Antispasmodic *ortho*-Substituted Phenoxyalkylamines

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The preparation of a series of *ortho*-substituted phenoxyalkylamines is reported. Several of the compounds proved to be potent papaverine-like agents, while exhibiting only weak anticholinergic properties. The spasmolytic activity *in vitro* as expressed by antibarium, anticholinergic, and antihistaminic potencies, and the acute toxicity in mice are recorded.

Since the pioneering work of Bovet on the antihistaminic properties of certain phenolic ethers, a great number of compounds derived from 2-phenoxyethylamine have been described, and a surprising diversity of biological activity attributable to the common structural feature has been uncovered. The variety of highly potent compounds include antihistaminics,[2] adrenergic postsynaptic neuron blocking agents,[3] general adrenolytics,[4] MAO inhibitors,[5] stimulants of autonomic ganglia[6] and of skeletal muscle,[7] antitussives,[8] and local anesthetics.[9]

About 15 years ago it was observed in this laboratory[2e] that the quaternary ammonium compounds corresponding to phenyltoloxamine were comparatively weak anticholinergic agents while retaining a considerable papaverine-like antispasmodic activity. This was in striking contrast to results from the closely related diphenylhydramine series.[2g]

During their investigation of phenyltoloxamine and related tertiary amines, Hoekstra, *et al.*,[2f] demonstrated a similar distribution of papaverine-like and anticholinergic *in vitro* activity. These findings prompted the study presented here of a series of basically substituted aryl ethers and their quaternary ammonium salts for evaluation as potential musculotropic antispasmodics. The compounds synthesized and investigated for biological effects were of two general types (I and II) where the bulky moiety R was derived

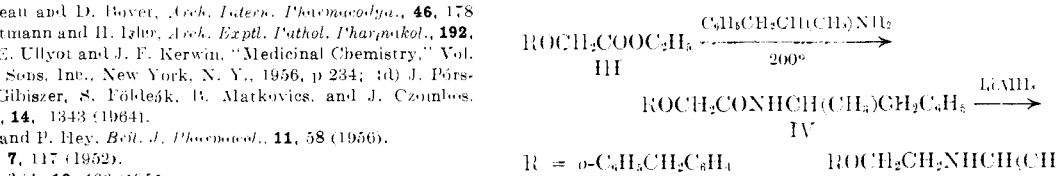
from 2-hydroxybenzophenones (Table I), 2-hydroxybenzhydrols and 2-hydroxytriphenylmethanols (Table II), and α-phenyl-*o*-cresols (Tables III and IV), and R′, R″ denotes hydrogen, aliphatic, alicyclic, and aromatically substituted alkyl groups. Quaternary ammonium salts were prepared from some typical members of each group of compounds.

The 2-dialkylaminopropyl ethers (type I) were most conveniently prepared by a nucleophilic displacement reaction of the *p*-toluenesulfonate esters of the corresponding 2-hydroxypropyl ethers with an excess of secondary amines in boiling benzene. Alternatively, the tertiary amines were synthesized *via* the 2-chloropropyl ethers in a similar manner. The secondary alcohols required in this synthesis were obtained by heating propylene oxide and the appropriate phenol in the presence of catalytical amounts of sodium at 140°.

The majority of the unbranched dialkylaminopropyl ethers of type II were obtained by the method described previously by Cheney.[3a,b] In the case of the 2-(3-dialkylaminopropoxy)benzhydrols listed in Table II (R_1 = H) it was found advantageous to first prepare the appropriate dialkylaminopropyl ethers of salicylaldehyde, which in a smooth Grignard reaction with phenylmagnesium bromide gave the desired benzhydryl ethers.

N-[2-(α-Phenyl-*o*-tolyloxy)ethyl]-α-methylphenethylamine (**48**) was prepared by aminolysis of (α-phenyl-*o*-tolyloxy)acetic acid ethyl ester[10] (III) with α-methylphenethylamine at 200° and subsequent reduction of the resulting amide (IV) with lithium aluminum hydride (see Scheme I). N-[2-(α-Phenyl-*o*-tolyloxy)ethyl]-2-indanamine (**49**) was prepared in a similar manner.

SCHEME I



(1) Correspondence should be addressed to this author.

(2) (a) L. C. Cheney, R. R. Smith, and S. B. Binkley, *J. Am. Chem. Soc.*, **71**, 61 (1949); (b) W. B. Wheatley, L. C. Cheney, and S. B. Binkley, *ibid.*, **71**, 64, 3795 (1949); (c) J. Mills, E. Rohrmann, W. G. Dinwiddie, and H. M. Lee, *Arch. Intern. Pharmacodyn.*, **80**, 119 (1949); (d) Ch. I. Morel and W. G. Stoll, *Helv. Chim. Acta*, **33**, 516 (1950); (e) J. Fakstorp and E. Hvorsen, *Acta Chem. Scand.*, **4**, 1610 (1951); (f) J. B. Hoekstra, D. Tisch, N. Rakieten, and H. L. Dickison, *J. Am. Pharm. Soc., Sci. Ed.*, **42**, 587 (1953); (g) S. Antonsen, *Acta Pharmacol. Toxicol.*, **9**, 47 (1953); (h) L. C. Cheney and S. B. Binkley, British Patents 743,106 (1956) and 741,082 (1957); U. S. Patents 2,703,324 (1955) and 2,768,207 (1956).

