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

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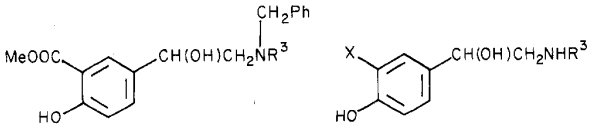
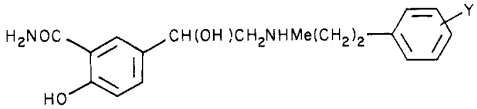
A series of phenethanolamines (**3**) based on salicylamide has been prepared and shown to possess β-adrenergic blocking properties. When the basic nitrogen atom was substituted by some aralkyl groups, the compounds also blocked α-adrenoceptors. The 1-methyl-3-phenylpropyl derivative labetalol (**34**) 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 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

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



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

(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

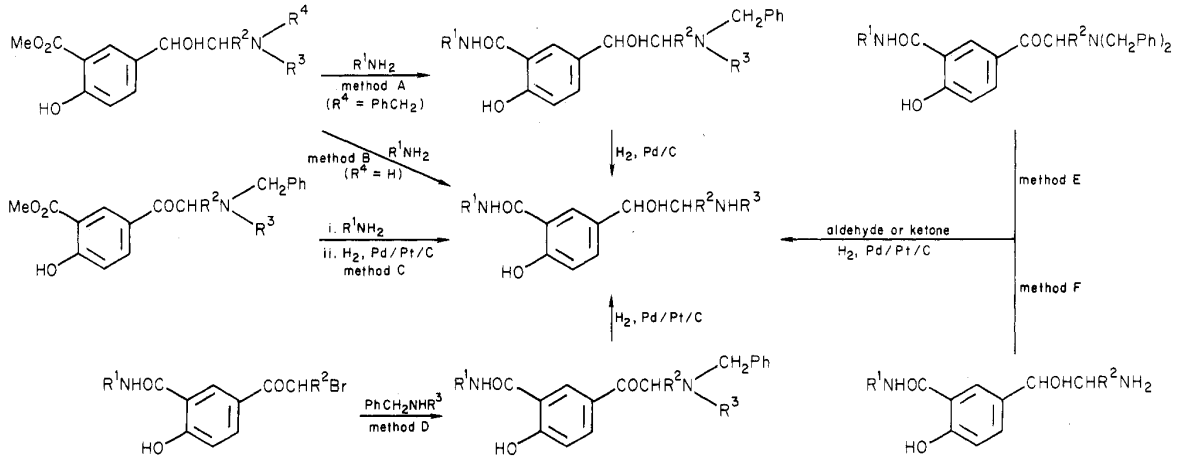
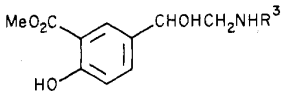


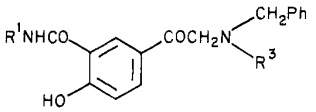
Table I. 5-(2-Amino-1-hydroxyethyl)salicylic Acid Esters [a]



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



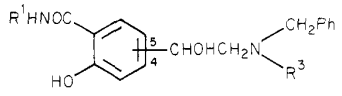
no.	R^1	R^3	formula	method	yield, %	crystn solvent [a]	mp, °C
14	H	Me_2CH	$C_{19}H_{22}N_2O_3 \cdot HCl$	C	77	Me	216-218
15	H	$PhCH_2$	$C_{23}H_{22}N_2O_3$	D	53	Ea	179-180
16	Me	Me_2CH	$C_{20}H_{24}N_2O_3 \cdot HCl$	C	64	Al-Ea	205-209
17	H	Me_3C	$C_{20}H_{24}N_2O_3 \cdot HCl$	C	80	Me	230 dec
18	H	$Ph(CH_2)_2CHMe$	$C_{26}H_{28}N_2O_3$	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).
(6) R. N. Brogden, R. C. Heel, T. M. Speight, and E. S. Avery, *Drugs*, **15**, 251 (1978).
(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 8053261 (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



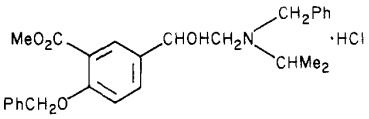
no.	R^1	R^3	position of side chain	formula	method	yield, %	crystn solvent[a]	mp, °C
19	H	Me_2CH	4	$C_{19}H_{24}N_2O_3$	A	53	B	155–156
20	Me	$Ph(CH_2)_2CHMe$	5	$C_{24}H_{26}N_2O_3 \cdot HCl$	A	65		183–185

[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.

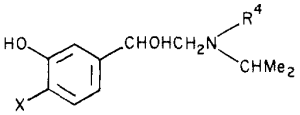
Since aminolyses of the phenolic ester **1** did not readily afford a hydroxamic acid **26** or a 2-hydroxyethyl amide **25**, these were prepared from the benzyloxy ester **73** with hydroxylamine and 2-aminoethanol, respectively, followed by hydrogenolysis of both benzyl protecting groups.



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.

