(C_{20}), 133.9 (C_6), 137.6 ($C_{1'}$), 134.3 (C_5), 170.4 (C(=O)Ac), 173.7 (C_1), 210.1 (C_{17}). Anal. ($C_{30}H_{36}NO_6Br$) C, H.

12-Azidocytochalasin C (4). 6,12-Dibromocytochalasin D (2; 0.040 g, 0.05 mmol) and sodium azide (0.100 g, excess) were dissolved in dry DMF (5 mL), the reaction mixture was stirred at room temperature for 48 h, and the solvent was removed under reduced pressure. The residue was extracted with dichloromethane and repeatedly washed with brine. The resulting organic layer was dried (anhydrous sodium sulfate), and solvent was removed under reduced pressure. The residue was purified by HPLC over a Whatman Partisil-10 Magnum 9 column, using ethyl acetate/hexane (1:1) as eluant, to give a white solid: yield 0.022 g (70%). Recrystallization from acetonitrile gave an analytical sample (4): mp 236–237 °C dec; mass spectrum (EI), m/e, no M^+ seen, 520 ($M^+ - N_2$); IR (KBr) 2100 (azide) cm^{-1}. Anal. ($C_{30}H_{36}N_4O_6$) C, H, N. Under identical conditions, 12-bromocytochalasin C (3) gave the same monoazido derivative.

12-Iodocytochalasin C (5). 12-Bromocytochalasin C (3; 0.080 g, 0.13 mmol), sodium iodide (0.200 g, excess), and acetone (20 mL) were stirred at room temperature for 24 h. The solvent was removed under reduced pressure. The residue was repeatedly extracted with dichloromethane, and the resulting organic layer, after washing with aqueous sodium thiosulfate solution and brine, was dried (anhydrous sodium sulfate). The solvent was removed under reduced pressure. The residue was purified by HPLC over a Whatman Partisil-10 Magnum 9 column, using ethyl acetate/hexane (1:1) as eluant. The major peak was collected, the solvent was removed, and the residue was crystallized from ethyl acetate/hexane (1:1) to give a pale yellow solid (5; 0.026 g, 30%). Repeated recrystallization from ethyl acetate/hexane (1:1) and preparative TLC (silica gel; benzene/acetone, 3:2) gave an analytical sample: mp 173–175 °C dec; ^1H and ^{13}C NMR shifts were consistent with this structure; mass spectrum (EI), m/e no M^+ seen, 505 ($M^+ - HI$). Anal. ($C_{30}H_{36}NO_6I$) C, H. Except in the dry state, 5 underwent rapid decomposition in solution to yield a variety of transformation and substitution products.

12-Cyanocytochalasin C (6). 12-Bromocytochalasin C (3; 0.180 g, 0.3 mmol) and sodium cyanide (0.400 g, excess) in DMF (15 mL) were stirred at room temperature for 24 h. After solvent removal under reduced pressure, the residue was extracted repeatedly with dichloromethane. The organic layer was repeatedly washed with aqueous hydrochloric acid (5%) and brine and dried (anhydrous sodium sulfate). The solvent was removed under reduced pressure. The residue was purified by HPLC on a Whatman Partisil-10 Magnum 9 column, using ethyl acetate/hexane (1:1) as eluant, to give a white solid (6): yield 0.073 g (45%). Repeated recrystallization from acetonitrile gave an analytical sample as a white solid: mp 240–242 °C dec; IR (KBr) 2250 (CN) cm^{-1}; mass spectrum (EI), m/e 532 (M^+); ^1H and ^{13}C shifts were in accord with the structure as given. Anal. ($C_{31}H_{36}N_2O_6$) C, H.

Acknowledgment. This research was supported by grants from the National Institute of Allergy & Infectious Diseases (AI-11902) and the Biomedical Research Support Program (RR-07174) of the National Institutes of Health. We thank Professors R. M. Silverstein and D. C. Dittmer for their helpful discussions and Jeannette Rasmussen for her excellent technical assistance.

