Reaction of 2-Hydroxy-1,4-naphthoquinone with Aldehydes. Synthesis of 2-Hydroxy-3-alk-1-enylnaphthoquinones

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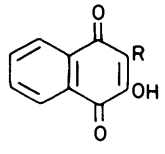
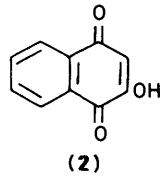
In the course of an unsuccessful attempt to prepare 2-(3,7-dimethylocta-1,6-dienyl)-3-hydroxy-1,4-naphthoquinone (**1a**) by acid catalyzed condensation of 2-hydroxy-1,4-naphthoquinone (**2**) with citronellal, a tetracyclic quinone (**3**) was obtained. This quinone was different from the two tetracyclic quinones, (**4**) and (**5**), previously obtained from a triethylamine catalyzed reaction. The quinone (**1a**) is shown to be an intermediate in the formation of (**4**) and (**5**). By adjusting the conditions (**1a**) can be isolated in a reasonable yield. Other 2-hydroxy-3-alk-1-enylnaphthoquinones are prepared similarly in variable yields. Primary and secondary products of this reaction are discussed.

In screening various compounds for pesticidal properties, we have prepared a series of 2-hydroxy-3-alk-1-enylnaphthoquinones (**1**; R = various alk-1-enyl groups)[1] by HCl-catalyzed condensation of 2-hydroxy-1,4-naphthoquinone (**2**) with aldehydes, after the procedure of Hooker.[2]



(**1a–e**)

a; R = CH=CHCH(Me)CH_2CH_2CH=CMe_2
b; R = CH=CHCHMe_2
c; R = CH=CEt_2
d; R = CH=CH$(CH_2)_5$Me
e; R = cyclohex-1-enyl



(**2**)

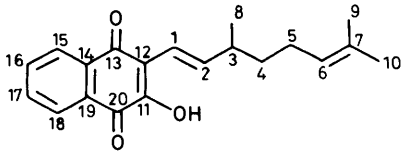
This procedure is useful for the preparation of lower homologues, but the large excess of aldehyde (*ca.* 5 equiv.) required makes product isolation difficult in the case of higher aldehydes. Furthermore, yields are consistently modest, often low. An alternative synthesis of these compounds is therefore desirable. In an attempt to synthesize (**1a**) using (+)-citronellal as the aldehyde reactant, no trace of the desired product could be detected. The reaction mixture was complex and the major quinone product isolated (38%) was the tetracyclic quinone (**3**). The presence of minor amounts of diastereoisomers of (**3**) in the mixture was indicated by g.c.–m.s.

2-Hydroxy-3-alk-1-enylnaphthoquinones are easily detected, both in solution and as t.l.c. spots, by the purple to violet colours of the anions formed upon reaction with triethylamine.

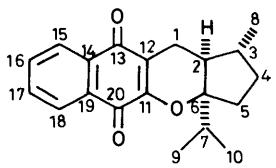
While this work was in progress, a report of the formation of the tetracyclic quinones (**4**) and (**5**) by the triethylamine catalyzed reaction of (**2**) with 1 equiv. of citronellal of unspecified chirality in refluxing toluene† was published.[3] We repeated this reaction in order to compare the products with the tetracyclic quinone (**3**). During the reaction, a transient compound giving the colour reaction expected for the hydroxyquinone (**1a**) was detected. On completion of the reaction, the mixture contained (**4**) and (**5**) and the structure and relative configuration suggested by the authors[3] was confirmed. We then tried to find conditions for optimizing the yield of (**1a**). Lowering the temperature gave a somewhat higher, but still unsatisfactory, steady-state concentration of (**1a**). More polar solvents appeared to slow down further reaction to (**4**) and (**5**), and from the reaction in refluxing acetonitrile a 20% yield of (**1a**) was obtained. A similar reaction in DMF at 40 °C gave a 28% yield accompanied by a new product (**6a**), (**4**) and (**5**) being hardly detectable.

The structures of compounds (**1a**), (**3**)—(**5**), and (**6a**) were assigned on the basis of their n.m.r. data (Tables 1 and 2). The assignment of the ^{1}H n.m.r. data was based on homodecoupling experiments, which in all cases allowed an unambiguous assignment of all the chemical shifts and coupling constants in Table 1. These data were consistent with the proposed structures and, for compounds (**4**) and (**5**), they were also in agreement with the published partial data.[3] The relative configuration of compounds (**4**) and (**5**) was easily deduced from the coupling constants $J_{1,2}$ = 11 Hz, which show that these protons are *trans* oriented. The large coupling constants $J_{3a,4}$ = 11 Hz and $J_{4,5a}$ = 12 Hz both show that the C-8 methyl group is equatorially oriented. The relative stereochemistry of carbons 2, 3, and 6 in compound (**3**) was determined from the coupling constants $J_{1e,2} = J_{1a,2} = J_{2,3}$ = 2.8 Hz. The five-membered ring must be *cis* fused to the pyran ring, *i.e.* 2-H and C-7 are *cis*, and from the small coupling constant $J_{2,3}$ it then follows that C-8 must be *cis* to C-7. The long-range couplings ($J_{1e,5e}$ = 1.8 Hz and $J_{2,4e}$ = 0.2 Hz) both agree with a 'W'-configuration and support the proposed stereochemistry. The assignment of the ^{13}C n.m.r. data in Table 2 is based on comparison with those of citronellal,[4] menthol,[4] and related naphthoquinone derivatives.[5,6] The assignment was furthermore confirmed by selective proton decoupling and 2-D heteronuclear shift correlation experiments, performed by using the pulse sequence described by Bax.[7] An example—compound (**5**)—is shown in Figures 1*a* and 1*b*, which depict the aromatic and aliphatic regions, respectively. The assignments based on this technique differ for the proton-bearing aromatic carbon atoms from those published,[5] the published data being based on comparison with model compounds and the use of shift reagents. Our assignments are based on the assumption that the proton at lowest