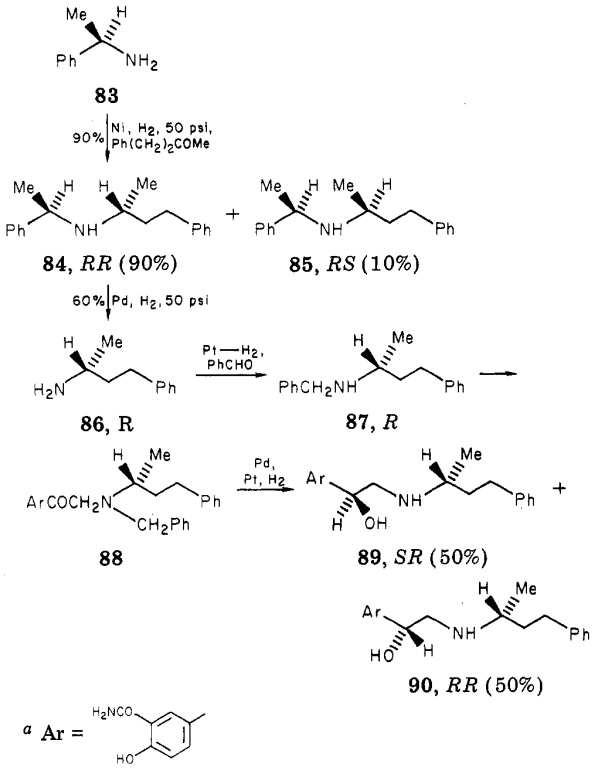
One compound, labetalol (**34**), was selected for development as an antihypertensive agent[4] and is now marketed as Trandate.

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).
(14) Y. Nakagawa, N. Shimamoto, M. Nakozawa, and S. Imai, *Jpn. J. Pharmacol.*, **30**, 743 (1980).
(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]



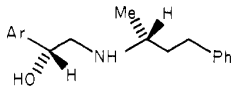
[a] Ar =

mers of labetalol according to method D.

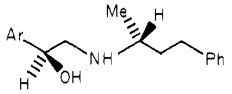
The (*R*)-amine **86** was prepared by asymmetric synthesis in a manner similar to that used to prepare some optically active amphetamine derivatives (Scheme II).[17] Commercially available (*R*)-(+)-α-methylbenzylamine **83** was reductively alkylated with 4-phenyl-2-butanone and hydrogen over Raney 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.



91, *RS*



92, *SS*

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.

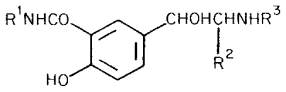
In general only one determination was made for each antagonist. Labetalol (**34**), however, has been more extensively investigated.[5,22b] Its α- and β-antagonist potencies, determined as above, are expressed as DR_{10} values in Table VII and, from experiments in vitro, as pA_2 values in Table VIII.

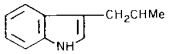
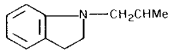
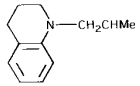
Structure–Activity Relationships. Arylethanolamines having alkyl groups on the basic nitrogen, compounds **21–27**, were β-adrenoceptor blocking agents, the most active of which, **22**, had an activity one-quarter that of propranolol.[24] Substitution on the amidic nitrogen generally afforded less active 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).
(20) V. P. Potapov, V. M. Dem'yanovich, and A. P. Terent'ev, *Zh. Obshch. Khim.*, **35**, 1538 (1965).
(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	$PhCONH\text{-}(4\text{-}c\text{-}C_5H_9N)\text{-}CH_2CHMe$	$C_{24}H_{32}N_4O_4$	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	$4\text{-}MeC_6H_4(CH_2)_2CHMe$	$C_{20}H_{26}N_2O_3 \cdot 0.5H_2O$ [i]	E	42	B	140-145	28		23	8
45	H	H	$4\text{-}CF_3C_6H_4(CH_2)_2CHMe$	$C_{20}H_{23}F_3N_2O_3$	E	45		131-133	36	360		
46	H	H	$2\text{-}FC_6H_4(CH_2)_2CHMe$	$C_{19}H_{23}FN_2O_3$	B	32	Et	145-150	4	14	12	24
47	H	H	$3\text{-}FC_6H_4(CH_2)_2CHMe$	$C_{19}H_{23}FN_2O_3$	B	39		146-150	2	7	16	75
48	H	H	$4\text{-}FC_6H_4(CH_2)_2CHMe$	$C_{19}H_{23}FN_2O_3 \cdot HCl$	B	90	Me-Ea	212-213	4	29	10	18
49	H	H	$4\text{-}ClC_6H_4(CH_2)_2CHMe$	$C_{19}H_{23}ClN_2O_3 \cdot HCl$	E	13	Me-Ea	227	10	50	34	26
50	H	H	$4\text{-}HOC_6H_4(CH_2)_2CHMe$	$C_{19}H_{24}N_2O_4 \cdot HCl$	F	23	Me-Ea	168-170	7	33	>30	
51	H	H	$4\text{-}MeOC_6H_4(CH_2)_2CHMe$	$C_{20}H_{26}N_2O_4$ [j]	F	63	Ea-B	152	5	57	27	43
52	H	H	$3,4\text{-}(MeO)_2C_6H_3(CH_2)_2CHMe$	$C_{21}H_{28}N_2O_5$	E	41	Ea-Pe	115-118	13	73	>10	
53	H	H	$3,4\text{-}(CH_2O_2)C_6H_3(CH_2)_2CHMe$	$C_{20}H_{24}N_2O_5 \cdot HCl$	B	81	Me-Ea	217-223	7	33	NA	
54	H	H	$4\text{-}MeO_2CC_6H_4(CH_2)_2CHMe$	$C_{21}H_{26}N_2O_5 \cdot 0.5H_2O$	E	90		140	6	100		
55	H	H	$4\text{-}H_2NOCC_6H_4(CH_2)_2CHMe$	$C_{20}H_{25}N_3O_4 \cdot HCl$	*k*	41	Me-Ea	195-196	6	17	NA	

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