Synthesis, Pharmacological Characterization, and Quantitative Structure−Activity Relationship Analyses of 3,7,9,9-Tetraalkylbispidines: Derivatives with Specific Bradycardic Activity†

Uwe Schön,* Jochen Antel, Reinhard Brückner, and Josef Messinger

Departments of Medicinal Chemistry and Pharmacology, Solvay Pharmaceuticals, P.O. Box 220, 30002 Hannover, Germany

Rainer Franke and Andreas Gruska

Consulting in Drug Design, Gartenstrasse 14, 16352 Basdorf, Germany

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A series of 3,7,9,9-tetraalkyl-3,7-diazabicyclo[3.3.1]nonane derivatives (bispidines) was synthesized and identified as potential antiischemic agents. Pharmacological experiments in vitro as well as in vivo are described, and the results are listed. For selection of those compounds fitting best to the desired profile of a specific bradycardic antianginal agent—decrease in heart rate without affecting contractility and blood pressure—these results were scored and ranked. Quantitative structure−activity relationship (QSAR) analyses were performed and discussed a posteriori by means of Hansch, nonelementary discriminant and factor analysis to get insight into the molecular features determining the biological profile. Highly significant equations were obtained, indicating hydrophobic and steric effects. Both pharmacological ranking and QSAR considerations showed compound **6** as the optimum within the structural class under investigation. Compound **6** (tedisamil, KC8857) has been selected as the most promising compound and was chosen for further pharmacological and clinical investigations as an antiischemic drug.

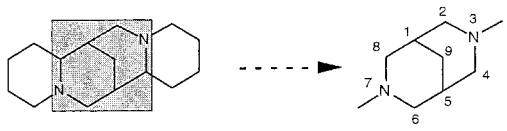
1. Introduction

Myocardial ischemia has been defined as an imbalance between the supply of oxygenated blood and the oxygen requirements of the myocardium. Major features of ischemia may include reduction in contractile function with a fall in blood pressure, ST-segment displacement, arrhythmias and the occurrence of anaerobic glycolysis, as evidenced by accumulation of its metabolic products. Research at Solvay Pharmaceuticals in the area of ischemic heart disease has been directed toward the development of compounds which improve the oxygen supply/demand ratio by selectively decreasing heart rate via a direct action on the sinus node. Compounds of this kind are being referred to as bradycardic antianginals or specific bradycardic agents, according to the definition of Kobinger.[1]

The skeleton of 3,7-diazabicyclo[3.3.1]nonane (bispidine[2]) constitutes the B and C rings of a variety of lupanine alkaloids, e.g., sparteine (Scheme 1), which is a tetracyclic alkaloid with antiarrhythmic properties.[3] Due to this structural relationship, compounds belonging to the ring system of bispidines have been the subject of considerable interest. For instance antiarrhythmic properties have been demonstrated for bispidine derivatives.[4] Studies about crystal structures, stereochemistry, and conformational analysis have been published.[5]

As part of our research program related to the synthesis of specific bradycardic agents, we decided to synthesize 3,7-diazabicyclo[3.3.1]nonane derivatives with a new cardiovascular profile. Within this field, we have focused our interest on the synthesis of 3,7,9,9-tetraalkylbispidine derivatives[6] (see Table 1 listing the synthesized compounds and Scheme 2 for general structures). The synthesis, pharmacological characterization, and quantitative structure−activity relationship (QSAR) analyses of 3,7,9,9-tetraalkyl-3,7-diazabicyclo-[3.3.1]nonane derivatives will be described, leading to **6** (tedisamil, KC8857) as the most promising compound selected for clinical development.

Scheme 1



2. Chemistry

Depending upon the substitution pattern of bispidine derivatives, several synthetic approaches are possible. For instance, using the Mannich reaction[7] or starting from pyridine derivatives[8] are known approaches. Our preferred sequence of reaction steps for the synthesis of 3,7,9,9-tetraalkylbispidines is summarized in Scheme 2. Condensation of alkylideneacetic acid esters **A**, which were synthesized by a Knoevenagel condensation, with unsubstituted (R = H) or substituted (R = R_1) cyanoacetic acid amides **B** yields unsubstituted or substituted dinitriles **C**.[9] Unsubstituted dinitriles **C** were also obtained by reaction of cyanoacetic esters with ketones in alcohol in the presence of ammonia.[10] Subsequently

* To whom correspondence should be addressed.

