stirring. After 10 min, 80 mL of water was added to the mixture, the pH was adjusted to 8 by the addition of 10% Na_2CO_3, and the mixture was extracted with AcOEt (100 mL × 2). The organic layer was dried over $MgSO_4$ and concentrated to 30 mL. The precipitated solid was filtered off to give **31** as yellow prisms: yield 0.6 g (68%); mp 184–186 °C.

2-(5-Ethylpyridin-2-yl)-5(6)-(acetylamino)benzimidazole (32). A mixture of 0.9 g (0.0038 mol) of **31** and 4 mL of Ac_2O was stirred at 100 °C for 20 min. The reaction mixture was concentrated in vacuo, and the resulting solid was recrystallized from MeOH two times to give **32** as colorless prisms: yield 0.61 g (58%); mp 295–296 °C.

Preparation of Pyridinecarboxylic Acid Derivatives. Pyridinecarboxylic acid derivatives were prepared by three general methods. 5-Methylpicolinic acid,[18] 5-ethylpicolinic acid,[19] 6-methylnicotinic acid,[20] and 6-chloropicolinic acid (mp 190 °C) were prepared by the oxidation (SeO_2 or $KMnO_4$) of picoline derivatives. 6-Ethylpicolinic acid,[21] 5,6-dimethylpicolinic acid, and 6-methoxypicolinic acid (identified as the methyl ester, mp 34–35 °C) were prepared by hydrolysis of the corresponding nitriles, which were synthesized the via the *N*-oxides. 5-Ethyl hydro-2,5-pyridinedicarboxylate[22] and 6-ethyl hydro-2,6-pyridinedicarboxylate[23] were prepared by means of partial hydrolysis of the corresponding diester.

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Synthesis and Structure–Activity Relationships among α-Adrenergic Receptor Agonists of the Phenylethanolamine Type

Gérard Leclerc,* Jean Claude Bizec,

Laboratoire de Chimie Organique, Faculté de Pharmacie, 67400 Illkirch-Graffenstaden, France

Nicole Bieth, and Jean Schwartz

Institut de Pharmacologie et de Médecine Expérimentale,[1b] Faculté de Médecine, 67000 Strasbourg, France.
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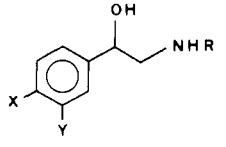
Nineteen arylethanolamine derivatives related to norepinephrine were prepared and tested for α-adrenergic stimulant activity. In one series the analogues possess a *p*-hydroxy function, while the meta position is substituted by methyl, ethyl, isopropyl, cyclohexyl, fluoro, chloro, iodo, carboxy, carbomethoxy, and methylsulfamido groups. The other series is meta hydroxylated with the para position substituted by the same groups. The influence of these groups upon the α-adrenergic activity is discussed, and the compounds are compared to octopamine, normetanephrine, norepinephrine, and norphenylephrine. It has been found that the introduction of an isopropyl, cyclohexyl, and fluoro group in the meta position of octopamine improves its affinity by three, five, and six times, respectively, whereas when these groups are introduced in the para position of norphenylephrine their effects are always detrimental. The most active compound, α-(aminomethyl)(4-fluoro-3-hydroxyphenyl)methanol (**44**), has about one-hundredth the affinity and the same intrinsic activity as norepinephrine.

Norepinephrine (**1a**) is the prototype of α-adrenergic



1a, Y = OH; X = OH; R = H
b, Y = OH; X = OH; R = *i*-Pr
c, Y = $NHSO_2Me$; X = OH; R = *i*-Pr
d, Y = $NHCONH_2$; X = OH; R = *t*-Bu

receptor agonists, and isoproterenol (**1b**) is a potent β-adrenergic agonist. Generally, agonist activity at the α-adrenergic receptor decreases with increasing size of the N-substituent in catecholamine-type molecules, while β activity is often enhanced by the same substitution. Furthermore, a great number of investigations have shown that the catechol moiety of the adrenergic agonists represents the most important part for high activity at adrenergic receptors.[2a,b] In particular, the influence of the *m*-hydroxy group has been emphasized. When one or both of these hydroxy groups in the 3 and 4 positions are absent, without any other aromatic substitution, the overall potency is generally reduced and there is especially a reduction in β activity. Larsen et al.[3] and Brittain et al.[2b]

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(2) (a) D. Bovet and F. Bovet-Nitti, in "Médicaments du Système Nerveux Végétatif", S. Karger, Ed., S. Xarger Publishing Co., Basel, Switzerland, 1948. (b) R. T. Brittain, D. Jack, and A. C. Ritchie, *Adv. Drug. Res.*, **5**, 197 (1970).
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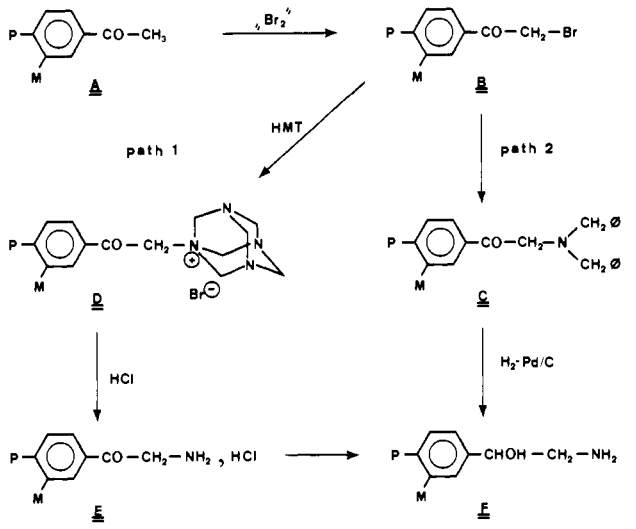
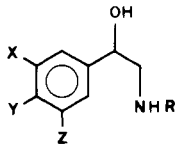
Scheme I



have shown that the phenolic hydroxy groups can be replaced by the acidic alkyl or arylsulfonamide substituents (soterenol, **1c**) or similar groups (carbuterol, **1d**) without altering the α and β activities.

