recrystallization from 1-propanol afforded 3.0 g (36%) of 3-(*N*-phthalimidino)propionic acid.

Serum Hypolipidemic Activity. Compounds were tested at 20 (mg/kg)/day and administered intraperitoneally to male mice at 11:00 a.m. On days 9 and 16, the blood was collected by tail-vein bleeding. The blood samples were collected between 8:00 and 9:30 a.m. in alkali-free nonheparinized microcapillary tubes, which were centrifuged for 3 min to obtain the serum.[2] We used duplicate 25-μL samples of nonhemolyzed serum in order to determine the milligram percent serum cholestrol levels by a modification of the Liebermann–Burchard reaction.[12] Using a separate group of mice, which were bled on day 14, we measured serum triglyceride levels (in milligram percent) using duplicate samples of 50 μL.[13]

(12) A. T. Ness, J. V. Pastewka, and A. C. Peacock, *Clin. Chem. Acta*, **10**, 229 (1964).
(13) Hycel Triglyceride Test, Hycel, Inc. 1975.

Acknowledgment. This research was supported by a National Institutes of Health grant (HL 25680). We thank Melba Gibson, Greg Webb, and Michelle Tousignant for their technical assistance.

Registry No. **1**, 81-07-2; **2**, 7499-06-9; **3**, 83747-19-7; **4**, 40506-05-6; **5**, 20158-91-2; **6**, 83747-20-0; **7**, 83747-21-1; **8**, 10312-42-2; **9**, 83747-22-2; **10**, 83747-23-3; **11**, 83747-24-4; **12**, 83747-25-5; **13**, 936-16-3; **14**, 83747-26-6; **15**, 83747-27-7; **16**, 83747-28-8; **17**, 85-41-6; **18**, 1515-72-6; **19**, 71510-39-9; **20**, 3416-57-7; **21**, 3783-77-5; **22**, 3197-25-9; **23**, 3339-73-9; **24**, 3130-75-4; **25**, 1147-76-8; **26**, 4443-26-9; **27**, 480-91-1; **28**, 50707-36-3; **29**, 83747-29-9; **30**, 83747-30-2; sodium saccharin, 128-44-9; ethyl 4-bromobutyrate, 2969-81-5; α-(bromomethyl)acrylic acid, 72707-66-5; methyl vinyl ketone, 78-94-4; ethyl 3-oxo-1,2-benzisothiazolinebutyrate 1,1-dioxide, 83747-31-3; 1-iodobutane, 542-69-8; ethyl 3-bromopropionate, 539-74-2; ethyl 3-(*N*-phthalimido)propionate, 4561-06-2; phthalimide, 85-41-6.

Synthesis and Antianxiety Activity of (ω-Piperazinylalkoxy)indan Derivatives

Ryoji Kikumoto,* Akihiro Tobe, Harukazu Fukami, and Mitsuo Egawa

Biosciences Laboratory, Research Center, Mitsubishi Chemical Industries Limited, 1000-Kamoshida, Midori-ku, Yokohama, Japan. *Received August 11, 1981*

A series of (ω-piperazinylalkoxy)indan derivatives has been synthesized and screened for potential antianxiety activities. The effect of structural modification of these molecules on activities has been systematically examined. Antianxiety activity was displayed by 5-[3-(4-phenyl-1-piperazinyl)propoxy]indan (**2**), 5-[3-[4-(4-fluorophenyl)-1-piperazinyl]-propoxy]indan (**8**), 6-fluoro-5-[3-(4-phenyl-1-piperazinyl)propoxy]indan (**33**), and 6-methyl-5-[3-(4-phenyl-1-piperazinyl)propoxy]indan (**42**), as determined in antifighting and anti-morphine tests. These derivatives in antianxiety tests were equipotent or more potent than chlordiazepoxide with less muscle-relaxant effect. They also showed weak neuroleptic-like action.

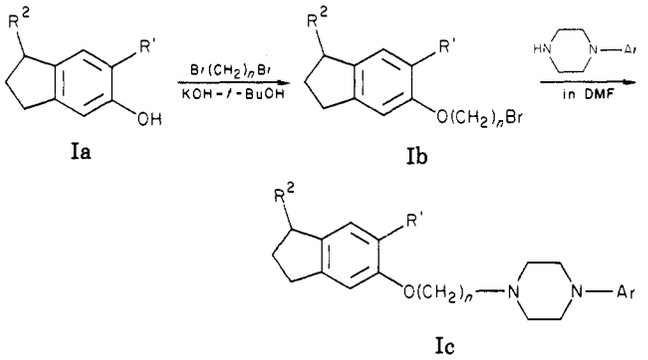
Although benzodiazepine tranquilizers are used with great clinical success in neurosis,[1,2] they are poorly effective in obsessional neurosis and they exhibit undesirable muscle-relaxant activity.[2,3] Recently, novel compounds without the benzodiazepine structure have been tried in the neurosis area with good results.[4,5]

Routine pharmacological screening in our laboratories of compounds directed toward new psychotropic agents has shown that some (ω-piperazinylalkoxy)indan derivatives antagonize the foot shock induced fighting behavior and the morphine-induced Straub's tail reaction in mice. We synthesized a wide variety of related compounds in order to find a new type of anxiolytic with novel properties. This paper describes the synthesis and primary pharmacological studies of (ω-piperazinylalkoxy)indan derivatives.

