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Studies on the Syntheses of Tetracycline Derivatives. I. Thermolytic Cycloaddition of *o*-Quinodimethanes with Naphthoquinone

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Naphthoquinone (**14**) reacted with the *o*-quinodimethanes, which were generated from the benzocyclobutenes (**9**, **10** and **11**), *o*-xylyl dibromide (**12**) and N-aminodihydroisoindole (**13**), to give the naphthacene-5,12-quinones (**15**, **16**, **17** and **18**), respectively.

The benzocyclobutenes[2] have a long history in organic chemistry and also in physical organic chemistry since Finkelstein[3] had prepared a benzocyclobutene itself in 1910. However, the field of benzocyclobutene chemistry lay dormant for about 50 years until Cava[4] repeated Finkelstein's synthesis.

Now, it has been well known[2] that the benzocyclobutenes (**1**) on heating give the reactive *o*-quinodimethanes (**2**), which can easily react stereoselectively and/or regioselectively with the olefins to afford the tetralin derivatives (**3**).[5] This fact indicated the benzocyclobutene derivatives to be key starting materials in synthetic organic chemistry, especially in the synthesis of natural products such as alkaloid, terpene, lignan, tetracycline, and anthracycline. Therefore we examined the thermolysis of benzocyclobutenes in the presence of the imines and reported the synthesis of isoquinolines and their related alkaloids[6] as shown in Chart 1.

Recently, we developed a new regioselective and stereoselective synthesis of the benzo[*b*]carbazole (**5**) by an intermolecular cycloaddition of *o*-quinodimethane (**4**) to indole,[7] and this finding suggests that the tetracycline (**6**), anthracycline (**7**) and lignan (**8**) would be synthesized from the appropriate *o*-quinodimethanes. We have investigated the synthesis of these type of compounds and here wish to report the synthesis of the polycyclic compounds as the model experiment for synthesis of **6**, **7** and **8**.

Heating of a mixture of 1-cyano-4,5-dimethoxybenzocyclobutene (**9**) and α-naphthoquinone (**14**) at 150—160° for 1.25 hr gave the naphthacene-5,12-quinone (**15**), mp 217—218°, whose structure, $C_{21}H_{13}O_4N$, was easily determined by infrared (IR) [ν_{max}^{KBr} cm^{-1}: 2220 (conjugated nitrile), 1670 (cross-conjugated carbonyl), 1610, 1590, and 1570 (aromatic absorption characteristic of naphthacene-5,12-quinone)],[8] ultraviolet (UV) (λ_{max}^{MeOH} nm: 325^{sh}, 292, 282,

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8) Z. Horii, Y. Ozaki, S. Yamamura, T. Nishikado, M. Hanaoka, and T. Momose, *Chem. Pharm. Bull.* (Tokyo), **22**, 93 (1974).