However, a catechol-like function is certainly not an indispensable feature, since high β-adrenergic activity can be exhibited by 3,5-dihydroxy derivatives (terbutaline, **1e**)



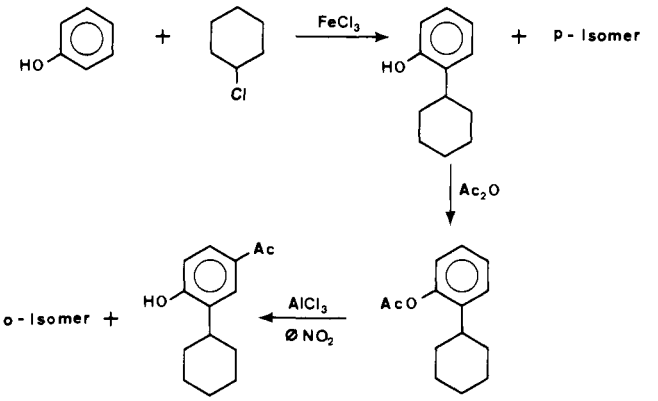
1e, Y = H; X = Z = OH; R = *t*-Bu
f, Y = OH; Z = H; X = CH_2OH; R = *t*-Bu
g, Y = NH_2; X = Z = Cl; R = *t*-Bu

or 3-(hydroxymethyl)-4-hydroxy derivatives (salbutamol, **1f**) and even by noncatecholic arylethanolamines that are not obviously related to catechols, such as clenbuterol (**1g**).[4,5]

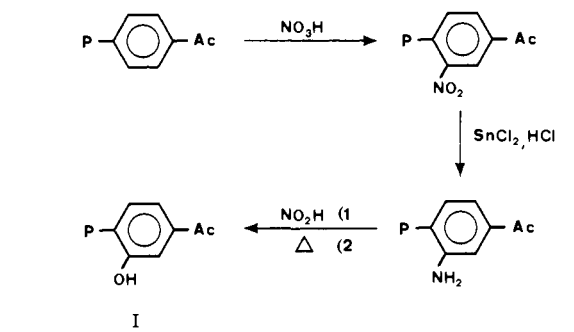
The role of the hydroxy or other similar functional groups remains unclear, and it has been proposed to be a water-ordering effect[6,7] or a metal-chelating effect.[8] In the hope of shedding some more light on the steric, electronic, or lipophilic role of the aromatic substituents, we have synthesized two series of compounds related to norepinephrine. In one series, the *p*-hydroxy function was maintained and the meta position was substituted. In the other series, the *m*-hydroxy function was maintained and the para position was substituted. In spite of the apparent simplicity of these molecules, most of them were not previously described, and, consequently, such a systematic study had never been undertaken.

In this paper, we report the synthesis and α-adrenergic agonist activity of these derivatives.

Scheme II



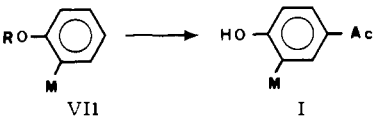
Scheme III



I

Chemistry. All the arylethanolamines, VI, reported here were prepared from the appropriate substituted acetophenone I following either path 1 or 2 as described in Scheme I.

In the *p*-hydroxy series, the starting ketones for the preparation of VI were generally prepared by acylation of the appropriate phenol VII (R = H), when it was available



VII I

(M = Me, Et, *i*-Pr, F, Cl, Br). For M = CO_2H or CO_2CH_3, the requisite acetophenone was obtained by a Fries rearrangement of acetylsalicylic acid (R = $COCH_3$). The 4-hydroxy-3-iodoacetophenone was obtained in satisfactory yield by iodination of 4-hydroxyacetophenone.[9] The 3-cyclohexyl-4-hydroxyacetophenone (**4**) was prepared in low yield following the procedure depicted in Scheme II. In the *m*-hydroxy series, the starting acetophenones, I, were usually obtained by the sequence shown in Scheme III. The decomposition of the diazonium salt into the corresponding acetophenone I was achieved satisfactorily only when electron-donating groups such as alkyl were present (P = Me, Et, *i*-Pr, cyclohexyl). When P = Cl, the decomposition of the diazonium sulfate in water at ca. 80 °C gave complex mixtures. When this decomposition was carried out in the presence of an enormous excess of cupric nitrate and cuprous oxide according to a recent procedure,[10] the expected phenol **16** was obtained in 16% yield. We found that the decomposition of the diazonium salt was best carried out in H_2SO_4/H_2O, which allowed the isolation of 4-bromo-3-hydroxyacetophenone and 4-chloro-3-hydroxyacetophenone in yields of 36 and 25%, respectively, but

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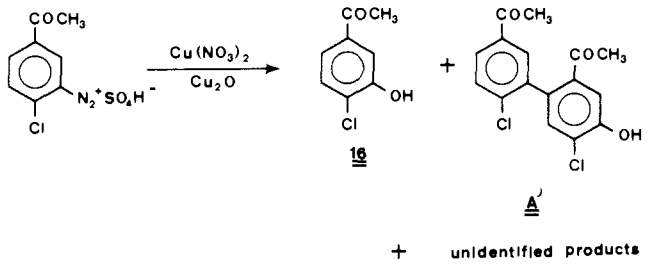


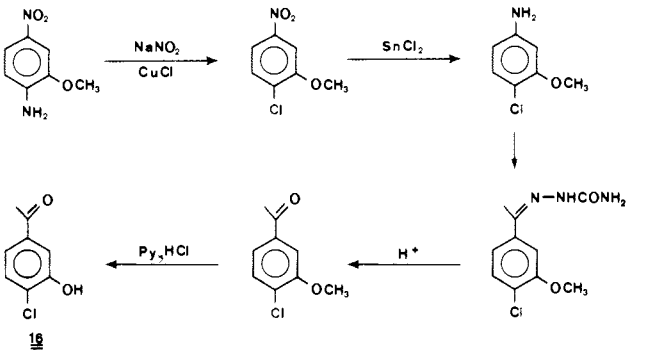
only traces of the 4-fluoro-3-hydroxyacetophenone.

