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Original article

Amino ketone and amino alcohol derivatives of benzoxazolinone: synthesis, adrenergic and antihypertensive properties

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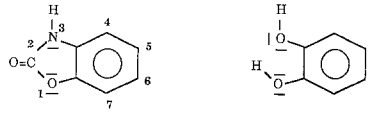
Summary — The concept of bioisosterism between benzoxazolinone and pyrocatechol has led to the synthesis of benzoxazolinone analogues of the catecholamines which display β- and α-blocking properties. In this paper, we report the synthesis of analogues in which the alkylamine moiety was replaced with 1-arylpiperazines or 4-benzylpiperidine. These compounds were investigated for α- and β-adrenoceptor blocking properties and for antihypertensive activity.

Résumé — Amino cétones et amino alcools dérivés de la benzoxazolinone: synthèse, propriétés adrénergiques et antihypertensives. *Le concept de bioisostérie entre la benzoxazolinone et le pyrocatéchol a conduit à la préparation d'analogues benzoxazolinoniques des catécholamines qui possèdent des propriétés ß et α bloquantes. Nous rapportons la synthèse de composés analogues dont l'atome d'azote de la chaîne latérale est inclus dans une structure de type aryl-1 pipérazine ou benzyl-4 pipéridine; l'étude pharmacodynamique a été orientée vers la recherche de propriétés adrénolytiques et antihypertensives.*

benzoxazolinone / amino ketones / amino alcohols / β- and α-adrenoceptor blocking properties / antihypertensive activity

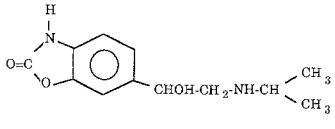
Introduction

Benzoxazolinone **I** has an acidic hydrogen atom, and displays steric and electronic characteristics similar to those of pyrocatechol. It can be considered a bioisoster of a pseudocyclic structure of pyrocatechol **II**.



I

II



III

The concept of bioisosterism has recently led to the synthesis of benzoxazolinone ethanolamines, analogues of the catecholamines, whose amino alcohol chain is in position 6 of the benzene ring of benzoxazolinone [1]. Pharmacodynamic studies have shown that these compounds display an affinity for adrenergic receptors, thus confirming the hypothesis of bioisosterism of the benzoxazolinone and pyrocatechol structures. 6-(2-isopropylamino-1-hydroxy) ethyl–2–benzoxazolinone **III**, which combines β_1-blocking with α–blocking activity [2], is currently being clinically investigated for its anti-hypertensive properties. In view of the pharmacological activity and potential clinical importance, we thought it useful to prepare a new series of compounds in which the nitrogen atom of the lateral chain was included in a heterocyclic group such as arylpiperazinyl or 4-benzyl-1-piperidinyl. Several investigators have, in fact, reported adrenolytic and hypotensive properties of 1-alkyl-4-aryl-piperazine [3], and some phenylethanolamine derivatives containing an arylpiperazine group have been described. An analogue of norepinephrine, pipratecol **IV**, is therapeutically used for its vasodilating properties. Some analogues of medroxalol, an α-and β-blocker, have been investigated [4]. In these analogues, the presence of an *ortho* substituent on the phenyl group of the aryl-piperazine moiety increases the α-blocking activity, and the *o*-methylated **V** derivative possesses the most favourable pharmacological profile.

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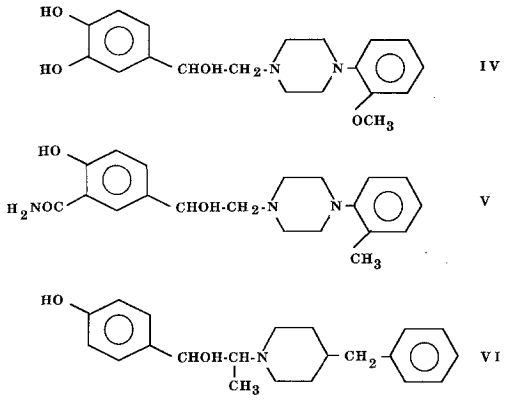
In addition, ifenprodil **VI**, which contains a 4-benzyl-1-piperidinyl group, is an α-blocker used therapeutically as a vasodilator.

Although it is not clear what role substituents on the aromatic ring of the phenylethanolamines play in the affinity for adrenergic receptors [5], some investigators have emphasized the importance of the presence of an acidic group [6–9]. To investigate this hypothesis, we synthesized homologues derived from 3-methyl benzoxazolinone, since the lack of an acidic hydrogen atom and the steric influence of the methyl group would, theoretically, decrease affinity for adrenergic receptors.