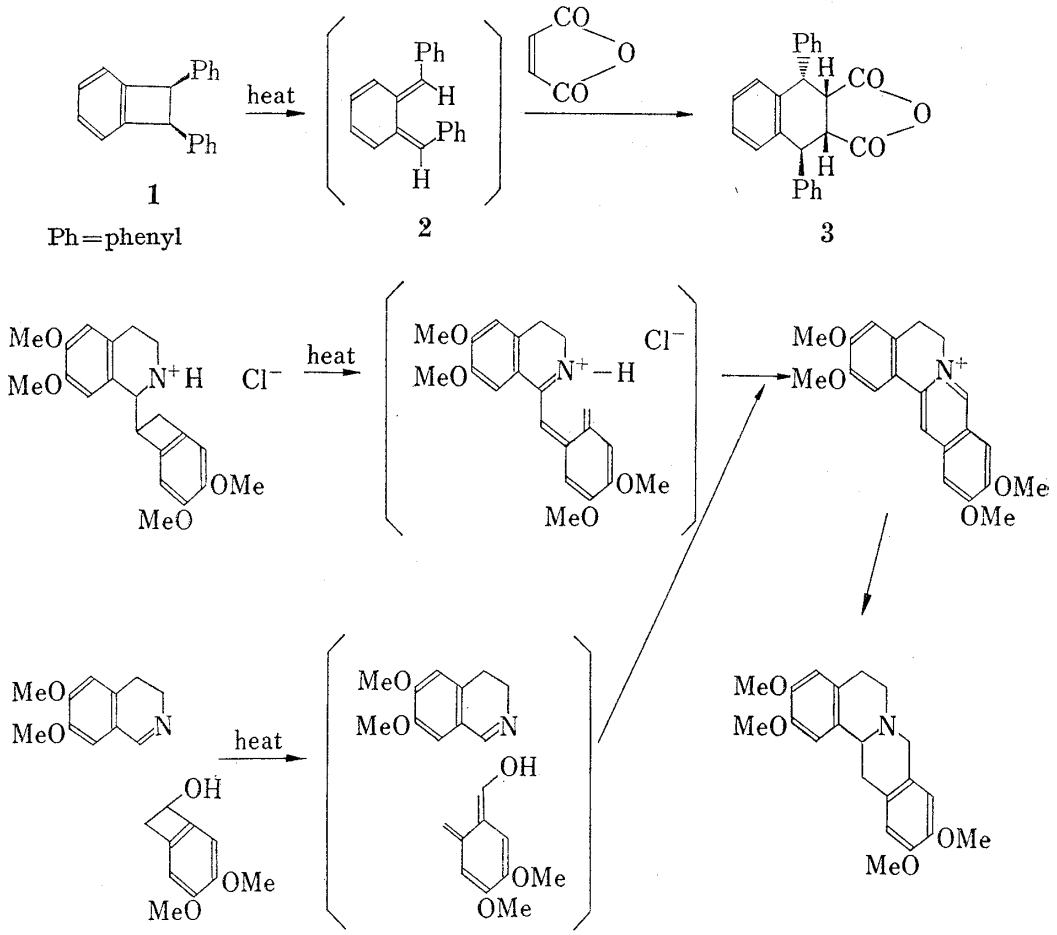

Chart 1

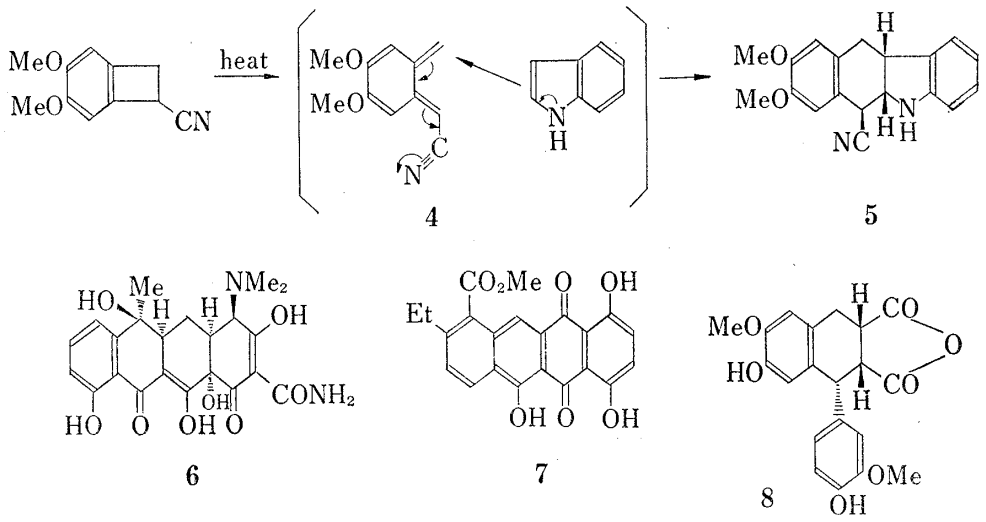

Chart 2

273 and 225[sh]) and nuclear magnetic resonance (NMR) spectra [$\delta(CF_3CO_2H)$ ppm: 4.16 and 4.20 (OMe), 7.55, 7.75 and 8.96 (each 1H, s, C_7-, C_{10}- and C_{11}–H), 7.88—8.00 (m, 2H, C_2– and C_3–H) and 8.28—8.42 (m, 2H, C_1– and C_4–H)]. Similarly, a monomethoxy analogue (**16**), mp 237—238°, *m/e* 313 (M^+), was obtained by a reaction of 1-cyano-5-methoxybenzocyclobutene (**10**) with naphthoquinone under the same conditions. This reaction would proceed by an intermolecular cycloaddition of naphthoquinone to the *o*-quinodimethanes (**9a** and **10a**),

generated by heating the benzocyclobutenes (**9** and **10**), followed by dehydrogenation by an unreactive naphthoquinone.

