Novel Cerebroprotective Agents with Central Nervous System Stimulating Activity. 1. Synthesis and Pharmacology of 1-Amino-7-hydroxyindan Derivatives

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To develop a novel cerebroprotective agent with central nervous system (CNS) stimulating activity, a series of 1-amino-7-hydroxyindan derivatives was synthesized, and their effects on the survival time of mice under hypoxic conditions were tested. CNS-stimulating activity was also evaluated by examining the promotional effect on the recovery from cerebral concussion induced coma in mice. Several compounds prolonged the survival time of mice in hypoxic conditions at a dose of 30 mg/kg (sc or ip) and 100 mg/kg (po). They also exhibited the promotional effects on recovery from coma at a dose of 100 mg/kg po. The three most potent compounds in both tests, 1-amino-7-hydroxy-6-(1-methylpropyl)indan (**20**), 1-amino-7-hydroxy-4,6-dimethyl-2-phenylindan (**30**), and 1-amino-7-hydroxy-2,2,4,6-tetramethylindan (**35**) were selected for further investigations. Structure–activity relationships were also discussed.

It is well-accepted that brain metabolism is highly dependent on oxygen supply to the brain and that oxygen deprivation is one of the common and most damaging conditions affecting brain functions. Such oxygen deprivation occurs in a variety of clinical situations including cardiac arrest, asphyxia, cerebral trauma, traffic accidents, stroke, and cerebral ischemia. When oxygen supply to the brain becomes deficient, cerebral function rapidly ceases, or in the survivor, neurological deficits occur resulting from the synaptic neurotransmitter dysfunctions or neuronal death.[1-5]

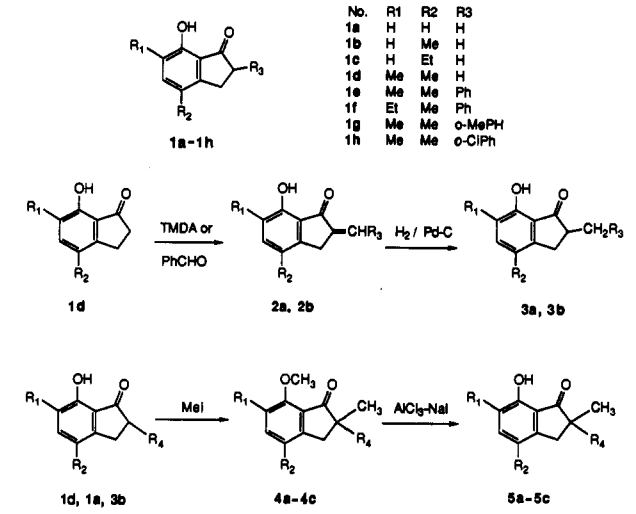
Central nervous system (CNS) depressants, barbiturates, have been reported to exert protective effects against brain damage in oxygen-deprivation conditions in experimental models[6,7] and also in man.[3] However, the protective effect has been observed only at a high dose, at which a marked sedation or motor depression has been known to be induced. These severe side effects made the barbiturate therapy a last-choice treatment. At present, there are no effective therapies available for use in the acute stage of ischemic–anoxic insult.[8]

On the other hand, CNS activators, cerebral metabolism enhancers, cerebral vasodilators, or neurotransmitter modifiers are currently used in the clinical treatment of symptoms in the chronic stage of ischemic–anoxic insults. However, the cerebroprotective effects of CNS activators have not been reported.

We have been interested in the development of a novel cerebroprotective drug which would possess CNS-stimulating activity and could be used throughout the period from acute to chronic stages of cerebral anoxic insult.

Though the mechanisms of barbiturate protection against brain damage have not been fully explained, one mechanism suggested its radical-scavenging action.[3] Recently, vitamin E (α-tocopherol), which seems to have no CNS depressive action, has been reported to protect against brain damage in the rat under hypoxic conditions by scavenging free oxygen radicals and by prevention of lipid peroxide formation.[9]

Scheme I



To find target compounds which would possess the desired dual activities, two pharmacological tests, the test for antihypoxic effect and for a promotional effect on recovery from coma, were used as primal screening tests. Barbiturates have been reported to prolong the survival of mice or rats in the test for antihypoxic effect.[10] The CNS activator thirotropine releasing hormone (TRH) has been known to show a promoting effect in the test for a promotional effect on recovery from coma.[11] In a random screening of compounds with a phenolic hydroxyl group, 1-amino-4,6-dimethyl-7-hydroxyindan (**13**), which had been prepared for the investigation of an antiinflammatory agent with a radical scavenging activity,[12] was found. This compound prolonged the survival of mice in the hypoxic conditions at a dose of 30 mg/kg sc. Furthermore, it promoted recovery from coma in mice at a dose of 100 mg/kg po. A series of the 1-amino-7-hydroxyindan derivatives was synthesized, and the dual activities were examined.

In this paper, the synthesis and preliminary pharmacological examination of the 1-amino-7-hydroxyindan derivatives are described.

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(2) Hall, E. D.; Braughler, J. M. *Free Radical Med.* **1989**, *6*, 303.
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(4) Nemoto, E. M. Brain and Heart Infarct, Springler Verlag: New York, 1977; p 306.
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(7) Yasuda, H.; Shuto, S.; Tsugami, T.; Nakajima, A. *Arch. Int. Pharmacodyn.* **1973**, *233*, 133.
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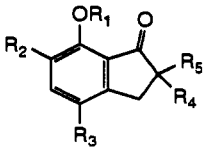
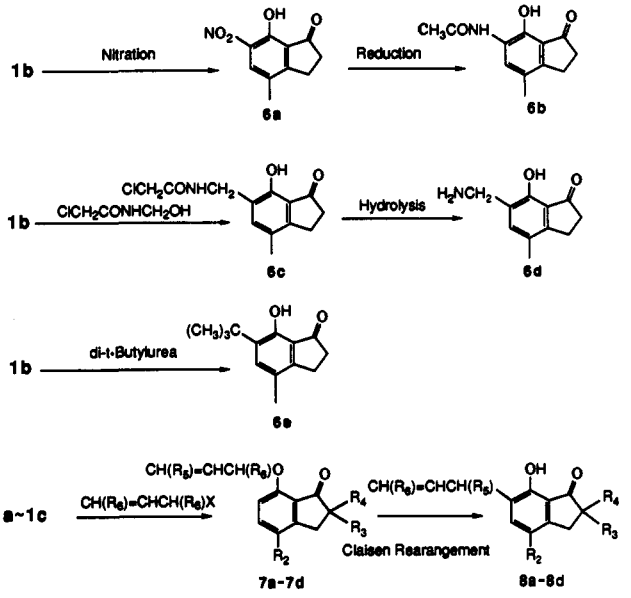
Table I. 7-Hydroxy-1-indanone and the 7-Methoxy-1-indanone Derivatives



no.	R_1	R_2	R_3	R_4	R_5	methods	% yield[a]	recryst solvent	mp, °C	formula	anal.[b]
1c	H	H	Et	H	H	A	35	EtOH	91.5–92.5	$C_{11}H_{12}O_2$	C, H
1e	H	Me	Me	Ph	H	B	77	EtOH	90.5–91	$C_{17}H_{16}O_2$	C, H
1f	H	Et	Me	Ph	H	B	68		oil	c	
1g	H	Me	Me	*o*-ClPh	H	B	69	EtOH	92–93	$C_{17}H_{15}O_2Cl$	C, H
1h	H	Me	Me	*o*-MePh	H	B	15	ether	118–120	$C_{18}H_{18}O_2$	C, H
2a	H	Me	Me	$=CH_2$		C	83	EtOH	131–134	$C_{12}H_{12}O_2 \cdot 0.6H_2O$	C, H
2b	H	Me	Me	$=CHPh$		D	95	EtOH	161–162	$C_{18}H_{16}O_2 \cdot 0.5H_2O$	C, H
3a	H	Me	Me	Me	H	C	27	hexane	84–85	$C_{12}H_{14}O_2 \cdot 0.5H_2O$	C, H[d]
3b	H	Me	Me	CH_2Ph	H	D	91	EtOH	107–108	$C_{18}H_{18}O_2$	C, H
4a	Me	Me	Me	Me	Me	E	54		oil	c	
4b	Me	Me	Me	CH_2Ph	Me	E	90		oil	c	
4c	Me	Me	Me	Ph	Me	E	79		oil	c	
5a	H	Me	Me	Me	Me	E	101	hexane	51–52	c	
5b	H	Me	Me	Ch_2Ph	Me	E	80	EtOH	86–87	$C_{19}H_{20}O_2$	C, H
5c	H	Me	Me	Ph	Me	E	79	EtOH	93–94	$C_{18}H_{18}O_2$	C, H
6b	H	$NHCOCH_3$	Me	H	H	F	52	MeOH	193–198	$C_{12}H_{13}NO_3$	C, H, N
6c	H	$CH_2NHCOCH_2Cl$	Me	H	H	G	80	EtOH	166–167.5	$C_{13}H_{14}NO_3Cl$	C, H, N
6d	H	CH_2NH_2	Me	H	H	G	39	EtOH	>300	$C_{11}H_{13}NO_2 \cdot HCl$	C, H, N
6e	H	$C(CH_3)_3$	Me	H	H	H	95	hexane	181–182	$C_{14}H_{18}O_2$	C, H
8a	H	$CH_2CH=CH_2$	H	H	H	I	48		oil	c	
8b	H	$CH_2CH=CH_2$	Me	H	H	I	84	petroleum ether	41–45	$C_{13}H_{14}O_2$	C, H
8c	H	$CH(CH_3)CH=CH_2$	Me	H	H	I	79	hexane	62.5–64	$C_{14}H_{16}O_2$	C, H
8d	H	$CH_2CH=CH_2$	Et	H	H	I	63		oil	c	

[a] Yields were not optimized in most cases. [b] C, H, N analyses were within ±0.4% of the calculated value. [c] This compound was isolated but not purified or analyzed before use in the next step; see the Experimental Section. [d] H: calcd, 7.59; found, 6.90.

