dry column, using ethyl acetate–methanol (2:1) as eluent, showed a broad red band on the column. The center portion of this band was cut out and extracted with acetone, and after removal of the solvent, the residue was precipitated from benzene solution with hexane to give 145 mg of red solid. The outer portions of the red band were similarly extracted and further purified on thick-layer chromatographic plates to give 368 mg of product: mp 262–263 °C; total yield, 415 mg (51%); TLC R_f 0.87 (A), 0.44 (B); UV max (CH_3OH) 260 nm (ϵ 14900), 273 (infl) (11850), 375 (14600), 483 (7480); UV max (0.01 M phosphate, pH 7, containing 10^{-5} M EDTA, 5% Me_2SO) 197 nm (ϵ 50429), 264 (15450), 381 (12553), 509 (8154). Anal. ($C_{62}H_{84}N_{11}O_{16}Cl\cdot 5H_2O$) C, H, N, Cl.

2-Deaminoactinomycin D (4). A solution of 118 mg of **3** in 10 mL of ethanol containing 120 μL of triethylamine was hydrogenated (1 atm) over 250 mg of Pd black at 75–85 °C for 32 h. Catalyst was removed from the colorless solution by filtering through Celite into a stirred solution of 100 mg of $K_3Fe(CN)_6$ in 3 mL of phosphate buffer, pH 7; after 15 min, the mixture was diluted with water and extracted several times with ethyl acetate. The extracts, washed and dried, were concentrated to give 95 mg of red solid residue, which was dissolved in ethyl acetate and precipitated with hexane, yielding 65 mg (57%) of product: mp 250–252 °C; TLC R_f 0.85 (A), 0.46 (B); UV max (CH_3OH) 257 nm (infl) (ϵ 16500), 372 (9940), 477 (6240); UV max (0.01 M phosphate, pH 7, containing 10^{-5} M EDTA, 5% Me_2SO) 196 nm (ϵ 49830), 261 (15860), 357 (9620), 504 (7360). Anal. ($C_{62}H_{85}N_{11}O_{16}\cdot 4H_2O$) C, H, N (% Cl found to be 0.0%).

Acknowledgment. The authors gratefully acknowledge support of this work by the National Cancer Institute (NIH), Public Health Research Grant CA16486-02. We also thank R. K. Johnson, Division of Cancer Treatment, National Cancer Institute, for in vivo testing of 1 vs. **4**; H. W. Boyer (University of California Medical School, San Francisco, Calif.) for *E. coli* strain pBR313 (RR1); J. C. Wang and R. Depew (Department of Chemistry, University of California, Berkeley, Calif.) for the *E. coli* ω enzyme and information about reaction conditions for the closed circular DNA experiments; and Dorris Taylor, Charlotte Elder, Nancy Charbeneau, Keith Hohlfeldt, and Lew Cary for technical assistance. Elemental analyses were performed by E. Meier, Department of Chemistry, Stanford University, Stanford, Calif.

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Synthesis and Antiallergic Activity of 2-Hydroxy-3-nitro-1,4-naphthoquinones[1]

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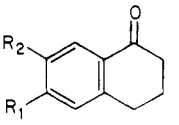
A selection of novel 2-hydroxy-3-nitro-1,4-naphthoquinones are shown to be potent inhibitors of rat passive cutaneous anaphylaxis (PCA) and to have highest potency with alkyl substitution at both C-6 and C-7. The most potent compounds were **7c** and **7e** which produced a 50% inhibition in the rat PCA test at doses of about 10 μM/kg following subcutaneous administration and showed activity after oral administration. Related 4-hydroxy-3-nitro-2(1*H*)-naphthalenones had no effect on rat PCA in doses up to 500 μM/kg.

2-Nitroindan-1,3-diones, **1**, and notably the 5,6-dimethyl derivative[2] have shown potent inhibition of the rat IgE mediated passive cutaneous anaphylaxis reaction in the rat (rat PCA).[3] Some of these compounds, moreover, will inhibit this reaction following oral administration. Our investigations into the limiting structural requirements for activity in the PCA test have led to other active classes of 2-nitro-1,3-dicarbonyl compounds of type **2** in which X may represent any one of the heteroatoms, oxygen,[4a] nitrogen,[4b] or sulfur.[4c]

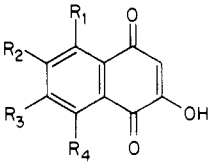
Table I. 3,4-Dihydro-1(2*H*)-naphthalenones



Compd	R_1	R_2	Mp or bp (mm), °C	Lit. mp, °C	Formula	Analyses	Yield, %[a]
6a[b]	Et	Et	118-122 (0.7)		$C_{14}H_{18}O$	C, H	89
6b	1,2-Cyclohexylene		48		$C_{14}H_{16}O$	C, H	80
6c	OMe	OMe	98-99	99[c]	$C_{12}H_{14}O_3$	C, H	73
6d	H	Me	34-35	35[d]	$C_{11}H_{12}O$		67
6e	H	OMe	65-66	66-67[e]	$C_{11}H_{12}O_2$		62
6f	H	OEt	34-36		$C_{12}H_{14}O_2$	C, H	60
6g	H	Br	72-73	76-77[f]	$C_{10}H_9BrO$	C, H, Br	77
6h	H	F	56-57		$C_{10}H_9FO$	C, H	63
6i	H	Ph	67		$C_{16}H_{14}O$	C, H	30

[a] Prepared by polyphosphoric acid cyclization of the appropriate 4-arylbutanoic acids following the procedure of ref 6. [b] See ref 5. [c] K. N. Campbell, A. Scharge, and B. K. Campbell, *J. Org. Chem.*, 15, 1135 (1960). [d] See ref 17. [e] R. D. Haworth and G. Sheldrick, *J. Chem. Soc.*, 1950 (1934). [f] L. F. Fieser and A. M. Seligman, *J. Am. Chem. Soc.*, 60, 170 (1938).