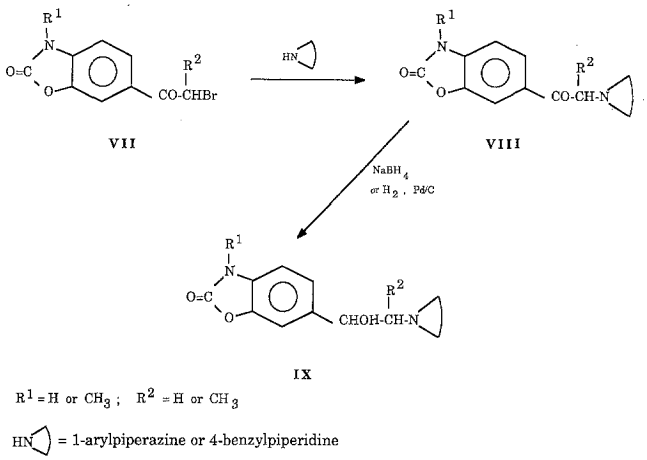
The pharmacological study of the benzoxazolinone amino alcohols and their amino ketone precursors was designed to evaluate their interaction with adrenergic receptors as well as to determine their antihypertensive properties.



Chemistry

The synthesis pathways are depicted in scheme 1. The 6-(bromoacyl)-2 benzoxazolinone **VII** was prepared *via* the acylation of benzoxazolinone or of *N*-methyl benzoxazolinone with either bromacetic acid or bromo-2 propionic acid. In these reactions, polyphosphoric acid was used as both solvent and catalyst [10, 11].

The amino ketones **VIII** (tables I and II) were obtained by condensation of the bromo ketones **VII** with 1-aryl-piperazine or 4-benzyl-piperidine. The amino alcohols **IX** (tables III and IV) were prepared by reduction of amino ketones **VIII**, either by catalytic hydrogenation on palladium charcoal (method A) or by the action of sodium borohydride (method B). When R_2 was a methyl group, these methods produced mixtures of diastereoisomeric amino alcohols, as shown by NMR: with method A, 75 to 80% of the erythro isomer and, with method B, 90% of the threo isomer. Fractional crystallization always permitted



Scheme 1.

isolation of the major epimer in pure form. The configuration was determined by NMR from the chemical shift and the coupling constant of the proton attached to the carbinol carbon atom. The erythro isomers had a doublet at δ 4.70-5.10 (J=4–5 Hz) and threo isomers had a doublet at δ 4.20–4.40 (J=9–10 Hz). These values corresponded to those reported for ephedrine and pseudoephedrine [12, 13], and other related structures [6, 9, 14–16].

Pharmacology

Compounds were examined for α-, β_1- and β_2-adrenoceptor blocking activity using classical *in vitro* techniques [17] and for antihypertensive effects in anaesthetized and conscious spontaneously hypertensive rats (SHR) [18].

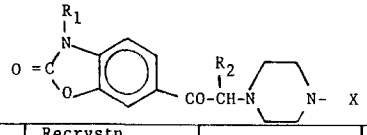
The *in vitro* preparations were characterized using the standard reference drugs propranolol, practolol and labetalol. pA_2 values for the reference and novel compounds were determined by the graphic method of Arunlakshana and Schild [19] and competitive antagonism assessed from the slope of the regression line of the Arunlakshana and Schild plot.

Antihypertensive activity was measured directly following intravenous administration in pentobarbitone-anaesthetized SHR or indirectly, using the tail-cuff method [18], following oral administration of the compound to groups of conscious SHR over a 2 d period. Blood pressure was recorded continuously from anaesthetized SHR and at 2 h post dosing in conscious SHR following stable control readings. Results were calculated as the mean percentage change in systolic blood pressure of each group and statistical differences in blood pressure between control and treated SHR determined using Student's *t*-test.

Results and Discussion

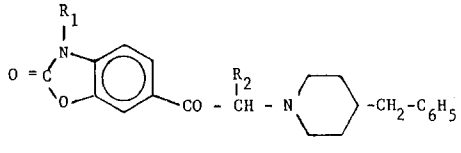
Of the amino ketones tested *in vitro* (table V) all were inactive in guinea-pig tracheal preparations which contain predominantly β_2-adrenoceptors but 3 compounds exhibited weak antagonism of the effects of isoprenaline in guinea-pig atria which contains predominantly β_1-adrenoceptors. The 3 compounds **10**, **15** and **20**, had calculated IC_{50} values of between 1-5 μM with Schild plot slopes significantly different from unity, suggesting that the interactions were not only weak but non-specific and therefore not necessarily at β_1-adrenoceptors. Additional experiments would however be required to confirm this suggestion. Of the 9 compounds tested for α-adrenoceptor blocking activity only compound **15** possessed competitive antagonistic effects in the guinea-pig vas deferens with a pA_2 of 5.30±0.12 and

Table I. Amino ketones with arylpiperazine structure.



