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SYNTHESIS AND SOME PROPERTIES OF 1,2-DIHYDRO-4,7-DIHYDROXYCYCLOBUTA[b]NAPHTHALENE-3,8-DIONE AND 1,2,5,6-TETRAHYDRO-4,7-DIHYDROXYDICYCLOBUTA[b,g]NAPHTHALENE-3,8-DIONE

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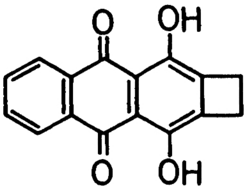
Title compounds have been first synthesized. The effects of strain due to the cyclobutene annelation are observed in the ^{13}C NMR chemical shifts, tautomeric equilibrium, reduction potentials, and Diels-Alder reactions with dienes; thermolytic Diels-Alder reactions with dienophiles give novel polycyclic hydroxyquinones.

Quinones annelated with small ring(s) are intriguing molecules from physicochemical and synthetic points of view.[1] We have recently reported the synthesis of 1,2-dihydro-3,10-dihydroxycyclobut[b]anthracene-4,9-dione (2,3-cyclobutaquinizarin) (1) and its usefulness as a synthetic intermediate for anthracyclinones (aglycons of antitumor antibiotics anthracyclines) and the related tetracyclic hydroxyquinones.[2] We here report the synthesis and some properties of 5,8-dihydroxy-1,4-naphthalenediones (naphthazarins) annelated with cyclobutene(s), the title compounds 2 and 3, which would be useful synthetic intermediates for polycyclic hydroxyquinones.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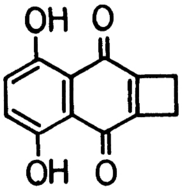
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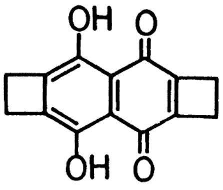
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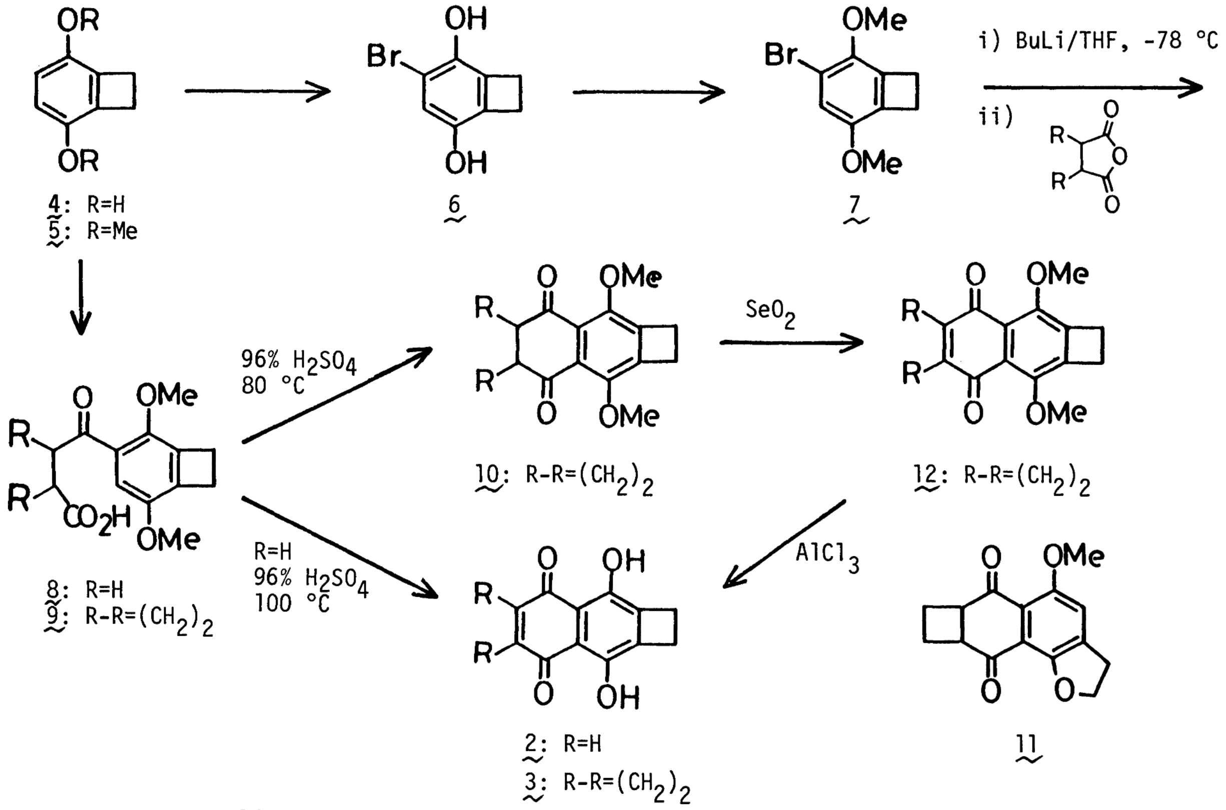
Although several methods for naphthazarin synthesis are known, they involve drastic conditions and lack in wide applicability.[3] Considering milder conditions and better applicability, we chose the following sequence. 3,6-Dihydroxy-1,2-dihydrobenzocyclobutene (4) was converted into 4-bromo-3,6-dimethoxy-1,2-dihydrobenzocyclobutene (7)[4] through bromination (dioxane dibromide, ether, 0 °C, 80%) giving the bromohydroquinone 6 followed by methylation (Me$_2$SO$_4$, K$_2$CO$_3$, acetone, reflux, 88%). Lithiation (BuLi, THF, -78 °C) of 7 and subsequent treatment with succinic anhydride gave the keto acid 8 in 81% yield. Similarly the keto acid 9 was obtained by reaction with *cis*-cyclobutane-1,2-dicarboxylic acid anhydride[5] in 63% yield. The keto acid 8 was also obtained by Friedel-Crafts acylation of the dimethyl ether 5 with succinic anhydride (AlCl$_3$, CH$_2$Cl$_2$, room temp) in 40-60% yield; however, the reaction was accompanied with formation of several by-products[6] due to ring opening of the cyclobutene moiety, and isolation of 8 was rather difficult. The lithiation-acylation process has advantages of avoiding the ring opening and general applicability to the introduction of electrophiles at C-4 of 5 which is a useful synthon for polycyclic quinones.7)

