Articles

Symbiotic Approach to Drug Design: Antihypertensive β-Adrenergic Blocking Agents

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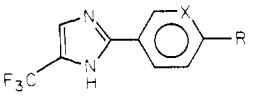
The symbiotic approach to drug design involves the incorporation of two mutually complementary biological activities into one entity by medicinal chemical hybridization. This approach has been applied to the design of the vasodilator/β-adrenoceptor antagonist 2-[3-(*tert*-butylamino)-2-hydroxypropoxy]-3-cyanopyridine (**3**). The vasodilating properties of this compound could be shown not to be due to β_2-adrenergic agonism. As might be expected of a compound directed at two separate pharmacologic goals, the structure–activity relationships are very restrictive and minor structural variations markedly affect the overall biological results. For example, alterations in the aminohydroxypropoxy group, as in **13**, which might have been expected to affect only β-adrenergic blockade, in fact were found to significantly influence the vasodilating properties. Thus, a bivalent drug such as **3** does not simply represent a combination of two separate activities into one molecule. Rather, the resulting biologic profile becomes an expression of the molecule as a whole. Regardless of the exact mechanism through which **3** may ultimately be found to exert its vasodilating effect, the application of the symbiotic approach to drug design has in this case led to compounds having the desired pharmacologic profile of two mutually supportive activities. Acute studies in man were terminated when **3** was found to be teratogenic in rabbits after chronic administration at high doses. In spite of the difficulties referred to above, we believe that this approach, in appropriate situations, represents a novel and useful strategy in drug design.

The rationale for the use of vasodilators such as hydralazine or minoxidil in combination with β-adrenoceptor antagonists is now well established as an approach to antihypertensive therapy,[2-16] and we have previously described our initial attempts to synthesize compounds designed to possess both these activities in a single entity. For such a bivalent drug to be of clinical value, the two biologic properties must be present in appropriate balance. The advantage of such a compound over a simple combination lies in the fact that the single entity would be absorbed, metabolized, and excreted at one rate in a given subject, thus maximizing the likelihood of a balanced profile during the entire course of drug action. In this assumption, of course, is recognized the less likely possibility that metabolic transformations may preferentially affect one activity component more than the other. In contrast, each drug in a combination would express its own individual profile of effectiveness depending upon its rate of absorption and duration of action; thus, the period of maximum interaction would be limited.

Although most compounds exhibit multiple actions in vivo, those that affect two or more biologic processes in a desirable and mutually beneficial manner are rare, and, moreover, in most cases of this type the discovery of the two activities in a single molecular species was fortuitous.[17-20] Few, if any, drugs capable of interacting with two distinct and separate processes have been prepared de novo by design. This failure may be the result of the fact that the two respective structure–activity relationships may prove mutually exclusive. We have recently reported our initial attempts directed toward combining both vasodilating and β-adrenergic blocking properties into a single entity by the introduction of a (*tert*-butylamino)-hydroxypropoxy side chain, a structural moiety associated with β-adrenergic receptor blockade, into our vasodilator (**1**).[21] The resulting compounds, exemplified by **2a,b**, were



1, X = N; R = H
2a, X = CH; R = $OCH_2CHOHCH_2NHC(CH_3)_3$
b, X = N; R = $OCH_2CHOHCH_2NHC(CH_3)_3$

found to lower blood pressure in spontaneously hypertensive (SH) rats of the Wistar–Okamoto strain and to exhibit peripheral vasodilating and β-adrenergic blocking properties in the dog.

Careful pharmacologic studies indicated that the reduction in peripheral vascular resistance induced by **2a,b** was due, in large part, to intrinsic β-sympathomimetic activity, as indicated by the observation that the peripheral vasodilation could be attenuated by pretreatment with a β-adrenergic blocking agent such as timolol. This was thought to be less than ideal because the β-adrenergic blocking component would tend on chronic administration to inhibit the β-sympathomimetic-induced increase in blood flow resulting in tachyphylaxis of the vasodilating effect. Thus, the introduction of the aminohydroxypropoxy group into **1** can be said to have resulted in the loss of a major portion of the intrinsic nonspecific vasodilating activity inherent in that structure.

This report describes the synthesis and evaluation of compounds exemplified by **3** which combine β-adrenoceptor blockade with a vasodilatory activity not due to β-adrenergic agonism. In the rat, these two activities are present in a balanced manner such that at a dose of **3** sufficient to induce vasodilation the drug is also exhibiting

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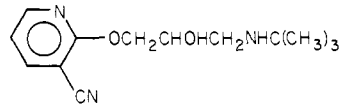

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substantial inhibition of the β-adrenergic receptors.

Chemistry. The compounds investigated, as part of this study, are listed in Table I. The parent 2-(3-pyridyl)-4-(trifluoromethyl)imidazole (1) was obtained from nicotinaldehyde and trifluoromethylglyoxal via a Radziszewski reaction as previously reported.[21a] The 2-[4-[3-*tert*-(butylamino)-2-hydroxypropoxy]phenyl]imidazoles **4a** and **5a,b** were prepared through the reaction of 4-[3-(*tert*-butylamino)-2-hydroxypropoxy]benzaldehyde or an appropriately substituted derivative with either glyoxal or phenylglyoxal.[21b] In the synthesis of the 4-methylimidazole derivative **4b**, the aminohydroxypropoxy side chain was introduced through reaction of 2-(4-hydroxyphenyl)-4-methylimidazole with (*S*)-2-phenyl-3-*tert*-butyl-5-(hydroxymethyl)oxazolidine, followed by deprotection with acid.[21b]