Chemistry. The (ω-piperazinylalkoxy)indan derivatives listed in Tables I and II were prepared by the ω-bromoalkoxylation of the corresponding indanol with α,ω-dibromoalkane in the presence of KOH in *t*-BuOH and followed by the amination with *N*-arylpiperazines (Scheme I).

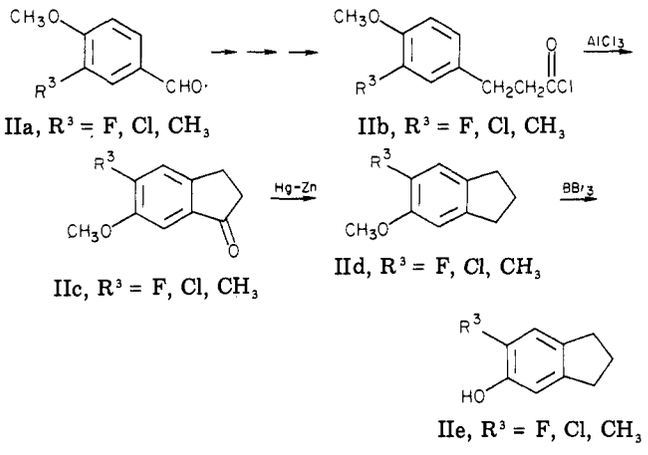
Indan derivatives with aromatic substituents were synthesized as follows (Scheme II). The 1-indanone derivatives (IIc) with fluoro, chloro, or methyl substituents were prepared by the Friedel-Craft cyclization[6] of the corresponding phenylpropionyl chlorides (IIb), which were

Scheme I



Ia Ib Ic

Scheme II



IIa, R^3 = F, Cl, CH_3 IIb, R^3 = F, Cl, CH_3

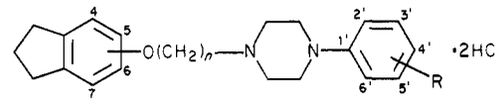
IIc, R^3 = F, Cl, CH_3 IId, R^3 = F, Cl, CH_3

IIe, R^3 = F, Cl, CH_3

(1) L. E. Holister, "The Benzodiazepines", S. Garattini, E. Mussini, and L. O. Randall, Eds., Raven Press, New York, 1973, p 367.
(2) R. N. Brogden, R. C. Heel, T. M. Speight, and G. S. Avery, *Drugs*, **20**, 161 (1980).
(3) M. Lader, *Arzneim.-Forsch. (Drug Res.)*, **30**, 910 (1980).
(4) K. Hirose, A. Matsushita, M. Eigyo, H. Jyoyama, A. Fujita, Y. Tsukinoki, T. Shiomi, and K. Matsubara, *Arzneim.-Forsch. (Drug Res.)*, **31**, 63 (1981).
(5) E. Wickstrom and K.-E. Giercksky, *Eur. J. Clin. Pharmacol.*, **17**, 93 (1980).