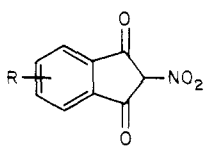
Table II. 2-Hydroxy-1,4-naphthoquinones



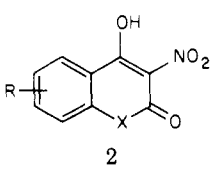
Compd	R_1	R_2	R_3	R_4	Mp, °C	Lit. mp, °C	Formula	Analyses	Yield, %	Method
5a	H	Me	H	H	190 (petr ether)	198[a]	$C_{11}H_8O_3$		40	B
5b	H	Me	Me	H	175-177 dec (petr ether)		$C_{12}H_{10}O_3$	C, H	55	B
5c[b]	H	Et	Et	H	105-109 (petr ether)		$C_{14}H_{14}O_3 \cdot 0.5H_2O$	C, H	63	A
5d	H	1,2-Cyclohexylene		H	193 (EtOH-H_2O)		$C_{14}H_{12}O_3$	C, H	17	A
5e	H	OMe	OMe	H	213-216 (EtOH)	212[c]	$C_{12}H_{10}O_5$	H; C[d]	87	A
5f	H	H	Me	H	206 (Me_2CO)	206[e]	$C_{11}H_8O_3$	H; C[f]	55	A
5g	H	H	OMe	H	216 (EtOH)	220-222[g]	$C_{11}H_8O_4$		97	A
5h	H	H	OEt	H	188 dec (EtOH)		$C_{12}H_{10}O_4$	C, H	46	A
5i	H	H	Br	H	216 (EtOH)		$C_{10}H_5BrO_3$	C, H, Br	34	A
5j	H	H	F	H	206-210 ($CHCl_3$)		$C_{10}H_5FO_3$	C, H	37	A
5k	H	H	Ph	H	190-192 (EtOH)		$C_{16}H_{10}O_3$	C, H	37	A
5l	H	H	H	Me	175-176 (petr ether)	176-177[h]	$C_{11}H_8O_3$		31	B
5m	H	H	H	OH	208-212 (AcOH)	215[h]	$C_{10}H_6O_4$		87	*h*

[a] See ref 9. [b] See ref 5. [c] H. R. Bentley, W. Dawson, and F. S. Spring, *J. Chem. Soc.*, 1763 (1952). [d] C: calcd, 61.54; found, 60.83. [e] L. F. Fieser et al., *J. Am. Chem. Soc.*, **70**, 3212 (1948). [f] C: calcd, 70.21; found, 69.70. [g] L. F. Fieser and R. H. Brown, *J. Am. Chem. Soc.*, 71, 3615 (1949); see ref 7. [h] See ref 11.

More recently we have shown the interchangeability of the nitro group of both 1 and 2 (X = O) by nitrile, although this change is accompanied by a slight loss of PCA activity.[5] We now wish to report our results on a related series of compounds, the 2-hydroxy-3-nitro-1,4-naphthoquinones 7.



1

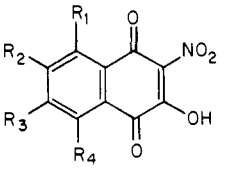


2

Chemistry. The 2-hydroxy-1,4-naphthoquinones, 5, which are key intermediates in the formation of the 3-nitro derivatives 7 were prepared by the two routes illustrated in Scheme I. The preferred route utilizes the 3,4-dihydro-1(2*H*)-naphthalenones 6 (Table I) which are readily available by polyphosphoric acid cyclization of 4-arylbutanoic acids.[6] Autoxidation of 6 in the presence of potassium *tert*-butoxide (method A)[7,8] results in the uptake of 2 equiv of oxygen to give, via the *o*-quinone intermediates,[8] the hydroxynaphthoquinones, 5, in moderate yield (Table II).