† Dedicated to Professor E. Winterfeldt on the occasion of his 65th birthday.

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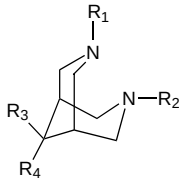
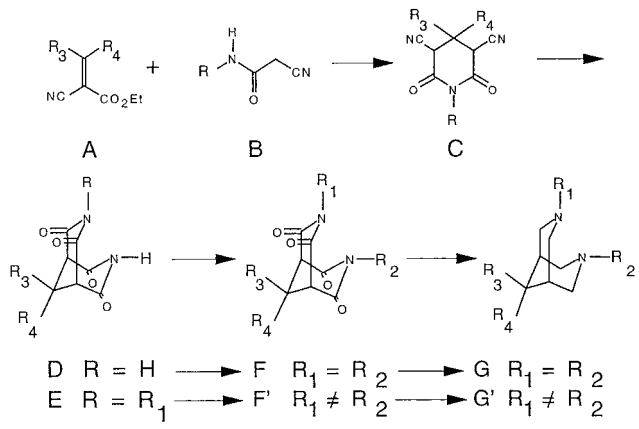
Table 1. Synthesized 3,7,9,9-Tetraalkyl-3,7-diazabicyclo[3.3.1]nonanes of Formula **G**



compd	R_1	R_2	R_3	R_4	bp (0.1 Torr), °C	% yield base	formula[f]	mp (salt), °C	analysis[g]
1	*n*-C_4H_9	*n*-C_4H_9	CH_3	CH_3	130	69	$C_{17}H_{34}N_2$·1Sa	113	C,H,N
2[a]	CH_3	CH_3	CH_3	CH_3	150−160/11	54	$C_{11}H_{22}N_2$·1Ox	188−190	C,H,N
3	CHM[c]	CHM	CH_3	C_2H_5	fp: 36	75	$C_{24}H_{44}N_2$·1Ox	157−158	C,H,N
4	*n*-C_4H_9	*n*-C_4H_9	CH_3	C_2H_5	180−200	83	$C_{18}H_{36}N_2$·1Ox	173−178	C,H,N
5	*n*-C_6H_{13}	*n*-C_6H_{13}	−$(CH_2)_4$−[e]		250	77	$C_{23}H_{44}N_2$		C,H,N
6	CPM[d]	CPM	−$(CH_2)_4$−		230	79	$C_{19}H_{32}N_2$·2HCl	195−197	C,H,N,Cl
7	*n*-C_4H_9	*n*-C_4H_9	*n*-C_4H_9	*n*-C_4H_9	210	76	$C_{23}H_{46}N_2$·1Ox	167−171	C,H,N
8	*n*-C_3H_7	*n*-C_3H_7	C_2H_5	C_2H_5	140−150	65	$C_{17}H_{34}N_2$·1Ox	185	C,H,N
9	*i*-C_3H_7	*i*-C_3H_7	*n*-C_3H_7	*n*-C_3H_7	150−160	58	$C_{19}H_{38}N_2$		C,H,N
10	*n*-C_6H_{13}	*n*-C_6H_{13}	C_2H_5	*n*-C_4H_9	230	40	$C_{25}H_{50}N_2$·1Ox	170−172	C,H,N
11	CHM	CHM	−$(CH_2)_5$−		fp: 102	75	$C_{26}H_{40}N_2$		C,H,N
12	CH3	*n*-C_6H_{13}	C_2H_5	C_2H_5	130	87	$C_{18}H_{36}N_2$·1Ox	201−203	C,H,N
13	*i*-C_3H_7	*i*-C_3H_7	CH_3	*n*-C_3H_7	150	51	$C_{17}H_{34}N_2$·1Ox	70	C,H,N
14	*i*-C_3H_7	*i*-C_3H_7	CH_3	CH_3	100−120	37	$C_{15}H_{30}N_2$·1.5Ox	56−60	C,H,N
15	*n*-C_4H_9	CHM	CH_3	CH_3	160	78	$C_{20}H_{38}N_2$		C,H,N
16	*i*-C_4H_9	*n*-C_4H_9	CH_3	CH_3	160−170	74	$C_{17}H_{34}N_2$·1Ox	120−125	C,H,N
17	*i*-C_3H_7	*i*-C_4H_9	−$(CH_2)_5$−		150	66	$C_{19}H_{36}N_2$·1.5Fu	104−107	C,H,N
18	*i*-C_3H_7	CHM	*n*-C_4H_9	*n*-C_4H_9	190−200	33	$C_{25}H_{48}N_2$		C,H,N
19	*n*-C_4H_9	*n*-C_4H_9	−$(CH_2)_3$−		170	83	$C_{18}H_{34}N_2$·1Ox	190−195	C,H,N
20	*n*-$C_{10}H_{24}$	*n*-$C_{10}H_{24}$	CH_3	CH_3	230	60	$C_{29}H_{58}N_2$·1Ox	155	C,H,N
21	allyl	allyl	CH_3	CH_3	160	24	$C_{15}H_{26}N_2$·1Sa	118−120	C,H,N
22	butenyl	butenyl	−$(CH_2)_5$−		175	46	$C_{20}H_{34}N_2$·1Sa	115−119	C,H,N
23	butenyl	butenyl	CH_3	CH_3	150	41	$C_{17}H_{30}N_2$·1Sa	85−89	C,H,N
24	butenyl	*i*-C_4H_9	*n*-C_3H_7	*n*-C_3H_7	170	82	$C_{21}H_{40}N_2$·1Sa	139−143	C,H,N
25	butenyl	*n*-C_4H_9	CH_3	CH_3	165	49	$C_{17}H_{32}N_2$·1Sa	162−163	C,H,N
26[b]	CH_3	*n*-C_6H_{13}	H	H	195	39	$C_{14}H_{28}N_2$·1Fu	142	C,H,N

