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A REVISED STRUCTURE FOR RHINACANTHONE

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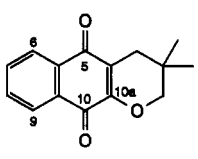
ABSTRACT.—Rhinacanthone [**2**], formerly regarded as a pyrano-1,4-naphthoquinone, has been shown to be an *o*-quinone on the basis of its uv-vis, ir, and COLOC nmr spectra, and the revised structure has been confirmed by X-ray crystallographic analysis. The isomeric *p*-quinone itself was also prepared, and its spectral properties and bioactivity were compared with those of rhinacanthone [**2**].

In 1991 an antifungal quinone (now named rhinacanthone) was isolated from the shrub *Rhinacanthus nasutus* Kuntze (Acanthaceae) and identified as **1** on the basis of spectroscopic evidence (1,2) and synthesis (3). Structure **1** is inconsistent with its visible (λ max 429 nm) and ir ($\nu_{C=O}$ 1698 and 1647 cm^{-1}) spectra, which closely resemble those of β-lapachone [**3**], which led us to re-examine the structure of rhinacanthone.

Rhinacanthone was converted into a yellow diol [**4**] by heating with aqueous NaOH (4). Following the procedures of Cassis *et al.* (5), treatment of **4** with dilute HBr at room temperature regenerated the orange quinone rhinacanthone whereas heating in dilute H_2SO_4 under reflux transformed **4** into an isomeric yellow quinone. Comparison of their uv-vis and ir spectra with those of authentic pyranonaphthoquinones (6,7) clearly indicated that the yellow quinone was a *p*-quinone similar to α-lapachone, while rhinacanthone was the isomeric *o*-quinone analogous to β-lapachone [**3**].



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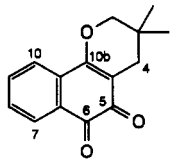

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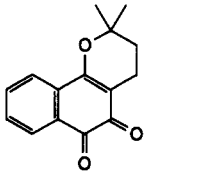

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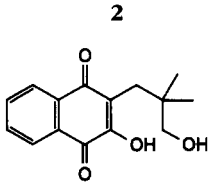

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These assignments were supported by some informative correlations in the COLOC nmr spectrum of each quinone. Rhinacanthone [**2**] showed correlations between H-10 and C-10b (δ 162.1, enolic carbon), H-4 and C-5 (δ 179.1), and H-7 and C-6 (δ 179.7), reflecting its *o*-quinone structure. On the other hand, the yellow quinone **1** had correlations between H-6 and C-5, and H-9 and C-10. Moreover, the enolic carbon C-10a (δ 154.3) of **1** had no correlation with any of the aromatic protons. It follows that this quinone must be represented by the structure **1**, and rhinacanthone by the *o*-quinone structure **2**. The results of X-ray structure analysis (Table 1 and Figure 1) confirmed this conclusion in all respects.

The 1991 synthesis (3) actually produced **2**, and not **1** as was supposed. In the last step, treatment of a mixture of **5** and **6** in the presence of *p*-toluenesulfonic acid, with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) would produce **7** and then **1**, as was expected, but under the acidic reaction conditions the latter evidently rearranged to the *o*-quinone **2** (4,6,7) (Figure 2).

Finally, comparison of the antifungal activities of **1** and **2** was carried out in the same manner as reported (1,2) by observing their inhibitory effects on the spore germination of *Pyricularia oryzae*,

TABLE 1. Coordinates ($\times 10^4$) and U_{eq} ($\times 10^3$) for Non-Hydrogen Atoms of Rhinacanthone [**2**] (with e.s.d.s. in parentheses).

Atom	*x/a*	*y/b*	*z/c*	U_{eq}*
O-1	1296 (3)	1768 (7)	4245 (3)	68 (2)
O-2	1153 (4)	−128 (8)	3058 (3)	73 (2)
O-3	4337 (3)	1554 (6)	4011 (2)	41 (1)
C-1	1955 (5)	1329 (9)	3937 (4)	47 (2)
C-2	1870 (5)	246 (10)	3265 (4)	52 (3)
C-3	2671 (4)	−285 (10)	2903 (4)	46 (2)
C-4	2639 (6)	−1318 (10)	2311 (4)	59 (3)
C-5	3374 (6)	−1872 (11)	1984 (4)	65 (3)
C-6	4168 (6)	−1359 (9)	2234 (4)	53 (3)
C-7	4223 (4)	−339 (9)	2825 (4)	42 (2)
C-8	3479 (4)	195 (8)	3168 (4)	36 (2)
C-9	3522 (4)	1200 (8)	3816 (4)	33 (2)
C-10	4447 (4)	2689 (9)	4598 (4)	42 (2)
C-11	3805 (4)	2417 (9)	5217 (4)	38 (2)
C-12	2898 (4)	2595 (9)	4896 (4)	45 (2)
C-13	2815 (4)	1725 (8)	4197 (4)	35 (2)
C-14	3963 (6)	3690 (10)	5786 (4)	62 (3)
C-15	3925 (5)	752 (9)	5532 (4)	49 (2)

