chlorobenzyl) derivative did not discolor on standing.

The chlorobenzyl derivatives showed increased extinction coefficients relative to the benzyl with the 4-chlorobenzyl compounds having the greatest effect. All of the dibenzylated structures had increased extinction coefficients relative to the monobenzylated products in the order 4-chlorobenzyl >> 2-chlorobenzyl = benzyl, although no significant change in absorption maximum was observed. In alkali, bathochromic shifts in reference to the 4-indanol were obtained and considerable increases in extinction coefficients were observed with the benzylated derivatives. In terms of the standards of Coggeshall and Glessner[23] no steric hindrance is indicated.

In contrast, in the 5-indanol series monobenzylation yielded significant increases in extinction coefficients and bathochromic shifts relative to the unsubstituted indanol, with alkali having an effect comparable to that observed with 5-indanol.

The spectra of the dibenzylated products in methanol were associated in all cases with a decrease in the extinction coefficient when compared to the monobenzylated product. Here apparently, the two benzyl groups in the position *ortho* to the phenolic hydroxyl introduce some steric inhibition[23] of resonance. With the ionic spectra a varying pattern is observed for the extinction coefficients relative to the monobenzylated indanols. The dibenzyl absorbs less, the di-2-chlorobenzyl the same and the di-4-chlorobenzyl more than the corresponding monobenzyl structure.

Experimental[24]

7-Benzyl-4-indanol and 5,7-Dibenzyl-4-indanol.—A mixture of 100 g. (0.74 mole) of 4-indanol, 62.8 g. (0.496 mole) of benzyl chloride and 32 g. of freshly fused anhydrous zinc chloride in 400 ml. of chloroform was refluxed with stirring for 12 hours, cooled and added to 1.6 l. of water. The chloroform phase was separated, dried (anhydrous magnesium sulfate), filtered and distilled. After removal of chloroform and unreacted 4-indanol, there was obtained 56 g. of 7-benzyl-4-indanol, b.p. 140–148° (0.1 mm.), which crystallized, m.p. 111–113°.

On further distillation there was obtained 20 g. of 5,7-dibenzyl-4-indanol, b.p. 174–205° (0.17 mm.).

6-(4-Chlorobenzyl)-5-indanol and 4,6-Di-(4-chlorobenzyl)-5-indanol.—A mixture of 12.5 g. (0.093 mole) of 5-indanol, 10 g. (0.062 mole) of *p*-chlorobenzyl chloride and 4 g. of freshly fused anhydrous zinc chloride was allowed to react as above. Upon distillation, there was obtained 8.82 g. of 6-(4-chlorobenzyl)-5-indanol, b.p. 138° (0.05 mm.), m.p. 73–74°.

On further distillation there was obtained 2.87 g. of 4,6-di-(4-chlorobenzyl)-5-indanol, b.p. 230° (0.05 mm.), m.p. 83–85°.

6-Benzyl-5-methoxyindan.—A solution of 30 g. (0.134 mole) of 6-benzyl-5-indanol and 32.8 g. (0.26 mole) of methyl sulfate in 100 ml. of acetone was treated with 27.6 g. (0.2 mole) of anhydrous potassium carbonate and heated under reflux with vigorous stirring for 4 hours. The cooled reaction mixture was filtered, the filtrate diluted with 100 ml. of water and extracted with three 100-ml. portions of ether. The ethereal extracts were combined, washed with 100 ml. of 6 *N* sodium hydroxide and the ether phase separated and dried over anhydrous magnesium sulfate. After filtration and evaporation of the ether, the product was collected, 16.9 g., b.p. 156–160° (0.5 mm.).

4-Methoxyindan.—In a similar manner 4-methoxyindan was obtained in 33% yield, b.p. 56–60° (0.1 mm.).

Anal. Calcd. for $C_{10}H_{12}O$: C, 81.0; H, 8.2. Found: C, 81.3; H, 8.2.

5-Methoxyindan.—In a similar manner 5-methoxyindan was obtained in 72% yield, b.p. 65–78° (1.0 mm.).

Anal. Calcd. for $C_{10}H_{12}O$: C, 81.0; H, 8.2. Found: C, 80.8; H, 8.4.

Acknowledgment.—The authors wish to express their appreciation to M. Blitz and his associates for the determination of the ultraviolet absorption spectra.

YONKERS 1, NEW YORK

(23) N. D. Coggeshall and A. S. Glessner, Jr., THIS JOURNAL, **71**, 3150 (1949).

