Dopaquinone and Related Compounds: Reactions with *o*-Phenylenediamine

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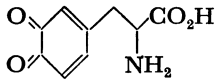
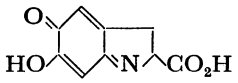
The oxidation of 4-substituted catechols including DOPA with *o*-chloranil or cerium(IV) sulfate to give the corresponding *o*-benzoquinones was examined. The trapping of *o*-benzoquinones with *o*-phenylenediamine immediately after oxidation was successfully used to isolate 2-substituted phenazines, the substituents being $-CH_3$, $-CH(CH_3)_2$, $-(CH_2)_2CO_2H$, $-(CH_2)_2CO_2CH_3$, $-CH{=}CHCO_2H$, $-CH{=}CHCO_2CH_3$, $-(CH_2)_2NHCOC_6H_5$, and $-CH_2CH(NHCOC_6H_5)CO_2CH_3$. Dopaquinone was identified in a protected form.

Raper[1] suggested the intermediacy of dopaquinone (I) in the melanogenesis of DOPA, and later Bu'Lock and Harley-Mason[2] reported the formation of dopachrome (II) based on the ultraviolet absorption spectrum. These intermediates are very unstable and have never been synthesized or trapped in spite of many reports on *o*-benzoquinones.[3-5]



I



II

Recently Horspool *et al.* have shown that 4-substituted *o*-benzoquinones react with arylamines at the 4- and 5-positions.[6] Also, it is known that dopamine or 5-hydroxydopamine is easily cyclized into the corresponding indoline derivative by mild oxidation. Thus, it was of interest to synthesize and trap dopaquinone or dopachrome. This paper will be concerned with the synthesis of dopaquinone and related compounds in neutral or acidic media as well as with their reactions with *o*-phenylenediamine.

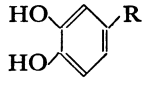
Results and Discussion

UV Spectral Studies. The oxidation of DOPA and related catechols were examined by means of the UV spectrum. Several oxidants are known to convert catechols to the corresponding *o*-benzoquinones: *e.g.*, *o*-chloranil,[3a] silver oxide,[7] cerium(IV) sulfate,[8] and potassium nitrosodisulfonate,[4a] among which *o*-chloranil is the best for the UV spectral studies. Equimolar solution of catechol and *o*-chloranil in ethanol were mixed, and the absorbance of the mixture was measured. The absorption maxima of the mixtures indicate that, in the case of catechols with no free amino group, the absorption of the corresponding quinone appears between 380—390 nm (Table 1). The absorbance of tetrachlorocatechol at 300 nm increased, while those of *o*-chloranil at 350 and 410 nm and catechol at 280 nm decreased. The isosbestic points were observed near 290 and 380 nm.

TABLE 1. THE ABSORPTION MAXIMA OF THE REACTION PRODUCTS OF 4-SUBSTITUTED CATECHOLS (IIIa—IIIh) WITH *o*-CHLORANIL

	λ_{max} (nm)		λ_{max} (nm)
IIIa	370	IIIe	385
IIIb	380	IIIf	384
IIIc	385	IIIg	—
IIId	386	IIIh	—

The final concentration of a substrate was 5×10^{-4} mol/l.



III

R

a : H
b : CH_3
c : $C(CH_3)_3$
d : $CH(CH_3)_2$
e : $(CH_2)_2CO_2H$
f : $(CH_2)_2NHCOC_6H_5$
g : $(CH_2)_2NH_2$
h : $CH_2CH(NH_2)CO_2H$

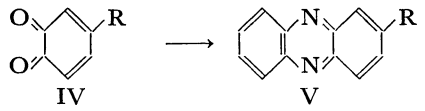
In the case of catechols with a free amino group, however, no absorption of *o*-benzoquinone appeared near 390 nm, while the absorptions at 350 and 410 nm of *o*-chloranil disappeared. These facts suggest that the oxidation by *o*-chloranil did not yield the corresponding *o*-benzoquinone. Dopamine (IIIg) did not show any absorption of *o*-benzoquinone after oxidation, but after 20 hr it showed an absorption at 470 nm which is similar to that of dopachrome.[9] DOPA (IIIh) itself did not show any absorption at 470—500 nm under similar oxidation conditions. Considering that dihydrocaffeic acid (IIIe), a desamino DOPA, gave a typical quinoid spectrum on oxidation, it could be concluded that a carboxyl group of DOPA has no relation to the instability of dopaquinone, but that an amino group contributes toward the cyclization of dopaquinone into an indoline derivative or an unidentified product.