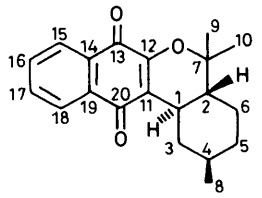
† Details of solvent communicated to us by Dr. A. V. Pinto.



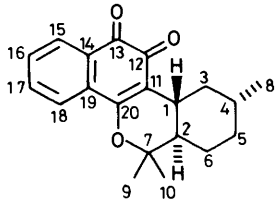
(1a)



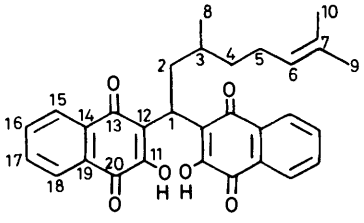
(3)



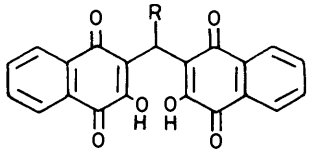
(4)



(5)



(6a)



(6b,c,f)

b; R = $CH_2CH(Me)_2$
c; R = $CH(Et)_2$
f; R = Ph

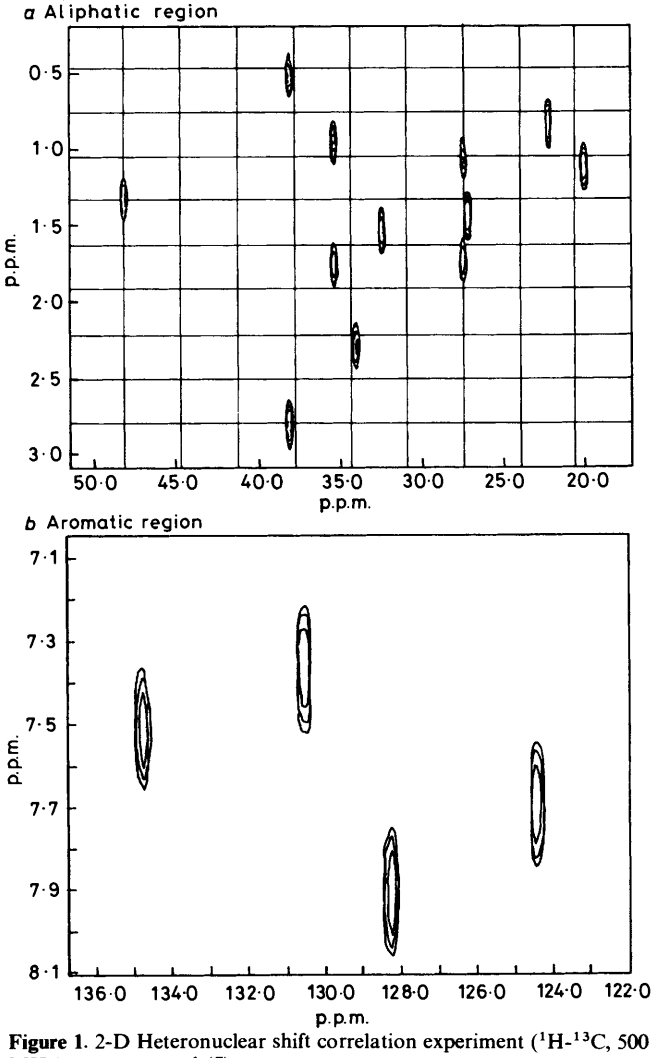


Figure 1. 2-D Heteronuclear shift correlation experiment (^1H-^{13}C, 500 MHz) on compound (**5**)

field in compounds (**1a**), (**3**), (**5**), and (**6a**) is 15-H, whereas in compound (**4**) it is 18-H.

When (**1a**) was refluxed in toluene with triethylamine for 3 h it was cleanly transformed into a mixture of (**4**) and (**5**), consistent with the assumption that (**1a**) is an intermediate in their formation.

However, when (**1a**) was subjected to the same reaction conditions as for the formation of compound (**3**), it was only partly converted into a complex mixture in which (**3**) could not be detected, either by t.l.c. or by g.c. Hence the formation of (**3**) remains unexplained.