(24) Descriptive data shown in Table I are not reproduced in this section.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, U. S. VITAMIN CORPORATION]

Indanols. II. Aminoalkyl Ethers

BY SEYMOUR L. SHAPIRO, KURT WEINBERG, THEODORE BAZGA AND LOUIS FREEDMAN

RECEIVED JANUARY 14, 1958

A series of disubstituted aminoalkyl ethers of 4-indanol, 7-benzyl(and chlorobenzyl)-4-indanol, 5-indanol and 6-benzyl-(and chlorobenzyl)-5-indanol and their salts have been prepared for pharmacologic evaluation. Significant responses such as hypotension, ganglionic block, anti-inflammatory activity and depression of the central nervous system have been noted with selected members of this series.

The indan ring is a structural component of pharmacologically active steroids and alkaloids. A variety of investigations[2–5] have been reported wherein the indan fragment has been derivatized in the search for pharmacologic activity in relatively simple structures.

The recent availability of 4-indanol and 5-indanol[6] made it attractive to consider evaluation of the aminoalkyl ethers of these phenols as broad spectrum[7] pharmacologic agents. Since benzylated phenol derivatives have proved more effective than the corresponding unsubstituted phenol,[8] the benzylated and chlorobenzylated indanols were

(1) Presented in part at the Meeting-in-Miniature, New York Section, American Chemical Society, March, 1958.

(2) F. C. Uhle, J. E. Krueger and A. E. Rogers, THIS JOURNAL, **78**, 1932 (1956); veratramine analogs.

(3) J. A. Barltrop, R. M. Acheson, P. G. Philpott, K. E. MacPhee and J. S. Hunt, *J. Chem. Soc.*, 2928 (1956); methadone analogs.

(4) D. B. Cowell and D. W. Mathieson, *J. Pharm. and Pharmacol.*, **9**, 549 (1957); adrenal cortical analogs.

(5) A. M. Akkerman, *Rec. trav. chim.*, **74**, 1281 (1955); analgesics.

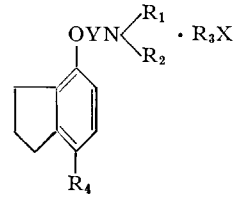
(6) Union Carbide Corp., New York, N. Y.

(7) C. Riffkin and N. Rubin, *J. Am. Pharm. Assoc., Sci. Ed.*, **45**, 317 (1956).

(8) (a) L. C. Cheney, R. R. Smith and S. B. Binkley, THIS JOURNAL, **71**, 60 (1949); (b) W. B. Wheatley, L. C. Cheney and S. B. Binkley, *ibid.*, **71**, 64 (1949); (c) **71**, 3795 (1949).

