(Fisher, SOX-1 Scintiverse; Packard scintillation counter) and analyzed for cholesterol content.[13]

Plasma Lipoprotein Fractions. Holtzman male rats (~400 g) were administered drugs at 20 (mg/kg)/day for 14 days. On day 14, blood was collected from the abdominal aorta. Serum was separated from whole blood by centrifugation at 3500 rpm. Aliquots (3 mL) were separated by density gradient ultracentrifugation according to the method of Hatch and Lees[29] and Havel et al.[30] into the chylomicrons, very low density lipoproteins, high density lipoproteins and low density lipoproteins. Each of the fractions were analyzed for cholesterol,[13] triglyceride,[7] neutral lipids,[26] phospholipids,[27] and protein levels.

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Registry No. 2, 520-03-6; 3, 83665-31-0; 4, 72801-61-7; 5, 40101-59-5; 6, 39953-63-4; 7, 83665-32-1; 8, 83665-33-2; 9, 41513-78-4; 10, 40101-51-7; 11, 5383-82-4; phthalic anhydride, 85-44-9; aniline, 62-53-3; anthranilic acid, 118-92-3; *m*-aminobenzoic acid, 99-05-8; *p*-aminobenzoic acid, 150-13-0.

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Hypolipidemic Activity of Phthalimide Derivatives. 3. A Comparison of Phthalimide and 1,2-Benzisothiazolin-3-one 1,1-Dioxide Derivatives to Phthalimidine and 1,2-Benzisothiazoline 1,1-Dioxide Congeners

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Previously it has been observed that N-substituted phthalimide derivatives with chain lengths of four carbon or oxygen atoms showed potent hypolipidemic activity in rodents at 20 (mg/kg)/day ip. The 1,2-benzisothiazolin-3-one 1,1-dioxide (saccharin) nucleus, itself, had also been observed to be active at the same dose. An investigation was undertaken to examine a series of 1,2-benzisothiazolin-3-one 1,1-dioxide analogues for their hypolipidemic activity in mice and to compare them to their respective phthalimide congeners. In addition, a series of 1,2-benzisothiazoline 1,1-dioxide and phthalimidine analogues was prepared, and their hypolipidemic activity was compared to the phthalimide analogues. These studies show that the respective congeners of 1,2-benzisothiazolin-3-one 1,1-dioxide compared favorably to phthalimide congeners in reducing serum triglyceride and cholesterol levels in male CF_1 mice at 20 (mg/kg)/day ip. Of the saccharin derivatives, 3-oxo-1,2-benzisothiazoline-2-propionic acid 1,1-dioxide was the most effective in lowering serum cholesterol levels by 53% after 16 days dosing and 3-oxo-1,2-benzisothiazoline-2-valeric acid 1,1-dioxide lowered serum triglycerides 56% after 14 days dosing. The 1,2-benzisothiazoline 1,1-dioxide and phthalimidine compounds were less active as hypolipidemic agents than their 1,2-benzisothiazolin-3-one 1,1-dioxide and phthalimide analogues, respectively.

The antihyperlipidemic activity of 1,2-benzisothiazolin-3-one 1,1-dioxide (saccharin 1) and its butan-3-one derivative (5) at 20 (mg/kg)/day ip in mice has previously been reported.[1] These two compounds compared favorably with phthalimide and 1-(*N*-phthalimido)butan-3-one in their ability to lower serum lipids.[1] A series of N-substituted phthalimide derivatives has been previously examined for hypolipidemic activity by this laboratory. Side-chain lengths of four carbon atoms or their equivalent for the N-substituted acids, esters, and ketones resulted in the best activity.[2] Thus, N-substituted derivatives of 1,2-benzisothiazolin-3-one 1,1-dioxide were synthesized and compared to their phthalimide congeners for hypolipidemic activity in mice. Preliminary studies have shown that the optimum dose for hypolipidemic activity for phthalimide and saccharin in rats and mice was 20 (mg/kg)/day.[3,4] The toxicity values (LD_{50}) of these derivatives were generally above 2 g/kg, indicating that utilization of the agents at 20 mg/kg was in the safe therapeutic range. No other deleterious side effects were observed for these agents when used in this dose range in mice.[1] A number of N-substituted 1,2-benzisothiazoline 1,1-dioxide (13) and phthalimidine (27) compounds were also prepared in order to study the importance of the carbonyl groups of the imide ring of these derivatives.