The experience obtained in the synthesis of (**1a**) was then applied to the synthesis of analogues. The results are presented in Table 3. Although the yields are still modest and the scope limited, the requirement of only a moderate excess of aldehyde, and consequently an easier work-up, makes this a better method than the acid catalyzed reaction in several cases. Ketones fail to react with (**2**) under HCl catalysis. With triethylamine, cyclohexanone does react, although less readily than do the aldehydes, and after reflux for 5 h in DMF the cyclohexenyl quinone (**1e**) (26%) was obtained. The open chain ketone heptan-2-one was unreactive under these conditions. In most of the reactions, the major products were the triethylammonium salts of the compounds of structure (**6**) involving two molecules of (**2**).

The compounds (**6c**) and (**6f**) were isolated and characterized in their salt form since the free acids and the diacetates were difficult to purify. Compounds (**6a**) and (**6b**) were characterized as free acids. Not surprisingly, benzaldehyde, lacking α-hydrogen atoms and thus unable to form products of type (**1**), gives the triethylammonium salt of (**6f**) as the only product. In the reaction of octanal an unexpected by-product was formed to which the structure (**7**) (two possible diastereoisomers) was tentatively assigned on the basis of analytical, u.v., i.r., m.s., and (poorly resolved) n.m.r. data.

The products (**6a**—**e**) are not formed *via* (**1a**—**e**); the latter, when heated with (**2**) and triethylamine, failed to give (**6a**—**e**). Under these conditions, and especially in toluene, (**1a**—**e**) are transformed into complex mixtures of completely different compounds among which (**8**) [from (**1b**)] and (**9a**) [from (**1c**)] have

Table 1. ^{1}H N.m.r. data[a] for compounds (**1a**), (**3**)—(**5**), and (**6a**)

(**1a**)			(**3**)			(**4**)		
Proton			Proton			Proton		
1-H	6.52	$J_{1.2}$ = 16.0; $J_{1.3}$ = 1.2[b]	1a-H	1.98	$J_{1a.1e}$ = 13.2; $J_{1a.2}$ = 2.8	1-H	2.43	$J_{1.2}$ = 11.0; $J_{1.3a}$ = 11.0; $J_{1.3e}$ = 3.0
			1e-H	1.38	$J_{1e.2}$ = 2.8; $J_{1e.5e}$ = 1.8			
2-H	6.90	$J_{2.3}$ = 8,0	2-H	3.05	$J_{2.3}$ = 2.8; $J_{2.4e}$ = 0.2	2-H	1.40	$J_{2.6e}$ = 3.6; $J_{2.6a}$ = 12.0
3-H	2.31	$J_{3.4}$ = 7.0; $J_{3.8}$ = 6.7	3-H	1.94	$J_{3.8}$ = 6.8; $J_{3.4}$ = 2.0; $J_{3.4a}$ = 5.0	3a-H	0.70	$J_{3a.3e}$ = 12.5; $J_{3a.4}$ = 11.0
						3e-H	2.85	$J_{3e.4}$ = 3.0; $J_{3e.5e}$ = 1.6
4-H	1.38	$J_{4.5}$ = 7.0	4a-H	1.57	$J_{4a.4e}$ = 14.0; $J_{4a.5e}$ = 7.5; $J_{4a.5a}$ = 11.5	4-H	1.64	$J_{4.8}$ = 6.6; $J_{4.5a}$ = 12.0; $J_{4.5e}$ = 3.6
			4e-H	1.24	$J_{4e.5a}$ = $J_{4e.5e}$ = 3.5			
5-H	1.92	$J_{5.6}$ = 6.8; $J_{5.10}$ = 1.5	5a-H	1.77	$J_{5a.5e}$ = 14.0	5a-H	1.08	$J_{5a.5e}$ = 12.0; $J_{5a.6a}$ = 12.0; $J_{5a.6e}$ = 3.6
			5e-H	1.74		5e-H	1.84	$J_{5e.6a}$ = $J_{5e.6e}$ = 3.6
6-H	5.06	$J_{6.9}$ = $J_{6.10}$ = 1.5				6a-H	1.18	$J_{6a.6e}$ = 12.0
						6e-H	1.84	
			7-H	1.94	$J_{7.9}$ = $J_{7.10}$ = 6.8			
8-H	1.04		8-H	1.12		8-H	0.94	
9-H	1.63		9-H	1.06		9-H	1.51	
10-H	1.54		10-H	0.96		10-H	1.15	
15-H	8.07	$J_{15.16}$ = 7.8; $J_{15.17}$ = 1.6; $J_{15.18}$ = 0.8	15-H	8.07	$J_{15.16}$ = 7.8; $J_{15.17}$ = 1.6; $J_{15.18}$ = 0.8	15-H	8.01	$J_{15.16}$ = 7.8; $J_{15.17}$ = 1.6; $J_{15.18}$ = 0.8
16-H	7.62	$J_{16.17}$ = 7.8; $J_{16.18}$ = 1.6	16-H	7.63	$J_{16.17}$ = 7.8; $J_{16.18}$ = 1.6	16-H	7.67	$J_{16.17}$ = 7.8; $J_{16.18}$ = 1.6
17-H	7.69	$J_{17.18}$ = 7.8	17-H	7.67	$J_{17.18}$ = 7.8	17-H	7.62	$J_{17.18}$ = 7.8
18-H	8.00		18-H	8.05		18-H	8.04	
OH	7.7							