Alternatively, 5 may be synthesized by amination followed by hydrolysis of substituted 1,4-naphthoquinones, 3,[9] where these are accessible by the cyclization and oxidation of readily available dienes. Substitution reactions in the quinonoid ring of 5-hydroxy-1,4-naphthoquinone (juglone) and some of its derivatives are known to be influenced by the nature of substituents present in the benzenoid ring, and of the two possible isomers one may predominate or be exclusive.[9,10] Furthermore, the work of Lyons and Thomson[9] has shown that electron-repelling substituents at position 6 of the naphthoquinone nucleus will cause aniline to react preferentially at position 2, whereas chlorine at position 6 will effect anilation at position 3. Derivatives substituted at the 5 position, however, have predominantly a C-3 directing effect for

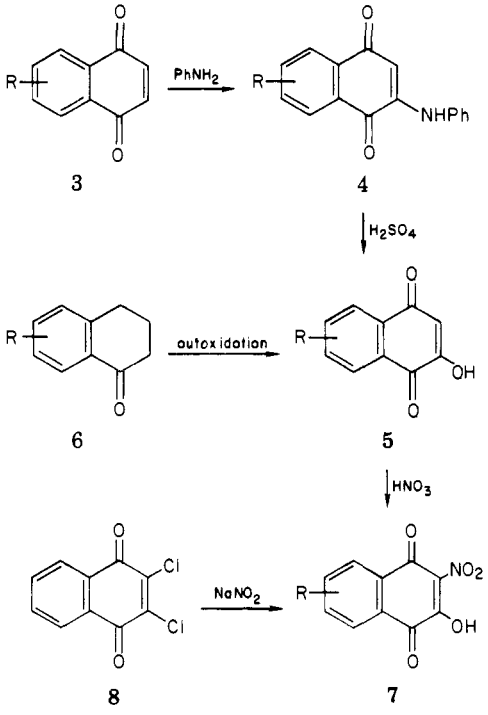
Table III. 2-Hydroxy-3-nitro-1,4-naphthoquinones



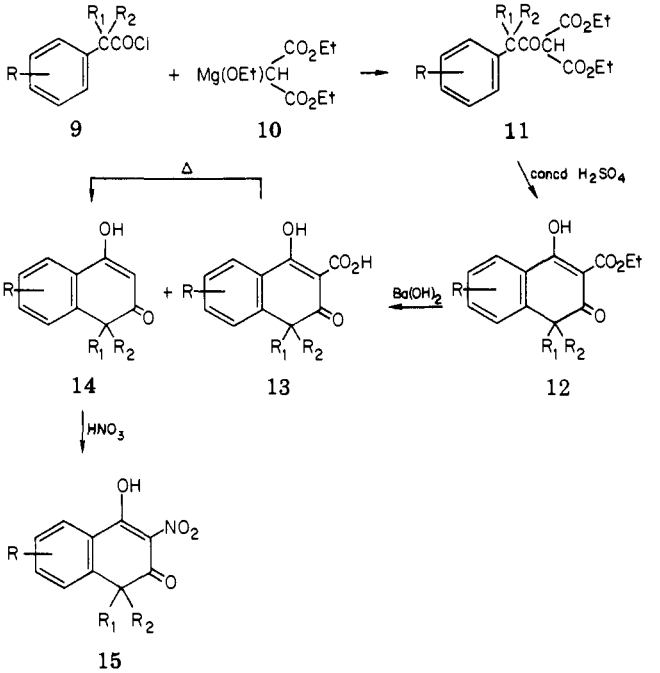
Compd	R_1	R_2	R_3	R_4	Mp, °C[a]	Formula	Analyses	Yield, %	Act. in rat PCA test, ED_{50},[b] μM/kg sc at T_{max}[c]
	Disodium cromoglycate								13.1 (9.6-18.2, 147, 56)
7a	H	H	H	H	162-163 dec[d]	$C_{10}H_5NO_5$	C, H, N	81	141 (48-419, 80, 24)
7b	H	Me	H	H	159-160 dec	$C_{11}H_7NO_5$	C, H, N	73	63.9 (21-172, 78, 15)
7c	H	Me	Me	H	169-170 dec	$C_{12}H_9NO_5$	C, H, N	87	11.0 (6.3-19.5, 122, 18)
7d	H	Et	Et	H	152 dec	$C_{14}H_{13}NO_5$	C, H, N	75	27.3 (7.5-154, 64, 17)
7e	H	1,2-Cyclohexylene		H	195-196 dec[e]	$C_{14}H_{13}NO_5$	C, H, N	81	7.3 (1.3-37, 56, 24)
7f	H	OMe	OMe	H	180-184	$C_{12}H_9NO_7$	C, H, N	79	42.8 (8.4-148, 78, 17)
7g	H	H	Me	H	160	$C_{11}H_7NO_5$	C, H, N	96	181 (*f*, -, 24)
7h	H	H	OMe	H	159 dec	$C_{11}H_7NO_6$	C, H, N	94	51.3 (18.2-142, 71, 23)
7i	H	H	OEt	H	158 dec	$C_{12}H_9NO_6$	C, H, N	99	68.2 (31.3-146, 85, 24)
7j	H	H	Br	H	172	$C_{10}H_4BrNO_5$	C, H, N, Br	81	>500
7k	H	H	F	H	152	$C_{10}H_4FNO_5$	C, H, N	81	>500
7l	H	H	Ph	H	172-173[g]	$C_{16}H_9NO_5$	C, H, N	91	>500
7m	H	H	H	Me	148-149 dec	$C_{11}H_7NO_5$	C, H, N	43	76.2 (31.3-177, 124, 17)
7n	H	H	H	OH	160-161.5 dec	$C_{10}H_5NO_6$	H, N; C[h]	51	>500

[a] Synthesized by method C and recrystallized from dilute HCl unless stated otherwise. [b] Figures in parentheses are 95% confidence limits, slope of inhibition/log dose line, number of animals used. [c] T_{max} refers to the time interval between sc administration of the drug and antigen challenge that produced maximum activity and was 10 min in each case. [d] A. Inoue, N. Kuroki, and K. Konishi, *Chem. Abstr.*, **54**, 4504*g* (1960), quote mp 160-161 °C. [e] Recrystallized from H_2O-EtOH-HCl. [f] Insufficient data to calculate confidence limits. [g] Recrystallized from EtOH-HCl. [h] C: calcd, 51.08; found, 50.31.