TABLE I

DERIVATIVES OF 4-INDANOL

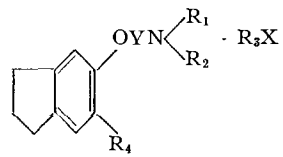


No.	Y	R_1	R_2	R_3X	R_4	B.p. °C.	B.p. Mm.	M.p.,[a,e] °C.	Yield,[f] %	Formula	Analyses[g] Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	$-(CH_2)_2-$	CH_3	CH_3	HCl	H			155–157[aa]	50	$C_{13}H_{20}ClNO$					5.8	5.8
2	$-(CH_2)_2-$	CH_3	CH_3	HPic.	H			139–141[ab]		$C_{19}H_{22}N_4O_8$	52.5	53.1	5.1	5.2	12.9	12.9
3	$-(CH_2)_2-$	CH_3	CH_3	CH_3I	H			175–177[ac]	42	$C_{14}H_{22}INO$	48.4	49.1	6.3	6.7		
4	$-(CH_2)_2-$	C_2H_5	C_2H_5	HCl	H			134–137[aa]	52	$C_{15}H_{24}ClNO$	67.0	67.0	8.9	9.0		
5	$-(CH_2)_2-$	C_2H_5	C_2H_5	CH_3I	H			100–104[aa]		$C_{16}H_{26}INO$	51.2	51.4	6.9	7.3	3.7	3.8
6	$-(CH_2)_2-$	i-C_3H_7	CH_3		H	104–108	0.03		69	$C_{15}H_{23}NO$	77.2	77.1	9.9	10.0	6.0	5.9
7	$-(CH_2)_2-$	i-C_3H_7	CH_3	HPic.	H			123–124		$C_{21}H_{26}N_4O_8$					12.1	12.2
8	$-(CH_2)_2-$	i-C_3H_7	CH_3	CH_3I	H			131–133[ad]	71	$C_{16}H_{26}INO$	51.2	51.2	6.9	6.9	3.7	3.6
9	$-(CH_2)_2-$	$-(CH_2)_4-$			H	128	.03		55	$C_{15}H_{21}NO$						
10	$-(CH_2)_2-$	$-(CH_2)_4-$		HPic.	H			145–146		$C_{21}H_{24}N_4O_8$	54.8	54.9	5.3	4.9	12.2	12.1
11	$-(CH_2)_2-$	$-(CH_2)_5-$			H	120–122	.09		31	$C_{16}H_{23}NO$	78.3	78.2	9.5	9.4		
12	$-(CH_2)_2-$	$-(CH_2)_5-$		CH_3I	H			115–117[ad]	50	$C_{17}H_{26}INO$					3.6	3.7
13	$-(CH_2)_2-$	$-(CH_2)_2O(CH_2)_2-$			H	128–138	.02		63	$C_{15}H_{21}NO_2$	72.8	73.2	8.6	8.7	5.7	5.7
14	$-(CH_2)_2-$	$-(CH_2)_2O(CH_2)_2-$		CH_3I	H			147–149[ad]	66	$C_{16}H_{24}INO$	49.4	49.4	6.2	6.4	3.6	3.9
15	$-(CH_2)_2-$	$-(CH_2)_6-$			H	130–136	.03		53	$C_{17}H_{25}NO$	78.7	78.8	9.7	10.2		
16	$-(CH_2)_2-$	$-(CH_2)_6-$		HPic.	H			210–213		$C_{23}H_{28}N_4O_8$	56.6	57.1	5.8	6.1		
17	$-(CH_2)_2-$	$-(CH_2)_6-$		CH_3I	H			124–125[ad]	73	$C_{18}H_{28}INO$	53.9	53.8	7.0	7.4	3.5	3.2
18	$-(CH_2)_2-$	$-C_6H_4CH_2CH_2-$[b]			H	162–174	.1		8	$C_{19}H_{21}NO$	81.7	81.8	7.6	8.0	5.0	5.1
19	$-CHCH_3CH_2-$	CH_3	CH_3		H	90–98	.1		42	$C_{14}H_{21}NO$	76.7	76.7	9.7	9.5		
20	$-CHCH_3CH_2-$	CH_3	CH_3	CH_3I	H			150–152[ad]	61	$C_{15}H_{24}INO$	49.9	49.9	6.6	6.8	3.9	3.8
21	$-CH_2)_3-$	CH_3	CH_3		H	92–98	.2		51	$C_{14}H_{21}NO$	76.7	77.1	9.7	9.6	6.4	6.0
22	$-(CH_2)_3-$	CH_3	CH_3	HPic.	H			150–152	45	$C_{20}H_{24}N_4O_8$	53.6	53.9	5.4	5.4	12.5	12.7
23	$-(CH_2)_3-$	CH_3	CH_3	CH_3I	H			225–226[ad]	59	$C_{15}H_{24}INO$	49.9	50.3	6.6	6.8		
24	$-(CH_2)_3-$	$-(CH_2)_5-$			H	128–132	.02		40	$C_{17}H_{25}NO$	78.7	78.9	9.7	9.7		
25	$-(CH_2)_3-$	$-(CH_2)_5-$		CH_3I	H			153–154[ad]	49	$C_{18}H_{28}INO$	53.9	53.8	7.0	7.0		
26	$-(CH_2)_3-$	$-(CH_2)_5-$		HPic.	H			151–153		$C_{23}H_{28}N_4O_8$	56.6	56.8	5.8	6.3		
27	$-(CH_2)_2-$	i-C_3H_7	CH_3		$C_6H_5CH_2-$	168–180	.12		72	$C_{22}H_{29}NO$	81.7	82.1	9.0	9.0	4.3	4.0
28	$-(CH_2)_2-$	i-C_3H_7	CH_3	CH_3I	$C_6H_5CH_2-$			171–173	70	$C_{23}H_{32}INO$	59.4	59.2	6.9	6.8	3.0	2.8
29	$-(CH_2)_2-$	$-(CH_2)_6-$			$C_6H_5CH_2-$	200–210	.45		55	$C_{24}H_{31}NO$	82.5	82.4	8.9	8.8	4.0	4.2
30	$-(CH_2)_3-$	CH_3	CH_3		$C_6H_5CH_2-$	162–170	.1		51	$C_{21}H_{27}NO$	81.5	82.0	8.8	8.7		
31	$-(CH_2)_3-$	CH_3	CH_3	CH_3I	$C_6H_5CH_2-$			195–198[ad]	35	$C_{22}H_{30}INO$	58.5	58.4	6.7	6.7	3.1	3.4
32	$-(CH_2)_3-$	CH_3	CH_3	C_3H_5Br[c]	$C_6H_5CH_2-$			98–102[ae]	40	$C_{24}H_{32}BrNO\cdot H_2O$	64.3	64.8	7.6	7.4	3.1	2.9
33	$-(CH_2)_3-$	CH_3	CH_3	$C_4H_7O_2Br$[d]	$C_6H_5CH_2-$			146–152[a]	52	$C_{25}H_{34}BrNO_3$	63.0	63.2	7.1	7.1	2.9	2.7
34	$-(CH_2)_3-$	CH_3	CH_3		2-$ClC_6H_4CH_2-$	162–173	.035		57	$C_{21}H_{26}ClNO$	73.4	73.6	7.6	7.3		
35	$-(CH_2)_3-$	CH_3	CH_3	CH_3I	2-$ClC_6H_4CH_2-$			192–194[ad]	59	$C_{22}H_{29}ClINO$	54.4	54.4	6.0	6.1	2.9	2.8

