Dopaquinone and Related Compounds. The Reaction with Cyclopentadiene

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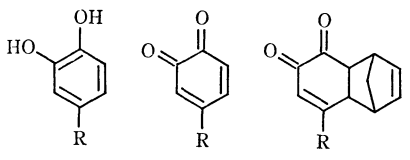
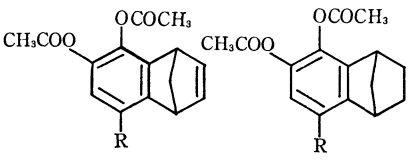
The trapping of *o*-quinones produced during the oxidation of 4-substituted catechols(I, R=CH_3, $CH_2CH_2CO_2H$, $CH_2CH_2NH_3Br$, $CH_2CH(NH_3Cl)CO_2CH_3$) in the presence of cyclopentadiene affords adducts, which are changed into 8-substituted 5,6-diacetoxy-1,4-dihydro-1,4-methanonaphthalenes(IV, R=CH_3, $CH_2CH_2CO_2H$, $CH_2CH_2NHCOCH_3$, $CH_2CH(NHCOCH_3)COCH_3$) by treatment with acetic anhydride-pyridine Dopaquinone (IIe) is trapped with cyclopentadiene, followed by acetylation and methylation with acetic anhydride–pyridine–methanol (13 : 2 : 2) to give the *N*-acetyl-2-(5,6-diacetoxy-1,4-dihydro-1,4-methanonaphthyl-8)-L-alanine methyl ester (IVd).

In a previous report we described the synthesis of dopaquinone protected by methylation and benzoylation.[1] However, free dopaquinone was labile to be isolated or trapped by *o*-phenylenediamine. We have continued to inquire into the method of trapping *o*-quinone[2] and have succeeded in proving the presence of free dopaquinone by trapping with cyclopentadiene.



I II III

(a) R: CH_3, (b) R: $CH_2CH_2CO_2H$
(c) R: $CH_2CH_2NH_3Br$, (d) R: $CH_2CHCO_2CH_3$ (NH_3Cl)
(e) R: CH_2CHCO_2H (NH_2)



IV V

(a) R: CH_3, (b) R: $CH_2CH_2CO_2H$
(c) R: $CH_2CH_2NHCOCH_3$, (d) R: $CH_2CHCO_2CH_3$ ($NHCOCH_3$)

Results and Discussion

The UV spectrum with time intervals of the equimolar mixture of the *N*-benzoyl-DOPA methyl ester (I, R=$CH_2CH(NHCOC_6H_5)CO_2CH_3$) and *o*-chloranil indicates a decrease in *o*-chloranil absorption at 350 and 410 nm as well as an increase in a new absorption near 380 nm attributable to the formation of a new *o*-quinone (Fig. a). On the contrary, the spectral change of the mixture of dopamine hydrobromide(I, R=$CH_2CH_2NH_3Br$) and *o*-chloranil does not show any formation of the *o*-quinone in spite of the decrease in *o*-chloranil (Fig. b). It is known that DOPA and dopamine are easily oxidized into the corresponding indoline derivatives.[3] Consequently, a similar reaction seems to have occurred in the latter case.

For the purpose of trapping this intermediate, the reaction with cyclopentadiene was examined. Substituted *o*-benzoquinones(II) are known to give adducts(III) with cyclopentadiene.[2] Also, it is known that these adducts can be acetylated in the reaction mixture to give a stable catechol diacetate(IV).[2b,2c] These reactions were applied to the trapping of the *o*-benzoquinone. As a typical model experiment, 4-