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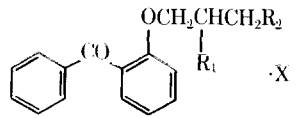
TABLE I

BASIC ETHERS OF 2-HYDROXYBENZOPHENONE



No.	R_1	R_2	X	Recrystn solvents[a]	Mp, °C	Formula	% C Calcd	% C Found	% H Calcd	% H Found	% N Calcd	% N Found	Mouse LD_{50} mg/kg ip 24 hr	Relative activity[b] *in vitro* Spasmolytic	Anticholinergic	Antihistaminic
1	$N(CH_3)_2$	H	HCl	A	176–177	$C_{18}H_{22}ClNO_2$	67.60	68.05	6.94	6.88	4.38	4.36	85[c]	20	0.07	0.07
2	$N(C_2H_5)_2$	H	HCl	B	147–148	$C_{20}H_{26}ClNO_2 \cdot H_2O$	65.65	65.48	7.64	7.72	3.84	3.83	108[c]	10	0.06	0.01
3	$N(C_3H_7)_2$	H	HI	C	136–137	$C_{22}H_{30}INO_2$	56.53	56.87	6.47	6.65	3.00	3.11	107[c]	5	0.01	<0.1
4	$N(C_4H_9)_2$	H	HI	C	102–104	$C_{24}H_{34}INO_2$	58.18	58.48	6.92	7.01	2.83	2.88	200–400[d]	2	<0.01	0.01
5	$C_5H_{10}N$[e]	H	HBr	A	133–134	$C_{21}H_{26}BrNO_2$	62.36	62.53	6.49	6.71	3.47	3.39	100–200[d]	4	0.01	0.02
6	H	$N(CH_3)_2$	HBr	A	87–89	$C_{18}H_{22}BrNO_2$	59.35	59.37	6.07	6.31	3.84	3.83	142[c]	5.8	<0.01	<0.1
7	H	$N(C_2H_5)_2$	H_3PO_4	D	187–189	$C_{20}H_{28}NO_6P$	58.67	58.85	6.90	7.17	3.42	3.61	100–200[d]	4	<0.01	<0.1
8	H	$N(C_3H_7)_2$	HI	A	121–123	$C_{22}H_{30}INO_2$	56.53	57.24	6.47	7.02	3.00	3.01	100–200[d]	2.8	<0.01	<0.1
9	H	$N(C_4H_9)_2$	HBr	A	131–132	$C_{24}H_{34}BrNO_2$	64.27	64.48	7.65	7.65	3.25	3.29	100–200[d]	1.3	<0.01	<0.1
10	H	$C_5H_{10}N$	HBr	A	157–159	$C_{21}H_{26}BrNO_2$	62.38	62.40	6.50	6.47	3.47	3.40	100–200[d]	<1	<0.01	<0.1
11	$CH_3N^+(C_2H_5)_2$	H	I^-	C	130–132	$C_{21}H_{28}INO_2$	55.62	55.92	6.22	6.25	3.09	3.14	50–100[d]	50	0.24	0.04
12	$C_5H_{10}N^+CH_3$	H	I^-	C	162–163	$C_{22}H_{28}INO_2$	56.77	56.79	6.07	6.24	3.01	3.07	80[d]	40	0.64	0.11

[a] Recrystallization solvents: (A) 2-propanol, (B) methyl ethyl ketone, (C) absolute, ethanol, (D) 90% ethanol. [b] The standards are taken as 1: spasmolytic = papaverine, anticholinergic = atropine, antihistaminic = diphenhydramine. [c] LD_{50} values calculated according to G. Kärber, *Arch. Exptl. Pharmakol.*, **162,** 480 (1931). [d] Approximate values for LD_{50} obtained from a behavioral observation test. [e] $C_5H_{10}N$ = piperidino.

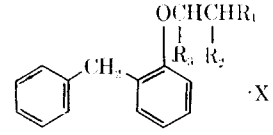
TABLE II: BASIC ETHERS OF 2-HYDROXYBENZHYDROLS