0022-2623/83/1826-0246$01.50/0

Table I. [ω-(4-Aryl-1-piperazinyl)alkoxy]indan Derivatives

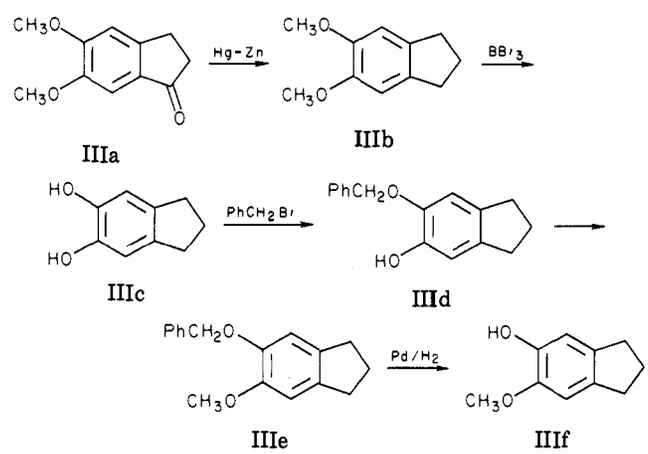


no.	R	n	substituted position of alkoxy	mp, °C	formula[a]	% inhibn:[b] antifighting potency		ED$_{50}$, mg/kg po anti-morphine potency	
1	H	2	5	195	$C_{21}H_{28}Cl_2N_2O$	0		17	
2	H	3	5	195-197	$C_{22}H_{30}Cl_2N_2O$	85	6.6	89	6.3
3	H	4	5	157-159	$C_{23}H_{32}Cl_2N_2O$	75		50	
4	H	5	5	153-155	$C_{23}H_{34}Cl_2N_2O$	27		25	
5	3'-F	3	5	195-197	$C_{22}H_{29}Cl_2FN_2O$	19		42	
6	3'-F	4	5	147-150	$C_{23}H_{31}Cl_2FN_2O$	15		17	
7	4'-F	2	5	199-202	$C_{21}H_{27}Cl_2FN_2O$	40		0	
8	4'-F	3	5	192-196	$C_{22}H_{29}Cl_2FN_2O$	88	7.5	100	6.0
9	4'-F	4	5	168-172	$C_{23}H_{31}Cl_2FN_2O$	70	12.0	100	11.1
10	4'-F	5	5	148-150	$C_{24}H_{33}Cl_2FN_2O$	58		71	
11	2'-Cl	3	5	241-242	$C_{22}H_{29}Cl_3N_2O$	40		42	
12	2'-Cl	4	5	143-145	$C_{23}H_{31}Cl_3N_2O$	85	14.5	42	30.0
13	3'-Cl	3	5	143-144	$C_{22}H_{29}Cl_3N_2O$	83	12.6	83	15.5
14	3'-Cl	4	5	206-207	$C_{23}H_{31}Cl_3N_2O$	37		0	
15	4'-Cl	3	5	192-193	$C_{22}H_{29}Cl_3N_2O$	43		58	
16	4'-Cl	4	5	160-163	$C_{23}H_{31}Cl_3N_2O$	31		33	
17	3',5'-Cl_2	3	5	222-226	$C_{22}H_{28}Cl_4N_2O$	0		0	
18	3',5'-Cl_2	4	5	212-215	$C_{23}H_{30}Cl_4N_2O$	0		0	
19	3'-CF_3	3	5	180-184	$C_{23}H_{29}Cl_2F_3N_2O$	0		73	
20	3'-CF_3	4	5	173-174	$C_{24}H_{31}Cl_2F_3N_2O$	8		100	12.5
21	3'-CF_3	5	5	141-142	$C_{25}H_{33}Cl_2F_3N_2O$	33		66	
22	2'-OCH_3	3	5	183	$C_{23}H_{32}Cl_2N_2O_2$	0		19	
23	2'-OCH_3	4	5	174-176	$C_{24}H_{34}Cl_2N_2O_2$	33		42	
24	4'-OCH_3	3	5	233-235	$C_{23}H_{32}Cl_2N_2O_2$	60		37	
25	4'-OCH_3	4	5	170-172	$C_{24}H_{34}Cl_2N_2O_2$	17		14	
26	4'-$COCH_3$	3	5	133-134	$C_{24}H_{32}Cl_2N_2O_2$	13		0	
27	2'-NO_2	3	5	209-212	$C_{22}H_{29}Cl_2N_3O_3$	8		43	
28	2'-NO_2	4	5	165-167	$C_{23}H_{31}Cl_2N_3O_3$	42	25.8	54	23.0
29	4'-NO_2	3	5	207-210	$C_{22}H_{29}Cl_2N_3O_3$	0		26	
30	4'-NO_2	4	5	198-200	$C_{23}H_{31}Cl_2N_3O_3$	0		22	
31	H	3	4	220-224	$C_{22}H_{30}Cl_2N_2O$	0		33	
32	4'-F	3	4	227-228	$C_{22}H_{29}Cl_2FN_2O$	5		25	

[a] Analyses for C, H, and N are within ±0.4% of the theoretical values. [b] Figures indicate percent inhibition at 25 mg/kg po of each compound.

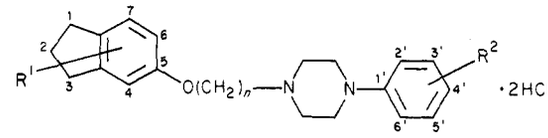
prepared from 3-substituted 4-methoxybenzaldehyde (IIa) by the usual methods.[7] The structure of the 1-indanone derivatives was assigned by ^{1}H NMR spectroscopy. In the spectra of the chloro and methyl derivatives, two benzene ring protons were shown as two singlet signals, suggesting para substitution. The spectrum of the fluoro compound showed two doublet signals with coupling constants of 5 and 4.5 Hz, respectively (ortho and meta coupling of H–F). Therefore, the benzene ring protons are para to each other. The other positional isomer of these derivatives could not be isolated. The 1-indanone derivatives (IIc) were converted to the corresponding 5-indanols (IIe) by the reduction of the carbonyl group with Hg–Zn and HCl[8] and then demethylation with BBr_3 in CH_2Cl_2.[9] 6-Methoxy-5-indanol (IIIf) was obtained from 5,6-dimethoxy-1-indanone (IIIa) and converted to 5,6-dihydroxyindan (IIIc). Monobenzylation, methylation, and then debenzylation gave 6-methoxy-5-indanol (IIIf) (Scheme III). 5-(3-Chloropropoxy)-6-nitroindan was prepared by nitrosation of 5-(3-chloropropoxy)indan with concentrated HNO_3 in AcOH. The structure was confirmed by ^{1}H NMR spectral analysis. The two benzene ring protons were shown as two singlet peaks, which confirm the para orientation. In the 6-hydroxyindan derivative, 6-(benzyloxy)-5-indanol was converted to 6-(benzyloxy)-5-(3-bromopropoxy)indan, which was aminated and then debenzylated by hydrogenolysis to afford 5-[3-(4-aryl-1-piperazinyl)propoxy]-6-hydroxyindan. 1-Phenyl- or 1-ethyl-5-indanol was prepared from 5-methoxy-1-indanone by Grignard reaction of 5-methoxy-1-indanone with phenyl- or ethylmagnesium bromide, dehydroxylation by hydrogenolysis, and then demethylation.