Structure–Activity Relationships for 2-Substituted Imidazoles as α_2-Adrenoceptor Antagonists[1]

Joan M. Caroon,[†] Robin D. Clark,*[,†] Arthur F. Kluge,*[,†] Ronald Olah,[†] David B. Repke,[†] Stefan H. Unger,[†] Anton D. Michel,[‡] and Roger L. Whiting*[,‡]

Institute of Organic Chemistry, Syntex Research, Palo Alto, California 94304, and Syntex Research Centre, Edinburgh, Scotland. *Received November 2, 1981*

Several 2-[(1,4-benzodioxan-2-yl)alkyl]imidazoles were prepared and evaluated for their blocking activity and relative selectivity on presynaptic (α_2) and postsynaptic (α_1) receptors in the isolated rat vas deferens. 1-Ethyl-2-[(1,4-benzodioxan-2-yl)methyl]imidazole (13) was the most selective α_2-adrenoceptor antagonist of the series and was, for practical purposes, devoid of α_1-adrenoceptor antagonist activity. The lipophilicity of 13 (log D = 2.31) indicated that it would have an excellent chance to enter the central nervous system. Compound 13 was selected for clinical evaluation as an antidepressant agent.

The pharmacological and functional differences between prejunctional α-adrenoceptors of the postganglionic sympathetic neurons and postjunctional α-adrenoceptors of the effector cells originally led to the designation α_1 and α_2, for the post- and prejunctional α-adrenoceptors, respectively, of noradrenergic neuroeffector junctions.[2] Subsequently, it has been recommended that the classification α_1 and α_2 should be used independently of the location and function of α-adrenoceptors and instead according to the relative affinity for agonists and antagonists, i.e., exclusively on the basis of their pharmacological specificity.[3,4] In general, α-adrenoceptors characterized as α_1 are only found at postjunctional locations, whereas α_2-adrenoceptors are located both prejunctionally and postjunctionally. Two examples that illustrate the varied roles and locations of α-adrenoceptors[5] are the inhibitory feedback effect on norepinephrine (NE) release at nerve endings[6] and the inhibition of adenylate cyclase in human platelets.[7]

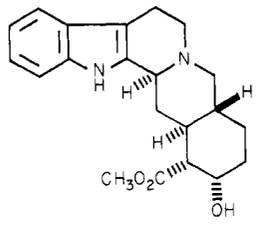
The study and therapeutic manipulation of α-adrenergic receptors are facilitated by having well-defined, selective receptor agonists and antagonists.[5a] Phenylephrine, a classic α_1-adrenoceptor agonist, operates as a vasoconstrictor and is used as a nasal decongestant. Prazosin, an

[†] Institute of Organic Chemistry.
[‡] Syntex Research Centre.

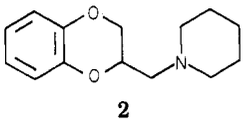
(1) Contribution no. 615 from the Institute of Organic Chemistry.
(2) Langer, S. Z. *Biochem. Pharmacol.* **1974**, *23*, 1793.
(3) Berthelsen, S.; Pettinger, W. A. *Life Sci.* **1977**, *21*, 595.
(4) Starke, K.; Langer, S. Z. *Adv. Biosci.* **1974**, *18*, 1.
(5) For reviews, see (a) Melchiorre, C. *Farmaco* **1980**, *35*, 535. (b) Hoffman, B. B.; Lefkowitz, R. J. *N. Engl. J. Med.* **1980**, 1390. (c) Rand, M. J.; Majewski, H., Medgett, I. C.; McCulloch, M. W.; Story, D. F. *Circ. Res., Suppl.* **1980**, *46*, I-70. (d) Lefkowitz, R. F. *Annu. Rep. Med. Chem.* **1980**, *15*, 217. (e) Timmermans, P. B. M. W. M.; Van Zwieten, P. A. *J. Auton. Pharmacol.* **1981**, *1*, 171.
(6) Langer, S. Z. *Br. J. Pharmacol.* **1977**, *60*, 481.
(7) Wood, C. L.; Arnett, C. D.; Clarke, W. R.; Tsai, B. S.; Lefkowitz, R. J. *Biochem. Pharmacol.* **1979**, *28*, 1277.