Scheme I



Scheme II

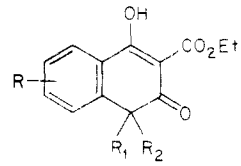


aniline irrespective of their nature.[11] Thus, reaction of **3** with aniline affords the anilino derivatives **4** which readily hydrolyze under acidic conditions[9] to the hydroxynaphthoquinones, **5** (Table II, method B). The dihydroxy derivative **5m** was prepared in two stages from juglone via the 4-mercaptotoluene derivative.[11]

Nitration of the intermediate 2-hydroxy-1,4-naphthoquinones, **5**, proceeded under mild conditions at room temperature (method C) to give high yields of the 3-nitro derivatives **7**. The parent compound, **7a**, was also synthesized from 2,3-dichloro-1,4-naphthoquinone, **8**, by reaction with ethanolic sodium nitrite,[12] but as a general procedure this method suffers from the relatively poor accessibility of the dichloro precursors and the possible ambiguity of structure from compounds with asymmetric substitution. Table III lists the properties and PCA data of nitro derivatives prepared by these methods.

The 4-hydroxy-3-nitro-2(1*H*)-naphthalenones **15** (R_1 = R_2 = Me) also required in this work are a novel class of compound and the route used in their synthesis is illustrated in Scheme II. The acid chlorides, **9**, are conveniently prepared from the appropriate arylacetonitrile by alkylation with dimethyl sulfate in the presence of sodamide (method D)[13] followed by hydrolysis with alcoholic potassium hydroxide (method E). Reaction of the resulting acids with thionyl chloride (method F) then effects near

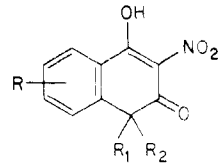
Table IV. 3-Carboethoxy-4-hydroxy-2(1*H*)-naphthalenones



Compd	R	R_1	R_2	Mp or bp (mm), °C	Formula	Analyses	Yield, %[a]
12a	H	H	Me	93 (EtOH)	$C_{14}H_{14}O_4$	C, H	33
12b	H	Me	Me	56-57 (EtOH-H_2O)	$C_{15}H_{16}O_4$	C, H	84
12c	6-Me	Me	Me	160 (1.0)	$C_{16}H_{18}O_4$	C, H	91
12d	8-Me	Me	Me	185 (1.0)	$C_{16}H_{18}O_4$	C, H	60

[a] Prepared by method G.

Table V. 4-Hydroxy-3-nitro-2(1*H*)-naphthalenones



Compd	R	R_1	R_2	Mp, °C	Formula	Analyses	Yield, %
15a	H	H	Me	210 dec (MeOH-H_2O)	$C_{11}H_9NO_4$	C, H, N	53
15b	H	Me	Me	86-89 (dil HCl)	$C_{12}H_{11}NO_4$	C, H, N	71[a]
15c	6-Me	Me	Me	110-112 (dil HCl)	$C_{13}H_{13}NO_4$	C, H, N	69[a]
15d	8-Me	Me	Me	115-117 (dil HCl)	$C_{13}H_{13}NO_4$	C, H, N	55[a]

[a] Prepared by method J.

quantitative conversion to **9**.

Condensation of **9** with ethoxymagnesium malonate **10** as described by Meyer and Bloch for phenylacetyl chloride[14] results in formation of the intermediate acylmalonates, **11**, which were cyclized in concentrated sulfuric acid (method G), without purification, to give good yields of the diketo esters **12** (Table IV). Mild hydrolysis of **12** with barium hydroxide in aqueous dioxane (method H)[14] resulted in the acids **13** accompanied, in the case of the *gem*-dimethyl derivatives **12b–d**, by varying amounts of the decarboxylated product **14**. Separation of **13** from **14** was simply accomplished in all cases. Thermolysis of 3-carboxy-4-hydroxy-1,1,6-trimethyl-2(1*H*)-naphthalenone, and its 1,1,8-trimethyl isomer, effected rapid and quantitative elimination of carbon dioxide to give the appropriate decarboxylated derivative **14**, although the more stabilized acid **13** (R = R_1 = H; R_2 = Me) was decarboxylated as described for 1,3-dihydroxy-2-naphthoic acid.[14]

Nitration of **14** (R = R_1 = H; R_2 = Me) in hot glacial acetic acid gave 1,3-dihydroxy-4-methyl-2-nitronaphthalene (**15a**) in moderate yield, although under similar conditions the *gem*-dimethyl derivative **14** (R = H; R_1 = R_2 = Me) oxidized to a nitrogen-free product, thought to be the *gem*-dimethylhomophthalic acid. Milder nitration in ether at 0 °C (method J) accomplished facile conversion of **14** (R = H or Me; R_1 = R_2 = Me) to their 3-nitro derivatives **15b–d** in moderate yield (Table V).

