Preparation and Pharmacological Evaluation of 1-(1,4-Benzoquinon-2-yl)-1,2,3,4-tetrahydronaphthalenes as Potent Cerebral Protective Agents[1)]

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Two new series of 1-(1,4-benzoquinon-2-yl)-1,2,3,4-tetrahydronaphthalenes (3, 4) were synthesized for evaluation of their pharmacological activities. These compounds showed significant anti-lipid peroxidation (ALP) activities with rat brain homogenate and some of them possessed a protective effect against hypobaric hypoxia in mice.

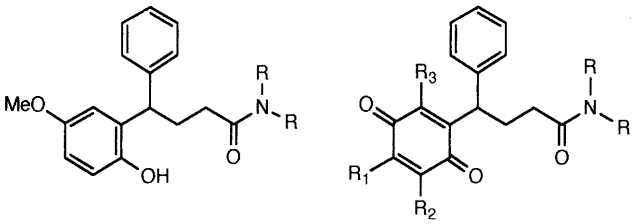
Key words 1,4-benzoquinone; tetrahydronaphthalene; anti-lipid peroxidation activity; hypobaric hypoxia; cerebral protective agent

In the therapy of diseases caused by a disorder in the oxygen supply mechanism in the central nervous system (CNS), CNS depressants such as barbiturates or steroids have been employed for the acute treatment of traumatic or ischemic injury. However, their use is limited because of the accompanying side effects on respiratory organs or the circulatory system.[2,3)] Oxygen free radicals have been proposed to mediate postischemic reperfusion damage in a variety of tissues, including the brain. There is now increasing pharmacological and biological evidence to support an important role of these radical species in the pathophysiology of acute cerebral ischemia.[4)] So, in recent years, considerable attention has been focused on the development of free radical scavenging enzymes[5)] or drugs[6)] to prevent postischemic injury and enhance functional recovery.

In the course of our studies on cerebral protective agents that affect cerebral blood flow, circulation and metabolism in the aged brain or in cerebral vascular diseases, we have reported the synthesis and pharmacological evaluation of some novel classes of compounds, 4,4-diarylbutanamides and related compounds (**1**)[1a)] and 4-(1,4-benzoquinon-2-yl)-4-arylbutanamides (**2**)[1c)] (Fig. 1). Many of these compounds showed potent cerebral protective activities in various screening assays such as anti-lipid peroxidation (ALP), hypobaric hypoxia, global ischemia, and so on. Among them, compound **2a** (SUN 4757) was most potent in the above assays and had low acute toxicity in mice ($LD_{50} > 1000$ mg/kg). In order to investigate more fully the structural requirements for exhibiting cerebral protective activities, we planned to synthesize the following two types of conformationally restricted analogues of **2a** (Fig. 2). (methylene units introduced as conformational restraints are indicated by broken lines.) In this paper, we report the synthesis of 2- or 3-substituted 1-(1,4-benzoquinon-2-yl)tetralin derivatives (**3** or **4**) and the results of screening tests of the synthesized compounds.

Chemistry The target molecules were synthesized *via* the routes shown in Charts 1—3. The 1-(1,4-benzoquinon-2-yl)-2-substituted tetralin derivatives (**3a—i**) ($n=1$ or 2) were prepared in 7 or 8 steps from tetralone (**5**) (Chart 1).

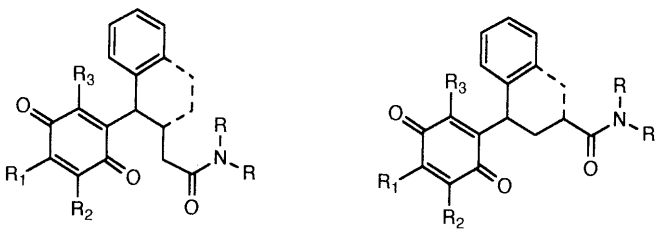
Ethoxycarbonylation of tetralone (**5**), followed by alkylation with ethyl bromoacetate or ethyl acrylate and subsequent hydrolysis and decarboxylation, gave **6a, b** ($n=1$ or 2).[7)] These compounds (**6a, b**) were transformed to the lactone derivatives (**7a, b**) ($n=1$ or 2) in 2 steps by standard methods [(1) $NaBH_4$ reduction, (2) lactonization]. Stereoisomers of **7a, b** were easily separated by column chromatography, and the stereochemistry of each isomer was confirmed by ^{1}H-NMR (coupling constants). The condensation reaction of **7a, b** ($n=1$ or 2) with 2,3-dimethoxy-5-methyl-1,4-hydroquinone catalyzed by Lewis acid (BF_3–Et_2O) or trifluoromethanesulfonic acid, followed by oxidation with cerium ammonium nitrate (CAN) afforded the benzoquinone derivatives (**3a, e**) (Y=OH, $n=1$ or 2) stereoselectively. These (**3a, e**) were transformed to amides by condensation with appropriate amines. Their stereochemistry was determined by ^{1}H-



1 **2**

2a : SUN4757 (R_1,R_2=MeO,R_3=Me, NR_2=thiomorpholino)