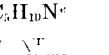
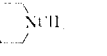
No.	R_1	R_2	X	Recrystn solvents[a]	Mp, °C	Formula	% C Calcd	% C Found	% H Calcd	% H Found	% N Calcd	% N Found	Mouse LD_{50}, mg/kg ip 24 hr	Relative activity[b] *in vitro* Spasmolytic	Anticholinergic	Antihistaminic
13	H	$N(CH_3)_2$	H_3PO_4	C	167–169	$C_{18}H_{26}NO_6P$	56.39	56.37	6.84	6.83	3.66	3.67	100–200[d]	1.3	0.01	0.22
14	H	$N(C_2H_5)_2$	H_3PO_4	B	167–169	$C_{20}H_{30}NO_6P$	58.39	58.54	7.36	7.41	3.42	3.47	200–400[d]	1.8	0.01	<0.1
15	H	$N(C_3H_7)_2$	HCl	E	140–142	$C_{22}H_{32}ClNO_2$	69.89	69.88	8.54	8.63	3.71	3.88	100–200[d]	2.5	<0.01	<0.1
16	H	$N(C_4H_9)_2$	HBr	A	119–121	$C_{24}H_{36}NO_2Br$	63.97	64.89	8.06	8.22	3.12	3.02	200–400[d]	1.5	<0.01	<0.1
17	H	$C_5H_{10}N$[e]	HBr	B	183–185	$C_{12}H_{28}BrNO_2$	62.06	62.10	6.96	6.82	3.46	3.39	100–200[d]	1.8	<0.01	<0.1
18	C_6H_5	$N(CH_3)_2$	HCl	F	206–208	$C_{29}H_{28}ClNO_2$	72.43	71.56	7.09	7.27	3.52	3.46	150[c]	6	0.01	<0.1
19	C_6H_5	$N(C_2H_5)_2$	HBr	D	185–188	$C_{26}H_{32}BrNO_2 \cdot 0.5H_2O$	65.13	65.60	6.95	6.97	2.92	2.99	100–200[d]	1.5	<0.01	<0.1
20	H	$N^+(CH_3)_3$	p-$CH_3C_6H_4SO_3^-$	E	152–156	$C_{26}H_{33}NSO_5$	66.22	66.10	7.05	6.93	2.97	3.15	50–100[d]	2	<0.01	<0.1
21	H	$CH_3^+N(C_2H_5)_2$	p-$CH_3C_6H_4SO_3^-$	E	132–134	$C_{28}H_{37}NSO_5$	67.30	67.82	7.46	7.56	2.81	2.77	25–50[d]	4	<0.01	<0.1
22	H	$CH_3N^+(C_3H_7)_2$	p-$CH_3C_6H_4SO_3^-$	E	164–165	$C_{30}H_{41}NSO_5$	68.28	68.10	7.84	7.83	2.66	2.73	100–200[d]	4	<0.01	<0.1
23	H	$CH_3N^+(C_4H_9)_2$	I^-	A	138–141	$C_{25}H_{38}INO_5$	58.71	59.79	7.49	7.59	2.74	2.61	100–200[d]	2	<0.01	<0.1
24	H	$C_5H_{10}N^+$–CH_3	p-$CH_3C_6H_4SO_3^-$	A	162–163	$C_{22}H_{30}INO_5$	56.53	56.53	6.48	6.72	3.00	3.02	50–100[d]	2.4	<0.01	<0.1
25	C_6H_5	$^+N(CH_3)_3$	p-$CH_3C_6H_4SO_3^-$	B	237–239	$C_{32}H_{37}SSO_5$	70.17	70.17	6.82	6.82	2.56	2.66	50–100[d]	33	0.23	<0.1
26	C_6H_5	$CH_3N^+(C_2H_5)_2$	p-$CH_3C_6H_4SO_3^-$	D	97–106	$C_{34}H_{41}NSO_5 \cdot 1.75H_2O$	67.09	67.13	7.38	7.35	2.35	2.30	25–50[d]	12	0.17	<0.1

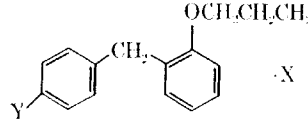
[a] Recrystallization solvents: (A) absolute ethanol, (B) 90% ethanol, (C) methanol, (D) chloroform–petroleum ether 1:1, (E) acetonitrile, (F) methanol–ether 2:1, (H) methyl ethyl ketone. [b–e] See corresponding footnotes in Table I.