Results and Discussion

As part of a study into the antiallergic activity of a series of compounds containing the 2-nitro-1,3-dicarbonyl moiety, we have investigated a range of homocyclic and heterocyclic compounds for their activities as inhibitors of rat passive cutaneous anaphylaxis. Structure–activity patterns which began to emerge from the 2-nitroindan-1,3-diones **1**[3] have recurred in the ring-expanded derivatives incorporating both oxygen[4a] and nitrogen[4b] (**2**, X = O and NR, respectively) and of the substituents studied, optimum activity results from alkyl substitution at both the C-5 and C-6 positions of **1** and the C-6 and C-7 positions of **2**. The ring-junction stereochemistry appears to exert a considerable influence on the biological activity. Within a series of cis-fused hydroaromatic 2-nitroindandiones, only marginal PCA activity was seen even when the substitution pattern was optimum.[15] Reduced 3-nitro-2-quinolones, on the other hand, having a planar ring junction, showed activity comparable to that of their aromatic analogues.[4b]

Few groups other than the nitro moiety appear to be compatible with good biological response, and of a wide range of replacements in both the indandione and 4-hydroxycoumarin series only the nitrile group was an effective substitute.[5]

In the current series, 2-hydroxy-3-nitro-1,4-naphthoquinones **7**, which may be considered as ring-expanded derivatives of **1** with the carbonyl moiety (i.e., **2** where X is C=O), show a high level of activity in the rat PCA test (see Table III), with greatest potency in those derivatives substituted at both C-6 and C-7 with alkyl groups (**7c–e**). The preferred compounds, **7c** and **7e**, were also active when administered orally, each having an $ED_{50} \approx 100$ μM/kg when given 10 min prior to antigen challenge. Other substitutions showed activity little different from the parent **7a** with the notable exception of the two halogenated derivatives **7j** and **7k** and the 7-phenyl derivative **7l**, which had low orders of activity. The structural requirements for activity of this series were therefore similar to those previously found for **1** and the ring-expanded compounds of general formula **2** where X = O and NR. Ring expansion with saturated carbon residues to give **15** (Table V), however, had a profound effect on activity with no compound showing inhibition of rat PCA in doses up to 500 μM/kg.

Experimental Section

Melting points were determined using a Büchi melting point apparatus and are recorded uncorrected. The structures of all compounds were consistent with their IR and NMR spectra, the

latter of which were determined as solutions in either $CDCl_3$ or Me_2SO-d_6. Where represented by elemental symbols the analyses of these elements fall within ±0.4% of the calculated values.

4-Arylbutanoic Acids. These compounds were prepared by reduction of the appropriate 3-aroylpropanoic acids either catalytically[16] or using the Clemmensen procedure[17] and had physical constants in agreement with literature values.

4-(4-Ethoxyphenyl)butanoic Acid. Granulated Zn/Hg [from Zn (26 g) and $HgCl_2$ (2.6 g)], prepared in the usual manner, was added to 3-(4-ethoxybenzoyl)propanoic acid[18] (22.2 g, 0.1 mol) and concentrated HCl (150 mL) and the mixture stirred at reflux for 5 h and filtered hot. The product, which crystallized on cooling, was removed by filtration, dried, and recrystallized [PhH–petroleum ether (40–60 °C)] to give 13.95 g (67%) of material of mp 63 °C. Anal. ($C_{12}H_{16}O_3$) C, H.

3,4-Dihydro-1(2*H*)-naphthalenones (Table I). These were prepared by the procedure of Koo[6] which is illustrated below for the 7-ethoxy derivative.

3,4-Dihydro-7-ethoxy-1(2*H*)-naphthalenone (6f). Finely powdered 4-(4-ethoxyphenyl)butanoic acid (77 g, 0.37 mol) was added in one portion to 85% polyphosphoric acid (500 g) at 70 °C and the thick mixture stirred at this temperature for 40 min. After cooling the dark red mass was poured onto ice–water (2 L) and the yellow solid which separated extracted into ether. The extracts were washed successively with H_2O, dilute $NaHCO_3$, and H_2O and dried ($MgSO_4$). Removal of the solvent in vacuo followed by distillation afforded 42.2 g (60%) of naphthalenone of bp 264–268 °C (0.1 mm) which crystallized on standing. Recrystallization from petroleum ether (bp 40–60 °C) gave material of mp 34–36 °C. Anal. ($C_{12}H_{14}O_2$) C, H.