(**5**)			(**6a**)		
Proton			Proton		
1-H	2.43	$J_{1.2}$ = 11.0; $J_{1.3a}$ = 11.0; $J_{1.3e}$ = 3.0	1-H	4.93	$J_{1.2}$ = 2.3; $J_{1.2'}$ = 9.0
2-H	1.48	$J_{2.6e}$ = 3.3; $J_{2.6a}$ = 11.0	2-H	2.32	$J_{2.2'}$ = 13.8; $J_{2.3}$ = 5.3
3a-H	0.65	$J_{3a.3e}$ = 12.3; $J_{3a.4}$ = 11.0	2'-H	1.91	$J_{2'.3}$ = 7.0
3e-H	2.93	$J_{3e.4}$ = 3.0; $J_{3e.5e}$ = 1.8	3-H	1.42	
4-H	1.66	$J_{4.8}$ = 6.6; $J_{4.5a}$ = 12.0; $J_{4.5e}$ = 3.6			
			4-H	1.46	
5a-H	1.05	$J_{5a.5e}$ = 12.0; $J_{5a.6a}$ = 12.0; $J_{5a.6e}$ = 3.6	4'-H	1.20	
5e-H	1.88	$J_{5e.6a}$ = $J_{5e.6e}$ = 3.6	5-H	2.00	
6a-H	1.17	$J_{6a.6e}$ = 12.00	5'-H	1.93	
6e-H	1.84		6-H	5.04	$J_{6.5}$ = $J_{6.5'}$ = 7.0
8-H	0.96		8-H	0.95	$J_{3.8}$ = 6.5
9-H	1.58		9-H	1.58	
10-H	1.25		10-H	1.53	
15-H	8.06	$J_{15.16}$ = 7.8; $J_{15.17}$ = 1.6; $J_{15.18}$ = 0.8	15-H	8.11	$J_{15.16}$ = 7.5; $J_{15.17}$ = 1.2; $J_{15.18}$ = 0.9
16-H	7.52	$J_{16.17}$ = 7.8; $J_{16.18}$ = 1.6	16-H	7.66	$J_{16.17}$ = 7.5; $J_{16.18}$ = 1.7
17-H	7.67	$J_{17.18}$ = 7.8	17-H	7.72	$J_{17.18}$ = 7.5
18-H	7.85		18-H	8.07	
			OH	8.5	

[a] 270 MHz, $CDCl_3$, 0.02M solutions; t = 300 K. [b] J values in Hz.

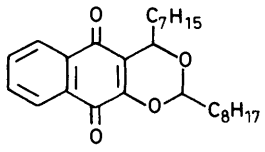
been characterized, both of them requiring redox reactions for their formation. The 1,4-quinone structure (**9a**) was preferred to the 1,2-quinone (**10a**) mainly on the basis of its orange colour, since the spectroscopic data were inconclusive. The orange colour was similar to that of the analogous compound dehydro-α-lapachone (**9b**) in contrast to the purple colour reported for the 1,2-quinone dehydro-β-lapachone (**10b**).[8,9] The formation of (**9a**) is analogous to the oxidative cyclisation of isolapachol (**1b**) to a mixture of (**9b**) and (**10b**) using DDQ as an oxidant,[9] but in the case of (**9a**), the nature of the oxidant is unknown.

Compounds of type (**6**), among these (**6a**), have previously been obtained from uncatalyzed reactions of (**2**) with aldehydes,[10] whereas substituted ammonium salts of (**6**; R = H) were isolated from the reaction of secondary amines and formaldehyde with (**2**) and are suggested to arise *via* addition of (**2**) to the intermediate (**11**; R = H).[11]

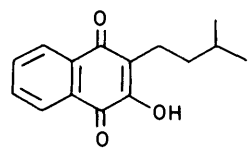
Experimental

Deuteriochloroform was used for all n.m.r. spectra (TMS as internal standard) and 96% ethanol for all u.v. spectra. I.r. spectra were recorded in KBr pellets.

Acid Catalysed Reaction of (+)-Citronellal with Hydroxynaphthoquinone (**2**): *Isolation of the Tetracyclic Quinone* (**3**).—2-Hydroxy-1,4-naphthoquinone (5.0 g, 0.029 mol) was dissolved in glacial acetic acid (100 ml) at 60 °C. (+)-Citronellal (9.0 g, 0.058 mol) was then added, followed by concentrated hydrochloric acid (30 ml). The mixture was stirred at 80 °C for 3 h, and subsequently poured onto ice. The mixture was extracted with hexane (3 × 30 ml) and the hexane phase washed, dried (Na_2SO_4) and evaporated to give a brown oil. Flash chromatography of the crude product gave a yellow solid (4.1 g), apparently a mixture of isomers judged by g.c.–m.s. Two



(7)



