2-[(1,4-Benzodioxan-2-yl)methyl]imidazole Hydrochloride (10). To a mixture of 35 g (200 mmol) of 4,[16a,b] 14 g of ethanol, and 100 mL of diethyl ether was added 12 g of HCl gas. The flask containing the mixture was tightly stoppered and left at 5 °C for 4 days, at which time the solid imidate hydrochloride 7 was isolated by filtration. After the solid was washed with diethyl ether, there was obtained 35 g (~68%), which was used without further purification. A mixture of 35 g (136 mmol) of 7, 19.91 g (183 mmol) of aminoacetaldehyde diethyl acetal, and 450 mL of ethanol was heated at reflux for 18 h. Evaporation of excess solvent left 61.6 g of an oily residue. This residue was mixed with 600 mL of 4 N HCl, and the mixture was stirred at 60 °C for 24 h. The mixture was filtered to remove a small amount of solid, and the filtrate was extracted with dichloromethane. The aqueous layer was basified with sodium hydroxide and thoroughly extracted with dichloromethane. Evaporation of solvent left a residue, which was filtered through 70 g of 70–230 mesh silica gel with 500 mL of 10% methanol–ethyl acetate. Evaporation of the filtrate left an oil. This material was taken up in 70 mL of 2-propanol, and an HCl salt was made by passing HCl gas into the solution. The salt was collected by filtration and was washed with diethyl ether: ^{13}C NMR (Me_2SO-d_6) δ 27.9 (t), 67.1 (t), 70.9 (d), 118.0 (d), 118.3 (d), 119.9 (d), 123.1 (d), 123.3 (d), 142.6 (s), 143.2 (s), 143.5 (s). Anal. ($C_{12}H_{13}ClN_2O_2$) C, H, N, Cl.

1-Ethyl-2-[(1,4-benzodioxan-2-yl)methyl]imidazole Hydrochloride (13). To a solution of 75 g (347 mmol) of 10 in 250 mL of DMF at 0 °C was added 20 g (41.6 mmol) of 50% sodium hydride in mineral oil in two equal portions. After 30 min at room temperature, 56.8 g (364 mmol) of ethyl iodide was added dropwise over 15 min at 0 °C. The mixture was then stirred for 30 min at room temperature. The mixture was poured into 700 mL of water, and the resulting mixture was extracted with three 200-mL portions of ethyl acetate. The combined extract was washed with 100 mL of water and then with two 250-mL portions of 5% HCl solution. The combined acid extract was washed with 100 mL of ethyl acetate and then made basic and concentrated ammonium hydroxide. The product was extracted with two 200-mL portions of ethyl acetate. Evaporation of solvent gave an oil, which was filtered through 100 g of 70–230 mesh silica gel with 500 mL of ethyl acetate. Evaporation of the filtrate gave 58.1 g of an off-white solid: mp 78–79 °C; NMR ($CDCl_3$) δ 1.35 (d, 2 H, J = 7 Hz), 3.05 (d, 2 H, J = 6 Hz), 3.72–4.85 (m, 5 H), 6.7–7.33 (m, 6 H).

The hydrochloride salt was prepared by passing excess HCl gas into a methanol solution of 13, followed by precipitation with diethyl ether, mp 174–175 °C. Anal. ($C_{14}H_{17}ClN_2O_2$) C, H, N.

2-[(1,4-Benzodioxan-2-yl)methyl]benzimidazole Hydrochloride (22). A mixture of 5 g (19.4 mmol) of 7, 2.16 g (20 mmol) of *o*-phenylenediamine, and 50 mL of ethanol was heated at reflux for 18 h. The solvent was evaporated, and the residue was suspended in 150 mL of 5% ammonium hydroxide. The product was extracted into ethyl acetate. Evaporation of the ethyl acetate gave an oil. The hydrochloride salt was prepared by passing excess HCl into a methanol solution of 22, followed by precipitation with diethyl ether: ^{13}C NMR (CD_3OD–D_2O) δ 29.14 (t), 67.40 (t), 70.98 (d), 114.44 (d), 117.85 (d), 117.98 (d), 122.89 (d), 127.05 (d), 131.83 (s), 142.69 (s), 143.31 (s), 150.14 (s). Anal. ($C_{16}H_{15}ClN_2O_2$) C, H, N.

Acknowledgment. We thank Paul Cheung for log D determinations and Dr. Michael Maddox, Ms. Janis Nelson, and Ms. Lilia Kurz for analytical assistance.

(30) Arunlakshana, O.; Schild, H. O. *Br. J. Pharmacol.* **1959**, *14*, 48.

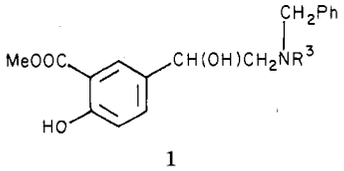
Arylethanolamines Derived from Salicylamide with α- and β-Adrenoceptor Blocking Activities. Preparation of Labetalol, Its Enantiomers, and Related Salicylamides

James E. Clifton, Ian Collins, Peter Hallett, David Hartley, Lawrence H. C. Lunts,* and Philip D. Wicks

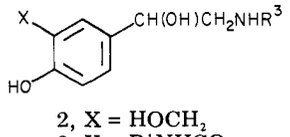
Chemistry Department, Glaxo Group Research Ltd., Ware, Hertfordshire, SG12 OD England. *Received August 20, 1981*

A series of phenethanolamines (3) based on salicylamide has been prepared and shown to possess β-adrenergic blocking properties. When the basic nitrogen atom was substituted by some aralkyl groups, the compounds also blocked α-adrenoceptors. The 1-methyl-3-phenylpropyl derivative labetalol (34) is antihypertensive in animals and man, and syntheses of its four stereoisomers are described. The enantiomer 90 with the *R* configuration at both asymmetric centers possessed most of the β-blocking activity but little α-blocking activity. That with the *S* configuration at the alcoholic carbon and the *R* configuration on the amino substituent, 89, is predominantly an α-adrenoceptor blocking agent.

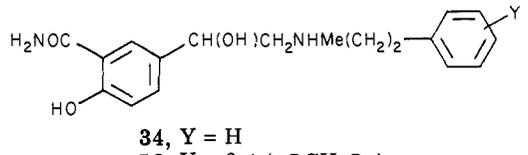
In a previous publication[1] we reported the preparation of the saligenins 2 from the salicyl esters 1 to give potent



1



2, X = $HOCH_2$
3, X = R^1NHCO



34, Y = H
53, Y = 3,4-(-OCH_2O-)

β$_2$-adrenoceptor stimulants. In an extension of this work, aimed at investigating the effect of analogous structures on adrenergic activity, we converted the esters 1 into the corresponding amides 3 and found that they blocked β-adrenoceptors.[2] Furthermore, when these amides were substituted on the basic nitrogen atom with specific aralkyl groups, the products possessed, in addition, α-adrenoceptor blocking activity and a capacity to produce rapid and long-lasting falls in blood pressure in the rat and dog.[3] This article describes a series of analogues 3 and the development of a novel antihypertensive agent, labetalol (34), operating by antagonism of α-adrenoceptors in which side effects, such as reflex tachycardia, are minimized by the concomitant antagonism of cardiac β-adrenoceptors. The biological activity of labetalol has been extensively reviewed.[4-6]

(1) D. T. Collin, D. Hartley, D. Jack, L. H. C. Lunts, J. C. Press, and P. Toon, *J. Med. Chem.*, **13**, 674 (1970).

(2) L. H. C. Lunts, P. Toon, and D. T. Collin, U. K. Patent 1 200 886 (1970).

(3) L. H. C. Lunts and D. T. Collin, U.K. Patent 1 266 058 (1972).