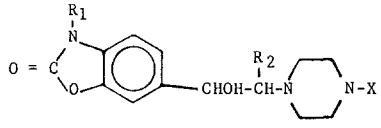
No	R_1	R_2	X	Recrystn solvent	mp, °C	Yield %	Formula	Anal.
1	H	H	$3\text{-}CF_3C_6H_4$	C_2H_5OH	205-210	64	$C_{20}H_{18}N_3F_3O_3$	C,H,N,F
2	H	H	$2\text{-}CH_3OC_6H_4$	C_2H_5OH	213	65	$C_{20}H_{21}N_3O_4$	C,H,N,O
3	H	H	$4\text{-}FC_6H_4$	C_2H_5OH	214-215	63	$C_{19}H_{18}N_3FO_3$	C,H,N,F
4	H	H	$2\text{-}CH_3C_6H_4$	C_2H_5OH	205.5-208	40	$C_{20}H_{21}N_3O_3$	C,H,N,O
5	H	CH_3	$3\text{-}CF_3C_6H_4$	C_2H_5OH	191-192	50	$C_{21}H_{20}N_3F_3O_3$	C,H,N,F
6	H	CH_3	$2\text{-}CH_3OC_6H_4$	CH_3COCH_3	225-226	52	$C_{21}H_{20}N_3O_4$	C,H,N,O
7	H	CH_3	$4\text{-}FC_6H_4$	C_2H_5OH	192-194	40	$C_{20}H_{20}N_3FO_3$	C,H,N,F
8	H	CH_3	$2\text{-}CH_3C_6H_4$	CH_3COCH_3	204-209	55	$C_{21}H_{23}N_3O_3$	C,H,N,O
9	CH_3	H	$3\text{-}CF_3C_6H_4$	C_2H_5OH	149	75	$C_{21}H_{20}N_3F_3O_3$	C,H,N,F
10	CH_3	H	$2\text{-}CH_3OC_6H_4$	CH_3COCH_3	186-187	72	$C_{21}H_{23}N_3O_4$	C,H,N,O
11	CH_3	H	$4\text{-}FC_6H_4$	CH_3COCH_3	192-195	75	$C_{20}H_{20}N_3FO_3$	C,H,N,F
12	CH_3	H	$2\text{-}CH_3C_6H_4$	CH_3CN	158-163	47	$C_{21}H_{23}N_3O_3$	C,H,N,O
13	CH_3	CH_3	$3\text{-}CF_3C_6H_4$	C_2H_5OH	115-116	84	$C_{22}H_{22}N_3F_3O_3$	C,H,N,F
14	CH_3	CH_3	$2\text{-}CH_3OC_6H_4$	CH_3COCH_3	195-196	75	$C_{22}H_{25}N_3O_4$	C,H,N,O
15	CH_3	CH_3	$4\text{-}FC_6H_4$	CH_3COCH_3	192-194	78	$C_{21}H_{22}N_3FO_3$	C,H,N,F
16	CH_3	CH_3	$2\text{-}CH_3C_6H_4$	CH_3CN	164-166	72	$C_{22}H_{25}N_3O_3$	C,H,N,O
17	CH_3	CH_3	C_6H_5	C_2H_5OH 95%	172-174	77	$C_{21}H_{23}N_3O_3$	C,H,N,O
18	CH_3	CH_3	2-pyrimidyl	C_2H_5OH 95%	185-188	78	$C_{19}H_{25}N_5O_3$	C,H,N,O

Table II. Amino ketones with benzylpiperidine structure.



No	R_1	R_2	Recrystn solvent	mp, °C	Yield %	Formula	Anal.
19	H	CH_3	C_2H_5OH	164-166	46	$C_{22}H_{24}N_2O_3$	C,H,N,O
20	CH_3	H	C_2H_5OH	168-169	78	$C_{22}H_{24}N_2O_3$	C,H,N,O
21	CH_3	CH_3	C_2H_5OH	155-156.5	80	$C_{23}H_{26}N_2O_3$	C,H,N,O

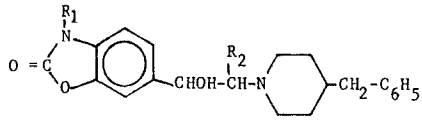
Table III. Amino alcohols with arylpiperazine structure.