Secondly, the reactions of the benzocyclobutene having no substituents on cyclobutene ring were examined. 4,5-Dimethoxybenzocyclobutene (**11**), which was obtained from the cyanobenzocyclobutene (**9**) by the reductive decyanation with lithium in liquid ammonia,[9] was heated with naphthoquinone (**14**) in boiling diethyl phthalate[10] to give the naphthacenequinone (**17**),[11] which also showed a typical pattern characteristic of this system at 1655, 1620, 1600 and 1585 cm^{-1} in IR spectrum and 232, 235, 257, 269, 275^{sh}, and 327 nm in UV spectrum. The NMR spectrum also supported this system by the presence of two deshielded protons at 8.54 ppm as singlets.

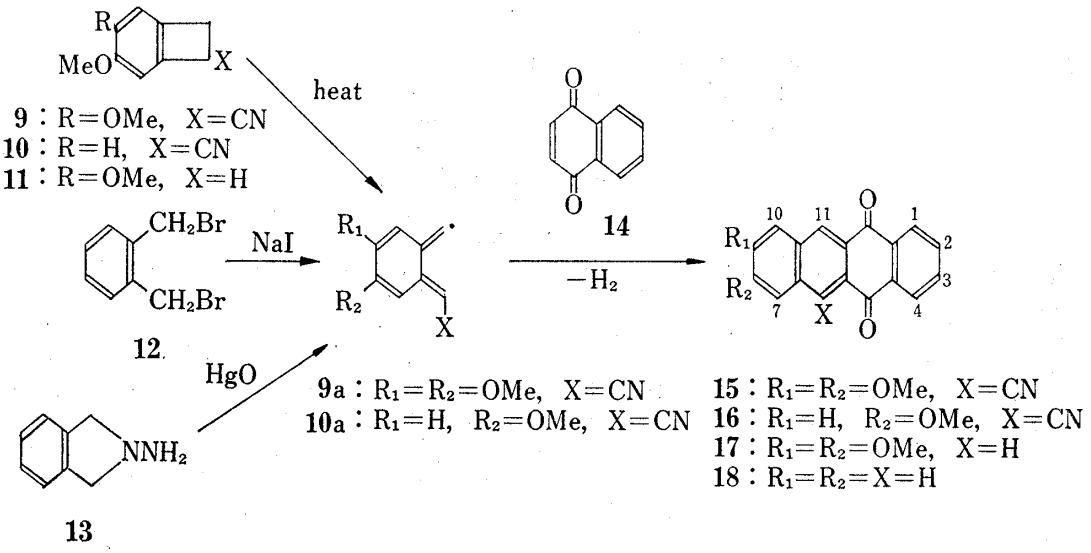

Chart 3

Ring opening reaction of the benzocyclobutenes having no substituents on aliphatic carbons to the corresponding *o*-quinodimethanes was carried out under the drastic conditions.[12] For example, 4-methoxybenzocyclobutene could not afford the cycloaddition product under the above reaction condition. Therefore, the syntheses of the naphthacenequinone under the mild conditions were investigated.

It has been reported that *o*-xylyl dibromides were converted into the corresponding benzocyclobutenes *via* *o*-quinodimethanes by a reaction with sodium iodide.[13,14] Therefore, the cycloaddition products would be obtained by a treatment of *o*-xylyl dibromides with sodium iodide in the presence of the appropriate olefins.[11] On the ground of this idea, *o*-xylyl dibromide (**12**) was heated at 60—70° with naphthoquinone in the presence of sodium iodide in dimethylformamide to afford the naphthacene-5,12-quinone (**18**),[15] mp 285—287°, whose structure was supported by IR and UV spectra showing a typical pattern of this system.

