inone (44). To a refluxing, stirred solution of 1-isopropyl-6-nitro-4-phenyl-2(1*H*)-quinazolinone (**43**, 12 g, 39 mmol) in EtOH (240 ml) and H_2O (80 ml) was added Fe filings (16 g). To this suspension was added dropwise a solution containing EtOH (80 ml), H_2O (20 ml), and 2 *N* HCl (4 ml). The refluxing was then continued for a further 3 hr. To the hot reaction mixture was added 2 *N* NaOH (4 ml) and the resulting suspension was then filtered hot (Celite). The filtrate was evaporated and the residue extracted with 2 *N* HCl-Et_2O. The acidic aqueous solution was made basic with concentrated NH_4OH (cooling) and extracted with CH_2Cl_2. The usual work-up of the organic phase gave a residue which was crystallized from EtOAc to yield **44**, 8.8 g (81%), mp 250–252°.

Reaction OO. 6-Dimethylamino-1-isopropyl-7-methyl-4-phenyl-2(1*H*)-quinazolinone (47). A mixture of 1-isopropyl-7-methyl-6-nitro-4-phenyl-2(1*H*)-quinazolinone (8 g, 25.8 mmol) and Raney Ni (*ca.* 8 g, wet with MeOH) in MeOH (200 ml) and dioxane (100 ml) containing HCHO (20 ml of a 37% solution in MeOH) was shaken under H_2 at room temperature and a pressure of 50 psi. After 2 hr no further uptake occurred and the mixture was filtered and the filtrate evaporated. The residue was crystallized from EtOAc to give **47**, 7.2 g (87%), mp 184–186°.

Reaction PP.[16] **1-Isopropyl-7-methyl-6-nitro-4-phenyl-2(1*H*)-quinazolinone.** To a cooled solution (0–5°) of 1-isopropyl-7-methyl-4-phenyl-2(1*H*)-quinazolinone (13.9 g, 50 mmol) in concentrated H_2SO_4 (50 ml) was added dropwise over 10 min a solution of KNO_3 (6.07 g, 60 mmol) in concentrated H_2SO_4 (15 ml). The resulting solution was allowed to warm to room temperature and then stirred for a further 2 hr. It was next poured onto ice and the solid obtained was filtered off. After drying the crude product was crystallized from EtOAc to give 11.7 g (72%), mp 192–194°.

Reactions SS and TT. 7-Diethylaminomethyl-1-isopropyl-4-phenyl-2(1*H*)-quinazolinone (48). To a solution of 1-isopropyl-7-methyl-4-phenyl-2(1*H*)-quinazolinone (**27**, 2.8 g, 10 mmol) in CCl_4 (250 ml) was added NBS (2 g, 20 mmol) and benzoyl peroxide (250 mg). The mixture was stirred and refluxed for 6 hr. It was then cooled, filtered, washed (H_2O), and dried (Na_2SO_4). A sample evaporated to dryness gave a residue which was shown by nmr to consist of 70% of the product, 7-bromomethyl-1-isopropyl-4-phenyl-2(1*H*)-quinazolinone, and 30% of unreacted starting material. To the bulk of the solution obtained above was added Et_2NH (5 ml). A precipitate rapidly formed and after 1 hr at room temperature this was filtered off. The filtrate was extracted with 2 *N* HCl and the acidic aqueous extract basified with 2 *N* NaOH. Extraction with Et_2O and the usual work-up gave the product, **48** (2.1 g, 60%), as a brown oil. The maleate salt was prepared and crystallized from Me_2CO, mp 174–176°.

Supplementary Material Available. A listing of the new intermediates and their physical constants will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 20× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $4.00 for photocopy or $3.00 for microfiche, referring to code number JMED-73-1237.

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β-Adrenoceptor Blocking Agents. 1. Cardioselective 1-Aryloxy-3-(aryloxyalkylamino)propan-2-ols

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A series of 1-aryloxy-3-(aryloxyalkylamino)propan-2-ols was synthesized and investigated for cardioselective β-adrenoceptor blocking activity. Several compounds exhibited potency comparable with that of propanolol, both *in vitro* and *in vivo*, and showed selectivity for cardiac *vs.* tracheal receptors. The cardiac depressant activity of the compounds was generally much less marked than that exhibited by propranolol. Compound **3** (tolamolol) has been shown to be a cardiac-selective β-adrenoceptor blocking agent in man.

Many β-adrenergic blocking agents have been described which antagonize the effects of catecholamines at β-adrenoceptors irrespective of whether the latter are β-1 or β-2 as classified by Lands and coworkers.[1] The discovery of practolol[2] showed that it is possible to develop blockers specific for the β-1 adrenoceptors and this prompted us to seek more potent cardioselective agents. We describe here the synthesis and biological activity of a new series of β-adrenoceptor blocking agents, some of which were more potent than practolol and exhibited comparable selectivity for myocardial receptors.

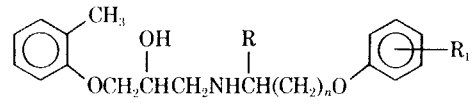
The compound which ultimately proved to be of greatest interest was 4-[2-(2-hydroxy-3-*o*-tolyloxypropylamino)ethoxy]benzamide hydrochloride (**3**, tolamolol,† Table I) a potent, orally active agent possessing selectivity for myocardial (β-1) *vs.* peripheral vascular (β-2) receptors in man.[3] In the dog heart-lung‡ and cat papillary muscle (Table I) preparations, **3** was appreciably less cardiac depressant than propranolol. These indications of negligible myocardial depression have been borne out in human studies.§ This compound is currently undergoing extensive clinical evaluation as a potential antianginal-antiarrhythmic agent.

Chemistry. The majority of the compounds listed in Tables I–III were synthesized *via* the two general routes illustrated in Scheme I. The epoxypropane derivatives **70** were obtained from the appropriate phenol and epichlorohydrin in essentially the manner described by Schwender.[4] The amines **71** and **72** were synthesized by catalytic

† British Pharmacopoeia Commission approved name.

‡ P. C. Sholfield, unpublished work, 1970.
§ A. R. Lorimer, *et al.*, to be published.