*U_{eq} defined as one third of the trace of the orthogonalized U_{ij} tensor.

the pathogen of rice blast disease. Rhinacanthone [**2**] showed a 100% inhibitory effect at 10 ppm, while the *p*-quinone **1** had no effect, even at 1,000 ppm.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Ir spectra were measured as KBr discs on a Jasco Ft/IR-500 spectrometer. ^{1}H- (500 MHz) and ^{13}C- (125 MHz) nmr spectra were recorded with TMS as internal standard in $CDCl_3$ on a JEOL JNM-A500 spectrometer. Mass spectra (70 eV) were measured on a Shimadzu GCMS 9020-DF spectrometer. Uv-vis spectra were taken on a Jasco Ubest-50 spectrometer.

2-HYDROXY-3-(3-HYDROXY-2,2-DIMETHYLPROPYL)-1,4-NAPHTHOQUINONE [**4**].—A mixture of **2** (4.00 g, 16.5 mmol) and 1% aqueous NaOH (100 ml, 25.0 mmol) was stirred and heated under reflux for 1.5 h. The reaction mixture was cooled to room temperature, neutralized with AcOH (1.43 ml, 25.0 mmol) and filtered. The filter cake was washed with H_2O and dried *in vacuo* to give 4.12 g (96%) of **4** as a yellow solid. Recrystallization from hexane/EtOAc afforded pure **4** as yellow microcrystals, mp 143–145°; ir ν max 3420, 1675, 1630, 1595, 1360 cm^{-1}; ^{1}H nmr δ 0.98 (6H, s), 2.62 (2H, s), 3.11 (2H, br d, J=6.4 Hz), 3.56 (1H, br t, J=6.4 Hz, OH), 7.63 (1H, br s, OH), 7.72 (1H, br t, J=1.5 and 7.5 Hz), 7.78 (1H, dt, J=1.5 and 7.5 Hz), 8.11 (1H, dd, J=1.5 and 7.5 Hz), 8.15 (1H, dd, J=1.5 and 7.5 Hz); ^{13}C nmr δ 25.2

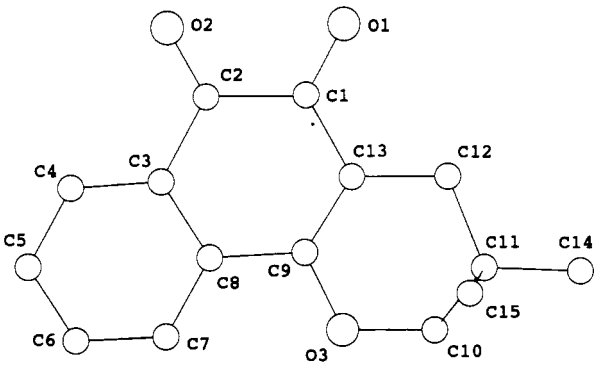

FIGURE 1. Perspective view of rhinacanthone [**2**] showing the crystallographic atom numbering scheme.

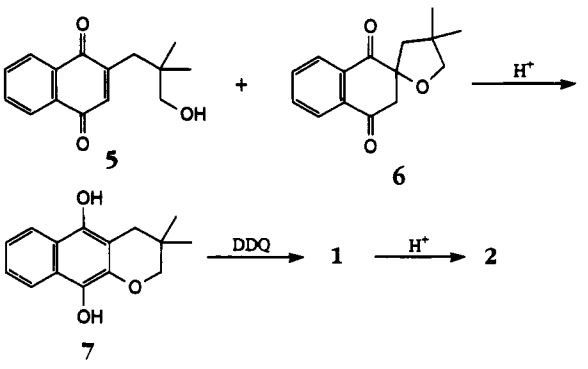

FIGURE 2. Possible pathway for the formation of **2**.

(two carbons), 30.7, 38.6, 69.9, 121.9, 126.3, 127.3, 129.4, 132.8, 133.3, 135.1, 155.0, 180.9, 186.4; hreims *m/z* 260.1042 ($C_{15}H_{16}O_4$ requires 260.1048).