Fig. 1



Type I (3) **Type II (4)**

Fig. 2

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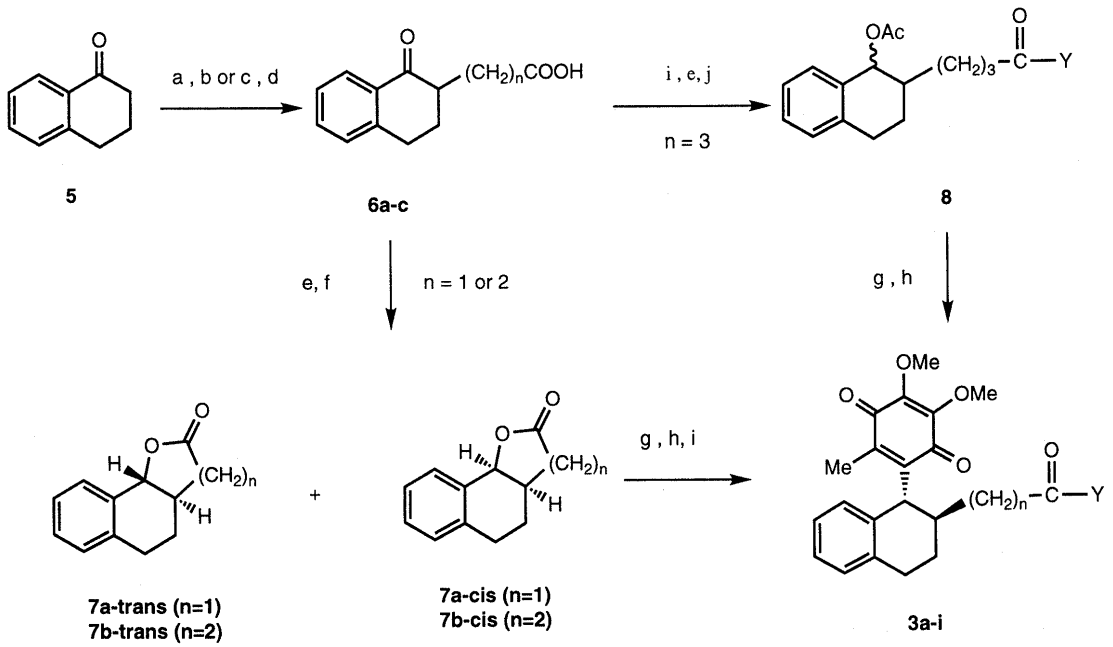


a: $(EtO)_2CO$, NaH b: $Br(CH_2)_nCO_2Et$, NaH c: $H_2C=CHCO_2Et$, NaOEt d: (1) $NaOH/H_2O$ (2) HCl e: $NaBH_4$ f: DCC g: 2,3-dimethoxy-5-methyl-1,4-hydroquinone, BF_3–Et_2O or CF_3SO_3H h: CAN i: HNR_2, DCC j: Ac_2O, DMAP, pyridine

Chart 1

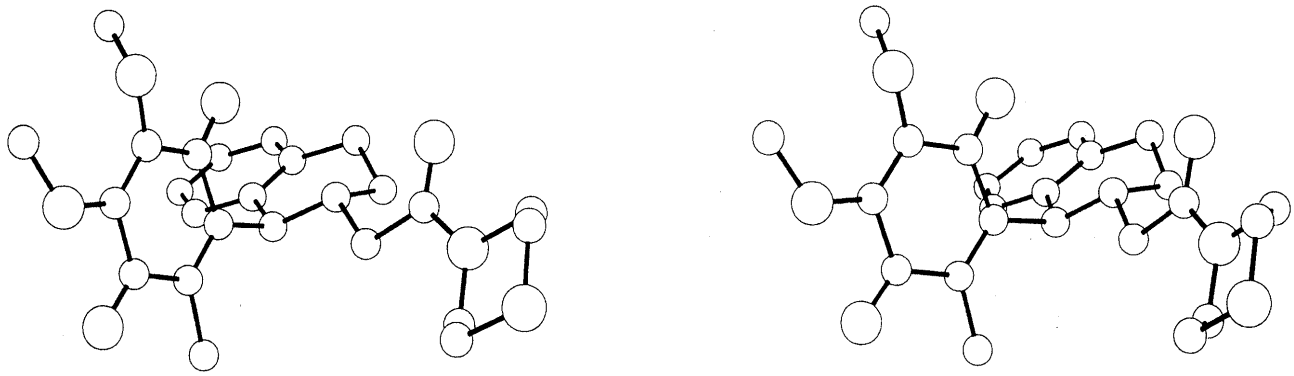


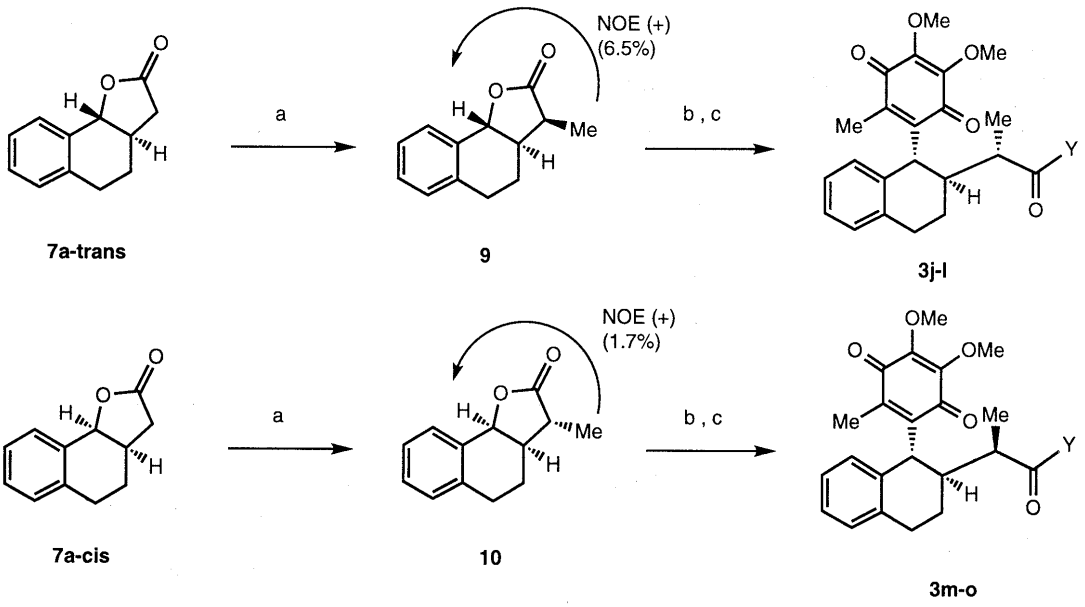
Fig. 3. Stereoscopic View of the Molecule of **3b**