2-Hydroxy-1,4-naphthoquinones (Table II). 3,5-Dihydroxy-1,4-naphthoquinone (**5m**) was prepared by the procedure of MacLeod and Thomson.[11]

Autoxidation of 3,4-Dihydro-1(2*H*)-naphthalenones. Method A.[7,8] **7-Ethoxy-2-hydroxy-1,4-naphthoquinone (5h).** A solution of 3,4-dihydro-7-ethoxy-1(2*H*)-naphthalenone (**6f**, 19 g, 0.1 mol) in dry *t*-BuOH (200 mL) was added to a 1 M solution of KO-*t*-Bu in dry *t*-BuOH (800 mL) which had previously been saturated with O_2 and the red solution vigorously stirred (or shaken) in an atmosphere of O_2 until 2 equiv were absorbed (ca. 0.5–1 h; exothermic reaction). The cooled solution was acidified with concentrated HCl, the bulk of the solvent removed in vacuo, and the product partitioned between water and $CHCl_3$. The organic phase was extracted with saturated aqueous $NaHCO_3$ from which the hydroxyquinone was isolated by acidification and filtration. Recrystallization of the dried yellow solid from EtOH gave 10.0 g (46%) of title compound of mp 188 °C dec. Anal. ($C_{12}H_{10}O_4$) C, H.

Hydrolysis of 2-Anilino-1,4-naphthoquinones. Method B.[9] **2-Anilino-6,7-dimethyl-1,4-naphthoquinone.** Aniline (0.5 mL) was added in one portion to a warm solution of 6,7-dimethyl-1,4-naphthoquinone[19] (1.08 g, 0.058 mol) in EtOH (20 mL) and the red solution refluxed on a steam bath for 1 h. The residue was stood at room temperature overnight and the precipitated red crystalline solid filtered off and washed well with EtOH to give, after recrystallization from aqueous AcOH, 0.54 g (34%) of title compound of mp 208–210 °C. Anal. ($C_{18}H_{15}NO_2$) C, H, N.

The following compounds were prepared by this procedure.

2-Anilino-6-methyl-1,4-naphthoquinone: yield 33%; mp 202–204 °C (aqueous AcOH) (lit.[9] mp 206 °C).

3-Anilino-5-methyl-1,4-naphthoquinone: yield 62%; mp 179–180 °C (PhH) (lit.[11] mp 179–180 °C).

6,7-Dimethyl-2-hydroxy-1,4-naphthoquinone (5b). 2-Anilino-6,7-dimethyl-1,4-naphthoquinone (3.1 g, 0.0136 mol) in concentrated H_2SO_4 (70 mL) was diluted with an equal volume of water and brought to reflux for 1 min. The product was poured into water, filtered, and dried in vacuo over P_2O_5. Recrystallization from petroleum ether (bp 100–120 °C) gave, after decolorizing, 1.29 g (55%) of yellow solid of mp 175–177 °C dec. Anal. ($C_{12}H_{10}O_3$) C, H.

Similarly were prepared the following compounds.

2-Hydroxy-6-methyl-1,4-naphthoquinone (5a): yield 40%; mp 198 °C [petroleum ether (bp 80–100 °C)] (lit.[9] mp 198 °C).

3-Hydroxy-5-methyl-1,4-naphthoquinone (5l): yield 48%; mp 175–177 °C [petroleum ether (bp 80–100 °C)] (lit.[11] mp 176–177 °C).

2-Hydroxy-3-nitro-1,4-naphthoquinones (Table III). General Procedure. Method C. A solution of the hydroxyquinone **5** (1.0 g) in $CHCl_3$ (100 mL) was stirred at room temperature during the dropwise addition of fuming HNO_3 (5.0 mL, *d* 1.52) over 1 h and then for a further 1 h. The dark solution was stripped of solvent in vacuo ($T < 20$ °C) and diluted with cold 5 N HCl (50 mL) and the yellow product filtered off and washed with 5 N HCl. Recrystallization from EtOH or dilute HCl afforded material of analytical purity in good yield.

2-Hydroxy-3-nitro-1,4-naphthoquinone (**7a**) was also prepared from 2,3-dichloro-1,4-naphthoquinone as previously described.[20]

2-Methyl-2-phenylpropanonitrile. Method D.[13] Fresh, finely powdered commercial $NaNH_2$ (90 g, 2.4 mol) and dry PhH (500 mL) were stirred during the addition of $PhCH_2CN$ (117 g, 1.0 mol) and the mixture refluxed for 2 h until evolution of NH_3 ceased. To the hot brown solution was cautiously added a solution of Me_2SO_4 (232 g, 2 mol) in its own volume of dry PhH such that the vigorous reaction was kept under control. After the addition was complete the near colorless solution was refluxed for 10 min and cooled. The flask was flushed with N_2, water (500 mL) was carefully added, and the phases separated. Distillation of the organic layer gave 76.5 g of oil of bp 104–107 °C (13 mm) which GLC showed to be a 1:1 mixture of mono- and dialkylated products. Recycling this product gave 56.5 g (39%) of pure nitrile of bp 100–106 °C (13 mm) [lit.[21] bp 81–82 °C (2.2 mm)].

The following compounds were prepared by this procedure.

2-Methyl-2-(*p*-tolyl)propanonitrile: yield, after recycling, 32%; bp 123 °C (13 mm) [lit.[22] bp 122–123 °C (12 mm)].

2-Methyl-2-(*o*-tolyl)propanonitrile: yield, after recycling, 32%; bp 122–130 °C (13 mm).