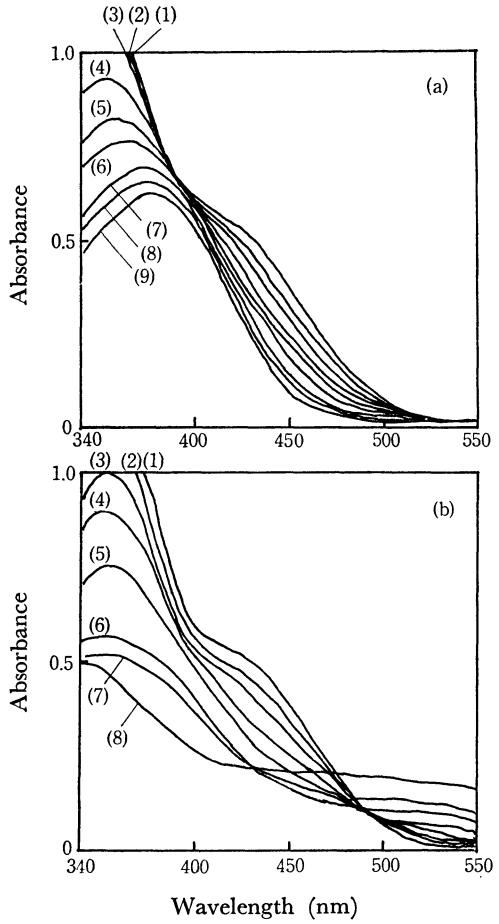


Fig. 1. Time-dependent UV and visible spectrum of the equimolar mixture of
(a) *N*-benzoyl-DOPA methyl ester and *o*-chloranil
(1) 2 min after addition of *o*-chloranil to the substrate; (2) 4 min; (3) 10 min; (4) 20 min; (5) 35 min; (6) 45 min; (7) 120 min; (8) 180 min; (9) 300 min.
(b) dopamine hydrobromide and *o*-chloranil
(1) 2 min after addition of *o*-chloranil to the substrate; (2) 5 min; (3) 30 min; (4) 45 min; (5) 105 min; (6) 200 min; (7) 280 min; (8) 20 hr.
conc. 5.00×10^{-4} mol/l in EtOH.

methylcatechol(Ia) was oxidized with *o*-chloranil in the presence of cyclopentadiene, the reaction mixture being warmed with acetic anhydride–pyridine to afford Compound IVa. The structure of IVa was confirmed by the NMR, IR, and UV spectra and elemental analysis. Furthermore, IVa was quantitatively hydrogenated to give Va.

Cyclopentadiene is known to give an adduct with *o*-chloranil,[4] but under the present experimental conditions it does not react with *o*-chloranil and only reacts selectively with the newly-formed *o*-quinones. The characteristic feature of this trapping method is that the labile adduct of an *o*-benzoquinone with cyclopentadiene is, without isolation, transformed into a stable compound by acetylation.

The trapping transformation is applied to the oxidation of dihydrocaffeic acid (Ib), and the IIb quinone is thus trapped in the form of an acetyl compound, IVb. The cyclic isomer of IIb, a lactone,[5] is not found. Next, the trapping of dopamine hydrobromide (Ic) was examined, Compound IVc was thus obtained. This is chemical proof of the dopaminequinone adduct with cyclopentadiene (IIIc). It is obvious that cyclopentadiene adds to IIc under conditions similar to those described above, without cyclization into an indoline derivative, the free amino group in IIc doing no harm to the trapping.

Finally, the trapping experiment was successful in giving Compound IVd from the DOPA methyl ester (Id) and IVd from DOPA itself. In the case of DOPA, the isolation of IV, R=$CH_2CH(NHCOC_6H_5)CO_2H$, is very difficult. Therefore, the isolation of IVd was carried out after the esterification of the carboxyl group with methanol.

