Chemistry, Pharmacology, and Structure–Activity Relationships with a New Type of Imidazolines Exerting a Specific Bradycardic Action at a Cardiac Site

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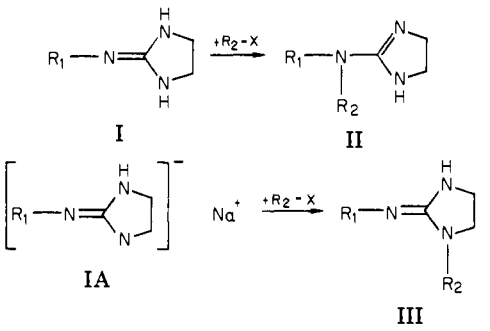
The reaction of alkyl halides with 2-(arylimino)imidazolidines (I) leads to imidazoline derivatives II, in which the side chain is situated at the bridge nitrogen atom between the phenyl group and the imidazoline ring. The new imidazolines (II) exert a specific bradycardic action at a cardiac site. Syntheses and pharmacology are shown and structure–activity relationships discussed. The results reveal that the imidazoline derivatives (II) represent a class of compounds with a novel type of cardiac action.

The well-known blood-pressure-lowering activity of the imidazolidine derivative clonidine (Scheme I; Ia)[1,2] stimulated a systematic preparation of compounds related to the 2-(arylimino)imidazolidines, I.[3] Our work during the last few years led to numerous molecular alterations[4] to find compounds with enhanced efficacy and possibly a pharmacological profile different from clonidine. One result of this approach was the synthesis of the imidazoline derivatives II characterized by an additional substitution at the exocyclic nitrogen atom. One of these compounds, 2-[*N*-allyl-*N*-(2,6-dichlorophenyl)amino]-2-imidazoline (alinidine) (**39**), was found to have an unexpected pharmacological profile.[5] This *N*-allyl derivative of clonidine exerted a specific bradycardic action with a direct attack at the atrial sinus node. A number of cardiovascular activities of this drug and the pharmacological differences from clonidine have been published recently.[6] In another paper[7] it was shown that alinidine (St 567; **39**) decreased electrocardiographic signs of experimentally induced myocardial ischemia. This indicated that drugs with "specific bradycardic action" reduce myocardial oxygen demand and, therefore, might be of value in the treatment of ischemic heart diseases.

This article presents the chemistry, physicochemical parameters, and the pharmacology of a number of imidazoline derivatives (II). The specificity of the bradycardic action of 2-[*N*-(cyclopropylmethyl)-*N*-(2,6-dibromophenyl)amino]-2-imidazoline (**1**)[8] is presented in comparison with other known compounds having direct bradycardic action, such as a cholinergic drug, an antiarrhythmic, and a so-called calcium antagonist. A rational test for quantitative evaluation of the direct bradycardic action in spinal rats was developed to test a greater number of compounds and to make it possible to compare structural elements and physicochemical parameters with the pharmacological efficacy.

Scheme I[a]



[a] R_1 = aryl (mono-, di- and trisubstituted, for example, by halogen, alkyl, CF_3); R_2 = alkyl, alkenyl, cycloalkylmethyl, thienylmethyl, etc.; X = Br, Cl; Ia (clonidine): R_1 = 2,6-dichlorophenyl.

Chemistry. Synthesis of Imidazolines of Type II. The approach taken in the design of these new compounds was based upon the fact that the nitrogen atoms in the 2-(arylimino)imidazolidines (I) can be selectively alkylated. The action of alkyl halides on the imidazolidines I led exclusively to alkylation of the exocyclic nitrogen atom and gave compounds II as the predominant reaction product.[9] In contrast, alkylation of the imidazolidine anion IA yields the isomeric compounds III (Scheme I),[10] which lack any bradycardic activity (unpublished results).

For the alkylation of I leading to imidazolines II, both polar (methanol) and nonpolar (toluene) solvents can be used. Details of the methods used are described under Experimental Section, and the results are summarized in Tables I–IV.

Physicochemical Properties of the Imidazolines II. Alkylation of the exocyclic nitrogen atom results in a shift of the exocyclic double bond (Scheme I) and a concomitant loss of conjugation with the aromatic π system. As a consequence of this, the pK_a values in the imidazolines II are considerably higher than those of the parent compounds I. As examples of the series I for clonidine (Ia) and for 2-[(2,6-dibromophenyl)imino]imidazolidine, pK_a values of 8.2 and 7.80, respectively, were published.[3,12] These values are considerably lower than those of the corresponding compounds of the series II, namely, **39** and all the substances listed in Table II.