Scheme IV represents an alternate method for the synthesis of 4-chloro-3-hydroxyacetophenone (**16**). Unexpected difficulties were encountered in the demethylation step, since HBr/AcOH, HBr/H_2O, and BBr_3/CH_2Cl_2 all gave very low yields of **16**. However, heating the methoxyacetophenone at 170–200 °C with pyridine hydrochloride gave **16** in 40% yield. The recently reported[9] iodination of phenol, which had been used in the synthesis of 4-hydroxy-3-iodoacetophenone (**8**), also provided access, although in low yields, to 4-iodo-3-hydroxyacetophenone (**18**).

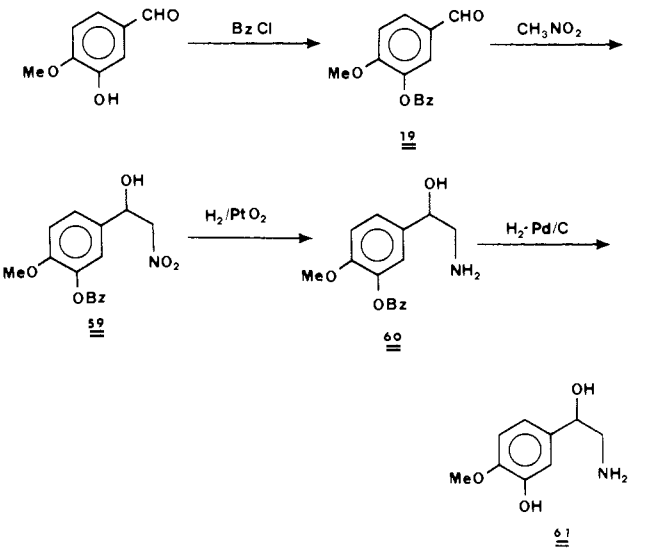
We at first used $CuBr_2$ in $EtOAc/CHCl_3$[11] for the bromination of the acetophenone derivatives I (Scheme I), but this procedure has proved much less satisfactory than dioxane dibromide. In particular, the yields were higher when the latter method was used, and the phenacyl bromides II were not contaminated with byproducts arising from nuclear bromination. Some dibromo derivatives were usually formed, but they could be removed quite easily. The known compounds[3] **50** and **58** were obtained by treating the acetophenone I with Br_2 in $CHCl_3$. However, when this procedure was applied to the other acetophenones, I, of our series, low yields of the phenacyl bromides were obtained. The aminoacetophenones III were easily prepared by the action of dibenzylamine on II. Catalytic hydrogenation (Pd/C) of III resulted in the reduction of the carbonyl group to the secondary hydroxyl function and removal of any benzyl groups present in the molecule. The synthesis of the *m*-Br and *m*-I derivatives **56** and **57** required a different strategy, since the catalytic hydrogenation caused the hydrogenolysis of the carbon–halogen bond prior to the complete reduction. The phenacyl bromide II was therefore condensed with hexamethylenetetramine (path 1, Scheme I), providing a quaternary salt which was hydrolyzed in hydrochloric acid/ethanol to the primary acetophenone V and further reduced by $NaBH_4/H_2O$ or BH_3/Me_2S in THF. The yields were diminished by the difficulties encountered in the isolation of V and VI. However, yields were greatly improved when the water solubility of V and VI was minimal, i.e., when lipophilic substituents like cyclohexyl, bromine, or iodine were present. The C–Cl bond hydrogenolysis of the *m*-chloro derivative **45** was minimized by using BH_3/MeS in THF to reduce the carbonyl function. Synthesis of 3-hydroxy-4-methoxyphenylethanolamine (**61**) was achieved as shown by Scheme V. Isovanillin was benzylated and then condensed with nitromethane[12] (KOH/EtOH, 12 °C). The nitro alcohol **59** was then reduced catalytically using PtO_2, and the benzyl group was removed in the last step by catalytic reduction using Pd catalyst.

Structure–Activity Relationships. The α-adrenergic agonist effects of the arylethanolamine derivatives described above are shown in Table II and are compared to the effects of octopamine, normetanephrine, norepinephrine, and norphenylephrine. As can be seen, all the compounds tested show moderate affinities and intrinsic activities which are of the same order as for norepinephrine. It is interesting to note the difference in the pharmacological potencies of comparable compounds in the meta and in the para series. Thus, it appears, contrary to our expectation, that molecules which bear a para phenolic group have considerably higher affinity than those having this group in the meta position. This finding is not in accord with earlier observations[3,13,14] showing that the hydroxy group in the meta position is more important for good activity that the hydroxy group in the para position of catecholamine derivatives. Several *p*-OH derivatives are more effective than octopamine but, nevertheless, do not show as high affinity as norepinephrine. Apart from compound **50**, which has been already reported by Larsen et al.[3] to be an α-adrenergic stimulant by virtue of the acidity of the methylsulfonamide group and its favorable spatial geometry, the most interesting compound is 44, which is meta fluorinated. When a comparison is made between the meta-halogenated derivatives, it appears that the affinity follows the sequence F > Cl > Br > I. The influence of an alkyl group in this position is less pronounced, but it seems that α-adrenergic affinity is increased by the size or the lipophilicity of the substituent: cyclohexyl > isopropyl, ethyl, or methyl. Compound **48** with a meta-carboxylic function is weakly active, although

Scheme IV



Scheme V



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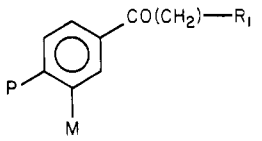
(12) J. Axelrod, S. Senoh, and B. Witkop, *J. Biol. Chem.*, **233**, 697 (1958).
(13) P. Pratesi and E. Grana, *Adv. Drug Res.*, **2**, 127 (1965).
(14) S. R. O'Donnell, *Eur. J. Pharmacol.*, **12**, 35 (1970).