Scheme II

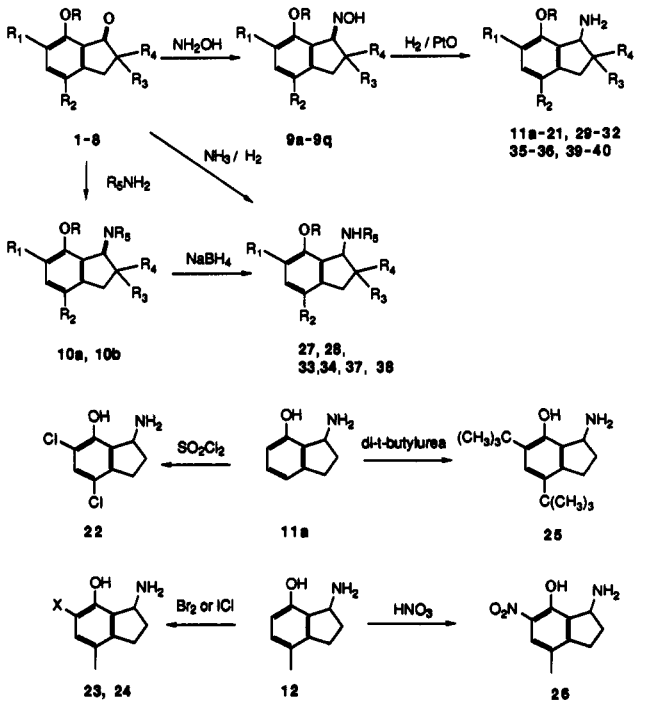


Chemistry

The 7-hydroxyl-1-aminoindans prepared are listed in Tables I–III, and their synthetic routes were outlined in Schemes I–III. The intermediates, indanones, were prepared by several methods as shown in Schemes I and II.

The methods of preparation of the simple 7-hydroxy-2-unsubstituted-1-indanone derivatives 7-hydroxy-1-indanone (**1a**),[13,14] 7-hydroxy-4-methyl-1-indanone (**1b**),[15,16]

Scheme III



and 4,6-dimethyl-7-hydroxy-1-indanone (**1d**)[17] have been reported. 6-Ethyl-7-hydroxy-1-indanone (**1c**) was prepared by the same method as reported for preparation of **1d**. The 2-phenyl-substituted-7-hydroxy-1-indanone derivatives (**1e–h**) were prepared by adopting the procedure reported

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(15) Hayes, N. F.; Thomson, R. H. *J. Chem. Soc.* **1956**, 1585.
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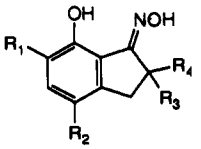
(17) Deana, A. A.; Stokker, G. E.; Schulz, E. M.; et al. *J. Med. Chem.* **1983**, *26*, 580.

Table II. 7-Hydroxy-1-indanone Oximes



no.	R_1	R_2	R_3	R_4	method	% yield[a]	recryst solvent	mp, °C	formula	anal.[b]
9a	H	H	H	H	J	62	MeOH	147–148.5	$C_9H_9NO_2$	C, H, N
9b	H	Me	H	H	J	96	MeOH	148–149.5	$C_{10}H_{11}NO_2$	C, H, N
9c	Me	Me	H	H	J	86	EtOH	133–136	$C_{11}H_{13}NO_2$	C, H, N
9d	$NHCOCH_3$	Me	H	H	J	90	MeOH	192.5–196	$C_{12}H_{14}N_2O_3 \cdot 0.5H_2O$	C, H, N
9e	$CH_2NHCOCH_2Cl$	Me	H	H	J	77	EtOH	195–197	$C_{13}H_{15}N_2O_3Cl$[c]	C, H, N
9f	$CH_2CH{=}CH_2$	H	H	H	J	74	hexane	104–104.5	$C_{12}H_{13}NO_2$	C, H, N
9g	$CH_2CH{=}CH_2$	Me	H	H	J	66	hexane	96.5–98.5	$C_{13}H_{15}NO_2$	C, H, N
9h	$CH(CH_3)CH{=}CH_2$	Me	H	H	J	73	hexane/ether	161.5–164	$C_{14}H_{17}NO_2$	C, H, N
9i	$CH_2CH{=}CH_2$	Et	H	H	J	78	hexane	91.5–92	$C_{14}H_{17}NO_2$	C, H, N
9j	$C(CH_3)_3$	Me	H	H	J	86	MeOH	221–224	$C_{14}H_{19}NO_2$	C, H, N
9k	Me	Me	Ph	H	K	63	EtOH	173–175	$C_{17}H_{17}NO_2$	C, H, N
9l	Et	Me	Ph	H	K	46	EtOH	148–149	$C_{18}H_{19}NO_2$	C, H, N
9m	Me	Me	o-ClC_6H_4	H	K	88	EtOH	182–183	$C_{17}H_{16}NO_2Cl$	C, H, N
9n	Me	Me	Me	H	K	70	hexane	104–105	$C_{12}H_{15}NO_2$	C, H, N
9o	Me	Me	Me	Me	K	89	hexane	156–157	$C_{13}H_{17}NO_2$	C, H, N
9p	Me	Me	Ph	Me	K	79	EtOH	181–183	$C_{18}H_{19}NO_2$	C, H, N

[a] Yields were not optimized in most cases. [b] C, H, N analyses were within ±0.4% of the calculated value. [c] C: calcd, 55.22; found, 55.67.

for the preparation of 2-cyclopentyl-6,7-dichloro-5-methoxy-1-indanone.[18]

Scheme I shows the preparation of the 2-substituted 7-hydroxy-1-indanones. Catalytic hydrogenation of the α,β-unsaturated cyclic ketone (**2a**), which was prepared by means of Mannich reaction of **1d** with *N,N,N′,N′*-tetramethyldiaminomethane (TMDM) in acetic anhydride,[19] afforded 7-hydroxy-2,4,6-trimethyl-1-indanone (**3a**). Aldol condensation of **1d** with benzaldehyde in the presence of diazabicyclo[5.4.0]undec-7-ene (DBU) gave 2-benzilydene-1-indanone (**2b**). Catalytic hydrogenation of **2b** yielded 2-benzyl-4,6-dimethyl-7-hydroxy-1-indanone (**3b**). Methylation of the 7-hydroxy-1-indanones with excess methyl iodide (MeI) in the presence of sodium hydride afforded 2,2-dimethyl-7-methoxy-1-indanones (**4a–4c**). Attempts at 2-monoalkylation of the 2-unsubstituted 1-indanones with MeI, isopropyl iodide, or benzyl bromide by the same procedure as described above were unsuccessful. Demethylation of **4a–4c** with aluminum chloride in acetonitrile in the presence of sodium iodide yielded the 7-hydroxy-2-methyl-substituted-1-indanones (**5a–c**).

Scheme II shows the chemical modifications of the 6-unsubstituted 7-hydroxy-1-indanons. Nitration of 7-hydroxy-4-methyl-1-indanone (**1b**) with fuming nitric acid in acetic acid gave 7-hydroxy-4-methyl-6-nitro-1-indanone (**6a**). Catalytic hydrogenation of **6a** in glacial acetic acid directly afforded 6-(acetylamino)-7-hydroxy-4-methyl-1-indanone (**6b**). Amidoalkylation of **1b** with *N*-(hydroxymethyl)-α-chloroacetoamide[20] in sulfuric acid yielded 6-[[(chloroacetyl)amino]methyl]-7-hydroxy-4-methyl-1-indanone (**6c**), and subsequent hydrolysis of **6c** with 6 N-hydrochloric acid gave 6-(aminomethyl)-7-hydroxy-4-methyl-1-indanone (**6d**).[21] Alkylation of **1b** with di-*tert*-butylurea in a 70% sulfuric acid solution[22] afforded the *tert*-butylated 1-indanone (**6e**). Alkylation of the 7-hydroxy-1-indanons (**1a–c**) with allyl halides gave the intermediate allyl ethers **7a–d**, which underwent Claisen rearrangement to afford **8a–d**.

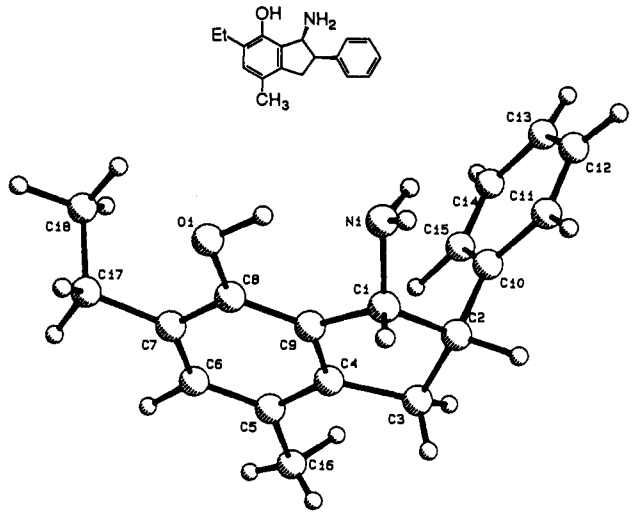


Figure 1. Perspective drawing of compound **31**, based on X-ray crystallographic data.

Scheme III shows the methods of preparation of the final compounds' 1-aminoindan derivatives (**11a–40**). 1-Amino-7-hydroxyindan (**11a**) has been known in the literature[23] and the positional isomers of **11a**, 4-, 5-, and 6-hydroxy-1-aminoindan, have been claimed in patents to be antidepressants.[24,25] However, the details of the preparation have not been reported. Another compound, 1-amino-4,6-dimethyl-7-hydroxyindan,[17] was reported after our patent application.[12] The methods of preparation of these compounds except 5-hydroxy-1-aminoindan, which could not be isolated for its instability, are included in the Experimental Section.

The 1-indanones (**1a–8d**) were converted to their oximes (**9a–q**) and subsequent catalytic hydrogenations of the oximes in the presence of platinum as a catalyst afforded the 1-aminoindans (**11a–21, 29–32, 35, 36, 39** and **40**).

(18) Woltersdorf, O. W., Jr.; deSolms, S. J.; Schultz, E. M., et al. *J. Med. Chem.* **1977**, *20*, 1400.
(19) desolms, S. J. *J. Org. Chem.* **1976**, *41*, 2650.
(20) Zaugg, H. E.; Martin, W. B. *Org. React.* **1965**, *14*, 52.
(21) Stokker, G. E.; Deana, A. A.; deSolms, S. J.; et al. *J. Med. Chem.* **1980**, *23*, 1414.
(22) Neurekar, N. B.; Sawardeka, S. R.; Pandit, T. S.; et al. *Chem. Ind.* **1983**, 206.
(23) Breslow, R.; McClure, D. E. *J. Am. Chem. Soc.* **1976**, *98*, 258.
(24) Ward, M.; Slough, G.; Williams, J.; et al., US Patent, 3,709,996, 1973.
(25) G. B. Patent, 1249375, 1971.