(1) W. Kobinger, in "Hypertension: Mechanisms and Management", G. Onesti, K. E. Kim, and J. H. Moyer, Eds., Grune & Stratton, New York, 1973, pp 369–380.
(2) C. H. Boehringer Sohn Ingelheim (inventors: H. Stähle, K.-H. Hauptmann, and K. Zeile), English Patent 1 034 938 (June 6, 1966); *Chem. Abstr.*, **65**, 12211 (1966).
(3) K.-H. Pook, H. Stähle, and H. Daniel, *Chem. Ber.*, **107**, 2644–2657 (1974).
(4) H. Stähle, *Med. Chem., Proc. Int. Symp., 4th, 1974*, 75–105 (1974).
(5) Code number St 567.
(6) W. Kobinger, C. Lillie, and L. Pichler, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **306**, 255–262 (1979).
(7) W. Kobinger, C. Lillie, and L. Pichler, *Eur. J. Pharmacol.*, **58**, 141–150 (1979).
(8) Code number STH 2148.
(9) H. Stähle and K.-H. Pook, *Liebigs Ann. Chem.*, **751**, 159–167 (1971).
(10) C. H. Boehringer Sohn Ingelheim (inventors: H. Stähle, H. Köppe, W. Kummer, and K. Stockhaus), DOS 2 308 883 (Feb 23, 1973/Aug 29 1974); *Chem. Abstr.*, **81**, 169545 (1974).

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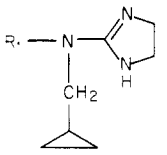
Table I. Chemical and Pharmacological Data of Imidazolines II (R_2 = Cyclopropylmethyl)



no.	R_1	reaction conditions: temp, °C	reaction conditions: time, h	% yield	mp, °C	log *P* (octanol/buffer, pH 7.4)	pK_a	mol formula	anal.	decrease in heart rate, spinal rats: D_{150},[a] mg/kg	decrease in heart rate, spinal rats: rel act.
1	2,6-Br_2-C_6H_3-	120 80	18 40	17 38.3	147-147.5	-1.12	10.88	$C_{13}H_{15}Br_2N_3$	C, H, Br, N	0.62	1.0
2	2,5-Br_2-C_6H_3-	125	72	38.0	161-163	-0.52	11.0	$C_{13}H_{15}Br_2N_3$	C, H, Br, N	5.0	0.12
3	2,4-Br_2-C_6H_3-	125	72	41.1	110-111	-0.31	11.2	$C_{13}H_{15}Br_2N_3$	C, H, Br, N	10.0	0.062
4	2,3-Br_2-C_6H_3-	125	17	16.4	99-102	-0.41	11.1	$C_{13}H_{15}Br_2N_3$	C, H, Br, N	7.5	0.083
5	3,4-Br_2-C_6H_3-	125	72	6.6	88-89			$C_{13}H_{15}Br_2N_3$	C, H, Br, N	>>10.0	<<0.062

[a] Dose which decreased heart rate by 150 beats/min, evaluated graphically; see Figure 2. For each substance, n = 6 animals, 3 cumulative doses per animal.

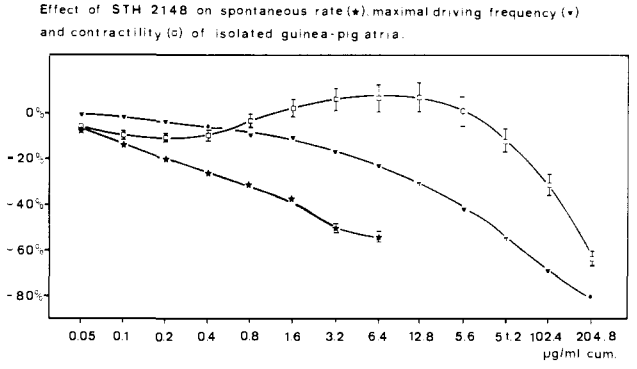


Figure 1. Isolated guinea pig atria. Effect of 1 on spontaneous rate (*), maximal driving frequency (▼), and contractility (□; electrical stimulation, 2.5 Hz). Abscissa: cumulative concentration of 1 in the organ bath. Ordinate: drug-induced changes in percent of control values; mean ± SEM is indicated when exceeding ±2%. Control values: atrial rate, 212 ± 4.3 beats/min (n = 10); contractility, 1.08 ± 0.045 g (n = 15); maximal driving frequency, 17.2 ± 0.744 beats/s (n = 10).

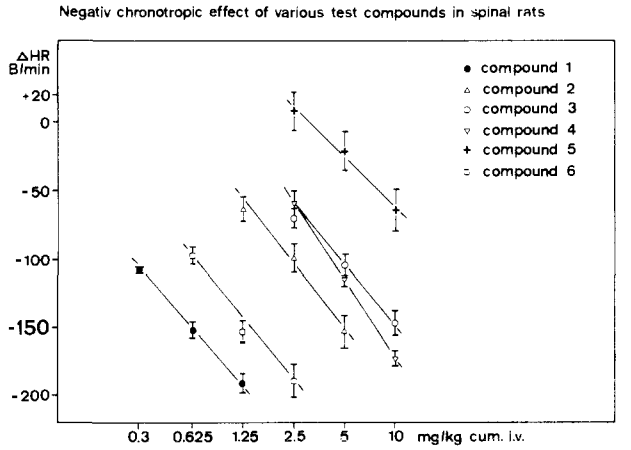


Figure 2. Decrease of heart rate in spinal rats. Test compounds 1–6 were injected cumulatively iv (abscissa); decrease in heart rate (HR) in beats/min (ΔB/min) are drawn on the ordinate (mean ± SEM; n = 6 animals).