Scheme III



(6) E. L. Martin and L. F. Fieser, "Organic Syntheses", Collect. Vol. 2, Wiley, New York, 1943, p 569.
(7) J. Koo, M. S. Fish, G. N. Walker, and J. Blake, "Organic Syntheses", Collect. Vol. 4, Wiley, New York, 1963, p 327.
(8) E. L. Martin, ref 6, p 499.
(9) J. F. McOmie, M. L. Watts, and D. E. West, *Tetrahedron*, **24**, 2289 (1967).

Table II. Substituted ω-(4-Aryl-1-piperazinyl)alkoxyindan Derivatives



no.	R^1	R^2	n	mp, °C	formula[a]	% inhibn:[b] antifighting potency		ED$_{50}$, mg/kg po antifighting potency		% inhibn:[b] anti-morphine potency		ED$_{50}$, mg/kg po anti-morphine potency	
33	6-F	H	3	212–213	$C_{22}H_{29}Cl_2FN_2O$	100	10.6			89	2.9		
34	6-F	H	4	142–148	$C_{23}H_{31}Cl_2FN_2O$	33				79			
35	5-F	4′-F	3	177	$C_{22}H_{28}Cl_2F_2N_2O$	100	12.5			97	1.0		
36	6-F	4′-F	4	148–151	$C_{23}H_{30}Cl_2F_2N_2O$	83	14.4			90	10.2		
37	6-F	3′-Cl	3	167–172	$C_{22}H_{28}Cl_3FN_2O$	92	13.8			92	14.5		
38	6-F	3′-CF_3	3	177–180	$C_{23}H_{28}Cl_2F_4N_2O$	0				20			
39	6-Cl	H	3	216–220	$C_{22}H_{29}Cl_3N_2O$	58	21.0			82	22.0		
40	6-Cl	4′-F	3	188–193	$C_{22}H_{28}Cl_3FN_2O$	83	14.3			100	11.5		
41	6-Cl	4′-Cl	3	163–169	$C_{22}H_{28}Cl_4N_2O$	33				36			
42	6-CH_3	H	3	198	$C_{23}H_{32}Cl_2N_2O$	83	16.0			94	18.5		
43	6-CH_3	4′-F	3	167–170	$C_{23}H_{31}Cl_2FN_2O$	50				31			
44	6-OH	H	3	208–213	$C_{22}H_{30}Cl_2N_2O$	17				0			
45	6-OH	4′-F	3	203–206	$C_{22}H_{29}Cl_2FN_2O_2$	25				0			
46	6-OH	3′-Cl	3	212–217	$C_{22}H_{29}Cl_2N_2O_2$	0				29			
47	6-OCH_3	H	3	170–173	$C_{23}H_{32}Cl_2N_2O_2$	50				65			
48	6-OCH_3	4′-F	3	159–162	$C_{23}H_{31}Cl_2FN_2O_2$	100	13.0			100	10.2		
49	6-OCH_3	3′-Cl	3	180–185	$C_{23}H_{31}Cl_3N_2O_2$	67	15.9			98	11.3		
50	6-NO_2	H	3	235–238	$C_{22}H_{29}Cl_2N_3O_3$	67				24			
51	6-NO_2	4′-F	3	203–205	$C_{22}H_{28}Cl_2FN_3O_3$	58				28			
52	3-Et	4′-F	3	powders	$C_{24}H_{33}Cl_2FN_2O$	67				44			
53	3-Ph	H	3	187–191	$C_{28}H_{35}Cl_2N_2O$	0				34			
54	3-Ph	4′-F	3	150–153	$C_{28}H_{34}Cl_2FN_2O$	17				32			

[a–c] See corresponding footnotes in Table I.

Results and Discussion

Pharmacological Activity. The compounds listed in Tables I and II were evaluated for their abilities to suppress the foot shock induced fighting behavior and the morphine-induced Straub's tail reaction in mice (further referred to as the antifighting and the anti-morphine activity, respectively).

Among the (ω-piperazinylalkoxy)indan derivatives, compound **2**, in which the 3-(4-phenyl-1-piperazinyl)-propoxy group was attached to the 5-position of indan, was one of the compounds with the highest antianxiety activity. Compound **31**, in which the side chain is linked at the 4-position, was much less active. Thus, 5-substituted derivatives are superior to 4-substituted ones in their antianxiety action. The potency changed according to the side-chain length in the ω-(4-phenyl-1-piperazinyl)alkoxy-type compounds. Namely, by changing the chain from three (**2**) to two (**1**) or five (**4**) carbon atoms, we reduced the activity. The change to four carbon atoms (**3**), however, brought about no reduction in the activity. The same relationships were observed in the ω-[4-(4-fluorophenyl)-1-piperazinyl]alkoxy-type compounds (**7–10**). Considering the above experimental results, the optimal side-chain moiety for antianxiety activity is a (4-phenyl-1-piperazinyl)propoxy or -butoxy group.