TABLE III

BASIC ETHERS OF α-PHENYL-*o*-CRESOL



No.	R_1	R_2	R_3	X	Recrystn solvents[a]	Mp, °C	Formula	% C Calcd	% C Found	% H Calcd	% H Found	% N Calcd	% N Found	Mouse LD_{50}, mg/kg ip 24 hr	Relative activity[b] *in vitro*: Spasmolytic	Relative activity[b] *in vitro*: Anticholinergic	Relative activity[b] *in vitro*: Antihistaminic
27	H	NH_2	CH_3	HCl	A	144–144.5	$C_{18}H_{20}ClNO$	69.19	69.11	7.23	7.66	5.04	4.71	100–200[d]	1.5	0.01	0.1
28	CH_3	$N(C_2H_5)_2$	H	HCl	A	111–113.5	$C_{20}H_{28}ClNO$	71.94	72.18	8.45	8.64	4.16	4.19	145[c]	17	0.03	0.1
29	CH_3	$N(C_3H_7)_2$	H	HCl	A	108.5–110	$C_{22}H_{32}ClNO$	72.98	73.67	8.92	9.09	3.86	3.94	210[c]	3	0.01	0.1
30	CH_3	$N(C_4H_9)_2$	H	HBr	A	89–92	$C_{24}H_{36}BrNO$	66.33	66.30	8.35	8.35	3.23	3.23	>200[c]	*f*		
31	CH_3N	$(CH_3)_3$ $(CH_3)C$	H	HBr	A	117–120	$C_{21}H_{30}BrNO$	64.27	64.40	7.70	7.77	3.56	3.48	184[c]	7	0.08	0.9
32	CH_3	C_4H_8N[e]	H	H_3PO_4	B	151–152	$C_{20}H_{28}NO_5P$	61.06	61.08	7.18	7.50	3.56	3.55	132[c]	3.5	0.03	<0.1
33	CH_3	$C_5H_{10}N$[e]	H	HCl	E	167–169	$C_{21}H_{28}ClNO$	72.91	73.04	8.15	8.28	4.04	4.05	133[c]	1.4	0.01	0.1
34	CH_3		H	2HCl	B	208–212	$C_{21}H_{30}$-Cl_2N_2O	63.46	63.63	7.67	7.62	7.06	7.16	200–400[d]	4	0.01	<0.1
35	$C_5H_{10}N$	H	CH_3	HCl	B	172.5–173.5	$C_{21}H_{28}ClNO$	72.91	72.95	8.15	8.21	10.25	10.22	200–400[d]	1.7	<0.01	<0.1
36	CH_3	$^+N(CH_3)_3$	H	*p*-$CH_3C_6H_4$-SO_3^-	C	165–166	$C_{26}H_{33}NSO_4$	68.54	68.23	7.31	7.37	3.07	3.09	37[c]	16	0.20	34
37	CH_3	$CH_3{}^+N(C_2H_5)_2$	H	I^-	C	120–122	$C_{21}H_{30}INO$	57.40	57.68	6.86	6.99	3.20	3.16	52[c]	70	0.35	1.93
38	CH_3	$(CH_3)_2N^+C(CH_3)_3$	H	I^-	C	136–137	$C_{22}H_{32}INO$	58.27	58.61	7.11	6.91	3.08	3.07	50–100[d]	15	0.13	0.67
39	CH_3	$C_9H_8N^+$–CH_3	H	I^-	F	117–125	$C_{21}H_{28}INO$	57.66	57.69	6.46	6.60	3.22	3.21	92[c]	45	0.40	0.27
40	CH_3	$C_5H_{10}N^+$–CH_3	H	*p*-$CH_3C_6H_4$-SO_3^-	D	125.5–126.5	$C_{29}H_{37}NSO_3$	70.26	70.28	7.52	7.61	2.82	2.87	95[c]	38	0.10	13
41	CH_3	$C_5H_{10}N^+$–C_2H_5	H	I^-	D	144.5–145.5	$C_{23}H_{32}NOI$	59.35	59.58	6.94	7.03	3.10	2.99	74[c]	13	0.05	0.73
42	CH_3	$C_5H_{10}N^+$–C_4H_7	H	HSO_4^-	C	140–142	$C_{24}H_{33}NO_5S$	64.10	64.20	7.86	7.90	3.12	3.17	25–50[d]	27	0.12	0.45
43	CH_3		H	I	C	171–173	$C_{20}H_{30}IN_2O$	56.65	57.27	6.70	6.71	6.01	6.15	25–50[d]	6	0.01	0.4



No.	R_1	Y	X	Recrystn solvents[a]	Mp, °C	Formula	% C Calcd	% C Found	% H Calcd	% H Found	% N Calcd	% N Found	Mouse LD_{50}, mg/kg ip 24 hr	Relative activity[b] *in vitro*: Spasmolytic	Relative activity[b] *in vitro*: Anticholinergic	Relative activity[b] *in vitro*: Antihistaminic
44	$N(C_2H_5)_2$	H	HCl	A	127–129	$C_{20}H_{28}ClNO$	71.94	71.84	8.45	8.53	4.16	4.16	155[c]	1.4	0.01	0.46
45	$N(C_2H_5)_2$	Cl	HI	B	104–106	$C_{20}H_{27}ClINO$	52.24	52.18	5.93	5.92	3.04	3.04	250[c]	2.2	0.01	
46	$N(C_4H_9)_2$	Cl	HCl	A	91–92	$C_{24}H_{35}Cl_2NO$	67.91	67.77	8.32	8.54	3.30	3.34	350[c]	*f*		
47	$CH_2N(CH_3)_2$	H	HCl	B	133–136	$C_{19}H_{26}ClNO$	71.43	71.43	8.21	8.20	4.38	4.38	100–200[d]	2.6	0.01	0.1

[a] Recrystallization solvents: (A) ethyl acetate, (B) absolute ethanol, (C) 2-propanol, (D) methyl ethyl ketone, (E) ethanol–ether 2:1, (F) acetone. [b] See corresponding footnotes in Table I. [c] Compound too insoluble to test. [d] C_4H_8N = pyrrolidinyl.