Accordingly, the partition coefficients in series II are lower (Tables I–IV) compared with the values of the corresponding compounds of the imidazolidines I [e.g., a log *P* for clonidine (Ia) and 2-[(2,6-dibromophenyl)imino]imidazolidine of 0.48 and 1.17, respectively].[11,12]

Pharmacology. Figure 1 presents the characteristics of one of the most active drugs of the series, 1, with respect to its direct effect upon myocardial actions. The rate of spontaneously beating atria was decreased in the lowest concentration range (left curve). In low concentrations the contractility was slightly increased; decreases in contractility (right curve), as well as in maximal driving frequency (a test for antiarrhythmic activity, middle curve), occurred in higher concentrations. These results are summarized in Table V where the concentrations are given, which decreased the parameters for 30% of their control values (EC_{30}). As reference substances, quinidine, verapamil, and carbachol were used. From the ratio of the EC_{30} values it can be seen that 1 exerted the greatest ratio between the bradycardic and the negative inotropic action, as well as a great ratio between bradycardic and antiarrhythmic action.

In spinal rats the iv injection of all tested substances decreased the heart rate. This effect was dose dependent; i.e., the stepwise injection of incremental doses produced a corresponding stepwise decrease of the heart rate.

In Figure 2, mean values (±SEM) are given for results with the compounds 1–6 as an example, and analoguous plots were gained with all other substances. From these log dose–response curves, those doses were evaluated which decreased heart rate by 150 beats/min (D_{150}). Results are given in Tables I–IV.

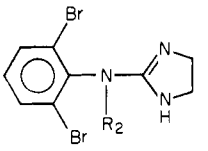
Discussion

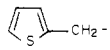
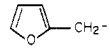
The bradycardic effect of 1 in isolated guinea pig atria, as well as the bradycardic effect of the compounds in spinal rats, prove the direct cardiac point of attack, independent of the central nervous system. The pattern of 1, as shown by the results in the isolated guinea pig atria, clearly differentiated this drug from other drugs with direct actions on cardiac pacemaker cells (see Table V): The "Ca antagonist" verapamil exerted a negative inotropic action in concentrations similar to those necessary for lowering of the atrial rate; the membrane-depressive antiarrhythmic drug, quinidine, decreased the maximal driving frequency in the same concentration range as the heart rate; carbachol strongly decreased contractility and even increased the maximal driving frequency.

Compound 1 exerted the same pharmacological pattern as was published for **39**.[6] No β-adrenoceptor blocking

(11) W. Hoefke, W. Kobinger, and A. Walland, *Arzneim.-Forsch (Drug Res.)*, **25**, 786-793 (1975).
(12) P. B. M. W. M. Timmermans, W. Hoefke, H. Stähle, and P. A. van Zwieten, *Progr. Pharmacol.*, 3(1), 1-97 (1980).

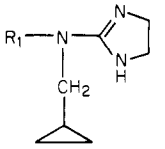
Table II. Chemical and Pharmacological Data of Imidazolines II (R_1 = 2,6-Dibromophenyl)