NMR (coupling constants, nuclear Overhauser effect (NOE) spectroscopy (NOESY)) and X-ray crystallography (in the case of compound **3b**) as *trans* (Fig. 3).[8]

2-Substituted tetralin derivatives (**3h, i**) ($n=3$) were also prepared by the method illustrated in Chart 1. 2-Ethoxycarbonyltetralone was alkylated with ethyl bromobutyrate, followed by hydrolysis and decarboxylation to afford **6c** ($n=3$). Compound **6c** was condensed with appropriate amines, followed by reduction and acetylation to afford **8** as diastereomeric mixtures. The condensation reaction of **8** with 2,3-dimethoxy-5-methyl-1,4-hydroquinone and CAN oxidation were carried out in the usual way to afford **3h, i**.

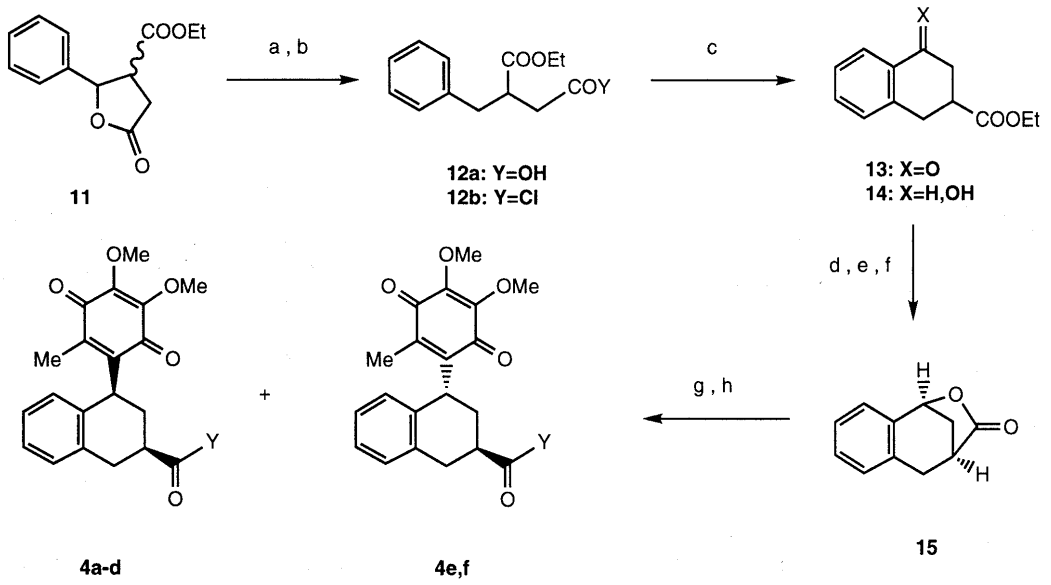
1-(1,4-Benzoquinon-2-yl)tetralin-2-isopropionic acids and related amides (**3j—o**) were synthesized as shown in Chart 2. Treatment of **7a**-*trans* and **7a**-*cis* with lithium isopropylcyclohexylamide, followed by alkylation with 1 eq of methyl iodide afforded **9** and **10**, respectively. Stereostructure of the lactone derivatives could be confirmed by NOE experiments in the ^1H-NMR spectrum. (In both compounds, enhancement of the signal of the proton on C9b was observed upon irradiating the proton of the introduced methyl group.) Condensation and subsequent oxidation reaction proceeded smoothly under usual conditions to give **3j, m** (Y=OH). They were converted to the corresponding amides in the usual way.

3-Substituted tetralin derivatives (**4a—f**) were prepared in 7 or 8 steps from the γ-butyrolactone derivative (**11**) easily obtained by aldol condensation of benzaldehyde and succinic anhydride[9] and subsequent esterification. Catalytic hydrogenation of **11** afforded the monoethyl succinate derivative (**12a**), which was transformed to the acid chloride (**12b**). This was converted to a tetralone derivative (**13**) by Friedel–Crafts reaction catalyzed by a Lewis acid. Reduction of **13** with $NaBH_4$ in EtOH followed by hydrolysis afforded **14** as a diastereomeric mixture, which was converted to the lactone (**15**) in a usual manner. [Stereoselectivity of the reduction was not confirmed and **15** was obtained from the *cis*-isomer.] Condensation reaction of **15** with 2,3-dimethoxy-5-methyl-1,4-hydroquinone and subsequent CAN oxidation was carried out under usual conditions to afford **4a** and **4e** as dia-



a: (1) *N*-isopropylcyclohexylamine, *n*-BuLi (2) MeI b: (1) 2,3-dimethoxy-5-methyl-1,4-hydroquinone, BF_3–Et_2O (2) CAN c: HNR_2, DCC

Chart 2



a: H_2, Pd b: $(COCl)_2$ c: $AlCl_3$ d: $NaBH_4$ e: NaOH, H_2O–THF f: DCC g: (1) 2,3-dimethoxy-5-methyl-1,4-hydroquinone, BF_3–Et_2O (2) CAN h: HNR_2, DCC

Chart 3

stereomeric mixtures.