Results and Discussion

After 14 days dosing of CF_1 male mice (~25 g) at 20 (mg/kg)/day ip, the 1,2-benzisothiazolin-3-one 1,1-dioxide (saccharin) and phthalimide derivatives significantly reduced serum triglyceride levels (Table II). Examination of the data for the substituted nuclei showed that phthalimide (17) was more active than 1,2-benzisothiazolin-3-one 1,1-dioxide (1) in lowering serum triglyceride levels. In general, the butyl (2 and 18) and pentyl (3 and 19) N-substituted derivatives of phthalimide and saccharin were less active than the N-substituted ketones and acids of this series of compounds in lowering serum triglyceride levels of mice. In the N-substituted ketone series, the propanone (20), butanone (21), and pentanone (22) derivatives of phthalimide were more active than the

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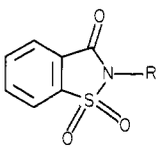
Table I. Physical and Chemical Characteristics of Cyclic Imides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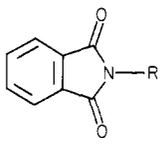
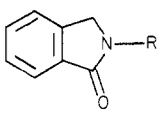

17-26


27-30

compd	R	mp or bp (mmHg), °C	crystn solvent	emp. formula	prep method or source	reaction temp, °C/time	yield, %
1	H			$C_7H_5NO_3S$	Ruger		
2	n-C_4H_9	121-128 (0.06)		$C_{11}H_{13}NO_3S$	method A	125/6.5 h	68
3	n-C_5H_{11}	57-58	EtOAc/H_2O	$C_{12}H_{15}NO_3S$	method A	reflux/6 h	44
4	CH_2COMe	144-145	MeOH	$C_{10}H_9NO_4S$	method A	125/2 h	84
5	$(CH_2)_2COMe$	120-122	MeOH	$C_{11}H_{11}NO_4S$	method B	80/2.5 h	9
6	$(CH_2)_3COMe$	96-97	MeOH	$C_{12}H_{13}NO_4S$	method A	100/12 h	12
7	$(CH_2)_2COOH$	155-166	H_2O	$C_{10}H_9NO_5S$	method A	135/8 h	52
8	$(CH_2)_3COOH$	117-118	EtOAc	$C_{11}H_{11}NO_5S$	method C	100/2 h	90
9	$(CH_2)_4COOH$	117-118	EtOH	$C_{12}H_{13}NO_5S$	method A	135/8 h	35
10	$(CH_2)_5COOH$	96-97	EtOAc	$C_{13}H_{15}NO_5S$	method A	135/8 h	17
11	$(CH_2)_2COOEt$	55-57	EtOH	$C_{12}H_{13}NO_5S$	method A	110/6 h	91
12	$CH_2C(CH_2)COOH$	226-228	MeOH	$C_{11}H_9NO_5S$	method A	120/5 h	26
13	H	111-112	EtOH	$C_7H_7NO_2S$	method D	RT/3 days	51
14	n-C_4H_9	135-140 (0.02)		$C_{11}H_{15}NO_2S$	method E	78/24 h	11
15	$(CH_2)_2COMe$			$C_{11}H_{13}NO_3S$	method F	68/0.5 h	10
16	$(CH_2)_2COOH$	103-106	EtOAc	$C_{10}H_{11}NO_4S$	method E	78/8.5 h	58
17	H				Aldrich		
18	n-C_4H_9	110-116 (0.12)			ref 2		88
19	n-C_5H_{11}	114-115 (0.03)			ref 2		83
20	CH_2COMe	124-127			ref 2		50
21	$(CH_2)_2COMe$	114-116			ref 2		80
22	$(CH_2)_3COMe$	73.5-75			ref 2		12
23	$(CH_2)_2COOH$	152-153			ref 2		39
24	$(CH_2)_3COOH$	117-118			ref 2		75
25	$(CH_2)_4COOH$	118.5-120			ref 2		70
26	$(CH_2)_5COOH$	108			ref 2		70
27	H	150-152		C_8H_7NO	method G	100/13 h	47
28	n-C_4H_9	128-129 (0.3)		$C_{12}H_{15}NO$	method H	100/5 h	52
29	$(CH_2)_2COMe$	60-63	ligroin	$C_{12}H_{13}NO_2$	method I	75/22 h	25
30	$(CH_2)_2COOH$	135-137	PrOH	$C_{11}H_{11}NO_3$	method J	100/5.5 h	36