no.	R_2	reaction conditions: temp, °C	reaction conditions: time, h	% yield	mp, °C	log *P* (octanol/buffer, pH 7.4)	pK_a	mol formula	anal.	decrease in heart rate, spinal rats: D_{150},[a] mg/kg	decrease in heart rate, spinal rats: rel. act.
6	CH_3-	80	16	63.7	125-127	−1.71	10.7	$C_{10}H_{11}Br_2N_3$	C, H, Br, N	1.4	0.44
7	C_2H_5-	110	16	20.5	135-137	−1.01	11.1	$C_{11}H_{13}Br_2N_3$	C, H, Br, N	0.75	0.83
8	*n*-C_3H_7-	110	16	37.2	155-156	−0.55	11.0	$C_{12}H_{15}Br_2N_3$	C, H, Br, N	0.65	0.95
9	*n*-C_4H_9-	100	16	26.7	136-138	−2.5	10.97	$C_{13}H_{17}Br_2N_3$	C, H, Br, N	1.35	0.46
10	*n*-C_5H_{11}-	100	18	30.8	135-137	0.32	11.0	$C_{14}H_{19}Br_2N_3$	C, H, Br, N	1.6	0.39
11	$CH_3CH(CH_3)$-	150	16	24.4	98-100	−0.82	11.2	$C_{12}H_{15}Br_2N_3$	C, H, Br, N	2.3	0.27
12	$CH_3CH(CH_3)CH_2$-	110	15	17.8	128-130	−0.64	11.02	$C_{13}H_{17}Br_2N_3$	C, H, Br, N	1.35	0.46
13	$CH_3CH(CH_3)CH_2CH_2$-	110	9	10.7	101-103	0.16	10.9	$C_{14}H_{19}Br_2N_3$	C, H, Br, N	1.3	0.48
14	CH_2=$CHCH_2$-	100	72	22.3	134-136	−0.75	10.7	$C_{12}H_{13}Br_2N_3$	C, H, Br, N	1.5	0.41
15	CH_2=$C(CH_3)CH_2$-	100	18	41.1	120-122	−0.66	10.71	$C_{13}H_{15}Br_2N_3$	C, H, Br, N	2.1	0.3
16	CH_3CH=$CHCH_2$-	78	2	39.3	82-84	−0.49	11.0	$C_{13}H_{15}Br_2N_3$	C, H, Br, N	0.7	0.88
17	$CH_3C(CH_3)$=$CHCH_2$-	78	8	43.6	187-188[b]	−0.14	10.75	$C_{14}H_{17}Br_2N_3$	C, H, Br, N[c]	3.5	0.18
18	CH_2=$CHCH_2CH_2$-	110	16	37.5	133-134	−0.63	11.20	$C_{13}H_{15}Br_2N_3$	C, H, Br, N	1.0	0.62
19	$CH_3C(=CH_2)CH_2CH_2$-	120	24	34.0	126.5-127.5	0.02	10.9	$C_{14}H_{17}Br_2N_3$	C, H, Br, N	1.03	0.6
20	CH≡CCH_2-	66	3	29.5	134-135	−0.18	10.1	$C_{12}H_{11}Br_2N_3$	C, H, Br, N	1.25	0.5
1	c-C_3H_5-CH_2-	120	18	17	147-147.5	−1.12	10.88	$C_{13}H_{15}Br_2N_3$	C, H, Br, N	0.62	1.0
		80	40	38.3							
21	c-C_4H_7-CH_2-	130	18	20.7	168-171	−0.06	10.9	$C_{14}H_{17}Br_2N_3$	C, H, Br, N	1.2	0.52
22	c-C_5H_9-CH_2-	110	20	7.5	151-153	0.32	10.9	$C_{15}H_{19}Br_2N_3$	C, H, Br, N	1.3	0.48
23	c-C_6H_{11}-CH_2-	140	20	31.9	157-158	0.27	11.2	$C_{16}H_{21}Br_2N_3$	C, H, Br, N	6.5	0.095
24	C_6H_5-CH_2-	110	0.25	57.9	87-91	−0.05	10.4	$C_{16}H_{15}Br_2N_3$	C, H, Br, N	2.5	0.25
25	c-C_5H_9-	117	8.5	27.6	120-122	−0.29	11.2	$C_{14}H_{17}Br_2N_3$	C, H, Br, N	1.0	0.62
26	c-C_6H_{11}-	117	10	4.0	147-149	0.14	11.3	$C_{15}H_{19}Br_2N_3$	C, H, Br, N	2.6	0.24
27		110	6	32.5	107-108	−0.10	10.51	$C_{14}H_{13}Br_2N_3S$	C, H, Br, N, S	1.9	0.33
28		110	5	25.1	114-115	−0.52	10.5	$C_{14}H_{13}Br_2N_3O$	C, H, Br, N	2.8	0.22

[a] Dose which decreased heart rate by 150 beats/min, evaluated graphically; see Figure 2. For each substance, n = 6 animals, 3 cumulative doses per animal. [b] Melting point of the hydrobromide. [c] Analyses of the hydrobromide.

Table III. Chemical and Pharmacological Data of Imidazolines II (R_2 = Cyclopropylmethyl)

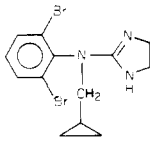
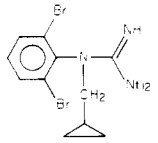
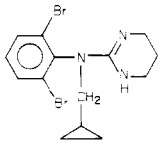
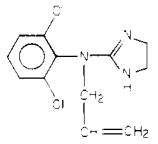