TABLE I (*Continued*)

No.	Y	R_1	R_2	R_3X	R_4	B.p. °C.	B.p. Mm.	M.p.,[a,e] °C.	Yield,[f] %	Formula	Analyses[g] Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
36	$-(CH_2)_3-$	CH_3	CH_3	C_3H_5Br[c]	2-$ClC_6H_4CH_2-$			81–84[ae]	39	$C_{24}H_{31}BrClNO\cdot H_2O$	59.7	59.5	6.8	7.2	2.9	2.9
37	$-(CH_2)_3-$	CH_3	CH_3	$C_4H_7O_2Br$[d]	2-$ClC_6H_4CH_2-$			148–150[ae]	39	$C_{25}H_{33}BrClNO_3$					2.7	2.8
38	$-(CH_2)_3-$	$-(CH_2)_5-$			2-$ClC_6H_4CH_2-$	178–194	.04		23	$C_{24}H_{30}ClNO$					3.7	3.8
39	$-(CH_2)_2-$	C_2H_5	C_2H_5		4-$ClC_6H_4CH_2-$	164–176	.06		50	$C_{22}H_{28}ClNO$	74.1	74.2	7.7	7.7	3.9	3.7
40	$-(CH_2)_2-$	C_2H_5	C_2H_5	HCl	4-$ClC_6H_4CH_2-$			134–136[ae]		$C_{22}H_{29}Cl_2NO$	67.0	67.1	7.4	7.1		
41	$-(CH_2)_2-$	*i*-C_3H_7	CH_3		4-$ClC_6H_4CH_2-$	186–196	.025		70	$C_{22}H_{28}ClNO$	73.8	74.1	7.8	7.7	3.9	3.7
42	$-(CH_2)_2-$	*i*-C_3H_7	CH_3	CH_3I	4-$ClC_6H_4CH_2-$			137–139[ad]	41	$C_{23}H_{31}ClINO$	55.3	55.2	6.2	6.1	2.8	2.7
43	$-(CH_2)_2-$	$-(CH_2)_6-$			4-$ClC_6H_4CH_2-$	206–210	.18		24	$C_{24}H_{30}ClNO$	75.1	75.1	7.8	7.8	3.7	3.8
44	$-(CH_2)_2-$	$-(CH_2)_6-$		CH_3I	4-$ClC_6H_4CH_2-$			198–200[ad]	29	$C_{25}H_{33}ClINO$					2.7	2.8
45	$-(CH_2)_2-$	$-C_6H_4CH_2CH_2-$[b]			4-$ClC_6H_4CH_2-$	256–268	.5		15	$C_{26}H_{26}ClNO$	77.3	77.1	6.4	6.3		
46	$-(CH_2)_3-$	CH_3	CH_3		4-$ClC_6H_4CH_2-$	186–190	.3		55	$C_{21}H_{26}ClNO$	73.4	73.8	7.6	7.6		
47	$-(CH_2)_3-$	CH_3	CH_3	HCl	4-$ClC_6H_4CH_2-$			166–168		$C_{21}H_{27}Cl_2NO$	66.3	66.7	7.1	7.0		
48	$-(CH_2)_3-$	CH_3	CH_3	CH_3I	4-$ClC_6H_4CH_2-$			254–256[ad]	58	$C_{22}H_{29}ClINO$	54.4	54.5	6.0	6.0	2.9	2.9
49	$-(CH_2)_3-$	CH_3	CH_3	$C_4H_7O_2Br$[d]	4-$ClC_6H_4CH_2-$			151–154[ac]	47	$C_{25}H_{33}BrClNO_3$	58.8	58.7	6.5	6.7	2.7	2.8
50	$-(CH_2)_3-$	$-(CH_2)_5-$			4-$ClC_6H_4CH_2-$	186–204	.14		21	$C_{24}H_{30}ClNO$					3.7	4.0