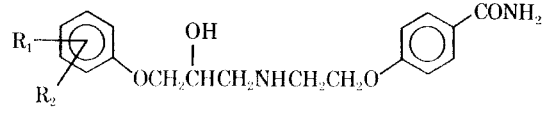
Table I



No.	n	R	R_1	Salt or base	Mp, °C	Analyses	Mol formula	Crystn solvent	Route	Adenylyl cyclase (rat) ID_{50} (heart), M	Adenylyl cyclase (rat) ID_{50} (lung), M	Select. ratio, heart/lung	Cat papillary muscle, ED_{50}, μg/ml	% inhibition of isoproterenol tachycardia in conscious dog: 2 hr after po drug (2 mg/kg)	% inhibition of isoproterenol tachycardia in conscious dog: 45 min after iv drug (0.25 mg/kg)
1	1	H	2-OCH_3	Maleate	103–105	C, H, N	$C_{19}H_{25}NO_4 \cdot C_4H_4O_4$	EtOH	A	3.2×10^{-6}					
2	1	H	2-$CONH_2$	Base	108–109	C, H, N	$C_{19}H_{24}N_2O_4$	C_6H_6	B_1	1.9×10^{-6}	1.5×10^{-6}	0.8[a]	>200[a]	46[b]	64[b]
3	1	H	4-$CONH_2$	Base	157–159	C, H, N	$C_{19}H_{24}N_2O_4$	EtOH–H_2O	B_1	1.2×10^{-6}	3.6×10^{-6}	3.0[c]	84[c]	51[b]	60[d]
3a	1	H	4-$CONH_2$	Base	138–142		$C_{19}H_{24}N_2O_4$			3.7×10^{-7}					
3b	1	H	4-$CONH_2$	Base	138–140		$C_{19}H_{24}N_2O_4$			7.6×10^{-6}					
4	1	H	3-$CONH_2$	HCl	191–195	C, H	$C_{19}H_{24}N_2O_4 \cdot HCl$	EtOH	B_2	4.2×10^{-6}	2.3×10^{-6}	0.6[a]	188[a]		
5	1	H	4-$CONHCH_3$	Oxalate	181–184	N	$C_{20}H_{26}N_2O_4 \cdot C_2H_2O_4$	H_2O	B_3	1.4×10^{-6}	2.4×10^{-6}	1.7[a]	62[b]	62[b]	65[b]
6	1	H	4-$CON(CH_3)_2$	Oxalate	124–127	C, H, N	$C_{21}H_{28}N_2O_4 \cdot C_2H_2O_4$	H_2O	B_3	4.8×10^{-6}	5.6×10^{-6}	1.2[a]	42[b]	41[b]	50[b]
7	1	H	4-CONHPh	Base	138–139	C, H, N	$C_{25}H_{28}N_2O_4$	EtOAc	B_3	7.5×10^{-7}	7.5×10^{-7}	1.0[a]		14[b]	
8	1	H	4-$CONHNH_2$	Base	91–92	C, H, N	$C_{19}H_{25}N_3O_4$	EtOH		2.2×10^{-6}	3.6×10^{-6}	1.6[a]		55[b]	54[a]
9	1	H	4-$CONHN(CH_3)_2$	Base	120–122	C, H, N	$C_{21}H_{29}N_3O_4$	EtOH–H_2O	B_3	1.1×10^{-5}	3.5×10^{-5}	3.2[a]	128[a]		28[b]
10	1	H	4-COOEt	HCl	138–139	C, H, N	$C_{21}H_{27}NO_5 \cdot HCl$	EtOH		1.4×10^{-6}					11[b]
11	1	H	4-SO_2NH_2	Base	123–125	C, H, N	$C_{18}H_{24}N_2O_5S$	EtOAc	A	7.8×10^{-6}	2.3×10^{-6}	0.3[a]		25[b]	52[b]
12	1	H	4-NO_2	Oxalate	176–181	C, H, N	$C_{18}H_{22}N_2O_5 \cdot C_2H_2O_4$	H_2O	B_3	3.0×10^{-6}			11[b]		
13	1	H	4-CH_2CONH_2	Base	129–130	C, H, N	$C_{20}H_{26}N_2O_4$	EtOAc	B_3	3.1×10^{-6}	6.4×10^{-6}	2.1[a]	239[a]		25[b]
14	2	H	4-$CONH_2$	Base	118–119	C, H, N	$C_{20}H_{26}N_2O_4$	EtOAc	B_1	7.5×10^{-6}	2.6×10^{-6}	0.4[a]	192[a]		37[b]
15	1	CH_3	4-$CONH_2$	Base	113–114.5	N	$C_{20}H_{26}N_2O_4$	MeOH–H_2O	C	$<1 \times 10^{-6}$				48[b]	72[b]
Propranolol										1.3×10^{-6}	2.0×10^{-7}	0.2[b]	9[d]	78[b]	74[d]
Practolol										1.1×10^{-4}	1.6×10^{-3}	15[b]	228[b]	64[b,e]	38[b]

Number of determinations for test procedures: [a] $n = 1$; [b] $n = 2$; [c] $n = 3$; [d] $n = 4$. [e] At a dose of 16 mg/kg.

Table II



No.	R_1	R_2	Salt or base	Mp, °C	Analyses	Mol formula	Crystn solvent	Route	Adenylyl cyclase (rat) ID_{50} (heart), M	Adenylyl cyclase (rat) ID_{50} (lung), M	Select. ratio, heart/lung	Cat papillary muscle, ED_{50}, μg/ml	% inhibition of isoproterenol tachycardia in conscious dog: 2 hr after po drug (2 mg/kg)	% inhibition of isoproterenol tachycardia in conscious dog: 45 min after iv drug (0.25 mg/kg)
16	2-Cl	H	HCl	234–238	C, H, N	$C_{18}H_{21}N_2O_4 \cdot HCl$	EtOH–H_2O	B_2	1.4×10^{-6}	6×10^{-6}	4.3[a]	97[a]	58[b]	38[b]
17	3-CH_3	H	Base	124–126	C, H, N	$C_{19}H_{24}N_2O_4$	EtOH	A	2.0×10^{-6}	1.6×10^{-5}	8.0[a]	171[b]	44[b]	65[b]