Compounds 33 and 34 were prepared by means of reductive amination of 1g and 1h, respectively, in the presence of 5% palladium on carbon as a catalyst. The 1-(alkylamino)indans (27 and 28) were obtained from the imines (10a and 10b) by reduction with sodium borohydride. In the catalytic hydrogenation of the oximes with allyl groups at the 6-position (9f–i), the reduction of the allyl groups was accompanied by that of the oxyimino group (17–21). Catalytic hydrogenation of the 2-phenyl-1-indanone oximes yielded only the 1,2-cis isomer (30–32). The 1,2-cis configuration of these derivatives was confirmed by X-ray crystallographic analysis of 6-ethyl-7-hydroxy-4-methyl-2-phenyl-1-aminoindan (31), as shown in Figure 1, or by NMR analysis. However, the reductive amination of 2-disubstituted 1-indanone 3b in the presence of 10% platinum on carbon as a catalyst afforded the 1:1 mixture of the 1,2-trans and 1,2-cis isomers, which were separated by column chromatography to give 37 and 38. Their conformations were confirmed by the examination of the nuclear Overhauser effect (NOE) as described in the Experimental Section.

Several 1-aminoindan derivatives were prepared by chemical modifications of the 1-amino-7-hydroxyindans. Chlorination of 11a by sulfuryl chloride in acetic acid gave 1-amino-4,6-dichloro-7-hydroxyindan (22), and alkylation of 11a with di-*tert*-butylurea in a diluted sulfuric acid solution afforded the *tert*-butylated 1-aminoindan 25. Bromination of 12 in acetic acid yielded the 6-brominated 1-aminoindan 23. Treatment of 12 with iodine monochloride in concentrated hydrochloric acid gave 6-iodo-1-aminoindan 24. Nitration of 12 with fuming nitric acid in acetic acid yielded 7-hydroxy-4-methyl-6-nitro-1-aminoindan (26).

Pharmacology

Two pharmacological tests, the test for antihypoxic effect[26] and for promotional effect on recovery from coma,[27] were used primarily as a screening test for finding our target compounds. In the test for antihypoxic effect, a series of 1-aminoindan derivatives were examined for their effects on the survival time of mice under hypoxic conditions. The CNS-stimulating activity of the compounds, which showed relatively high potency in the test for antihypoxic effect, was evaluated in terms of its promoting effect on recovery from coma in mice in which coma was induced by cerebral concussion. This test has been reported as the experimental model for the cerebral trauma.[27] The results are summarized in Table III.

In the initial stage of the investigations, several drugs and the antioxidants were examined in order to find a leading compound with the dual activities in these two tests.

The activity of pentobarbital sodium on the survival time of mice was confirmed in the test for antihypoxic effect, when administered by intraperitoneal (ip) injection above 20 mg/kg, whereas the CNS activators tricyclic antidepressant imipramine hydrochloride and TRH shorten the survival time. An antioxidant, vitamin E, was inactive in this test at a dose of 100 mg/kg intravenation (iv) injection; however the butylated hydroxytoluene (BHT) prolonged the survival time when administered by ip injection at a dose of 100 mg/kg. Nootropics mechlophenoxate and CDP-choline were found to be inactive.

In the test for promotional effect on recovery from coma, the promoting effect of TRH was confirmed when administered by iv injection. However, this compound was inactive when administered orally. Pentobarbital sodium retarded recovery from coma. Tricyclic antidepressants and antioxidants were found to be inactive in this test. No actual drug examined could be found to possess dual activities. In a random screening on the compounds with the phenolic hydroxyl groups using those two tests, 1-amino-4,6-dimethyl-7-hydroxyindan hydrochloride (13) was found to have dual activities. A series of 1-amino-7-hydroxyindan derivatives was synthesized, and their dual activities were examined. Structure–activity relationships are discussed below with the data indicated in Table III.

Structure–Activity Relationships

First, the activities of the positional isomers of 1-amino-7-hydroxyindan were examined in the test for antihypoxic effect (11a–c), and the 7-hydroxy isomer (11a) was found to prolong the survival of mice, whereas the 6- and 4-hydroxy isomers were inactive in this test. Therefore further comparison of the activity of various substituents was made within the 7-hydroxy isomers series.

Subsequently, the effects of aromatic substitution in the 2-unsubstituted 1-aminoindan series were examined. Introduction of a single alkyl group to the 4- or 6-position in compound 11a decreased the potency (12 or 17), but that of two methyl groups to the 4- and 6-position increased the potency (13). Replacement of one of the methyl groups in compound 13 with a more bulky alkyl group slightly reduced in the potency (13 ≥ 20 ≥ 21 ≥ 16 ≥ 18 ≥ 19). Replacement of the methyl group at the 4- or 6-position in compound 13 with more polar aminomethyl, chlorine, and nitro substituents gave inactive compounds (15, 22, and 26). The compound with an acetoamido substituent at the 6-position was found to shorten the survival time (14). In this series, compound 13 was the most potent, and the potency of the compound was comparable to that of pentoparbital sodium.

The effect of the substitution of the amino group at the 1-position in compound 13 was then examined and it was found that the replacement of the amino group with the methylamino or butylamino substituent gave inactive compound (27 and 28).

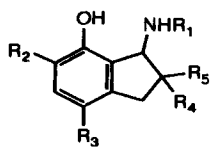
The effect of the 2-substitution in compound 13 was next examined. Introduction of a single methyl group to the 2-position did not change the potency (29), but that of the bulky phenyl and benzyl group to the 2-position reduced the potency (30, 34). Dimethyl substitution at the 2-position in compound 13 was found to increase the potency (35). Replacement of one of the methyl groups in compound 35 with a more bulky benzyl or phenyl moiety reduced the potency (36–38).

The effect of the phenolic hydroxyl group in the compounds 30 and 35 was finally examined, and replacement of the hydroxyl group with a methoxy substituent gave inactive compounds 39 and 40, respectively. This result indicated that the phenolic hydroxyl group in compound 30 and 35 was essential to the activity in the test. In the 2-substituted-1-aminoindan series, compounds 29 and 35 were found to have potency comparable to that of 13.

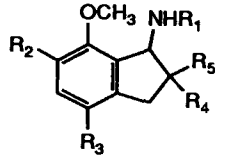
In the next step, we examined the CNS-stimulating activity of several compounds which showed relatively high potency in the antihypoxia test. In the test for promotional effect on recovery from coma, compound 11a was inactive. Introduction of two methyl groups to the 4- and 6-position in the compound 11a revealed the activity (13). In contrast to the antihypoxia test, the replacement of one of the methyl groups in the compound 13 with a bulky branched alkyl substituent significantly increased the potency (20). Introduction of a single methyl group to 2-position of 13

(26) Nakanishi, M.; Yasuda, H.; Tsumagari, T. *Life Sci.* 1973, *13*, 467.
(27) Manaka, M.; Sano, K. Igaku No Ayumi 1977, *102*, 867.

Table III. The 1-Aminoindan Derivatives and Their Cerebroprotective and CNS-Stimulating Activities



(11a - 38)



(39 and 40)

no.	R_1	R_2	R_3	R_4	R_5	method	% yield[a]	recryst[b] solvents	mp, °C	formula[c]	cerebroprotective activity:[d] SVT[e] sc[h] (ip)[i]	cerebroprotective activity:[d] SVT[e] po[j]	CNS stimulating activity[d] RRT[f] po[j]	CNS stimulating activity[d] SMT[g] po[j]	n[k]
11a	H	H	H	H	H	L	76	a	224–226	$C_9H_{11}NO$·HCl	nt	204.8 ± 17.3**	102.0 ± 16.0	99.1 ± 20.4	10
12	H	H	Me	H	H	L	32	c	235–237	$C_{10}H_{13}NO$·HCl	157.8 ± 20.0	98.4 ± 20.4	40.1 ± 7.8**	42.6 ± 6.0**	9
13	H	Me	Me	H	H	L	35	a	229–230 dec	$C_{11}H_{15}NO$·HCl	303.4 ± 16.1*	255.7 ± 46.5**	51.4 ± 8.0**	61.4 ± 13.6*	10
14	H	$NHCOCH_3$	Me	H	H	L	36	d	213–215 dec	$C_{12}H_{16}N_2O_2$·HCl·$0.25H_2O$	46.8 ± 4.5*	nt	nt	nt	
15	H	CH_2NH_2	Me	H	H	L	24	e	>200 dec	$C_{11}H_{16}N_2O$·2HCl	74.3 ± 7.7	110.2 ± 21.1	69.9 ± 21.8	79.3 ± 19.9	7
16	H	$C(CH_3)_3$	Me	H	H	L	90	f	186–188	$C_{14}H_{21}NO$·HCl	252.8 ± 28.6*,[j]	nt	90.6 ± 14.1	113.5 ± 11.5	10
17	H	$CH_2CH_2CH_3$	H	H	H	L	24	g	175–176 dec	$C_{12}H_{17}NO$·HCl	138.0 ± 13.3*	158.0 ± 29.0*	70.5 ± 6.1	79.5 ± 8.9	9
18	H	$CH_2CH_2CH_3$	Me	H	H	L	33	g	174–175.5	$C_{13}H_{19}NO$·HCl	244.6 ± 42.7*	205.3 ± 71.9*	nt	nt	
19	H	$CH_2CH(CH_3)_2$	Me	H	H	L	45	e	186–187	$C_{14}H_{21}NO$·HCl	281.4 ± 69.2*	149.9 ± 16.0	59.3 ± 7.7**	76.1 ± 7.5	10
20	H	$CH(CH_3)CH_2CH_3$	Me	H	H	L	37	e	177.5–179	$C_{14}H_{21}NO$·HCl	276.5 ± 88.1**	234.8 ± 45.0**	18.9 ± 7.9**	23.3 ± 8.4**	10
21	H	$CH_2CH_2CH_3$	Et	H	H	L	52	g	156–158 dec	$C_{14}H_{21}NO$·HCl	194.3 ± 50.3	206.8 ± 54.1**	94.4 ± 15.6	116.3 ± 14.1	8
22	H	Cl	Cl	H	H	N	31	i	238–239 dec	$C_9H_9NOCl_2$·HCl	65.8 ± 9.2	nt	nt	nt	
23	H	Br	Me	H	H	N	20	i	178–179 dec	$C_{10}H_{12}NOBr$·HBr	308.0 ± 29.8**	130.1 ± 25.9	81.5 ± 12.2	83.4 ± 8.6	10
24	H	I	Me	H	H	N	43	i	>200 dec	$C_{10}H_{12}NOI$·HCl	184.6 ± 1.5*	nt	81.1 ± 10.4	92.3 ± 19.4	10
25	H	$C(CH_3)_3$	$C(CH_3)_3$	H	H	O	86	a	225–226.5	$C_{17}H_{27}NO$·HCl·$0.1H_2O$	171.3 ± 22.3*,[j]	119.2 ± 13.2	160.2 ± 33.1	157.6 ± 27.6	10
26	H	NO_2	Me	H	H	P	28	a	>200 dec	$C_{10}H_{12}N_2O_3$·HCl	189.7 ± 71.4	nt	nt	nt	
27	Me	Me	Me	H	H	Q	75	h	121–122	$C_{12}H_{17}NO$	177.5 ± 42.2	nt	57.9 ± 7.5**	55.8 ± 6.5**	10
28	n-C_4H_9	Me	Me	H	H	Q	70	a	143–144	$C_{15}H_{23}NO$·HCl	nt	187.3 ± 45.0	55.3 ± 8.7*	57.7 ± 11.5**	8
29	H	Me	Me	Me	H	L	18	a	183–185	$C_{12}H_{17}NO$·HCl·$0.6H_2O$	nt	237.7 ± 14.4**	79.1 ± 8.8	71.0 ± 6.7	10
30	H	Me	Me	Ph	H	L	45	a	135–136	$C_{17}H_{19}NO$	185.7 ± 26.5*,[j]	149.1 ± 12.3**	31.1 ± 8.1**	37.6 ± 7.0**	8
31	H	Et	Me	Ph	H	L	24	a	79–80	$C_{18}H_{21}NO$	nt	97.4 ± 8.0	89.2 ± 7.8	94.4 ± 11.4	10
32	H	Me	Me	o-ClC_6H_4	H	L	18	a	194–197	$C_{17}H_{16}NOCl$·$C_4H_4O_4$·$0.5H_2O$[l]	nt	151.0 ± 10.8**	35.8 ± 13.3**	33.8 ± 9.9**	8
33	H	Me	Me	o-MeC_6H_4	H	M	27	k	157 dec	$C_{18}H_{21}NO$·HCl	nt	161.3 ± 22.3*	44.4 ± 8.3**	45.9 ± 10.0**	10
34	H	Me	Me	CH_2Ph	H	M	18	a	145–146	$C_{18}H_{21}NO$·HCl·$0.5H_2O$	nt	148.0 ± 18.7*	47.0 ± 14.6**	38.6 ± 9.0**	10
35	H	Me	Me	Me	Me	M	69	a	231–233 dec	$C_{13}H_{19}NO$·HCl·$0.1H_2O$	298.1 ± 90.7**	288.0 ± 80.3**	37.2 ± 12.3**	53.9 ± 16.4**	10
36	H	Me	Me	Ph	Me	L	15	a	206–208 dec	$C_{18}H_{21}NO$·HCl·$0.1H_2O$	nt	171.6 ± 12.1*	34.1 ± 8.6**	34.7 ± 8.0**	10
37	H	Me	Me	CH_2Ph	Me	M	12	a	143–145	$C_{19}H_{23}NO$	nt	167.3 ± 14.9**	29.9 ± 11.1**	32.6 ± 10.7**	8