On the other hand, Carpino[16] prepared the benzocyclobutenes by mild oxidation of N-aminodihydroisoindoles. This synthetic reaction proceeded mildly although the selection of reaction conditions is very difficult. Therefore, we examined the synthesis of naphthacene-

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quinones from the N-aminodihydroisoindoles *via* the benzocyclobutenes or the corresponding *o*-quinodimethanes. Thus, an oxidation of N-aminodihydroisoindole (**13**) or its hydrochloride with mercuric oxide prepared freshly in an aqueous solution at 0° in the presence of naphthoquinone (**14**) afforded, in poor yield, the expected naphthacenequinone (**18**), which was indentical with that prepared from *o*-xylyl dibromide (**12**) in spectral and melting point comparisons.

Thus, we synthesized the naphthacene-5,12-quinones through the *o*-quinodimethane intermediates, and this reaction would provide a useful route for the synthesis of tetracycline, anthracycline, and lignan.

Experimental[17]

6-Cyano-8,9-dimethoxynaphthacene-5,12-quinone (15)——A mixture of 302 mg (1.6 mmole) of 1-cyano-4,5-dimethoxybenzocyclobutene (**9**) and 252 mg (1.6 mmole) of α-naphthoquinone (**14**) was heated at 150—160° for 75 min in a current of N_2. After cooling, the reaction mixture was washed with ether and then with AcOEt. The residue was recrystallized from $CHCl_3$–ether to give 120 mg (20.5%) of the naphthacenequinone (**15**) as a yellow powder, mp 217—218°. *Anal.* Calcd. for $C_{21}H_{13}O_4N$: C, 73.46; H, 3.82; N, 4.08. Found: C, 73.52; H, 3.96; N, 3.92. IR ν_{max}^{KBr} cm^{-1}: 2220 (CN), 1670 (C=O), 1610, 1590, and 1570 (Ar). UV λ_{max}^{MeOH} nm: 325^{sh}, 292, 282, 273, 225^{sh}. NMR δ (CF_3CO_2H) ppm: 4.16 (3H, s, OMe), 4.20 (3H, s, OMe), 7.55 (1H, s, 7-H), 7.75 (1H, s, 10-H), 7.88—8.00 (2H, m, 2-H and 3-H), 8.28—8.42 (2H, m, 1-H and 4-H), 8.96 (1H, s, 11-H).

6-Cyano-8-methoxynaphthacene-5,12-quinone (16)——A mixture of 557 mg (3.5 mmole) of 1-cyano-5-methoxybenzocyclobutene (**10**) and 620.1 mg (3.9 mmole) of α-naphthoquinone (**14**) was treated as above to give 110 mg (10.0%) of the naphthacenequinone (**16**) as a yellow powder from $CHCl_3$–ether, mp 237—238°. *Anal.* Calcd. for $C_{20}H_{11}O_3N$: N, 4.47; M^+ (*m/e*) 313. Found: N, 4.22; M^+ (*m/e*) 313. IR ν_{max}^{KBr} cm^{-1}: 2220 (CN), 1670 (C=O), 1610, 1590 and 1570 (Ar). UV λ_{max}^{MeOH} nm: 355^{sh}, 328^{sh}, 306, 290, 260. NMR δ (CF_3CO_2H) ppm: 4.12 (3H, s, OMe), 7.52 (1H, dd, J=7.5 and 2 Hz, 9-H), 7.80 (1H, d, J=2 Hz, 7-H), 7.88—7.95 (2H, m, 2-H and 3-H), 8.16 (1H, d, J=7.5 Hz, 10-H), 8.32—8.48 (2H, m, 1-H and 4-H), 9.08 (1H, s, 11-H).