The transformation of 8 to 2 was achieved in a single step in 40% yield by heating at 100 °C in 96% H_2SO_4 for 1 h. Oxidation and demethylation have apparently ocurred under the reaction conditions. However, the similar reaction of 9 (96% H_2SO_4, 80 °C, 1.5 h) gave mainly the unoxidized cyclization product 10 (48%) and the rearranged product 11 (14%), and only traces of oxidized products were obtained. Oxidation of 10 with selenium dioxide (2.0 equiv., dioxane, reflux, 1 h) gave the quinone 12 in 52% yield. Demethylation of 12 to 3 was smoothly effected by $AlCl_3$ in dichloromethane at room temperature.



The averaged ^{13}C chemical shifts of the four O-bonded carbons of 2 (δ_{av}=170.7) and 3 (δ_{av}=169.2) are 1.8 and 3.0 ppm higher than that of 2,3-dimethylnaphthazarin (13) (δ_{av}=172.5) and 2,3,6,7-tetramethylnaphthazarin (14) (δ_{av}=172.2), respectively, indicating the effect of strain due to the cyclobutene annelation (Table 1).1c) Between the two tautomers in 13, 13B is known to be thermodynamically much favored over 13A,8) the fact being also seen in the large ^{13}C chemical shift difference ($\Delta\delta$=27.5) between C-1,4 and C-5,8. In 2, however, only slight predominance of 2B over 2A is suggested by the small difference ($\Delta\delta$=3.8). This suggestion is substantiated in the equilibrated mixture of the diacetate 15 whose ^{1}H NMR spectrum at 37 °C shows 15A/15B=3/7.9)

The reduction potentials of 2 and 3 lie between those of naphthazarin and 13, reflecting the strain (Table 2). The same trend has been observed in the corresponding *p*-benzoquinone series.1)