Experimental

1,4-Dihydro-8-methyl-1,4-methanonaphthalene-5,6-diol Diacetate (IVa). *(a)*: An ethereal solution of *o*-chloranil (2.00 g) was slowly added to a solution of 4-methylcatechol (1.00 g) in 20 ml of ether with stirring under nitrogen at −78 °C. After the mixture had been stirred for 1 hr, cyclopentadiene (1 ml) was added, the mixture was then stirred for an additional 4 hr at −78 °C and for 12 hr at room temperature. After the evaporation of the solvent, a mixture of acetic anhydride (35 ml) and pyridine (1 ml) was added to the residue, and the mixture was heated at 80—90 °C for 2 hr. A precipitate of tetrachlorocatechol diacetate was then removed, and the filtrate was evaporated and chromatographed on silica-gel to yield 1.66 g (74%) of IVa; white solid (sublimed); mp 90—91 °C; UV λ_{max}^{EtOH} (ε): 271 (430) and 280(355) nm; NMR ($CDCl_3$): δ 2.20(s, 3H), 2.23(m, 2H), 2.25(s, 6H), 3.82(m, 1H), 3.95(m, 1H), 6.48(s, 1H), and 6.73(m, 2H); IR (KBr): 3000, 2930, and 1770 cm^{-1}. Found: C, 70.58; H, 5.97%. Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92%.

(b) A solution of *o*-chloranil (400 mg) in THF (10 ml) was added to a mixture of Ia (200 mg) and cyclopentadiene (0.2 ml) in THF (10 ml) at −78 °C. After the evaporation of the solvent, the residue was treated as has been described in *(a)*.

(c) At room temperature, a solution of *o*-chloranil (600 mg) in THF was added to a mixture of Ia (300 mg) and cyclopentadiene (1 ml) in THF. After 5 hr stirring and the removal of the solvent, the residue was treated with acetic anhydride–pyridine to yield 544 mg of IVa (75%).

(d) A solution of cerium(IV) sulfate (1.27 g) in 20% aqueous sulfuric acid (20 ml) was added to a mixture of Ia (200 mg) and cyclopentadiene (1 ml) in THF (20 ml) under nitrogen at −5 °C. After having been stirred overnight at room temperature, the mixture was extracted with ethyl acetate, washed, dried, and treated with acetic anhydride–pyridine to give 179 mg of IVa (37%).

(e) An aqueous solution of hydrochloric acid(2 M, 2 ml) was added to a solution of Ia (300 mg) and cyclopentadiene (1 ml) in THF (30 ml), a solution of *o*-chloranil (600 mg) was then dropped into the mixture at room temperature, and the mixture was stirred for 5 hr. The yield was 483 mg (66.5%).

3-(5,6-Diacetoxy-1,4-dihydro-1,4-methanonaphthyl-8-)propionic Acid(IVb). Dihydrocaffeic acid (500 mg) gave 508 mg (56%) of IVb by the method (*b*) described in the preceding section; white needles from benzene; mp 131—132 °C; UV λ_{max}^{EtOH} (ε): 273(800) and 280(760) nm; NMR($CDCl_3$): δ 2.23(s, 3H), 2.25(m, 2H), 2.27(s, 3H), 2.4—3.0(m, 4H), 3.83(m, 1H), 4.02(m, 1H), 6.55(s, 1H), 6.75(m, 2H), and 7.77 (broad s, 1H, D_2O exchangeable); IR (KBr): 3200—3500, 1765, and 1700 cm^{-1}. Found: C, 65.39; H, 5.57%. Calcd for $C_{18}H_{18}O_6$: C, 65.44; H, 5.49%.

N-Acetyl-2-(5,6-diacetoxy-1,4-dihydro-1,4-methanonaphthyl-8-)ethylamine(IVc). Dopamine hydrobromide(Ic, 500 mg) gave 304 mg (42%) of IVc by the (*c*) method except that methanol was used instead of THF; glassy solid; NMR ($CDCl_3$): δ 1.90(s, 3H), 2.25, 2.30(s, 3H×2, and 2H), 2.75 (t, J=7 Hz, 2H), 3.28(t, J=7 Hz, 2H), 3.85(m, 1H), 4.00 (m, 1H), 6.30(broad m, 1H, D_2O exchangeable), 6.50 (s, 1H), and 6.75(m, 2H); IR (KBr): 3400, 3300, 2950, 1770, and 1650 cm^{-1}.