The 2-[3-(*tert*-butylamino)-2-hydroxypropoxy]pyridines **3**, **6**, and **8–12** were prepared from the corresponding 2-halo derivative on reaction with (*S*)-2-phenyl-3-*tert*-butyl-5-(hydroxymethyl)oxazolidine as described for the 5-cyano analogue **6**.[21a] The 2-halo-3-(trifluoromethyl)pyridine required for the synthesis of **11** was obtained through treatment of 2-chloronicotinic acid with SF_4/HF. The 3-(methylsulfonyl) moiety present in **12** was introduced through peroxide oxidation of the corresponding 3-(methylthio)-2-[3-(*tert*-butylamino)-2-hydroxypropoxy]-pyridine. The intermediate 2-chloro-3-(methylthio)-pyridine was synthesized through diazotization of 2-chloro-3-aminopyridine and reaction of the resulting fluoroborate salt with $NaSCH_3$.[21c]

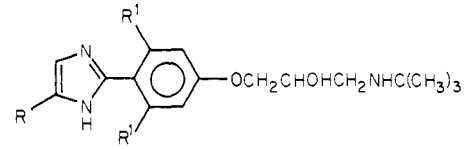
The use of (*S*)-2-phenyl-3-isopropyl-5-(hydroxymethyl)oxazolidine in place of the *tert*-butyl derivative in the reaction with 2-chloro-3-cyanopyridine allowed for the synthesis of the isopropyl analogue **13**. This oxazolidine was obtained through the reductive amination of *d*-glyceraldehyde acetonide with isopropylamine.

Discussion

Our approach, directed toward a reduction in the β-agonist component of the prototype **2a,b**,[21b] was based on the premise that the affinity of the β-adrenergic receptor is determined by the aminohydroxypropoxy side chain, while activation of the receptor is induced by an interaction of an acidic proton of the bound drug with the binding site. In this view, the intensity of binding to this site then determines the degree of receptor activation and resulting β-agonist activity. The partial agonism exhibited by **2** was ascribed to the interaction of the acidic imidazole proton with the binding site.

In an attempt to reduce the β-sympathomimetic component, compounds related to **2a,b**, structurally modified to interfere with the postulated interaction, were synthesized. For example, to reduce the acidic character of the imidazole proton, the strongly electronegative trifluoromethyl substituent was replaced by groups such as hydrogen and methyl, as in **4a,b**. Both compounds, especially **4b**, induced modest increases in iliac arterial blood flow in dogs under conditions in which the β-adrenergic receptors were blocked by timolol, thus indicating that the vasodilation produced was not via stimulation of the β_2-adrenergic receptors.

Attempts were also made to reduce the postulated interaction of the acidic proton with the activator site by

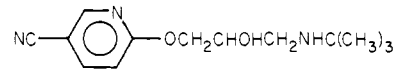


4a, R = R^1 = H
b, R = CH_3; R^1 = H
5a, R = C_6H_5; R^1 = H
b, R = CF_3; R^1 = CH_3

increasing steric bulk in appropriate portions of the molecule, as illustrated by compounds **5a,b**. These modifications induced the desired reduction of the undesirable timolol-sensitive vasodilator component but unfortunately also severely attenuated any residual intrinsic vasodilator response. The introduction of such steric restraints as in **5a** did, however, produce a desirable shift of β-adrenergic blocking activity toward selectivity for the cardiac β_1 receptor.

In a third more successful approach designed to introduce vasodilation not due to β-agonist activity, the trifluoromethylimidazole moiety was replaced with substituents incapable of acting as phenolic equivalents. Since it would be expected that the trifluoromethylimidazoyl substituent would exert an overall effect of electron withdrawal, electronegative groups such as cyano and trifluoromethyl were introduced into the 3 and/or 5 positions of the pyridine ring, thus maintaining the meta relationship between the pyridine nitrogen and the substituent as is found in **2**.

The aminohydroxypropoxy moiety was first introduced into a position para to the cyano group as in **6**. This



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compound was essentially devoid of any vasodilator-type antihypertensive activity in the dog, the entire vasodilator component having been eliminated by this modification. However, when the cyano group was placed ortho to the side chain but still meta to the hetero atom as in **3**, entirely different pharmacological properties were observed. In acute studies, the antihypertensive activity exhibited by **3** in SH rats did not differ significantly from other potent compounds such as **2a**. Using the method of Watson and Ludden,[27] single oral doses of **3** from 0.078 to 1.25 mg/kg produced a dose-dependent fall in arterial pressure with a duration of action exceeding 12 h at 1.25 mg/kg. This compound was 3.8 times more potent than hydralazine in the SH rat and was the most active member of the series. Vasodilating activity of **3** was determined by intraarterial administration in the dog extremity;[21] at a dose of 1600 μg ia, a significant increase in iliac arterial blood flow was observed. Significantly, however, the mechanism of this vasodilation was different from that observed with **2** since pretreatment with timolol (2 mg/kg, iv), which reduced the effects of **2** on iliac blood flow, did not attenuate those of **3**. Thus, it can be inferred that **3** does not increase skeletal muscle blood flow by an interaction with vascular β_2 adrenoceptors and that a desired mode of vasodilation had been achieved. This argument is also supported by the observation that no intrinsic β-agonist activity could be observed in vitro in isolated cat papillary muscle or in the reserpinized isolated rat atria preparation.