Oxidation of 4-Substituted Catechols to o-*Benzoquinone.* 4-Isopropylcatechol (IIId), as a model compound of DOPA, was oxidized by *o*-chloranil according to the method which Horner *et al.*[3a] used in the oxidation of homocatechol, but 4-isopropyl-*o*-benzoquinone was an oily product and could not be obtained in a pure state. Therefore, cerium(IV) sulfate[8] was used as the oxidant. The acidic media are favorable for the stability of the quinone produced. The *o*-benzoquinone was obtained as a dark red oil which showed UV absorption band at 390 and 540 nm and an NMR spectrum characteristic of 4-substituted *o*-benzoquinone ring[10] (see Experimental), but an attempt at purification was unsuccessful. Therefore, it became necessary to trap such an unstable *o*-benzoquinone as a stable crystalline compound.

Reaction of o-*Benzoquinones with* o-*Phenylenediamine.* One of the most common methods of trapping *o*-benzoquinones is the reaction with *o*-phenylenediamine to give a phenazine derivative.[3a] On the other hand, Horspool *et al.*[6] have pointed out the possibility of substitution on the 4- or 5-position of *o*-benzoquinone upon treatment with arylamine. However, when the oily 4-isopropyl-*o*-benzoquinone was treated with *o*-phenylenediamine, 2-isopropylphenazine(Vb) was obtained in a 53% yield as yellow needles (Table 2).

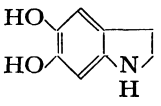
TABLE 2. PHENAZINES (V) DERIVED FROM 4-SUBSTITUTED *o*-BENZOQUINONES (IV)

Phenazines	R	Yield%	mp °C
Va	CH_3	76	116—116.5
Vb	$CH(CH_3)_2$	53	90— 91
Vc	$(CH_2)_2CO_2H$	67	186—188 (dec)
Vd	$(CH_2)_2CO_2CH_3$	44	92— 93
Ve	$CH{=}CHCO_2H$	12	257—258 (dec)
Vf	$CH{=}CHCO_2CH_3$	13	152—153
Vg	$(CH_2)_2NHCOC_6H_5$	37	171—172
Vh	$CH_2CHCO_2CH_3$ $NHCOC_6H_5$	31	211—212

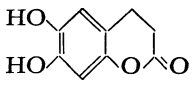


IV V

The quinones (IVc and IVd) from dihydrocaffeic acid and its methyl ester were also oily substances, but their corresponding phenazines (Vc and Vd) were crystals. The quinone from dihydrocaffeic acid is an isomer of a catechol (VII),[11] just as VI is a formal isomer of the unisolable dopamine quinone. However, the presence of these compounds could not be detected among the oxidation products. The quinone from caffeic acid was very unstable and could not be identified even by the NMR spectrum, but the trapping of this quinone to give the phenazine derivative (Vf) was successful. As is shown in Table 2, the method of trapping unstable *o*-benzoquinone by *o*-phenylenediamine is useful for the identification of dopaquinone related compound.



VI



VII

Finally, DOPA was protected by methylation and benzoylation and then oxidized by cerium(IV) sulfate to give a dark red oil showing the UV and NMR spectra characteristic of 4-substituted *o*-benzoquinone, which was then converted into the crystalline phenazine derivative.

Experimental

Oxidation of 4-Isopropylcatechol (IIId). To a solution of IIId (137 mg) in chloroform (7 ml), we poured an ice-cooled solution of cerium(IV) sulfate (aq. 734 mg) in 20% sulfuric acid (13 ml), after which the mixture was stirred for 5 min. Then a solution of cerium(IV) sulfate (aq. 73.4 mg) in 20% sulfuric acid (2 ml) was added and the mixture was stirred for 1 min. The organic layer was washed three times with 0.01 M sulfuric acid, dried over anhydrous sodium sulfate, and then concentrated to give a red oil.