no.	R_1	reaction conditions: temp, °C	reaction conditions: time, h	% yield	mp, °C	log *P* (octanol/buffer, pH 7.4)	pK_a	mol formula	anal.	decrease in heart rate, spinal rats: D_{150},[a] mg/kg	decrease in heart rate, spinal rats: rel. act.
1	2,6-Br_2-C_6H_3-	120	18	17	147-147.5	−1.12	10.88	$C_{13}H_{15}Br_2N_3$	C, H, Br, N	0.62	1.0
		80	40	38.3							
29	2,6-Cl_2-C_6H_3-	110	32	10.6	126-129	−0.92	10.9	$C_{13}H_{15}Cl_2N_3$	C, H, Cl, N	0.65	0.95
30	2,6-F_2-C_6H_3-	78	20	16.0	112-114	−1.41	10.3	$C_{13}H_{15}F_2N_3$	C, H, F, N	4.8	0.13
31	2-Br-6-Cl-C_6H_3-	78	24	23.3	136-137	−0.79	10.8	$C_{13}H_{15}BrClN_3$	C, H, X,[b] N	0.42	1.48
32	2-Br-6-F-C_6H_3-	78	23	30.8	120	−1.03	10.7	$C_{13}H_{15}BrFN_3$	C, H, X,[b] N	1.5	0.41
33	2-Cl-6-F-C_6H_3-	130	16	28.0	116-118	−0.98	10.8	$C_{13}H_{15}ClFN_3$	C, H, Cl, F, N	0.74	0.84
34	2-F-6-CF_3-C_6H_3-	120	18	58.4	126-127	−0.95	10.7	$C_{14}H_{15}F_4N_3$	C, H, F, N	1.8	0.34
35	2-Cl-6-CH_3-C_6H_3-	130	16	30.3	127-128	−0.99	11.3	$C_{14}H_{18}ClN_3$	C, H, Cl, N	1.85	0.34
36	2-Br-C_6H_4-	78	120	23.8	96.5-98.5	−1.30	11.2	$C_{13}H_{16}BrN_3$	C, H, Br, N	4.4	0.14

[a] Dose which decreased heart rate by 150 beats/min, evaluated graphically; see Figure 2. For each substance, n = 6 animals, 3 cumulative doses per animal. [b] X means total halogen.

effect or cholinergic effect was found with **39**, and similar results were also obtained for **1** (unpublished results). In contrast to clonidine, the compounds **39** and **1** lacked a distinct hypotensive effect in intact rats and the pronounced stimulation of α-adrenoceptors in spinal rats (ref 6 and unpublished results). It will be assumed now that the other compounds listed in Tables I–IV lowered the heart rate by similar mode of actions as **1** and **39**. It may

Table IV. Chemical and Pharmacological Data of a Guanidine and Tetrahydropyrimidine Derivative Compared to an Imidazoline II[a]

no.	structure	reaction conditions: temp, °C	reaction conditions: time, h	% yield	mp, °C	log *P* (octanol/buffer, pH 7.4)	pK_a	mol formula	anal.	decrease in heart rate, spinal rats: D_{150},[b] mg/kg	decrease in heart rate, spinal rats: rel act.
1		120 80	18 40	17 38.3	147-147.5	-1.12	10.88	$C_{13}H_{15}Br_2N_3$	C, H, Br, N	0.62	1.0
37[c]		78	34	28.7	270[d]	-0.63	11.9	$C_{11}H_{13}Br_2N_3$	C, H, Br, N	>10.0	<0.062
38[e]		125	18	4.5	128-130	-1.03	12.4	$C_{14}H_{17}Br_2N_3$	C, H, Br, N	1.1	0.56
39		65	4	57.2	127-129	-1.66	10.42	$C_{12}H_{13}Cl_2N_3$	C, H, Cl, N	2.5	0.25

[a] For comparison, data are also given for alinidine (39). [b] Dose which decreased heart rate by 150 beats/min, evaluated graphically; see Figure 2. For each substance, $n = 6$ animals, 3 cumulative doses per animal. [c] Synthesized by action of chloromethylcyclopropane on *N*-(2,6-dibromophenyl)guanidine according to the reaction conditions described in Table IV. [d] Melting point of the hydrochloride. [e] For synthesis, see C. H. Boehringer Sohn, Ingelheim (inventors: H. Stähle, H. Köppe, W. Kummer, W. Kobinger, C. Lillie and L. Pichler), German Patent Application P 28 31 600.9 (July 19, 1978).

Table V. Effects of Substances on Spontaneous Frequency, Contractility, and Maximal Driving Frequency in Isolated Guinea Pig Atria[a]

substance	decrease in: atrial rate: EC_{30}, μg/mL	decrease in: contractility: EC_{30}, μg/mL	decrease in: max driving freq: EC_{30}, μg/mL	ratio of EC_{30}: contractility/atrial rate	ratio of EC_{30}: max driving freq/atrial rate
1	0.65 (10)	95 (15)	12 (10)	146	18
quinidine	7.2 (9)	62 (10)	6.5 (6)	8.6	0.90
verapamil	0.20 (8)	0.24 (6)	6.5 (7)	1.2	32
carbachol	0.029 (20)	0.0065 (8)	increase[b] (6)	0.22	

[a] EC_{30} = concentration which reduced predrug value by 30%, evaluated from curves as in Figure 1. Number of experiments are in parentheses. [b] EC_{30} of increase = 0.090 μg/mL.

be pointed out that the spinal rat preparation, as used in this study, practically excludes bradycardic effects other than those directly attacking the heart.