18	4-CH_3	H	Base	181–183	C, H, N	$C_{19}H_{24}N_2O_4$	EtOH–H_2O	A	1.7×10^{-5}	2.6×10^{-5}	1.5[a]			
19	2-OCH_3	H	Base	108–112	C, H, N	$C_{19}H_{24}N_2O_5$	EtOH–H_2O	A	1.3×10^{-6}	3.4×10^{-6}	2.6[a]	228[a]	74[b]	70[b]
20	3-OCH_3	H	Base	103–106	C, H, N	$C_{19}H_{24}N_2O_5$	EtOH	A	5.8×10^{-6}	3.8×10^{-6}	0.8[a]	64[b]	67[b]	66[b]
21	4-OCH_3	H	Base	165–167	C, H, N	$C_{19}H_{24}N_2O_5$	EtOH	A	7.4×10^{-5}	3.0×10^{-4}	4.1[a]			
22	3-Cl	H	Base	120–123	C, H, N	$C_{18}H_{21}ClN_2O_4$	EtOH	A	2.5×10^{-6}	1.4×10^{-5}	5.6[a]		49[b]	50[b]
23	2-Ph	H	Base	124–125	C, H, N	$C_{24}H_{26}N_2O_4$	EtOAc	A	1.2×10^{-6}	8.3×10^{-7}	0.7[a]		63[b]	61[b]
24	H	H	Base	135–137	C, H, N	$C_{18}H_{22}N_2O_4$	*i*-PrOH	A	1.3×10^{-6}	2.3×10^{-5}	17.5[a]			32[b]
25	2-CH_3	4-Cl	Base	136–140	C, H, N	$C_{19}H_{25}ClN_2O_4$	EtOH	A	2.7×10^{-5}	7.2×10^{-6}	0.3[a]			0[b]
26	4-NHCOCH_3	H	HCl	265–267	C, H, N	$C_{20}H_{25}N_3O_5 \cdot HCl$	H_2O	B_3	8.7×10^{-5}	3.4×10^{-4}	3.9[a]	>256[a]		33[b]
27	4-NHCOCH_3	2-CH_3	Base	181–182	C, H, N	$C_{21}H_{27}N_3O_5$	EtOH–H_2O	A	2.1×10^{-5}	4.1×10^{-4}	19.5[a]	229[b]	30[d]	45[d]
28	4-NHCOCH_3	3-CH_3	Base	168–171	C, H, N	$C_{21}H_{27}N_3O_5$	EtOH	A	2.7×10^{-4}	1.7×10^{-3}	6.3[a]			17[b]
29	4-CH_2NHCOCH_3	2-OCH_3	Base	162–164	C, H, N	$C_{22}H_{29}N_3O_6$	MeOH	A	4.0×10^{-5}	2.3×10^{-4}	5.8[a]			
30	3-NHCOCH_3	H	Base	164–165	C, H, N	$C_{20}H_{25}N_3O_5$	EtOH–H_2O		9.8×10^{-6}	1.4×10^{-4}	1.5[a]			
31	4-NHCOC$_2$H$_5$	H	Base	187–189	C, H, N	$C_{21}H_{27}N_3O_5$	MeOH	A	2.2×10^{-5}	4.3×10^{-4}	19.5[b]	18[b]		
32	4-NHCOOC$_2$H$_5$	H	Base	176–178	C, H, N	$C_{21}H_{27}N_3O_6$	EtOH–H_2O	A	7.0×10^{-5}	9.2×10^{-4}	13.1[a]			
33	4-CH_2NHCOCH_3	H	Base	177	C, H, N	$C_{21}H_{27}N_3O_5$	MeOH	A	1.8×10^{-5}	1.0×10^{-4}	5.6[a]		46[b]	44[b]
34	3-CH_2NHCOCH_3	H	Base	142–144	C, H, N	$C_{21}H_{27}N_3O_5$	EtOH–H_2O	A	3.9×10^{-5}	$>1 \times 10^{-4}$	>5[a]			
35	2-$CONH_2$	H	Base	178–180	C, H, N	$C_{19}H_{23}N_3O_5$	EtOH–H_2O	A	5.5×10^{-5}	3.6×10^{-5}	0.6[a]			37[b]
36	4-CH_2CONHCH_3	H	Base	182–184	C, H, N	$C_{21}H_{27}N_3O_5$	EtOH–H_2O	A	4.0×10^{-5}	1.2×10^{-4}	3.0[a]			

Number of determinations for test procedures: [a] $n = 1$; [b] $n = 2$; [c] $n = 3$; [d] $n = 4$.

reduction of the azido derivatives **73** and amination[5] of chlorohydrins **74**, respectively. Azides **73** were prepared by the action of sodium azide on β-haloethoxybenzenes **75** *via* a method similar to that described by Smith and Brown[6] for β-azidoethylbenzene.

The remaining compounds were synthesized using the routes outlined in Scheme II. Compounds **30**, **51**, and **63** were prepared by acylation of the appropriate amines **76**, **77**, and **78**, which in turn were obtained by reduction of the corresponding nitro derivatives **79**, **80**, and **81**. The ester **10** (obtained from **3** *via* the nitrosocarboxylic acid **82**) was converted to the hydrazide **8** by the action of hydrazine hydrate. The branched compounds **15** and **69** were prepared by reduction of the imines **83**, obtained from the reaction of amines **72** with ketones **84**. Ketones **84** were synthesized from chloroacetone and appropriate phenols using the method of Hurd and Perletz.[7]

Racemic **3** was resolved using *d*- and *l*-mandelic acids. The mandelate salts were crystallized to constant rotation and converted to the enantiomeric free bases **3a** and **3b**, which possessed approximately equal and opposite optical rotations.

Pharmacology. β-Adrenoceptor blocking potency and selectivity were estimated *in vitro* by the antagonism of isoproterenol-stimulated adenylyl cyclase preparations obtained from rat heart and lung homogenates, as described by Burges and Blackburn.[8] Results are quoted (Tables I–III) as the molar concentrations required to give 50% inhibition of the isoproterenol response (ID_{50} values). The heart/lung enzyme selectivity ratio is quoted as ID_{50} (lung)/ID_{50} (heart).

β-Blocking activity was determined in conscious dogs (Tables I–III) by measuring the percentage inhibition of isoproterenol-induced tachycardia following intravenous and oral administration of the compound.[9]

Cardiac-depressant activity was estimated *in vitro* using electrically stimulated cat right ventricular papillary muscle. The results are recorded (Tables I–III) as the concentration of compound required to produce 50% depression of contractile amplitude.