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Scheme I

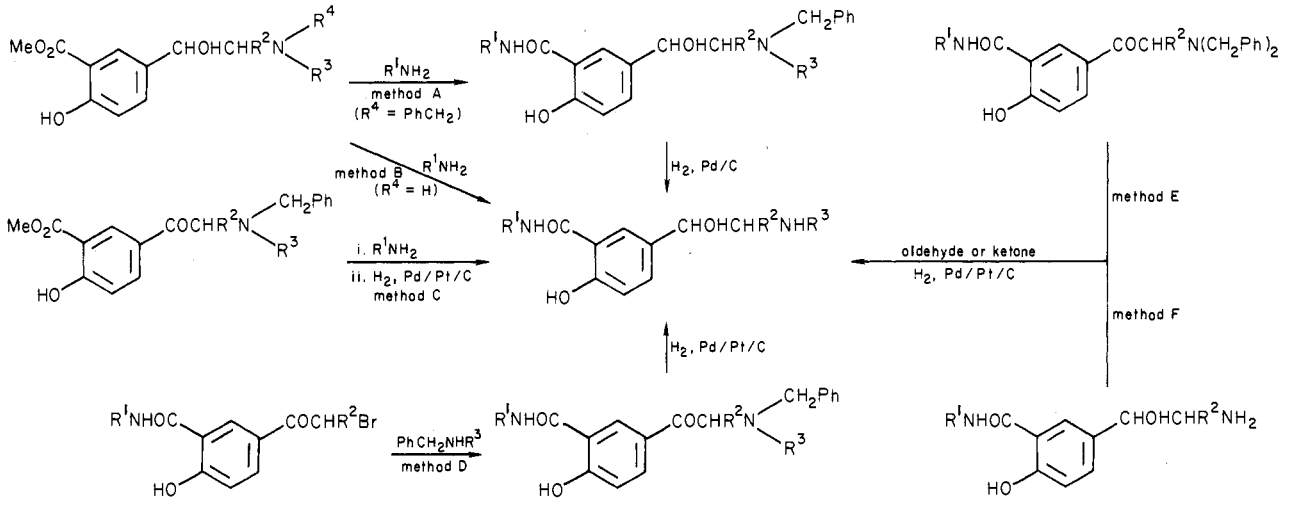
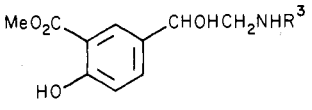


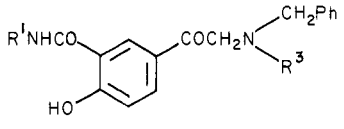
Table I. 5-(2-Amino-1-hydroxyethyl)salicylic Acid Esters[a]



no.	R^3	formula	method	yield, %	crystn solvent[b]	mp, °C
4	2-$FC_6H_4(CH_2)_2CHMe$	$C_{20}H_{24}FNO_4 \cdot HCl$	E[c]	76	Ea-Pe	139-143
5	4-$FC_6H_4(CH_2)_2CHMe$	$C_{20}H_{24}FNO_4 \cdot HCl$	E[c]	75	Me-Ea	159-163
6	3,4-$(CH_2O_2)C_6H_3(CH_2)_2CHMe$	$C_{21}H_{25}NO_6 \cdot HCl$	E[c]	93	Ea-Pe	187-191
7	4-$AcNHC_6H_4(CH_2)_2CHMe$	$C_{22}H_{28}N_2O_5$	E[c]	51	Ea-Pe	105
8	$PhCO(CH_2)_2$	$C_{19}H_{21}NO_5 \cdot HCl$	*d*	34	Ip	165-167
9	$PhCHOH(CH_2)_2$	$C_{19}H_{23}NO_5$	*e*	28	Ea	145-148
10	$PhCH_2CH(CO_2Et)CHMe$	$C_{23}H_{29}NO_5 \cdot HCl$	F[f]	65	Ea-Pe	176-177
11	PhCONH-(4-c-C_5H_9N)-CH_2CHMe	$C_{25}H_{33}N_3O_5$	E[c]	51		157-162
12	$PhNHCH_2CHMe$	$C_{19}H_{24}N_2O_4 \cdot 2HCl$	E[c]	84	Me-Ea	183-185
13	$PhNHCOCH_2CHMe$	$C_{20}H_{24}N_2O_5$	E[c]	57	Et	124-128

[a] For analogous esters not described in this table, see ref 1. [b] Al = EtOH; B = PhH; Ea = EtOAc; Et = Et_2O; Ip = *i*-PrOH; Me = MeOH; Pe = petroleum ether (bp 60–80 °C). [c] Reductive alkylation of the *N*,*N*-dibenzylglycyl ester (Scheme I). [d] See Experimental Section. [e] Reduction of **8** with $NaBH_4$. [f] Reductive alkylation of the primary amine ester (Scheme I).

Table II. 5-(N-Substituted-glycyl)salicylamides



no.	R^1	R^3	formula	method	yield, %	crystn solvent[a]	mp, °C
14	H	Me_2CH	$C_{19}H_{22}N_2O_3 \cdot HCl$	C	77	Me	216-218
15	H	$PhCH_2$	$C_{23}H_{22}N_2O_3$	D	53	Ea	179-180
16	Me	Me_2CH	$C_{20}H_{24}N_2O_3 \cdot HCl$	C	64	Al-Ea	205-209
17	H	Me_3C	$C_{20}H_{24}N_2O_3 \cdot HCl$	C	80	Me	230 dec
18	H	$Ph(CH_2)_2CHMe$	$C_{26}H_{28}N_2O_3$	D	68	Ip	116-120

[a] See footnote *b* to Table I.

Lately, other phenethanolamines have been shown to combine β-adrenoceptor blocking activity with α-blocking or vasodilating properties,[7-9] and one of our analogues, medroxalol (**53**), has been the subject of detailed biological investigation.[8] In addition, other β-adrenergic agents that induce a fall in peripheral resistance without reflex tach-

(4) R. T. Brittain, D. M. Harris, D. Jack, and D. A. Richards, *Pharmacol. Biochem. Prop. Drug Subst.*, **2**, 299 (1979).
(5) R. T. Brittain and G. P. Levy, *Br. J. Clin. Pharmacol.*, **3** (Suppl), 681 (1976).
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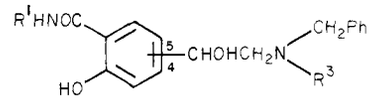
(7) K. Imai, K. Niigata, T. Fujikura, S. Hashimoto, and T. Takenaka, Japanese Patent 7961139 (1979); *Chem. Abstr.*, **92**, 22283*w* (1980). Yamanouchi Pharmaceutical Co. Ltd., Japanese Patent 80 53261 (1980); *Chem. Abstr.*, **94**, 46962 (1981).
(8) (a) J. M. Grisar, G. P. Claxton, T. M. Bare, R. C. Dage, H. C. Cheng, and J. K. Woodward, *J. Med. Chem.*, **24**, 327 (1981). (b) H. C. Cheng, O. K. Reavis, Jr., J. M. Grisar, G. P. Claxton, D. L. Weiner, and J. K. Woodward, *Life Sci.*, **27**, 2529 (1980). (c) R. C. Dage, H. C. Cheng, and J. K. Woodward, *J. Cardiovasc. Pharmacol.*, **3**, 299 (1981).
(9) R. E. Philion, D. K. Phillips, S. C. Laskowski, D. C. Schlegel, R. R. Lorenz, P. H. Hernandez, and H. E. Lape, "Abstracts of Papers", 176th National Meeting of the American Chemical Society, Miami Beach, FL, Sept 1978, American Chemical Society, Washington, DC, 1978, Abstr MEDI 024.

Table III. (2-Amino-1-hydroxyethyl)salicylamides



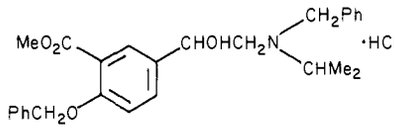
no.	R^1	R^3	position of side chain	formula	method	yield, %	crystn solvent[a]	mp, °C
19	H	Me_2CH	4	$C_{19}H_{24}N_2O_3$	A	53	B	155–156
20	Me	$Ph(CH_2)_2CHMe$	5	$C_{24}H_{26}N_2O_3 \cdot HCl$	A	65		183–185

[a] See footnote *b* to Table I.

ycardia have been reported, e.g., prizidolol,[10] MK-761,[11] and bucindolol;[12] these compounds, however, are aryloxypropanolamines.

Chemistry. The amides **3** were generally prepared from the corresponding esters **1**[1] by treatment with a methanolic solution of the appropriate amine or ammonium hydroxide at room temperature, followed by removal of any benzyl group by catalytic hydrogenation (Scheme I, methods A and B). This procedure was preferable to aminolysis of the intermediate glycyl esters, followed by hydrogenation (method C). A less flexible but otherwise satisfactory route involved the reaction of 5-(bromoacetyl)salicylamide with an *N*-benzylamine, followed by catalytic reduction of the ketone and removal of the *N*-benzyl group (method D). The substituent R^3 could also be introduced by reductive alkylation of dibenzylamino ketones (method E) or primary arylethanolamines (method F) with the appropriate carbonyl compound. Amides obtained by these routes are listed in Tables II–IV.

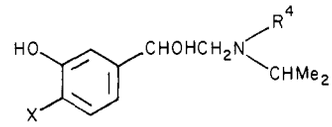
Since aminolyses of the phenolic ester 1 did not readily afford a hydroxamic acid **26** or a 2-hydroxyethyl amide **25**, these were prepared from the benzyloxy ester **73** with hydroxylamine and 2-aminoethanol, respectively, followed by hydrogenolysis of both benzyl protecting groups.



73

Phenethanolamine esters were made by the method previously described;[1] new compounds are shown in Table I.

The 4-substituted salicylamides were much less accessible, and only the isopropylamino derivative **74** was prepared from the corresponding benzylamino ester **75**[1] by method A.