Subsequently, the effect of substitution on the phenyl group of the (4-phenyl-1-piperazinyl)propoxy or -butoxy group was examined. The substituted derivatives with F (**5–10**), Cl (**11–16**), Cl_2 (**17** and **18**), OCH_3 (**22–25**), $COCH_3$ (**26**), and NO_2 (**27–30**) groups on the phenyl group indicated, on the whole, that an increase in bulk or an increase in polarity of the substituents decreases the activity. The ortho-substituted compounds decreased or eliminated the activities (**11**, **22**, and **27**). The introduction of a *m*-CF_3 group (**19** and **20**) diminished the anti-morphine activity but increased the antifighting effect. In substitutions on the phenyl group of the phenylpiperazinyl moiety, none of the derivatives with small lipophilic substituents, especially fluoro, possessed high activity.

On substitution of the indan at the 6-position (Table II) with highly polar groups (NO_2 or OH), the activity decreased or disappeared (**44–46**, **50**, and **51**). The introduction of halogens, methyl, and methoxy groups resulted in equipotent or slightly less active analogues compared with the unsubstituted derivatives. Surprisingly, among the compounds with a fluoro group at the 6-position (**33–38**), there were derivatives that were 2 to 7 times more potent (**33**, **35**, and **36**) compared with the ones that are unsubstituted at the 6-position (**2**, **8**, and **9**). Since antifighting activity is a better measure of antianxiety effects than anti-morphine activity, these increases in activity were interesting. The activites of 3-phenylindan derivatives (**53** and **54**) were exceedingly weak.

The properties of compounds **2**, **8**, **33**, and **42**, of which ED_{50} values were under 10 mg/kg po in either the antifighting or the anti-morphine effect, were studied further pharmacologically and compared with those of chlordiazepoxide, diazepam, and chlorpromazine. The results are given in Tables III and IV.

In the antifighting test, compounds **2**, **8**, **33**, and **42** were 1.4 to 4.3 times more potent than chlordiazepoxide but less active than diazepam. In the anti-morphine tests, **33** and **42** were equipotent with chlordiazepoxide, and **2** and **8** were two times as active. In order to examine the selectivity in their antianxiety activites, we calculated the ratios (B/A) of the antifighting effect (A) to the muscle-relaxant action (B) (Table III). The B/A values of these four derivatives (2.18–5.41) were larger than that of chlordiazepoxide (0.64), and **8**, **33**, and **42** were superior to diazepam (3.00).

These four compounds also exhibited activities in open-field tests, anti-methamphetamine tests, and hypothermic tests (Table IV). That is, the potencies of **2**,

Table III. Pharmacology: Antianxiety Property and Acute Toxicity

compd	ED_{50},[a] mg/kg po: antifighting effect (A)	anti-morphine effect	muscle-relaxant action (B)	toxicity: LD_{50},[a] mg/kg po	B/A[b]
2	6.6 (3.5-11.6)	6.3 (3.5-11.1)	14.1 (8.3-24.1)	>1500	2.18
8	7.5 (3.2-15.3)	6.0 (3.5-10.2)	28.0 (18.8-44.4)	>2000	3.73
33	2.9 (0.8-5.6)	10.6 (8.5-13.3)	14.5 (8.1-19.2)	>2000	5.00
42	8.5 (6.8-12.9)	16.0 (12.8-21.6)	46.0 (31.4-66.0)	>2000	5.41
chlordiazepoxide	12.5 (6.6-20.0)	13.0 (8.7-19.5)	8.0 (6.8-12.4)	700 (394-1421)	0.64
diazepam	1.6 (0.6-5.1)	1.2 (0.7-2.2)	4.8 (2.0-8.4)	620 (382-1188)	3.00

[a] 95% confidence limits in parentheses. [b] Ratio of the antifighting effect to muscle-relaxant action.

Table IV. Pharmacology: Neuroleptic-like Property

compd	ED_{50},[a] mg/kg po: inhibitory effect in open-field test	anti-methamphetamine effect	hypothermic action at 30 mg/kg po: Δt °C	cataleptogenic action: ED_{50},[a] mg/kg po
2	11.7 (8.4-17.0)	>100	-2.3	>100
8	10.3 (8.1-13.2)	43 (20-79)	-5.0	50 (26-93)
33	9.3 (7.3-13.9)	>100	-2.9	>100
42	16.6 (11.9-23.1)	>100	-2.5	56 (30-71)
chlorpromazine	10.1 (7.0-13.5)	15 (10-24)	-1.5	17 (10-29)
chlordiazepoxide	slight increase[b]	>30	+0.2	>30
diazepam	increase[b]	>30	-0.1	>30

[a] 95% confidence limits in parentheses. [b] Drug induced an increase in ambulation at 3 to 20 mg/kg po.