Discussion

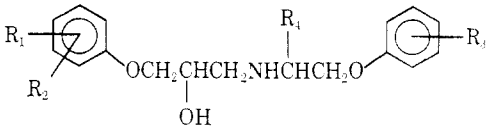
Hitherto, isopropyl and *tert*-butyl have been the most commonly employed N substituents in β-adrenoceptor blocking agents of the phenylethanolamine and phenoxypropanolamine type (*e.g.*, sotalol and propranolol). In this investigation an initial objective was to evaluate new types of side chain, with a view to the discovery of potent, novel agents exerting a selective β-blocking action on the heart.

A high level of β-blocking activity was displayed *in vitro* by the phenoxyethyl derivative **1**, but only weak, short-lived activity was observed *in vivo* (anesthetized rat and cat). The 2-carbamoyl analog **2** showed greatly improved potency and duration *in vivo* (conscious dog, Table I), but even more interesting was the 4-carbamoyl isomer **3**, which proved to be a highly potent β-blocking agent with a good duration of activity. Furthermore, studies both *in vitro* and *in vivo* have revealed selectivity for cardiac β-receptors in the rat (Table I), guinea pig,= and dog.** In human volunteer studies, **3** showed selectivity for blockade of cardiac *vs.* peripheral vascular responses to isoproterenol, being approximately equiselective with practolol in this test.[3] The cardiac depressant activity of **3** was *ca.* nine times less than that of propranolol *in vitro* (cat papillary muscle, Table I). In the dog heart–lung prepara-

= K. R. Adam, J. R. C. Baird, R. A. Burges, and J. Linell, paper in preparation.

** S. M. Boyles, paper in preparation.

Table III



No.	R_1	R_2	R_3	R_4	Salt or base	Mp, °C	Analyses
37	4-$NHCOCH_3$	H	4-$NHCOCH_3$	H	Base	198–200	N
38	4-$CH_2NHCOCH_3$	H	4-$NHCOCH_3$	H	Base	176–177	C, H, N
39	4-$NHCO(CH_2)_2CH_3$	H	4-$NHCOCH_3$	H	Base	206–207	C, H, N
40	4-$NHCONH_2$	H	4-$NHCOCH_3$	H	Base	185–187	C, H, N
41	4-$NHCOCH_3$	3-CH_3	4-$NHCOCH_3$	H	Base	144–146	C, H, N
42	4-CH_2CONH_2	H	4-$NHCOCH_3$	H	Base	190–192	C, H, N
43	4-$NHCOCH(CH_3)_2$	H	4-$NHCOCH_3$	H	Base	219–220	C, N
44	4-$NHCOOC_2H_5$	H	4-$NHCOCH_3$	H	Base	166–168	C, H, N
45	4-$N(CH_3)COCH_3$	H	4-$NHCOCH_3$	H	Base hydrate	77–80	C, H, N
46	4-$(CH_2)_2NHCOCH_3$	H	4-$NHCOCH_3$	H	Base	174–175	C, H, N
47	4-$NHCOOCH_3$	H	4-$NHCOCH_3$	H	Base	195–197	C, H, N
48	4-$NHCOCH_3$	H	4-$NHCOC_2H_5$	H	Base	204–205	C, H, N
49	4-$NHCOCH_3$	H	4-$NHCOCH_3$; 3-CH_3	H	Base	143–144	C, H, N
50	4-$CH_2NHCOC_2H_5$	H	4-$NHCOCH_3$	H	Base	171–173	C, H, N
51	3-$NHCOCH_3$	H	4-$NHCOCH_3$	H	HCl	237–239	C, H, N
52	4-NHCHO	H	4-$NHCOCH_3$	H	Base	153–155	C, H
53	2-$NHCOCH_3$	H	4-$NHCOCH_3$	H	Base	159–60	C, H, N
54	4-$CH_2NHCOCH_3$	2-CH_3	4-$NHCOCH_3$	H	Base hydrate	104–106	C, H, N
55	4-$NHCOCH_3$	H	4-CH_2CONH_2	H	Base	196–197	C, H
56	4-$CH_2NHCOCH_3$	2-CH_3O	4-$NHCOCH_3$	H	Base	150–152	N
57	4-$NHCOCH_3$	H	4-$CH_2NHCOCH_3$	H	Base	171–173	C, H, N
58	4-$CH_2NHCOCH_3$	H	4-$CH_2NHCOCH_3$	H	Base	187–188	C, H, N
59	3-$CONH_2$	H	4-$NHCOCH_3$	H	Base	138–141	C, H, N
60	4-$NHCOCH_3$	2-Cl	4-$NHCOCH_3$	H	Base	186–188	C, H, N
61	4-$NHCOCH_3$	H	2-$NHCOCH_3$	H	Base	152–154	C, H
62	4-$NHCOCH_3$	H	4-NHCHO	H	Base	154–156	C, H, N
63	4-$NHCOCH{=}CH_2$	H	4-$NHCOCH_3$	H	HCl	241–243	C, H, N
64	4-$NHCOCH_3$	H	4-$NHCOOCH_3$	H	Base	164–166	C, H, N
65	4-$NHCOCH_3$	H	4-SO_2NH_2	H	Base	158–160	C, H, N
66	4-$NHCOCH_3$	2-CH_3	4-$NHCOCH_3$	H	Base	178–180	C, H, N
67	4-$NHCOC_2H_5$	H	4-$NHCOCH_3$	H	Base	203	C, H, N
68	4-$NHCOCH_3$	2-$CHCH{=}CH_2$	4-$NHCOCH_3$	H	Base	147–149	N
69	4-$NHCOCH_3$	H	4-$NHCOCH_3$	CH_3	Base	165–167	C, H, N

Number of determinations for test procedures: [a]$n = 1$; [b]$n = 2$; [c]$n = 3$; [d]$n = 4$.

tion, 3 was five times less active than propranolol in causing a 25% reduction in cardiac contractility.‡ Only minor decreases in myocardial contractility have been demonstrated in man following intravenous administration of 3.§