The N-Acetyl-2-(5,6-diacetoxy-1,4-dihydro-1,4-methanonaphthyl-8-)-L-alanine Methyl Ester(IVd) from DOPA methyl Ester. DOPA methyl ester hydrochloride (Id, 1.00 g) gave 668 mg (41%) of IVd by the (*c*) method; glassy solid; NMR ($CDCl_3$): δ 1.77(s, 3H), 2.24 2.29(s, 3H×2, and 2H), 3.10(d, J=7 Hz, 2H), 3.68(s, 3H), 3.83(m, 1H), 3.97(m, 1H), 4.83(q, J=7 Hz, 1H), 6.23(broad d, J=7 Hz, D_2O exchangeable), 6.45(s, 1H), and 6.75(m, 2H).

N-Acetyl-2-(5,6-diacetoxy-1,4-dihydro-1,4-methanonaphthyl-8-)L-alanine Methyl Ester(IVd) from DOPA. DOPA (Ie, 500 mg) was dissolved in hydrochloric acid (2M, 2 ml) and diluted to 30 ml with THF, to this mixture a solution of *o*-chloranil (625 mg) in THF was then added under nitrogen at room temperature, followed by the addition of cyclopentadiene (2 ml). After stirring for 2 hr, the solvent was removed and the residue was placed in a mixture of methanol (20 ml), acetic anhydride (130 ml), and pyridine (20 ml). The mixture was heated with stirring at 90—100 °C for 1 hr. Then the solvent was removed, and precipitates of tetrachlorocatechol diacetate were separated by filtration. Ethyl acetate was added to the filtrate, which was then washed with water, dried over anhydrous sodium sulfate, and evaporated to afford a residue which was subsequently purified by column chromatography on silica-gel, and eluted by ethyl acetate–benzene. The yield was 140 mg (14%) of IVd.

1,2,3,4-Tetrahydro-8-methyl-1,4-methanonaphthalene-5,6-diol Diacetate(Va). The catalytic hydrogenation of IVa with platinum oxide in acetic acid gave Va quantitatively as colorless prisms from cyclohexane; mp 99—100 °C; UV λ_{max}^{EtOH} (ε): 266(290) and 273(250) nm; NMR ($CDCl_3$): δ 1.0—2.0(m, 6H), 2.26(s, 3H), 2.29(s, 6H), 3.32(m, 1H), 3.43(m, 1H), and 6.67(s, 1H); IR(KBr): 2950 and 1765 cm^{-1}. Found: C, 70.11; H, 6.60%. Calcd for $C_{16}H_{18}O_4$: C, 70.05; H, 6.61%.

N-Acetyl-2-(5,6-diacetoxy-1,2,3,4-tetrahydro-1,4-methanonaphthyl-8-)-ethylamine(Vc). Colorless prisms from benzene; mp 140 °C; UV λ_{max}^{EtOH} (ε): 267(460) and 274(420) nm; ($CDCl_3$): δ 1.0—2.0(m, 6H), 1.96(s, 3H), 2.29(s, 3H), 2.31(s, 3H), 2.80(m, 2H), 3.3—3.6(m, 2H×2), 5.85(broad m, 1H, D_2O exchangeable), and 6.71(s, 1H); IR (KBr): 3250, 3070, 2960, 1770, and 1640 cm^{-1}. Found: C, 66.32; H, 6.63; N, 4.13%. Calcd for $C_{19}H_{23}O_5N$: C, 66.07; H, 6.71; N, 4.06%.

The N-Acetyl-2-(5,6-diacetoxy-1,2,3,4-tetrahydro-1,4-methanonaphthyl-8-)-L-alanine Methyl Ester(Vd). Glassy solid; UV λ_{max}^{EtOH}: 267 and 274 nm; NMR ($CDCl_3$): δ 1.0—2.0(m, 6H), 1.97(s, 3H), 2.23(s, 3H), 2.28(s, 3H), 3.06(d, J=7 Hz, 2H), 3.46(m, 2H), 3.67(s, 3H), 4.81(broad q, J=7 Hz, 1H), 6.30(broad d, J=7 Hz, 1H, D_2O exchangeable), and 6.60(s, 1H); IR (KBr): 3400, 3300, 2970, 1770, 1750, and 1660 cm^{-1}; MS: *m/e* 403 (M^+).

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