DERIVATIVES OF 5-INDANOL



· R_3X

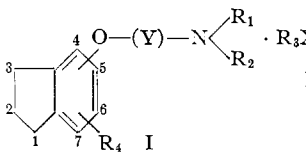
No.	Y	R_1	R_2	R_3X	R_4	B.p. °C.	B.p. Mm.	M.p.,[a,e] °C.	Yield,[f] %	Formula	Analyses[g] Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
51	$-(CH_2)_2-$	C_2H_5	C_2H_5	HCl	H			138–139	37	$C_{15}H_{24}ClNO$	67.0	66.8	8.9	8.8	5.2	5.2
52	$-(CH_2)_2-$	$-(CH_2)_4-$			H	128–135	0.15		51	$C_{15}H_{21}NO$	77.9	78.0	9.2	9.3	6.1	5.8
53	$-(CH_2)_2-$	$-(CH_2)_4-$		HPic.	H			124–126		$C_{21}H_{24}N_4O_8$	54.8	54.7	5.3	5.0	12.2	11.9
54	$-(CH_2)_2-$	$-(CH_2)_4-$		CH_3I	H			116–117[ad]	59	$C_{16}H_{24}INO$	51.5	51.4	6.4	6.4	3.8	3.8
55	$-(CH_2)_2-$	$-(CH_2)_5-$			H	122–130	.03		38	$C_{16}H_{23}NO$	78.3	78.6	9.5	9.4	5.7	5.8
56	$-(CH_2)_2-$	$-(CH_2)_5-$		CH_3I	H			118–120[ad]	50	$C_{17}H_{26}INO$	52.7	52.9	6.7	7.1	3.6	3.6
57	$-(CH_2)_2-$	$-(CH_2)_2O(CH_2)_2-$			H	128–136	.05		65	$C_{15}H_{21}NO_2$					5.7	5.7
58	$-(CH_2)_2-$	$-(CH_2)_2O(CH_2)_2-$		CH_3I	H			198–200[ad]	99	$C_{16}H_{24}INO_2$	49.4	49.3	6.2	6.3	3.6	3.9
59	$-(CH_2)_2-$	$-(CH_2)_6-$			H	146–150	.08		55	$C_{17}H_{25}NO$	78.7	79.4	9.7	9.5		
60	$-(CH_2)_2-$	$-(CH_2)_6-$		HPic.	H			168–170		$C_{23}H_{28}N_4O_8$					11.5	11.2
61	$-(CH_2)_2-$	$-(CH_2)_6-$		CH_3I	H			164–165[ad]	83	$C_{18}H_{26}INO$	53.9	54.2	7.0	6.8		
62	$-(CH_2)_2-$	$-C_6H_4CH_2CH_2-$[b]			H	190–192	.2	77–79	19	$C_{19}H_{21}NO$	81.7	81.7	7.6	7.4		
63	$-CHCH_3CH_2-$	CH_3	CH_3		H	83–93	.03		52	$C_{14}H_{21}NO$	76.7	77.3	9.7	9.6		
64	$-CHCH_3CH_2-$	CH_3	CH_3	HPic.	H			127–129	23	$C_{20}H_{24}N_4O_8$	53.6	53.7	5.4	5.2		
65	$-CHCH_3CH_2-$	CH_3	CH_3	CH_3I	H			119–124[ad]	44	$C_{15}H_{24}INO$	49.9	50.0	6.6	7.0	3.9	3.8
66	$-(CH_2)_3-$	CH_3	CH_3		H	96–100	.04		42	$C_{14}H_{21}NO$	76.7	77.4	9.7	9.6		
67	$-(CH_2)_3-$	CH_3	CH_3	CH_3I	H			196–197[ad]	52	$C_{15}H_{24}INO$					3.9	4.0
68	$-(CH_2)_3-$	$-(CH_2)_5-$			H	148–156	.15		62	$C_{17}H_{25}NO$	78.7	78.7	9.7	9.8		
69	$-(CH_2)_3-$	$-(CH_2)_5-$		HPic.	H			122–124		$C_{23}H_{28}N_4O_8$	56.6	56.8	5.8	5.7	11.5	11.4
70	$-(CH_2)_3-$	$-(CH_2)_5-$		CH_3I	H			141–142[ad]	91	$C_{18}H_{28}INO$	53.9	53.9	7.0	6.9		
71	$-(CH_2)_2-$	*i*-C_3H_7	CH_3		$C_6H_5CH_2-$	188–192	.8		23	$C_{22}H_{29}NO$	81.7	82.1	9.0	9.2	4.3	4.0

TABLE I (*Continued*)