No [a]	R_1	R_2	X	method [b]	recrystn solvent	mp, °C	Yield [c] %	Formula	Anal.
22	H	H	3-$CF_3C_6H_4$	A	C_2H_5OH 50%	170	90	$C_{20}H_{20}N_3F_3O_3, H_2O$ [d]	C,H,N,F
23	H	H	2-$CH_3OC_6H_4$	A	C_2H_5OH 50%	175-176	90	$C_{20}H_{23}N_3O_4$	C,H,N,O
24	H	H	4-FC_6H_4	A	C_2H_5OH	224-225	88	$C_{19}H_{20}N_3FO_3$	C,H,N,F
25	H	H	2-$CH_3C_6H_4$	A	C_2H_5OH	197-201	33	$C_{20}H_{23}N_3O_3$	C,H,N,O
26 E	H	CH_3	3-$CF_3C_6H_4$	A	C_2H_5OH	187-188	75	$C_{21}H_{22}N_3F_3O_3$	C,H,N,F
27 E	H	CH_3	2-$CH_3OC_6H_4$	A	C_6H_6	192	65	$C_{21}H_{25}N_3O_4$	C,H,N,O
28 E	H	CH_3	2-$CH_3C_6H_4$	A	C_2H_5OH	220-230	55	$C_{21}H_{25}N_3O_3$	C,H,N,O
29	CH_3	H	3-$CF_3C_6H_4$	B	C_2H_5OH	139	90	$C_{21}H_{22}N_3F_3O_3$	C,H,N,F
30	CH_3	H	2-$CH_3OC_6H_4$	B	C_2H_5OH	126-127	90	$C_{21}H_{25}N_3O_4$	C,H,N,O
31	CH_3	H	4-FC_6H_4	B	CH_3OH	208-208,5	90	$C_{20}H_{22}N_3FO_3$	C,H,N,F
32	CH_3	H	2-$CH_3C_6H_4$	B	C_2H_5OH	164-166	65	$C_{21}H_{25}N_3O_3$	C,H,N,O
33 E	CH_3	CH_3	3-$CF_3C_6H_4$	A	C_2H_5OH	148	66	$C_{22}H_{24}N_3F_3O_3$	C,H,N,F
34 T	CH_3	CH_3	3-$CF_3C_6H_4$	B	C_2H_5OH	192	86	$C_{22}H_{24}N_3F_3O_3$	C,H,N,F
35 E	CH_3	CH_3	2-$CH_3OC_6H_4$	A	C_2H_5OH	183-184	70	$C_{22}H_{27}N_3O_4$	C,H,N,O
36 T	CH_3	CH_3	2-$CH_3OC_6H_4$	B	C_6H_6	232-233	88	$C_{22}H_{27}N_3O_4$	C,H,N,O
37 E	CH_3	CH_3	4-FC_6H_4	A	C_2H_5OH	157	61	$C_{21}H_{24}N_3FO_3$	C,H,N,F
38 T	CH_3	CH_3	4-FC_6H_4	B	C_2H_5OH	217	84	$C_{21}H_{24}N_3FO_3$	C,H,N,F
39 E	CH_3	CH_3	2-$CH_3C_6H_4$	A	C_6H_6	175-178	75	$C_{22}H_{27}N_3O_3$	C,H,N,O
40 T	CH_3	CH_3	2-$CH_3C_6H_4$	B	C_2H_5OH	190-193	80	$C_{22}H_{27}N_3O_3$	C,H,N,O
41 T	CH_3	CH_3	C_6H_5	B	C_6H_6	197-200	87	$C_{21}H_{25}N_3O_3$	C,H,N,O
42 T	CH_3	CH_3	2-pyrimidyl	B	C_2H_5OH 95%	193-195	88	$C_{19}H_{23}N_5O_3$	C,H,N,O

[a]All products were racemic. Diastereoisomer: E = erythro, T = threo. [b]Capital letters refer to synthetic methods in the experimental section. [c]Yield of pure product. [d]Monohydrate.

Table IV. Amino alcohols with benzylpiperidine structure.



No [a]	R_1	R_2	Method [b]	Recrystn solvent	mp, °C	Yield [c] %	Formula	Anal.
43	CH_3	H	B	C_2H_5OH	156	90	$C_{22}H_{26}N_2O_3$	C,H,N,O
44 E	CH_3	CH_3	A	C_2H_5OH	181.5-182	75	$C_{23}H_{28}N_2O_3$	C,H,N,O
45 T	CH_3	CH_3	B	C_2H_5OH	183-183.5	25	$C_{23}H_{28}N_2O_3$	C,H,N,O

[a,b,c]See corresponding footnotes to table III.

