulting residue was chromatographed on 20 g of silica gel using benzene as an eluant to give 120 mg of 6-methoxy-2-methylbenzaldehyde (**16**), whose distillation at 70°/4 mmHg gave a colorless liquid. *Anal.* Calcd. for $C_9H_{10}O_2\cdot 0.33\ H_2O$: C, 69.21; H, 6.55. Found: C, 69.19; H, 6.50. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1690 (–CHO), 1598, 1580. NMR (CCl_4) δ: 2.53 (3H, s CH_3) 3.83 (3H, s, OCH_3), 7.36∼6.63 (3H, m, ArH), 10.05 (1H, s, CHO). Evaporation of the former benzene–ether (5: 1) eluant gave a yellow powder, whose recrystallization from EtOH afforded 48 mg of **15** as pale yellow plates, mp 228—229°. *Anal.* Calcd. for $C_{21}H_{16}O_4$: C, 75.89; H, 4.85. Found: C, 75.50; H, 4.77. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1665 (>C=O), 1585. NMR ($CDCl_3$) δ: 1.50 (3H, t, J=7, $CH_2\underline{CH_3}$), 4.05 (3H, s, OCH_3), 4.23 (2H, q, J=7 Hz, $\underline{CH_2}CH_3$), 7.83—6.67 (5H, m, ArH), 8.33 (1H, d, J=9, 7-H), 8.71 (1H), 9.23 (1H) (each s, 12-H, 5-H). UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm: 300. MS *m/e*: 332 (M^+). The final elution gave a brown powder, whose recrystallization from MeOH afforded 63 mg of **11** as brown needles, mp 180°, identical with the authentic sample which was obtained in the above reaction.

6-Ethoxy-1,4-naphthoquinone (**20**)——a) To a solution of 150 mg of dihydronaphthalene (**10**) and 15 ml of MeOH, a solution of 1.3 g of Fremy's salt in 60 ml of water was added. The mixture was set aside for 24 hr at room temperature and then extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated to give 98 mg of **20** as a yellow powder, mp 114—115° (from petroleum ether). *Anal.* Calcd. for $C_{12}H_{10}O_3$: C, 71.28; H, 4.99. Found: C, 71.32; H, 5.04. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1660 (>C=O), 1590. NMR ($CDCl_3$) δ: 1.50 (3H, t, J=7 Hz, –$CH_2\underline{CH_3}$), 4.15 (2H, q, J=7 Hz, $\underline{CH_2}CH_3$), 6.86 (2H, s, –CO–C$\underline{H}$=C$\underline{H}$–CO–), 7.13 (1H, dd, J=3, 8 Hz, 7-H), 7.46 (1H, d, J=3, 5-H), 7.96 (1H, d, J=8 Hz, 8-H).

b) To a solution of 200 mg of tetrahydronaphthoquinone (**8**) and 20 ml of MeOH, was added a solution of 5 g of Fremy's salt and 300 ml of water. The mixture was set aside for 24 hr at room temperature and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated to give 130 mg of **20** as a yellow powder, whose recrystallization from petroleum ether gave a yellow powder, mp 113—115°, identical with the sample prepared by the method (a) mentioned above.

Reaction of Benzocyclobutenol (**14**) **and Naphthoquinone** (**20**)——A mixture of 190 mg of benzocyclobutenol (**14**) and 280 mg of naphthoquinone (**20**), and 10 ml of dry toluene was heated at 110—120° for 72 hr in a current of N_2. After cooling, the crystals separated were collected by filtration, washed with ether and recrystallized from EtOH to give 245 mg of **15** as yellow plates, mp 230—233°, which were identical with the authentic sample prepared as before. The above filtrate was evaporated to give a residue, which was chromatographed on silica gel using benzene as an eluant to give 25 mg of **16**, identical with the authentic sample prepared as mentioned above.

6-Ethylenedioxy-5,6,7,8-tetrahydro-1,4-naphthoquinone (**24**)——A mixture of 100 mg of β-tetralone (**11**), 5 ml of ethylene glycol, 50 mg of *p*-TsOH (monohydrate) and 20 ml of CH_3CN was heated at 80—90°

for 2.5 hr in a current of N_2. After cooling, the solvent was evaporated, and 10 ml of 10% NH_4OH was added to the resulting residue, which was extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and evaporated to afford a syrup, which was chromatographed on 20 g of silica gel using benzene–ether (10: 1) as an eluant to give 34 mg of a yellow gum (**24**), bp 150—160°/4 mmHg. *Anal.* Calcd. for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49. Found: C, 64.96; H, 5.38. IR $\nu_{\max}^{CHCl_3}$ cm^{-1}: 1655 (>C=O), 1600. NMR ($CDCl_3$) δ: 2.66—1.70 (2H, m, $-C\underline{H}_2-$), 2.89—2.59 (4H, m, $-C\underline{H}_2-C=C-C\underline{H}_2-$), 4.01 (4H, s, $-O-C\underline{H}_2C\underline{H}_2-O-$), 6.67 (2H, s, $_{\underline{H}}\rangle=\langle_{\underline{H}}$). UV $\lambda_{\max}^{EtOH}$ nm: 248. MS *m/e*: 220 (M^+).

Reaction of 14 and 24——A mixture of 330 mg of **24**, 260 mg of benzocyclobutenol (**14**), and 5 ml of dry toluene was heated at 110—120° for 3 days in a current of N_2. After cooling, the solvent was evaporated and the residue was chromatographed on 20 g of silica gel using benzene as eluant to give 83 mg of **16**, prepared in the above reaction. A further benzene eluant gave 106 mg of tetracycline-compound (**25**) as a yellow powder, mp 218—224°, after recrystallization from EtOH. *Anal.* Calcd. for $C_{21}H_{18}O_5 \cdot 0.33\,H_2O$: C, 70.81; H, 5.28. Found: C, 70.74; H, 5.32. IR $\nu_{\max}^{CHCl_3}$ cm^{-1}: 1660 (>C=O), 1620. NMR ($CDCl_3$) δ: 3.10—2.73 (6H, m, $3\times CH_2$), 3.98 (7H, s, $OC\underline{H}_3$, $O-C\underline{H}_2C\underline{H}_2-O$), 7.63—6.86 (3H, m, ArH), 8.10 (1H), 8.90 (1H) (each, s, ArH). UV $\lambda_{\max}^{EtOH}$ nm: 430, 276.

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