corresponding ketones (**4**–**6**) of saccharin. The biological data for the N-substituted acids of the two series were mixed. The propionic acid derivative (**23**) of phthalimide was more effective in lowering serum triglyceride levels than the propionic acid (**7**) of saccharin, but the butyric (**8**) and valeric acid (**9**) of saccharin was more active than the butyric (**24**) and valeric acids (**25**) of phthalimide.

Examination of the effects of saccharin and phthalimide derivatives on mouse serum cholesterol levels after 16 days administration at 20 mg/kg ip demonstrated marked reductions by all of the agents. Of the N-substituted derivatives, the butyl (**2** and **18**), pentyl (**3** and **19**), and propionic acid (**7** and **23**) demonstrated the best activity in lowering serum cholesterol levels, i.e., greater than 40% reduction. Many of the N-substituted saccharin and phthalimide derivatives produced essentially the same magnitude of reduction of serum cholesterol levels, e.g., the butyl (**2** and **18**), pentyl (**3** and **19**), and butanone derivatives (**5** and **21**). The propanone derivative of saccharin (**4**) was more active than the propanone derivative of phthalimide (**20**). The propionic (**7**) and valeric (**9**) acid derivatives of saccharin were more active than their phthalimide congeners (**23** and **25**). In fact, compound **23** was the most active compound in lowering serum cholesterol levels in both series of compounds studied.

Two miscellaneous saccharin derivatives were tested. 3-Oxo-α-methylene-1,2-benzisothiazolinepropionic acid 1,1-dioxide (**12**) was not markedly active in either screen. On the other hand, ethyl 3-oxo-1,2-benzisothiazoline-2-butyrate 1,1-dioxide (**11**) demonstrated activity in both screens, lowering serum triglycerides 49% and serum cholesterol levels 39% at 20 (mg/kg)/day.

The conversion of a carbonyl function of a cyclic imide, C(=O)N(R)C(=O), to a methylene to afford the corresponding lactam C(=O)N(R)CH_2 had a significant effect on hypolipidemic activity in CF_1 male mice at 20 (mg/kg)/day. The reduction of an imido carbonyl group of phthalimide, **17**, and three phthalimide N-substituted derivatives (**18**, **21**, and **23**) to the corresponding phthalimidine derivatives (**27**–**30**) resulted in a decrease from 8 to 42% in hypocholesterolemic activity (on day 16) in every case. Reduction of an imido carbonyl to form the phthalimidino congeners resulted in a decrease of 25–35% in hypotriglyceridemic activity on day 14. The exception to reduction in hypotriglyceridemic activity was *N*-*n*-butylphthalimidine (**28**), which was not lower than 18.

A similar, although less marked, effect was noted with the reduction of 1,2-benzisothiazolin-3-one 1,1-dioxide (saccharin), **1**, and the three N-substituted derivatives (**2**, **5**, and **7**) to the corresponding 1,2-benzisothiazoline 1,1-dioxide congeners (**13**–**16**). Hypocholesterolemic activity was decreased in every case (12–19% on day 16), as was hypotriglyceridemic activity (9–35%), again with the exception of *N*-*n*-butyl-1,2-benzisothiazoline 1,1-dioxide (**14**).