74, X = H_2NOC; R^4 = H
75, X = MeO_2C; R^4 = CH_2Ph

Hitherto unreported ketones used in the reductive alkylation of amines (methods E and F) are listed in Table V. They were prepared either by catalytic reduction of an unsaturated ketone (method G) or by alkylation of an amine or phenoxide with chloroacetone (method H).

$$ArCH{=}CHCOMe \xrightarrow[\text{method G}]{H_2,\ Pd/C} ArCH_2CH_2COMe$$

$$ArOH + ClCH_2COMe \xrightarrow[\text{method H}]{} ArOCH_2COMe$$

$$XNH + ClCH_2COMe \xrightarrow[\text{method H}]{} XNCH_2COMe$$

X = ArMe or heterocyclyl residue

Representative examples are given under Experimental Section.

When the substituent R^3 was asymmetric, the products usually contained approximately 50% of each racemic pair of diastereoisomers. Their ratio could be assessed from the NMR spectra of their hydrochlorides. When determined in an isotropic solvent such as pyridine, two doublets due to the methyl group were observed at τ 9.02; these doublets were separated by 1 Hz using a 60-MHz spectrometer.

One compound, labetalol (**34**), was selected for development as an antihypertensive agent[4] and is now marketed as Trandate.

Stereochemistry. Labetalol (**34**) contains two asymmetric centers and, therefore, consists of two racemic compounds. The method of preparation of labetalol hydrochloride (method D) and its crystallization from ethanol–ethyl acetate consistently provided material with a mp of 188–191 °C. This product was a 50:50 mixture of the two components as assessed by NMR spectra in pyridine, by GLC,[13] and by HPLC. Under carefully controlled conditions, it was possible to separate these racemic substances by fractional crystallization. Crystallization of the hydrochloride six times from ethanol gave "racemate I hydrochloride", mp 220 °C, whereas "racemate II" was preferentially obtained by four recrystallizations of labetalol base from ethanol, followed by conversion into the hydrochloride, mp 183 °C. Comparison of these two racemic modifications with labetalol (Table IV) showed that the α-blocking activity resided mainly in "racemate I", whereas the β-blocking activity is due almost entirely to "racemate II". These results have been confirmed in a recent publication.[14]

In order to correlate the biological activity with stereochemical structure, we synthesized the four individual enantiomers.[15] This required the preparation of the *R* and *S* forms[16] of 1-methyl-3-phenylpropanamine and their conversion into the corresponding mixtures of diastereo-

(10) A. Bell, M. J. Boyce, W. I. Burland, and D. D. Underwood, *Br. J. Clin. Pharmacol.*, **9**, 299P (1980).
(11) J. J. Baldwin, W. C. Lumma, G. F. Lundell, G. S. Ponticello, A. W. Raab, E. L. Engelhardt, R. Hirschmann, C. S. Sweet, and A. Scriabine, *J. Med. Chem.*, **22**, 1284 (1979).
(12) *J. Am. Med. Assoc.*, **242**, 2467 (1979).
(13) G. Munro, J. H. Hunt, L. R. Rowe, and M. B. Evans, *Chromatographia*, 11, 440 (1978).
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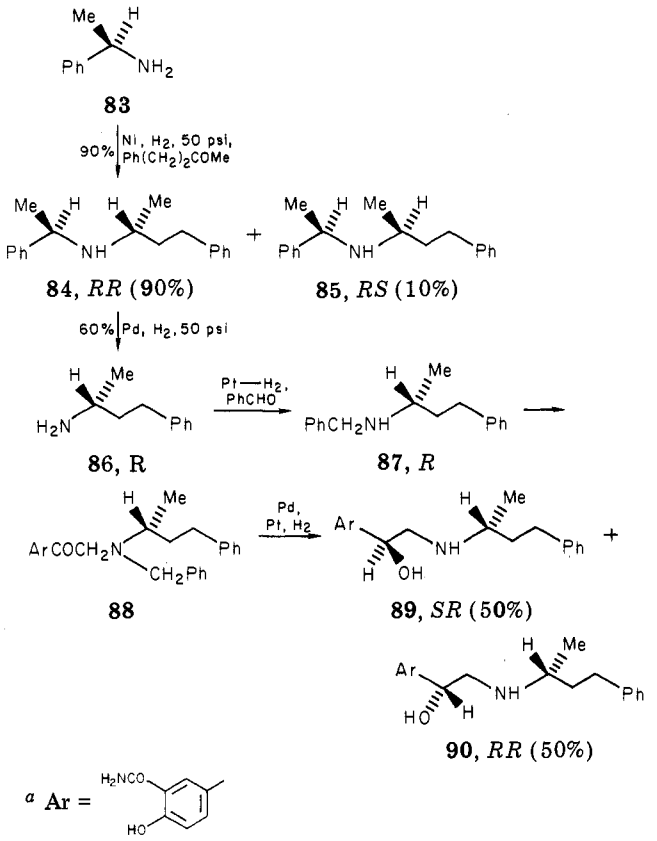
(15) Since this work was completed a synthesis of these enantiomers has been disclosed: E. H. Gold and W. Chang, Eur. Pat. Appl. 9702 (1980).
(16) R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, 12, 81 (1956).

Scheme II[a]

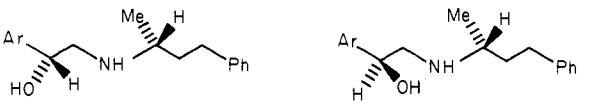


mers of labetalol according to method D.

The (*R*)-amine **86** was prepared by asymmetric synthesis in a manner similar to that used to prepare some optically active amphetamine derivatives (Scheme II).[17] Commercially available (*R*)-(+)-α-methylbenzylamine **83** was reductively alkylated with 4-phenyl-2-butanone and hydrogen over Raney nickel catalyst at 50 psi to give a mixture containing the (*RR*)-amine **84** and the (*RS*)-amine **85** in a ratio of 9:1. This mixture was converted into the corresponding hydrochlorides and recrystallized twice from methanol–ethyl acetate to give the (*RR*)-amine **84** as its hydrochloride in 37% yield with an enantiomeric purity of >99% as determined by GLC.[13] Since the amine was too hindered to react with phenacyl halides, it was hydrogenolyzed over palladium on carbon at 50 psi to give the primary (*R*)-amine **86**. This amine has been prepared previously by resolution of the (*RS*)-amine with (−)-mandelic acid,[18] (+)-tartaric acid,[19] and (−)-dibenzoyltartaric acid,[20] and its stereochemistry has been assigned by degradative[18,19] and ORD[19,20] procedures. In view of the fact that the Czech[19] and Dutch[18] workers arrived at opposite conclusions, we confirmed that the levorotatory isomer (−)-**86** had the *R* configuration by X-ray crystallography of the hydrochloride of the corresponding *N*-benzylamine **87**.[21]

Reductive alkylation of the (*R*)-amine **86** with benzaldehyde and hydrogen over a platinum catalyst gave the *N*-benzyl derivative **87**, which was converted into a 1:1 mixture of the SR + RR diastereomers **89** and **90** by method D. Although these compounds could be separated by fractional crystallization, a more efficient procedure utilized high-pressure liquid chromatography of their *O,N*-dibenzyl derivatives using a Waters Associates Prep. LC-system 500. Each isomer was isolated in approximately 35% yield, and debenzylation gave the (*RR*)- and (*SR*)-amines **89** and **90** in greater than 99% enantiomeric purity. The absolute configuration of the hydrochloride of the *RR* enantiomer was established by X-ray crystallography.[21]

Starting with the commercially available (*S*)-(+)-α-methylbenzylamine, we obtained the *SS* and *RS* enantiomers, **92** and **91**, in a similar manner.



Biological Test Procedures.[5,22] Adrenoceptor blocking activities were determined in the anesthetized dog. The β-adrenoceptor blocking activity was assessed by the ability of the drug to antagonize the effects of intravenously administered (−)-isoproterenol on heart rate and blood pressure. Antagonism of the pressor response to phenylephrine was used as a measure of α-blocking activity. The results were analyzed in the form of a Schild plot,[23] and in each instance the dose required to cause a 10-fold displacement of the agonist dose–response curve, the DR_{10} value, was calculated. These data are expressed in Table IV as equipotent doses relative to propranolol (β-blockade) and phentolamine (α-blockade), respectively. If required, the absolute DR_{10} values can be derived from these results using DR_{10} values shown for the reference compounds in Table VII.

In general only one determination was made for each antagonist. Labetalol (**34**), however, has been more extensively investigated.[5,22b] Its α- and β-antagonist potencies, determined as above, are expressed as DR_{10} values in Table VII and, from experiments in vitro, as pA_2 values in Table VIII.

Structure–Activity Relationships. Arylethanolamines having alkyl groups on the basic nitrogen, compounds **21–27**, were β-adrenoceptor blocking agents, the most active of which, **22**, had an activity one-quarter that of propranolol.[24] Substitution on the amidic nitrogen generally afforded less active compounds, **23–27**. The 4-isomer, **74**, had a β-blocking activity one-tenth that of propranolol and five times that of its 5-isomer, **21**.