8, and 33 in the open-field test were equal to that of chlorpromazine, although only 8 was active in the anti-methamphetamine test. In hypothermic activity, they were more potent than chlorpromazine. On the other hand, they displayed only weak cataleptogenic activity, but diazepam and chlordiazepoxide induced an increase in ambulation at 3 to 20 mg/kg po and hardly showed anti-methamphetamine effect, hypothermic action, or cataleptogenesity to a high dose, 30 mg/kg po. The above results suggest that these compounds possess neuroleptic-like activity with weak catatonic side effects; these latter activities appeared at higher doses than needed to produce antianxiety effects.

These indan derivatives display antianxiety properties with weak muscle-relaxant side effects and with weak neuroleptic-like activity.

Experimental Section

Chemistry. Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. All compounds were analyzed for C and H or C, H, and N, and analytical results were within ±0.4% of the theoretical values. Compounds were checked by IR spectra on a JASCO IR-A2. ^1H NMR spectra were taken on a JEOL PS-100 (Me_4Si as internal standard).

Preparation of (ω-Piperazinylalkoxy)indans. The (ω-piperazinylalkoxy)indans were all prepared by the same general method, and the procedure is exemplified by the preparation of compound **2**.

5-(3-Bromopropoxy)indan (Scheme I). To a solution of KOH (7.5 g, 0.13 mol) in H_2O (7.5 mL) were added *t*-BuOH (100 mL), 5-indanol (15.0 g, 0.11 mol), and 1,3-dibromopropane (90 g, 0.45 mol), and the mixture was stirred for 2 h under reflux. The reaction mixture was evaporated, extracted with benzene, washed with H_2O, and dried (Na_2SO_4). After evaporation of the solvent, the residual oil was distilled under reduced pressure to give 25.8 g (91%) of 5-(3-bromopropoxy)indan, bp 121 °C (1 mmHg). Anal. ($C_{12}H_{51}OBr$) C, H.

5-[3-(4-Phenyl-1-piperazinyl)propoxy]indan Dihydrochloride (2). A solution of 5-(3-bromopropoxy)indan (25.5 g, 0.1 mol), *N*-phenylpiperazine (17.8 g, 0.11 mol), and Et_3N (15.0 g, 0.15 mol) in DMF (300 mL) was stirred at 80 °C for 2 h. The resulting mixture was poured into H_2O and extracted with AcOEt. The extract was washed with saturated NaCl solution, dried (Na_2SO_4), and evaporated to a syrup, which was dissolved in EtOH (100 mL). Ethanolic HCl 20% (40 mL) was added to the solution to give crystals, which were recrystallized from EtOH to obtain 35.0 g (85.6%) of **2**, mp 195–197 °C. Anal. ($C_{22}H_{28}N_2O\cdot 2HCl$) C, H, N. Other compounds prepared are listed in Tables I and II.

Preparation of 6-Substituted 5-Indanols. 5-Fluoro-6-methoxy-1-indanone (IIc, R^3 = F; Scheme II). To a solution of fine pulverized anhydrous $AlCl_3$ (15.0 g, 0.11 mol) in CS_2 (70 mL) was added dropwise 3-(3-fluoro-4-methoxyphenyl)propionyl chloride [IIb, R^3 = F; 20.2 g, 0.09 mol; bp 115–117 °C (1 mmHg)], which was prepared from 3-fluoro-4-methoxybenzaldehyde (IIa, R^3 = F), at 0–10 °C while stirring. After the addition, the reaction mixture was stirred vigorously for 1 h, poured into cold 2 N HCl solution, and then extracted with AcOEt. The extract was washed with saturated NaCl solution, dried (Na_2SO_4), and evaporated to dryness. The residue crystallized from AcOEt–*n*-hexane to give 16.0 g (96%) of 5-fluoro-6-methoxy-1-indanone (IIc, R^3 = F), mp 148 °C. Anal. ($C_{10}H_9FO_2$) C, H.

6-Fluoro-5-indanol (IIe, R^3 = F; Scheme II). Water (40 mL), concentrated HCl (50 mL), toluene (50 mL), and IIc (R^3 = F; 20.0 g, 0.11 mol), in that order, were added to Hg–Zn, which was prepared from Zn powder (50.0 g) and $HgCl_2$ (5.0 g). The mixture was stirred vigorously under reflux for 6 h. The mixture was extracted with benzene. The extract was washed with H_2O, dried (Na_2SO_4), and evaporated, and the residue was distilled at 78–80 °C (3 mmHg) to obtain 17.0 g (92%) of 6-fluoro-5-methoxyindan (IId, R^3 = F). To a solution of IId (R^3 = F; 17.0 g, 0.10 mol) in CH_2Cl_2 (150 mL) was added BBr_3 (11.4 mL, 0.12 mol) dropwise under stirring at 0–5 °C. After the addition, the reaction was stirred for 1 h at 0–5 °C and then at room temperature for 2 h and then H_2O was added dropwise to decompose the boron complex. The organic layer was washed with H_2O and evaporated, and the residue was distilled at 82–83 °C (5 mmHg) to give 14.5 (88%) of 6-fluoro-5-indanol (IIe, R^3 = F). Anal. (C_9H_9FO) C, H.