Table I. Acetophenone Intermediates



no.	P	M	R_1	prepn method[a]	yield,[b] %	crystn solvent[c]	mp, °C	formula
1	OH	CH_3	H	A	96	benzene	107-109[d]	$C_9H_{10}O_2$
2	OH	C_2H_5	H	A	60	benzene/hexane	89-91[e]	$C_{10}H_{12}O_2$
3	OH	*i*-C_3H_7	H	A	44	hexane	139-140[f]	$C_{11}H_{14}O_2$
4	OH	C_6H_{11}	H	B	15	hexane	147-148[g]	$C_{14}H_{18}O_2$
5	OH	F	H	A	74	$CHCl_3/CCl_4$	127-129	$C_8H_7FO_2$
6	OH	Cl	H	A	98	$EtOH/H_2O$	92-95[h]	$C_8H_7ClO_2$
7	OH	Br	H	A	86	hexane	125-128[i]	$C_8H_7B_2O_2$
8	OH	I	H	C	57	$CHCl_3/CCl_4$	153-154[j]	$C_8H_7IO_2$
9	OH	CO_2H	H	D	82	EtOH	215-216[k]	$C_9H_8O_4$
10	OH	CO_2CH_3	H	D	82	MeOH	58-61[l]	$C_{10}H_{10}O_4$
11	OBzl	$NHSO_2CH_3$	H	*n*	16	2-PrOH	140-142[m]	$C_{16}H_{17}NO_4S$
12	CH_3	OH	H	E	40	CCl_4	119-120	$C_9H_{10}O_2$
13	C_2H_5	OH	H	E	46	benzene/hexane	94-95	$C_{10}H_{12}O_2$
14	*i*-C_3H_7	OH	H	E	50	hexane	97-100[o]	$C_{11}H_{14}O_2$
15	C_6H_{11}	OH	H	E	48	CCl_4	165-167	$C_{14}H_{18}O_2$
16	Cl	OH	H	F, G	10	CCl_4	103-104	$C_8H_7ClO_2$
17	Br	OH	H	H	22	CCl_4	122-123	$C_8H_7B_2O_2$
18	I	OH	H	C	15	$CHCl_3/CCl_4$	134-135	$C_8H_7IO_2$
19				*P*		cyclohexane	59-60[p]	$C_{15}H_{14}O_3$
20	$NHSO_2CH_3$	OBzl	H	*n*	18	2-PrOH	145-146[q]	$C_{16}H_{17}NO_4S$
21	OH	CH_3	Br	I	79			
22	OH	C_2H_5	Br	I	63			
23	OH	*i*-C_3H_7	Br	I	55			
24	OH	C_6H_{11}	Br	I	95			
25	OBzl	F	Br	J	35			
26	OBzl	Cl	Br	J	33			
27	OH	Br	Br	I	82			
28	OH	I	Br	I	87			
29	OH	CO_2H	Br	I	69	benzene		
30	OH	CO_2CH_3	Br	I	76	CCl_4		
31	OBzl	$NHSO_2CH_3$	Br	K	94	2-PrOH	118-120[r]	$C_{16}H_{16}BrNO_4S$
32	CH_3	OH	Br	I	42	CCl_4		
33	C_2H_5	OH	Br	I	67			
34	*i*-C_3H_7	OH	Br	I	78			
35	C_6H_{11}	OH	Br	I	51			
36	Cl	OH	Br	I	84			
37	Br	OH	Br	I	79			
38	I	OH	Br	I	75			
39	$NHSO_2CH_3$	OBzl	Br	K	94	2-PrOH	165-167[s]	$C_{16}H_{16}BrNO_4S$

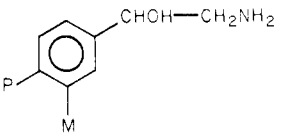
[a] For synthesis, see Experimental Section: A = Friedel-Crafts acylation; B and D = Fries acylation; C = iodination; E = nitration, followed by reduction and diazotation; F, G, and H = new procedures described under Experimental Section; I = dioxane dibromide; J = cuprous bromide; K = bromine in chloroform. [b] For ketones 1-20 the yield is based on the commercially available product. For bromo ketones 21-39 the yield is based on ketones 1-20. [c] Unless otherwise indicated, bromo ketones 21-39 were not recrystallized and were used as such for the next step. In these cases, melting points and microanalysis are not given. [d] Lit.[19] mp 104 °C. [e] J. P. Begué and M. Fetizon, *Bull. Soc. Chim. Fr.*, 78 (1969), reported mp 95 °C. [f] P. Demerseman, J. P. Lechartier, A. Cheutin, R. Reynaud, R. Royer, and P. Rumpf, *Bull. Soc. Chim. Fr.*, 1700 (1962), reported mp 140 °C. [g] Lit.[21] mp 148-149 °C. [h] N. M. Shah and S. R. Parikh, *J. Indian Chem. Soc.*, 36, 784 (1959), reported mp 96 °C. [i] J. A. Donnelly and J. J. Murphy, *J. Chem. Soc. C*, 18, 2597 (1970), reported mp 129 °C. [j] Lit.[9] mp 154-156 °C. [k] *Beilstein*, 3rd suppl., 8, 4227 (1971), gave mp 217 °C. [l] W. Borsche and J. Barthenheir, *Justus Liebigs Ann. Chem.*, 553, 250 (1942), reported mp 62 °C. [m] Lit.[3] mp 141.5-142.5 °C. [n] See ref 3. [o] Y. Kawase, R. Royer, M. Hubert-Habart, A. Cheutin, L. Rene, J. P. Buisson, and M. L. Desvoye, *Bull. Soc. Chim. Fr.*, 3131 (1964), reported mp 100-101 °C. [p] Benzyloxyisovanilline (19), mp 59-60 °C, was prepared in 89% yield from isovanillin by benzylation with benzyl chloride in the presence of aqueous potassium hydroxide, according to E. Späth and A. Mechoff, *Chem. Ber.*, 67, 1215 (1934), who reported mp 62-63 °C. [q] Lit.[3] mp 146.5-147.5 °C. [r] Lit.[3] mp 118.5-121.5 °C. [s] Lit.[3] mp 166-168 °C.

a considerable variety of substituents can replace the meta-phenolic group of isoproterenol, including $MeSO_2NH$-, $HOCH_2$-, $HOCH_2CH_2$-, and $MeSO_2NHCH_2$-,[2] without greatly affecting the β-agonist activity. The poor activity of **48** could be due to the strongly acidic carboxylic group which may drastically affect the concentration of unprotonated amine present.