Table V. α– and β-adrenoceptor blocking activity of the reference compounds and the amino ketones.

Compound N°	Rat vas deferens		Guinea-pig			
			Atria		Trachea	
	pA_2 value	Slope	pA_2 value	Slope	pA_2 value	Slope
Practolol	I		6.76 ± 0.09	1.0	I	
Propranolol	I		8.06 ± 0.05	1.0	7.36 ± 0.17	1.0
Labetalol	5.67 ± 0.43	1.0	7.60 ± 0.14	1.0	6.18 ± 0.24	1.0
3	I		I		I	
5	I		I		I	
7	I		I		I	
9	I		I		I	
10	I		5.40 ± 0.39	> 1.0	I	
11	I		I		I	
14	I		I		I	
15	5.30 ± 0.12	1.0	5.90 ± 0.08	> 1.0	I	
20	I		5.30 ± 0.48	> 1.0	I	

Results are mean ± SEM values calculated from 3 or 4 experiments using different preparations. The slope of the Schild-plot is also given and when different from unity is indicative of non-competitive kinetics. See methods section for additional details. I refers to compounds inactive in the test at concentrations up to 100 μM.

in this respect was some 2.5 times less potent than labetalol.

As in the amino ketone series, all amino alcohols synthesized were inactive in guinea-pig tracheal preparations even at the high concentration of 100 μM (table VI). At β_1-adrenoceptors in guinea-pig atria the majority of the compounds antagonized the positive inotropic effects of isoprenaline, however, 5 of these active compounds had Schild-plot slopes different from unity so it is not possible to ascribe these effects to a definitive interaction at β_1-adrenoceptor sites. Of the 6 remaining compounds, the activity exhibited ranged from calculated IC_{50} values of 0.1–100 μM and only compound **26** had inhibitory potency equivalent, or close to that of the reference drugs (see table VI). Compound **26** also competitively antagonized contractile responses to noradrenaline in rat vas deferens preparations, being more potent than labetalol in this respect. Similarly, compounds **23**, **25** and **30** also exhibited competitive α-adrenoceptor blocking activity in this test but 2 other compounds, **32** and **35**, although antagonizing responses to noradrenaline, had non-competitive kinetics making assessment of their site of action problematic.

All amino alcohols were tested in either anaesthetized or conscious SHR but only 2 amino ketones, compounds **10** and **15**, were selected for *in vivo* testing. The latter 2 compounds were selected since they exhibited a certain activity, albeit weak and non-competitive, in atrial preparations (pA_2 values 5.4 and 5.9 respectively) with compound **15** in addition having weak α-adrenoceptor antagonist effects (pA_2 = 5.3). In anaesthetized SHR, both compounds lowered systolic blood pressure to the same extent ($\approx$ 40%) but the antihypertensive effects were transient ($\leq$ 10 min) and did not warrant additional studies (table VII). Of the **11** amino alcohols tested in anaesthetized SHR *via* the intravenous route, all lowered systolic blood pressure but with the majority of compounds, this effect was transient and inferior to that of the reference drugs (table VII). From this test, 4 compounds are of interest (compounds **23**, **30**, **36** and **44**), for their long-lasting effects on blood pressure. Compounds **23** and **30** exhibited weak competitive β-adrenoceptor blocking activity in atrial tissue (pA_2's 5.85 and 5.55 respectively) coupled with competitive effects at α-adrenoceptor (pA_2's 6.0 and 5.72 respectively). Compound **36** was, however, inactive in

Table VI. α– and β-adrenoceptor blocking activity of the amino alcohols.

Compound N°	Rat vas deferens		Guinea-pig		
			Atria		Trachea
	pA_2 value	Slope	pA_2 value	Slope	pA_2 value
22	I		I		I
23	6.00 ± 0.23	1.0	5.85 ± 0.09	1.0	I
24	I		5.43 ± 0.50	1.0	I
25	6.37 ± 0.53	1.0	6.06 ± 0.32	> 1.0	I
26	6.12 ± 0.23	1.0	6.93 ± 0.10	1.0	I
29	I		5.40 ± 0.19	> 1.0	I
30	5.72 ± 0.25	1.0	5.55 ± 0.50	1.0	I
31	I		I		I
32	6.94 ± 0.16	> 1.0	5.74 ± 0.21	1.0	I
33	I		I		I
34	I		I		I
35	6.14 ± 0.31	> 1.0	5.65 ± 0.40	1.0	I
36	I		I		I
37	I		5.21 ± 0.43	> 1.0	I
38	I		I		I
42	I		I		I
43	I		5.70 ± 0.28	> 1.0	I
44	I		5.53 ± 0.28	> 1.0	I