2-Methyl-2-phenylpropanoic Acid. Method E. 2-Methyl-2-phenylpropanonitrile (56.5 g, 0.39 mol) was added to a solution of KOH (111 g, 1.96 mol) in MeOH (300 mL) and the mixture stirred in an autoclave at 140–150 °C for ca. 20 h. The cooled solution was concentrated in vacuo, diluted with water, and acidified with HCl to give the acid as a white crystalline solid. Filtration and recrystallization from EtOH gave 57.4 g (90%) of material of mp 80 °C (lit.[23] mp 80–81 °C).

By the same procedure the following compounds were prepared.

2-Methyl-2-(*p*-tolyl)propanoic acid: yield 91%; mp 78–80 °C (petroleum ether) (lit.[22] mp 82 °C).

2-Methyl-2-(*o*-tolyl)propanoic acid: yield 46%; mp 99–101 °C (from H_2O containing a trace of EtOH). Anal. ($C_{11}H_{14}O_2$) C, H.

Acid Chlorides 9. Method F. These were prepared from the acids by refluxing for 5 h with a tenfold excess of $SOCl_2$, followed by removal of excess reagent in vacuo and distillation, and were used without further purification.

2-Phenylpropanoyl chloride: prepared from commercially available acid; yield 83%; bp 92 °C (13 mm) [lit.[24] bp 75–76 °C (3 mm)].

2-Methyl-2-phenylpropanoyl chloride: yield 83%; bp 107 °C (13 mm).

2-Methyl-2-(*p*-tolyl)propanoyl chloride: yield 90%; bp 118–122 °C (13 mm).

2-Methyl-2-(*o*-tolyl)propanoyl chloride: yield 91%; bp 114–118 °C (13 mm).

3-Carboethoxy-4-hydroxy-2(1*H*)-naphthalenones. Method G[14] **(Table IV). 3-Carboethoxy-1,1-dimethyl-4-hydroxy-2(1*H*)-naphthalenone (12b).** Anhydrous EtOH (45 mL) was added to a mixture of dry Mg (6.75 g, 0.26 g-atom) and dry diethyl malonate (20 g, 0.125 mol) containing 0.5 mL of dry CCl_4. The ensuing vigorous reaction was controlled by external cooling and when complete a further 20 g (0.125 mol) of diethyl malonate was rapidly added. When the reaction subsided, anhydrous Et_2O (100 mL) was added and the product heated for 1 h at reflux. 2-Methyl-2-phenylpropanoyl chloride (53.0 g, 0.29 mol) in dry Et_2O (50 mL) was then added over 30 min with stirring. After a further 10 min at reflux, the mixture was cooled in ice and water (50 mL) slowly added. Separation of the oily layer followed by washing with water (2 × 50 mL) and evaporation under reduced pressure gave 83 mL of crude ester **11**. This ester was added in one portion, without cooling, to three volumes of concentrated H_2SO_4 and the orange solution set aside for 7 days. On pouring onto crushed ice (1 kg) and water (500 mL) a yellow crystalline solid separated which after filtration and recrystallization from aqueous EtOH

afforded 54.5 g (84%) of colorless naphthalenone **12b**: mp 56–57 °C; ν_{max} (mull) 1670, 1620, 1560 cm^{-1}; NMR δ ($CDCl_3$) 1.46 (3 H, t, J = 7.5 Hz, ester CH_3), 1.60 (6 H, s, *gem*-Me_2), 4.51 (2 H, quartet, J = 7.5 Hz, ester CH_2), 7.32–7.70 (3 H, complex m, aromatics less H-5), 8.27 (1 H, dd, H-5), one low-field exchangeable proton (OH). Anal. ($C_{15}H_{16}O_4$) C, H.

Using the same procedure the other compounds shown in Table IV were prepared.

Hydrolysis of 3-Carboethoxy-4-hydroxy-2(1*H*)-naphthalenones. Method H.[14] **3-Carboxy-1,1-dimethyl-4-hydroxy-2(1*H*)-naphthalenone and 1,1-Dimethyl-4-hydroxy-2(1*H*)-naphthalenone.** A solution of ester **12b** (11.7 g, 0.045 mol) in dioxane (150 mL) was stirred at 100 °C under N_2 during the addition of a solution of $Ba(OH)_2 \cdot 8H_2O$ (20 g) in water (250 mL) over 1 h and then for a further 3 h. The mixture was filtered hot and the solid added to a cold 7% v/v solution of H_2SO_4 (100 mL). After several minutes the solid was filtered off and extracted with hot EtOH to give, on evaporation, 2.71 g (26%) of 3-carboxy-1,1-dimethyl-4-hydroxy-2(1*H*)-naphthalenone as a white solid of mp 136–137 °C: ν_{max} (mull) 2500 (br), 1675, 1610, 1565, 1495 cm^{-1}. Anal. ($C_{13}H_{12}O_4$) C, H.

Evaporation of the aqueous dioxane phase afforded an oily solid to which was added EtOH and one-tenth its volume of 5 N H_2SO_4. The precipitated $BaSO_4$ was removed by filtration and the filtrate diluted with water. Azeotropic removal of the bulk of the EtOH in vacuo resulted in precipitation of 2.84 g (34%) of 1,1-dimethyl-4-hydroxy-2(1*H*)-naphthalenone: mp 194–196 °C; ν_{max} (mull) 2500 (br), 1630, 1590, 1530 (sh), 1500 cm^{-1}; NMR δ (Me_2SO) 1.46 (6 H, s, *gem*-Me_2), 5.68 (1 H, sharp exchangeable s, methine C-H), 7.27–7.78 (3 H, complex m, aromatics less H-5), 8.00 (1 H, dd, H-5), one broad low-field exchangeable proton (OH). Anal. ($C_{12}H_{12}O_2$) C, H.