Structure–activity investigations revealed that the presence of a 4 substituent in the phenoxypropanolamine ring invariably led to decreased potency. This point is illustrated by comparison of **3** with **17** and **18**; **19** with **20** and **21**; and **3** with **25** and **27**. Branching in the side chain, as in **15** and **69**, did not lead to a significantly improved activity profile. Lengthening the side chain to propyl, as in **14**, led to reductions in selectivity and in activity in the conscious dog, compared with **3**. Close analogs of **3** which showed appreciable cardiac selectivity included **17** and **24**. Compound **24** exhibited excessive intrinsic sympathomimetic activity and was of no further interest. The 3-meth-

Scheme I

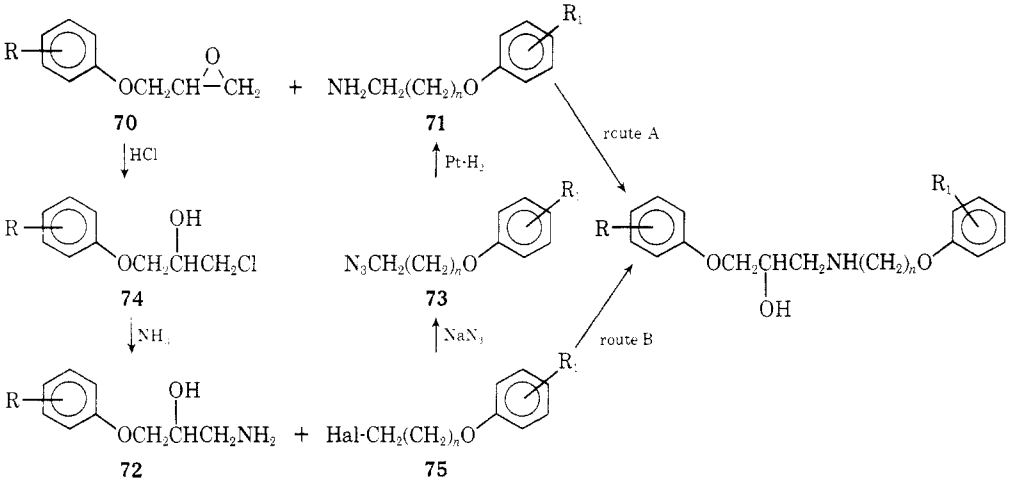


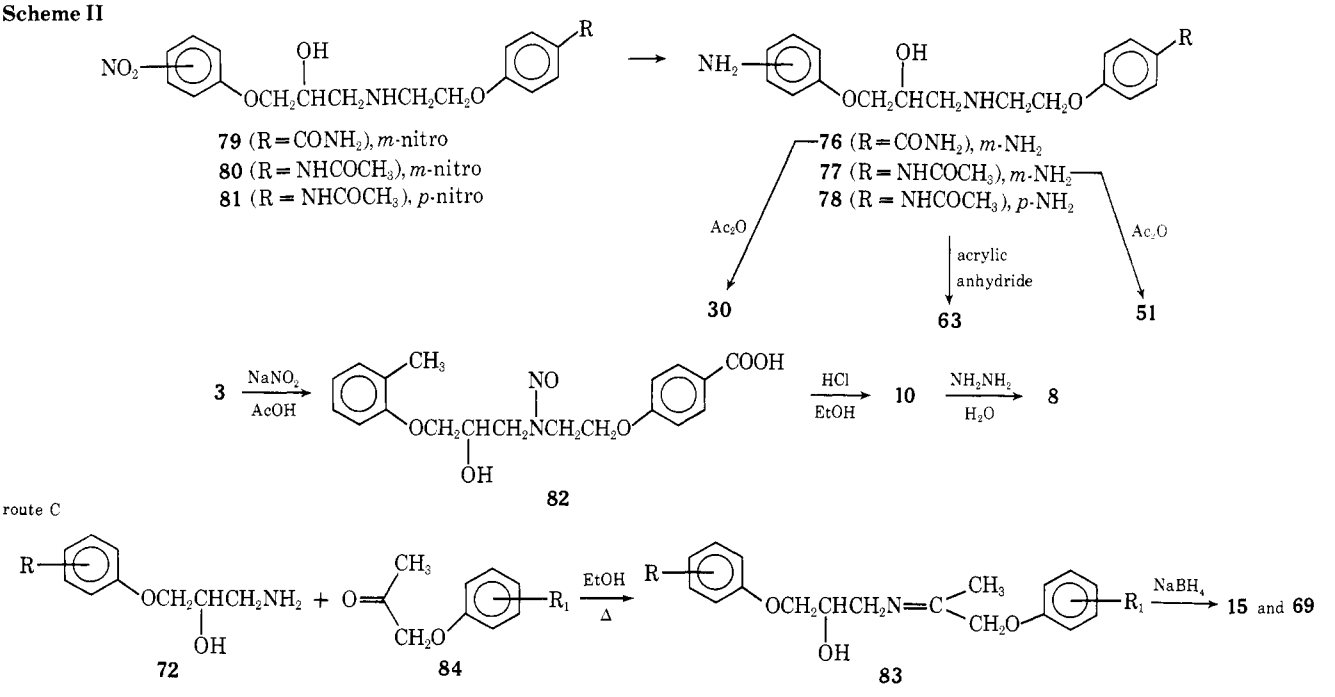
Table III (*Continued*)