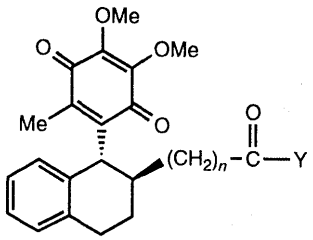
This result suggests that this acid-catalyzed reaction proceeds through a cationic intermediate and the steric (or thermodynamic) effect of the substituent at the 3-position is not significant. Each isomer could be separated by column chromatography and the stereochemistry was determined by ^{1}H-NMR (NOE). [In **4a** (*cis*-isomer), NOE between C(1)-H and C(3)-H was observed.] They were transformed to amides by condensation with appropriate amines.

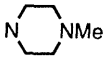
The chemical structures of the above-mentioned compounds were determined on the basis of spectroscopic data [infrared (IR), ^{1}H-NMR, and mass (MS) spectra] and elemental analyses. The physiological data are summarized in Tables 1—3.

Pharmacological Evaluation The ALP activity[10] and antihypoxic activity[11] of the compounds synthesized are listed in Table 4. These compounds are analogues of **2a** (SUN4757), in which rotation about the C(3)–C(4) bond is restricted by cyclization, *via* introduction of methylene units at the *ortho*-position of the benzene ring from the C(2)- or C(3)-position of the butanamide moiety (see Fig. 2). The results of pharmacological evaluation of activity against hypobaric hypoxia in mice are summarized in Table 4.

Compound **3b**, in which a six-membered ring was introduced as conformational restraint, retained the same level of protective activity as the parent (**2a**) (ED_{min}:

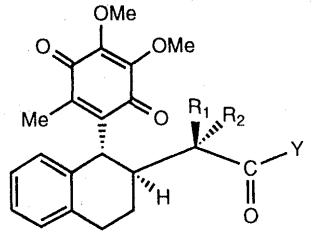
Table 1. Physical Data for **3a—i**



Compound	*n*	Y	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd			Found		
						C	H	N	C	H	N
3a	1	OH	63	*a)*	$C_{21}H_{22}O_6$	68.10	5.99		68.15	6.03	
3b	1		89	150—151	$C_{25}H_{29}NO_6$	68.32	6.65	3.19	68.27	6.79	3.13
3c	1		63	156—157	$C_{25}H_{29}NO_5S$	65.91	6.42	3.07	65.64	6.56	3.09
3d	1		69	*b)*	$C_{26}H_{32}N_2O_5$	69.01	7.13	6.19	69.22	7.25	6.21
3e	2	OH	55	*b)*	$C_{22}H_{24}O_6$		384.1574*c)*			384.1596*c)*	
3f	2		82	117—118	$C_{26}H_{31}NO_6$	68.86	6.89	3.09	68.93	6.95	3.04
3g	2		79	*a)*	$C_{26}H_{31}NO_5S$		469.1923*c)*			469.1938*c)*	
3h	3		38	*b)*	$C_{27}H_{33}NO_6$		467.2308*c)*			467.2340*c)*	
3i	3		30	*b)*	$C_{27}H_{33}NO_5S$		483.2080*c)*			483.2045*c)*	

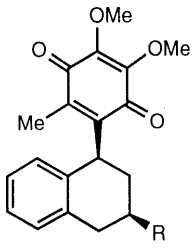
a) Not measured because the compound is extremely hygroscopic. *b)* Obtained as an oil. *c)* Determined by high-resolution mass spectrometry.

Table 2. Physical Data for **3j—o**

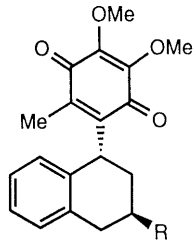


Compound	R_1	R_2	Y	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd			Found		
							C	H	N	C	H	N
3j	H	Me	OH	48	154—155	$C_{22}H_{24}O_6$	68.74	6.29		68.66	6.32	
3k	H	Me		70	167—169	$C_{26}H_{31}NO_6$	68.86	6.89	3.09	68.72	6.85	3.02
3l	H	Me		74	165—167	$C_{26}H_{31}NO_5S$	66.50	6.65	2.98	66.46	6.62	3.02
3m	Me	H	OH	49	157—159	$C_{22}H_{24}O_6$	68.74	6.29		68.75	6.30	
3n	Me	H		73	134—136	$C_{26}H_{31}NO_6$	68.86	6.89	3.09	68.63	6.88	3.02
3o	Me	H		78	108—109	$C_{26}H_{31}NO_5S$	66.50	6.65	2.98	66.48	6.67	3.00

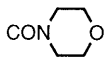
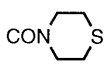
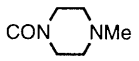
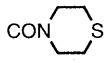
Table 3. Selected Physical Data for **4a—f**



4a—d



4e, f

Compound	R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd			Found		
					C	H	N	C	H	N
4a	COOH	47	76—78	$C_{20}H_{20}O_6$		356.1206[a]			356.1234[a]	
4b		49	80—82	$C_{24}H_{27}NO_6$		425.1838[a]			425.1799[a]	
4c		58	87—89	$C_{24}H_{27}NO_5S$	65.28	6.16	3.17	65.31	6.17	3.21
4d		47	69—71	$C_{25}H_{30}N_2O_5$	68.47	6.90	6.39	68.44	6.95	6.44
4e	COOH	20	156—159	$C_{20}H_{20}O_6$		356.1206[a]			356.1302[a]	
4f		54	58—60	$C_{24}H_{27}NO_6S$	65.28	6.16	3.17	65.30	6.20	3.19

a) Determined by high-resolution mass spectrometry.