In the *p*-alkyl series the situation is the reverse of that pertaining in the *m*-alkyl series, since the increase in affinity decreases with increasing size of the group: cyclohexyl < isopropyl < ethyl < methyl. However, in the *p*-halogeno derivatives, the increase in affinity follows the sequence Cl > Br > I, already observed for the *m*-halogeno derivatives. The best compound among the para-substituted derivatives is **55**, which is 70 times less active than norphenylephrine. The *p*-methoxy compound **61** is about 20 times less active than its positional isomer, normetanephrine, and about 1000 times less active than norphenylephrine.

In conclusion, this study shows that the introduction of various groups in the meta position of octopamine can improve the existing α-adrenergic affinity, whereas when

Table II. Physical and Biological Properties of Arylethanolamine Derivatives



compd	P	M	prepn method[a]	mp, °C	crystn solvent[b]	emp formula	yield,[c] %	α-adrenergic effect: pD2 ± SEM[d] (n)	α-adrenergic effect: intrinsic act.[e]
40	OH	CH_3	N + O	188-192	R	$C_9H_{13}NO_2 \cdot HCl$	39	5.96 ± 0.06 (4)	1.0
41	OH	C_2H_5	N + O	149-150.5	R	$C_{10}H_{15}NO_2 \cdot HCl$	46	6.09 ± 0.07 (4)	0.9
42	OH	i-C_3H_7	N + O	188-190	R	$C_{11}H_{17}NO_2 \cdot$ oxalate	53	6.53 ± 0.04 (4)	1.2
43	OH	C_6H_{11}	N + O	209-211	R	$C_{14}H_{21}NO_2 \cdot HCl$	41	6.73 ± 0.08 (4)	1.1
44	OH	F	N + O	199-201	R	$C_8H_{10}FNO_2 \cdot HCl$	20	6.78 ± 0.08 (8)	1.0
45	OH	Cl	N + O + P	187-189	R	$C_8H_{10}ClNO_2 \cdot HCl$	17	5.85 ± 0.05 (4)	1
46	OH	Br	L + M	209-211	R	$C_8H_{10}BrNO_2 \cdot HCl$	33	5.57 ± 0.05 (8)	1.1
47	OH	I	L + P	191-193	S	$C_8H_{10}INO_2 \cdot$ maleate	19	5.50 ± 0.14 (4)	0.9
48	OH	CO_2H	N + O	208 dec	R	$C_9H_{11}NO_4 \cdot HCl$	69	4.07 ± 0.03 (4)	1.0
49	OH	CO_2CH_3	N + O	202.5-204	R	$C_{10}H_{13}NO_4 \cdot HCl$	48	4.85 ± 0.12 (4)	0.9
50	OH	$NHSO_2CH_3$	N + O	201-203[f]	R	$C_9H_{14}N_2O_4S \cdot HCl$	23	7.19 ± 0.05 (6)	1.1
51	CH_3	OH	N + O	190.5-191.5	R	$C_9H_{13}NO_2 \cdot$ oxalate	28	5.66 ± 0.07 (4)	1.3
52	C_2H_5	OH	N + O	234-235	R	$C_{10}H_{15}NO_2 \cdot 0.5$oxalate$\cdot 0.5H_2O$	28	5.20 ± 0.07 (4)	1.1
53	i-C_3H_7	OH	N + O + P	197.5-198.5	T	$C_{11}H_{17}NO_2 \cdot HCl$	60	5.00 ± 0.10 (4)	0.7
54	C_6H_{11}	OH	L + M	>260	U	$C_{14}H_{21}NO_2 \cdot HCl$	45	4.86 ± 0.17 (4)	0.7
55	Cl	OH	L + M	203-205	R	$C_8H_{10}ClNO_2 \cdot$ oxalate	53	6.35 ± 0.09 (4)	1.1
56	Br	OH	L + M	205-207	R	$C_8H_{10}BrNO_2 \cdot H_3PO_4$	24	5.58 ± 0.05 (6)	1.0
57	I	OH	L + P	237-239	R	$C_8H_{10}INO_2 \cdot$ oxalate	11	4.99 ± 0.05 (4)	0.9
58	$NHSO_2CH_3$	OH	N + O	185-187[f]	V	$C_9H_{14}N_2O_4S \cdot HCl$	32	3.20 ± 0.03 (4)	0.8
61	OCH_3	OH	Q	235.5-236.5	R	$C_9H_{13}NO_3 \cdot 0.5$oxalate	23[g]	4.97 ± 0.05 (4)	1.0
NM[h]	OH	OCH_3						6.23 ± 0.06 (6)	0.9
OC[h]	OH	H						6.08 ± 0.05 (8)	1.1
NP[h]	H	OH						8.21 ± 0.05 (8)	1.0
NE[h]	OH	OH						8.80 ± 0.05 (26)	1.0