38	H	Me	Me	CH$_2$Ph	M	12	a	130–131	$C_{19}H_{23}NO \cdot 0.1H_2O$	nt	197.0 ± 15.6**	33.0 ± 11.4**	28.8 ± 8.5**	10
39	H	Me	Me	Ph	Me	L	63	a	247–249 dec	$C_{19}H_{23}NO \cdot HCl \cdot 0.25H_2O$	nt	117.9 ± 16.8	25.0 ± 6.8**	23.9 ± 6.4**	10
40	H	Me	Me	Me	Me	L	39	a	239–240 dec	$C_{14}H_{21}NO \cdot HCl \cdot 0.1H_2O$	nt	164.3 ± 29.6	43.6 ± 7.9**	39.2 ± 8.1**	9
11b[m]										nt	78.0 ± 8.3	nt	nt	
11c[n]										nt	103.9 ± 9.3	nt	nt	
vitamin E										96.7 ± 12.7[o]	178.1 ± 34.6	92.2 ± 8.9	83.5 ± 9.2	10
butylated hydroxytoluene (BHT)										358.8 ± 37.1**,[o]	87.6 ± 14.6	69.6 ± 15.2	80.9 ± 15.0	10
pentobarbital sodium										306.7 ± 46.0**,[p]	nt	494.0 ± 0.0**,[p]	283.0 ± 0.0**,[p]	5
thirotropine release hormone (TRH)										43.4 ± 2.0**,[q]	nt	40.8 ± 7.2**,[r]	40.9 ± 7.3**,[r]	10
imipramine hydrochloride										nt	67.9 ± 4.7**	113.4 ± 24.1	115.5 ± 22.0	10
mechlophenoxate										133.0 ± 40.1[q]	106.0 ± 10.8	53.8 ± 8.0**,[s]	63.8 ± 7.5**,[s]	10
CDP-cholin										88.8 ± 2.8[t]	nt	38.4 ± 8.2**,[t]	47.5 ± 7.9**,[t]	10

[a] Yields were not optimized in most cases. [b] A = EtOH, B = acetone, C = hexane, D = EtOH/ether, E = hexane/AcOEt. [c] C, H, N analyses were within ±0.4% of the calculated value. [d] All values are represented as percent of control ± standard error (SEM). Significance determined by Wilcoxon sum test, * $p < 0.05$, ** $p < 0.01$, nt = not tested. [e] Survival time. [f] Time for recovery (in seconds) of righting reflex. [g] Time for recovery (in seconds) of spontaneous movement. [h] Subcutaneous injection of 30 mg/kg unless otherwise indicated. [i] Intraperitoneal injection of 30 mg/kg. [j] Oral administration of 100 mg/kg unless otherwise indicated. [k] Numbers of the mice used in the test for promotional activity. [l] Fumaric acid. [m] 1-Amino-6-hydroxyindan hemifumarate. [n] 1-Amino-4-hydroxyindan hydrochloride. [o] 100 mg/kg ip. [p] 40 mg/kg ip. [q] 3 mg/kg iv. [r] 2.5 mg/kg iv. [s] 200 mg/kg po. [t] 300 mg/kg iv.

diminished the potency, but introduction of a bulkier phenyl and benzyl group to the 2-position of compound **13** enhanced the potency (**30** and **34**). Introduction of chlorine or methyl substituent to the 2-phenyl moiety in the compound **30** did not change the potency. Disubstitution of the 2-position in compound **13** with dimethyl, methyl and benzyl, or methyl and phenyl groups enhanced the potency (**35–38**).

Finally, the effect of the phenolic hydroxyl group in compounds **30** and **35** was examined. Replacement of the phenolic hydroxyl group with a methoxy substituent did not change the potency (**39** and **40**). This result indicated the hydroxyl group in this series was not essential to the activity in the test in contrast to the test for antihypoxic effect.

From the structure–activity relationships, compounds **20**, **30**, and **35**, which possessed relatively high potency in the test for antihypoxic effect and for promotional effect on recovery from coma, were selected for further pharmacological and toxicological investigations. In the toxicological studies, those compounds were administered orally to rats for 2 weeks (30, 150, 500, or 700 mg/kg per day) and the general symptoms and mortality were examined. All rats examined were dead at a high dosage of 500 mg/kg per day after 2 weeks of administrations. General symptoms, tremor, and salivation were observed at doses higher than 150 mg/kg. All compounds were found to possess hypothermia at a dose of 30 mg/kg and above.

Because of the unsatisfactory results from the toxicological examinations, further investigations are necessary to find a safer compound with fewer side effects such as hypothermia and tremor, or without lethal effects up to 1000 mg/kg, but with the dual activities.

Conclusion

For the purpose of developing a novel cerebroprotective agent with CNS-stimulating effects, a series of 1-amino-7-hydroxyindan derivatives was synthesized, and their cerebroprotective and CNS-stimulating effects were examined in the tests described in this paper. For the first time, we found several compounds in this series to have the dual activities. From the structure–activities relationships, the structure requirements for possessing the dual activites were found in this series as follows: (1) an unsubstituted amino group in the 1-position is preferred to a substituted group; (2) a phenolic hydroxyl group at the 7-position is essential to the activity in the antihypoxia test; and (3) the presence of alkyl groups at the 4- and 6-position is necessary, and the replacement of the alkyl group with a more polar substituent than an alkyl group diminished the potency. The three most potent compounds in this series were selected for toxicological examination. However, the compounds selected were found to have several side effects, including tremor and hypothermia. Further investigations are necessary to find a safer compound possessing the desired dual activity.

Experimental Section

Melting points were determined by a Yanagimoto Micro Melting Point Apparatus and were uncorrected. ^{1}H NMR spectra were recorded on a Varian EM 390 NMR spectrometer using tetramethylsilane (TMS) or 3-(trimethylsilyl)propionic acid-d_5 (TSP) as an internal standard. Elemental analyses for carbon, hydrogen, and nitrogen were carried out with a Yanaco MT-5 CHN Corder. Where analyses are indicated only symbols of elements, analytical results obtained are within ±0.4% of the theoretical values. All compounds were routinely checked by TLC with Merck silica gel 60 F254 precoated plates.

Method A. Preparations of the 7-Hydroxy-1-indanones. 4-Ethyl-7-hydroxy-1-indanone (1c). This compound was

prepared by the same procedure reported for 7-hydroxy-1-indanone (1a),[14] 7-hydroxy-4-methyl-1-indanone (1b),[15] and 4,6-dimethyl-7-hydroxy-1-indanone (1d)[17] except that the intermediate ester was not isolated. Yield: 62.2 g (35%) of colorless needles (from EtOH). Mp: 91.5–92.5 °C. ^{1}H NMR ($CDCl_3$): δ 1.21 (3 H, t, J = 7.5 Hz, CH_3), 2.57 (2 H, q, J = 7.5 Hz, CH_2), 2.58–2.78 (2 H, m, CH_2), 2.92–3.13 (2 H, m, CH_2), 6.67 (1 H, d, J = 8.5 Hz, 6-H), 7.29 (1 H, d, J = 8.5 Hz, 5-H), 8.98 (1 H, s, OH). Anal. ($C_{11}H_{12}O_2$): C, H.