Examination of several compounds in the clonidine series clearly demonstrated that a maximal penetration of the blood–brain barrier was obtained for log *P* values of approximately 2.0.[12,13] Comparing log *P* values in series I[12] and II revealed smaller log *P* values in series II. Therefore, one would expect a much smaller penetration of the imidazolines II through the blood–brain barrier.

Gross inspection of Tables I–IV reveals no obvious correlation between the bradycardic activity (D_{150}) of the new imidazolines II and the parameters log *P* and pK_a. However, certain structural properties were found to be essential for the observed pharmacological activity. It became evident from our investigations with the dibromo derivatives shown in Table I that the bradycardic activity of these imidazolines is markedly influenced by the position of the substituents in the aromatic ring, which in turn determines the stereochemical conformation of the molecule. It can be noted that compounds with 2,6-substituents exhibit optimal bradycardic activity. The observed bradycardic activity and the bulk of the nonaromatic side chain, R_2, on the exocyclic nitrogen atom (Table II) show that maximum activity can be expected for compounds where R_2 contains 2–5 carbon atoms. In this series the introduction of the cyclopropylmethyl moiety led to the compound with the greatest bradycardic potency (1). Comparison of compounds with R_2 = cyclopropylmethyl revealed that optimum activity was obtained for compounds with bromine or chlorine in the 2,6 position of the aromatic ring, respectively (Table III).

The importance of the five-membered imidazoline ring can be seen. Ring opening to the guanidine or ring expansion to a six-membered ring leads to a decrease of activity (Table IV). It was previously found in the imidazolidine I series that for an interaction between the drug and the peripheral postsynaptic α-adrenoceptor at least one of the two aromatic substituents should be located in the ortho position. In compounds with one substituent in the ortho position, a partial rotation around the C–N axis is possible; therefore, a total inhibition of free rotation is not essential for an optimal drug–receptor interaction

(13) E. J. Lien, *Med. Chem., Proc. Int. Symp., 4th, 1974*, 319–342 (1974).

for the imidazolidines I.[12] In contrast, in the imidazoline II series a disubstitution in the ortho, ortho prime position is essential for a bradycardic activity. This disubstitution completely inhibits a rotation around the C–N axis and thereby the establishment of a coplanar conformation is also inhibited.

The results of our structure–activity correlations for the imidazolines II disclose the following optimal structural elements for a specific bradycardic activity: (1) a guanidine moiety fixed within the aminoimidazoline system; (2) an increase in basicity of the guanidine grouping by means of the introduction of a nonaromatic N-substituent with a concomitant shift of the conjugated C=N double bond to an isolated C=N double bond; (3) a conformationally aplanar structure for the molecule by means of the introduction of bulky halogen substituents in the 2 and 6 positions of the phenyl ring; (4) a pK_a value greater than in series I; (5) a log P value lower than in series I. The criteria listed above do not completely coincide with those known for α-adrenergics of the imidazolidine I type. Thus, a molecular basis could be found for the biological differences between the compounds of types I and II.

Experimental Section

Chemistry. Melting points were determined in open glass capillaries with a Büchi-Tottoli apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory of C.H. Boehringer Sohn Ingelheim. Analyses (C, H, Br, Cl, F, N, and S) for all compounds reported in this paper were within ±0.4% of the theoretical values. All TLC chromatograms were carried out on precoated silica gel F 254 plates (E. Merck, Darmstadt). The following solvent systems were used: A, benzene–dioxane–concentrated ammonia–ethanol (50:40:5:5); B, ethyl acetate–2-propanol–concentrated ammonia (70:50:20); C, toluene–dioxane–concentrated ammonia–ethanol (50:40:15:5). Detection was with iodoplatinate.[14] NMR spectra were recorded on a Varian XL-100 spectrometer with Me_4Si as internal standard. Mass spectra were obtained on a Varian MAT-CH-7 spectrometer. pK_a values and partition coefficients (P) were determined according to methods described by Timmermans and van Zwieten.[15]

Examples of Synthesis of Imidazolines II. 2-[*N*-Allyl-*N*-(2,6-dichlorophenyl)amino]-2-imidazoline (39). A mixture of 2-[(2,6-dichlorophenyl)imino]imidazolidine (Scheme I, Ia; 230 g, 1 mol), allyl bromide (181.5 g, 1.5 mol), and anhydrous Na_2CO_3 (64 g) in 800 mL of absolute methanol was refluxed with stirring for 4 h. After standing overnight, the insoluble inorganic material was removed by filtration through charcoal. Evaporation of the filtrate to dryness left a slightly colored solid residue, which was dissolved in approximately 2 L of 1 N HCl. The solution was treated with charcoal, filtered, and then made alkaline with 20% aqueous NaOH. The resulting oily residue was stirred with approximately 500 mL of petroleum ether; the solid which formed was filtered and triturated with petroleum ether for a second time in a mortar. The precipitate was collected by filtration and washed with water and petroleum ether. After drying at 60 °C, it afforded 154.6 g (57%) of the base, mp 127–129 °C. The analytical sample was recrystallized from MeOH–H_2O: mp (hydrobromide) 193–194 °C; TLC R_f 0.56 (system A), 0.75 (system B); NMR (CD_6SO) δ 7.58 (m, 3 H, aryl), 5.94 (m, 1 H, –CH=), 5.20 and 5.32 (d, 2 H, $=CH_2$), 4.38 (d, 2 H, N-CH_2-allyl), 3.85 (s, 4 H, -CH_2CH_2-imidazoline); MS (70 eV) M^+ 269, 271, 273 (2Cl), M - H 268, 270, 272 (2Cl), M - Cl 234, 236 (1Cl). Anal. ($C_{12}H_{13}Cl_2N_3$) C, H, Cl, N.