3,4-DIHYDRO-3,3-DIMETHYL-2H-NAPHTHO-[2,3-B]PYRAN-5,10-DIONE [**1**].—A mixture of **4** (0.300 g, 1.15 mmol) and 20% aqueous H_2SO_4 (300 ml) was stirred and heated under reflux. After 6 h, the mixture was diluted with H_2O and extracted with Et_2O. The Et_2O solution was washed with saturated aqueous $NaHCO_3$, H_2O, and brine, then dried ($MgSO_4$), and concentrated *in vacuo*. The residue was recrystallized from hexane/EtOAc to give 0.210 g (75%) of **1** as bright-yellow needles, mp 150.5–152.0°; ir ν max 1680, 1640, 1615, 1595, 1575 cm^{-1}; ^1H nmr δ 1.07 (6H, s), 2.40 (2H, s), 3.90 (2H, s), 7.68 (1H, dt, J=2.0 and 7.5 Hz), 7.71 (1H, dt, J=2.0 and 7.5 Hz), 8.08 (1H, dd, J=2.0 and 7.5 Hz), 8.11 (1H, dd, J=2.0 and 7.5 Hz); ^{13}C nmr δ 24.9 (two carbons), 27.8, 32.4, 76.4, 120.9, 126.0, 126.2, 130.9, 132.1, 133.0, 133.9, 154.3, 179.4, 184.4; uv λ max (MeOH) (log ϵ) 250 (4.40), 280 (4.16), 332 (3.52) nm; hreims *m/z* 242.0938 ($C_{15}H_{14}O_3$ requires 242.0942).

3,4-DIHYDRO-3,3-DIMETHYL-2H-NAPHTHO-[1,2-B]PYRAN-5,6-DIONE, RHINACANTHONE [**2**].—A mixture of **4** (0.200 g) and 32% aqueous HBr (20 ml) was stirred at room temperature for 6 h. The mixture was worked up in the same manner as described for **1** to give 0.179 g (96%) of **2** as orange needles, mp 151.5–152.0°; ir ν max 1700, 1645, 1605, 1570, 1520, 1390, 1370, 1300, 1230 cm^{-1}; ^1H nmr δ 1.08 (6H, s), 2.34 (2H, s), 3.98 (2H, s), 7.51 (1H, dt, J=1.5 and 7.5 Hz), 7.66 (1H, dt, J=1.5 and 7.5 Hz), 7.81 (1H, dd, J=1.5 and 7.5 Hz), 8.06 (1H, dd, J=1.5 and 7.5 Hz); ^{13}C nmr δ 24.7 (two carbons), 27.9, 31.9, 77.1, 113.2, 124.0, 128.6, 129.8, 130.6, 131.8, 134.8, 161.9, 178.9, 179.5; uv-vis λ max (MeOH) (log ϵ) 255 (4.45), 262 (4.39, sh), 279 (3.95), 333 (3.44), 429 (3.43) nm; hreims *m/z* 242.0950 ($C_{15}H_{14}O_3$ requires 242.0942). These spectral data are virtually identical with those of natural rhinacanthone.

X-RAY DIFFRACTION ANALYSIS OF **2**[1].—Crystal data: $C_{15}H_{14}O_3$, mol wt 242.28, orthorhombic, space group Pbca, a=15.413(5), b=8.463(4), c=18.385(10) Å (from 14 random oriented reflections), V=2398(2) Å^3, Z=8, F(000)=1024, D_c=1.342 g/cm^3, MoKα radiation (λ=0.71069 Å), μ=0.09 mm^{-1}. Crystal dimensions 0.9×0.3×0.14 mm. A total of 2451 reflections with $0 \leq h \leq 18$, $0 \leq k \leq 10$, $0 \leq 1 \leq 21$, $2\theta \leq 50°$ was recorded using a Nicolet P3 diffractometer (θ/2θ scan). Two standard reflections measured after every fifty reflections showed no significant variation. A total of 881 reflections with $F > 4\sigma(F)$ was retained for solving and refining the structure, and corrected for Lorentz and polarization effects. The structure was solved by direct methods. Non-hydrogen atoms were refined anisotropically by full-matrix least squares, minimizing $\Sigma w(F_o - F_c)^2$, with $w^{-1} = \sigma^2(F) + 0.001928F^2$. Hydrogen atoms were placed in calculated positions with C-H=0.95 Å and refined riding upon the C to which they were attached with separate group Uiso for methyl, methylene, and aryl hydrogen. Final residuals are: R=0.072, R_w=0.074, GOF=1.57, $|\Delta\rho| < 0.27$ e/Å^3. All computations were performed on the SUN SPARCserver (UNIX operating system) of the Computing Centre of the University of Aberdeen. Structure solution and refinement software: SHELXS86 (8) and SHELX76 (9). PLOTAID (10) was used to prepare Figure 1. Final non-hydrogen atomic coordinates are included in Table 1.

[1]Hydrogen coordinates, thermal parameters, and bond distances and angles have been deposited with the Cambridge Crystallographic Data Centre and can be obtained on request from Dr. Olga Kennard, University Chemical Laboratory, 12 Union Road, Cambridge CB2 1EZ, UK.

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