No.	Y	R_1	R_2	R_3X	R_4	B.p. °C.	B.p. Mm.	M.P.,[a,c] °C.	Yield,[f] %	Formula	Analyses[g] Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
72	$-(CH_2)_2-$	$-(CH_2)_6-$			$C_6H_5CH_2-$	196–201	.08		46	$C_{24}H_{31}NO$	82.5	82.6	8.9	9.1		
73	$-(CH_2)_2-$	$-(CH_2)_6-$		CH_3I	$C_6H_5CH_2-$			125–127[ad]	43	$C_{25}H_{34}INO$	61.1	60.8	6.9	7.1	2.9	3.0
74	$-(CH_2)_3-$	CH_3	CH_3		2-$ClC_6H_4CH_2-$	166–172	.035		52	$C_{21}H_{26}ClNO$	73.4	73.4	7.6	7.4		
75	$-(CH_2)_3-$	CH_3	CH_3	CH_3I	2-$ClC_6H_4CH_2-$			257–259[ad]	50	$C_{22}H_{29}ClINO$	54.4	54.4	6.0	6.0	2.9	3.0
76	$-(CH_2)_3-$	CH_3	CH_3	C_3H_5Br[c]	2-$ClC_6H_4CH_2-$			140–146[ae]	56	$C_{24}H_{31}BrClNO\cdot H_2O$	59.7	59.6	6.8	6.8	2.9	2.9
77	$-(CH_2)_3-$	CH_3	CH_3	$C_4H_7O_2Br$[d]	2-$ClC_6H_4CH_2-$			144–147[ae]	40	$C_{25}H_{33}BrClNO_3$	58.8	58.7	6.5	6.5	2.7	2.8
78	$-(CH_2)_3-$	$-(CH_2)_5-$			2-$ClC_6H_4CH_2-$	180–186	.015		17	$C_{24}H_{30}ClNO$					3.7	4.0
79	$-(CH_2)_2-$	CH_3	CH_3		4-$ClC_6H_4CH_2-$	160–166	.25		54							
80	$-(CH_2)_2-$	CH_3	CH_3	HCl	4-$ClC_6H_4CH_2-$			165–166[ae]	41	$C_{20}H_{25}Cl_2NO$	65.6	65.6	6.8	6.9	3.8	3.7
81	$-(CH_2)_2-$	C_2H_5	C_2H_5		4-$ClC_6H_4CH_2-$	170–180	.55		56							
82	$-(CH_2)_2-$	C_2H_5	C_2H_5	HCl	4-$ClC_6H_4CH_2-$			147–148[ae]	50	$C_{22}H_{29}Cl_2NO$	67.0	67.0	7.4	7.2	3.6	3.7
83	$-(CH_2)_2-$	*i*-C_3H_7	CH_3		4-$ClC_6H_4CH_2-$	184–190	.06		59	$C_{22}H_{28}ClNO$	73.8	74.1	7.8	8.2		
84	$-(CH_2)_2-$	*i*-C_3H_7	CH_3	CH_3I	4-$ClC_6H_4CH_2-$			138–140[ad]	77	$C_{23}H_{31}ClINO$	55.3	55.4	6.2	6.4		
85	$-(CH_2)_2-$	$-(CH_2)_6-$			4-$ClC_6H_4CH_2-$	210–214	.2		39	$C_{24}H_{30}ClNO$	75.1	75.0	7.8	8.0	3.7	3.9
86	$-(CH_2)_2-$	$C_6H_4CH_2CH_2-$[b]			4-$ClC_6H_4CH_2-$	242–252	.22		11	$C_{26}H_{26}ClNO$	77.3	76.9	6.4	6.4		
87	$-(CH_2)_3-$	CH_3	CH_3		4-$ClC_6H_4CH_2-$	180	.03		73							
88	$-(CH_2)_3-$	CH_3	CH_3	HCl	4-$ClC_6H_4CH_2-$			215–217[aa]		$C_{21}H_{27}Cl_2NO$	66.3	66.2	7.1	7.5	3.7	3.8
89	$-(CH_2)_3-$	CH_3	CH_3	CH_3I	4-$ClC_6H_4CH_2-$			183–185[ad]	71	$C_{22}H_{29}ClINO$	54.4	53.8	6.0	5.8	2.9	3.3
90	$-(CH_2)_3-$	CH_3	CH_3	C_3H_5Br[c]	4-$ClC_6H_4CH_2-$			136–138[ad]	74	$C_{24}H_{31}BrClNO$	62.0	61.7	6.7	6.4	3.0	2.9
91	$-(CH_2)_3-$	CH_3	CH_3	$C_4H_7O_2Br$[d]	4-$ClC_6H_4CH_2-$			177–178[ad]	68	$C_{25}H_{33}BrClNO_3$	58.8	59.1	6.5	6.0	2.7	2.8
92	$-(CH_2)_2-$	*i*-C_3H_7	CH_3		H	108–112	.05		65	$C_{15}H_{23}NO$	77.2	77.0	9.9	10.2	6.0	6.0
93	$-(CH_2)_2-$	*i*-C_3H_7	CH_3	HPic.	H			156–157		$C_{21}H_{26}N_4O_8$	54.5	54.9	5.7	5.7	12.1	12.3
94	$-(CH_2)_2-$	*i*-C_3H_7	CH_3	CH_3I	H			113–115[ad]	83	$C_{16}H_{26}INO$	51.2	51.3	6.9	7.2	3.7	3.7
95	$-(CH_2)_3-$	$-(CH_2)_5-$			4-$ClC_6H_4CH_2-$	178–193	.015		23	$C_{24}H_{30}ClNO$	75.1	75.2	7.8	8.1	3.7	3.9