0022-2623/82/1825-0666$01.25/0

example of a potent and selective α_1-adrenoceptor antagonist, is used in the control of hypertension.[8] Clonidine, a potent α_2-adrenoceptor agonist, which also manifests α_1-adrenoceptor agonist properties, is useful in the therapy of hypertension.[9] Two examples of α_2-adrenoceptor antagonists are yohimbine (1) and piperoxan (2). Both



1

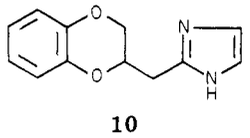


2

compounds have been examined in a variety of in vitro preparations. They are reported to be potent but not very selective when assayed in the rat vas deferens[10] or the guinea pig ileum.[11] Yohimbine is about 30 times more selective as an antagonist of the α_2-adrenoceptor than the α_1-adrenoceptor in rat vas deferens;[10] however, it appears to be about 100 times more potent as an antagonist of the α_2-adrenoceptor in the rabbit pulmonary artery.[12,13]

A therapeutic role for specific α_2-adrenoceptor antagonist has not yet been defined by a clinical agent. When one considers the presently known locations and functions of α_2-adrenoceptors, one can easily imagine that an antagonist might have some potential as a cardiovascular or CNS agent. For example, it is known that postsynaptic α_2-adrenoceptors mediate the vasoconstriction caused by the α_2-adrenoceptor agonist azepexol (B-HT 933) and that this vasoconstriction can be antagonized by the α_2-adrenceptor antagonists rauwolscine and yohimbine.[14] Also, a presynaptic α_2-adrenoceptor antagonist could lead to increased levels of NE at the neuroeffector junction through inhibition of the negative feedback of NE at the prejunctional α_2-adrenoceptor. Such a result might be therapeutically useful in the treatment of depression, since one would achieve the same effect of increasing extraneuronal NE as one achieves currently through the use of blockers of NE neuronal uptake.[15]

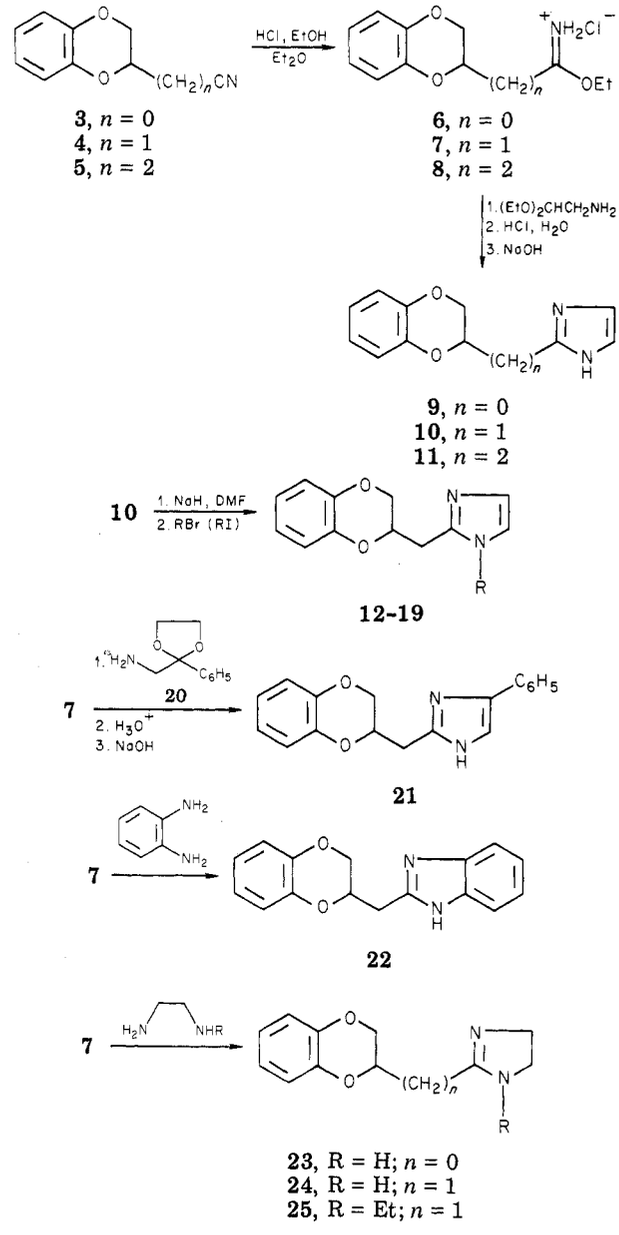
By screening a number of congeners of piperoxan, we identified the imidazole **10** as a selective α_2-adrenoceptor