Method B. Preparations of the 7-Hydroxy-2-phenyl-1-indanones. 4,6-Dimethyl-7-hydroxy-2-phenyl-1-indanone (1e). A mixture of 2,4-dimethylphenol (308 g, 2.52 mol) and phenylacetyl chloride (389 g, 2.52 mol) was stirred at 90 °C for 1 h. Aluminum chloride (660 g, 4.95 mol) was added in small portions to the mixture at this temperature. After 2 h of stirring at 100 °C, the hot mixture was poured into an ice–water mixture (2 L) with vigorous stirring and extracted with $CHCl_3$. The extract was washed, dried, and concentrated to give an oily product. Vacuum distillation gave 4,6-dimethyl-2-(phenylacetyl)phenol (433.3 g, 72%). Bp: 170–193 °C (0.4 mmHg). ^{1}H NMR ($CDCl_3$): δ 2.20 (3 H, s, CH_3), 2.26 (3 H, s, CH_3), 4.24 (2 H, s, CH_2), 7.14 (1 H, s, 3-H), 7.27 (5 H, s, aromatic H), 7.47 (1 H, s, 5-H), 12.54 (1 H, s, OH).

Acetic anhydride (350 mL) was added to a mixture of 4,6-dimethyl-2-(phenylacetyl)phenol (433.8 g, 1.81 mol) in TMDM (539.3 g, 5.28 mol) with ice cooling and the resulting mixture was stirred for 3 h at room temperature. The mixture was poured into ice–water. The precipitated crystals were filtered, washed, and dried to give α-styryl 2-(4,6-dimethyl-1-hydroxyphenyl) ketone (425.5 g, 93%), which was used in the next step without further purification. Mp: 83–84 °C. ^{1}H NMR ($CDCl_3$): δ 2.16 (3 H, s, CH_3), 2.26 (3 H, s, CH_3), 5.45 (1 H, s, =CH), 5.96 (1 H, s, =CH), 7.14 (1 H, s, 3-H), 7.11–7.55 (7 H, s, aromatic H, 3,5-H), 12.22 (1 H, s, OH).

α-Styryl 2-(4,6-dimethyl-1-hydroxyphenyl) ketone (400 g, 1.59 mol) was added in portions to concentrated H_2SO_4 (1 L) and the mixture was stirred for 1 h at room temperature. The reaction mixture was poured into ice water and extracted with CH_2Cl_2. The extract was washed, dried, and evaporated to dryness. Recrystallization from EtOH afforded 1e (310.9 g, 77%) as colorless prisms. Mp: 90.5–91 °C. ^{1}H NMR ($CDCl_3$): δ 2.23 (6 H, s, CH_3), 3.04 (1 H, dd, J = 3 Hz, 18 Hz, 3-H), 3.47 (1 H, dd, J = 9 Hz, 18 Hz, 3-H), 3.90 (1 H, dd, J = 3 Hz, 9 Hz, 2-H), 7.07-7.43 (6 H, m, aromatic H), 9.02 (1 H, s, OH). Anal. ($C_{17}H_{15}O_2$): C, H.

Compounds 1f–h were prepared in a manner similar to that of 1d from the corresponding phenols and the phenylacetyl chlorides.

Method C. Preparation of 7-Hydroxy-2,4,6-trimethyl-1-indanone (3a). 7-Hydroxy-4,6-dimethyl-2-methylidene-1-indanone (2a). Acetic anhydride (100 mL) was added in drops to a mixture of 1d (52.8 g, 300 mmol) and TMDM (74.9 g, 730 mmol) at room temperature. After 5 h of stirring, the mixture was poured into ice–water and extracted with AcOEt. The extract was washed, dried, and evaporated to dryness. Recrystallization from EtOH afforded 2a (31 g, 55%). Mp: 131–134 °C. ^{1}H NMR ($CDCl_3$): δ 2.19 (3 H, s, CH_3), 2.22 (3 H, s, CH_3), 3.45–3.55 (2 H, m, CH_2), 5.60–5.70 (1 H, m, =CH), 6.20–6.30 (1 H, m, =CH), 7.10 (1 H, s, 5-H), 9.15 (1 H, s, OH). Anal. ($C_{12}H_{12}O_2 \cdot 0.6H_2O$): C, H.

7-Hydroxy-2,4,6-trimethyl-1-indanone (3a). Compound 2a (31 g, 165 mmol) was dissolved in EtOH (300 mL) and hydrogenated in the presence of 5% palladium on carbon (2 g) as a catalyst under 3 kg/cm^3 hydrogen pressure at room temperature for 2 h. After removal of the catalyst by filtration, the filtrate was evaporated to give an oily product, which was crystallized from n-hexane. Yield: 8.46 g (27%) as colorless granulars. Mp: 84–85 °C. ^{1}H NMR ($CDCl_3$): δ 1.24 (3 H, d, J = 7.5 Hz, CH_3), 2.15 (6 H, s, CH_3), 2.42 (1 H, dd, J = 3 Hz, 16.5 Hz, 3-H), 2.74 (1 H, qd, J = 7.5 Hz, 3 Hz, 3-H), 3.17 (1 H, dd, J = 7.5 Hz, 16.5 Hz, 2-H), 7.09 (1 H, s, 5-H), 9.04 (1 H, s, OH). Anal. ($C_{12}H_{14}O_2 \cdot 0.5H_2O$): C; H: calcd, 7.59; found, 6.90.

Method D. Preparation of 2-Benzyl-4,6-dimethyl-7-hydroxy-1-indanone (3b). 2-Benzylidene-4,6-dimethyl-7-hydroxy-1-indanone (2b). A mixture of 1d (150 g, 850 mmol), benzaldehyde (117.8 g, 1.11 mol), and DBU (166 mL, 1.11 mol) in EtOH (1.5 L) was refluxed for 5 h, and cooled to room temperature. The precipitated crystals were filtered, washed with cold EtOH (500 mL), and dried. Recrystallization from EtOH gave 2b (214 g, 95%) as colorless prisms. Mp: 161–162 °C. ^{1}H NMR ($CDCl_3$): δ 2.18 (3 H, s, CH_3), 2.22 (3 H, s, CH_3), 3.71 (2 H, s, 3-H), 7.08 (1 H, s, 5-H), 7.30–7.70 (6 H, m, aromatic H), 9.04 (1 H, s, OH). Anal. ($C_{18}H_{16}O_2 \cdot 0.5H_2O$): C, H.

2-Benzyl-4,6-dimethyl-7-hydroxy-1-indanone (3b). Catalytic hydrogenation of 2b (70 g, 265 mmol) in glacial acetic acid (1 L) in the presence of palladium black (5 g) as a catalyt under an atmospheric hydrogen pressure gave 3b (64 g, 91%). mp: 107–108 °C. ^{1}H NMR($CDCl_3$) δ 2.11 (3 H, s, CH_3), 2.19 (3 H, s, CH_3), 2.40–3.50 (5 H, m, 2-H, 3-H, benzyl H), 7.13 (1 H, s, 5-H), 7.25 (5 H, s, aromatic H), 9.04 (1 H, s, OH). Anal. ($C_{18}H_{18}O_2$): C, H.

Method E. Preparation of 7-Hydroxy-2,2,4,6-tetramethyl-1-indanone (5a). 7-Methoxy-2,2,4,6-tetramethyl-1-indanone (4a). Sodium hydride (60%, 32.16 g, 800 mmol) was added in small portions to a solution of 1d (117.4 g, 670 mmol) in DMF (1 L) at room temperature and the mixture was stirred for 0.5 h. Then, MeI (102.6 g, 720 mmol) was added to the mixture and the mixture was stirred for 40 min. Again, sodium hydride (64.3 g, 1.6 mol) and MeI (209.2 g, 1.34 mol) were added to the mixture, and stirring was continued for 1 h at 60 °C. After the formed NaI was filtered off, the filtrate was evaporated under reduced pressure to give an oil, which was dissolved in ether (1 L). The ether solution was washed, dried, and evaporated to give 4a as a reddish brown oil (79.1 g, 54%). This compound was used in the next step without further purification. ^{1}H NMR ($CDCl_3$): δ 1.20 (6 H, s, CH_3), 2.20 (3 H, s, CH_3), 2.25 (3 H, s, CH_3), 2.80 (2 H, s, CH_2), 3.90 (3 H, s, OCH_3), 7.20 (1 H, s, 5-H).

Compounds 4b and 4c were prepared in a manner similar to that of 4a from the corresponding 1-indanones.

7-Hydroxy-2,2,4,6-tetramethyl-1-indanone (5a). Aluminum chloride (103.2 g, 770 mmol) was added in portions to a mixture of 4a (79 g, 360 mmol) and NaI (115.4 g, 770 mmol) in acetonitrile (390 mL) with ice cooling, and the mixture was stirred for 1 h at 70 °C. After solvent was removed by distillation, ice was added to the residue and the resulting mixture was extracted with AcOEt. The extract was washed, dried, and evaporated to give 5a as an oil (74.9 g, 101%), which was crystallized by standing overnight at room temperature. Mp: 51–52 °C. ^{1}H NMR ($CDCl_3$): δ 1.30 (6 H, s, CH_3), 2.20 (3 H, s, CH_3), 2.24 (3 H, s, CH_3), 2.83 (2 H, s, 3-H), 7.20 (1 H, s, 5-H), 9.10 (1 H, s, OH). Anal. ($C_{13}H_{16}O_2$): C, H.

Compounds 5b and 5c were prepared in a manner similar to that of 5a from 4b and 4c, respectively.

Method F. Preparation of 6-(Acetylamino)-7-hydroxy-4-methyl-1-indanone (6b). 7-Hydroxy-4-methyl-6-nitro-1-indanone (6a). A solution of fuming HNO_3 (23.4 g, 370 mmol) in acetic acid (50 mL) was added in drops to a solution of 1b (25.6 g, 158 mmol) in acetic acid (250 mL). After 5 h of stirring at room temperature, the mixture was evaporated to dryness and the residue was washed with ether to give 6a (25.7 g, 79%) as yellow needles. This compound was used without further purification. Mp: 154–157 °C; ^{1}H NMR ($CDCl_3$): δ 2.32 (3 H, s, CH_3), 2.73 (2 H, s, 2-H), 3.14 (2 H, s, 3-H), 8.10 (1 H, s, 5-H), 10.91 (1 H, s, OH).

6-(Acetylamino)-7-hydroxy-4-methyl-1-indanone (6b). A mixture of 6a (11.5 g, 56 mmol) and 5% palladium on carbon (1.5 g) as a catalyst in glacial acetic acid (500 mL) was hydrogenated under atmospheric hydrogen pressure at room temperature. After removal of the catalyst by filtration, the filtrate was evaporated under reduced pressure. Recrystallization from MeOH gave 6b (6.34 g, 52%) as reddish orange needles. Mp: 193–198 °C. ^{1}H NMR (DMSO-d_6): δ 2.1 (3 H, s, $COCH_3$), 2.17 (3 H, s, CH_3), 2.45–3.10 (4 H, m, 2,3-H), 7.67 (1 H, s, 5-H), 9.25–10.00 (2 H, br, OH and NH). Anal. ($C_{12}H_{13}NO_3$): C, H, N.