[a] Recrystallizing solvent: [aa] ethanol–ethyl acetate; [ab] water (all picrates were recrystallized from water); [ac] ethanol–heptane; [ad] acetonitrile; [ae] butyl acetate. [b] NR_1R_2 represents the 1-indolinyl derivative. [c] C_3H_5 represents allyl. [d] $C_4H_7O_2$ represents $-CH_2COOC_2H_5$. [e] Melting points are not corrected. [f] Yields are based on distilled or recrystallized product. [g] Analyses by Weiler and Strauss, Oxford, England.

prepared and converted to aminoalkyl ethers. Typical of the structures prepared is I.



I

Y = alkylene or isoalkylene containing 2–3 carbon atoms
R_1, R_2 = alkyl and arylalkyl
R_3X = quaternizing group
R_4 = hydrogen, benzyl and chlorobenzyl

Formal structural relationship[2-5,7,8] indicated evaluation of these compounds as hypotensive agents, antihistamines, central nervous system depressants and anti-inflammatory agents, and responses in all of these categories were noted on testing.

The substituted benzylindanols were prepared by the zinc chloride catalyzed condensation of the required benzyl halide with the indanol following Buu-Hoï and Demerseman[9] and have been described in another paper.[10]

The indanols and monobenzylated indanols were treated with disubstituted aminoalkyl chlorides in aqueous alcoholic potassium hydroxide to yield the required disubstituted aminoalkyl ethers of the corresponding indanols.

2-(1-Indolinyl)-ethyl chloride could not be obtained in workable amounts by treatment of 2-(1-indolinyl)-ethanol with thionyl chloride, and instead the 2-chloroethyl ether of the indanol, prepared by treatment of the indanol with ethylene chlorobromide, was treated with indoline to give the desired product. The compounds which were prepared are described in Table I.

Experimental[11]

β-Disubstituted Aminoalkanols and β-Disubstituted Aminoalkylchloride Hydrochlorides.—The required aminoalcohols were obtained commercially or were prepared by procedures described in the literature[12,13] and were converted to the corresponding chloride with thionyl chloride.[12] A typical procedure is described.

2-(1-Hexamethylenimyl)-ethyl Chloride.—To a cooled solution of 30 ml. of thionyl chloride in 100 ml. of benzene there was added with continued cooling (10°) and stirring, 25 g. (0.175 mole) of 2-(1-hexamethylenimyl)-ethyl alcohol. After the addition was complete (30 minutes), the reaction mixture was refluxed for 2 hours, the volatiles removed *in vacuo* and the residue dissolved in water. After washing with ether, the aqueous phase was neutralized with 40% sodium hydroxide and extracted with two 200-ml. portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate, filtered, the ether evaporated and the residue distilled *in vacuo*. There was obtained 18.42 g. (65.3%) of 2-(1-hexamethylenimyl)-ethyl chloride, b.p. 80–82° (0.1 mm.).

Anal. Calcd. for $C_8H_{16}ClN$: N, 8.7. Found: N, 9.0.

4-(2-[N-Isopropyl-N-methyl]-aminoethoxy)-indane (Compound 6).—To a solution of 4.02 g. (0.03 mole) of 4-indanol in 25 ml. of ethanol and 14 ml. of water containing 5.2 g. (0.9 mole) of potassium hydroxide there was added slowly (over 15 minutes) with cooling (10°), a solution of 6.1 g. (0.045 mole) of isopropylmethylaminoethyl chloride in 60 ml. of ethanol. The reaction mixture was stirred and refluxed for 3 hours, cooled, filtered and volatiles removed *in vacuo*. The residue was suspended in 100 ml. of water and extracted with three 100-ml. portions of ether. The combined ethereal extracts were extracted with two 60-ml. portions of 3 *N* hydrochloric acid. The acid phase was separated, made strongly alkaline with 40% sodium hydroxide and the product extracted with two 100-ml. portions of ether. The combined ether extracts were dried, filtered, the ether removed and the residual oil distilled. There was obtained 4.8 g. (69%) of product, b.p. 104–108° (0.03 mm.).