Table 4. Pharmacological Evaluation of Selected Compounds

Compd.	Hypobaric hypoxia (% of control) (mg/kg, i.p.)			(mg/kg, *p.o.*)		ALP (%)[c]
	50	25	12.5	50	25	
3a	96			96		92[c]
3b	181**[a]	215**	215**	148*[b]	145	100
3c	105			115		95
3d	133*			136**	139*	100
3e	102			129*		90
3f	223**	205**	162**	179*	114	100
3g	111			119		100
3h	96			86		95
3i	106			117		95
3l	105			130		90
3o	97			93		95
4c	120			141		90
4f	95			98		95
2a	160**	142**	175**	100		81

a) and *b*) Significant differences *versus* control [*, $p<0.05$; **, $p<0.01$]. *c*) Anti-lipid peroxidation activity (% inhibition at 10^{-4} M in rat brain homogenate).

2a = 6.25 mg/kg, i.p. and **3b** = < 12.5 mg/kg, i.p.). Among this series (**3a—i**), compound **3f** ($n=2$) also showed significant activity. These new compounds were more effective than the parent (**2a**) in oral administration (ED_{min}: **3b, f** = 50 mg/kg, *p.o.* and **2a** = no effect at 50 mg/kg, *p.o.*). Compounds **3j—o**, which were prepared as analogues of **3b** with reduced flexibility owing to the introduction of an additional methyl group, did not show enhanced activity (no effect at 50 mg/kg, i.p. and *p.o.*). In contrast, the other six-membered constrained system (**4**) is detrimental to antihypoxic activity. For example, a significant decrease in cerebral protective activity was observed for **4c** and **4f** (no effect at 50 mg/kg, i.p. and *p.o.*). Most of the compounds in this series showed significant ALP activity (over 80% inhibition at 10^{-4} M) and a large difference in IC_{50} values of the ALP activity was not caused by the structural modifications described in this report. These results suggest that the biological activity of these benzoquinones in an *in vivo* functional model may depend on their preferred conformation or lipophilic–hydrophilic nature. But other factors, such as chemical (or biological) stability or bioavailability, should also be taken into consideration.

In conclusion, 2-substituted 1-(1,4-benzoquinon-2-yl)-tetralin derivatives which have one or two carbon unit(s) between the tetralin nucleus and the amide function expressed anti-hypoxic activity. Compounds **3b** and **3f** were found to show cerebral protective activity in animal models (such as normobaric hypoxia, KCN anoxia, hemicolinium-3 anoxia and global ischemia) designed as extensive screening test, and they had high LD_{50} values (> 1000 mg/kg). The results of further investigation of the biological properties of these compounds will be reported in due course.

Experimental

Melting points were determined on a Yanaco melting point apparatus and are uncorrected. The ^{1}H-NMR spectra were recorded on a JEOL JNM-GX270 spectrometer, using tetramethylsilane as an internal standard, and IR spectra were obtained with either a Hitachi 260-10 or a Nicolet 5DX instrument. Elemental analyses were performed on a Perkin-Elmer 240B elemental analyzer. MS were obtained with a Hitachi M80 instrument with a direct inlet system.

1-Tetralone-2-acetic Acid (6a) For preparation of this compound, the conventional procedure gave reproducible results. A suspension of 1-tetralone (10 g, 68.4 mmol), sodium hydride (60%, 3.56 g, 89.0 mmol) and diethyl carbonate (32 g, 0.27 mol) was refluxed for 1 h, then poured into ice-water, adjusted with concentrated hydrochloric acid to a pH of **1** to **2**, and extracted with ether. The extract was washed with water and then dried over magnesium sulfate. After evaporation of the solvent, the crude product was purified by flash column chromatography with hexane–ethyl acetate (9 : 1).

The obtained compound (8.60 g, 39.4 mmol) was dissolved in tetrahydrofuran (THF) (220 ml) and then sodium hydride (60%, 1.90 g, 47.5 mmol) was added under ice-cooling. The mixture was stirred for 30 min, then ethyl bromoacetate (10.0 g, 59.9 mmol) was added, and stirring was continued at room temperature for 3 h. The reaction mixture was poured into ice-water, and extracted with ether. The organic solution was washed with water, dried and evaporated in a conventional manner. The crude product was purified by flash column chromatography with hexane–ethyl acetate (5 : 1). The obtained compound (9.03 g, 29.7 mmol) was dissolved in a mixture of 2 N aqueous sodium hydroxide solution (100 ml) and dioxane (50 ml), followed by heating under reflux for 8 h. The reaction mixture was diluted with water, then adjusted to a pH of 1 to 2 with concentrated hydrochloric acid, and extracted with ether. The organic layer was washed with water, dried and evaporated in a conventional manner to afford **6a** (5.40 g, 26.5 mmol). ^{1}H-NMR ($CDCl_3$) δ: 1.85—2.10 (1H, s), 2.15—2.35 (1H, m), 2.35—2.60 (1H, m), 2.85—3.25 (4H, m), 7.15—7.40 (2H, m), 7.48 (1H, t), 8.03 (1H, d). IR (KBr): 1710, 1682 cm^{-1}. MS *m/z*: 204 (M^+).

1-Tetralone-2-propionic Acid (6b) Ethyl 1-tetralone-2-carboxylate (5.00 g, 22.9 mmol) was added into an ethanolic solution (300 ml) of sodium ethoxide prepared from 158 mg (6.70 mmol) of sodium, and then ethyl acrylate (2.99 g, 29.9 mmol) was added, followed by stirring at room temperature for 4 h.