In a further attempt to establish that the vasodilating component of **3** was distinct from, and not dependent upon, an interaction with the β-adrenergic receptor, a basic ether function was introduced into the 2 position of the

Table I. Comparative Cardiovascular Effects of Compounds on Arterial Pressure of Spontaneously Hypertensive Rats and on Iliac Blood Flow and β-Adrenergic Blockade in Anesthetized Dogs

	activity in SH rat					activity in anesthetized dogs								
						increase in iliac blood flow, mL/min ± SE						blockade of isoproterenol-induced hypotension & tachycardia		
									after timolol: dose, μg/kg iv[g]				est ED_{50},[b] μg/kg iv	
compd	dose, mg/kg	route[c]	no. of SHR	max fall in MAP,[a] mmHg ± SE	duration of effect h	no. of dogs	dose, mg ia[f]	before timolol	320	800	2000	no. of dogs	MAP[a]	HR[e]
hydralazine	0.5	po	4	15 ± 5	4	3	400	78 ± 12						
	1	po	6	30 ± 5	6	3	1600	66 ± 14						
	2	po	4	40 ± 3	>7	3	3200	53 ± 9						
propranolol	1.25	po	6	12 ± 3	8									
	5	po	8	7 ± 4	<8			NT				7	19 (14-27)	51 (35-86)
	20	po	5	14 ± 6	12									
timolol	0.312	po	6	32	8									
	0.625	po	5	0				NT				8	1.3 (1.0-1.6)	2.4 (1.9-3.4)
	1.25	po	6	-1										
1	8	po	8	48 ± 3	>6	3	800	108 ± 20	99 ± 14					
	2	po	4	39 ± 6	6									
	1	po	7	21 ± 4	2	3	800	93 ± 20		76 ± 11				
2a	5	po	5	49 ± 8	18	5	1600	79 ± 8			15 ± 4	4	36 (28-46)	9 (6-11)
	1.25	po	5	36 ± 8	18									
	0.312	po	4	21 ± 4	7									
2b	20	ip	2	40	>7	6	1600	103 ± 22		38 ± 11		3	58	2.5
(S)-3	1.25	po	4	47 ± 5	>12	3	1600	98 ± 20			90 ± 36			
	0.312	po	8	30 ± 4	1	4	250			62 ± 19		4	5.2 (3.5-8.1)	1.5 (1.2-1.9)
	0.078	po	4	19 ± 2		4	64			38 ± 9				
(R)-3	1.25	po	3	22 ± 3		2	64				13 ± 3			
	5.0	po	4	27 ± 4	1	2	250				22 ± 18			
	20.0	po	4	40 ± 4	4	3	1600				82 ± 33	2	100	100
4a	20	ip	2	33	1	4	1600	36 ± 18	31 ± 20			4	>1000[d]	67[d]
4b	20	po	4	41 ± 5	8-12									
	5	po	4	19 ± 5	<8	4	1600	60 ± 5	33 ± 6			2	>1000[d]	30[d]
	1.25	po	3	24 ± 6	<6									
5a	20	po	2	54	>24									
	5	po	4	30 ± 7	4	2	1600	46			42	2	83	38
	1.25	po	4	20 ± 6										
5b	20	po	2	30	18									
	5	po	3	19 ± 5	4	2	1600	7						
6	20	po	2	15		1	1600	-13			+19			
						3	1600	-5		-1				
7	20	ip	2	49	1	2	1600	100			72			
8	20	po	2	55	4									
	5	po	2	30	2	2	1600	35 ± 15		18 ± 3		1	>30	30
	1.25	po	2	15										

9a	20	po	4	21 ± 4	8	2	1600	33 ± 8			3 ± 18	2	2.6	1.5
	5	po	4	16 ± 6										
9b	5	po	2	5		1	1600	70			43	1	<10	<10
10	20	po	3	33 ± 4										
	5	po	4	10 ± 5		1	1600				30	1	70	10
11	20	po	4	36 ± 6	18	1	1600	100			145			
	1.25	po	4	28 ± 2	4	4	250			60 ± 1		3	<1	<1
	0.312	po	4	15 ± 2			64			41 ± 8				
12	20	po	2	13		1	1600	33		8				
	5	po	2	12		1	1600	10						
13	20	ip	2	59	8									
	5	ip	2	26	2									
	20	po	2	40	4	4	1600	59 ± 6			48	1	30	5

[a] MAP = mean arterial pressure. [b] 95% confidence limits are given in parentheses. [c] ip = intraperitoneal; po = per os. [d] Data for S isomer. [e] HR = heart rate. [f] ia = intra-arterial administration. [g] iv = intravenous administration.

pyridine ring in place of the aminohydroxypropoxy moiety as in **7**. Although such a substituent would not be ex-

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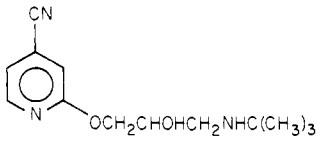
pected to interact with the β-adrenergic receptor, **7** was, nevertheless, found to be a vasodilator on the order of **3** in potency, as determined by the observed increase in iliac blood flow in the dog model. This in itself does not eliminate the possibility of an adrenergically mediated mechanism for **3**, but it does imply that **3** has within its structure elements which may induce vasodilation through an interaction not directly involving classical β-adrenergic receptors.

As a β-adrenoceptor antagonist, **3** was equipotent to timolol, as determined by the blockade of isoproterenol-induced hypotension and tachycardia in dogs.[21] This potent adrenoceptor antagonism cannot account for the antihypertensive activity observed in SH rats, since it has been reported by several investigators that β-adrenergic blocking agents do not lower arterial pressure in SH rats following acute administration.[28] For example, as indicated in Table I, timolol, although equipotent to **3** as an adrenoceptor antagonist, does not lower arterial pressure in the rat acutely. Since β-adrenergic blocking agents do not produce acute antihypertensive effects in the SH rat, this model was used to identify compounds possessing a biologic activity independent of β-adrenoceptor blockade. Only those compounds acutely antihypertensive in the SH rat, i.e., exhibiting >20 mmHg fall in mean arterial pressure, were studied further to define their mode of action. Such acute antihypertensive activity, in combination with increased peripheral blood flow not attenuated by timolol pretreatment, would strongly suggest the presence of the desired two parameters in the same molecule.