2-[*N*-(Cyclopropylmethyl)-*N*-(2,6-dibromophenyl)amino]-2-imidazoline (1). A mixture of 48 g (0.145 mol) of 2-[(2,6-dibromophenyl)imino]imidazolidine and 14.1 g (0.152 mol) chloromethylcyclopropane in 120 mL of toluene was heated in an autoclave at 120 °C for 20 h in the presence of 24 mL of triethylamine. After the mixture cooled, the toluene which contained mostly unreacted starting material was removed by decantation. The remaining resinous material was dissolved in approximately 200 mL of MeOH, and the solvent was subsequently removed in vacuo. The residue was dissolved in 100 mL of 1 N HCl and then extracted with ether. The pH of the aqueous layer was adjusted to pH 8 with 9 mL of 50% KOH and again extracted with ether; this was followed by exhaustive extraction with ether at increasing pH values to remove all impurities (TLC). Addition of 5 mL of 50% KOH quantitatively precipitated the 2-[*N*-(cyclopropylmethyl)-*N*-(2,6-dibromophenyl)amino]-2-imidazoline from the aqueous phase. After filtration, the solid residue was washed three times with water (30 mL each) and dried to yield 9.3 g (17%), mp 147–147.5 °C. The analytical sample was recrystallized from MeOH–H_2O: mp (hydrobromide) 207 °C; TLC R_f 0.55 (system A), 0.45 (system C); NMR (CD_6SO) δ 7.83 (d, 2 H, aryl), 7.37 (t, 1 H, aryl), 3.84 (m, A_2B_2, 4 H, -CH_2CH_2-imidazoline), 3.64 (d, 2 H, N-CH_2-), 1.08 (m, 1 H, –CH-cyclopropyl), 0.32–0.6 and 0.10–0.27 (m, 4 H, -CH_2CH_2-cyclopropyl); MS (70 eV) M^+ 371, 373, 375 (2Br), M - H 370, 372, 374 (2Br), M - C_4H_6 317, 319, 321 (2Br), M - Br 292, 294 (1 Br). Anal. ($C_{13}H_{15}Br_2N_3$) C, H, Br, N. According to the above-described examples, the imidazolines in Tables I–IV were synthesized. The reaction conditions are shown in Tables I–IV.

Pharmacological Methods. Two sets of experiments were performed. One series in isolated guinea pig atrial preparations is presented to demonstrate the specific bradycardic action of one compound, 1. The other series was done in spinal rats, in which the bradycardic action of all compounds was quantified.

Experiments in Isolated Guinea Pig Atria. Guinea pigs of various breeds, 300–500 g of either sex, were killed by a blow on the head, the heart was removed, and the atria were dissected. The preparation was suspended in 40 mL of modified Tyrode's solution (136.8 mM NaCl, 2.68 mM KCl, 0.26 mM $MgCl_2$, 0.42 mM NaH_2PO_4, 11.9 mM $NaHCO_3$, 1.8 mM $CaCl_2$, 15 mM glucose), gassed with a mixture of 98% O_2 + 2% CO_2. The resting tension on the muscle was 1 g. Mechanograms were recorded isometrically via a strain gauge on a multichannel recorder.

Drug effects on atrial rate (bradycardic effect) were tested in spontaneously beating atria, bath temperature 37 °C, after a equilibrium period of at least 30 min, until the rate did not change by more than 5 beats/min. Effects on contractility (inotropic effect, expressed in grams) were tested in electrically stimulated left atria (rectangular pulses, 3 ms, 1.5 times threshold voltage; 2.5 Hz), bath temperature 30 °C, equilibrium period 20 min. Effects on maximal driving frequency (antiarrhythmic effect) were tested in electrically stimulated left atria (rectangular pulses, 1 ms, 3 times threshold voltage). After a 15-min equilibration at 1 Hz, frequency was increased by 1 Hz every 10 s until contractions did not follow every stimulus.[16] The stimulation runs were interspersed by resting periods of 5 min with stimulation at 0.5 Hz. The control value was determined as the mean of three predrug tests. Five and ten minutes after the substance was added, the maximal driving frequency was determined and the average of these two trials evaluated. In all three types of experiments the test substance was added cumulatively whereby the concentration was doubled every 10 min. A separate atrium perparation was used for each experiment.