Conclusion

The N-substituted derivatives of 1,2-benzisothiazolin-3-one 1,1-dioxide (saccharin) demonstrated potent hypolipidemic activity in mice and compared favorably to their respective N-substituted phthalimide congeners. 3-Oxo-1,2-benzisothiazolin-2-valeric acid 1,1-dioxide (**9**) was the most potent derivative in the triglyceride screen, causing a 56% reduction, whereas 3-oxo-1,2-benzisothiazoline-2-propionic acid 1,1-dioxide (**7**) was the most effective, low-

Table II. Hypolipidemic Activity of Cyclic Imides at 20 mg/kg in CF_1 Male Mice

compd	% control		
	14th day serum triglyceride	9th day serum cholesterol	16th day serum cholesterol
1	51 ± 16[a]	68 ± 11[a]	67 ± 10[a]
2	76 ± 9[a]	76 ± 13[b]	56 ± 7[a]
3	62 ± 8[a]	106 ± 11	58 ± 7[a]
4	66 ± 8[a]	95 ± 10	52 ± 5[a]
5	51 ± 7[a]	60 ± 8[a]	62 ± 6[a]
6	77 ± 9[a]	73 ± 7[a]	77 ± 7[a]
7	67 ± 7[a]	96 ± 8	47 ± 5[a]
8	48 ± 8[a]	85 ± 6[b]	73 ± 6
9	44 ± 6[a]	96 ± 8	68 ± 8[a]
10	55 ± 6[a]	90 ± 9	76 ± 7[a]
11	61 ± 7[a]	97 ± 8	71 ± 8[a]
12	101 ± 7	85 ± 7[a]	85 ± 10
13	86 ± 4[a]	82 ± 8[a]	80 ± 11[a]
14	76 ± 6	71 ± 10[a]	68 ± 7[a]
15	78 ± 9[a]	87 ± 5[a]	81 ± 6[a]
16	76 ± 6[a]	73 ± 9[a]	59 ± 6[a]
17	44 ± 8[a]	63 ± 8[a]	57 ± 7[a]
18	82 ± 6	72 ± 10[a]	54 ± 6[a]
19	75 ± 6[a]	76 ± 8[a]	58 ± 7[a]
20	48 ± 10[a]	80 ± 16	67 ± 12[a]
21	58 ± 7[a]	67 ± 11[a]	63 ± 7[a]
22	59 ± 13[a]	71 ± 6[a]	63 ± 5[a]
23	58 ± 10[a]	74 ± 7[a]	55 ± 11[a]
24	59 ± 14[a]	80 ± 7[a]	68 ± 6[a]
25	54 ± 5[a]	83 ± 9[b]	77 ± 4[a]
26	51 ± 12[a]	81 ± 6[a]	67 ± 3[a]
27	78 ± 7[a]	89 ± 6	87 ± 14
28	80 ± 8	68 ± 9[a]	62 ± 7[a]
29	83 ± 6[a]	88 ± 4[a]	84 ± 8[a]
30	88 ± 9	87 ± 8[b]	97 ± 8
1% CMC[c]	100 ± 6	100 ± 5	100 ± 8

[a] $p \leq 0.001$. [b] $p \leq 0.010$. CMC = carboxymethylcellulose.

ering serum cholesterol levels by 53%. Both carbonyl groups of the cyclic imide system of phthalimide derivatives were required for potent hypolipidemic activity. The carbonyl in the saccharin (1,2-benzisothiazolin-3-one 1,1-dioxide) series was also required for significant hypolipidemic activity in mice at 20 (mg/kg)/day.

Experimental Section

Chemistry. Melting points were determined on a Mel-Temp apparatus and are uncorrected. Infrared spectra were obtained with a Perkin-Elmer 297 spectrophotometer. NMR data were obtained with a Bruker WM 250 spectrophotometer. Silica gel 60, 230–400 mesh (E. Merck), was utilized for column chromatography. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ, and are within ±0.4%.

Method A. Sodium saccharin (0.02–0.10 mol) was dissolved in 80–200 mL of DMF, and a 10% excess of an equimolar amount of bromoalkanes, bromo ketone, bromoalkanoic acid, ethyl 4-bromobutyrate, or α-(bromomethyl)acrylic acid was added. The reaction mixture was allowed to react, and the volatile material was removed under vacuum. The residue was dissolved in CH_2Cl_2 and washed with water. The CH_2Cl_2 layer was evaporated under vacuum, and the residue was purified by distillation or recrystallization.