Some analogues when substituted on the basic nitrogen by specific aralkyl groups showed good α-blocking activity in addition to β-blockade, and compounds having this combination of effects, e.g., **34**, **46**, **47**, and **48**, caused rapid and sustained lowering of blood pressure in DOCA hypertensive rats and in conscious normotensive and renal hypertensive dogs.[4] An apparently satisfactory balance between β- and α-adrenergic blockade was shown by labetalol (**34**), which was 4–16 times more potent at β- than at α-receptors.[5] In these compounds, the capacity to block α-adrenoceptors appears to be associated with the aral-

(17) D. E. Nichols, C. F. Barfknecht, D. B. Rusterholz, F. Benington, and R. D. Morin, *J. Med. Chem.*, **16**, 480 (1973).
(18) J. van Dijk, V. G. Keizer, and H. D. Moed, *Recl. Trav. Chim. Pays-Bas*, **82**, 189 (1963).
(19) O. Cervinka, E. Kroupova, and O. Belovsky, *Collect. Czech. Chem. Commun.*, **33**, 3551 (1968).
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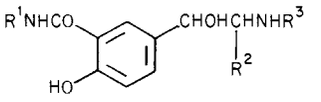
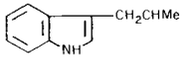
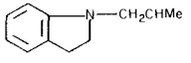
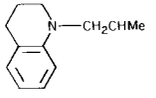
(21) P. Murray-Rust, "Molecular Structure and Biological Activity", W. L. Duaz, Ed., Elsevier, Amsterdam, in press.
(22) (a) J. B. Farmer, I. Kennedy, G. P. Levy, and R. J. Marshall, *Br. J. Pharmacol.*, **45**, 660 (1972). (b) I. Kennedy and G. P. Levy, *ibid.*, **53**, 585 (1975).
(23) O. Arunlakshana and H. O. Schild, *Br. J. Pharmacol.*, **14**, 48 (1959).
(24) C. H. Blackburn, L. J. Byrne, V. A. Cullum, J. B. Farmer, and G. P. Levy, *J. Pharm. Pharmacol.*, **21**, 488 (1969).

Table IV. 5-(2-Amino-1-hydroxyethyl)salicylamides



no.	R¹	R²	R³	formula	method	yield, %	crystn solvent [a]	mp, °C	activity (dose ratio): β-blockade [b] heart rate	β-blockade [b] blood press.	α-blockade: [c] blood press.	ratio, DR_{10} (α)/ DR_{10} (β₁)
21	H	H	Me_2CH	$C_{12}H_{18}N_2O_3 \cdot HCl$	C	73	Me-Ea	207-208	50			
22	H	H	Me_3C	$C_{13}H_{20}N_2O_3 \cdot HCl$	C	75	Me-Ip	203-204	4			
23	Me	H	Me_2CH	$C_{13}H_{20}N_2O_3 \cdot HCl$	C	71	Al	208-209	>50			
24	$PhCH_2$	H	Me_2CH	$C_{19}H_{24}N_2O_3 \cdot HCl$	B	44	Me-Ea	211-212	>50			
25	$HO(CH_2)_2$	H	Me_2CH	$C_{14}H_{22}N_2O_4 \cdot HCl$	*d*	83	Ip	195	>50			
26	OH	H	Me_2CH	$C_{12}H_{18}N_2O_4$ [e]	*d*	30		186-188	20			
27	NH_2	H	Me_3C	$C_{13}H_{21}N_3O_3 \cdot H_2O$	B	78		>300	100			
28	H	H	$PhCH_2CHMe$	$C_{18}H_{22}N_2O_3 \cdot HCl$	E	87	Me-Ea	195-196	43	38	15	3
29	H	H		$C_{20}H_{23}N_3O_3 \cdot C_6H_8O_7 \cdot 0.5H_2O$ [f]	E	6		frothed 90	43	23		
30	H	H		$C_{20}H_{25}N_3O_3$	E	40	B	126-130	70	37	18	2
31	H	H		$C_{21}H_{27}N_3O_3$ [g]	E	37	B	125-129	70	97	NA [u]	
32	H	H	PhCONH-(4-c-C_5H_9N)-CH_2CHMe	$C_{24}H_{32}N_4O_4$	B	86	Ea-Pe	120-125	36	100	NA	
33	H	H	$Ph(CH_2)_3$	$C_{18}H_{22}N_2O_3 \cdot HCl$	F	30	Me-Ea	199-200	13	87	59	36
34	H	H	$Ph(CH_2)_2CHMe$	$C_{19}H_{24}N_2O_3 \cdot HCl$	D	67	Al-Ea	187-189	4	17	8	16
35	H	H	$Ph(CH_2)_2CMe_2$	$C_{20}H_{26}N_2O_3 \cdot 0.5H_2O$	B	80		152-154	5	13	⩾10	
36	H	H	Ph_2CHCH_2CHMe	$C_{25}H_{28}N_2O_3 \cdot HCl$	E	27	Al	220	16	93	24	11
37	H	H	$PhCH_2CH(CO_2Et)CHMe$	$C_{22}H_{28}N_2O_3 \cdot HCl$	B	83	Me-Ea	168	48	16	NA	
38	H	H	$PhCH(OH)CH_2CH_2$	$C_{18}H_{22}N_2O_4 \cdot H_2O$ [h]	B	80		80-94	31	20	10	3
39	H	H	$PhNHCH_2CHMe$	$C_{18}H_{23}N_3O_3$	B	30	Ea-Pe	124-126	9	29	NA	
40	H	H	$PhNMeCH_2CHMe$	$C_{19}H_{25}N_3O_3 \cdot 0.5H_2O$	E	58	Et	128-131	24	18	9	3
41	H	H	$PhNEtCH_2CHMe$	$C_{20}H_{27}N_3O_3 \cdot 0.5H_2O$	E	44	B	132-137	26	90	NA	
42	H	H	$PhNCHMe_2CH_2CHMe$	$C_{21}H_{29}N_3O_3 \cdot H_2O$	E	66	Ea-Pe	137-141	127	160	NA	
43	H	H	$PhNAcCH_2CHMe$	$C_{20}H_{25}N_3O_4 \cdot HCl \cdot 0.5H_2O$	E	14		120-125	6	126	NA	
44	H	H	4-$MeC_6H_4(CH_2)_2CHMe$	$C_{20}H_{26}N_2O_3 \cdot 0.5H_2O$ [i]	E	42	B	140-145	28		23	8
45	H	H	4-$CF_3C_6H_4(CH_2)_2CHMe$	$C_{20}H_{23}F_3N_2O_3$	E	45		131-133	36	360		
46	H	H	2-$FC_6H_4(CH_2)_2CHMe$	$C_{19}H_{23}FN_2O_3$	B	32	Et	145-150	4	14	12	24
47	H	H	3-$FC_6H_4(CH_2)_2CHMe$	$C_{19}H_{23}FN_2O_3$	B	39		146-150	2	7	16	75
48	H	H	4-$FC_6H_4(CH_2)_2CHMe$	$C_{19}H_{23}FN_2O_3 \cdot HCl$	B	90	Me-Ea	212-213	4	29	10	18
49	H	H	4-$ClC_6H_4(CH_2)_2CHMe$	$C_{19}H_{23}ClN_2O_3 \cdot HCl$	E	13	Me-Ea	227	10	50	34	26
50	H	H	4-$HOC_6H_4(CH_2)_2CHMe$	$C_{19}H_{24}N_2O_4 \cdot HCl$	F	23	Me-Ea	168-170	7	33	>30	
51	H	H	4-$MeOC_6H_4(CH_2)_2CHMe$	$C_{20}H_{26}N_2O_4$ [j]	F	63	Ea-B	152	5	57	27	43
52	H	H	3,4-$(MeO)_2C_6H_3(CH_2)_2CHMe$	$C_{21}H_{28}N_2O_5$	E	41	Ea-Pe	115-118	13	73	>10	
53	H	H	3,4-$(CH_2O_2)C_6H_3(CH_2)_2CHMe$	$C_{20}H_{24}N_2O_5 \cdot HCl$	B	81	Me-Ea	217-223	7	33	NA	
54	H	H	4-$MeO_2CC_6H_4(CH_2)_2CHMe$	$C_{21}H_{26}N_2O_5 \cdot 0.5H_2O$	E	90		140	6	100		
55	H	H	4-$H_2NOCC_6H_4(CH_2)_2CHMe$	$C_{20}H_{25}N_3O_4 \cdot HCl$	*k*	41	Me-Ea	195-196	6	17	NA	