6-Methoxy-5-indanol (IIIf, Scheme III). 5,6-Dimethoxyindan (IIIb; 44.0 g, 94%) was obtained from 5,6-dimethoxy-1-indanone (IIIa; 50.5 g, 0.26 mol) by the same method for the preparation of IId (R^3 = F). The demethylation of IIIb (25.0 g, 0.14 mol) gave 18.3 g (87%) of 5,6-dihydroxyindan (IIIc). To a solution of crude IIIc (15.7 g, 0.10 mol) in 1.6 N NaOEt (60 mL) was added dropwise benzyl bromide (17.0 g, 0.10 mol), and the mixture was stirred for 6 h at room temperature. The reaction mixture was evaporated, and the residue was taken up in Et_2O. The solution was washed with 1 N NaOH and saturated NaCl solution, dried (Na_2SO_4), and then evaporated. The residual oil

was distilled at 151–154 °C (1 mmHg) to give 8.1 g (32%) of 5-(benzyloxy)-6-indanol (IIId). To a solution of IIId (6.5 g, 27 mmol) in DMF (30 mL) was added NaH (0.84 g, 35 mmol) under cooling. CH_3I (8.0 g, 56 mmol) was added dropwise to the mixture, which was stirred for 1 h at room temperature. The reaction mixture was poured into H_2O and extracted with benzene. The extract was washed with H_2O, dried (Na_2SO_4), and evaporated to a syrup, which was hydrogenolyzed with Palladium Black (0.5 g) in EtOH (50 mL) under atmospheric pressure of H_2 for 2 h at room temperature. The catalyst was filtered off, and the filtrate was evaporated to give oily crude 6-methoxy-5-indanol (IIIf). The crude oil of IIIf was alkylated with 5.9 g (80%) of 5-(3-bromopropoxy)-6-methoxyindan, bp 135–138 °C (1 mmHg). Anal. ($C_{13}H_{17}BrO_2$) C, H.

Pharmacology. Antifighting Activity.[10] For each group were used six selected pairs of mice, which were foot shocked through the grid floor with a current of 1.5 mA at 28 V. Fighting episodes were observed for 2 min at 1 h after oral doses of the test compounds. The ED_{50} was defined as the dose in which the number of fighting episodes was reduced by 50%, compared with that (about 16.5 as mean) of the control group (six pairs of mice).

Anti-morphine Activity.[11] For each group were used six mice, which were administered the test compounds (po) 1 h before the treatment with morphine (20 mg/kg ip). Straub's tail reaction served as an index of the CNS stimulant action of morphine.

Muscle-Relaxant Action (Traction Test in Mice).[12] Forepaws of mice (eight per group) were placed on a horizontal wire bar, 30 cm in height, 1 h after administration of the test compounds (po). Failure to place the hind feet onto the wire within 5 s was judged to be a measured muscle-relaxant activity. The ED_{50} was defined as the dose that causes muscle relaxation in 50% of the animals used.

Inhibitory Action of Ambulation in Open-Field Tests.[13] Open field was a square box (100 × 100 cm, 30 cm in height), the bottom and wall of which were painted black. The apparatus was placed in a dark room illuminated by a 100-W lamp. Each group consisted of five rats. The test compounds were administered orally 1 h before observation. Performance of the rats in the open field was observed for 3 min, and the number of ambulations was counted. The ED_{50} was defined as the dose that decreased the number of ambulations by 50% compared with that of the control group.

Anti-methamphetamine Activity.[14] Each group of six rats was given orally the test compounds; 1 h thereafter, the same rats were administered intraperitoneally 5 mg/kg of methamphetamine. Each animal was assigned a stereotyped score of 0 to 4 according to the following criteria: sleep and eyes closed = 0; motionless and eyes open = 1; moving around the cage = 2; sniffing = 3; continuous licking or gnawing = 4. The ED_{50} was defined as the dose that reduced average stereotyped scores by 50% compared with those of the control group.

Hypothermic Action.[15] Six mice were used for each group, and the test compounds were administered orally 1 h before the test. Rectal temperature was recorded with an electronic thermister. The results are expressed in degrees of hypothermia, compared with the nontreated group.

Cataleptogenic Action.[16] Six mice were used for each group, and the test compounds were administered orally 1 h before the test. Forepaws were put on a horizontal steel bar, and the animals were forced to maintain an abnormal position. When the animals could keep the posture for over 30 s, it was interpreted as positive response of the catalepsy. the ED_{50} was defined as the dose that caused catalepsy in 50% of the animals used.