Not surprisingly, the structural requirements for the bivalent activity exhibited by **3** are extraordinarily restrictive. The relative positions of the two substituents, the configurations around the chiral center, and the substituents in the 3 position and on the aliphatic nitrogen are among the most critical determinants of the biological profile. A detailed study on the effect of structural variation will be published later, and, therefore, only those examples most suitable for the illustration of the interaction of molecular structure and biological properties are presented in this article.

The relative positions of the cyano group and the aminohydroxypropoxy moiety to each other and to the heteroatom have a significant impact on the antihypertensive activity as determined in the SH rat. This is best illustrated by the dramatic decrease in the acute antihypertensive activity when the cyano group is located in the 4 or 5 positions as in **6** and **8**. This effect of the cyano group in a location other than the 3 position may be due to a steric interaction, since diminished activity was also observed with **9a,b**. Extensive substitution studies which further strengthen this steric argument have been conducted, details of which will be described in future reports.

The aminohydroxypropoxy side chain which is common to β-adrenergic blocking agents and to **3** is characterized by the presence of a chiral center. Of the two enantiomers, those having the S configuration have been found to be the more active as β-adrenergic blocking agents. However,



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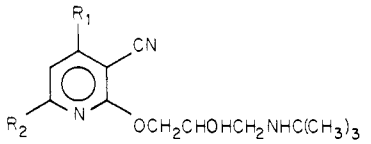
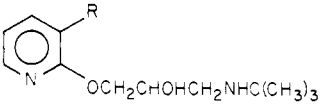


9a, $R_1 = R_2 = CH_3$
b, $R_1 = H$; $R_2 = CH_3$

the expected decrease in potency of (*R*)-**3** as a β-adrenoceptor antagonist was coupled with an overall reduction in antihypertensive activity in spite of the fact that this enantiomer was nearly equivalent to (*S*)-**3** as a vasodilator. This decrease in antihypertensive activity seen with (*R*)-**3** may reflect the inability of the compound to inhibit an increase in heart rate and cardiac output caused by vasodilation.

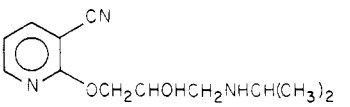
The nature of the substituent in the 3 position significantly affects antihypertensive and vasodilating potency; the 3-unsubstituted, the 3-(trifluoromethyl), and 3-(methylsulfonyl) derivatives **10–12** serve as illustrations.



10, R = H
11, R = CF_3
12, R = H_3CSO_2

Replacement of the cyano group present in **3** with hydrogen yields a compound having only marginal antihypertensive activity and essentially no vasodilating effect after timolol pretreatment. The favorable effect observed with the 3-cyano substituent on vasodilation and antihypertensive activity is also seen with the trifluoromethyl group. These moieties are similar electronically and in molecular radius. The introduction of a methylsulfonyl group into the 3 position, a group similar in electronic effects to cyano but larger in size, virtually eliminates vasodilating and antihypertensive activities. The 3 substituent is not only required for maximum effect, but the size and electronegativity of the group itself substantially influence the induced biological activities.

Thus, a satisfactory bivalent antihypertensive drug does not simply result from combining pharmacophoric elements. Rather, it appears mandatory that the two activities be delicately balanced to achieve the desired results. Considering these restraints, it is not surprising that the acceptable structure–activity relationships around a drug such as **3** are extremely narrow such that the two pharmacologic actions and the balance between them become properties of the molecule as a whole. For example, alteration of the *N*-alkyl group in the aminohydroxypropoxy side chain yielded dramatic results. With most known β-adrenergic blocking agents, the structural latitude allowed with this moiety is unusually large; i.e., changes ranging from isopropyl and *tert*-butyl to dimethoxyphenethyl and *p*-carbamoylphenoxyethyl are tolerated. In contrast, with **3** even the modest change of *tert*-butyl to isopropyl, as in **13**, resulted in a dramatic decrease in first day onset antihypertensive activity in the rat and a significant reduction in vasodilating activity in the dog while retaining potent β-adrenergic blockade.



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Of the compounds prepared, only the cyano and trifluoromethyl derivatives **3** and **11** meet the requirements for a potent β-adrenergic receptor blocking/vasodilating agent apparently not dependent on β-sympathomimetic activity for the reduction in peripheral resistance. Regardless of the exact mechanism through which **3** may ultimately be found to exert its vasodilating effect, the application of the symbiotic approach to drug design has in this case led to compounds having the desired pharmacologic profile of two mutually supportive activities. Acute studies in man were terminated when **3** was found to be teratogenic in rabbits after chronic administration at high doses.

Experimental Section

Infrared spectra were obtained on Perkin-Elmer Model 137 and 257 spectrophotometers and optical rotation measurements on a Perkin-Elmer 141 polarimeter. NMR spectra were determined in the indicated solvent on a Varian T-60 using tetramethylsilane as an internal standard for proton spectra and external fluorotrichloromethane for ^{19}F spectra. Chemical shifts are given in δ and coupling constants in hertz (Hz). Splitting patterns are designated as s, singlet; br s, broad singlet; fs s, finely split singlet; d, doublet; t, triplet; q, quartet; p, pentet; and m, multiplet. Mass spectra were taken on an AEI MS-902 mass spectrometer and run at an ionizing voltage of 70 eV and at an ionizing current of 100 mA. Spectra were collected and processed by a DS50 Data Acquisition System. Melting points were determined on a Thomas-Hoover apparatus, in open capillary tubes, and are uncorrected. Microanalyses are within 0.4% of theoretical values when indicated by symbols of the elements.

Silica gel 60 (E. Merck, Darmstadt) and aluminum oxide 90 (activity grade II, E. Merck, Darmstadt) were used for column chromatography. Organic solutions were dried over Na_2SO_4, filtered, and concentrated to dryness on a Buchi rotary evaporator under water-aspirator pressure (20 mm).