10

antagonist. Compound **10** showed a selectivity ratio (α_2/α_1) of 76 through a comparison of pA_2 values obtained using rat vas deferens (vide infra). Compound **10** was therefore taken as a lead structure for further modification.

Scheme I

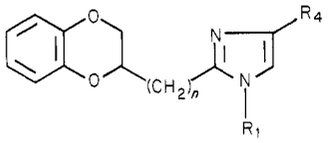


Our goals were to define a structure–activity description for this series and also to identify a highly selective α_2-adrenoceptor antagonist for exploratory studies in man.

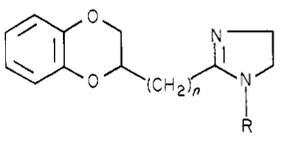
Chemistry. Nitriles **3–5**[16] were transformed into imidate hydrochlorides **6–8** using ethanol, diethyl ether, and dry HCl. Condensation of imidate hydrochlorides **6–8** with aminoacetaldehyde diethyl acetal, followed by acid-catalyzed hydrolysis and ring closure, gave the homologous series of imidazoles, **9–11**. The low overall yield (3%) of **11** probably relates to the fact that imidate **8** was an oil and, thus, of unknown purity. The 4-phenylimidazole **21** was obtained through condensation of **7** with amine ketal **20**.[17] *N*-Alkyl-substituted derivatives of imidazole **10** were made by condensing the sodium salt of **10** with various halides. Benzimidazole **22** obtained by condensation of **8** with *o*-phenylenediamine. Condensation of **6** and **7** with

(8) Brogden, R. N.; Heel, R. C.; Speight, T. M.; Avery, G. S. *Drugs* **1977**, *14*, 163.
(9) Wilkinson, P. R.; Raftery, E. B. *Br. J. Clin. Pharmacol.* **1977**, *4*, 289.
(10) Michel, A. D.; Whiting, R. L. *Br. J. Pharmacol.* **1981**, *74*, 256P.
(11) Drew, G. M. *Br. J. Pharmacol.* **1978**, *64*, 293.
(12) Borowski, E.; Starke, K.; Ehrl, H.; Endo, T. *Neuroscience* **1977**, *2*, 285.
(13) Weitzell, R.; Tanaka, T.; Starke, K. *Naunyn-Schmiedegerg's Arch. Pharmacol.* **1979**, *308*, 127.
(14) Timmermans, P. B. W. M.; VanZweiten, P. A. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1980**, *313*, 17.
(15) For a review of "second generation" antidepressant drugs, see Leonard, B. E. *Neuropharmacology* **1980**, *19*, 1175.
(16) (a) Marini-Bettolo, G. B.; Renzi, L.; Milani, C.; Bovet, D. *Rend. Ist. Super. Sanita* **1959**, *22*, 207; *Chem. Abstr.* **1960**, *54*, 1522h. (b) Leonard, F.; Koo, J. Belgian Patent 613 211, 1962; *Chem. Abstr.* **1962**, *57*, 16633c. (c) Leonard, F.; Koo, J. U.S. Patent 3 149 108; 1964; *Chem. Abstr.* **1964**, *61*, 13320a.
(17) Adachi, J.; Sato, N. *J. Org. Chem.* **1972**, *37*, 221.