8,9-Dimethoxynaphthacene-5,12-quinone (17)——A mixture of 328.4 mg (2 mmole) of 4,5-dimethoxybenzocyclobutene (**11**), 316.4 mg (2 mmole) of α-naphthoquinone (**14**) and 25 ml of diethyl phthalate was heated on boiling and distilled slowly until almost 20 ml of distillate was collected. Ether was added to a cooled residue and the separated powder was collected by centrifugalation and recrystallized from CH_2Cl_2 to give 480.2 mg (75.4%) of the naphthacenequinone (**17**) as an orange powder, mp>270° (lit.[11] mp 300°), whose NMR spectrum was identical with that of the authentic sample.[11] IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1655 (C=O), 1620, 1600 and 1588 (Ar). UV λ_{max}^{MeOH} nm: 327, 275^{sh}, 269, 257, 235, 232. NMR δ ($CDCl_3$) ppm: 3.99 (6H, s, 2× OMe), 7.20 (2H, s, 7-H and 10-H), 7.72 (2H, m, 2-H and 3-H), 8.33 (2H, m, 1-H and 4-H), 8.54 (2H, s, 6-H and 11-H).

Naphthacene-5,12-dione (18)——a) From *o*-Xylyl Dibromide (**12**): A mixture of 1 g (3.79 mmole) of *o*-xylyl dibromide (**12**), 1 g (6.30 mmole) of α-naphthoquinone (**14**), 3 g (20.0 mmole) of NaI and 10 ml of DMF was heated at 60—70° for 6 hr. On cooling, 100 ml of water was added, and the mixture was decolorized by addition of saturated aqueous $NaHSO_3$. The resulting solution was extracted with ether, and the extract was washed with water, dried over anhyd. Na_2SO_4, and evaporated. The residue was chromatographed on 20 g of silica gel using CH_2Cl_2 as the eluant to give 196.0 mg (20.0%) of naphthacene-5,12-dione (**18**) as yellow needles after recrystallization from tetrachloroethane-ether, mp 285—287° (lit.[15] mp 285°). IR ν_{max}^{KBr} cm^{-1}: 1675 (C=O). UV λ_{max}^{MeOH} nm: 315^{sh}, 282, 245^{sh}, 238. Mass Spectrum *m/e*: 258 (M^+), 230 (M^+—CO), 202 (230—CO). NMR δ (CF_3CO_2H) ppm: 7.45—8.05 (6H, m, 2-H, 3-H, 7-H, 8-H, 9-H, and 10-H), 8.05—8.32 (2H, m, 1-H and 4-H), 8.46 (2H, s, 6-H and 11-H).

b) From N-Aminodihydroisoindole (**13**): To a solution of N-aminoisoindole (**13**) [generated from 60 mg (0.35 mmole) of its hydrochloride[16] and 10 ml of 10% NaOH in $CHCl_3$] and 68 mg (0.43 mmole) of α-naphthoquinone (**14**) in 15 ml of $CHCl_3$ was added in small portions 2 g of HgO[18] prepared freshly with stirring at 0°. After stirring for 10 min, undissolved materials were filtered off, and the filtrate was evaporated. The residue was subjected to silica gel thin-layer chromatography developed with $CHCl_3$. Evaporation of an appropriate part (*Rf* 0.61) gave 30 mg (25.3%) of **18** as yellow needles from $CHCl_3$–EtOH, mp 285—287°, which was identical with the sample prepared by method a).

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

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c) From N-Aminodihydroisoindole (**13**) Hydrochloride: To a solution of 60 mg (0.35 mmole) of N-aminodihydroisoindole (**13**) hydrochloride and 68 mg (0.43 mmole) of α-naphthoquinone (**14**) in 10 ml of DMF was added 2 g of HgO with stirring at 0°. After stirring for 20 min, an undissolved substance was filtered off and the solvent was distilled off. The residue was diluted with 10 ml of 5% HCl and extracted with ether. The extract was washed with water, dried over K_2CO_3, and evaporated to give a brown gum, which was subjected to silica gel thin-layer chromatography as above to give 16 mg (17.6%) of the naphthacenequinone (**18**) after recrystallization from $CHCl_3$–EtOH, mp 285—287°, identical with the above sample.

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