Acute Toxicity. Eight mice were for each group, and the test compounds were administered orally. The LD_{50} was calculated according to the method of Litchfield and Wilcoxon.[17]

Acknowledgment. The authors thank M. Sugano and N. Hashimoto for their technical assistance and Dr. S. Hattori, Assistant General Manager of the Research Center, Mitsubishi Chemical Industries Limited, for his valuable advice and encouragement throughout this work. We are also indebted to members in Systems Engineering and the Analytical Laboratory, Mitsubishi Chemical Industries Limited, for elemental analyses.

Registry No. **1**, 83802-46-4; **2**, 78114-61-1; **3**, 78114-62-2; **4**, 83802-47-5; **5**, 83802-48-6; **6**, 83802-49-7; **7**, 83802-50-0; **8**, 78114-63-3; **9**, 78114-64-4; **10**, 83802-51-1; **11**, 78114-71-3; **12**, 83815-93-4; **13**, 78114-73-5; **14**, 83802-52-2; **15**, 78114-65-5; **16**, 78129-75-6; **17**, 83802-53-3; **18**, 83802-54-4; **19**, 78114-66-6; **20**, 78114-67-7; **21**, 83802-55-5; **22**, 78114-69-6; **23**, 83802-56-6; **24**, 78114-70-2; **25**, 83802-57-7; **26**, 78114-72-4; **27**, 83802-58-8; **28**, 83802-59-9; **29**, 83802-60-2; **30**, 83802-61-3; **31**, 83802-62-4; **32**, 83802-63-5; **33**, 78114-74-6; **34**, 78114-78-0; **35**, 78114-75-7; **36**, 78114-79-1; **37**, 78114-77-9; **38**, 78114-76-8; **39**, 78114-82-6; **40**, 78114-83-7; **41**, 83802-64-6; **42**, 78114-80-4; **43**, 78114-81-5; **44**, 78114-87-1; **45**, 78114-88-2; **46**, 78114-89-3; **47**, 78114-84-8; **48**, 78114-85-9; **49**, 78114-86-0; **50**, 78114-90-6; **51**, 78114-91-7; **52**, 83802-65-7; **53**, 83802-66-8; **54**, 83802-67-9; Ia (R^1, R^2 = H), 1470-94-6; Ib (n = 2; R^1, R^2 = H), 82827-58-5; Ib (n = 3; R^1, R^2 = H), 78114-95-1; Ib (n = 4; R^1, R^2 = H), 82827-59-6; Ib (n = 5; R^1, R^2 = H), 83802-68-0; Ib (n = 3; R^1 = CH_3O; R^2 = H), 83802-76-0; IIb (R^3 = F), 83802-70-4; IIc (R^3 = F), 83802-71-5; IId (R^3 = F), 83802-72-6; IIe (R^3 = F), 83802-73-7; IIIa, 2107-69-9; IIIb, 59078-28-3; IIIc, 3598-20-7; IIId, 83802-74-8; IIIe, 83815-94-5; IIIf, 83802-75-9; 1,2-dibromoethane, 106-93-4; 1,3-dibromopropane, 109-64-8; 1,4-dibromobutane, 110-52-1; 1,5-dibromopentane, 111-24-0; *N*-phenylpiperazine, 92-54-6; *N*-(3-fluorophenyl)-piperazine, 3801-89-6; *N*-(4-fluorophenyl)piperazine, 2252-63-3; *N*-(2-chlorophenyl)piperazine, 39512-50-0; *N*-(3-chlorophenyl)-piperazine, 6640-24-0; *N*-(4-chlorophenyl)piperazine, 38212-33-8; *N*-(3,5-dichlorophenyl)piperazine, 55827-50-4; *N*-[3-(trifluoromethyl)phenyl]piperazine, 15532-75-9; *N*-(2-methoxyphenyl)-piperazine, 35386-24-4; *N*-(4-methoxyphenyl)piperazine, 38212-30-5; *N*-(4-acetylphenyl)piperazine, 51639-48-6; *N*-(2-nitrophenyl)piperazine, 59084-06-9; *N*-(4-nitrophenyl)piperazine, 6269-89-2; 4-indanol, 1641-41-4; 4-(3-bromopropoxy)indan, 83802-69-1.

(10) L. O. Randall, C. L. Scheckel, and R. F. Banziger, *Curr. Ther. Res.*, **7**, 590 (1965).
(11) H. Takagi, T. Ueoka, Y. Suzuki, and R. Tachikawa, *Folia Pharmacol. Jpn.*, **66**, 107 (1970).
(12) S. Courvoisier, R. Ducrot, and L. Julou, "Psychotropic Drugs", S. Garattini and V. Ghetti, Eds., Elsevier, Amsterdam, 1957, p 373.
(13) P. A. Janssen, C. J. E. Niemegeers, and K. H. I. Schellenkens, *Arzneim.-Forsch.*, **15**, 104 (1965).
(14) R. M. Quinton and G. Halliwell, *Nature (London)*, **200**, 178 (1963).
(15) G. E. Johnson, *Acta Physiol. Scand.*, **60**, 181 (1964).
(16) S. Ueki, M. Fujiwara, and K. Inoue, *Folia Pharmacol. Jpn.*, **72**, 585 (1976).
(17) J. T. Litchfield, Jr., and F. W. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949).