Method G. Preparation of 6-(Aminomethyl)-7-hydroxy-4-methyl-1-indanone (6d). 6-[[(Chloroacetyl)amino]-methyl]-4-methyl-7-hydroxy-1-indanone (6c). A mixture of 1b (39.3 g, 243 mmol) and 2-(chloroacetyl)-N-(hydroxymethyl)-acetamide (30 g, 279 mmol) was added to concentrated H_2SO_4 (250 mL) while being ice cooled. After being allowed to stand overnight at room temperature, the mixture was poured into ice–water (500 mL). The precipitated crystals were filtered, washed, and recrystallized from EtOH to give 6c (49 g, 80%) as

colorless needles. Mp: 166–167.5 °C. ^{1}H NMR ($CDCl_3$) δ 2.23 (3 H, s, CH_3), 2.60–3.07 (4 H, m, 2,3-H), 4.03 (2 H, s, CH_2), 4.46 (2 H, d, J = 6 Hz, CH_2), 7.20 (1 H, br, NH), 7.30 (1 H, s, 5-H), 9.14 (1 H, br, OH). Anal. ($C_{13}H_{14}NO_3Cl$): C, H, N.

6-(Aminomethyl)-7-hydroxy-4-methyl-1-indanone (6d). A mixture of **6c** (3 g, 12 mmol) and concentrated HCl (30 mL) in EtOH (60 mL) was refluxed for 8 h and evaporated to dryness. Recrystallization from EtOH afforded **6d** (1 g, 37%) as pale yellow flakes. Mp: 300 °C dec. ^{1}H NMR (DMSO-d_6): δ 2.22 (3 H, s, CH_3), 2.6–2.8 (2 H, m, 2-H), 2.85–3.1 (2 H, m, 3-H), 3.97 (2 H, s, CH_2N), 7.55 (1 H, s, 5-H), 8.4–9.5 (3 H, br, NH_3^+). Anal. ($C_{11}H_{13}NO_2$·HCl): C, H, N.

Method H. Preparation of 7-Hydroxy-4-methyl-6-*tert*-butyl-1-indanone (6e). A mixture of **1b** (3.4 g, 21 mmol) and di-*tert*-butylurea[21] (5 g, 40 mmol) was added to 70% H_2SO_4 (20 mL). After 2 h of stirring at 65 °C, the mixture was poured onto ice (200 g) with vigorous stirring and the precipitated crystals were filtered, washed, and dried. Recrystallization from *n*-hexane gave **6e** (4.8 g, 95%) as colorless needles. Mp: 181–182 °C. ^{1}H NMR ($CDCl_3$): δ 1.38 (9 H, s, CH_3), 2.23 (3 H, s, CH_3), 2.58–2.75 (2 H, m, 3-H), 2.80–3.00 (2 H, m, 2-H), 7.20 (1 H, s, 5-H), 9.70 (1 H, s, OH). Anal. ($C_{14}H_{18}O_2$): C, H.

Method I. Preparation of the 6-Allyl-7-hydroxy-1-indanones (8a–d). 7-(Allyloxy)-1-indanone (7a). Allyl bromide (16.7 g, 140 mmol) was added to a mixture of **1a** (13.4 g, 90 mmol) and potassium hydroxide (7.15 g, 110 mmol) in MeOH (200 mL) and the mixture was refluxed for 6 h. After filtration, the filtrate was evaporated to dryness and extracted with chloroform (200 mL). The extract was washed, dried, and evaporated to give **7a** (12.1 g, 71%) as a dark brown oil. This compound was used in the next step without further purification. ^{1}H NMR ($CDCl_3$): δ 2.50–2.72 (2 H, m, 2-H), 2.93–3.16 (2 H, m, 3-H), 4.52–4.73 (2 H, m, CH_2), 5.17–5.62 (2 H, m, $=CH_2$), 5.80–6.27 (1 H, m, —CH=), 6.73 (1 H, d, J = 7.5 Hz, aromatic H), 6.95 (1 H, d, J = 7.5 Hz, aromatic H), 7.45 (1 H, dd, J = 7.5 Hz, 7.5 Hz, 5-H).

6-Allyl-7-hydroxy-1-indanone (8a). A mixture of **7a** (12 g, 64 mmol) in 1,2,3,4-tetrahydronaphthalene (30 mL) was refluxed for 4 h under a nitrogen atmosphere and evaporated under reduced pressure to give an oily material. This oily material was purified by passing through a silica gel column (hexane, then hexane–methylene chloride 2:1) to give **8a** (5.8 g, 48%) as pale brown oil. ^{1}H NMR ($CDCl_3$): δ 2.55–2.90 (2 H, m, 2,3-H), 2.93–3.13 (2 H, m, 3-H), 3.35 (2 H, d, J = 6 Hz, CH_2), 4.87–5.17 (2 H, m, $=CH_2$), 5.69–6.20 (1 H, m, —CH=), 6.83 (1 H, d, J = 7.5 Hz, 4-H), 7.30 (1 H, d, J = 7.5 Hz, 5-H), 9.25 (1 H, br, OH).

Compounds **8b–d** were prepared in a manner similar to that of **8a** by the reaction of the corresponding allyl halides with **1b** and **1c**, respectively.

Preparations of the 1-Indanone Oximes Listed in Table II. Method J. 7-Hydroxy-4-methyl-1-indanone Oxime (9b). This compound was prepared by adaptation of the procedure reported for preparation of 4,6-dimethyl-7-hydroxy-1-indanone oxime (**9c**).[17] A mixture of **1b** (16.2 g, 100 mmol), NH_2OH·HCl (28 g, 400 mmol), and K_2CO_3 (56 g, 410 mmol) in MeOH (400 mL) was refluxed for 3 h and evaporated to dryness. The residue was extracted with AcOEt and the extract was washed, dried, and evaporated to dryness. Recrystallization from MeOH gave **9b** (17.06 g, 96%) as colorless needles. Mp: 148–149.5 °C. Anal. ($C_{10}H_{11}NO_2$) C, H, N. ^{1}H NMR ($CDCl_3$): δ 2.13 (3 H, s, CH_3), 2.85 (4 H, s, 2,3-H), 6.60 (1 H, d, J = 9 Hz, 6-H), 6.96 (1 H, d, J = 9 Hz, 5-H), 7.00–8.40 (2 H, br, N-OH and OH).

Compounds **9a**, **9c–j** were prepared in a manner similar to that of **9b** from the corresponding 1-indanones.

Method K. 4,6-Dimethyl-7-hydroxy-2-phenyl-1-indanone Oxime (9k). A mixture of **1e** (310 g, 1.23 mol), NH_2OH·HCl (128.2 g, 1.84 mol), and pyridine (500 mL) was refluxed for 2 h. Recrystallization from EtOH gave **9k** (63%) as a pale yellow powder. Mp: 173–715 °C. ^{1}H NMR ($CDCl_3$): δ 2.13 (3 H, s, CH_3), 2.24 (3 H, s, CH_3), 2.86 (1 H, dd, J = 3 Hz, 18 Hz, 3-H), 3.45 (1 H, dd, J = 9 Hz, 18 Hz, 3-H), 4.53 (1 H, dd, J = 3 Hz, 9 Hz, 2-H), 6.93 (1 H, s, 5-H), 7.22 (5 H, s, aromatic H), 8.37 (1 H, s, OH). Anal. ($C_{17}H_{17}NO_2$): C, H, N.

Compounds **9l–p** were prepared in a manner similar to that of **9k** from the corresponding 2-substituted-1-indanones **1f**, **1h**, **4a**, **4c**, and **5a**.

Method L. Preparations of the 7-Hydroxy-1-aminoindans. 1-Amino-7-hydroxyindan Hydrochloride (11a). Oxime **9a** (9.0 g, 55 mmol) was hydrogenated in a Parr apparatus in the presence of platinum oxide (1.0 g) as a catalyst in glacial acetic acid (200 mL) under 3 kg/cm^3 hydrogen pressure. After filtration, the filtrate was evaporated to give the amine, which was converted to its hydrochloride. Recrystallization from EtOH gave **11a** (7.75 g, 76%) as colorless needles. Mp: 224–226 °C. ^{1}H NMR (DMSO-d_6): δ 1.95–2.10 (1 H, m, 2-H), 2.35–2.49 (1 H, m, 3-H), 2.79 (1 H, m, 2-H), 3.00–3.20 (1 H, m, 3 H), 4.70–4.74 (1 H, m, 1-H), 6.70 (1 H, d, J = 9 Hz, 6-H), 6.75 (1 H, d, J = 9 Hz, 4-H), 7.18 (1 H, t, J = 9 Hz, 5-H). Anal. ($C_9H_{11}NO$·HCl): C, H, N.

1-Amino-6-hydroxyindan Hemifumarate (11b). The crude amine, which was prepared in a manner similar to that of **11a** from 6-hydroxy-1-indanone oxime (2.3 g, 15 mmol), was dissolved in EtOH and converted to its fumarate by addition of an EtOH solution of fumaric acid. Recrystallization from EtOH–hexane afforded **11b** (0.67 g, 17%) as a colorless powder. Mp: 209.5–210.5 °C dec. ^{1}H NMR (DMSO-d_6): δ 1.90–1.98 (1 H, m, 2-H), 2.38–2.46 (1 H, m, 2-H), 2.66–2.78 (1 H, m, 3-H), 2.86–2.94 (1 H, m, 3-H), 4.58 (1 H, t, J = 7.5 Hz, 1-H), 6.73 (1 H, dd, J = 3 Hz, 9 Hz, 5-H), 6.97 (1 H, d, J = 3 Hz, 7-H), 7.07 (1 H, d, J = 9 Hz, 4-H). Anal. ($C_9H_{11}NO$·0.5$C_4H_4O_4$): C, H, N.

1-Amino-4-hydroxyindan Hydrochloride (11c). This compound, **11c**, was prepared from 4-hydroxy-1-indanone[28] (14.8 g, 100 mmol) in a manner similar to that of **11a**. Recrystallization from EtOH gave a colorless powder (2.8 g, 15%). Mp: 249–250 °C. Anal. ($C_9H_{11}NO$·HCl·0.1H_2O): C, H, N. ^{1}H NMR (DMSO-d_6): δ 1.90–1.98 (1 H, m, 2-H), 2.38–2.46 (1 H, m, 2-H), 2.66–2.78 (1 H, m, 3-H), 2.86–2.94 (1 H, m, 3-H), 4.58 (1 H, t, J = 7.5 Hz, 1-H), 6.73 (1 H, dd, J = 3 Hz, 9 Hz, 5-H), 6.97 (1 H, d, J = 3 Hz, 7-H), 7.07 (1 H, d, J = 9 Hz, 4-H).