The picrate, prepared from aqueous picric acid and recrystallized from water, melted at 123–124°.

The methiodide quaternary salt (compound 8) was prepared by treating 2.0 g. of the above base in 12 ml. of acetonitrile with 15 ml. of methyl iodide. After standing 3 hours, 25 ml. of ethyl acetate and 15 ml. of ether were added and the reaction mixture was allowed to crystallize at 10° over 13 hours. After filtration, rinsing of the precipitate with ether and recrystallization from acetonitrile there was obtained 2.3 g. of the methiodide, m.p. 131–133°.

6-(4-Chlorobenzyl)-5-(3-dimethylaminopropoxy)-indan Hydrochloride. (Compound 88).—A mixture of 25.9 g. (0.1 mole) of 6-(4-chlorobenzyl)-5-indanol and 16.8 g. (0.3 mole) of potassium hydroxide in a solution of 200 ml. of ethanol and 50 ml. of water was treated with a solution of 23.7 g. (0.15 mole) of dimethylaminopropyl chloride hydrochloride in 200 ml. of ethanol and processed as described above. The product obtained in 25 g. yield (72.5%) boiled at 180° (0.03 mm.). The hydrochloride was prepared from a solution of 2.5 g. of the base in 4.65 ml. of 1.54 *N* hydrochloric acid and, on standing 1 hour, 1.72 g. of the hydrochloride was separated.

5-(2-[1-Indolinyl]-ethoxy)-indan (Compound 62).—The preparation of this and allied indolinylethyl ethers did not proceed by the general methods as described above. The following procedure was used.

2-Chloroethyl ether of 5-indanol was prepared by slowly adding dropwise (over 30 minutes) a solution of 23.45 g. (0.175 mole) of 5-indanol in 150 ml. of ethanol and 80 ml. of water to 154.7 g. (1.07 moles) of ethylene chlorobromide. Heating (75°) and stirring were maintained for 3 hours and the volatiles then removed. The residual oil was suspended in water and then extracted with three 200-ml. portions of ether. The combined ethereal extracts were dried, filtered and the ether removed. The oily residue, distilled at 73–85° (0.01–0.03 mm.), afforded 16.08 g. (49%) of 5-(2-chloroethoxy)-indan which was used directly below.

A solution of 17.0 g. (0.086 mole) of this halo ether and 21.4 g. (0.18 mole) of indoline in 50 ml. of toluene was refluxed for 6 hours. The formed indoline hydrochloride, 4.0 g., was separated. The filtrate was made alkaline with 6 *N* sodium hydroxide and extracted with three 100-ml. portions of ether. The combined ethereal extracts were dried (anhydrous magnesium sulfate), filtered, the ether removed and the residue distilled. There was obtained 4.6 g. (19%) of product which boiled at 190–192° (0.2 mm.) and crystallized on standing, m.p. 77–79°.

Pharmacology.—The compounds were screened for pharmacologic activity with the following significant responses[14]: **long-lasting hypotensive response,** compounds 11, 13, 30, 33, 34, 46, 48, 49, 50, 77, 78, 95; **antihistamine response,** compounds 30, 49, 80, 82; compounds 77 and 78 potentiate histamine; **ganglionic block,** compounds 4, 11, 40, 46, 49; **anti-inflammatory response** (units per Gram), compounds 23 (17), 40 (5), 47 (10), 51 (10), 58 (9), 82 (8); **depression of motor activity** (% decrease/test level mg./kg. subcutaneous/subcutaneous $LD_{min.}$): compounds 34 (22/10/400), 49 (24/20/750), 77 (35/20/350), 88 (45/10/300).

In general, where noteworthy pharmacologic effects were found, they were observed in the aminoalkyl ethers of both 4-indanol and 5-indanol.

Acknowledgment.—The authors wish to express their appreciation to Dr. G. Ungar for the pharmacologic results.

YONKERS 1, NEW YORK

(9) Ng. P. Buu-Hoï and P. Dermerseman, *J. Org. Chem.*, **20**, 1129 (1955).

(10) S. L. Shapiro, T. Bazga, K. Weinberg and L. Freedman, THIS JOURNAL, **80**, 3726 (1958).

(11) Descriptive data shown in the tables are not reproduced in the Experimental section.

(12) D. G. Doherty, R. Shapira and W. T. Burnett, Jr., THIS JOURNAL, **79**, 5667 (1957).

(13) F. F. Blicke, U. S. Patent 2,748,713.

(14) For more detailed reference to the pharmacologic tests used, see S. L. Shapiro, H. Soloway and L. Freedman, *J. Am. Pharm. Assoc., Sci. Ed.*, **46**, 333 (1957).