Mol formula	Crystn solvent	Route	Adenylyl cyclase (rat) ID$_{50}$ (heart), *M*	Adenylyl cyclase (rat) ID$_{50}$ (lung), *M*	Select. ratio	Cat papillary muscle, ED$_{50}$, μg/ml	% inhibition of isoproterenol tachycardia in conscious dog: 2 hr after po drug (2 mg/kg)	% inhibition of isoproterenol tachycardia in conscious dog: 45 min after iv drug (0.25 mg/kg)
$C_{21}H_{27}N_3O_5$	EtOH	B_3	3.3×10^{-5}	2.0×10^{-3}	60[a]	>256[a]	51[b]	62[b]
$C_{22}H_{29}N_3O_5$	EtOH–H_2O	A	8.8×10^{-6}	3.3×10^{-4}	38[a]	99[d]	43[b]	65[b]
$C_{23}H_{31}N_3O_5$	EtOH–H_2O	A	1.7×10^{-5}	2.0×10^{-4}	12[a]			32[b]
$C_{20}H_{26}N_4O_5$	EtOH–H_2O	A	1.8×10^{-4}	4.3×10^{-4}	2.4[a]	250[a]		
$C_{22}H_{29}N_3O_5$	EtOH–H_2O	A	1.6×10^{-4}	1.5×10^{-3}	9.4[a]	205[a]		
$C_{21}H_{27}N_3O_5$	EtOH–H_2O	A	2.3×10^{-5}	9.1×10^{-4}	40[a]	256[a]	37[b]	
$C_{23}H_{31}N_3O_5$	EtOH–H_2O	A	2.6×10^{-4}	1.5×10^{-3}	5.8[a]			8[b]
$C_{22}H_{29}N_3O_6$	EtOH–H_2O	A	2.1×10^{-5}	5.1×10^{-4}	24[a]		20[b]	42[b]
$C_{22}H_{29}N_3O_5 \cdot H_2O$	Me_2CO	A	5.0×10^{-5}	5.3×10^{-4}	11[a]			28[b]
$C_{23}H_{31}N_3O_5$	EtOH	A	3.0×10^{-5}	6.5×10^{-4}	22[a]		37[b]	40[b]
$C_{21}H_{27}N_3O_6$		A	1.4×10^{-4}	3.5×10^{-3}	25[a]			27[b]
$C_{22}H_{29}N_3O_5$	DMA–H_2O	B_3	1.8×10^{-4}	8.9×10^{-4}	5.0[a]			32[b]
$C_{22}H_{29}N_3O_5$	EtOH–H_2O	B_3	1.8×10^{-4}	$>1 \times 10^{-3}$	>10[a]			4[b]
$C_{23}H_{31}N_3O_5$	EtOH–H_2O	A	2.7×10^{-5}	2.0×10^{-4}	7.5[a]			
$C_{21}H_{27}N_3O_5 \cdot HCl$	H_2O		1.0×10^{-4}		~3[a]			42[b]
$C_{20}H_{25}N_3O_5$	EtOH	A	4.1×10^{-5}	6.5×10^{-4}	16[a]		39[b]	27[b]
$C_{21}H_{27}N_3O_5$	EtOH	A	2.3×10^{-4}	2.4×10^{-4}	1.0[a]			21[b]
$C_{23}H_{31}N_3O_5 \cdot H_2O$	MeOH	A	8.7×10^{-6}	1.9×10^{-4}	22[a]		19[b]	52[b]
$C_{21}H_{27}N_3O_5$	MeOH–H_2O	A	9.2×10^{-5}	3.0×10^{-4}	3.2[a]		43[b]	50[b]
$C_{23}H_{31}N_3O_6$	EtOAc–EtOH	A	5.0×10^{-5}	2.8×10^{-4}	5.6[a]		7[b]	38[b]
$C_{22}H_{29}N_3O_5$	EtOH–H_2O	A	5.2×10^{-4}	1.2×10^{-3}	2.3[a]			2[b]
$C_{23}H_{31}N_3O_5$	EtOH–H_2O	A	1.2×10^{-4}	2.7×10^{-4}	2.2[a]			39[b]
$C_{20}H_{25}N_3O_5$	BuOH	A	1.2×10^{-4}	2.7×10^{-4}	2.2[a]			17[b]
$C_{21}H_{26}ClN_3O_5$	EtOH–H_2O	A	8.5×10^{-6}	1.3×10^{-4}	15[a]			47[b]
$C_{21}H_{27}N_3O_5$	*i*-PrOH	A	1.5×10^{-3}	5.4×10^{-4}	0.4[a]			+8[b]
$C_{20}H_{25}N_3O_5$	EtOH	A	1.3×10^{-5}	6.3×10^{-4}	48[a]			36[b]
$C_{22}H_{27}N_3O_5 \cdot HCl$	H_2O		2.9×10^{-5}	2.7×10^{-4}	9.3[a]			16[b]
$C_{21}H_{27}N_3O_6$	EtOH	A	1.8×10^{-4}	1.2×10^{-3}	6.7[a]			17[b]
$C_{19}H_{25}N_3O_6S$	EtOH	A	3.8×10^{-4}	1.2×10^{-4}	0.3[a]			13[b]
$C_{22}H_{29}N_3O_5$	EtOH	A	1.7×10^{-5}	2.8×10^{-3}	165[d]	189	45[d]	47[b]
$C_{22}H_{29}N_3O_5$	EtOH–H_2O	A	3.4×10^{-5}	1.6×10^{-3}	47[a]	124	22[b]	
$C_{24}H_{31}N_3O_5$	EtOAc–EtOH	A	5.6×10^{-6}	1.4×10^{-4}	28[a]		33[b]	57[b]
$C_{22}H_{29}N_3O_5$	EtOH	C	2.4×10^{-5}	1.4×10^{-3}	59[a]	208	21[b]	44[b]

yl derivative **17** displayed an activity profile almost comparable with **3** but was less efficacious following oral administration in the conscious dog.

Greatest selectivity was found in compounds possessing an amidic 4 substituent in the aromatic nucleus of the phenoxypropanolamine moiety, *e.g.*, **37, 42, 44, 62, 66,**

Scheme II



and **67**. Unfortunately, however, as noted earlier, substitution at this position also resulted in decreased potency, usually by *ca.* tenfold compared with **3**. Only minor changes in potency and myocardial selectivity were observed when the amidic function was separated from the ring by one and two methylene units, as in **38** and **46**. Within a particular series, positional changes in a ring substituent often resulted in marked changes in activity. For example, considerable differences in potency and selectivity *in vitro* occurred between **37**, **51**, **53**, and **61**.

The desired combination of selectivity for cardiac β-receptors and oral efficacy proved to be particularly elusive. Compound **3** was finally selected for progression to clinical evaluation from several potential candidates, *e.g.*, **27**, **38**, and **66**, on the basis of a good overall activity profile and lack of toxicity in early trials.

Speculation concerning the role of the side chain in **3** suggested that interactions of the type postulated by Bloom and Goldman[10] in their receptor model for β-receptor stimulation might be important. Thus, the phenoxyethyl N substituent may be visualized as interacting with the adenine portion of the substrate ATP and the carbamoyl substituent contributing to the interaction, possibly through H bonding. Some support for this speculation was derived from the results of a Hansch analysis in a series of α-branched compounds closely related to and including **15**, which suggested that H bonding might contribute significantly to potency in the 4-carbamoyl series.†† It is difficult, however, to reconcile such speculation with more recent models[11] in which β-receptor stimulation is regarded as an allosteric interaction involving the β-receptor on the outside of the membrane and a catalytic site promoting the conversion of ATP to cAMP on the inside.