[a] For synthesis, see Experimental Section: L = HMT; M = $NaBH_4$; N = dibenzylamine; O = catalytic reduction; P = BH_3 reduction; Q = see Experimental Section. [b] R = CH_3CN/H_2O; S = 95% EtOH/Et_2O; T = not recrystallized; U = H_2O; V = 2-PrOH. [c] Yield expressed from the bromo ketone, except for 61. [d] Rat aorta pD_2 values plus or minus standard error of the mean with the number of experiments in parentheses. [e] Intrinsic activity as the ratio of the maximum response to each compound to the maximum response to norepinephrine; norepinephrine = 1. [f] 50, lit.[3] mp 173.5-174 °C; 58, lit.[3] mp 185.5-186.5 °C. [g] Yield expressed from the aryl aldehyde 19: see footnote *p* in Table I. [h] Abbreviations used are: NM, normetanephrine; OC, octopamine; NP, norphenylephrine; NE, norepinephrine.

the same groups are introduced in the para position of norphenylephrine their effects are always detrimental. However, none of these newly synthesized substituted hydroxyphenylethanolamines is as active as norepinephrine; the most active derivatives, **43** and **44**, have about one-hundredth the potency of norepinephrine.

Experimental Section

Pharmacology. Helically cut strips of rat aorta, 1.5- to 2-cm long and 3- to 4-mm wide, were prepared as described by Liebau, Distler, and Wolff.[16] Preparations were suspended in 20-mL baths, containing Krebs–Henseleit solution, kept at 37 °C, and bubbled with a mixture of 95% oxygen and 5% carbon dioxide. They were set up at a resting tension of 2 g and allowed to stabilize for approximately 2 h before the experiment. The contractions of rat aortic strips were elicited by increased and cumulative doses first of a freshly prepared norepinephrine solution and then of one of the derivatives. Contractile responses gradually increased to reach a maximum after 25 min. After three or four washings, relaxation was complete. After a 1-h rest, the second curve was taken. The contractions were recorded isometrically on a polygraph by means of a force-displacement transducer.

pD_2 values ($pD_2 = -\log K_A$; K_A = the dissociation constant of the agonist receptor complex; in fact, the pD_2 value is identical with the $-\log ED_{50}$) were determinated by the method of Ariens and Van Rossum.[17] Intrinsic activity is expressed as the ratio of the maximum response to each compound to the maximum response to norepinephrine.[18]

Chemistry. Melting points were obtained on a calibrated Kofler hot-stage apparatus and are uncorrected. Infrared spectra were measured in $CHCl_3$ solution with a Beckman IR 33 spectrophotometer. NMR spectra were recorded on a Perkin-Elmer spectrometer using Me_4Si as an external reference. Compounds in Table II were analyzed for C, H, and N and gave results within ±0.4% of the theoretical values. All the phenylethanolamine derivatives **40–61** were analyzed by mass spectrometry on a Hewlett Packard 5992 A model, after derivatization with pentafluoropropionyl anhydride. Retention times and pattern fragmentations of these catecholamine derivatives were characteristic[15] and allowed a clear distinction from their amino ketone

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precursors. Most significantly, in all cases major fragments were observed for $(CH_2{=}NH\text{-}PFP)^+$ and $(Ar\text{-}CH{=}OH)^+$.

4-Hydroxy-3-methylacetophenone (1). Method A. To a solution of 129.8 g (1.2 mol) of *o*-cresol in 300 mL of CS_2, cooled in an ice–salt bath, were added under mechanical stirring 336 g of $AlCl_3$, by portions, and then dropwise 94.2 mL (1.32 mol) of acetyl chloride. After stirring for 1 h at ambient temperature, the solution was heated at reflux for 12 h. After cooling, the reaction mixture was poured onto crushed ice–concentrated HCl, extracted several times with Et_2O. The ether extracts were dried and evaporated, and the residue was recrystallized from benzene to afford 44 g (96%) of 1, mp 107–109 °C (lit.[19] mp 104 °C).

3-Cyclohexyl-4-hydroxyacetophenone (4). Method B. A mixture of 470 g (5 mol) of phenol, 118 g (1 mol) of cyclohexyl chloride, and 1 g of $FeCl_3{\cdot}12H_2O$ was heated for 20 min at 140–185 °C.[20] Distillation at reduced pressure allowed the recovery of 343 g of phenol. The remaining crystalline residue was slurried with petroleum ether (40–60 °C) to give 42.9 g of a white powder consisting mainly of *p*-cyclohexylphenol contaminated by some ortho isomer. The mother liquors were cooled (acetone–dry ice) to give, after filtration, 49 g (28%) of the ortho isomer pure enough to be used as such for the next step.

It was quantitatively converted to 2-cyclohexylphenyl acetate by heating it under reflux for 6 h with Ac_2O.

A mixture of 42 g of this acetate and 30 g of $AlCl_3$ in 200 mL of nitrobenzene was heated at 85 °C for 4 h. The mixture was hydrolyzed with crushed ice–concentrated HCl and diluted with EtOAc. The organic phase, which contained a mixture of para and ortho isomers, was shaken with 10% NaOH. The sodium salt of 4 which precipitated (sodium salt of 3-cyclohexyl-2-hydroxyacetophenone remained dissolved) was filtered off and acidified to give 23 g (55%) of 4, mp 147–148 °C (lit.[21] mp 148–149 °C).

4-Hydroxy-3-iodoacetophenone (8). Method C. To a solution of 20.4 g (0.15 mol) of *p*-hydroxyacetophenone in 1.25 L of concentrated NH_4OH was added rapidly, with stirring, a solution of 121 g of KI (0.73 mol) and 38.3 g (0.15 mol) of I_2 in 300 mL of H_2O. Stirring at room temperature was continued overnight (color changed from gray to yellow), after which the mixture was filtered and concentrated. The brown oil that formed was extracted with EtOAc. The extract was dried over $MgSO_4$, filtered, and evaporated to afford the crude iodophenol. It was dissolved in 500 mL of 10% aqueous NaOH, filtered, and reprecipitated with concentrated HCl to give 8 as a bright-yellow product, 22.4 g (57%). It was recrystallized from $CHCl_3$–CCl_4 to give 8, mp 153–154 °C (lit.[9] mp 154–156 °C).