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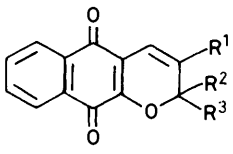
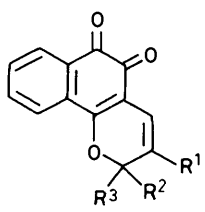


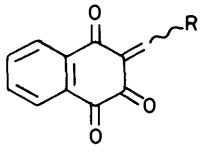
(9)

a; R^1 = Et, R^2 = H, R^3 = Me
b; R^1 = H, R^2 = R^3 = Me



(10)

a; R^1 = Et, R^2 = H, R^3 = Me
b; R^1 = H, R^2 = R^3 = Me



(11)

crystallizations from heptane gave the most abundant isomer (3.4 g, 38%), m.p. 140—141 °C (Found: C, 77.25; H, 7.15. $C_{20}H_{22}O_3$ requires C, 77.39; H, 7.15%); $\nu_{max.}$ 1 675, 1 640, 1 607, and 1 575 cm^{-1}; $\lambda_{max.}$ (log ε) 251 (4.35), 281 (4.04), 338 (3.36), and 383 (3.08) nm; *m/z* 310 (M^+, 8%) and 267 (8).

Tetracyclic quinones (**4**) *and* (**5**). The published procedure[3] was followed using toluene as solvent and (+)-citronellal (FLUKA). The isolated products were both crystallized from ethanol and heptane, successively, and had m.p. (**4**) 147—149 °C (lit.,[3] 135—136 °C); and (**5**) 166—167 °C (lit.,[3] 147—148 °C).

Triethylamine Catalysed Reactions of Aldehydes with Hydroxynaphthoquinone (**2**)

(*a*) (+)-*Citronellal.*—(*i*) *In* MeCN: *isolation of* (**1a**), (**4**), *and* (**5**). A mixture of (**2**) (11.0 g, 63 mmol), (+)-citronellal (10.0 g, 65 mmol), and triethylamine (14 g, 140 mmol) in MeCN (500 ml) was refluxed for 14 h. MeCN was then evaporated off and the residue chromatographed on silica gel with methylene chloride–hexane (1:3) as the eluant, giving, in order of elution (**1a**), (**4**), and (**5**). (**1a**), orange plates (4.0 g, 20%), m.p. 43—45 °C (from pentane) (Found: C, 76.6; H, 7.0. $C_{20}H_{22}O_3$ requires C, 77.39; H, 7.15%); $\nu_{max.}$ 3 330, 1 655, 1 630, 1 608, and 1 591 cm^{-1}; $\lambda_{max.}$ (log ε) 270 (4.47), 335sh, and 444 (3.40) nm; (**4**), yellow prisms (6.6 g, 34%), m.p. 146—148 °C; (**5**), orange needles (5.3 g, 27%), m.p. 165—166 °C.

(*ii*) *In* DMF: *isolation of* (**1a**) *and* (**6a**). A solution of (**2**) (5.2 g, 30 mmol), (+)-citronellal (5.0 g, 32 mmol), and triethylamine (12 g, 120 mmol) in DMF (20 ml) was left at 40 °C for 4 days. Diethyl ether (250 ml) was added and the ether phase was washed with 2M sulphuric acid and then with water, dried (Na_2SO_4), and evaporated. The semicrystalline residue was refluxed with ethyl acetate–hexane (1:9) (200 ml), cooled, and filtered to give bright yellow needles of (**6a**) (4.6 g, 63%), m.p. 165—167 °C (from toluene) (Found: C, 74.7; H, 5.9. $C_{30}H_{28}O_6$ requires C, 74.36; H, 5.82%); $\nu_{max.}$ 3 400, 1 660, 1 645, and 1 590 cm^{-1}; $\lambda_{max.}$ (log ε) 272 (4.62), 324 (3.59), and 421 nm (3.40); *m/z* 484 (M^+, 23%) and 310 (18). The filtrate was concentrated and chromatographed on silica gel (eluant: CH_2Cl_2–hexane, 1:3) to afford (**1a**) (2.6 g, 28%), m.p. 40—44 °C.

(*b*) *Isovaleraldehyde.*—(*i*) *In* MeCN: *isolation of* (**1b**) *and* (**6b**). A mixture of (**2**) (5.2 g, 30 mmol), isovaleraldehyde (4.0 g, 47 mmol), and triethylamine (12 g, 120 mmol) in MeCN (25 ml) was refluxed for 80 min. Diethyl ether (200 ml) was added and the solution washed once with 2M sulphuric acid and twice with water. Chromatography on silica gel (eluant: CH_2Cl_2) gave isolapachol (**1b**) (2.6 g, 36%), m.p. 123—124 °C (lit.,[12] 120 °C); δ_H (60 MHz) 1.13 (6 H, d, *J* 6.8 Hz), 2.57 (1 H, oct., *J* 6.8 Hz), 6.6 (1 H, d, *J* 17 Hz), 7.1 (1 H, dd, J_1 17, J_2 6.8 Hz), 7.6—8.3 (4 H, m), and 8.95 (1 H, s, OH); followed by (**6b**), yellow prisms (3.0 g, 48%), m.p. 169—170 °C (from aqueous ethanol) (Found: C, 72.3; H, 4.9. $C_{25}H_{20}O_6$ requires C, 72.11; H, 4.84%); $\nu_{max.}$ 3 400, 1 660, 1 645, and 1 590 cm^{-1}; $\lambda_{max.}$ (log ε) 255 (4.54), 273 (4.52), 329 (3.67), and 40 nm (3.41); δ_H (60 MHz) 0.98 (6 H, d, *J* 6 Hz), 1.6 (1 H, m), 2.11 (2 H, dd, J_1 7.5, J_2 6.5 Hz), 4.95 (1 H, t, *J* 7.5 Hz), 7.6—8.3 (8 H, m), and 8.3 (2 H, br s, OH); *m/z* 416 (M^+, 12%), 383 (8), and 359 (10).