The levo enantiomer **3a** of tolamolol was considerably more potent than the dextro enantiomer **3b** (rat adenylyl cyclase, Table I), in keeping with published results on other β-adrenoceptor blocking agents, for example, propranolol and alprenolol.[12]

Experimental Section

Chemistry. All melting points are uncorrected and were obtained using an Electrothermal capillary melting point apparatus. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

General Methods. Route A (Scheme I). 3-Aryloxy-1,2-epoxypropanes **70** (1 mol) and 1-amino-2-aryloxyethanes **71** (1 mol) were dissolved in the minimum quantity of EtOH and allowed to stand overnight. If product crystallized out it was recovered by filtration and recrystallized from the appropriate solvent; otherwise the EtOH was evaporated *in vacuo* to obtain the product, which was then recrystallized. Oily products were dissolved in EtOH–Et_2O and precipitated as the salt by addition of ethereal oxalic acid or HCl. The salts were purified by recrystallization.

Route B (Method 1). 3-Aryloxyalkyl halides **75** (1 mol), aryloxypropanolamines **72** (1 mol), $NaHCO_3$ (1 mol), and EtOH were refluxed together for 16 hr. The mixture was cooled, filtered, and evaporated *in vacuo* to give a crude product which was either recrystallized from the appropriate solvent or converted to the salt as in method A.

Route B (Method 2). 3-Aryloxyalkyl halides **75** (1 mol) and aryloxypropanolamines **72** (1 mol) were refluxed together in xylene for 6 hr. During this time product hydrohalide was precipitated and after cooling was collected by filtration or decantation. Subsequent recrystallization gave the pure salt.

Route B (Method 3). 1-Amino-3-aryloxypropan-2-ols **72** (3 mol) and aryloxyalkyl halides **75** (1 mol) were fused together at 140° for 2 hr. The reaction mixture was cooled and dissolved in $CHCl_3$ followed by cooling at 4° for several hours. Occasionally product hydrochloride precipitated during this time and was recrystallized from the appropriate solvents. Alternatively, the mixture was rebasified (Na_2CO_3) and the $CHCl_3$ extract was dried and evaporated to give a mixture of **72** and product. Excess **72** could be partially removed by extraction with ether or by distillation *in vacuo* and the residual product was then purified by crystallization of the base or the oxalate salt (prepared as in method A).

Route C (Scheme II). Aryloxyacetones **84** (1 mol), aryloxypropanolamines **72** (1 mol), and EtOH were refluxed together for 2 hr. The resultant imines **83** were reduced by the addition of excess $NaBH_4$ at 20°. After stirring for 30 min excess $NaBH_4$ was destroyed by the addition of AcOH, followed by rebasification to pH 10 (10% Na_2CO_3) and extraction with $CHCl_3$. Evaporation of the extract followed by recrystallization from the appropriate solvent gave the pure product. Alternatively, the product was purified as the salt as in method A.

4-[2-[2-Hydroxy-3-(4-acryloylaminophenoxy)propylamino]-ethoxy]acetanilide (63). The amino derivative **78** (4 g, 0.011 mol) was dissolved in dilute HCl and the pH adjusted to 4. Acryloyl chloride (1 g, 0.011 mol) was added slowly while the pH was maintained at 4 by the addition of 10% Na_2CO_3. The mixture was stirred at pH 4 for 3 hr. The hydrochloride of **63** was recovered by filtration and recrystallized from water (1 g, 20%), mp 241–243° (C, H, N).

The acetamido derivatives **30** and **51** were prepared in a similar manner from the amino compounds **76** and **77** and acetic anhydride.

4-[2-[*N*-[3-(2-Methylphenoxy)-2-hydroxypropyl]-*N*-nitroso-amino]ethoxy]benzoic Acid (82). Compound **3** (5 g, 0.015 mol) in AcOH (400 ml) and H_2O (200 ml) was treated portionwise with $NaNO_2$ (40 g, 0.58 mol) in H_2O (200 ml). The mixture was then cooled, while concentrated HCl (36 ml) was added slowly, and then allowed to stand for 12 hr. Water (3 vol) was added and the mixture was extracted with EtOAc. The extract was washed (H_2O), dried ($MgSO_4$), and evaporated to dryness *in vacuo* to give the crude product as an oily paste (3 g, 54%). Recrystallization from MeOH gave a crystalline product, mp 127–129°.

4-[2-[2-Hydroxy-3-(3-nitrophenoxy)propylamino]ethoxy]-benzamide (79). 3-(3-Nitrophenoxy)-1,2-epoxypropane (25 g, 0.128 mol) and 4-(2-aminoethoxy)benzamide (23 g, 0.128 mol) were dissolved in EtOH and allowed to stand 24 hr. The precipitated product was recovered by filtration and recrystallized from MeOH to give pure **79** (27 g, 56%), mp 140–141°. Similarly prepared were **4-[2-[2-hydroxy-3-(3-nitrophenoxy)propylamino]ethoxy]acetanilide (80)**, mp 107–109° (C, H, N), and **4-[2-[2-hydroxy-3-(4-nitrophenoxy)propylamino]ethoxy]acetanilide (81)**, mp 177–179° (C, H, N).

4-[2-[2-Hydroxy-3-(3-aminophenoxy)propylamino]ethoxy]-benzamide (76). The nitro derivative **79** (12 g, 0.032 mol) in MeOH (1000 ml) was hydrogenated over PtO_2 at room temperature and a pressure of 50 psi until uptake ceased. The catalyst was removed and the solvent evaporated *in vacuo* to give the crude product (9 g, 81.5%), mp 148–150°. Similarly prepared were **4-[2-[2-hydroxy-3-(3-aminophenoxy)propylamino]ethoxy]-acetanilide (77)**, mp 217–219°, and **4-[2-[2-hydroxy-3-(4-amino-phenoxy)propylamino]ethoxy]acetanilide (78).**

4-[2-(2-Hydroxy-3-*o*-tolyloxypropylamino)ethoxy]benzoic Acid Ethyl Ester (10). The nitrosobenzoic acid derivative **82** (50 g, 0.134 mol) was dissolved in EtOH (350 ml) saturated with HCl gas. The mixture was refluxed while HCl gas was bubbled in to maintain saturation. On allowing the mixture to cool the hydrochloride of **10** crystallized out and was recrystallized from EtOH as white crystals (20.7 g, 38%), mp 138–139°.