General Preparation of 2-[3-(*tert*-Butylamino)-2-hydroxypropoxy]pyridines. The (*tert*-butylamino)hydroxypropoxy moiety was introduced through the reaction of (*S*)-2-phenyl-3-*tert*-butyl-5-(hydroxymethyl)oxazolidine[22] with the 2-halopyridines. The synthesis of (*S*)-2-[3-(*tert*-butylamino)-2-hydroxypropoxy]-3-cyanopyridine hydrochloride (**3**) is presented as an example; all other compounds, except the methylsulfonyl derivative **12**, were prepared by essentially the same procedure utilizing the appropriately substituted 2-halopyridine in place of 2-chloro-3-cyanopyridine. The following were prepared by literature procedures: 2-chloro-3-cyano-4,6-dimethylpyidine,[23] 2-chloro-3-cyano-6-methylpyridine,[24] 2-chloro-4-cyanopyridine[25] and 2-chloro-5-cyanopyridine.[26] The synthesis of 2-fluoro-3-(trifluoromethyl)pyridine is included in this section; 2-chloropyridine was obtained commercially.

NaH (13.82 g, 0.29 mol, 50% emulsion in mineral oil) was added portionwise to a solution of (*S*)-2-phenyl-3-*tert*-butyl-5-(hydroxymethyl)oxazolidine (72 g, 0.29 mol) in DMF (400 mL) under N_2 at 0–4 °C. After completion of the addition, the mixture was heated on a steam bath for 30 min and stirred at 25 °C for 4 h. A solution of 2-chloro-3-cyanopyridine (42.6 g, 0.31 mol) in DMF (200 mL) was then added dropwise over a period of 1.5 h. After stirring for 18 h at 25 °C, the reaction mixture was poured onto ice–H_2O and extracted with Et_2O. The combined extracts were washed with H_2O, 1.2 N HCl, and H_2O. The acid layer and last H_2O wash were combined and heated on a steam bath for 30 min and maintained at 25 °C for 30 min. The acid solution was extracted with C_6H_6 and was poured into a cold solution of saturated Na_2CO_3 and extracted with EtOAc (4 × 400 mL). The organic extracts were dried, filtered, and concentrated. The residue was dissolved in absolute EtOH (75 mL) and added to a hot solution of fumaric acid (27.9 g) in absolute EtOH (400 mL).

After cooling, the mixture was filtered to yield a solid, which was treated with saturated aqueous Na_2CO_3 (300 mL) and extracted with EtOAc. The organic layer was dried, filtered, and concentrated. The residue was dissolved in *i*-PrOH and added to a cold solution of 3 N HCl–EtOH (50 mL). After cooling, the mixture was filtered to yield 52.5 g (63%) of (*S*)-**3**: mp 170–174 °C; $[\alpha]^{25}_D$ −11.87 (1 N HCl); NMR (Me_2SO-d_6) δ 1.1 (s, 9 H), 2.5 (d, 2 H, *J* = 6 Hz), 3.8 (p, 1 H), 4.4 (d, 2 H, *J* = 6 Hz), 7.3 (dd, 1 H, *J* =5 and 7 Hz), 8.3 (m, 2 H). Anal. ($C_{13}H_{19}N_3O_2$·HCl) C, H, N.

The *R* isomer, (*R*)-**3**, was obtained by the same procedure, starting with (*R*)-2-phenyl-3-*tert*-butyl-5-(hydroxymethyl)oxazolidine prepared from (*R*)-glycolamine.[21] The hydrochloride melted at 168–170 °C. Anal. ($C_{13}H_{19}N_3O_2$·HCl) C, H, N.

(*S*)-2-[3-(*tert*-Butylamino)-2-hydroxypropoxy]-4-cyanopyridine (8): yield 60%; mp 80–82 °C (Et_2O–petroleum ether); NMR ($CDCl_3$) δ 1.15 (s, 9 H), 2.85 (m, 5 H), 4.1 (p, 1 H), 4.35 (d, 2 H, *J* = 4 Hz), 7.5 (d, 1 H, *J* = 4 Hz), 8.4 (d, 1 H, *J* = 4 Hz), 8.6 (s, 1 H); IR (Nujol) 3150, 2220 cm^{-1}. Anal. ($C_{13}H_{19}N_3O_2$) C, H, N.

(*S*)-2-[3-(*tert*-Butylamino)-2-hydroxypropoxy]-5-cyanopyridine (6):[21a] yield 24%; mp 105–106 °C (methylcyclohexane); NMR ($CDCl_3$) δ 1.1 (s, 9 H), 2.6 (m, 2 H), 3.9 (m, 1 H), 4.4 (d, 2 H, *J* = 6 Hz), 7.85 (d, 1 H, *J* = 8 Hz), 7.75 (dd, 1 H, *J* = 8 and 2 Hz), 8.4 (d, 1 H, *J* = 2 Hz). Anal. ($C_{13}H_{19}N_3O_2$) C, H, N.

2-[2-(Dimethylamino)ethoxy]-3-cyanopyridine Hydrochloride (7). To 2-(dimethylamino)ethanol (1.3 g, 0.015 mol) in DMF (25 mL) was added 57% NaH in mineral oil (0.63 g, 0.015 mol). After stirring for 0.5 h at 23 °C, a solution of 2-chloro-3-cyanopyridine (2 g, 0.015 mol) in DMF (10 mL) was added. The reaction mixture was stirred for 20 h, concentrated to 10 mL, and added to H_2O (25 mL). The solution was extracted with $CHCl_3$; the organic layer was dried, filtered, and concentrated. The resulting oil was dissolved in Et_2O and treated with HCl in MeOH to yield, after recrystallization from Et_2O–*i*-PrOH, 0.8 g (23%) of **7**, mp 148–150 °C. Anal. ($C_{10}H_{13}N_3O$·HCl) C, H, N.