[a] Welner, S.; Ginsburg, D. Synthesis of Potential Analgesics. *Isr. J. Chem.* **1966,** *4,* 39−45. [b] Binnig, F.; Raschak, M.; Treiber, H. J. Neue Antiarrhythmika. DT 248792, **1976**. [c] CHM = cyclohexylmethyl. [d] CPM = cyclopropylmethyl. [e] Indication for spirocyclic ring. [f] Sa = salicylic acid; Ox = oxalic acid; Fu = fumaric acid. [g] Compounds gave satisfactory analyses within ±0.4% of theoretical calculations unless otherwise stated.

Scheme 2



the 2,4,6,8-tetraoxo-3,7-diazabicyclo[3.3.1]nonane derivatives of formula **D** and **E** were prepared by cyclization of **C** under strong acidic conditions.[11] The monoalkylation of the diimides of formula **E** or dialkylation of **D** is carried out under basic conditions, for example with sodium hydride or potassium carbonate in dimethylformamide. Finally the reduction of the substituted tetraoxo derivatives of formula **F** yields the bispidines of formula **G** which could be isolated as free base or crystalline salts (see Table 1). Diimides of formula **F** were reduced with lithium aluminum hydride. In the case of an unsaturated side chain, reduction had to be performed by means of sodium bis(2-methoxyethoxy)aluminum hydride in order to avoid reduction of double bonds.

3. Pharmacology

Bradycardic antianginal agents are beneficial in cardiac ischemia due to **reduction in oxygen demand** by selectively decreasing heart rate via a direct action on the heart's pacemaker, the sinus node. The relative prolongation of the diastole caused by the reduction of the heart rate leads to an **increased oxygen supply**.

As a main objective, bradycardic antianginal agents should exert selective bradycardic activity without affecting contractility and blood pressure. Additional effects on refractoriness (antiarrhythmic activity) may be of benefit.

Pharmacological investigations were performed in two in vitro models, spontaneously beating right and electrically paced left atria both isolated from guinea pigs, and one in vivo model, anesthetized rats (see the Experimental Section). Selection of the compounds according to the objectives given above was done by scoring potency and selectivity parameters and ranking these scores. The parameters which were determined from these in vitro and in vivo models (Table 2) are as follows:

Sinus Rate (SR). The rate of a spontaneously beating right atrium reflects the activity of the sinus node and provides information on direct effects on automaticity for the compound tested.