TABLE IV

SECONDARY AMINO ETHERS

·HCl

No.	R_1	Q	Recrystn solvents[a]	Mp, °C	% C Calcd	% C Found	% H Calcd	% H Found	% N Calcd	% N Found	% Cl Calcd	% Cl Found	Mouse LD_{50}, mg/kg ip 24 hr	Relative activity[b] *in vitro* — Spasmolytic	Relative activity[b] *in vitro* — Anticholinergic	Relative activity[b] *in vitro* — Antihistaminic
48	$CH(CH_3)CH_2C_6H_5$	$>CH_2$	A	163–165	75.50	75.41	7.39	7.41	3.68	3.84	9.28	9.73	200–400[d]	1.7	0.01	0.1
49		$>CH_2$	A	172–173	75.80	76.00	6.89	6.95	3.69	3.79	9.34	9.62	100–200[d]	1	0.01	0.1
50	$CH_2CH_2C_6H_4OH$-*p*	$>CH_2$	A	165–167	72.00	72.20	6.84	6.91	3.65	3.60	9.25	9.57	400–600[d]	1	0.01	0.1
51	$CH(CH_3)CH_2C_6H_5$	$>C{=}O$	B	143–147	72.78	72.85	6.71	6.62	3.48	3.54	8.99	8.96	100–200[d]	1	0.01	0.1

[a] Recrystallization solvents: (A) absolute ethanol, (B) acetonitrile. [b–d] See corresponding footnotes in Table I.

A modification of this method was applied to the synthesis of N-[2-(α-phenyl-*o*-tolyloxy)ethyl]-*p*-hydroxyphenethylamine (**50**), in which case the amide linkage was formed by the reaction of 2-(α-phenyl-*o*-tolyloxy)ethylamine[11] with *p*-hydroxyphenylacetic acid methyl ester.[12] The extreme insolubility of the intermediate amide and the well-known complications arising from the precipitation of the lithium phenoxide during the lithium aluminum hydride reduction resulted in poor yields of the secondary amine (**50**).

The presence of a carbonyl group made it necessary to devise another route to 2-[2-(α-methylphenethylamino)ethoxy]benzophenone (**51**) (Scheme II). Treatment of 2-(α-methylphenethylamino)ethanol[13] (V) with 2 moles of *p*-toluenesulfonyl chloride in pyridine gave the *p*-toluenesulfonamido-*p*-toluensulfonate ester (VI), which on reaction with the sodium salt of 2-hydroxybenzophenone at 160° yielded the *p*-toluenesulfonamide (VII). Removal of the protecting group without causing rupture of the ether linkage was effected by prolonged treatment at room temperature with 48% HBr and phenol in glacial acetic acid.[14]

SCHEME II

The starting phenols were prepared essentially as described earlier.[2a,b,15,16] A detailed description of the synthesis of (*o*-hydroxyphenyl)diphenylmethanol[17] is, however, included in the Experimental Section. The quaternary ammonium salts were obtained in a conventional manner by reaction of the free tertiary amines with alkylating agents in acetone.

The antispasmodic activities recorded in Tables I–IV were determined on the isolated guinea pig ileum according to a modification of the method of Magnus.[18] Barium chloride, carbaminoylcholine, and histamine hydrochloride were employed as agonists, and the spasmolytic, anticholinergic, and antihistaminic potencies were expressed as multiples of papaverine hydrochloride, atropine sulfate, and histamine hydrochloride, respectively. The compounds of this series were found

(11) Prepared from α-phenyl-*o*-tolyloxyacetonitrile in 80% yield by $LiAlH_4$ reduction.

(12) H. Salkowski, *Chem. Ber.*, **22**, 2146 (1889).

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(15) M. Kulka, *ibid.*, **76**, 5469 (1954).

(16) (a) C. Graebe and F. Ullmann, *Chem. Ber.*, **29**, 824 (1896); (b) F. Ullmann and I. Goldberg, *ibid.*, **35**, 2811 (1902).

(17) (a) A. Bayer, *Ann. Chem.*, **354**, 167 (1907); (b) J. vanAlphen, *Rec. Trav. Chim.*, **46**, 800 (1927).

(18) (a) K. Hermansen, *Acta Pharmacol. Toxicol.*, **17**, 277 (1960); (b) R. Magnus, *Arch. Ges. Physiol.*, **102**, 123 (1904).

to be moderately strong to strong antagonists of spasms induced by barium ions on the guinea pig ileum *in vitro*, while, with few exceptions, exhibiting a relatively low order of anticholinergic and antihistaminic activity. Some of the more promising members (**1**, **11**, **28**, **29**, **30**, and **40**) have been further studied with regard to their utility as antispasmodics directly active on plain muscle.

In addition, a variety of other effects were observed in the tertiary and quaternary members of the series. Notable among them are antagonism of tremorine-induced hypothermia and analgesia,[19] antagonism of the phenyl-*p*-quinone-induced writhing syndrome,[20] local anesthetic activity,[21] and prevention of the tussive response to stimulation of the cat's laryngeal nerve.[22] A more detailed account of the pharmacology of the compounds described will be published elsewhere.

Experimental Section

All melting points are corrected and were determined in a capillary tube. Microanalyses were carried out by Analytica AB, Sollentuna, Sweden.

The experimental procedures given below are representative for the compounds listed in Tables I–IV.