56	H	H	4-$Me_2NC_6H_4(CH_2)_2CHMe$	$C_{21}H_{29}N_3O_3 \cdot 0.5H_2O$ [l]	E	76	Ea–Pe	138–146	29	133	NA
57	H	H	4-$AcNHC_6H_4(CH_2)_2CHMe$	$C_{21}H_{27}N_3O_4 \cdot HCl$ [m]	B	94	Me–Ea	170–171	24	200	NA
58	H	H	4-(c-$C_5H_{10}N)C_6H_4(CH_2)_2CHMe$	$C_{26}H_{33}N_3O_3 \cdot 2HCl \cdot 1.5H_2O$ [n]	E	27	E	130–133	84	267	NA
59	H	H	4-$FC_6H_4(CH_2)_2CHEt$	$C_{20}H_{25}FN_2O_3$ [o]	E	15	B	90–96 dec	27		NA
60	H	H	4-$FC_6H_4CH_2CMe_2CH_2$	$C_{20}H_{25}FN_2O_3 \cdot HCl \cdot H_2O$ [p]	E	42	Me–Ea	174–177	307	326	NA
61	H	H	$PhCO(CH_2)_2$	$C_{18}H_{20}N_2O_4 \cdot HCl$	*q*	32	Ip	165–169	71	477	6
62	H	H	4-$FC_6H_4OCH_2CHMe$	$C_{18}H_{21}FN_2O_4 \cdot HCl$	E	73	Me–Ea	142–144	7	110	67
63	H	H	2-$MeOC_6H_4OCH_2CHMe$	$C_{19}H_{24}N_2O_5$ [r]	F	53	B	125–127	29	133	19
64	H	H	3,4-$(CH_2O_2)C_6H_3OCH_2CHMe$	$C_{19}H_{22}N_2O_6$	E	17	Ea	110–112	3	45	NA
65	H	H	4-$MeC_6H_4NMeCH_2CHMe$	$C_{20}H_{27}N_3O_3$	E	65	B	112–119	52	90	NA
66	H	H	4-$FC_6H_4NMeCH_2CHMe$	$C_{19}H_{24}FN_3O_3$	E	61	B	125–129	36	100	27
67	H	H	4-$HOC_6H_4NMeCH_2CHMe$	$C_{19}H_{25}N_3O_4 \cdot 1.5HCl$	E	18		125–145	30	113	NA
68	H	H	4-$MeOC_6H_4NMeCH_2CHMe$	$C_{20}H_{27}N_3O_4$ [s]	E	40	B	105–110	12	50	NA
69	H	H	$PhNHCOCH_2CHMe$	$C_{19}H_{23}N_3O_4$	B	94	Et	163–169	156	540	NA
70	H	H	$Ph(CH_2)_3CHMe$	$C_{20}H_{26}N_2O_3 \cdot 0.5H_2O$	F	42	Ea	149	39	167	35
71	H	Me [t]	$Ph(CH_2)_3$	$C_{19}H_{24}N_2O_3$	F	30	Ea–Pe	168–170	51	130	10
72	Me	H	$Ph(CH_2)_2CHMe$	$C_{20}H_{26}N_2O_3 \cdot HCl$	A	28		203–207	40	>300	10

0.5	7	2	2
75			
5			
	6		

[a] See footnote *b* in Table I. IPa = *i*-PrOAc. [b] Equipotent dose compared to propranolol (in the anesthetized dog). [c] Equipotent dose compared to phentolamine (in the anesthetized dog). [d] See text. [e] Anal. C: calcd, 56.7; found, 56.2. [f] $C_6H_8O_7$ = citric acid. [g] Anal. N: calcd, 11.4; found, 10.8. [h] Anal. N: calcd, 8.0; found, 7.5. [i] Anal. N: calcd, 8.0; found, 8.8. [j] Anal. N: calcd, 7.8; found, 7.3. [k] Ammonolysis of the ester **54**. [l] Anal. C: calcd, 66.3; found, 65.8. [m] Anal. C: calcd, 59.8; found, 59.3. [n] Anal. H: calcd, 7.5; found, 7.0. [o] Anal. C: calcd, 66.65; found, 65.9. N: calcd, 7.8; found, 8.8. [p] Anal. N: calcd, 6.8; found, 7.3. [q] See Experimental Section. [r] Anal. C: calcd, 63.3; found, 62.5. [s] Anal. N: calcd, 11.2; found, 10.7. [t] Erythro isomer. [u] NA = not active.

kylamine portion of the molecule, and for optimum $\alpha + \beta$ blocking activity, this moiety requires (a) a three-atom separation of aryl from nitrogen, since compounds with a two-carbon and four-carbon chain, **28** and **70**, respectively, were less active than their corresponding analogues with a three-carbon chain, **34**, but retained some α-adrenoceptor blocking activity, and (b) a 1-methyl substituent, since its replacement by hydrogen or ethyl led to less active compounds, **33** and **59**, respectively. The *gem*-dimethyl analogue **35** was a good β-antagonist, but it was much less active at α-adrenoceptors.

Substitution in the aromatic ring was generally disadvantageous, but the profile of activity of the fluoro derivatives, **46–48**, was similar to that of the unsubstituted compound **34** with a less favorable ratio of β to α potency in **47**. Replacement of the CH_2 group situated adjacent to the aryl group by O, NH, or *N*-alkyl afforded less active compounds, e.g., **62**, **39**, and **40**. Effects of alteration of structure on α-adrenoceptor blocking activity were unpredictable. Several compounds, e.g., **40**, **61**, and **72**, had an apparently higher ratio of α to β blockade but only at the expense of the latter.

The biological activities of the individual enantiomers of labetalol are shown in Table VI. From these results it may be seen that the β-adrenoceptor blocking activity is almost entirely due to the *RR* enantiomer. In particular, the *R* configuration for the chiral center bearing the hydroxyl group is consistent with that of other arylethanolamines known to act at β-adrenoceptors.[25] On the other hand, the α-blocking activity is mainly due to the *SR* isomer and, to a lesser extent, to the *SS* isomer. This observation is difficult to interpret, since labetalol represents the first arylethanolamine with potent α-blocking activity. However, if this antagonism is mediated by direct interaction with the α-receptor and not via an allosteric site, then it appears that the α-receptor will accommodate arylethanolamines with the chiral center bearing the hydroxyl group having either an *R* (as in epinephrine[25g]) or *S* configuration.

α-Blockers, such as phentolamine (Regitine) or thymoxamine (Opilon), are known to lower blood pressure by inhibiting the stimulant effects of norepinephrine at vascular α-adrenoceptors. As a consequence, they dilate peripheral arterioles and cause a decrease in total peripheral resistance. This action is effective in lowering blood pressure in hypertensive patients but, in addition, it can cause postural hypotension plus an unpleasant and often unacceptable reflex tachycardia resulting from physiological efforts to maintain blood pressure.[26] Therefore, nonselective α-blockers are seldom used on their own to treat hypertension. Conversely, the antihypertensive effect caused by β-blockers, such as propranolol (Inderal), is accompanied by a reduction in cardiac output. This mechanism would not be expected to cause rapid falls in blood pressure because the decrease in cardiac output is offset by an increase in peripheral resistance.[26] Consequently, the simultaneous administration of drugs that block both α- and β-receptors would be expected to have an additive effect in lowering blood pressure while mini-

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Table V. Ketones

no.	structure	formula	method[a]	yield, %	crystn solvent[b]	mp or bp (mm), °C
76	4-$FC_6H_4(CH_2)_2COMe$	$C_{10}H_{11}FO$	G	76		79 (1.25)
77	4-$AcNHC_6H_4(CH_2)_2COMe$	$C_{12}H_{15}NO_2$	G	100	Al	130-132
78	4-$FC_6H_4OCH_2COMe$	$C_9H_9FO_2$[c]	H	d		oil
79	4-$FC_6H_4NMeCH_2COMe$	$C_{10}H_{12}FNO$	H	69[d]		88-92 (0.2)
80	4-$MeC_6H_4NMeCH_2COMe$	$C_{11}H_{15}NO$	H	80[d]		95 (0.05)
81	PhCONH-(4-c-C_5H_9N)-CH_2COMe	$C_{15}H_{20}N_2O_2$[e]	H	60	Ea	117-120
82		$C_{12}H_{15}NO\cdot HCl$	H	30[d]		118-120

[a] See text. [b] See footnote b to Table I. [c] Anal. C: calcd, 64.3; found, 63.8. [d] Purified via complex with $NaHSO_3$. [e] Anal. C: calcd, 69.2; found, 68.6.

Table VI. Adrenoceptor Blocking Properties of Labetalol and Its Enantiomeric Components[28]

compd	blockade of cardiac β_1 receptors[a]	blockade of vascular β_2 receptors[a]	blockade of α_1-vascular receptors[b]
labetalol (34)	2.4	8	7.8
RR isomer (90)	1.1	3.7	50.9
SS isomer (92)	70.4	309	19.8
RS isomer (91)	15.9	86	34.4
SR isomer (89)	56.8	377	4.5
RR + *SR* isomers	1.2	6.9	5.8

[a] Propanolol = 1. [b] Phentolamine = 1. See footnotes b and c to Table IV.