Table 2. Parameters Measured, Selectivity Quotients Defined, and Effective Concentrations/Doses Calculated in the Pharmacological Investigations[a]

measured parameter and defined selectivity quotient		effective concentration/dose	abbrev[a]
sinus rate	SR	EC_{75}	SR75
force of contract.	F	EC_{75}	F75
funct ref period	FRP	EC_{125}	FRP125
select. quot F	F/SR		SelF
select. quot FRP	FRP/SR		SelFRP
heart rate	HR	ED_{75}	HR75
diast art. press.	DAP	ED_{125}	DAP125
RαT-interval	RαT	ED_{125}	RαT125
select. quot DAP	DAP/HR		SelDAP
select. quot RαT	RαT/HR		SelRαT

[a] Abbreviations used in the text.

Force of Contraction (F). The peak force of contraction of a stimulated left atrium provides information on a direct effect on contractility in cardiac muscle.

Functional Refractory Period (FRP). The functional refractory period is the shortest interval between a double stimulus causing a double contraction. The FRP provides information on effects on refractoriness, the ability of re-excitation.

Heart Rate (HR). The heart rate provides information on in vivo bradycardic activity of the compound tested.

Diastolic Arterial Pressure (DAP). The diastolic arterial blood pressure provides information on the peripheral resistance of the cardiovascular system and selectivity regarding bradycardia.

RαT-Interval.[12−14] The RαT-interval of the rat ECG reflects the time from ventricular excitation to recovery; effects on refractoriness in vivo can be judged from the RαT-interval.

Furthermore the results of the in vitro models (guinea pig atria) and the in vivo model (anesthetized rat) were scored separately but according to a similiar procedure (see Table 3):

First Score (Desired Effects). The EC_{75} values for the desired effects, i.e., decrease in sinus rate or heart rate, were divided into seven groups and scores of 0 to 6 points assigned to these groups (Table 3, first column).

Second Score (Undesired Effects). The selectivity quotients for the ratio of desired versus undesired effects, i.e., force of contraction or diastolic arterial pressure, were also divided into seven groups and scores of 0 to −6 points assigned to the so-formed groups (Table 3, second column).

Third Score (Additional Effects). The selectivity quotients for the ratio of desired versus additional effects, i.e., refractory period or RαT-interval, were divided into seven groups as well and scores of 0 to 6 points assigned to the so-formed groups (Table 3, third column).

Table 3. Score Points Assigned to Parameters and Selectivity Quotients of the Pharmacological Investigations in Vitro and in Vivo

In Vitro Experiments (Guinea Pig Atria)

potency desired effect sinus rate SR75		selectivity versus undesired effect force of contraction F75/SR75 (SelF)		selectivity versus additional effect funct refractory period FRP125/SR75 (SelFRP)	
pts	range (μmol/L)	pts	range	pts	range
6	<1	0	>20	6	<0.1
5	1−2.5	−1	10−20	5	0.1−0.2
4	2.5−5	−2	5−10	4	0.2−0.5
3	5−10	−3	3−5	3	0.5−2
2	10−20	−4	2−3	2	2−4
1	>20	−5	1−2	1	4−10
0	not reached	−6	<1	0	>10

In Vivo Experiments (Anesthetized Rat)

potency desired effect heart rate HR75		selectivity versus undesired effect diastolic arterial pressure DAP125/HR75 (SelDAP)		selectivity versus additional effect RαT-interval RαT125/HR75 (SelRαT)	
pts	range (μmol/L)	pts	range	pts	range
6	<5	0	>10	6	<0.1
5	5−7.5	−1	4−10	5	0.1−0.2
4	7.5−12.5	−2	2−4	4	0.2−0.5
3	12.5−25	−3	0.5−2	3	0.5−2
2	25−40	−4	0.2−0.5	2	2−4
1	>40	−5	0.1−0.2	1	4−10
0	not reached	−6	<0.1	0	>10

4. QSAR Analyses

A QSAR analysis was performed a posteriori to obtain a statistical rating of the compounds, to unveil previously hidden structure activity relations of the different substituent patterns, and to get an insight into the molecular features determining the biological profile. In fact, we wanted to check if the synthesized compounds included the structural optimum within the investigated group of bispidines or if an untested combination of substituents would improve the desired pharmacological profile.