Method B. Saccharin (18.32 g, 0.10 mol) was suspended in ethyl acetate, a catalytic amount of sodium ethoxide was added, and the reaction was heated to 70 °C. Methyl vinyl ketone (7.36 g, 0.105 mol) was added, and the solution was refluxed for an additional 2.5 h, neutralized with acetic acid, and evaporated to a residue, which was dissolved in $CHCl_3$ and washed with 1.0 N NaOH solution. The $CHCl_3$ was evaporated in vacuo to yield a yellow solid, which upon recrystallization from ethanol afforded 2.24 g (9%) of 3-oxo-1,2-benzisothiazoline-2-butan-3-one 1,1-dioxide.

Method C. Ethyl 3-oxo-1,2-benzisothiazolinebutyrate 1,1-dioxide was hydrolyzed to the corresponding acid (compound 8) by refluxing in 0.5% HCl for 2 h. The acid that precipitated on cooling was purified by recrystallization from EtOAc.

Method D. Utilizing the procedure of Childress and Baum,[9] 18.3 g (0.076 mol) of saccharin was slowly added to 3.9 g (0.103 mol) of $LiAlH_4$ in 200 mL of THF. The reaction mixture was allowed to stir for 3 days at room temperature under anhydrous conditions. The excess $LiAlH_4$ was destroyed with EtOAc, 500 mL of 10% H_2SO_4 was slowly added, and the organic layer was separated and washed with 5% Na_2CO_3, dried over anhydrous Na_2SO_4, and evaporated in vacuo to yield 6.6 g (51%) of 1,2-benzisothiazoline 1,1-dioxide. The compound was purified by recrystallization from EtOH.

Method E. To a solution of 0.022 g-atom of sodium in 100 mL of MeOH was added 0.02 mol of 1,2-benzisothiazoline 1,1-dioxide and either 1-iodobutane or ethyl 3-bromopropionate. The mixture was allowed to react and then neutralized with AcOH and evaporated in vacuo. The residue was mixed with CH_2Cl_2 and washed with 5% NaOH and then water. The CH_2Cl_2 layer was evaporated in vacuo and the residue was purified by distillation or recrystallization.

Method F. 1,2-Benzisothiazoline 1,1-dioxide (0.5 g, 0.003 mol) was dissolved in 10 mL of MeOH, 2 drops of 20% NaOH was added, and the solution was set to reflux. Methyl vinyl ketone (0.35 g, 0.005 mol) was slowly added, and the solution was refluxed an additional 2.5 h, neutralized with AcOH, and evaporated in vacuo to a light brown solid. Preparative TLC (silica gel GF, 100 μm, ether) afforded 0.07 g (10%) 1,2-benzisothiazoline butan-3-one 1,1-dioxide.

Method G. Phthalimide (5.88 g, 0.04 mol) was added to a mixture of 26 g (0.40 mol) of freshly activated zinc dust in 200 mL of glacial acetic acid. The reaction mixture was heated to 100 °C for 13 h and filtered while hot, and the filtrate was evaporated to a white solid residue. The residue was added to 75 mL of 10% NaOH and extracted with chloroform, and the chloroform extracts were evaporated to yield a white solid, which upon recrystallization from methanol/water afforded 2.5 g (47%) of phthalimidine.

Method H. Powdered zinc (32.7 g, 0.5 mol) was amalgamated by shaking it with a solution containing 2.6 g of mercuric chloride, 5 mL of concentrated HCl, and 68 mL of water. The supernatant was decanted, and 25 mL of water was added to the freshly amalgamated zinc, followed by the addition of 10.2 g (0.05 mol) of *N*-*n*-butylphthalimide and 34 mL of concentrated HCl. The reaction mixture was refluxed for 5 h and filtered while hot, and the filtrate was extracted with CH_2Cl_2. Evaporation of the CH_2Cl_2 extract gave a clear oil, which upon fractional distillation afforded 3 g (32%) of *N*-*n*-butylphthalimidine. Repeated fractional distillation gave a analytical sample of *N*-*n*-butylphthalimidine.

Method I. Applying the general procedure of Butula et al.,[10] 2.17 g (0.01 mol) of 1-(*N*-phthalimido)butan-3-one was dissolved in 20 mL of glacial acetic acid, and 3 g of 5% Pd on $BaSO_4$ was added. The reaction mixture was shaken under hydrogen (initial pressure 32.5 psig) at 75 °C for 22 h, on a Parr catalytic hydrogenation apparatus (final pressure 13 psig). Filtration and evaporation of the filtrate gave a clear oil, which upon column chromatography (EtOAc) afforded 0.5 g (25%) of 1-(*N*-phthalimidino)butan-3-one, mp 60–63 °C. Recrystallization of an analytical sample from ligroin gave 1-(*N*-phthalimidino)propionic acid.