Table VII. Relative Adrenoceptor-Blocking Actions of Labetalol, Phentolamine, and Propranolol in the Anesthetized Dog[a,b]

drug	α-blockade: DR_{10}, mg/kg, for antagonism of PE-induced vasopressor responses	β-blockade: DR_{10}, mg/kg,[c] for antagonism of IP-induced	
		positive chronotropy (β_1 response)	vasodepression (β_2 response)
labetalol	8.4 (6.7-10.4)	0.53 (0.4-0.6)	0.53 (0.4-0.8)
phentolamine	1.2 (0.9-1.6)	>10.0	>10.0
propranolol	>3.0	0.13 (0.09-0.17)	0.03 (0.02-0.04)

[a] Reference 4. [b] 95% confidence limits are given in parentheses. [c] IP = isoproterenol; PE = phenylephrine.

mizing the side effects of either drug given independently. Although this therapeutically beneficial procedure has been established by Majid et al.,[27] using a combination of phentolamine and oxprenolol, it has the disadvantage that the absorption, pharmacokinetics, and metabolism of each drug are different and this may lead to problems in providing a balanced control of blood pressure. This is less likely to be the case with labetalol (34), where the biological activity is mainly due to the independent actions of two structurally related compounds, the *RR* and *SR* diastereomers.[28]

More recently, pharmacological studies have shown that labetalol is selective in blocking α_1-adrenoceptors[4,29,30] (see Table IX) and that it possesses additional vasodilating actions that may contribute to the overall antihypertensive effect of the drug.[31,32]

Human pharmacology has confirmed the α- and β-adrenoceptor blocking activities of labetalol,[33] and clinical experience has shown it to be efficacious in reducing high blood pressure with minimal side effects.[34] In practice, postural hypotension has rarely been observed when the drug is administered at recommended doses.[6,34,35]

Experimental Section

Melting points were determined in open capillary tubes on a Townson-Mercer apparatus and have not been corrected. Compounds gave satisfactory UV, IR, and NMR spectral data and were obtained, respectively, on Perkin-Elmer Model 137 and 402 UV spectrophotometers, Unicam SP 100 and Perkin-Elmer 357 IR spectrophotometers, and Varian Associates A-60A and Perkin-Elmer R12B spectrometers. Microanalyses were determined on a F & M 185 CHN analyzer and by Dr. A. Bernhardt, 5251 Elbach über Engelskirchen, West Germany. Where analyses are indicated only by the symbols of the elements, analytical values obtained were within ±0.4% of the calculated values. Unless stated otherwise, C, H, and N analyses of compounds in the Tables were all within ±0.4% of the calculated values. Optical rotations were determined on the AA-10 automatic polarimeter in methanol

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Table VIII. Comparison of Adrenoceptor-Blocking Actions of Labetalol, Propranolol, and Phentolamine in Isolated Tissues [a,b]

preparation	type of receptor	agonist	labetalol		propranolol		phentolamine	
			pA_2	slope	pA_2	slope	pA_2	slope
rat vas deferens	α	norepinephrine	7.45 (7.19–7.79)	1.03 (0.88–1.19)	not tested		8.22 (8.06–8.41)	1.22 (0.98–1.38)
rat aortic strip	α	norepinephrine	7.42 (6.98–7.81)	0.92 (0.86–1.20)	not tested		8.32 (8.01–8.69)	1.05 (0.85–1.24)
rabbit aortic strip	α	norepinephrine	7.44 (7.01–7.72)	1.21 (0.99–1.38)	<4.0		8.43 (8.11–8.92)	0.96 (0.88–1.16)
guinea pig left atrium	β	isoproterenol	8.31 (7.82–8.53)	0.95 (0.79–1.17)	8.81 (8.42–9.37)	1.23 (0.98–1.47)	<5.0	
guinea pig trachea	β	isoproterenol	8.10 (7.82–8.53)	0.90 (0.71–1.09)	8.33 (8.03–8.76)	0.82 (0.67–0.96)	not tested	

[a] Reference 5. [b] 95% confidence limits are in parentheses.

Table IX. Relative Blocking Actions of Labetalol,[a] Phentolamine, Thymoxamine, and Piperoxan at α_1- and α_2-Adrenoceptors [b]

drug	α-antagonist activity (pA_2 values): postsynaptic adrenoceptors, α_1 (rat, rabbit aorta)	presynaptic adrenoceptors, α_2 (guinea pig ileum)
labetalol	7.0–7.5	<5.0
phentolamine	7.5–8.5	8.5
thymoxamine	7.0–7.5	4.5
piperoxan	6.5–7.0	7.6

[a] Selectivity of other analogues was not determined. [b] Reference 4.

at 22 °C unless stated otherwise.

The isomeric purity of labetalol (34) and its isomers were determined by GLC.[13] The isomeric purity of their *O,N*-dibenzyl derivatives were determined by HPLC on Partisil 10 using a 20 × 0.5 cm column and eluting with hexane–ethyl acetate–ammonia (SG 0.880) (55:45:0.1) at 250 psi; detection was by UV at 280 nm.

Each general method discussed in the theoretical part of this paper is described here by only one representative example. Hydrogenations were carried out at room temperature and atmospheric pressure unless stated otherwise.

Methyl 2-Hydroxy-5-[1-hydroxy-2-[(3-oxo-3-phenylpropyl)amino]ethyl]benzoate Hydrochloride (8) (See Table I). A suspension of methyl 5-[2-[(2-amino-1-hydroxyethyl)amino]ethyl]-2-hydroxybenzoate hydrochloride[1] (2.47 g, 0.01 mol) in EtOH (70 mL), PhCOMe (4.8 g, 0.04 mol), and paraformaldehyde (0.7 g) was stirred under reflux for 6 h. Solvent was removed under reduced pressure, and the residue was triturated with Et_2O (200 mL) and recrystallized.

Preparation of Salicylamides (See Tables II–IV). Method A. 2-Hydroxy-4-[1-hydroxy-2-[*N*-(1-methylethyl)-*N*-(phenylmethyl)amino]ethyl]benzamide (19). A solution of methyl 2-hydroxy-4-[1-hydroxy-2-[*N*-(1-methylethyl)-*N*-(phenylmethyl)amino]ethyl]benzoate (**75**; 3.05 g, 0.089 mol) (prepared by methods previously described[1]) in EtOH (50 mL) with NH_4OH (SG 0.880, 30 mL) was left to stand at room temperature for 1 week and evaporated to dryness. The residue was extracted with Et_2O, the filtered extract was evaporated, and the product was crystallized from benzene to give the amide **19**.

2-Hydroxy-4-[1-hydroxy-2-[(1-methylethyl)amino]ethyl]benzamide Benzoate Salt (74). The preceding amide (0.46 g, 0.001 mol) in MeOH (10 mL) was hydrogenated in the presence of 10% Pd/C (0.1 g) for 19 min. Catalyst and solvent were removed to leave a glassy residue, which crystallized from a mixture of Et_2O and EtOAc as white prisms: yield 0.24 g; mp 114–116 °C. The base was converted into a benzoate salt, **74**, that crystallized from *i*-PrOH as colorless prisms, mp 146–152 °C.

Method B. 5-(2-Amino-1-hydroxyethyl)-2-hydroxybenzamide Hydrochloride. A solution of methyl 5-(2-amino-1-hydroxyethyl)-2-hydroxybenzoate hydrochloride[1] (5 g, 0.02 mol) in NH_4OH (SG 0.880, 100 mL) was left at room temperature for 8 days and evaporated under reduced pressure. The residue crystallized from MeOH–EtOAc to give the amide hydrochloride 3.5 g (62%), which did not melt below 400 °C. Anal. ($C_9H_{12}N_2O_3$·HCl) C, H, N.

Method C. 2-Hydroxy-5-[[*N*-(1-methylethyl)-*N*-(phenylmethyl)amino]acetyl]benzamide Hydrochloride (14). A solution of methyl 2-hydroxy-5-[[*N*-(1-methylethyl)-*N*-(phenylmethyl)amino]acetyl]benzoate hydrochloride[1] (15 g, 0.04 mol) in MeOH (125 mL) and NH_4OH (SG 0.880, 125 mL) was left to stand at room temperature for 6 days and evaporated to dryness. The residue was extracted into Et_2O (3 × 150 mL) and treated with HCl in Et_2O to precipitate an oil, which when boiled with EtOAc afforded colorless crystals of **14**.

2-Hydroxy-5-[1-hydroxy-2-[(1-methylethyl)amino]ethyl]benzamide Hydrochloride (21). A solution of **14** (4.15 g, 0.011 mol) in MeOH (250 mL) was hydrogenated in the presence of 10% Pd/C (1 g) until uptake of H_2 ceased (40 min). Catalyst and

solvent were removed to yield the hydrochloride.

Method D. 2-Hydroxy-5-[[*N*-(1-methyl-3-phenylpropyl)-*N*-(phenylmethyl)amino]acetyl]benzamide (18). 5-(Bromoacetyl)-2-hydroxylbenzamide[37] (2.6 g, 0.01 mol) and *N*-(1-methyl-3-phenylpropyl)phenylmethylamine (4.8 g, 0.02 mol) in EtCOMe (50 mL) were refluxed for 40 min. Solvent was removed by evaporation, and the residue was treated with benzene. The mixture was filtered, the filtrate was evaporated to dryness, and the residual base was treated with excess HCl in EtOH. The hydrochloride of 18 crystallized from the solution, mp 139–141 °C.