Table 1. ^{13}C NMR chemical shifts of naphthazarins$^{a)}$

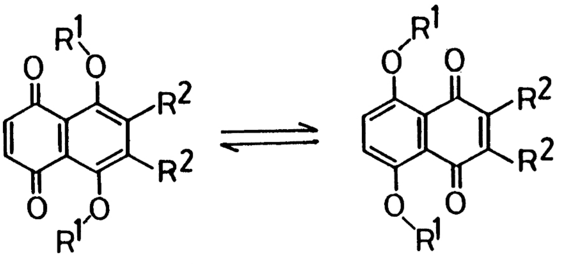
Carbon No. Compound	1	2	3	4	5	6	7	8	9	10	Others
naphthazarin$^{b)}$	172.9	134.6	134.6	172.9	172.9	134.6	134.6	172.6	111.9	111.9	
13	186.2	144.4	144.4	186.2	158.7	129.4	129.4	158.7	111.6	111.6	12.5
2$^{c,d)}$	172.6$^{e)}$	152.0	152.0	172.6$^{e)}$	168.8$^{e)}$	133.1	133.1	168.8$^{e)}$	112.7	112.7	28.1
14	172.2	141.1	141.1	172.2	172.2	141.1	141.1	172.2	f)	f)	12.5
3$^{c,d)}$	169.2	150.5	150.5	169.2	169.2	150.5	150.5	16.92	113.7	113.7	28.1

a) δ ppm from $(CH_3)_4Si$ in $CDCl_3$. b) M. Kobayashi, Y. Terui, K. Tori, and N. Tsuji, tetrahedron Lett., 619 (1976). c) This work. d) Numbering is based on that of naphthazarin. e) Assignment was made based on the long range coupling (4.3 Hz) observed for the signal at δ 168.8.
f) The signal was not cleanly observed due to poor solubility.

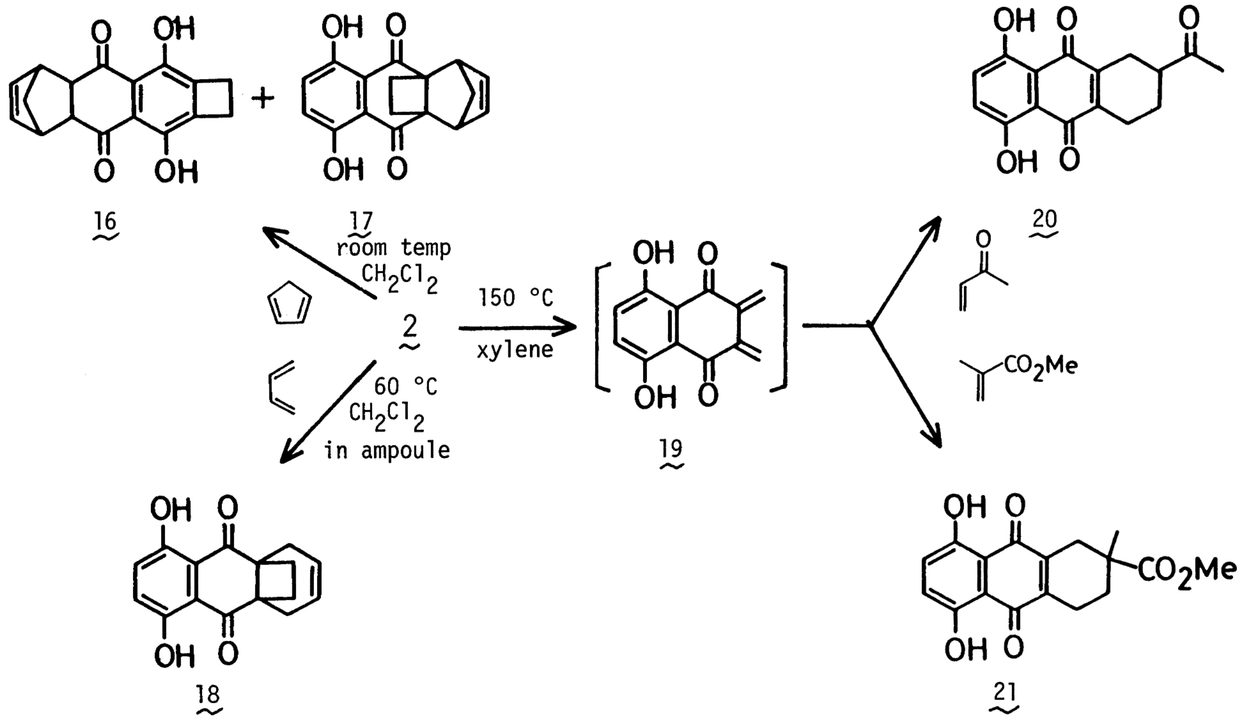
Table 2. Reduction potentials of naphthazarins$^{a)}$

	$^{1}E_{1/2}$$^{b)}$	$^{2}E_{1/2}$$^{b)}$
naphthazarin	-0.56	-1.11
2	-0.59	-1.16
3	-0.64	-1.19
13	-0.69	-1.21

a) Measured by cyclic voltametry using a glassy carbon electrode; 0.1 M Et_4NClO_4-CH_3CN, sweep rate 100 mV s^{-1}, 25°C. b) V vs. SCE.