(*S*)-2-[3-(*tert*-Butylamino)-2-hydroxypropoxy]-3-cyano-4,6-dimethylpyridine hydrochloride hemihydrate (9a): yield 22%; mp 177–178 °C (Et_2O–*i*-PrOH); NMR (Me_2SO-d_6) δ 1.35 (s, 9 H), 2.4 (s, 6 H), 3.05 (m, 2 H), 3.35 (br s, 1 H exch), 4.4 (m, 3 H), 5.95 (br s, 1 H, exch), 7.0 (s, 1 H), 9.0 (br s, 1 H exch); IR (Nujol) 3190, 2220 cm^{-1}; MS *m/e* 278 (M + 1), 262 (M −15), 115, 86. Anal. Calcd for $C_{15}H_{23}N_3O_2$·HCl·0.5H_2O: C, 55.81; H, 7.80; N, 13.02. Found: C, 56.26; H, 7.64; N, 13.09.

(*S*)-2-[3-(*tert*-Butylamino)-2-hydroxypropoxy]pyridine (10): yield 45%; mp 89–91 °C (C_6H_{14}); NMR ($CDCl_3$) δ 1.1 (s, 9 H), 2.7 (d, 2 H, *J* = 6 Hz), 2.9 (br s, 2 H exch), 4.0 (p, 1 H), 4.4 (d, 2 H, *J* = 6 Hz), 6.8 (m, 2 H), 7.6 (m, 1 H), 8.1 (dd, 1 H, *J* = 6 and 2 Hz). Anal. ($C_{12}H_{20}N_2O_2$) C, H, N.

(*S*)-2-[3-(*tert*-Butylamino)-2-hydroxypropoxy]-3-cyano-6-methylpyridine hydrochloride (9b): yield 21%; mp 208–210 °C (H_3CCN); NMR (Me_2SO-d_6) δ 1.3 (s, 9 H), 2.5 (s, 3 H), 3.1 (m, 2 H), 4.5 (m, 3 H), 7.1 (d, 1 H, *J* = 8 Hz), 8.2 (d, 1 H, *J* = 8 Hz). Anal. ($C_{14}H_{21}N_3O_2$·HCl) C, H, N.

(*S*)-2-[3-(*tert*-Butylamino)-2-hydroxypropoxy]-3-(trifluoromethyl)pyridine (11): yield 62%; mp 112–113.5 °C ($CHCl_3$–C_6H_{14}); NMR ($CDCl_3$) δ 1.1 (s, 9 H), 2.62 (br s, 2 H, exch), 2.75 (d, 1 H, *J* = 2 Hz), 2.84 (s, 1 H), 3.99 (p, 1 H, *J* = 5 Hz), 4.5 (d, 2 H, *J* = 5 Hz), 6.99 (dd, 1 H, *J* = 5 and 7 Hz), 7.91 (d, 1 H, *J* = 7.5 Hz), 8.35 (d, 1 H, *J* = 5 Hz); ^{19}F NMR (CCl_3F) 63.2 ppm (s, 3 F). Anal. ($C_{13}H_{19}F_3N_2O_2$) C, H, N.

2-Fluoro-3-(trifluoromethyl)pyridine. Into a stainless-steel bomb were placed 2-chloro-3-pyridinecarboxylic acid (50 g, 0.32 mol), SF_4 (254 g), and HF (40 mL), and the contents were heated at 150 °C. After 16 h, the bomb was cooled and vented, and the material was poured onto ice. The solution was adjusted to pH 6 with 10 N NaOH and the product extracted with $CHCl_3$. The organic layer was dried, filtered, and distilled at atmospheric pressure to yield 21.3 g (37%) of 2-fluoro-3-(trifluoromethyl)-pyridine: bp 134–137 °C; NMR ($CDCl_3$) δ 7.42 (t, 1 H, *J* = 6 Hz), 8.05 (t, 1 H, *J* = 8 Hz), 8.44 (d, 1 H, *J* = 6 Hz); ^{19}F NMR (CCl_3F) 62.6 (d, 3 F, *J* = 11 Hz), 66.3 ppm (m, 1 F).

Preparation of 2-[3-(*tert*-Butylamino)-2-hydroxypropoxy]-3-(methylsulfonyl)pyridine Maleate Salt (12). 2-Chloro-3-(methylthio)pyridine. A solution of $NaNO_2$ (6.9 g, 0.1 mol) in H_2O (20 mL) was added with stirring to a solution of 3-amino-2-chloropyridine (12.2 g, 0.095 mol) in 48–50% fluoroboric acid (40 mL) and 95% EtOH (75 mL) at 0–4 °C. After complete addition, the solution was allowed to stir for 5 min and diluted with Et_2O, and the resulting fluoroborate salt was filtered and washed with Et_2O. To a suspension of the fluoroborate salt (21.7 g) in H_3CCN (200 mL) cooled in an ice bath was added a suspension of $NaSCH_3$ (7 g, 0.1 mol) in H_3CCN (200 mL). The solution was then allowed to stir at 25 °C overnight. The suspension was concentrated and the residue was triturated with $CHCl_3$, filtered, and concentrated. Distillation of the residual oil at 0.2 mm at 105–108 °C gave 2.2 g of 2-chloro-3-(methylthio)pyridine (23%): NMR ($CDCl_3$) δ 2.50 (s, 3 H), 7.3 (m, 2 H), 8.05 (dd, 1 H). Anal. (C_6H_6ClNS) C, H, N.