3-Hydroxy-4-iodoacetophenone (18) was prepared similarly in 15% yield and could only be purified by column chromatography (SiO_2, $CHCl_3$).

5-Acetyl-2-hydroxybenzoic Acid (9). Method D. Under ice cooling, 240 g (1.8 mol) of well-pulverized $AlCl_3$ was added to 150 mL of nitrobenzene, followed by 100 g (0.55 mol) of acetylsalicylic acid. The mixture was mechanically stirred for 1 h. After that time, the thick paste was carefully decomposed with a mixture of crushed ice and concentrated HCl, steam distilled, and filtered hot to yield 82 g (82%) of white needles, which crystallized from alcohol to afford 9, mp 215–216 °C (lit.[22] mp 216–217 °C).

Methyl 5-Acetyl-2-hydroxybenzoate (10). Method D. This compound was prepared in 96% yield by heating 32.6 g of 9 in 200 mL of MeOH containing 2 mL of H_2SO_4 during 24 h. It was recrystallized from MeOH to give colorless prisms, mp 58–61 °C (lit. mp 62 °C; see footnote *l* in Table I).

3-Hydroxy-4-methylacetophenone (12). Method E. The nitration of 4-methylacetophenone and reduction of the nitro group with $SnCl_2$ were carried out according to ref 23. Compounds 13 and 14 were prepared similarly.

Acetylation[24] of cyclohexylbenzene yielded 91% of 4-cyclohexylacetophenone, which was converted as above to 15.

4-Chloro-3-hydroxyacetophenone (16). Method F. 4-Chloro-3-aminoacetophenone was prepared by nitration of 4-chloroacetophenone, followed by reduction as in ref 23. It was diazotized in fluoroboric acid according to ref 25; the diazonium salt (35 g) was added in small portions to 300 mL of boiling H_2SO_4 containing a few drops of an antifoam emulsion. After the N_2 evolution had ceased, the solution was cooled and extracted with benzene. The organic phase was extracted with 1 N NaOH, and the aqueous phase was washed three times with ether, decolorized with C norit, cooled, filtered, and acidified with 2 N HCl to afford 4 g (18% yield) of 4-chloro-3-hydroxyacetophenone.

When the diazonium sulfate (prepared from 13 g of the amino derivative) was decomposed in the presence of large amounts of $Cu(NO_3)_2$ and Cu_2O according to ref 10, compound 16 was obtained after column chromatography (SiO_2: EtOAc/hexane, 1:9). 16: yield 2.2 g (16%); mp 103–104 °C; ^1H NMR ($CDCl_3$) δ 2.57 (s, 3 H, $COCH_3$), 6.37 (s, 1 H, OH), 7.5 and 7.65 (m, 2 H and 1 H, ArH).

4-Chloro-3-hydroxyacetophenone (16). Method G. 4-Chloro-3-methoxyaniline[26] was converted to 4-chloro-3-methoxyacetophenone using a procedure described by Beech et al.[27] A mixture of 18.5 g (0.1 mol) of methoxyacetophenone and 21.5 g of pyridine hydrochloride was heated at 170–200 °C for 2 h. The cooled solution was poured into 500 mL of water and extracted with ether. The ethereal extract was dried ($MgSO_4$) and evaporated. The brown residue was purified by column chromatography (SiO_2; $CHCl_3$/EtOAc, 9:1) to yield 6.8 g (40%) of 16, mp 103–104 °C (lit.[19] mp 96 °C).

4-Bromo-3-hydroxyacetophenone (17). Method H. 4-Bromoacetophenone was nitrated and reduced as in method E. Decomposition of the diazonium fluoroborate was carried out in H_2SO_4/H_2O as in method F: yield 36%.

4-Hydroxy-3-methylphenacyl Bromide (21). Method I. A solution of 163.6 g (0.66 mol) of dioxane dibromide was added dropwise with stirring to 90.1 g (0.6 mol) of 1 dissolved in a mixture of 500 mL of dioxane and 500 mL of ether. After the addition was complete, the solution was stirred for 2 h at room temperature. The solvents were rotary evaporated, and the brown oil was induced to crystallize by scratching: 107 g (78%) of violet crystals were filtered off, which could be recrystallized from benzene.

4-(Benzyloxy)-3-fluorophenacyl Bromide (25). Method J. Bromination using $CuBr_2$ in EtOAc–$CHCl_3$[11] was applied for the synthesis of 25 and 26. The product which crystallized from the reaction mixture was used as such for the next step.

α-(Aminomethyl)(4-hydroxy-3-methylphenyl)methanol (40). Method N plus O. A mixture of 57 g (0.25 mol) of phenacyl bromide 21 and 98.2 g (0.5 mol) of dibenzylamine in 400 mL of methyl ethyl ketone was stirred at room temperature for 12 h. The dibenzylamine hydrobromide, which appeared within 2 min, was removed by filtration and washed with methyl ethyl ketone (50 mL). The combined solutions were evaporated under reduced pressure and diluted with 400 mL of ether. The dibenzylamine hydrobromide which precipitated was filtered off, and the ethereal solution was bubbled with HCl gas. The gummy precipitate was triturated with a mixture of acetone and ether, filtered, and recrystallized from EtOAc/MeOH (6:4) to afford 67 g (70% yield) of peach cream crystals of [(dibenzylamino)methyl]-4-hydroxy-3-methylacetophenone hydrochloride.

A solution of 53.5 g (0.14 mol) of the above aminoacetophenone hydrochloride in 1.3 L of EtOH, with 5.35 g of 10% Pd/C, was

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hydrogenated under 1 kg/cm^2 of hydrogen pressure. Consumption of the calculated quantity of hydrogen was complete in 98 h. After removal of the catalyst and evaporation of the solvent, the residue was triturated with MeCN. The crystals thus obtained were filtered off and dissolved in 28 mL of water, and 800 mL of MeCN was added. Insoluble crystals separated and they were collected by filtration to give 16 g (56% yield) of **40**, mp 188–192 °C. The homogeneity of **40** was checked by TLC using *n*-BuOH–AcOH–H_2O (4:1:1).