(*ii*) *In* DMF. The procedure described for (+)-citronellal was followed, but using isovaleraldehyde (4.0 g, 47 mmol). Chromatography (CH_2Cl_2) gave isolapachol (**1b**) (2.4 g, 33%), m.p. 120—122 °C.

Table 2. ^{13}C N.m.r. data[a] for compounds (**1a**), (**3**)—(**5**), and (**6a**)

Carbon	Compd. (**1a**)	(**3**)	(**4**)	(**5**)	(**6a**)
1	117.0	23.9	34.6	34.0	31.1
2	149.4	31.1	48.2	48.1	37.3
3	38.7	37.1	38.9	38.1	31.0
4	36.9	24.3	32.8	32.4	36.9
5	25.8	29.6	35.3	35.4	25.2
6	124.3	83.9	27.6	27.5	124.8
7	131.4	31.4	81.5	82.5	131.0
8	20.2	17.5	22.3	22.3	19.5
9	25.6	17.1	27.0	27.2	25.4
10	17.6	17.0	19.4	20.1	17.5
11	151.2	157.0	123.9	116.9	154.7, 154.6
12	118.6	125.0	154.3	179.0[b]	124.1, 123.6
13	184.2	183.0	180.2	180.4[b]	185.2, 185.1
14	132.6	132.2	131.0	132.0	132.8
15	126.9	126.1[b]	125.9[b]	128.3	127.0
16	132.9	132.7	133.8	130.6	132.9
17	134.7	133.5	132.7	134.8	134.8
18	125.8	126.0[b]	126.0[b]	124.4	126.1
19	129.3	131.3	132.9	130.4	129.5
20	181.2	179.5	184.4	161.6	181.4, 181.3

[a] 67.89 MHz, $CDCl_3$, 0.3M solutions. *t* = 300 K. [b] Assignments may be reversed.

Table 3. Products from the triethylamine catalysed reaction of 2-hydroxy-1,4-naphthoquinone with aldehydes

Aldehyde	Solvent	Products (isolated yield %)		
(+)-Citronellal	MeCN	(**1a**) (20)	(**4**) (34)	(**5**) (27)
(+)-Citronellal	DMF	(**1a**) (28)	(**6a**) (63)	
$(Me)_2CHCH_2CHO$	MeCN	(**1b**) (36)	(**6b**) (48)	
$(Me)_2CHCH_2CHO$	DMF	(**1b**) (33)	(**6b**) (not isolated)	
$(Et)_2CHCHO$	Toluene	(**1c**) (0)	(**6c**) (83)[a]	
$(Et)_2CHCHO$	DMF	(**1c**) (0)	(**6c**) (46)	
Octanal	DMF	(**1d**) (30)	(**7**) (9)	
Cyclohexanone	DMF	(**1e**) (26)		
Benzaldehyde	Toluene		(**6f**) (89)[a]	

[a] Isolated as triethylammonium salt.