The following compounds were obtained by this method.

3-Carboxy-4-hydroxy-1,1,6-trimethyl-2(1*H*)-naphthalenone and 4-Hydroxy-1,1,6-trimethyl-2(1*H*)-naphthalenone. The 3-carboxy derivative **13** (R = 6-Me; $R_1 = R_2$ = Me) was isolated in low yield by the procedure described above, presumably due to its ready decarboxylation. The pure acid had mp (EtOH) 146 °C with effervescence and resolidification and final melting at 224–226 °C: ν_{max} (mull) 2600 (br), 1665, 1600, 1555, 1495 cm^{-1}. Anal. ($C_{14}H_{14}O_4$) C, H.

The total yield of the decarboxylated product **14** (R = 6-Me; $R_1 = R_2$ = Me) from both the solid and the dioxane phases was 63%, the product having mp (EtOH) 226–229 °C. Anal. ($C_{13}H_{14}O_2$) C, H.

Quantitative conversion of the 3-carboxy derivative to the decarboxylated product occurred on gentle heating above the melting point.

3-Carboxy-4-hydroxy-1,1,8-trimethyl-2(1*H*)-naphthalenone and 4-Hydroxy-1,1,8-trimethyl-2(1*H*)-naphthalenone. Hydrolysis of **12d** as described above gave 45% of the carboxylic acid **13** (R = 8-Me; $R_1 = R_2$ = Me) of mp (EtOH) 160 °C with effervescence and final melting at 224–226 °C. Anal. ($C_{14}H_{14}O_4$) C, H. From the dioxane phase 10% of the decarboxylated material **14** (R = 8-Me; $R_1 = R_2$ = Me) of mp (EtOH) 224–227 °C was isolated. Anal. ($C_{13}H_{14}O_2$) C, H.

Heating the acid to 175 °C for 1 min effected a quantitative conversion to the decarboxylated material. This procedure could be used as a synthetic route to analogous compounds.

1,3-Dihydroxy-4-methyl-2-naphthoic acid: yield 67%; mp 155 °C (dilute HCl). Anal. ($C_{12}H_{10}O_4$) C, H. No attempt was made in this case to isolate material from the dioxane phase.

1,3-Dihydroxy-4-methylnaphthalene. A suspension of 1,3-dihydroxy-4-methyl-2-naphthoic acid (6.5 g, 0.03 mol) in water (25 mL) was refluxed for 4 h under N_2 and the resulting solution treated with charcoal and filtered hot. The product separated on cooling as a white solid which after filtration and drying gave a yield of 3.55 g (70%) of material of mp 108–110 °C. Anal. ($C_{11}H_{10}O_2 \cdot 0.75H_2O$) C, H.

1,3-Dihydroxy-4-methyl-2-nitronaphthalene (15a). Concentrated HNO_3 (2.5 mL, *d* 1.42) was added in one portion to a solution of 1,3-dihydroxy-4-methylnaphthalene (1.56 g, 0.009 mol) in glacial AcOH (15 mL) whereby the mixture became warm. The yellow solution was gently warmed on a steam bath for 1 min, cooled rapidly in ice, and diluted with water. The precipitated yellow nitro derivative was separated and recrystallized from aqueous MeOH to give 1.04 g (53%) of solid of mp 210 °C dec. Anal. ($C_{11}H_9NO_4$) C, H, N.

General Procedure for Compounds 15b–d (Table V). Method J. Fuming HNO_3 (2 mL, *d* 1.52) was added dropwise to a stirred suspension of the naphthalenone **14** (0.006 mol) in anhydrous Et_2O (15 mL) at 0 °C, and the mixture stirred for a further 1.5 h at this temperature. The resulting clear solution was diluted with cold 5 N HCl (30 mL) and the Et_2O removed in vacuo at 0 °C. The product, which separated as a pale yellow solid, was filtered off, washed well with 5 N HCl, and recrystallized from a large volume of water by slow addition of concentrated HCl.

Passive Cutaneous Anaphylaxis. Rat PCA was carried out as previously described.[4b] Compounds were administered to male Wistar rats of 250–300 g in phosphate-buffered saline (PBS, isotonic saline buffered with 0.05 M, pH 7.2, Sorenson buffer, Difco Laboratories), neutralized with sodium bicarbonate when necessary, or, for insoluble compounds, as a suspension in a 1:1 mixture of PBS and 1% methylcellulose in distilled water, at 2 mL/kg of body weight. Control animals received the same volume of carrier fluid. Five to eight rats were used for each treatment and control group. Treatments were randomized.

Acknowledgment. The authors express their thanks to Mr. N. J. Morgan for his assistance with two of the syntheses.

References and Notes

(1) All compounds are named as derivatives of 2-hydroxy-1,4-naphthoquinone for consistency throughout although some compounds are more accurately named as derivatives of 3-hydroxy-1,4-naphthoquinone.
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