UV $\lambda_{max}^{CHCl_3}$: 390 and 580 nm; NMR ($CDCl_3$): δ 1.23 (d, J=7 Hz, 6H), 2.65 (septet, J=7 Hz, 1H), 6.2 (broad s, 1H), 6.4 (d, J=11 Hz, 1H), and 7.0 (dd, J=11 and 2 Hz, 1H); IR (film): 2940, 1735, 1680, 1665, 1280, 815, and 755 cm^{-1}.

Found: C, 71.40; H, 6.77%. Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71%. R_f: 0.705(*n*-butyl acetate-heptane 1 : 1, DMF impregnated paper.[12]

Oxidation of N-Benzoyl DOPA Methyl Ester (IIIi). To a solution of IIIi (60 mg) in methanol-ethyl acetate (1 : 5) we added an ice-cooled solution of cerium(IV) sulfate (170 mg) in 20% sulfuric acid (4 ml) after which the mixture was vigorously stirred for 1 min. Then a solution of cerium(IV) sulfate (2 mg) in sulfuric acid was added to complete the reaction. The organic layer was washed three times with dilute sulfuric acid, dried over anhydrous sodium sulfate, and then concentrated to afford a dark red oil.

UV $\lambda_{max}^{CHCl_3}$: 386 and 580 nm; NMR ($CDCl_3$): δ 3.0 (broad d, J=7 Hz, 2H), 5.0 (broad t, J=7 Hz, 1H), 6.2 (broad s, 1H), 6.3 (d, J=10 Hz, 1H), and 7.0 (dd, J=10 and 2 Hz, 1H).

Phenazines. A typical example is shown below in the case of 2-methylphenazine.

2-Methylphenazine (IV).[13] A solution of 4-methylcatechol (IIIb) (170 mg) in chloroform was mixed with a solution of cerium(IV) sulfate in 20% sulfuric acid and stirred for 1 min. The organic layer was washed, dried and transferred into an ethereal solution of *o*-phenylenediamine with stirring at room temperature. After the mixture had stood for six days, the ether was distilled off and a mixture of acetic anhydride and pyridine (1 : 1, v/v) was added to the residue. After standing overnight, the reaction mixture was heated *in vacuo* to remove the acetic anhydride and pyridine. The residue was purified by column chromatography(benzene-ethyl acetate 5 : 1, silica gel) to give a yellow powder, which was recrystallized from ethanol to give yellow needles; 161 mg (76%), mp 116—116.5 °C (lit,[4] 117 °C).

2-Isopropylphenazine (Vb). 4-Isopropylcatechol (IIId) (150 mg) gave 115 mg (54%) of Vb; yellow needles, mp 90—91 °C; UV λ_{max}^{MeOH} (ε): 252 (124000) and 365 nm (13800); NMR ($CDCl_3$): δ 1.43 (d, J=7 Hz, 6H), 3.20 (septet, J=7 Hz, 1H), and 7.6—8.3 (m, 7H); IR (KBr): 1643, 1512, 1370, 835, and 758 cm^{-1}. Found: C, 81.22; H, 6.41; N, 12.55%. Calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60%.

3-(2-Phenazinyl)propionic Acid (Vc). Dihydrocaffeic acid (IIIe) (364 mg) gave 338 mg (67%) of Vc; yellow prisms, mp 186—188 °C (dec): UV λ_{max}^{MeOH} (ε): 254 (124000) and 363 nm (15300); NMR (CF_3CO_2H): δ 3.16 (t, J=7 Hz, 2H), 3.50 (t, J=7 Hz, 2H), and 8.2—8.8 (m, 7H); IR (KBr): 1720, 1640, 825, and 775 cm^{-1}. Found: C, 71.19; H, 4.90; N, 11.08%. Calcd for $C_{15}H_{12}N_2O_2$: C, 71.41; G, 4.80; N, 11.11%.