1-Amino-7-hydroxy-4-methylindan Hydrochloride (12). Yield: 5.3 g (32%) as colorless needles. Mp: 235–237 °C. ^{1}H NMR (DMSO-d_6): δ 2.22 (3 H, s, CH_3), 1.8–3.10 (4 H, m, 2,3-H), 4.54–4.82 (1 H, m, 1-H), 6.67 (1 H, d, J = 9 Hz, 6-H), 6.95 (1 H, d, J = 9 Hz, 5-H), 7.90–8.65 (3 H, br, NH_3^+), 9.60 (1 H, br, OH). Anal. ($C_{10}H_{13}NO$·HCl): C, H, N.

Compounds **13–21**, **29–32**, **36**, **39**, and **40** were prepared in a manner similar to that of **11a** from the corresponding oximes.

Method M. Preparation of 1-Amino-4,6-dimethyl-7-hydroxy-2-(2-methylphenyl)indan Hydrochloride (33). A mixture of **1g** (32 g, 120 mmol) and a 10% solution of ammonia in MeOH (150 mL) was heated in a stainless steel tube at 100 °C for 10 h and cooled to room temperature. The precipitated crystals were filtered, washed, and dried to give the imine, which was directly used in the next step without further purification. The imine was suspended in AcOEt and hydrogenated in the presence of 5% palladium on carbon as a catalyst under an atmospheric hydrogen pressure for 4 h. After filtration, the filtrate was evaporated to dryness. The residue was purified by passing through a silica gel column (CH_2Cl_2 and AcOEt). The AcOEt eluents were combined and evaporated to dryness to give the amine, which was converted to its hydrochloride. Recrystallization from water gave **33** (10 g, 27%) as a colorless powder. Mp: 157 °C dec. ^{1}H NMR (DMSO-d_6): δ 2.17 (6 H, s, CH_3), 2.40 (3 H, s, CH_3), 2.91 (1 H, dd, J = 6 Hz, 15 Hz, 3-H), 3.60 (1 H, dd, J = 12 Hz, 15 Hz, 3-H), 3.80–4.17 (1 H, m, 2-H), 4.80–5.10 (1 H, m, 1-H), 6.96 (1 H, s, 5-H), 7.10–7.30 (4 H, m, aromatic H), 7.43–8.00 (3 H, br, NH_3^+), 9.10 (1 H, br, OH). Anal. ($C_{18}H_{21}NO$·HCl): C, H, N.

Compound **34** was prepared in a manner similar to that of **33** from **3b**.

1-Amino-2-benzyl-7-hydroxy-2,4,6-trimethylindan (36 and 37). A mixture of **5b** (5.6 g, 19 mmol) and an ammonia-saturated MeOH solution (60 mL) in a sealed stainless steel tube was heated for 10 h and evaporated to dryness. The residue was dissolved in AcOEt (100 mL) and hydrogenated under atmospheric hydrogen pressure at room temperature in the presence of 10% platinum on carbon as a catalyst. After filtration, the filtrate was evaporated to give a mixture of the crude amines, which was subjected to silica gel column chromatography. The second eluents

(28) Cannon, J. G.; Dushin, R. G.; Long, J. P.; et al. *J. Med. Chem.* **1985**, *28*, 515.

with CH_2Cl_2 were evaporated and recrystallized from EtOH to give **37** (0.7 g, 12%) as yellow flakes. Mp: 130–131 °C. ^1H NMR ($CDCl_3$): δ 1.24 (3 H, s, CH_3), 2.08 (3 H, s, CH_3), 2.17 (3 H, s, CH_3), 2.50 (1 H, d, J = 15 Hz, 3-H), 2.77 (1 H, d, J = 15 Hz, 3-H), 2.87 (2 H, s, $-CH_2-$), 4.43 (1 H, s, 1-H), 6.73 (1 H, s, 5-H), 7.27 (5 H, s, aromatic H). Anal. ($C_{19}H_{23}NO \cdot 0.1H_2O$): C, H, N.

In the NMR studies, the NOE of the proton in the 1-position of compound **37** on the methylene proton in 2-benzyl moiety (15%) was observed, whereas that on the 2-methyl proton was not observed.

The third eluents with hexane–ethyl acetate (1:1) were evaporated to dryness and recrystallized from EtOH to give **36** (0.7 g, 12%) as pale yellow prisms. Mp: 143–145 °C. ^1H NMR ($CDCl_3$): δ 1.17 (3 H, s, CH_3), 2.07 (1 H, d, J = 15 Hz, 3-H), 2.10 (3 H, s, CH_3), 2.20 (3 H, s, CH_3), 2.40 (2 H, s, $-CH_2-$), 2.70 (1 H, d, J = 15 Hz, 3-H), 4.30 (1 H, s, 1-H), 6.67 (1 H, s, 5-H), 6.90–7.07 (2 H, m, aromatic H), 7.15–7.27 (3 H, m, aromatic H). Anal. ($C_{19}H_{23}NO$): C, H, N.

In contrast to compound **36**, the NOE of the proton in the 1-position of compound **37** on the 2-methyl proton was observed (16%), but that on the methylene proton in 2-benzyl moiety was not observed.

Method N. Halogenation of the 1-Amino-7-hydroxyindans. 1-Amino-4,6-dichloro-7-hydroxyindan Hydrochloride (22). Sulfuryl chloride (1.53 g, 1.1 mmol) was added to a solution of **11a** (1 g, 5.4 mmol) in acetic acid (60 mL) with ice cooling, and the mixture was stirred for 3 h and evaporated to dryness. Recrystallization from 2-propanol–ether gave **22** (0.43 g, 31%) as colorless prisms. Mp: 238–239 °C dec. ^1H NMR (DMSO-d_6): δ 2.05–2.25 (1 H, m, 2-H), 2.35–2.50 (1 H, m, 2-H), 2.75–2.80 (1 H, m, 3-H), 3.05–3.25 (1 H, m, 3-H), 4.9–5.00 (1 H, m, 1-H), 7.53 (1 H, s, 5-H), 8.00–9.20 (4 H, br, NH_3^+ and OH). Anal. ($C_9H_9NOCl_2 \cdot HCl$): C, H, N.

1-Amino-6-bromo-7-hydroxy-4-methylindan Hydrobromide (23). This compound was prepared in a manner similar to that of **22** from **12** (5 g, 25 mmol) and bromine (4.8 g, 30 mmol). Recrystallization from 2-propanol afforded **23** (1.64 g, 20%) as yellow needles. Mp: 178–179 °C dec. ^1H NMR (DMSO-d_6): δ 2.18 (3 H, s, CH_3), 1.80–3.35 (4 H, m, 2,3-H), 4.75–5.05 (1 H, m, 1-H), 7.35 (1 H, s, 5-H), 7.6–9.2 (3 H, br, NH_3^+), 11.0 (1 H, s, OH). Anal. ($C_{10}H_{12}NOBr \cdot HBr$): C, H, N.

1-Amino-7-hydroxy-6-iodo-4-methylindan Hydrochloride (24). A solution of iodine monochloride (0.85 g, 5 mmol) in concentrated HCl (5 mL) was added to a solution of **12** (1 g, 5 mmol) in water (20 mL) at room temperature, and the mixture was stirred for 2 h and then ice cooled. The precipitated crystals were filtered, washed, and dried to give **24** (0.7 g, 43%) as yellow needles. Mp: >200 °C dec. Anal. ($C_{10}H_{12}NOI \cdot HCl$): C, H, N. ^1H NMR (DMSO-d_6): δ 2.01–2.15 (1 H, m, 2-H), 2.13 (3 H, s, CH_3), 2.30–2.50 (1 H, m, 2-H), 2.70–2.85 (1 H, m, 3-H), 2.95–3.15 (1 H, m, 3-H), 4.90 (1 H, d, J = 7.5 Hz, 1-H), 7.53 (1 H, s, 5-H), 8.15–8.60 (3 H, br, NH_3^+), 9.80–10.05 (1 H, br, OH).

Method O. Preparation of 1-Amino-4,6-di-*tert*-butyl-7-hydroxyindan Hydrochloride (25). A mixture of **11a** (5.56 g, 30 mmol) and di-*tert*-butylurea (6.96 g, 40 mmol) was added in small portions of 70% H_2SO_4 (20 mL) at 70 °C. After 2 h of stirring at this temperature, the reaction mixture was poured onto crushed ice (500 g) with vigorous stirring and made basic by addition of sodium hydroxide. The precipitates were collected by filtration and dissolved in ether (400 mL). The ether solution was washed, dried, and evaporated to give the amine, which was converted to its hydrochloric acid salt. Recrystallization from EtOH afforded **25** (7.7 g, 86%) as colorless pyramidals. Mp: 225–226.5 °C. ^1H NMR ($CDCl_3$): δ 1.31 (9 H, s, CH_3), 1.40 (9 H, s, CH_3), 2.30–3.30 (4 H, m, 2,3-H), 4.30–4.60 (1 H, m, 1-H), 7.15 (1 H, s, 5-H), 8.10–8.70 (4 H, br, NH_3^+ and OH). Anal. ($C_{17}H_{27}NO \cdot HCl \cdot 0.1H_2O$): C, H, N.

Method P. Preparation of 1-Amino-7-hydroxy-4-methyl-6-nitroindan Hydrochloride (26). A solution of fuming HNO_3 (3.9 g, 60 mmol) in acetic acid (10 mL) was added to a mixture of **12** (5.75 g, 29 mmol) and acetic anhydride (3.27 mL) in acetic acid (40 mL) while the reaction temperature was kept under 20 °C. After 6 h of stirring at room temperature, the mixture was evaporated to dryness and washed with ether. Recrystallization from EtOH afforded **26** (2 g, 28%) as yellow needles. Mp: 200 °C dec. ^1H NMR (DMSO-d_6): δ 2.22 (3 H, s, CH_3), 2.00–3.45 (4 H, m, 2,3-H), 4.70–5.00 (1 H, m, 1-H), 7.82 (1 H, s, 5-H), 8.40–9.70 (3 H, br, NH_3^+), 11.00 (1 H, br, OH). Anal. ($C_{10}H_{12}N_2O_3 \cdot HCl$): C, H, N.