Results are mean ± SEM values calculated from 3 or 4 results using different preparations. The slope of the Schild-plot is also given and when different from unity is indicative of non-competitive kinetics. See Methods section for additional details. I refers to compounds inactive in the test at concentrations up to 100 μM.

all 3 *in vitro* tests whereas compound **44** possessed weak non-competitive effects in atrial tissue. Given the interesting antihypertensive activity of compound **36** and the fact that this may not be related to α- or β-adrenoceptor blockade *per se*, it was decided to confirm the efficacy of this compound in conscious SHR *via* the oral route before embarking on additional studies. Orally at 30 mg/kg in SHR, significant falls in blood pressure were observed with compound **36** and also with compounds **25**, **31** and **38** with no tachyphylaxis over the d 2 dosing period (table VIII). Compound **42** was active on d 1 but tachyphylaxis was observed on 2 d. Compounds **31** and **36** were the most active compounds in this test and will be subjected to additional studies; firstly over a longer time period to definitively rule out the possibility of tachyphylaxis occurring and secondly, to identify the mechanism(s) responsible for the antihypertensive effects since both compounds had no α- or β-adrenoceptor blocking activity *in vitro*.

Table VII. Effect of intravenous administration of certain selected amino ketones and the amino alcohols on the blood pressure of pentobarbitone-anaesthetized SHR.

Compound N°	Dose (mg/kg I.V.)	Basal values (mmHg)		% Δ Pressure		Duration of effect (min)
		SBP	DBP	SBP	DBP	
Propranolol	5	253±30	210±24	-64	-54	30
Practolol	20	230±10	173±15	-31	-32	45
Labetalol	5	241±10	150±8	-34	-31	>45
10	5	228±13	175±9	-39	-57	10
15	10	190±10	155±5	-39	-51	2
23	15	240±11	178±11	-46	-48	>45
24	15	213±13	163±9	-40	-65	3
26	20	232±13	169±5	-49	-62	5
29	5	219±9	163±10	-33	-36	2
30	1.25	233±11	185±9	-45	-44	>45
35	20	228±17	168±13	-57	-69	10
36	2.5	247±13	193±12	-42	-42	>45
37	20	217±8	173±8	-38	-52	3
38	20	205±19	160±17	-37	-48	3
43	20	218±4	166±11	-43	-54	15
44	5	223±17	168±17	-47	-61	>45

Results are given as mean values obtained in 3–6 animals. See Methods section for additional details.

Table VIII. Effect of certain selected amino alcohols on the blood pressure of conscious SHR after oral administration of 30 mg/kg.

Compound N°	Basal SBP (mmHg)	% Δ SBP from basal values		
		Day 1		Day 2
		2 h	24 h	2 h
22	197±8	+1	+5	0
25	211±4	-8 *	-1	-18 *
28	231±3	-5	+2	-3
31	204±7	-25 *	-20*	-41 *
32	209±2	-9 *	+1	-10 *
33	217±6	-5	-9	-10 *
34	216±11	-2	+5	+4
36	202±6	-12	-2	-30 *
38	200±4	-15 *	-11	-24 *
39	208±3	-5 *	-3	-3
40	208±3	+1	0	-1
42	200±5	-20 *	+5	-6

Results are the mean changes observed in groups of 5 animals. Asterisks indicate statistically significant changes with respect to the vehicle treated control group. $P<0.05$ Paired Student's test. See Methods section for further details.

Conclusion

For the amino alcohols that interacted with adrenergic receptors, it is possible to make some inferences regarding the influence of structure on the biological activity. The presence of an acid hydrogen atom in the aromatic moiety does not constitute a major criterion for affinity to α- or β_1-adrenoceptors; the pairs of compounds **23** and **30**, **25** and **32**, have very similar pA_2 values. The presence of *ortho* substituted arylpiperazine groups (compounds **23**, **25**, **30**, **32**, **35**) is a favourable factor for α-adrenoceptor blocking potency which confirms the results of a previous study [4]. No clear structure–activity relationship was evident at β_1-adrenoceptors; compound **26** was the most active compound in this respect but activity (pA_2 = 6.93) was much less than that observed with labetalol (pA_2 = 7.6).

The results in both conscious and anaesthetized SHR permit one to conclude that the amino alcohol derivatives of benzoxazolinone have antihypertensive activity. This activity may be accounted for in such compounds as **23**, **30**, **25** and **32** by their α- and β_1-adrenergic blocking action. Others, such as compounds **31**, **36** and **38**, show no adrenergic interference and consequently their antihypertensive activity must be due to another mechanism.