(*c*) *2-Ethylbutyraldehyde.*—(*i*) *In toluene: isolation of the triethylammonium salt of* (**6c**). A mixture of (**2**) (8.7 g, 50 mmol), 2-ethylbutyraldehyde (5.0 g, 50 mmol), and triethylamine (10 g, 100 mmol) in toluene (100 ml) was refluxed for 3.5 h. Diethyl ether (200 ml) was added and the precipitated crystals were filtered off and washed with diethyl ether to give the triethylammonium salt of (**6c**) (11.0 g, 83%), vermilion prisms (from aqueous methanol), m.p. 170—172 °C (Found: C, 72.45; H, 7.05; N, 2.6. $C_{32}H_{37}NO_6$ requires C, 72.29; H, 7.01; N, 2.64%); $\nu_{max.}$ 3 440, 1 668, 1 630, 1 593, and 1 564 cm^{-1}; δ_H (270 MHz) 0.79 (6 H, t, *J* 7.4 Hz), 1.33 (9 H, t, *J* 7.2 Hz), 1.4 (4 H, m), 2.9 (1 H, m), 3.32 (6 H, q, *J* 7.2 Hz), 5.39 (1 H, d, *J* 12.0 Hz), 7.52 (2 H, dt, J_1 1.5, J_2 7.5 Hz), 7.65 (2 H, dt, J_1 1.5, J_2 7.5 Hz), 7.96 (2 H, dd, J_1 1.5, J_2 7.5 Hz), and 8.17 (2 H, dd, J_1 1.5, J_2 7.5 Hz); δ_C (67.89 (MHz) 8.3 (q), 9.8 (q), 21.9 (t), 32.4 (d), 35.5 (d), 45.9 (t), 124.4 (s), 124.6 (s), 125.0 (d), 126.5 (d), 130.8 (s), 131.3 (d), 133.4 (d), 162.2 (s), 184.2 (s), and 184.9 (s) p.p.m.; *m/z* 430 (M^+ − Et_3N, 18%), 360 (8), 342 (7), 314 (7), and 256 (40). When the triethylammonium salt of (**6c**) was dissolved in CH_2Cl_2 and shaken with concentrated aqueous HCl, an amorphous orange precipitate formed, which was assumed to be (**6c**). This product had identical R_F value and u.v. absorptions (256, 275, 333, and 410 nm) with those of the salt when run on h.p.l.c. with an MeCN–aqueous phosphate buffer (pH 2) as eluant, but could not be purified for analysis. When the salt was refluxed with an excess of acetyl chloride–triethylamine in CH_2Cl_2 a rather unstable diacetate could be isolated after repeated chromatography (silica gel/CH_2Cl_2) and several crystallizations from methanol. A satisfactory elemental analysis could not be obtained; m.p. 168—170 °C; $\nu_{max.}$ 1 771, 1 672, and 1 595 cm^{-1}; δ_H (60 MHz) 0.92 (6 H, t *J* 7 Hz), 1.4 (4 H, m), 2.43 (6 H, s), 3.1 (1 H, m), 4.92 (1 H, d, *J* 11.5 Hz), and 7.6—8.3 (8 H, m); *m/z* (M^+, 6%), 472 (47), 430 (100), 360 (22), and 342 (36).

(*ii*) *In* DMF: *isolation of* (**6c**). A mixture of (**2**) (5.2 g, 30 mmol), 2-ethylbutyraldehyde (5.0 g, 50 mmol) and triethylamine (12 g, 120 mmol) in DMF (20 ml) was kept at 40 °C for 4 days. After dilution to 100 ml with diethyl ether, the triethylammonium salt of (**6c**) (3.4 g, 46%) crystallized at −20 °C, and was filtered off and washed with diethyl ether; it had m.p. 169—171 °C.

(*d*) *Octanal in* DMF: *Isolation of* (**1d**) *and* (**7**).—The procedure described for citronellal was followed using 5.8 g (47 mmol) of octanal. Chromatography on silica gel with CH_2Cl_2–hexane (1:1) as eluant gave (**1d**) (2.6 g, 30%) followed by (**7**) (1.1 g, 9%). (**1d**): Minute orange plates (from heptane), m.p. 93—94 °C (Found: C, 76.05; H, 7.0. $C_{18}H_{20}O_3$ requires C, 76.03; H, 7.09%); $\nu_{max.}$ 1 655, 1 648, 1 628, 1 604, and 1 590 cm^{-1}; $\lambda_{max.}$ (log ε) 270 (4.34), 284sh, 308sh, 335sh, and 448 (3.17) nm; δ_H (60 MHz) 0.9 (3 H, distorted t, *J ca.* 6 Hz), 1.4 (8 H, m), 2.3 (2 H, distorted q, *J ca.* 7 Hz), 6.6 (1 H, d, *J* 17 Hz), 7.17 (1 H, dt, J_1 17, J_2 7 Hz), and 7.6—8.3 (4 H, m); *m/z* 284 (M^+, 24%) and 213 (100). (**7**): Yellow needles, m.p. 105—106.5 °C (from heptane) (Found: C, 75.9; H, 9.05. $C_{26}H_{36}O_4$ requires C, 75.69; H, 8.80%); $\nu_{max.}$ 1 675, 1 645, 1 618, 1 593, and 1 575 cm^{-1}; $\lambda_{max.}$ (log ε) 251 (4.32), 277 (4.15), 339 (3.38), and 381 (3.04) cm^{-1}; δ_H (60 MHz) 0.8—2.0 (30 H, m), 3.2 (1 H, m), 5.7 (1 H, m), and 7.6—8.3 (4 H, m); *m/z* 412 (M^+, 100%) and 384 (20).

(*e*) *Cyclohexanone in* DMF: *Isolation of* (**1e**).—A mixture of (**2**) (5.2 g, 30 mmol), cyclohexanone (3.5 g, 35 mmol), and triethylamine (12 g, 120 mmol) in DMF (20 ml) was refluxed for 5 h. After cooling, the mixture was acidified with 2M sulphuric acid and extracted with diethyl ether. The ether phase was washed with water, dried (Na_2SO_4) and evaporated. The residue was triturated several times with hot heptane, the heptane phase evaporated, and the residue chromatographed on silica gel with ethyl acetate–hexane (1:6) as eluant to give (**1e**) as orange needles (2.0 g, 26%), m.p. 91—92 °C (from heptane) (Found: C, 75.8; H, 5.6. $C_{16}H_{14}O_3$ requires C, 75.58; H, 5.55%); $\nu_{max.}$ 3 365, 1 658, 1 645, 1 635, and 1 592 cm^{-1}; $\lambda_{max.}$ (log ε) 252 (4.26), 274 (4.26), 327 (3.46), and 407 (3.11) nm; δ_H (60 MHz) *ca.* 1.7 (4 H, m), *ca.* 2.3 (4 H, m), 5.9 (1 H, m), 7.6—8.3 (4 H, m), and *ca.* 7.8 (1 H, br s); *m/z* 254 (M^+, 78%), 226 (38), and 188 (100).