2-(2-*p*-Tolylsulfonyloxypropoxy)benzophenone.—A mixture of 0.5 g of sodium dissolved in 268 g (1.35 moles) of 2-hydroxybenzophenone[15,16] and and 86.5 g (1.49 moles) of propylene oxide was heated in an autoclave for 4 hr at 140°.[23] The product was distilled *in vacuo* and the fraction boiling at 180–210° (1–3 mm) was collected (247 g). Redistillation afforded 218 g (65%), bp 157–162° (0.15–0.25 mm), of the desired alcohol, which was converted to the *p*-tolylsulfonyl ester by a standard procedure.[24] The crude ester could not be crystallized and was used directly in the preparations of the compounds listed in Table I, by the typical method described below for **1**.

2-(2-Dimethylaminopropoxy)benzophenone Hydrochloride (1).—A solution of 21.4 g (0.47 mole) of dimethylamine in 240 ml of dry benzene was added to a solution of 78 g (0.19 mole) of 2-(2-*p*-tolylsulfonyloxypropoxy)benzophenone in 80 ml benzene, and the mixture was heated in an autoclave for 16 hr at 140°.[25] The solvent was removed under reduced pressure, the residue was treated with 450 ml of 15% NaOH, and the separated oily product was extracted repeatedly with ether. The combined extracts were washed with water and dried and the solvent was removed. The oily residue was distilled *in vacuo* giving 46 g (85%) of the free base, bp 143–144.5° (0.15 mm). The base (21.3 g, 0.075 mole) was converted to the hydrochloride by treatment with excess 3 *N* HCl, evaporation to dryness of the resulting solution under reduced pressure, and crystallization of the residue from 2-propanol; yield 12.3 g, mp 169–174.5°. Three further recrystallizations from 2-propanol furnished an analytical sample, mp 176.5–177.5°.

2-(3-Dimethylaminopropoxy)benzophenone Hydrobromide (6).—To a stirred solution of 5.75 g (0.25 g-atom) of Na in 600 ml of dry methanol was added 49.5 g (0.25 mole) of 2-hydroxybenzophenone, and the mixture refluxed for 10 min. After evaporation of the solvent under reduced pressure and removal of the last traces of water by codistillation with toluene, the residue was suspended in 250 ml of dry toluene. To this, 30.4 g (0.25 mole) of 3-dimethylaminopropyl chloride in toluene solution was added with efficient stirring, and the mixture refluxed for 18 hr. After the addition of 250 ml of water, the toluene layer was separated and washed with water, and the product was extracted with 3 *N* HCl. The combined acid extracts were washed with ether (discarded) and the purified base was precipitated with 30% NaOH. Isolation of the product in the usual manner and distillation *in vacuo* yielded 50.6 g (71%) of an oil, bp 161–166° (0.3 mm). The free base (15.0 g, 0.05 mole) was converted to the corresponding hydrobromide by treatment with HBr in ether solution, 17.5 g (90%), mp 84–86°. Four recrystallizations from 2-propanol furnished an analytical sample, mp 87–89°.

2-(3-Dimethylaminopropoxy)benzaldehyde.—Salicylaldehyde (61.1 g, 0.5 mole) was added with stirring to a solution of 11.5 g of Na (0.5 g-atom) in 600 ml of dry methanol, and the mixture refluxed for a few minutes to complete the reaction. The methanol was slowly evaporated under reduced pressure, the solid residue was suspended in 200 ml of toluene, and the solvent was distilled to secure anhydrous conditions. 3-Dimethylaminopropyl chloride (73 g, 0.6 mole) in 600 ml of dry toluene was then added to a suspension of the sodium salicylaldehyde in 300 ml of toluene. The mixture was refluxed with stirring for 18 hr and cooled, and the precipitated salt was filtered. The filtrate was concentrated under reduced pressure, and the residue was distilled *in vacuo*; yield 82 g (71%), bp 108–109° (0.25–0.32 mm), $n^{20}D$ 1.5141. Calcd for $C_{12}H_{17}NO_2$: N, 6.76. Found: N, 6.74.

2-(3-Dimethylaminopropoxy)benzhydrol (13). A solution of 26.7 g (0.120 mole) of 2-(3-dimethylaminopropoxy)benzaldehyde in 70 ml of dry ether was slowly added with stirring to an ethereal solution of phenylmagnesium bromide, prepared from 12.6 g (0.52 g-atom) of Mg and 101 g (0.62 mole) of bromobenzene in 250 ml of dry ether. The mixture was refluxed for 4 hr in a dry atmosphere and left standing overnight at room temperature. The complex was decomposed with 245 ml of 3 *N* HCl, and the precipitate was recovered by filtration and washing with ether. The crude hydrochloride was dissolved in hot water, and the free base was liberated with 225 ml of 30% NaOH. The yield of crystalline product was 30.8 g (83%), mp 95–101°. The free base (10 g, 0.035 mole) was dissolved in methanol and treated with 41.3 ml of 0.85 *M* phosphoric acid. Recovery and recrystallization of the phosphate from methanol gave 8.8 g (66%), mp 167.5–169°, of **13**.