2-Hydroxy-5-[1-hydroxy-2-[(1-methyl-3-phenylpropyl)-amino]ethyl]benzamide Hydrochloride (34). A solution of the preceding hydrochloride (0.75 g, 0.0016 mol) in EtOH (20 mL) was hydrogenated in the presence of a mixture of 10% PdO/C (0.05 g) and 10% Pt/C (0.05 g). Removal of catalyst and solvent gave the hydrochloride.

Method E. 2-Hydroxy-5-[1-hydroxy-2-[(1-methyl-2-phenylethyl)amino]ethyl]benzamide Hydrochloride (28). A solution of 15 (9.35 g, 0.025 mol), 3-phenyl-2-propanone (4.02 g, 0.03 mol), and acetic acid (1.5 mL) in MeOH (200 mL) was hydrogenated in the presence of 10% PdO/C (1.0 g) and 10% Pt/C (1.0 g) catalysts. When absorption of H_2 was complete (33 h), catalysts and solvent were removed, and the residual oil in EtOH was treated with EtOAc and HCl in Et_2O to precipitate the hydrochloride 28.

Method F. 2-Hydroxy-5-[1-hydroxy-2-[(3-phenylpropyl)amino]ethyl]benzamide Hydrochloride (33). A suspension of 5-(2-amino-1-hydroxyethyl)-2-hydroxybenzamide hydrochloride (2.3 g, 0.01 mol) in MeOH (50 mL) was neutralized with NaOH (0.4 g, 0.01 mol) in MeOH (10 mL), concentrated, and heated on the steam bath for 1 h with a solution of phenylpropanal (1.34 g, 0.01 mol) in EtOH (100 mL). The cooled solution was hydrogenated in the presence of 10% PdO/C (0.5 g) and 10% Pt/C (0.5 g). After absorption of 1 mol of H_2, catalyst and solvent were removed, and the residue was treated with 2 N HCl and Et_2O. Some insoluble gummy hydrochloride was separated, and the aqueous acidic solution was neutralized with $NaHCO_3$ and extracted with EtOAc. Addition of HCl in Et_2O to the organic solution precipitated a hydrochloride, which was combined with the above gum and crystallized from MeOH–EtOAc to give 33.

***N*,2-Dihydroxy-5-[1-hydroxy-2-[(1-methylethyl)amino]-ethyl]benzamide (26).** A solution of methyl 5-[1-hydroxy-2-[*N*-(1-methylethyl)-*N*-(phenylmethyl)amino]ethyl]-2-(phenylmethoxy)benzoate hydrochloride[1] (73; 4 g, 0.008 mol) in MeOH (30 mL) was added to a solution of NH_2OH (from 32.6 g of NH_2OH·HCl and 11 g of Na in MeOH) (300 mL). After 6 weeks at room temperature, the solution was evaporated and the residue was extracted with Et_2O (3 × 150 mL). Evaporation of the extract afforded an oil, which was dissolved in hot cyclohexane and cooled to yield *N*-hydroxy-5-[1-hydroxy-2-[*N*-(1-methylethyl)-*N*-(phenylmethyl)amino]ethyl]-2-(phenylmethoxy)benzamide as a white solid: yield 2.2 g (58%); mp 134–137 °C dec; recrystallization from cyclohexane raised the mp to 138–140 °C. Anal. ($C_{26}H_{30}N_2O_4$) C, H, N. This amine (1.45 g, 0.0033 mol) in MeOH (32 mL) was hydrogenated in the presence of 10% Pd/C (0.4 g) suspended in H_2O (8 mL). When the theoretical amount of H_2 had been absorbed (15 min), the catalyst and solvents were removed and the residue was triturated with THF, followed by EtOH, to yield 26.

2-Hydroxy-5-[1-hydroxy-2-[(3-oxo-3-phenylpropyl)-amino]ethyl]benzamide Hydrochloride (61). A suspension of 5-(2-amino-1-hydroxyethyl)benzamide hydrochloride (1.2 g, 0.005 mol), paraformaldehyde (0.4 g), and acetophenone (2.4 g, 0.005 mol) in EtOH (50 mL) was refluxed for 6 h and filtered, and the filtrate was evaporated under reduced pressure. The residual oil was triturated with dry Et_2O and crystallized twice from *i*-PrOH.

Preparation of Ketones (See Table V). Method G. 4-(4-Fluorophenyl)-2-butanone (76). 4-(4-Fluorophenyl)-3-buten-2-one[38] (2.90 g, 0.018 mol) in EtOAc (3.50 mL) was hydrogenated in the presence of 10% Pd/C (0.6 g). When uptake of H_2 had ceased (20 min), the catalyst and solvent were removed, and the ketone 76 was purified by distillation.

Method H. 3-[(4-Fluorophenyl)methylamino]-2-propanone (79). 3-Chloro-2-propanone (33.3 g, 0.36 mol) was added dropwise over a period of 10 min to a stirred mixture of 4-fluoro-*N*-methylbenzamine[39] (22.5 g, 0.18 mol) and $NaHCO_3$ (36 g) in EtOH (90 mL). After 21 h at reflux, the mixture was filtered, and the filtrate was evaporated under reduced pressure. The residue in 5 N HCl (100 mL) was washed with Et_2O (3 × 150 mL) and basified (pH 14) with NaOH. Extraction with Et_2O (3 × 200 mL) gave the crude ketone as a red oil. This was purified by treating a solution in EtOH (300 mL) with a solution of $NaHSO_3$ (32.4 g) in H_2O (70 mL). After 4 h at 0 °C, the precipitate was filtered off, washed with EtOH, and dissolved in 2 N HCl (200 mL). The solution was washed with Et_2O (2 × 125 mL), adjusted to pH 14 with NaOH, and extracted with Et_2O (2 × 200 mL). The dried ($MgSO_4$) ethereal extract was evaporated to give the pure ketone 79.

Preparation of the Enantiomeric Components of Labetalol (34). [*R*-(*R,*R**)]-α-Methyl-*N*-(1-phenylethyl)benzenepropanamine Hydrochloride (84).** (*R*)-(+)-α-Methylbenzylamine (83; 36.3 g, 0.3 mol) and benzylacetone (74 g, 0.5 mol) in EtOH (400 mL) were hydrogenated at 50 psi in the presence of Raney nickel (~4 g) for 120 h. The catalyst and the solvent were removed, and the residue was dissolved in CH_2Cl_2 (900 mL). The organic solution was washed with 2 N HCl (4 × 150 mL) (to remove any α-methylbenzylamine) and H_2O (200 mL) and then dried and evaporated. The residue was triturated with Et_2O and collected: yield 78.8 g (91%); isomer ratio by GLC, 90:10 (*RR*/*SR*). The solid was recrystallized twice from MeOH–EtOAc as white needles: yield 37%; mp 223–224.5 °C; $[\alpha]_D$ +58°. Anal. ($C_{18}H_{23}N$·HCl) C, H, N.

Similarly prepared from (*S*)-(−)-α-methylbenzylamine was the (*SS*)-amine: yield 43%; mp 219–222 °C; $[\alpha]_D$ −62°. Anal. ($C_{18}H_{23}N$·HCl) H, N; C: calcd, 74.59; found, 75.2.

(*R*)-α-Methylbenzenepropanamine Hydrochloride (86). [*R*-(*R**,*R**)]-α-Methyl-*N*-(1-phenylethyl)benzenepropanamine hydrochloride (11.8 g, 0.04 mol) was basified with saturated $NaHCO_3$ solution and extracted with EtOAc. The extracts were dried and evaporated. The residue was dissolved in EtOH (300 mL) and hydrogenated at 50 psi for 20 h over 10% PdO/C (4.0 g). The catalyst and solvent were removed, and a solution of the residue in Et_2O was treated with ethereal HCl to give white needles: yield 5.3 g (70%); mp 114–115 °C (from CH_2Cl_2–Et_2O); $[\alpha]_D$ +9.3° [lit.[18] 113.5–114.5 °C; $[\alpha]_D$ +6.8° (H_2O)].

Similarly prepared was the hydrochloride of the (*S*)-amine: yield 76%; mp 114–115 °C; $[\alpha]_D$ −10.0° [lit.[18] 113–114 °C; $[\alpha]_D$ −7.2° (H_2O)].

(*R*)-α-Methyl-*N*-(phenylmethyl)benzenepropanamine Hydrochloride (87). (*R*)-α-Methylbenzenepropanamine hydrochloride (4 g, 0.022 mol) was basified with saturated $NaHCO_3$ solution (100 mL) and extracted with CH_2Cl_2 (4 × 100 mL). The combined extracts were dried and evaporated. The residue was dissolved in absolute EtOH (100 mL) containing PhCHO (2.51 g, 0.023 mol), and the solution was stirred at room temperature for 0.5 h. The ethanolic solution was hydrogenated over prereduced 5% PtO/C (1 g) in EtOH (50 mL) for 16 h. The catalyst and the solvent were removed, and the residue was purified by chromatography on a column of silica and elution with Et_2O. The product was dissolved in dry Et_2O, and the solution was treated with an excess of ethereal HCl to give the salt: yield 8.65 g (73%); mp 186–188 °C (CH_2Cl_2–Et_2O); $[\alpha]_D$ +5.0°. Anal. ($C_{17}H_{21}N$·HCl) C, H, N.