Method Q. Preparation of the 1-(Alkylamino)-7-hydroxyindans. 4,6-Dimethyl-7-hydroxy-1-(methylamino)-indan (27). A mixture of **1d** (1.76 g, 10 mmol) and methylamine (40% solution in MeOH, 2 mL) in MeOH (20 mL) was refluxed for 1 h. Then, $NaBH_4$ (1 g, 26 mmol) was added in small portions to the mixture with ice cooling. After 1 h of stirring at room temperature, the reaction mixture was evaporated. The residue was dissolved in water (100 mL), and insoluble materials were collected by filtration, washed with water, and dried. Recrystallization from ether–hexane afforded **27** (1.43 g, 75%) as colorless prisms. Mp 121–122 °C. ^1H NMR ($CDCl_3$) δ 2.02 (3 H, s, CH_3), 2.08 (3 H, s, CH_3), 2.40 (3 H, s, CH_3), 2.40–2.90 (4 H, m, 2,3-H), 4.10–4.40 (1 H, m, 1-H), 6.60 (1 H, s, 5-H), 7.20 (2 H, br, NH and OH). Anal. ($C_{12}H_{17}NO$): C, H, N.

1-(Butylamino)-4,6-dimethyl-7-hydroxyindan Hydrochloride (28). A solution of **1d** (1.76 g, 10 mmol) and *n*-butylamine (14.6 g, 100 mmol) in EtOH (100 mL) was refluxed for 8 h and cooled to room temperature. Then $NaBH_4$ (1.0 g, 26 mmol) was added in small portions to the mixture. After 1 h of stirring at room temperature, the reaction mixture was worked up in a manner similar to that of **27** to give the amine, which was converted to its hydrochloride. Recrystallization from EtOH afforded **28** (1.88 g, 70%) as colorless needles. mp: 143–144 °C. ^1H NMR ($CDCl_3$): δ 0.83 (3 H, t, J = 6 Hz, CH_3), 1.1–2.0 (4 H, m, $-CH_2CH_2-$), 2.10 (3 h, s, CH_3), 2.08 (3 H, s, CH_3), 2.18 (3 H, s, CH_3), 2.10–3.40 (6 H, m, 2,3-H and CH_2), 4.40–4.70 (1 H, m, 1-H), 6.80 (1 H, s, 5-H), 7.20 (1 H, br, OH), 8.80–9.30 (2 H, br, NH_2^+). Anal. ($C_{15}H_{23}NO \cdot HCl$): C, H, N.

Pharmacology. Test for Antihypoxic Effect. This test was conducted by a procedure similar to that reported.[26] ICR strain male mice (weighing 20–30 g) were used as the test animals. The test compounds were administered to a group of 10 mice 0.25 h (iv, sc, or ip injection) or 1 h (oral administration) before the test as indicated in Table III. The groups of mice were placed in a glass desiccator equipped with a vacuum pump and a manometer. The inside pressure of the desiccator was reduced to 210 mmHg by sucking out the inside air with a vacuum pump, and the stop bulb was closed.

The survival time of the mouse was determined as the length of time from the beginning of the vacuum pump operation to the cessation of the respiration of the mouse. Under the above hypoxic conditions, the survival times of control animals were found to be 130–180 s. For convenience, the survival time of the mouse which lived longer than 900 s was taken as 900 s. Activity of the compound in the test was defined as the ratio (%) of the survival time of the mice treated with the test compound to that of the control group. The results are shown in Table III as SVT. Statistical analysis was performed by the Wilcoxon sum test (number of animals used: n = 10).

Test for Promoting Effects on Recovery from Coma. The procedure used was similar to that reported as the experimental model for the head injury.[27] ICR strain male mice (weighing 20–30 g) were used as the test animals. The head of the test mouse was fixed on a pillow made of foamed polystyrene resin by holding the neck of the mouse. A plastic tuve (22 mm i.d.) was placed vertically over the head and the mouse received a concussion by dropping an acrylate cylindrical rod (weighing 20 g) through the tube from a 40-cm height to strike the vertex. Clonic convulsion occurred for 1–10 s, followed by loss of consciousness (righting reflex); the mice then remained motionless in a crouching or prone position for some time. The time required for the reappearance of the righting reflex (RRT) after concussion and the time between recovery of the righting reflex and the appearance of spontaneous movement (SMT) were used as indicators of the promoting effect on recovery from coma.

Each of the test compounds was administered orally 1 h before concussion was induced. The same amount of physiological saline was administered to the mouse of the control group. After the test, the brains of all mice tested were subjected to postmortem examinations and those mice showing contused wound of the brain were excluded from the determination. The numbers of animals used in this test are shown in parentheses in the last column in Table III. Activity of the compound in the test was defined as

the ratio (%) of RRT or SMT of the mice treated with the test compound to that of the control group. The results are shown in Table III. Statistical analysis was performed by the Wilcoxon sum test.

Crystallography. Crystals of 31 ($C_{18}H_{21}NO$) suitable for X-ray analysis were crystallized with space group symmetry $P2_1/a$ from EtOH. The cell dimensions and intensities were measured on a Rigaku AFC5S diffractometer using Mo Kα radiation with graphite monochromator (λ = 0.71069 Å) with a $\omega - 2\theta$ scan mode within 2θ less than 45° at room temperature. Cell constants determined were a = 16.294 (2) Å, b = 10.981 (1) Å, c = 17.929 (2) Å, and β = 107.178 (9)° with Z = 8 for a calculated density of 1.159 g/cm^3. A total of 4187 independent reflections was collected. The linear absorption coefficient for Mo Kα is 0.66 cm^{-1}. Azimuthal scans of several reflections indicated no need for an absorption correction. The data were collected for Lorentz and polarization effects. The structure was solved by a direct method.[29] The resulting E map revealed the position of non-hydrogen atoms. The structure was refined by using a full-matrix least-squares technique by minimizing $\Sigma\omega(|F_o| - |F_c|)$ with $\omega = (1/2F_o)^2$. Thermal parameters were refined anisotropically for all non-hydrogen atoms and isotropically for the H atoms. The final refinement was based on 2442 observed reflections [$I > 3.00\sigma(I)$] and 518 variable parameters, and converged (largest parameter shift was 1.67 times its ESD) with unweighted and weighted agreement factors of

$$R = \frac{\sum\omega(|F_o| - |F_c|)}{\sum\omega|F_o|} = 0.059$$

$$R_\omega = \left(\frac{\sum\omega(|F_o| - |F_c|)^2}{\sum\omega(F_o)^2}\right)^{1/2} = 0.081$$

The standard deviation of an observation weight was 1.46. The weighting scheme was based on counting statistics and included a factor (p = 0.03) to weight the intense reflections. Plots of $\sum\omega(|F_o| - |F_c|)$ versus $|F_o|$, reflection order in data collection, sin θ/n, and various classes of indices showed no usual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.32 and −0.23 e/Å^3, respectively. Neutral atom scattering factors were taken from Cromer and Waber.[30] All calculations were performed with the TEXAN[31] crystallographic software package of Molecular Structure Corporation. The correct configuration for 31 is shown in the computer drawing in Figure 1.

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Registry No. 1a, 6968-35-0; 1b, 67901-82-0; 1c, 72806-67-8; 1d, 84174-65-2; 1e, 133497-34-4; 1f, 133497-35-5; 1g, 133497-36-6; 1h, 133497-37-7; 2a, 133497-38-8; 2b, 103234-30-6; 3a, 133497-39-9; 3b, 133497-40-2; 4a, 133497-41-3; 4b, 133497-42-4; 4c, 133497-43-5; 5a, 93748-03-9; 5b, 133497-44-6; 5c, 133497-45-7; 6a, 93747-59-2; 6b, 93747-61-6; 6c, 103234-37-3; 6d, 133497-46-8; 6e, 133497-47-9; 7a, 93747-67-2; 8a, 93747-71-8; 8b, 93747-68-3; 8c, 133497-48-0; 8d, 93747-72-9; 9a, 73045-35-9; 9b, 100072-76-2; 9c, 84174-67-4; 9d, 93747-81-0; 9e, 93747-80-9; 9f, 94727-58-9; 9g, 93747-82-1; 9h, 133497-49-1; 9i, 93747-86-5; 9j, 100072-77-3; 9k, 133497-50-4; 9l, 133497-51-5; 9m, 133497-52-6; 9n, 133497-53-7; 9o, 93747-87-6; 9p, 133497-54-8; 11a, 133497-55-9; 11a·free base, 133497-56-0; 11b, 133497-58-2; 11c, 133497-59-3; 12, 133497-60-6; 12·free base, 133497-61-7; 13, 133497-62-8; 13·free base, 133497-63-9; 14, 133497-64-0; 14·free base, 133497-65-1; 15, 133497-66-2; 15·free base, 133497-67-3; 16, 133497-68-4; 16·free base, 133497-69-5; 17, 133497-70-8; 17·free base, 133497-71-9; 18, 133497-72-0; 18·free base, 133497-73-1; 19, 133497-74-2; 19·free base, 133497-75-3; 20, 93747-30-9; 20·free base, 93747-31-0; 21, 133497-76-4; 21·free base, 133497-77-5; 22, 133497-78-6; 22·free base, 133497-79-7; 23, 133497-80-0; 23·free base, 133497-81-1; 24, 133497-82-2; 24·free base, 133497-83-3; 25, 133497-84-4; 25·free base, 133497-85-5; 26, 133497-86-6; 26·free base, 133497-87-7; 27, 133497-88-8; 28, 133497-89-9; 28·free base, 133497-90-2; 29, 133497-91-3; 29·free base, 133497-92-4; 30, 133497-93-5; 31, 133497-94-6; 32, 133497-96-8; 32·free base, 133497-95-7; 33, 103246-88-4; 33·free base, 103233-84-7; 34, 133497-97-9; 34·free base, 103284-75-9; 35, 133497-98-0; 35·free base, 133497-99-1; 36, 133498-00-7; 36·free base, 133498-01-8; 37, 133498-02-9; 38, 133498-03-0; 39, 103284-78-2; 39·free base, 103233-86-9; 40, 133498-04-1; 40·free base, 133498-04-1; TMDM, 51-80-9; $ClCH_2CONHCH_2OH$, 2832-19-1; 2,4-dimethylphenol, 105-67-9; phenylacetyl chloride, 103-80-0; 4,6-dimethyl-2-(phenylacetyl)phenol, 93433-76-2; α-styryl 2-(4,6-dimethyl-1-hydroxyphenyl)ketone, 133498-05-2; benzaldehyde, 100-52-7.

Supplementary Material Available: Fractional coordinates, temperature parameters, bond distances, and bond angles for 31 (11 pages). Ordering information is given on any current masthead page.

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