1-o-Hydroxyphenyl)diphenylmethanol.[17]—Salicylic acid methyl ester (50.7 g, 0.333 mole) in 100 ml of dry ether was added dropwise with stirring to an ethereal solution of phenylmagnesium bromide, prepared from 48.6 g (2.0 g-atoms) of Mg and 392 g (2.5 moles) of bromobenzene in 800 ml of dry ether, and the mixture refluxed for 2 hr. After standing overnight, the complex was decomposed by the careful addition with stirring of 600 ml of 10% NH_4Cl, and the suspension was filtered. The ether layer was separated, washed with water, and dried, and the solvent was removed. The solid residue was recrystallized from petroleum ether (62.7 g) then from 67% alcohol, yielding 58.2 g (62%), mp 141–142°, lit.[17] 142°) of the pure carbinol.

N,N-Dialkyl-3-(α-phenyl-*o*-tolyloxy)propylamines (Table III, **44–46**) were prepared from α-phenyl-*o*-cresol according to the general method described in the literature.[26]

N,N-Dialkyl-1-methyl-2-(α-phenyl-*o*-tolyloxy)ethylamines (Table III, **28–43**) were prepared by aminolysis of 1-(α-phenyl-*o*-tolyloxy)-2-propanol *p*-toluenesulfonate with the appropriate secondary amines according to the procedure described in detail for 2-(2-dimethylaminopropoxy)benzophenone hydrochloride (**1**).

Quaternary Ammonium Salts.—The quaternary ammonium salts listed in the Tables I–IV were prepared from their corresponding bases by reaction with the appropriate alkylating agents (alkyl halides, *p*-toluenesulfonyl esters) in acetone.

N-[2-(α-Phenyl-*o*-tolyloxy)ethyl]-α-methylphenethylamine Hydrochloride (48). A mixture of 10.8 g (0.04 mole) of α-phenyl-*o*-tolyloxyacetic acid ethyl ester (III)[19] and 5.41 g (0.04 mole) of α-methylphenethylamine was heated first at 140° for 1 hr, then at 200° for another 3 hr while allowing the ethanol formed to escape. The syrupy reaction product, consisting of crude *N*-(α-methylphenethyl)-(α-phenyl-*o*-tolyloxy)acetamide (IV), was dissolved in 50 ml of dry ether and slowly added with stirring to a suspension of 2.22 g (0.058 mole) of $LiAlH_4$ in 100 ml of dry ether. The mixture was refluxed for 12 hr and, after cooling, treated successively with 1.9 ml of water, 1.4 ml of 20% NaOH, and 6.4 ml of water. The stirring was continued for 1 hr, the hydroxide precipitate was filtered, the ether layer was dried ($MgSO_4$), and the solvent was removed. The residue (13.2 g) was distilled *in vacuo* yielding 9.8 g (72%) of a product boiling diffusely from 195–216° (0.15 mm). Conversion of the base to its hydrochloride with dry HCl in ether solution gave 6.07 g (56%), mp 156–163°, of **48**. After three recrystallizations from ethanol it melted at 163–167°.

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(25) T. M. Laakso and D. D. Reynolds, *J. Am. Chem. Soc.*, **73**, 3518 (1951).

N-[2-(α-Phenyl-*o*-tolyloxy)ethyl]-2-indanamine (49), bp 238–248° (0.36–0.50 mm), yield 51%, hydrochloride mp 172–173°, was prepared similarly from 2-aminoindane[26] and α-phenyl-*o*-tolyloxyacetic acid ethyl ester (III) *via* N-(2-indanyl)-(α-phenyl-*o*-tolyloxy)acetamide, mp 188–192.8°, yield 80%.

N-(2-indanyl)-(α-phenyl-*o*-tolyloxy)acetamide, mp 188–192.8°, yield 80%.

Anal. Calcd for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 79.78; H, 6.49; N, 4.04.

2-(α-Phenyl-*o*-tolyloxy)ethylamine.—A solution of 34.6 g (0.155 mole) of α-phenyl-*o*-tolyloxyacetonitrile[2h,27] in 200 ml of dry ether was slowly added to 11.7 g (0.308 mole) of $LiAlH_4$ suspended in 200 ml of dry ether with efficient stirring. The mixture was refluxed for 13 hr and, after cooling, treated with 10.1 ml of water, 7.5 ml of 30% NaOH, and finally 34.2 ml of water. After stirring for 1 hr, the precipitate was filtered and washed thoroughly with ether. The combined filtrate was dried ($MgSO_4$), the solvent was removed, and the residue (35.2 g) was distilled *in vacuo*. The fraction boiling at 149.5–162° (0.38–0.52 mm) was redistilled, yielding 28.2 g (80%) of V, bp 148.5–151° (0.48–0.52 mm).

Anal. Calcd for $C_{15}H_{17}NO$: C, 79.25; H, 7.54; N, 6.16. Found: C, 79.40; H, 7.75; N, 5.74.

N-[2-(α-Phenyl-*o*-tolyloxy)ethyl]-*p*-hydroxyphenylacetamide.—A mixture of 23.4 g (0.103 mole) of 2-(α-phenyl-*o*-tolyloxy)-ethylamine (V) and 17.1 g (0.103 mole) of *p*-hydroxyphenylacetic acid methyl ester[12] was heated to 140° for 30 min, then to 200° for 3 hr, while the alcohol formed during the reaction escaped. The syrupy residue was recrystallized from alcohol; mp 126.6–131.6°, yield 24.4 g (65%). A sample prepared for analysis melted at 131–132.8°.