Similarly prepared was the (*S*)-amine: yield 77%; mp 186–188 °C; $[\alpha]_D$ −6°. Anal. ($C_{17}H_{21}N$·HCl) C, H, N.

(*R*)-2-Hydroxy-5-[[*N*-(1-methyl-3-phenylpropyl)-*N*-(phenylmethyl)amino]acetyl]benzamide (88). A suspension of the hydrochloride (87; 4.5 g, 0.0163 mol) in saturated $NaHCO_3$ solution was extracted with EtOAc (4 × 100 mL). The combined

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extracts were washed with $NaHCO_3$ solution, dried, and evaporated. The residual amine in EtCOMe (125 mL) containing propylene oxide (20 mL) was treated with 5-(bromoacetyl)-salicylamide[37] (3.85 g, 0.0149 mol), and the mixture was heated under reflux for 2.5 h. The solvents were removed, and a solution of the residue in EtOAc was washed with saturated $NaHCO_3$ solution, dried, and evaporated. The product in EtOAc was filtered through a column of silica (240 g) to give white microcrystals: yield 67%; mp 122–123° C (from *i*-PrOH); $[\alpha]_D$ +18°. Anal. ($C_{26}H_{28}N_2O_3$) C, H, N.

Similarly prepared was the corresponding (*S*)-glycyl compound: yield 68%; mp 122–124 °C; $[\alpha]_D$ −20°. Anal. ($C_{26}H_{28}N_2O_3$) C, H, N.

2-Hydroxy-5-[1-hydroxy-2-[(1-methyl-3-phenylpropyl)-amino]ethyl]benzamide Hydrochloride (*RR*/*SR* isomers, 1:1, 90 and 89). A solution of (*R*)-2-hydroxy-5-[[*N*-(1-methyl-3-phenylpropyl)-*N*-(phenylmethyl)amino]acetyl]benzamide (88; 4.6 g, 0.011 mol) in EtOH (500 mL) containing AcOH (1 mL) was hydrogenated over 10% Pd/C (0.5 g) and 10% PtO/C (0.5 g) at room temperature and pressure. The absorption of H_2 (0.505 L, theoretical 0.495 L) required 18 h. The suspension was filtered, and the filtrate was evaporated at reduced pressure to afford the crude product as a yellow gum: yield 5 g; isomer ratio by GLC, 51.2:48.8 (*RR*/*SR*). This gum was converted into a hydrochloride: yield 2.6 g (64%); mp 191–192 °C; $[\alpha]_D$ +10.6°; isomer ratio by GLC, 52.2: 47.8 (*RR*/*SR*). Anal. ($C_{19}H_{24}N_2O_3$·HCl) C, H, N.

The analogue, (*S*)-2-hydroxy-5-[[*N*-(1-methyl-3-phenylpropyl)-*N*-(phenylmethyl)amino]acetyl]benzamide (16.2 g), was converted similarly into the mixture of hydrochlorides of the *SS* + *RS* isomers of labetalol (92 and 91): yield 8.85 g (62%); $[\alpha]_D$ −10.9°; mp 191–192 °C. Anal. ($C_{19}H_{24}N_2O_3$·HCl) C, H, N.

[*R*-(*R,*R**)]-5-[1-Hydroxy-2-[*N*-(1-methyl-3-phenylpropyl)-*N*-(phenylmethyl)amino]ethyl]-2-(phenylmethoxy)benzamide (*RR* Isomer) and [*S*-(*R**,*S**)]-5-[1-Hydroxy-2-[*N*-(1-methyl-3-phenylpropyl)-*N*-(phenylmethyl)amino]ethyl]-2-(phenylmethoxy)benzamide (*SR* Isomer).** A suspension of 2-hydroxy-5-[1-hydroxy-2-[(1-methyl-3-phenylpropyl)amino]ethyl]benzamide hydrochloride (*RR* + *SR* isomers; 82.1 g, 0.225 mol) was stirred in saturated $NaHCO_3$ solution (1 L). The organic base was filtered off and dried. A mixture of the base (72 g, 0.220 mol), $PhCH_2Cl$ (59.25 g, 0.470 mol), anhydrous K_2CO_3 (225 g), and NaI (17.5 g) in EtCOMe (2.7 L) was stirred at reflux for 5 h. The cooled solution was filtered, and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in EtOAc (128 mL), and aliquots were injected onto the column of a Waters Prep LC/system 500 and eluted with hexane–EtOAc–NH_3 (SG 0.880) (55.45:0.1) at 350 mL min^{-1}. The appropriate fractions from all the separations were combined and evaporated under reduced pressure to afford the *RR* isomer (yield 55.7 g; isomer ratio by HPLC, 98.7:1.3) and the *SR* isomer [yield 57.5 g; isomer ratio by HPLC, 98.7:1.3 (*SR*:*RR*)] as gums. The two products were rechromatographed to effect further purification. The *RR* isomer (40.2 g, 35.3%) was obtained with an isomer ratio of 99.9:0.1 and $[\alpha]_D$ −30.1°. The *SR* isomer (35.7 g, 31.3%) was obtained with an isomer ratio of 99.8:0.2 and $[\alpha]_D$ +3.5°.

In a similar manner, the *SS* and *RS* isomers were isolated, with an isomeric purity by HPLC of >99.6%, from a 1:1 mixture of their hydrochlorides.

[*R*-(*R)]-2-Hydroxy-5-[1-hydroxy-2-[(1-methyl-3-phenylpropyl)amino]ethyl]benzamide Hydrochloride (*RR* isomer, 90).** [*R*-(*R**,*R**)]-5-[1-Hydroxy-2-[*N*-(1-methyl-3-phenylpropyl)-*N*-(phenylmethyl)amino]ethyl]-2-(phenylmethoxy)benzamide (19.1 g, 0.038 mol) in EtOH (220 mL) was hydrogenated over 10% Pd/C (1 g) until the theoretical volume of H_2 (1.68 L) had been absorbed. The catalyst was filtered off, and the solvent was evaporated under reduced pressure to give the base as a gum, which slowly solidified: yield 11.7 g (94.9%); $[\alpha]_D$ −21.7°; isomeric purity by GLC >99%. This base in EtOAc was converted into the hydrochloride: yield 16.9 g (87%); mp 195–196 °C;[40] $[\alpha]_D$ −28.9°; isomeric purity by GLC >99%. Anal. ($C_{19}H_{24}N_2O_3$·HCl) C, H, N.

In a similar manner were prepared the *SR* isomer (89: $[\alpha]_D$ +34.2°; isomeric purity by GLC >99%; hydrochloride: recrystallized from *i*-PrOH–hexane; mp 174–175 °C; $[\alpha]_D$ +51.7°; isomeric purity by GLC >99%. Anal. ($C_{19}H_{24}N_2O_3$·HCl) C, H, N), the *SS* isomer (92: $[\alpha]_D$ +21.8°, isomeric purity by GLC >99%; hydrochloride: mp 137–139 °C; $[\alpha]_D$ +28.5°; isomeric purity by GLC 97%. Anal. ($C_{19}H_{24}N_2O_3$·HCl) C, H, N), and the *RS* isomer (91: $[\alpha]_D$ −36.2°; isomeric purity by GLC >99%; hydrochloride: mp 174–176 °C; $[\alpha]_D$ −48.6°; $[\alpha]_D$ calcd to dry wt −50.1°; isomeric purity by GLC 94%. Anal. ($C_{19}H_{24}H_2O_3$·HCl·0.13$C_4H_8O_2$)[41] C, H, N.

Biological Determinations.[5] α-Adrenoceptor and β-adrenoceptor blocking potencies were determined in anesthetized dogs. Anesthesia was induced with thiopentone (25 mg/kg) intravenously and maintained with barbitone (250 mg/kg) intraperitoneally. Animals were bilaterally vagotomized and were artificially respired with room air through a cuffed endotracheal tube using a stroke volume of 13 mL/kg and a rate of 20 strokes/min. Blood pressure was recorded from a femoral artery, and the pulse pressure was used to trigger a heart rate meter.

One agonist–antagonist combination was tested in each dog. Dose–response curves were obtained by the sequential intravenous injection of increasing doses of agonist before and from 15 min after administration of cumulative doses of antagonist. Antagonists were tested at three or more dose levels in each experiment. More detailed descriptions of the methods used are given in the papers by Daly et al.[36] and Kennedy and Levy.[22b]

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(40) A polymorphic form, mp 137–139 °C has also been obtained.
(41) The hydrochloride of the *RS* isomer contained entrained EtOAc.