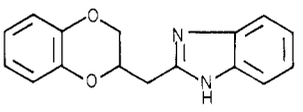
Table I. Substituted Imidazoles, Imidazolines, and Benzimidazoles



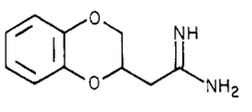
9-19, 21



23-25



22



26

compd	n	R_1	R_4	mp,[a] °C[a]	yield, %	formula	log D[d]
				A. Imidazoles (9-19, 21)			
9	0	H	H	225-227	45[b]	$C_{11}H_{10}N_2O_2 \cdot HCl$	1.76
10	1	H	H	223-228	32[b]	$C_{12}H_{12}N_2O_2 \cdot HCl$	1.92
11	2	H	H	159-160	3[b]	$C_{13}H_{14}N_2O_2 \cdot HCl$	1.99
12	1	CH_3	H	158-164	13[c]	$C_{13}H_{14}N_2O_2 \cdot HCl$	1.93
13	1	C_2H_5	H	174-175	70[c]	$C_{14}H_{16}N_2O_2 \cdot HCl$	2.31
14	1	n-C_3H_7	H	123-126	13[c]	$C_{15}H_{18}N_2O_2 \cdot HCl \cdot 0.25H_2O$	2.40
15	1	i-C_3H_7	H	105-106	28[c]	$C_{15}H_{18}N_2O_2$	
16	1	n-C_4H_9	H	143-145	8[c]	$C_{16}H_{20}N_2O_2 \cdot HCl$	
17	1	$C_6H_5CH_2$	H	104-105	25[c]	$C_{19}H_{18}N_2O_2 \cdot HCl \cdot 0.75H_2O$	>2.5
18	1	2,6-Cl_2-C_6H_3-CH_2	H	217-218	49[c]	$C_{19}H_{17}Cl_2N_2O_2 \cdot HCl$	
19	1	3-CH_3O-C_6H_4-CH_2	H	105-106	48[c]	$C_{20}H_{20}N_2O_3 \cdot HCl$	
21	1	H	C_6H_5	190-192	78[b]	$C_{18}H_{16}N_2O_2 \cdot HCl \cdot 0.25H_2O$	>2.5
				B. Imidazolines (23-25)			
23[e]	0	H		195-196	42[b]	$C_{11}H_{12}N_2O_2 \cdot HCl$	0.33
24[f]	1	H		235-236	40[b]	$C_{12}H_{14}N_2O_2 \cdot HCl$	0.28
25	1	C_2H_5		88-90	27[b]	$C_{14}H_{19}N_2O_2 \cdot HCl \cdot H_2O$	
				C. Other			
22				230-232	27[b]	$C_{16}H_{14}N_2O_2 \cdot HCl$	3.29
26[g]						$C_{10}H_{12}N_2O_2 \cdot HCl$	

[a] Salts were precipitated from methanol by the addition of diethyl ether. Bases were recrystallized using ethyl acetate-hexane. [b] Yield from starting nitrile. [c] Yield from **10**. [d] 1-Octanol distribution coefficient determined by HPLC method at pH 7.4 (phosphate buffer, sodium chloride, 0.004 M dimethyloctylamine). See Unger, S. H.; Chaing, G. H. *J. Med. Chem.* **1981**, *24*, 262. [e] Reference 18. [f] Reference 19. [g] Reference 21.

Table II. α_2- and α_1-Adrenoceptor pA_2 Values[a]