(*S*)-2-[3-(*tert*-Butylamino)-2-hydroxypropoxy]-3-(methylthio)pyridine Maleate Salt. The preparation of (*S*)-2-[3-(*tert*-butylamino)-2-hydroxypropoxy]-3-(methylthio)-pyridine was similar to **3** using 2-chloro-3-(methylthio)pyridine in place of 2-chloro-3-cyanopyridine: yield 32%; mp 148–149 °C; NMR ($CDCl_3$) δ 1.1 (s, 9 H), 2.4 (s, 3 H), 2.8 (m, 4 H), 3.95 (p, 1 H), 4.45 (d, 2 H, *J* = 4 Hz), 6.9 (dd, 1 H, *J* = 7 and 4 Hz), 7.4 (dd, 1 H, *J* = 8 and 2 Hz), 7.85 (dd, 1 H, *J* = 4 and 2 Hz). Anal. ($C_{13}H_{22}N_2O_2S$·$C_4H_4O_4$) C, H, N.

(*S*)-2-[3-(*tert*-Butylamino)-2-hydroxypropoxy]-3-(methylsulfonyl)pyridine Maleate Salt (12). A solution of 30% H_2O_2 (20 mL) was added to (*S*)-2-[3-(*tert*-butylamino)-2-hydroxypropoxy]-3-(methylthio)pyridine (0.6 g, 0.0022 mol) in AcOH (8 mL). After stirring at 25 °C overnight, the mixture was poured into saturated aqueous Na_2CO_3 and extracted with $CHCl_3$. The organic layer was dried, filtered, and concentrated. The residue was dissolved in Et_2O and treated with maleic acid in *i*-PrOH to yield 0.6 g (63%) of **12**: mp 98–100 °C; NMR (Me_2SO-d_6) δ 1.25 (s, 9 H), 3.2 (m, 2 H), 3.3 (s, 3 H), 4.4 (m, 3 H), 6.1 (s, 2 H, olefinic protons of maleic acid), 7.4 (dd, 1 H, *J* = 8 and 5 Hz), 8.1 (dd, 1 H, *J* = 8 and 2 Hz), 8.55 (dd, 1 H, *J* = 5 and 2 Hz); IR (Nujol) 1370 and 1160 cm^{-1}; MS *m/e* 287 (M − 15), 114, 86. Anal. ($C_{13}H_{22}N_2O_4S$·$C_4H_4O_4$) C, H, N.

(*S*)-2-[3-(Isopropylamino)-2-hydroxypropoxy]-3-cyanopyridine (13). The isopropyl analogue (**13**) was prepared by essentially the same procedure as used for the synthesis of **3**, except (*S*)-2-phenyl-3-isopropyl-5-(hydroxymethyl)oxazolidine was used in place of 2-phenyl-3-*tert*-butyl-5-(hydroxymethyl)oxazolidine: yield 58%; mp 127–128 °C (C_6H_6); NMR ($CDCl_3$) δ 1.1 (d, 6 H, *J* = 6 Hz), 2.7 [m, 5 H (2 H exch)], 4.0 (p, 1 H), 4.5 (d, 2 H, *J* = 6 Hz), 7.0 (dd, 1 H, *J* = 8 and 6 Hz), 8.0 (dd, 1 H, *J* = 2 and 8 Hz), 8.5 (dd, 1 H, *J* = 2 and 6 Hz). Anal. ($C_{12}H_{17}N_3O_2$) C, H, N.

(*S*)-2-Phenyl-3-isopropyl-5-(hydroxymethyl)oxazolidine. (*S*)-2-Phenyl-3-isopropyl-5-(hydroxymethyl)oxazolidine was prepared according to the procedure of Weinstock[22] for the 3-*tert*-butyl analogue. In the reductive amination of *d*-glyceraldehyde acetonide, isopropylamine was used in place of *tert*-butylamine. The compound was purified by distillation and used without further treatment: yield 68%; bp 121–128 °C at 0.05 mm.

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References and Notes

(1) Present address: Wyeth Laboratories, Radnor, Pa. 19087.
(2) (a) Freis, E. D. *Physiol. Rev.* **1960**, *40*, 27; (b) Frohlich, E. D.; Tarazi, R. C.; Dustan, H. P. *Am. J. Med. Sci.* **1969**, *257*, 9.
(3) Koch-Weser, J. *Arch. Intern. Med.* **1974**, *133*, 1017.
(4) Massingham, R.; Hayden, M. L. *Eur. J. Phamacol.* **1975**, *30*, 121.
(5) Graham, R. M.; Muier, M. R.; Hayes, J. M. *Clin. Exp. Pharmacol. Physiol.* **1976**, *3*, 173.
(6) Kincaid-Smith, P. *Am. J. Cardiol.* **1973**, *32*, 575.
(7) Tarazi, R. C.; Dustan, H. P. *Am. J. Cardiol.* **1972**, *29*, 633.
(8) Conway, J. "Modern Trends in Cardiology", Oliver, M. F., Ed.; Butterworths: London, 1974; p 376.