The reaction mixture was worked up in a usual way and the crude product was subjected to hydrolysis and decarboxylation by a similar procedure to that used for the synthesis of **6a**, to afford **6b** (3.71 g, 17.0 mmol). ^{1}H-NMR ($CDCl_3$) δ: 1.70—2.05 (2H, m), 2.10—2.40 (2H, m), 2.40—2.70 (3H, m), 2.90—3.10 (2H, m), 7.10—7.40 (2H, m), 7.46 (1H, t), 8.01 (1H, d). IR (KBr): 1706, 1678 cm^{-1}. MS *m/z*: 218 (M^+).

1-Tetralone-2-butyric Acid (6c) Ethyl 1-tetralone-2-carboxylate (10.0 g, 45.9 mmol) was dissolved in 1,2-dimethylethane (DME) (50 ml) and added to a suspension of sodium hydride (60%, 2.30 g, 57.5 mmol) in DME (250 ml) under ice-cooling. Then ethyl 4-bromobutyrate (14.4 g, 71.8 mmol) was added, followed by heating under reflux for 6 h. The reaction mixture was poured into ice-water, followed by extraction with ether. The organic solution was washed with water, dried, evaporated and purified. The product was subjected to hydrolysis and decarboxylation by a similar procedure to that used for the synthesis of **6a**, to afford **6c** (3.98 g, 17.2 mmol). ^{1}H-NMR ($CDCl_3$) δ: 1.40—2.10 (5H, m), 2.10—2.60 (4H, m), 2.85—3.10 (2H, m), 7.05—7.55 (4H, m), 8.02 (1H, d). IR ($CDCl_3$): 1708, 1679 cm^{-1}. MS *m/z*: 232 (M^+).

(3a*R,9b*R**)- and (3a*R**,9b*S**)-3a,4,5,9b-Tetrahydronaphtho[1,2-*b*]furan-2(3*H*)-one (7a)** Sodium borohydride (2.24 g, 58.9 mmol) was added to a solution of (**6a**) (4.00 g, 19.6 mmol) in ethanol (100 ml) under ice-cooling, followed by stirring at room temperature for 5 h. The reaction mixture was concentrated under reduced pressure, then diluted with water, adjusted to a pH of 1 to 2 with concentrated hydrochloric acid and extracted with ether. The extract was concentrated and the crude product was dissolved in methylene chloride (220 ml). This solution was treated with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, and the mixture was stirred at room temperature for 3 h.

The solution was washed with water, dried and evaporated, and the crude product was purified by flash column chromatography with hexane–ethyl acetate (5 : 2) to obtain two isomers, (**7a**-*trans*) (1.91 g, 10.2 mmol) and (**7a**-*cis*) (0.64 g, 3.4 mmol).

(**7a**-*trans*): ^{1}H-NMR ($CDCl_3$) δ: 1.65—1.95 (1H, m), 2.10—2.55 (3H, m), 2.55—2.85 (1H, m), 2.85—3.15 (2H, m), 4.97 (1H, d, J=10.4 Hz), 7.00—7.50 (4H, m). IR (KBr): 1782 cm^{-1}. MS *m/z*: 188 (M^+).

(**7a**-*cis*): ^{1}H-NMR ($CDCl_3$) δ: 1.50—1.75 (1H, m), 1.80—2.00 (1H, m), 2.30—2.50 (1H, m), 2.60—3.00 (4H, m), 5.42 (1H, d, J=6.1 Hz), 7.05—7.55 (4H, m). IR (KBr): 1766 cm^{-1}. MS *m/z*: 188 (M^+).

(4a*R,10b*R**)- and (4a*R**,10b*S**)-3,4,4a,5,6,10b-Hexahydro-2*H*-naptho[1,2-*b*]pyran-2-one (7b)** Using a procedure similar to that described above, **7b**-*trans* (1.33 g, 6.58 mmol) and **7b**-*cis* (0.57 g, 2.82 mmol) were obtained from **6b** (3.81 g, 17.5 mmol).

(**7b**-*trans*): ^{1}H-NMR ($CDCl_3$) δ: 1.45—1.80 (2H, m), 1.80—2.20 (3H, m), 2.55—3.10 (4H, m), 5.10 (1H, d, J=10.4 Hz), 7.00—7.30 (3H, m), 7.50—7.70 (1H, m). IR (KBr): 1726 cm^{-1}. MS *m/z*: 202 (M^+).

(**7b**-*cis*): ^{1}H-NMR ($CDCl_3$) δ: 1.60—2.00 (3H, m), 2.10—2.40 (2H, m), 2.40—2.70 (2H, m), 2.70—3.00 (2H, m), 5.32 (1H, d, J=5.2 Hz), 7.00—7.55 (4H, m). IR ($CDCl_3$): 1728 cm^{-1}. MS *m/z*: 202 (M^+).

Mixture of (1*R,2*R**)- and (1*R**,2*S**)-1-Acetoxy-1,2,3,4-tetrahydronapthalene-2-butanamides (8)** A solution of **6c** (499 mg, 2.15 mmol) and thiomorpholine (276 mg, 2.68 mmol) in methylene chloride (30 ml) was treated with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (620 mg, 3.23 mmol), followed by stirring at room temperature for 3 h. The reaction mixture was washed with 1 N hydrochloric acid and water, and dried. After evaporation of the solvent, the residue was dissolved in EtOH (20 ml), and this solution was treated with sodium borohydride (122 mg, 3.21 mmol) under ice-cooling, followed by stirring at room temperature for 6 h. Conventional work-up gave a crude product, which was acetylated in a mixture of acetic anhydride, pyridine and methylene chloride. After evaporation, the residue was purified by flash column chromatography to afford **8a** (600 mg, 1.66 mmol) as a diastereomeric mixture.