compd	$pA_2 \pm SE\,(n)$[b] α_2	$pA_2 \pm SE\,(n)$[b] α_1	selectivity ratio[c]
9	5.60 ± 0.21 (3)	<4.00 (2)	>39.8
10	6.10 ± 0.13 (9)	4.22 ± 0.22 (6)	75.9
11	6.21 ± 0.14 (4)	4.20 ± 0.15 (4)	102.3
12	6.20 ± 0.28 (9)	4.33 ± 0.08 (6)	74.1
13	6.71 ± 0.21 (9)	<4.00 (6)	>512.9
14	6.57 ± 0.19 (3)	4.20 ± 0.13 (2)	234.4
15	6.56 ± 0.14 (2)	4.30 ± 0.21 (2)	182
16	6.84 ± 0.11 (2)	<4.50 (2)	>218.8
17	6.84 ± 0.13 (3)	5.00 (3)[d]	69.2
18	6.00 ± 0.14 (2)	<5.00 (2)	>10
19	6.58 ± 0.21 (2)	5.00 (2)[d]	38.0
20	5.50 ± 0.13 (2)	<5.00 (2)	>3.2
21	5.51 ± 0.16 (2)	<5.00 (2)	>3.2
23	7.80 ± 0.33 (3)	5.80 ± 0.30 (2)[e]	100.0
24	7.00 ± 0.18 (3)	5.00 ± 0.21 (3)	100.0
25	6.70 ± 0.19 (4)	5.00 ± 0.21 (4)	50.1
26	5.40 ± 0.21 (3)	<5.00 (2)	>2.5
rauwolscine	7.92 ± 0.09 (6)	6.27 ± 0.08 (6)	44.7
yohimbine	7.71 ± 0.08 (12)	6.21 ± 0.06 (12)	31.6
piperoxan	7.40 ± 0.21 (3)	6.40 ± 0.14 (3)	10.0
phentolamine	8.03 ± 0.07 (12)	7.94 ± 0.07 (12)	1.23

[a] Determined using isolated rat vas deferens. [b] SE = standard error; n = number of determinations. [c] Ratio of antilogs of pA_2 (α_2)/pA_2 (α_1). [d] At this concentration the compound was an agonist. [e] Compound produces contractures of vas at concentrations greater than 10^{-6} M.

1,2-diamines gave the imidazolines **23**,[18-20] **24**,[19] and **25**. Condensation of the free base of **7** with ammonium chloride in ethanol gave amidine **26**.[21] These reactions are summarized in Scheme I.

Results and Discussion

The compounds in Table I were tested for α_1- and α_2-adrenergic blocking potential using the isolated rat vas deferens. The vasa were transversely bisected, and the

(18) Chapleo, C. B.; Myers, P. L. *Tetrahedron Lett.* **1981**, 4839.
(19) Krapcho, J.; Lott, W. A. U.S. Patent 2979511, 1961; *Chem. Abstr.* **1961**, *55*, 18780*d*.
(20) (a) Mouille, P.; Dabire, H.; Fournier, B.; Schmitt, H. *Eur. J. Pharmacol.* **1981**, *73*, 367. (b) Mouille, P.; Dabire, H.; Andrejak, M.; Schmitt, *H. C. R. Hebd. Seances Acad. Sci.* **1980**, *290*, 1553.
(21) Augstein, J.; Green, S. M.; Monro, A. M.; Potter, G. W. H.; Worthing, C. R.; Wrigley, T. I. *J. Med. Chem.* **1965**, *8*, 446.

prostatic and epididymal portions were used separately because of their different sensitivities to agonists and their different response to electrical stimulation.[22-24]

Antagonist activity at the α_2-adrenoceptor was assessed in the prostatic portions of the vasa by determining the pA_2 value against the inhibitory effect of the α_2-adrenoceptor-mediated inhibitory effect of xylazine[25] on electrically stimulated contractions. Antagonist affinity at the α_1-adrenoceptor was assessed by determination of the pA_2 value against the contractile effect of amidephrine, a selective α_1-adrenoceptor agonist in epididymal portions of vasa.[26] These results are listed in Table II.

The data in Table II are indexed according to potency and selectivity for the α_2-adrenoceptor relative to the α_1-adrenoceptor. All of the compounds with the exception of **23**[27] were less potent than the standard yohimbine. Many of the compounds, however, were more α_2-adrenoceptor selective than was yohimbine. The most selective of the series was the *N*-ethylimidazole **13**. We observed a selectivity ratio of more than 513 for **13**. In fact, no detectable affinity for the α_1-adrenoceptor was observed for **13** at concentrations up to 10^{-4} M. We were unable to examine **13** at concentrations higher than 10^{-4} M because the compounds salted out of solution. The selectivity value for **13** makes it the most selective α_2-adrenoceptor antagonist reported to date.