Anal. Calcd for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88. Found: C, 76.40; H, 6.47; N, 3.82.

N-[2-(α-Phenyl-*o*-tolyloxy)ethyl]-*p*-hydroxyphenethylamine Hydrochloride (50).—In the upper part of a Soxhlet apparatus was placed 21.6 g (0.06 mole) of N-[2-(α-phenyl-*o*-tolyloxy)ethyl]-*p*-hydroxyphenylacetamide. In the bottom flask a suspension of 11.4 g (0.6 mole) of $LiAlH_4$ in 600 ml of dry ether was prepared, and the extraction continued under reflux until the amide had disappeared (162 hr). To the cooled, stirred suspension was added in succession 11.2 ml of water, 8.6 ml of 20% NaOH, and 58.4 ml of water. The precipitate was filtered and washed with ether and then suspended in 400 ml of 3 *N* HCl. Extraction with three 100-ml portions of chloroform followed by filtration of the insoluble product gave 6.64 g of the crude product, mp 150–155°. Recrystallization from ethanol yielded 4.28 g, mp 160.4–163.6°, which on further purification gave a final yield of 3.2 g (14%) of the analytically pure hydrochloride.

N-*p*-Tolylsulfonyl-N-[2-(*p*-tolylsulfonyloxy)ethyl]-α-methylphenethylamine (VI).—To a solution of 35.9 g (0.2 mole) of 2-(α-methylphenethylamino)ethanol in 240 ml of dry pyridine was added in small portions 85.4 g (0.5 mole) of *p*-tolylsulfonyl chloride with efficient stirring and cooling in an ice–salt mixture. The temperature was kept below 10°, then poured on 1 l. of ice–water, and the organic phase was extracted with two 500-ml portions of ether. The ether layer was decolorized and freed from black, tarry impurities by washing twice with 250-ml portions of 3 *N* HCl, separating, and drying ($MgSO_4$). Removal of the solvent left a yellow syrup (55.6 g, 57%) that resisted all attempts of crystallization. Elemental analysis (*Anal.* Calcd for $C_{25}H_{29}NO_5S_2$: N, 2.87; S, 13.15. Found: N, 2.64; S, 12.61.) showed the material to be sufficiently pure for use in the next step.

N-(α-Methylphenethyl)-N-[2-(*o*-benzoylphenoxy)ethyl]-*p*-toluenesulfonamide (VII).—2-Hydroxybenzophenone (21.2 g, 0.1 mole) was added to a solution of 2.46 g (0.1 g-atom) of Na in 50 ml of alcohol. To this, 52.1 g (0.1 mole) of VI dissolved in 100 ml alcohol was added, and the mixture was heated in an autoclave to 160° for 24 hr. The solvent was then removed *in vacuo*, and the residue was treated with 300 ml of 10% NaOH. Extraction of the oily precipitate with ether, and evaporation of the solution to dryness gave 50 g (91%) of a syrup that could not be crystallized.

Anal. Calcd for $C_{31}H_{31}NSO_4$: N, 2.73; S, 6.24. Found: N, 2.60; S, 6.09.

2-[2-(α-Methylphenethylamino)ethoxy]benzophenone Hydrochloride (51).—A mixture of 22.4 g (0.04 mole) of VII, 100 g of 36.7% dry HBr in glacial acetic acid, and 8.23 g (0.08 mole) of phenol was left standing at room temperature for 6 days. The dark solution was evaporated to dryness *in vacuo* and the residue was distributed between 200 ml of 15% NaOH and 200 ml of ether. The ether phase was washed with 15% NaOH and water, dried ($MgSO_4$), and treated with dry HCl. The resulting oily suspension was evaporated to dryness *in vacuo*, and the residue was recrystallized from acetonitrile; yield 10.8 g, mp 134–137°. Repeated recrystallizations from acetonitrile and 2-propanol gave the analytically pure hydrochloride **51** (7.23 g, 42%), mp 142.5–147°.

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(26) 2-Aminoindane was prepared in practically quantitative yield by a Schmidt reaction on indane-2-carboxylic acid chloride.

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Serotonin Inhibitors. III.[1] Compounds Related to 2′-(3-Dimethylaminopropylthio)cinnamanilide[2,3]

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The preparation of 24 compounds related to 2′-(3-dimethylaminopropylthio)cinnamanilide and their antiserotonin activity on the rat uterus are reported. Four of these compounds are highly active in this test procedure.

We have previously reported the synthesis and antiserotonin activity of I[3] and several of its analogs. Following the pharmacological studies of this series of compounds,[4–7] I was selected for evaluation in man.

Preliminary clinical studies have shown that I exhibits antidepressant action, is effective in the treatment of spastic bronchial disease and gastrointestinal hyperfunctioning states, and apparently possesses

(1) Previous paper: J. Krapcho, E. R. Spitzmiller, C. F. Turk, and J. Fried, *J. Med. Chem.*, **7**, 376 (1964).

(2) Presented in part before the Division of Medicinal Chemistry, 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965.

(3) Cinanserin is the approved generic name for 2′-(3-dimethylaminopropylthio)cinnamanilide (I).

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