Experimental protocols

Chemistry

Melting points were determined on a Büchi SMP-20 capillary melting-point apparatus and are uncorrected. All compounds were homogeneous according to TLC analysis; TLCs were performed on fluorescent silica gel plates with C_6H_6:C_6H_{12}:CH_3COCH_3 (3:3:4) as eluant, and spots were detected by UV and by exposure to I_2 vapour. Elemental analysis were performed by the Analytical Center, CNRS, Vernaison (France); analytical results for the elements indicated were within ±0.4% of the theoretical values. IR spectra (KBr pellets)

were obtained with a Beckman Acculab IV or a Perkin-Elmer 297 spectrophotometer. ^{1}H NMR spectra were recorded at 60 MHz on a Jeol C 60 HL spectrometer; chemical shifts are expressed in parts per million downfield from internal tetramethylsilane, and coupling constants are expressed in Hz. IR and ^{1}H NMR spectra of all compounds were consistent with the assigned structures. Spectral data are described here only for some representative examples.

Preparation of amino ketones: general procedure

A solution of 6-(2-bromoacyl)-2-benzoxazolinone or 6-(2-bromoacyl)-3-methyl-2-benzoxazolinone (0.03 mol) in hot dioxane (100 ml) was added dropwise to a stirred solution of the corresponding 1-arylpiperazine or 4-benzyl piperidine (0.03 mol) and triethylamine (4.55 g, 0.045 mol) in dioxane (30 ml).

After the mixture was stirred at room temperature for 15 h, the precipitate was filtered. The filtrate was evaporated under vacuum, and the residue added to the precipitate. The mixture was stirred in water (500 ml). The solid was collected by filtration, dried, and crystallized from the appropriate solvent.

6-[4-(3-Trifluoromethylphenyl)-1-piperazinyl] acetyl– 2 benzoxazolinone ***1***
IR cm^{-1} 1785 (O-CO-N), 1685 (C=O). ^{1}H NMR (DMSO–d_6) δ: 2.50-3 (4H, m), 3-3.50 (4H, m), 3.86 (2H, s), 6.90-7.60 (5H, m), 7.88 (1H, d, J = 1.8), 7.93 (1H, m, J = 8.5, J = 1.8), 9 (1H, br s, exch).

6{2-[4-(2-methoxyphenyl)-1-piperazinyl] propionyl}-3-methyl-2-benzoxazolinone ***14***
IR cm^{-1} 1775 (O-CO-N), 1675 (C=O). ^{1}H NMR (DMSO-d_6) δ: 1.24 (3H, d, J = 6.5), 2.50-2.80 (4H, m), 2.80-3.10 (4H, m), 3.40 (3H, s), 3.78 (3H, s), 4.25 (1H, q, J = 6.5,), 6.89 (4H, s), 7.30 (1H, d, J = 8.5), 8.02 (1H, d, J = 1.8), 8.10 (1H, m, J = 8.5, J = 1.8).

3-Methyl-6-[2-(4-benzyl-1-piperidinyl) propionyl]-2 benzoxazolinone ***21***
IR cm^{-1} 1790 (O-CO-N), 1670 (C=O). ^{1}H NMR (DMSO–d_6) δ: 1.15 (3H, d, J = 6.5), 0.70-3.30 (11H, m), 3.38 (3H, s), 4.15 (1H, q, J = 6.5), 7.19 (5H, s), 7.30 (1H, d, J = 8.5), 7.96 (1H, d, J = 1.8), 8.05 (1H, m, J = 8.5, J = 1.8).

Preparation of amino alcohols

Method A
A 10% palladium-charcoal catalyst (0.5 g) was added to a suspension of the corresponding amino ketone (5 g) in ethanol (500 ml). The mixture was hydrogenated under 1422 psi at 100°C for 10 h. After cooling, the catalyst was removed. The filtrate was evaporated under vacuum, and the residue was crystallized from the appropriate solvent.

Method B
Sodium borohydride (1.13 g, 0.03 mol) was added in portions to a stirred suspension of the corresponding amino ketone (0.015 mol) in methanol (300 ml). The mixture was stirred at room temperature for 1 h and then evaporated under vacuum. The residue was treated with water (100 ml). The resulting solid was filtered, dried, and crystallized from the appropriate solvent.

3-Methyl-6-{2-[4-(3-trifluoromethylphenyl)-1-piperazinyl]-1-hydroxyethyl}-2 benzoxazolinone ***29***
IR cm^{-1} 3120 (O-H), 1775 (O-CO-N). ^{1}H NMR [$(CD_3)_2CO$] δ: 2.55 (2H, d, J = 6.5), 2.60-2.90 (4H, m) 3.20-3.50 (4H, m), 3.37 (3H, s), 4.15 (1H, br s, exch), 4.88 (1H, t, J = 6.5), 6.95-7.55 (7H, m).