Substitutions on the imidazole moiety were used to probe the structure–activity relationships for potency and for selectivity at the α_2-adrenoceptor. Modification of **9** by insertion of a methylene group between the 2 position of the 1,4-benzodioxane and the 2 position of the imidazole gave a more active and a more selective compound, **10**. Addition of another methylene did not markedly increase activity or selectivity. The potency and selectivity changes that accompanied alkyl substitution of the imidazole nitrogen of **10** showed a straightforward correlation with substituent bulk/lipophilicity by rising to a maximum with ethyl (**13**) and then falling off with more bulky/lipophilic substituents. This correlation did not appear to hold for the two imidazolines **24** and **25**, where it was found that the more potent and more selective compound was the unsubstituted compound **24**. Comparison of the pA_2 values of amidine **26** with those for **10** and **24** showed that the addition of carbon-4 and -5 to give an imidazole or an imidazoline led to enhanced α_2-adrenoceptor affinity.

For an α_2-adrenoceptor antagonist to function as an antidepressant by increasing NE levels at neuroeffector junctions, it would have to penetrate into the central nervous system. Timmermans et al. have determined the brain concentrations of several clonidine analogues in anesthetized rats following an intravenous dosing.[28] They obtained an excellent correlation of ED_{30} (dose causing a 30% drop in blood pressure) with the log of the distribution coefficient between 1-octanol and pH 7.4 buffer (log *D*). The optimal log *D* was found to be 2.16. It is interesting to compare that result with the log *D* values reported in Table I. The *N*-ethylimidazole **13**, which has excellent selectivity for the α_2-adrenoceptor, has a log *D* of 2.31; therefore, **13** is sufficiently lipophilic to penetrate into the CNS in a nearly optimal manner by analogy to the clonidine-like α_2-adrenoceptor agonists.

Our goal in this study was to prepare a highly selective α_2-adrenoceptor antagonist for testing in man. The *N*-ethylimidazole **13** was the best compound in our series. Its α_2-adrenoceptor selectivity was more than 18 times that of yohimbine and more than 11 times that of rauwolscine. It was, for practical purposes, devoid of α_1-adrenoceptor activity. Because of these features, 1-ethyl-2-[(1,4-benzodioxan-2-yl)methyl]imidazole (**13**) was selected for clinical evaluation of its tolerance in man and for its efficacy as an antidepressant.[29]

Experimental Section

Melting points (uncorrected) were obtained on a Fisher-Johns apparatus. Infrared spectra were obtained with a Perkin-Elmer 237 grating instrument. ^{13}C and ^1H NMR spectra were obtained with a Bruker 90 and with a Bruker WM 300 spectrometer, respectively. Mass spectra were obtained in either an Atlaswerke CH-4 or CH-7 instrument. Combustion analysis were obtained from Syntex Analytical Research and from Alfred Bernhardt, Muhlheim/Ruhr.

pA_2 Values. The α_1- and α_2-adrenoceptor blockade was assessed using the method outlined by Michel and Whiting.[10] Vasa deferentia were removed from male (200–300 g) Sprague–Dawley rats and placed in a petri dish containing oxygenated Krebs–bicarbonate solution (NaCl, 119 mM; KCl, 4.7 mM; $MgSO_4 \cdot 7H_2O$, 1.0 mM; $KH_2PO_4 \cdot 2H_2O$, 1.2 mM; $CaCl_2 \cdot 6H_2O$, 2.5 mM; $NaHCO_3$, 25.0 mM; glucose, 11.1 mM).

Connective tissue was removed, and the vasa were transversely bisected. Prostatic portions, 12 mm in length, and epididymal portions, 14 mm in length, were prepared. Stainless-steel threads (0.0004-cm diameter) were tied through the walls of the lumen at each end of the bisected portions, and the tissues were mounted under 0.5-g tension in 30 (prostatic portions) or 10 mL (epididymal portions) organ baths containing oxygenated Krebs–bicarbonate solution at 37 °C. Isometric contractions of the tisues were monitored on a Devices MX4 recorder and a Tektronix DM63 storage oscilloscope. The antagonist was added to the Krebs–bicarbonate solution bathing one tissue while the contalateral protion served as a control.