Method J. Mossy zinc (50 g, 0.76 mol) was placed in a solution containing 4.0 g of mercuric chloride, 7.5 mL of concentrated HCl, and 100 mL of water. The supernatant was decanted, and 40 mL of water was added to the freshly amalgamated zinc, followed by the addition of 9.5 g (0.038 mol) of 3-(*N*-phthalimido)propionic acid ethyl ester[11a] and 50 mL of concentrated HCl. The reaction mixture was refluxed for 5.5 h and filtered while hot. A white solid precipitated from the filtrate upon cooling, which upon

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(10) Lj. Butula, D. Kolbah, and I. Butula, *Croat. Chem. Acta*, 44, 484 (1972).
(11) (a) Prepared by stirring 3-(*N*-phthalimido)propionic acid in ethanol containing a catalytic amount of concentrated H_2SO_4, mp 66–69 °C (lit.[11b] mp 66–67 °C). (b) S. Chodroff, R. Kapp, and C. O. Beckman, *J. Am. Chem. Soc.*, **69**, 259 (1947).

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]

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(13) Hycel Triglyceride Test, Hycel, Inc. 1975.

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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

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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.

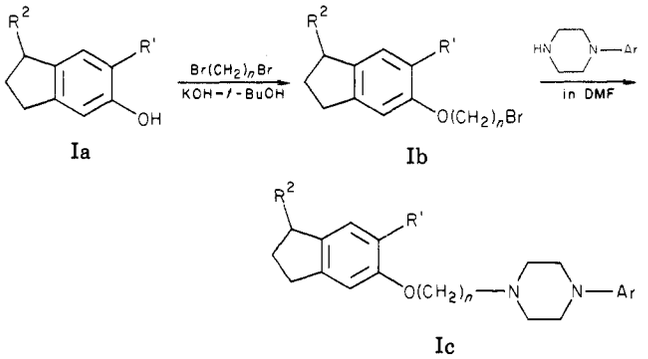
Although benzodiazepine tranquilizers are used with great clinical success in neurosis,[1,2] they are poorly effective in obsessional neurosis and they exhibit undesirable muscle-relaxant activity.[2,3] Recently, novel compounds without the benzodiazepine structure have been tried in the neurosis area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

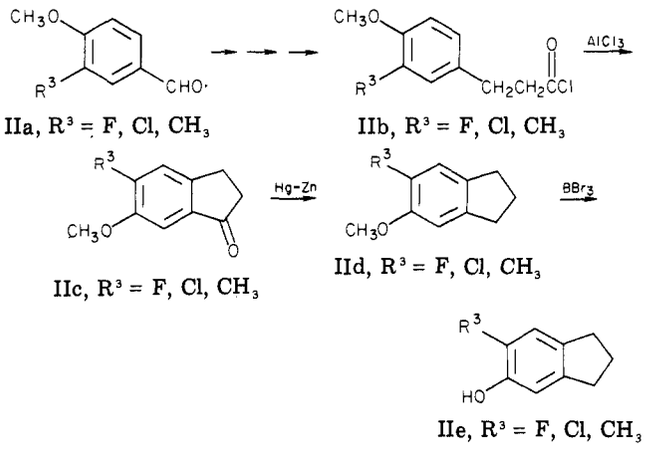
Chemistry. The (ω-piperazinylalkoxy)indan derivatives listed in Tables I and II were prepared by the ω-bromoalkoxylation of the corresponding indanol with α,ω-dibromoalkane in the presence of KOH in *t*-BuOH and followed by the amination with *N*-arylpiperazines (Scheme I).

Indan derivatives with aromatic substituents were synthesized as follows (Scheme II). The 1-indanone derivatives (IIc) with fluoro, chloro, or methyl substituents were

Scheme I



Scheme II



prepared by the Friedel-Craft cyclization[6] of the corresponding phenylpropionyl chlorides (IIb), which were

(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).

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