Erythro-3-methyl-6-{2-[4-(3-trifluoromethylphenyl)-1-piperazinyl]-1-hydroxypropyl}-2-benzoxazolinone ***33***
IR cm^{-1} 3160 (O-H), 1780 (O-CO-N). ^{1}H NMR ($CDCl_3$) δ: 0.95 (3H, d, J = 7), 2.60-3.50 (9H, m), 3.42 (3H, s), 3.50 (1H, br s, exch), 5.04 (1H, d, J = 4), 6.85-7.55 (7H, m).

Threo-3-methyl-6-{2-[4-(3-trifluoromethylphenyl)-1-piperazinyl]-1-hydroxypropyl}-2-benzoxazolinone ***34***
IR cm^{-1} 3390 (O-H), 1780 (O-CO-N). ^{1}H NMR ($CDCl_3$) δ: 0.85 (3H, d, J = 7), 2.50-3.40 (9H, m), 3.40 (3H, s), 4.36 (1H, d, J = 9.8), 4.70 (1H, br s, exch), 6.80-7.60 (7H, m).

Pharmacological methods

α-Adrenoceptor blocking activity

Vasa deferentia were removed from Wistar rats, cut open longitudinally and mounted under 1 g tension in 10 ml organ baths containing Krebs'solution at 31°C gassed with 95% O_2 and 5% CO_2. Cumulative concentration-response curves were constructed to noradrenaline (0.01–10 μM) followed by thorough washing of the tissue. When reproducible control curves were obtained, the compound under study was added to the organ bath 3 min before commencing the concentration-response curve to noradrenaline.

β-Adrenoceptor blocking activity

Cardiac β_1-adrenoceptors
Guinea-pig left atria were mounted, under 0.5 g resting tension, in isolated organ baths containing Krebs'solution at 37°C gassed with 95% O_2; 5% CO_2 and driven at 1.6 Hz (supramaximal voltage and 1 ms pulse width). Cumulative concentration-response curves to isoprenaline (0.01-10 μM) were constructed followed by washing. When reproducible curves were obtained, the compound under study was added to the organ bath 15 min before repeating the concentration-response curve to isoprenaline.

Tracheal β_2-adrenoceptors
Spiral strips of guinea pig trachea were mounted under 2 g resting tension in isolated organ baths containing Krebs' solution at 37°C gassed with 95% O_2, 5% CO_2. Cumulative concentration-response curves to isoprenaline (0.01-10 μM) were constructed followed by thorough washing of the preparation. Once stable control concentration–response curves to isoprenaline were obtained, the compound under study was added to the organ bath 15 min before repeating the concentration-response curve to isoprenaline.

In all *in vitro* experiments, each preparation was exposed to 3 ascending concentrations (0.1–10 μM) of the compound under study. Recordings were made on Sefralm flat-bed recorders using Ifelec isometric force transducers. pA_2 values were determined according to the method of Arunlakshana and Schild [19] and competitive antagonism assessed from the slope of the regression line of the Arunlakshana and Schild plot. Results are presented as mean ± SEM values from at least 3 preparations.

Antihypertensive activity in spontaneously hypertensive rats (SHR)

Male SHR (Charles River, France) weighing 180-220 g were used in these experiments.

Studies in anaesthetized SHR
Groups of 3–6 male SHR were anaesthetized with pentobarbitone (45 mg/kg IP), intubated and the carotid artery cannulated for blood pressure measurements (Bell and Howell transducers, Beckman polygraph). A jugular vein was also cannulated to permit injection of test compounds. Compounds were injected over a 1 min period in increasing doses (1-20 mg/kg IV) at intervals of 1 h, until blood pressure fell by about 50%. Maximal changes in systolic and diastolic blood pressure due to the test substances were recorded and results expressed in terms of the percentage difference from control values. Results shown in table VII are the mean values from groups of 3–6 animals.

Studies in conscious SHR
Systolic blood pressure was recorded indirectly from the tail artery of groups of 5 trained male SHR using the tail-cuff method [18]. Animals were pre-warmed for 20 min in a ventilated chamber maintained at 39°C prior to each measurement. Compounds were administered orally for 2 consecutive days at a dose of 30 mg/kg. Blood pressure was measured 2 h and 24 h after compound administration. The mean percentage change in systolic blood pressure of each group was calculated and statistical differences in blood pressure of treated and control, vehicle-treated SHR determined using the paired Student's *t*-test.

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