For α_2-adrenoceptor studies, the prostatic portion of the vas deferens was used. Responses were elicited from contralateral prostatic portions of vasa deferentia by supramaximal single-pulse nerve stimulation (0.3-ms duration, 15 V, 15 mA) every 5 min using an S88 Grass stimulator and a pulse power amplifier. After a 45-min equilibration period, the cumulative concentration of xylazine was increased when consecutive responses to field stimulation were identical (usually 20 min). Results were expressed as a percentage of the maximal inhibition of the response to single-pulse nerve stimulation obtained in the control tissue.

For α_1-adrenoceptor studies, the epididymal portion of the vas deferens was used. After a 45-min equilibration period, concentration–response curves to amidephrine were constructed for each tissue. Each concentration of agonist was allowed to act for 45 s, or until a maximal response was obtained, before replacing the bathing fluid. A 6-min dose cycle was used, the Krebs–bicarbonate solution being replaced 4 times between additions. Responses were expressed as a percentage of the maximal response obtained in the control tissue.

The antagonistic potency of the test compounds at α-adrenoceptors was expressed in terms of their pA_2 value. These values were obtained from the ratio of the doses of agonist causing 50% of the maximal resonse in the presence and absence of the test compound, according to the method of Arunlakshana and Schild.[30]

(22) Brown, C. M.; McGrath, J. C.; Summers, R. J. *Br. J. Pharmacol.* **1979**, *66*, 553.
(23) Kasuya, Y.; Suzuki, N. *Arch. Int. Pharmacodyn.* **1979**, *241*, 24.
(24) McGrath, J. C. *J. Physiol.* **1978**, *283*, 23.
(25) Docherty, J. R.; MacDonald, A.; McGrath, J. C. *Br. J. Pharmacol.* **1979**, *67*, 421P.
(26) Flavahan, N. A.; McGrath, J. C. *Br. J. Pharmacol.* **1981**, *72*, 585P.
(27) After the submission of this paper, a report appeared on compound **23** (RX 781094A) which claimed it to be a potent, selective α_2-adrenoceptor antagonist: Chapleo, C. B.; Doxey, J. C.; Myers, P. L.; Roach, A. G. *Br. J. Pharmacol.* **1981**, *74*, 842.
(28) (a) Timmermans, P. B. M. W. M.; Van Zwieten, P. A. *Prog. Brain Res.* **1977**, *47*, 391. (b) Timmermans, P. B. M. W. M.; Brands, A.; Van Zwieten, P. A. *Arch. Pharm. (Weinheim, Ger.)* **1977**, *300*, 217.
(29) A full report of the animal pharmacology of **13** will be published elsewhere.

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.

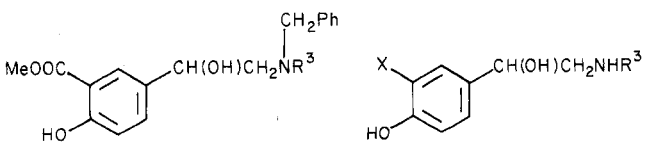
Arylethanolamines Derived from Salicylamide with α- and β-Adrenoceptor Blocking Activities. Preparation of Labetalol, Its Enantiomers, and Related Salicylamides

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*

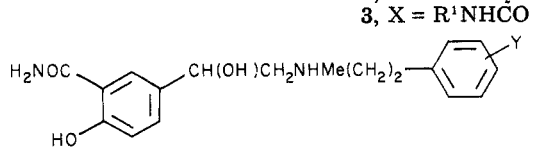
A series of phenethanolamines (**3**) based on salicylamide has been prepared and shown to possess β-adrenergic blocking properties. When the basic nitrogen atom was substituted by some aralkyl groups, the compounds also blocked α-adrenoceptors. The 1-methyl-3-phenylpropyl derivative labetalol (**34**)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

0022-2623/82/1825-0670$01.25/0