α-(Aminomethyl)(3-chloro-4-hydroxyphenyl)methanol (45). Method N plus O plus P. A mixture of 14.4 g (0.0425 mol) of phenacyl bromide **26** and 16.8 g (0.085 mol) of dibenzylamine in 100 mL of methyl ethyl ketone was stirred at 50 °C for 12 h to afford 6.4 g (0.012 mol) of [(dibenzylamino)-methyl]-4-(benzyloxy)-3-chloroacetophenone hydrobromide (see the synthesis of **40**). This salt was then reduced catalytically and the reaction was stopped after 3 equiv of hydrogen was absorbed. The aminoacetophenone thus obtained (3.3 g) was heated with 1 equiv of sodium ethoxide to afford 2.5 g of the corresponding base. It was reduced with 4 mL of BH_3–Me_2S, as in the synthesis of **47**, and purified as its hydrochloride salt to give 1.65 g (61%) of **45**, mp 187–189 °C.

α-(Aminomethyl)(3-bromo-4-hydroxyphenyl)methanol (46). Method L plus M. A solution of 29.4 g (0.1 mol) of 4-hydroxy-3-bromophenacyl bromide (**27**) and 14 g (0.1 mol) of hexamethylenetetramine in 400 mL of $CHCl_3$ was stirred at 50 °C for 30 min. The abundant precipitate was collected by filtration and washed with $CHCl_3$. The quaternary complex was suspended in 100 mL of EtOH and 50 mL of HCl and heated at 50 °C for 4 h. After 0.5 h, the mixture was homogeneous and aminophenone hydrochloride began to crystallize. The mixture was cooled on ice and filtered. The crystalline product, which consists of the amine hydrochloride and ammonium chloride, was stirred for 10 min with 50 mL of H_2O, cooled to 0 °C, and filtered. The product was dried in vacuo over $CaCl_2$ to yield 18 g (54%) of 3-bromo-4-(hydroxyamino)acetophenone hydrochloride.

To a solution of the above aminoacetophenone hydrochloride in 100 mL of water was added dropwise 4 g of $NaBH_4$ in a minimum of water. After 6 h, 2 N HCl was added until a clear solution was obtained. Most of the water was evaporated and the semisolid residue was slurried with 50 mL of cold water. The crystals obtained were dissolved in a minimum of EtOH, and CH_3CN added up to a volume of ca. 400 mL. After 12 h, colorless crystals of **46** were collected: yield 8.8 g (33%); mp 209–211 °C.

α-(Aminomethyl)(4-hydroxy-3-iodophenyl)methanol (47). Method L plus P. A solution of 33.5 g (0.1 mol) of 4-hydroxy-3-iodophenacyl bromide (**28**) and 14 g (0.1 mol) of hexamethylenetetramine was heated at 50 °C, for 30 min, and the quaternary salt thus obtained was hydrolyzed, as in the synthesis of **46**, to yield 21 g (71%) of 4-hydroxy-3-(iodoamino)phenone hydrochloride, which gave 10 g (54%) of the corresponding base by treatment with aqueous $NaHCO_3$.

This base (vacuum dried) was suspended in 250 mL of anhydrous THF under N_2. To this was slowly added 8.9 mL of BH_3–Me_2S complex, and the solution was heated at 60 °C overnight. Anhydrous MeOH (10 mL, 3 equiv) was then carefully added. The solvents were removed to give 5.1 g (51% yield) of a yellow solid, which was dissolved in 45 mL of EtOH and treated with a hot solution of 2.1 g of maleic acid, in 80 mL of EtOAc, to give 3.6 g of white crystals of **47**. The analytic sample was recrystallized from ethanol–ether (1:2).

α-(Aminomethyl)(3-hydroxy-4-methoxyphenyl)methanol (61). Method O. Compound **61** was obtained from 3-(benzyloxy)-4-methoxybenzaldehyde following essentially the procedure described by Axelrod et al.[12] for the synthesis of DL-normetanephrine. However, as difficulties were encountered in the purification procedure, based upon fractional crystallization, we used instead column chromatography (SiO_2, $CHCl_3$) and obtained **59** in 34% yield.

It was recrystallized from cyclohexane–benzene to afford slightly yellow needles: IR ($CHCl_3$) 3600 (free OH), 3400 (bonded OH), 1550 cm^{-1} (NO_2); mp 92–93 °C.

To a suspension of Platinum black, prepared from 1.4 g of PtO_2 in 150 mL of absolute ethanol saturated with hydrogen, was added a solution of 5.7 g of the above nitro alcohol in 300 mL of absolute ethanol. After 2–3 h of stirring, the NO_2 function was reduced, as indicated by TLC. The Pt catalyst was filtered off, and the solvent was evaporated under reduced pressure. The crystalline residue was slurried with EtOAc and filtered to give 2.5 g (48%) of **60**.

This product was then dissolved in 250 mL of absolute ethanol containing 500 mg of 10% Pd/C and hydrogenated at atmospheric pressure. During 0.5 h, 210 mL of hydrogen (0.94 equiv) was absorbed. When HCl was added at this stage, as described in ref 12, only 2-ethoxy-2-(3-hydroxy-4-methoxyphenyl)ethylamine was obtained, as evidenced by microanalysis, NMR, and MS.

After the catalyst was filtered and carefully washed with hot ethanol, the combined filtrate was evaporated to dryness. The crude crystals (1.1 g) were dissolved in anhydrous THF and mixed with 0.72 g of oxalic acid dissolved in THF. The oxalate (1.55 g) was recrystallized from MeCN–H_2O to afford **61**: mp 235.5–236.5 °C (lit.[28] mp 170–172 °C for the hydrochloride salt).

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