Thiomorpholine Amides (**8a**): ^{1}H-NMR ($CDCl_3$) δ: 1.20—1.55 (2H, m), 1.55—1.90 (4H, m), 1.90—2.00 (1H, m), 2.04, 2.10 (3H, each s), 2.20—2.45 (2H, m), 2.50—2.70 (4H, m), 2.70—3.00 (2H, m), 3.60—4.00 (4H, m), 5.79, 6.08 (1H, d, s-like), 7.00—7.40 (4H, m). IR ($CHCl_3$): 1724, 1638 cm^{-1}. MS *m/z*: 361 (M^+).

Morpholine Amides (**8b**): ^{1}H-NMR ($CDCl_3$) δ: 1.20—1.55 (2H, m), 1.55—1.90 (4H, m), 1.90—2.20 (1H, m), 2.04, 2.10 (3H, each s), 2.20—2.40 (2H, m), 2.70—3.00 (2H, m), 3.35—3.75 (8H, m), 5.78, 6.07 (1H, each d), 7.05—7.40 (4H, m). IR ($CHCl_3$): 1728, 1636 cm^{-1}. MS *m/z*: 345 (M^+).

(1*R,2*R**)-1-(5,6-Dimethoxy-3-methyl-1,4-benzoquinon-2-yl)-1,2,3,4-tetrahydro-2-naphthaleneacetic Acid (3a)** 2,3-Dimethoxy-5-methyl-1,4-hydroquinone (636 mg, 3.46 mmol) and boron trifluoride–ether complex (566 mg, 3.99 mmol) were added to a solution of **7a**-*trans* or *cis* (500 mg, 2.66 mmol) in 1,2-dichloroethane (20 ml), followed by stirring at room temperature for 16 h. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in a mixture of acetonitrile (15 ml) and water (5 ml). To this solution, CAN (4.74 g, 8.65 mmol) was added, followed by stirring at room temperature for 30 min. The reaction mixture was diluted with water, then extracted with ether. The extract was washed with water, dried and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography with 2—5% methanol–methylene chloride to afford **3a** (620 mg, 1.68 mmol). The physical data are listed in Table 1.

(1*R,2*R**)-1-(5,6-Dimethoxy-3-methyl-1,4-benzoquinon-2-yl)-1,2,3,4-tetrahydro-2-naphthalenepropionic Acid (3e)** Compound **3e** was synthesized by similar procedure to that used for the synthesis of **3a** from **7b**-*trans* or -*cis*. The physical data are listed in Table 1.

(1*R,2*R**)-1-(5,6-Dimethoxy-3-methyl-1,4-benzoquinon-2-yl)-1,2,3,4-tetrahydro-2-naphthaleneacetamides (3b)** A solution of **3a** (348 mg, 0.94 mmol) and thiomorpholine (145 mg, 1.41 mmol) in methylene chloride (20 ml) was treated with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (270 mg, 1.41 mmol), followed by stirring at room temperature for 4 h. The usual work-up and purification by silica gel column chromatography with hexane–ethyl acetate afforded **3b** (270 mg, 0.59 mmol). Compounds **3c, d, f**—**i** were synthesized by a similar procedure to that described above. The physical data are listed in Table 1.

(1*R,2*S**)-1-(5,6-Dimethoxy-3-methyl-1,4-benzoquinon-2-yl)-1,2,3,4-tetrahydro-2-napthalenebutanamides** Compounds **3h, i** were synthesized by the similar procedure to that used for the synthesis of **3a** from **8a, b**. The physical data are listed in Table 1.

(3*R,3a*S**,9b*S**)-3a,4,5,9b-Tetrahydro-3-methylnaptho[1,2-*b*]furan-2(3*H*)-one (9)** A solution of **7a**-*trans* (1.00 g, 5.32 mmol) in THF (5 ml) was added to a solution of lithium isopropylcyclohexylamide, prepared from isopropylcyclohexylamine (750 mg, 5.32 mmol) and *n*-BuLi (1.57 M solution in hexane, 3.39 ml) in THF (20 ml), at −78 °C, followed by stirring at same temperature for 30 min. Then methyl iodide (793 mg, 5.59 mmol) was added, followed by further stirring at the same temperature for 2 h. The reaction mixture was poured into water and extracted with ether. The organic solution was washed with water, dried and evaporated. The crude product was purified by flash column chromatography with hexane–ethyl acetate (6 : 1) to afford **9** (430 mg, 2.13 mmol). ^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, d), 1.65—1.90 (1H, m), 1.90—2.10 (1H, m), 2.35—2.60 (2H, m), 2.60—2.95 (2H, m), 5.52 (1H,

d), 7.00—7.55 (4H, m). IR ($CHCl_3$): 1770 cm^{-1}. MS *m/z*: 202.

Compound **10** was obtained by a similar procedure from **7a**-*cis*. ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, d), 1.70—1.95 (1H, m), 1.95—2.15 (1H, m), 2.25—2.45 (1H, m), 2.70—2.90 (1H, m), 2.90—3.10 (2H, m), 5.13 (1H, d), 7.05—7.50 (5H, m). IR ($CHCl_3$): 1778 cm^{-1}. MS *m/z*: 202 (M^+).

(1*R,2*S**)-1-(5,6-Dimethoxy-3-methyl-1,4-benzoquinon-2-yl)-2-[1-(*S**)-carboxyethyl]-1,2,3,4-tetrahydronaphthalene (3j) and the Isomer (3m)** These compounds were prepared by a similar procedure to that used for the synthesis of **3a**. Compounds **3k,l** and **3n,o** were prepared by a similar procedure to that used for the synthesis of **3b**. The physical data for these compounds are listed in Table 2.