(9) Clarkson, R. "Antihypertensive Agents", Engelhardt, E. L., Ed.; American Chemical Society: Washington, D.C., 1976; pp 1-25.
(10) Pettinger, W. A.; Mitchell, H. C. *N. Engl. J. Med.* **1973**, *289*, 167; *Clin. Pharmacol. Ther.* **1973**, *14*, 143.
(11) Bennett, C.; Wilburn, R. *Clin. Res.* **1974**, *22*, 262A.
(12) Chidsey, C. *Clin. Sci. Mol. Med.* **1973**, *45* (suppl. I) 171S.
(13) Pettinger, W.; Campbell, W.; Keeton, K. *Circ. Res.* **1973**, *33*, 82.
(14) Pettinger, W.; Keeton, K. *Clin. Res.* **1973**, *21*, 472.
(15) Gottlieb, T. B.; Kratz, F. H.; Chidsey, C. A. *Circulation* **1972**, *45*, 571.
(16) Gilmore, E.; Weil, J.; Chidsey, C. *N. Engl. J. Med.* **1970**, *282*, 521.
(17) Cragoe, E. J., Jr.; Schultz, E. M.; Schneeberg, J. D.; Stokker, G. E.; Woltersdorf, O. W., Jr.; Fanelli, G. M., Jr.; Watson, L. S. *J. Med. Chem.* **1975**, *18*, 225.
(18) Simpson, G. M.; Angus, J. W. S. *Curr. Ther. Res.* **1967**, *9*, 24.
(19) Sugerman, A. A. *Curr. Ther. Res.* **1966**, *8*, 479.
(20) Dujovne, C. A.; Azarnoff, D. L.; Huffman, D. H.; Pentikainen, P.; Hurwitz, A.; Shoeman, D. W. *Clin. Pharmacol. Ther.* **1975**, *19*, 352.
(21) (a) Baldwin, J. J.; Hirschmann, R.; Lumma, P. K.; Lumma, W. C., Jr.; Ponticello, G. S.; Sweet, C. S.; Scriabine, A. *J. Med. Chem.* **1977**, *20*, 1024; (b) Baldwin, J. J.; Engelhardt, E. L.; Hirschmann, R.; Lundell, G. F.; Ponticello, G. S.; Ludden, C. T.; Sweet, C. S.; Scriabine, A.; Share, N. N.; Hall, R. *J. Med. Chem.* **1979**, *22*, 687; (c) Baldwin, J. J.; Hartman, R. D.; Lumma, W. C., Jr.; Ponticello, G. S. *J. Org. Chem.* **1979**, *44*, 3080.
(22) Weinstock, L. M.; Mulvey, D. M.; Tull, R. *J. Org. Chem.* **1976**, *41*, 3121.
(23) Jahine, H.; Zaher, H. A.; Sayed, A. A.; Seada, M. *J. Prakt. Chem.* **1974**, *316*, 337.
(24) Matsumoto, I.; Tomimoto, K.; Okazawa, M.; Yoshizawa, J. *Chem. Abstr.* **1974**, *81*, 105306e.
(25) Yasuyuki, S. *Yakugaku Zasshi* **1961**, *81*, 1204; *Chem. Abstr.* **1962**, *56*, 3445d.
(26) Forrest, H. S.; Walker, J. *J. Chem. Soc.* **1948**, 1939.
(27) Watson, L. S.; Ludden, C. T. "New Antihypertensive Drugs", Scriabine, A.; Sweet, C. S., Eds.; Spectrum Publications: Holliswood, N.Y., 1976; pp 87-96.
(28) ref 27, p 227.

Ultraviolet Photoelectron Spectroscopy of Cyclic Amidines. 1. Electronic Structure of Some α-Adrenergic Benzylimidazolines

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Slight changes in the structure of the 2-benzylimidazolines are able to produce drastic changes in pharmacological action and potency. In order to determine whether electronic effects are involved, as well as to reveal some aspects of the electronic structure of these compounds, UV-photoelectron spectra of 2-benzylimidazoline and some substituted analogues, including naphazoline, oxymetazoline, tetrahydrozoline, and xylometazoline, have been recorded. Assignments of various ionization energies (IE's) to particular molecular orbitals have been made on the basis of correlation of IE's of similar molecules, substituent effects, differences in intensity between He(I) and He(II) spectra, and results of modified CNDO/s calculations. It turned out that there is no conjugative electronic interaction between the phenyl and imidazoline ring. The methyleneimidazoline substituent proved to be a weak electron-withdrawing group. The CNDO/s method in conjunction with Koopmans' theorem predicts rather well the energy levels of orbitals possessing predominant π character. The location of the energy levels of orbitals with mainly n_N character is not correctly estimated by CNDO/s. The electronic properties, measured with photoelectron spectroscopy, do not seem to be related to the qualitative pharmacological action of the 2-benzylimidazolines, but for the sympathomimetic compounds naphazoline, oxymetazoline, tetrahydrozoline, and xylometazoline a correlation has been found between first aromatic IE and potency of the drug on both the peripheral and central α-adrenergic receptor level.

In 1939, Hartmann and Isler[1] carried out an extensive investigation into the pharmacological activity of a great number of benzylimidazolines. It turned out that slight alterations in the chemical structure of these molecules were able to bring about drastic changes in pharmacological action and activity. Some compounds showed sympatholytic activity, e.g., 2-benzylimidazoline, whereas others, such as naphazoline, exerted sympathomimetic activity. Mujic and van Rossum[2] have shown that sympathomimetic activity of these compounds was the result of direct α-adrenergic receptor stimulation. Investigating the relationship between chemical structure and pharmacological activity, Struijker Boudier et al.[3] found that, in addition to the increase of molar volume, differences in the pK_a were playing an important role. Differences in the pK_a within a series of structurally narrow related molecules are known to be closely connected with differences in electronic structure. Although for benzylimidazolines much is known about the influence of substituents on the pharmacological activity in a variety of biological tests, little information is available regarding the effect of these substituents on the electronic structure. With the development of UV photoelectron spectroscopy (UPS), a new experimental method has come at our disposal to gain some insight into the electronic structure of molecules. According to Koopmans' theorem, the ionization energies (IE_i), which are directly measured with UPS, are related to the actual orbital energy levels (ϵ_i), as shown in eq 1.[4] In this approximation, relaxation and

$$IE_i = -\epsilon_i \quad (1)$$

correlation effects are not taken into account. Nevertheless, it is customary to regard the photoelectron spectrum as a direct representation of the molecular orbital energy diagram.

Quantum mechanical calculation provide considerable information about the electronic properties of molecules and are used as an aid in the interpretation of the photoelectron spectra. For this latter purpose, the semiempirical CNDO/s method has proven quite reliable.[5-7]

Recently, the UPS technique has been successfully applied to the determination of the electronic structure

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