2A R^1=H, R^2-R^2=$(CH_2)_2$ 2B
13A R^1=H, R^2=CH_3 13B
15A R^1=$COCH_3$, R^2-R^2=$(CH_2)_2$ 15B



The effect of strain is also significant on the Diels-Alder reactions of 2. Reaction of 2 with cyclopentadiene (room temp, CH_2Cl_2) gave two adducts, 16 and 17,$^{10)}$ in 70% and 28% yields, respectively. Butadiene exclusively afforded the adduct 18 in 96% yield, providing a synthetic way for novel propellanes. These results contrast with the exclusive reaction of 13 at the unsubstituted carbons.$^{8)}$ The cyclobutene ring of 2 thermally opened more readily than that of 1 to generate the reactive intermediate 19 which could be trapped with dienophiles. Thus, heating a xylene solution of 2 and methyl vinyl ketone (4 equiv.) in a sealed glass tube at 150 °C for 1 h gave the tricyclic adduct 20 in 80% yield. Similarly methyl methacrylate gave the adduct 21 in 62% yeild. These results indicate 2 (and 3) to be a useful synthon for polycyclic hydroxyquinones.

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4) Satisfactory combustion analyses and/or Mass spectra were obtained for all the new compounds. Some physical data are following: 2: red fine needles, mp 145 °C decomp., ^{1}H NMR ($CDCl_3$) δ 3.09 (s, 4H), 7.03 (s, 2H), 12.57 (s, 2H); 3: red needles, mp 150 °C decomp., ^{1}H NMR ($CDCl_3$) δ 3.10 (s, 8H), 12.91 (s, 2H); 7: mp 135-136 °C; ^{1}H NMR ($CDCl_3$) δ 3.0-3.5 (m, 4H), 3.43 (s, 3H), 3.89 (s, 3H), 6.83 (s, 1H); 8: mp 154-158 °C; 9: mp 160-162 °C; 10: mp 179-180 °C; ^{1}H NMR ($CDCl_3$) δ 2.2-2.5 (m, 4H), 3.3-3.7 (m, 2H), 3.44 (s, 4H), 3.91 (s, 6H); 11: mp 174-176 °C, 2.1-2.8 (m, 4H), 3.26 (t, J=8.5 Hz, 2H), 3.4-3.7 (m, 2H), 3.87 (s, 3H), 4.75 (t, 8.5 Hz, 2H), 7.14 (s, 1H); 12: mp 148 °C decomp., ^{1}H NMR ($CDCl_3$) δ 2.96 (s, 4H), 3.46 (s, 4H), 3.97 (s, 6H); 15: ^{1}H NMR ($CDCl_3$, 37 °C) δ for 15A, 2.38(s), 3.19(s), 6.66; for 15B, 2.38(s), 2.97(s), 7.24(s) (the integrated ratio 15A/15B=3/7); 16: mp 134 °C decomp. ^{1}H NMR ($CDCl_3$) δ 1.55 (m, 2H), 3.13 (s, 4H), 3.36 (m, 2H), 3.64 (m, 2H), 5.99 (m, 2H), 12.76 (s, 2H); 17: mp 229 °C decomp., ^{1}H NMR ($CDCl_3$) δ 1.61 (dt, J=10.1 Hz, 1H), 2.0-2.5 (m, 5H), 3.35 (m, 2H), 5.96 (m, 2H), 7.16 (s, 2H), 12.60 (s, 2H); 18: mp 87-89 °C, ^{1}H NMR ($CDCl_3$) δ 2.1-2.8 (m, 8H), 6.06 (m, 2H), 7.24 (s, 2H), 12.59 (s, 2H); 20: mp 136-137 °C; 21: mp 148-152 °C.

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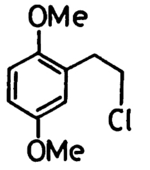
6) The by-products were identified as a and b.



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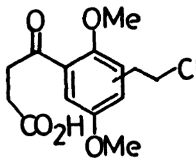

b

7) Thermolytic Diels-Alder reactions of 5 give adducts in high yields which can be oxidized to the corresponding quinones; to be published elsewhere.

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10) The stereochemistries of 16 and 17 were assigned as shown in analogy with the adducts from 1,2,3,6-tetrahydrobenzocyclobutene-3,6-dione.[1)]

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