Methyl 3-(1-Phenazinyl)propionate (Vd). The methyl ester of dihydrocaffeic acid (392 mg) gave 235 mg (44%) of Vd; yellow sticks, mp 92—93 °C; UV λ_{max}^{EtOH} (ε): 253 (143000) and 364 nm (20500); NMR ($CDCl_3$): δ 2.81 (t, J=7 Hz, 2H), 3.24 (t, J=7 Hz, 2H), 3.69 (s, 3H), and 7.5—8.3 (m, 7H): IR (KBr): 1740, 1640, 840, and 760 cm^{-1}. Found: C, 71.94; H, 5.23; N, 10.52%. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52%.

3-(2-Phenazinyl)-2-propenoic Acid (Ve). Caffeic acid (900 mg) gave 150 mg (12%) of Ve; dark yellow needles, mp 257—258 °C (dec); UV λ_{max}^{MeOH} (ε): 238 (21000), 282 (62000), 358 (7200), 380 (11000), and 395 nm (13000); NMR (CF_3CO_2H): δ 7.04 (d, J=15.6 Hz, 1H), 8.03 (d, J=15.6 Hz, 1H), and 8.3—8.8 (m, 7H); IR (KBr): 1690, 1620, 1290, 820, and 740 cm^{-1}. Found: C, 70.80; H, 4.06; N, 11.08%. Calcd for $C_{15}H_{10}N_2O_2$: C, 70.26; H, 4.03; N, 11.20%.

Methyl 3-(2-Phenazinyl)-2-propenoate (Vf). The methyl ester caffeic acid (388 mg) gave 68 mg (13%) of Vf; yellow needles, mp 152—154 °C; UV λ_{max}^{EtOH} (ε): 238 (19900) 285 (83500), 377 (16900), and 395 nm (15500); NMR

($CDCl_3$): δ 3.82 (s, 3H), 6.57 (d, J=16 Hz, 1H), and 7.6—8.3 (m, 8H); IR (KBr): 1725, 1630, 1312, 1290, 820, and 750 cm^{-1}. Found: C, 72.20; H, 4.60; N, 10.55%. Calcd for $C_{16}H_{12}N_2O_2$: C, 72.71; H, 4.58; N, 10.60%.

N-Benzoyl-3-(2-phenazinyl)ethylamine (Vg). *N*-Benzoyldopamine (IIIf) (376 mg) gave 178 mg (37%) of Vg; yellow needles, mp 171—172 °C; UV λ_{max}^{MeOH} (ε): 253 (107000) and 365 nm (13400); NMR ($CDCl_3$): δ 3.17 (t, J=7 Hz, 2H), 3.85 (q, J=7 Hz, 2H), 6.60 (broad s, 1H), and 7.2—83. (m, 12H); IR (KBr): 3320, 1640, 1550, 820, and 750 cm^{-1}. Found: C, 76.80; H, 5.25;N, 13.03%. Calcd for $C_{21}H_{17}N_3O$: C, 77.04; H, 5.23; N, 12.84%.

Methyl 3-(2-Phenazinyl)-2-benzoylaminopropionate (Vh). The methyl ester of N-benzoyldopa (IIIi) (100 mg) gave 38 mg (31%) of Vh; yellow needles, mp 211—212 °C; UV λ_{max}^{EtOH} (ε): 225 (25500), 254 (127000), and 363 nm (16800); IR(KBr): 3270, 1745, 1640, 815, and 760 cm^{-1}. Found: C, 71.83; H, 5.09; N, 11.16%. Calcd for $C_{23}H_{19}N_3O_3$: C, 71.67; H, 4.97; N, 10.90%.

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13) Preparations of 2-substituted phenazines have been reported; Vb was synthesized by heating catechol with *o*-phenylenediamine in the presence of metallic oxides,[a] while Vc, Ve, and Vf were prepared from 2-phenazinecarboxaldehyde and malonic acid.[b] However, these methods are different from ours and the analytical details have not been described in these reports. a) Shell International Research Maatschappij N. V. Neth. appl. 6511395, March 4, 1965 [*Chem. Abstr.*, **66**, 2279e (1966)]. b) Yu. S. Rozum, *Ukrain. Khim. Zhur.*, **33**, 776 (1956) [*Chem. Abstr.*, **51**, 8762 (1957)].