Experiments in Spinal Rats. Male rats of the strain Chbb:THOM, weighing between 200 and 250 g, were anesthetized with pentobarbital sodium, 50 mg/kg ip. The trachea was cannulated and atropine sulfate, 1 mg/kg sc, was injected. The medulla was sectioned at C_1, the brain was destroyed, and artificial respiration was performed. The heart rate was registered continously on an ink-writing polygraph by means of an instantaneous beat to beat recording tachograph triggered by the electrocardiogram (ECG). Test substances were injected cumulatively via the jugular vein. Thereby the dose was doubled every 2 min, a time when the maximal effect of the test substances was already achieved. Each animal received three doses; each substance was tested in six animals. The highest dose was 10 mg/kg cumulatively. The ECG was recorded before the first and after the last cumulative dose at a paper speed of 60 mm/s. The heart rate

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was evaluated 2 min after injection of the test substance, immediately before the next cumulative dose. Mean values of the drug-induced changes (in beats/minute) were plotted against the logarithm of the dose. From the linear dose–response curves this dose was graphically evaluated, which decreased heart rate by 150 beats/min (= D_{150}).

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Notes

Studies on Several 7-Substituted *N,N*-Dimethyltryptamines

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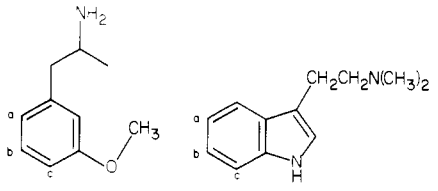
Several 7-substituted derivatives of *N,N*-dimethyltryptamine (DMT) were prepared and evaluated in the rat fundus serotonin receptor assay and in a behavioral (discriminative stimulus) assay in rats. Both 7-Me- and 5-OMe-7-Me-DMT possess a higher pA_2, and 5,7-$(OMe)_2$-DMT a lower pA_2, than that of DMT itself. Like DMT, all three of these compounds produce behavioral effects in rats which are similar to those of the hallucinogen 5-OMe-DMT. Although 7-Et- and 7-Br-DMT possess a higher serotonin receptor affinity than DMT, neither produce behavioral effects which parallel those of 5-OMe-DMT. In contrast, 6-Me-DMT and its 5-OMe derivative do not interact with the serotonin receptors in a competitive manner and are inactive in the discriminative stimulus assay.

Examination of the serotonin (5-hydroxytryptamine, 5-HT) receptor affinities of phenylalkylamine analogues has revealed certain similarities with the affinities of tryptamine analogues.[1-3] For example, N,N-dimethylation of the terminal amine, in either series, halves affinity, while α-methylation has no effect on affinity when racemates are examined. Working on the assumption that the 4 position of the phenylalkylamines might correspond to the 7 position of the tryptamines,[4,5] the a–c positions of 1 would



1 2

correspond to the a–c positions of **2**. By examining methoxy substitution at the a, b, and c positions of 1 (pA_2 = 5.93)[3a] we see that there is an effect on affinity which essentially parallels that seen with the corresponding substitution in compound **2** (pA = 6.00).[2] Methoxylation at the a-position of 1 and **2** enhances the affinity of the parent compound by 10-fold, while methoxylation at b halves affinity. Methoxylation of 1 at c decreases affinity by threefold, while c methoxylation of **2** decreases affinity by just more than fourfold. Furthermore, demethylation of the a-position methoxy group (i.e., 2-methoxy of 1, 5-methoxy of **2**) results in an additional doubling of affinity.[3b]

There is also evidence that an example of 1 produces behavioral effects in animals that are similar to its corresponding **2** analogue. In a series of discriminative stimulus experiments, rats were trained to distinguish between administration of saline and 5-methoxy-*N,N*-dimethyltryptamine (5-OMe-DMT, **3**; i.e., the a-methoxy analogue of **2**). When these animals were challenged with doses of 2,5-dimethoxyphenylisopropylamine (2,5-DMA, **4**; i.e., the a-methoxy analogue of 1), generalization occurred; that is, the animals could not distinguish between the interoceptive cues produced by certain doses of 2,5-DMA (**4**) and those produced by the training dose of 5-OMe-DMT (**3**). The ED_{50} values determined for **3** and **4** in this assay were 0.40 and 0.59 mg/kg, respectively.[6]

Para methylation, ethylation, and bromination are known to enhance the hallucinogenic potency of compound **4**;[7] these changes also result in an increased 5-HT receptor affinity.[3a] Thus, it was of interest to synthesize several examples of 7-substituted derivatives of *N,N*-dimethyltryptamine (DMT, **2**) and to explore their 5-HT receptor affinities and behavioral properties.

Chemistry. With the exception of 6-methylindole and 5-methoxy-6-methylindole, the requisite indoles were prepared in two steps via the recently reported SASK[8]

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