Ethyl 1,2,3,4-Tetrahydro-4-oxo-2-naphthoate (13) β-Ethoxycarbonyl-γ-phenyl-γ-butyrolactone (**11**) (*trans* isomer > 80%) (3.30 g, 14.1 mmol) was added to a suspension of palladium–black [prepared from 1.00 g of palladium chloride] in dioxane (40 ml), followed by stirring at room temperature for 16 h under a hydrogen gas stream. After filtration, the filtrate was concentrated under reduced pressure to afford β-ethoxycarbonyl-γ-phenylbutyric acid (**12a**) (3.32 g). Then 1.30 g (5.51 mmol) of the obtained compound (**12a**) was added to oxalyl chloride (20 ml), followed by stirring at room temperature for 5 h. After removal of excess reagent, the residue was dissolved in 1,2-dichloroethane (70 ml). To this solution, anhydrous aluminum chloride (806 mg, 6.06 mmol) was added under ice-cooling, followed by stirring at room temperature for 16 h. The reaction mixture was poured into 1 N aqueous hydrochloric acid, and extracted with ether. The organic solution was washed with water, dried and evaporated. The crude product was purified by silica gel column chromatography with hexane–ethyl acetate (2 : 1) to give **13** (864 mg, 3.96 mmol). ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, s), 2.70—3.05 (2H, m), 3.05—3.35 (3H, m), 4.17 (2H, q), 7.20—7.40 (2H, m), 7.50 (1H, t), 8.03 (1H, d). IR ($CHCl_3$): 1728, 1683 cm^{-1}. MS *m/z*: 218 (M^+).

3-Oxo-1,3,4,5-tetrahydro-1,4-methano-2-benzoxepin (15) Sodium borohydride (1.51 g, 39.7 mmol) was added to a solution of **13** (2.88 g, 13.2 mmol) in ethanol (80 ml) under ice-cooling and the mixture was stirred at room temperature for 4 h, then concentrated under reduced pressure. The residue was diluted with 2 N hydrochloric acid and extracted with ether. The organic solution was washed, dried and evaporated, and the crude product was dissolved in a mixture of 3% aqueous potassium hydroxide (100 ml) and dioxane (50 ml). This solution was stirred at room temperature for 8 h, then poured into water, adjusted to pH 1 to 2 with concentrated hydrochloric acid and extracted with ether. The organic solution was washed with water, dried and evaporated, and the crude product was dissolved in methylene chloride (500 ml). To this solution, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (5.03 g, 26.2 mmol) was added, followed by stirring at room temperature for 4 h. The mixture was washed with water, dried and evaporated. The crude product was purified by silica gel column chromatography with hexane–ethyl acetate (3 : 1) to afford **15** (971 mg, 5.58 mmol). ^{1}H-NMR ($CDCl_3$) δ: 2.20 (1H, d), 2.60—2.80 (1H, m), 2.90—3.30 (3H, m), 5.29 (1H, d), 7.00—7.40 (4H, m). IR ($CHCl_3$): 1768 cm^{-1}. MS *m/z*: 174 (M^+).

(1*R,3*R**)- and (1*R**,3*S**)-1-(5,6-Dimethoxy-3-methyl-1,4-benzoquinon-2-yl)-1,2,3,4-tetrahydronaphthalene-3-carboxylic Acid (4a, e)** 2,3-Dimethoxy-5-methyl-1,4-hydroquinone (654 mg, 3.55 mmol) and boron trifluoride–ether complex (582 mg, 4.10 mmol) were added to a solution of **15** (476 mg, 2.74 mmol) in 1,2-dichloroethane (20 ml) at room temperature and the reaction mixture was stirred at same temperature for 16 h. It was then concentrated under reduced pressure and the residue was dissolved in a mixture of acetonitrile (15 ml) and water (5 ml). To this solution, CAN (4.87 g, 8.89 mmol) was added, followed by stirring at room temperature for 30 min. The reaction mixture was poured into water and extracted with ether.

The organic solution was washed with water, dried and evaporated. The crude product was purified by silica gel column chromatography with 5% methanol–methylene chloride to afford **4a** (120 mg), **4e** (83 mg) and **4a**+**4e** (450 mg). The physical data of these compounds are listed in Table 3.

Compounds **4b—d,f** were synthesized by the similar method to that used for the synthesis of compound **3b** from **4a** or **4e** and their physical data are listed in Table 3.

Pharmacological Evaluation ALP Activity Assay: The supernatant fraction of rat brain homogenate was prepared according to the method of Stocks *et al.*[10] The whole brain except the cerebellum of male Wistar rats weighing 200—250 g was obtained after decapitation and homogenized in an ice-cold phosphate–saline buffer (50 mM, pH 7.4) at a volume of 9 ml per 1 g tissue. The homogenate was centrifuged for 15 min at $1000 \times g$, and the supernatant was stored at -30 °C for later assay. To utilize the stocked supernatant, the sample was diluted 3-fold with the same phosphate-saline buffer. The diluted sample (1 ml) was incubated at 37 °C for 30 min either with the test compound dissolved in 10 μl of dimethyl sulfoxide or with the vehicle. After the addition of 2.0 ml of ice-cold 35% $HClO_4$, the resulting mixture was centrifuged at $1000 \times g$ for 15 min. The lipid peroxide in the supernatant was determined by the thiobarbituric acid (TBA) method and expressed as malondialdehyde (MDA) per mg of protein.

An assay for cerebral protective activity (hypobaric hypoxia) was carried out according to the method described by Nakanishi *et al.*[11] The ED_{min} was determined as the minimum effective dose at which the drug significantly prolongs the survival time in mice under a hypoxic condition as compared with the vehicle-treated group. The initial dose administered was 25 or 50 mg/kg (i.p., *p.o.*) and the subsequent dose was reduced to 1/2 of the initial when it was effective. The statistical evaluation was carried out by means of the F-test followed by Studient's *t*-test.

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References and Notes

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