(*f*) *Benzaldehyde in Toluene: Isolation of the Triethylammonium Salt of* (**6f**).—A mixture of (**2**) (5.2 g, 30 mmol), benzaldehyde (3.2 g, 30 mmol), and triethylamine (10 g, 100 mmol) in toluene (100 ml) was refluxed for 2.5 h. After cooling, diethyl ether was added to a total volume of 250 ml. The precipitated orange prisms were filtered off and dissolved in CH_2Cl_2 (25 ml). Under reflux, methanol (100 ml) was gradually added, and the mixture cooled to yield the triethylammonium salt of (**6f**) (7.2 g, 89%), m.p. 225—226 °C (Found: C, 74.35; H, 5.9; N, 2.7. $C_{33}H_{31}NO_6$ requires C, 73.73; H, 5.81; N, 2.61%); $\nu_{max.}$ 3 420, 1 663, 1 636, 1 597, and 1 570 cm^{-1}; δ_H (60 MHz) 1.05 (9 H, t, *J* 7.4 Hz), 2.95 (6 H, q, *J* 7.4 Hz), 6.94 (1 H, s), 7.0—7.5 (5 H, m), 7.6—8.3 (4 H, m), *ca.* 7.3 (1 H, br s), and *ca.* 11 (1 H, br s); *m/z* 436 (M^+ − Et_3N, 5%).

Reaction of Isolapachol (**1b**) *in Triethylamine–Toluene: Isolation of* (**8**).—Isolapachol (**1b**) (4.8 g, 20 mmol) and triethylamine (5.0 g, 50 mmol) in toluene (50 ml) was refluxed until t.l.c. showed full conversion of (**1b**) (7 h). The mixture was diluted with diethyl ether and washed with 2M sulphuric acid. Drying (Na_2SO_4) and evaporation gave a complex mixture from which (**8**) (1.1 g, 23%) was isolated by chromatography on silica gel (eluant CH_2Cl_2); m.p. 95—96 °C (lit.,[2] 93.5—94.5 °C); $\nu_{max.}$ 3 360, 1 655, 1 645, and 1 591 cm^{-1}; $\lambda_{max.}$ (log ε) 251 (4.25), 281 (3.92), 339 (3.26), and 383 (3.00) nm; δ_H (500 MHz) 0.95 (6 H, d, *J* 6.9 Hz), 1.41 (2 H, distorted q, *J* 7—8 Hz), 1.62 (1 H, nonet, *J* 7 Hz), 2.59 (2 H, distorted t, *J* 8 Hz), 7.25 (1 H, s), 7.65 (1 H, t, *J* 8 Hz), 7.72 (1 H, t, *J* 8 Hz), 8.06 (1 H, d, *J* 8 Hz), and 8.10 (1 H, d, *J* 8 Hz); *m/z* 244 (M^+, 40%), 189 (18), and 188 (100). When a similar reaction was carried out in the presence of (**2**) (20 mmol) an analogous result was obtained, and (**6b**) could not be detected in the reaction mixture.

Reaction of (**1c**) *in Triethylamine–Toluene: Isolation of* (**9a**).—A mixture of (**1c**)[1] (0.51 g, 2 mmol) and triethylamine (0.30 g, 3 mmol) in toluene (10 ml) was refluxed for 4.5 h. After cooling, the mixture was diluted to 100 ml with diethyl ether, washed successively with 2M sulphuric acid and water, dried (Na_2SO_4) and evaporated. Crystallisation of the residue from methanol gave (**9a**) as orange triangular plates (0.27 g, 54%), m.p. 103—104 °C (Found: C, 74.9; H, 5.6. $C_{16}H_{14}O_3$ requires C, 75.58; H, 5.55%); $\nu_{max.}$ 1 662, 1 645, 1 590, and 1 570 cm^{-1}; $\lambda_{max.}$ (log ε) 265 (4.27), 280 (4.26), 332 (3.33), and 459 nm (3.23); δ_H (60 MHz) 1.20 (3 H, t, *J* 7.0 Hz), 1.47 (3 H, d, *J* 7.2 Hz), 2.20 (2 H, dq, J_1 2, J_2 7.0 Hz), 5.13 (1 H, q, *J* 7. 2 Hz), 6.47 (1 H, q, *J* 2 Hz), and 7.6—8.3 (4 H, m); *m/z* 254 (M^+, 38%), 239 (100), and 225 (56). In the presence of equimolar amounts of (**2**), this reaction gave a similar result, and no (**6c**) was formed.

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