4-[2-(2-Hydroxy-3-*o*-tolyloxypropylamino)ethoxy]benzoic Hydrazide (8). The ester hydrochloride **10** (5 g, 0.012 mol) was dissolved in excess hydrazine hydrate (7.2 g, 0.144 mol) containing a small quantity of ethanol. The mixture was refluxed for 1 hr, allowed to stand for 12 hr at room temperature, and then poured into H_2O. The precipitated hydrazide **8** was recrystallized from EtOH (2.5 g, 58%), mp 91–92°.

Resolution of 3. Racemic **3** (50 g, 0.145 mol) in hot MeOH (2000 ml) was treated with a hot methanolic solution of D(−)-mandelic acid (22.1 g, 0.145 mol). The mixture was evaporated *in vacuo* to give the mandelate salt of **3** (70.7 g): mp 138–140°; $[\alpha]^{25}_{578}$ −33.7° (MeOH). The mandelate was recrystallized repeatedly from EtOH to give *d*-**3** D(−)-mandelate (2.34 g): $[\alpha]^{25}_{578}$ −23.8° (MeOH); mp 156–157°. *d*-**3** D(−)-mandelate (0.25 g) in H_2O was treated with $NaHCO_3$ (0.07 g) in H_2O and the crystalline *d* isomer (0.16 g) **3b** was recovered by filtration: mp 138–140°; $[\alpha]^{25}_{578}$ +9.2° (MeOH).

The above procedure was repeated with racemic **3** using L(+)-mandelic acid to give *l*-**3** L(+)-mandelate (2.6 g): mp 157–158°; $[\alpha]^{25}_{578}$ +21.9° (MeOH). Basification of this as described above

†† M. S. Tute and A. Cañas-Rodriguez, unpublished work, 1970.

gave the *l* isomer **3a**: mp 138–142°; $[\alpha]^{25}_{578}$ −10.6° (MeOH).

Equal portions of **3a** and **3b** were ground together to obtain a mixture melting point of 156–159°, coincident with that of racemic **3** (157–159°).

Pharmacology. Cardiac depressant activity was estimated using electrically stimulated (frequency 1 Hz, voltage 10–15% above threshold, pulse width 1 msec) cat right ventricular papillary muscle, under 1 g of tension, suspended in oxygenated Krebs solution at 37°. After equilibration, contraction amplitude was measured and cumulative doses (0.25–256 μg/ml) of drug were added every 10 min, doubling the concentration each time. Results were calculated on the concentration of drug causing 50% depression of contraction amplitude.

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Partly Reduced Biphenyls as Central Nervous System Agents. 3. *cis*- and *trans*-4-Aryl-4-methoxycyclohexylamines

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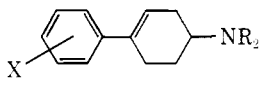
The two isomeric 4-tolyl-4-methoxycyclohexylamines were prepared and their configurations determined. A series of analogs bearing differing substitution in the aromatic ring was then synthesized by stereoselective routes, starting from the corresponding substituted cyclohexanones. The thus produced amines were converted to the 4′-fluoro-4-butyrophenones and selected compounds to the piperidines. The products were tested in a series of assays for CNS activity; the former were particularly active on both overt behavior and biochemical parameters.

We have recently reported on the preparation and intriguing CNS activity of the substituted arylcyclohexylamines **1** and **2**.[1,2] The effects of substitution at the ring carbon bearing the aromatic ring in the phenylpiperidines on biological activity have been amply documented.[3,4] It was thus of some interest to determine the effect on activity of the corresponding modification in our previously reported series.



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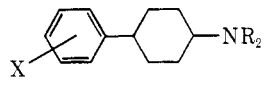

2

Synthesis. The key intermediate for the present work was the hydroxycyclohexanones **3**, obtained as described earlier,[1] from the reaction of hydroxycyclohexanone with appropriate arylmagnesium bromides. Treatment with MeOH in the presence of a catalytic amount of CF_3CO_2H led cleanly to the ketal. This was then alkylated by means of NaH and CH_3I (Scheme I). The crude alkylation product was then deketalized with aqueous Me_2CO; since the alkylations seldom went to completion, chromatography was employed to separate the product.

Reduction of the ketone **6c** by means of $NaBH_4$ gave a mixture of diols in the ratio of 17:3. Careful chromatography afforded the less polar minor isomer as a gum and the major isomer as a crystalline solid. The nmr spectrum of the latter showed H_a as a peak at δ 3.65 ($W_{1/2}$ = 20 Hz); the corresponding proton in the minor isomer appears at δ 4.0 ($W_{1/2}$ = 10 Hz). This then leads us to assign the major isomer to the equatorial series and the minor product to the axial series. If the tolyl group is in the expected equatorial orientation, the major alcohol is thus the trans compound. In practice, the crude reduction mixtures were purified so as to isolate only the major isomer. These alcohols were then taken on to the corresponding mesylates **8**. Displacement with NaN_3 in DMF led by SN2 reaction to the azides of the opposite configuration to that of starting mesylate. Reduction by means of $LiAlH_4$ completed the preparation of the primary cis amines. (Cis and trans in this context refer to the relationship of the aromatic ring and the amine.)

Preparation of the trans amines started by formation of the oximes **10**. Treatment with Ac_2O in pyridine gave the corresponding acetate. Reduction to the amines **12** was achieved by treatment with B_2H_6 in THF. Since the steric requirements of this reaction are quite similar to the $NaBH_4$ reduction of the ketones, the product should be the equatorial (trans) amine. The fact that the products are clearly isomeric with the corresponding compounds obtained by the inversion route bears out the assignment.

Treatment of the amines with the neopentyl glycol ketal of *p*-fluoro-4-chlorobutyrophenone in DMF followed by deketalization in aqueous methanol gave the corresponding alkylation products. Three of the primary amines in the cis series were taken on to the piperidines by means of 1,5-diiodopentane. It should be noted that in all cases where salts of the amines were prepared care was taken to avoid working with an excess of acid to preclude elimination of the benzylic methoxyl group.

Pharmacology. The effects of the substituted amines on both behavioral and biochemical end points are sum-