QSAR analyses were performed for all biological activities mentioned above by means of Hansch[15] or nonelementary discriminant[16] analysis. Factor analysis[17] was used to investigate the structure of biological data. Physicochemical properties of the compounds or substituents, respectively, are described by log *P*, Taft's E_s, Verloop's STERIMOL parameters, molar refractivity, Rekker's *f* values, aliphatic σ values.[18,19] Taft's E_s and molar refractivity both characterize substituent bulk while the STERIMOL parameters according to Verloop measure the dimension of substituents in different directions of space; in the present case the best results were obtained with molar refractivity as steric parameter. Rekker's *f* values as used here represent substituent hydrophobicity, and log *P* measures the hydrophobicity of the whole molecule. Aliphatic σ values express the electron-attracting power of substituents. In addition, the following indicator variables were used: I1 (saturated and unbranched substituents in R_2 equal to or greater than *n*-butyl), I2 (unsaturation in the R_1 substituent), I3 (branched substituent in R_2), I4 (occurrence of a ring in R_3 and R_4), I5 (branch in R_1 and/or R_2), I6 (branching or ring structures in R_1 and/or R_2). All parameters significantly appearing in the resulting QSARs are summarized in Table 4. As the molecules are symmetrical with respect to R_3 and R_4, R_1 and R_2 were so defined that R_2 is always the larger substituent. In case where the substituents R_3 and R_4 are examined together, the abbreviation R_{34} is used. The correlations between parameters are shown in Table 5. Table 5 shows high correlations between *f* values and molar refractivities for all positions of substitution as is to be expected for the type of substituents varied. As

Table 4. Parameters Used in Hansch and Discriminant Analyses[a]

compd	log *P*	MR(R_1)	*f*(R_1)	MR(R_2)	*f*(R_2)	MR(R_{34})	*f*(R_{34})	I1	I2	I3	I4	I5	I6
1	3.88	19.61	2.51	19.61	2.51	11.30	1.54	1	0	0	0	0	0
2	1.61	5.65	0.77	5.65	0.77	11.30	1.54	0	0	0	0	0	0
3	6.65	31.34	3.67	31.34	3.67	16.15	2.20	0	0	0	0	0	1
4	4.37	19.61	2.51	19.61	2.51	16.15	2.20	1	0	0	0	0	0
5	5.47	28.90	3.71	28.90	3.71	18.59	2.40	1	0	0	1	0	0
6	4.19	18.18	2.05	18.18	2.05	18.59	2.40	0	0	0	1	0	1
7	7.03	19.61	2.51	19.61	2.51	39.22	5.02	1	0	0	0	0	0
8	3.85	14.96	1.97	14.96	1.97	21.00	2.86	0	0	0	0	0	0
9	4.51	14.96	1.84	14.96	1.84	29.92	3.94	0	0	1	0	1	1
10	8.26	28.90	3.71	28.90	3.71	30.11	3.94	1	0	0	0	0	0
11	7.43	31.34	3.67	31.34	3.67	24.25	2.94	0	0	0	1	0	1
12	4.88	5.65	0.77	28.90	3.71	21.00	2.86	1	0	0	0	0	0
13	3.53	14.96	1.84	14.96	1.84	20.61	2.74	0	0	1	0	1	1
14	2.48	14.96	1.84	14.96	1.84	11.30	1.54	0	0	1	0	1	1
15	4.98	19.61	2.51	31.34	3.67	11.30	1.54	0	0	0	0	0	1
16	3.70	19.59	2.63	19.61	2.51	11.30	1.54	1	0	0	0	1	1
17	4.29	14.96	1.84	19.59	2.63	24.25	2.94	0	0	1	1	1	1
18	7.61	14.96	1.84	31.34	3.67	39.22	5.02	0	0	0	0	1	1
19	4.24	19.61	2.51	19.61	2.51	13.94	1.86	1	0	0	1	0	0
20	9.64	47.50	5.87	47.50	5.87	11.30	1.54	1	0	0	0	0	0
21	2.70	14.49	1.08	14.49	1.08	11.30	1.54	0	1	0	0	0	0
22	4.49	19.09	1.62	19.09	1.62	24.25	2.94	0	1	0	1	0	0
23	3.13	19.09	1.62	19.09	1.62	11.30	1.54	0	1	0	0	0	0
24	5.32	19.09	1.62	19.59	2.63	29.92	3.94	0	1	1	0	1	1
25	3.42	19.09	1.62	19.61	2.51	11.30	1.54	1	1	0	0	0	0
26	3.18	5.65	0.77	28.90	3.71	2.06	0.46	1	0	0	0	0	0

[a] For the definition of indicator variables, see text.

Table 5. Correlation Matrix[a]

	log *P*	MR(R_1)	MR(R_2)	MR(R_{34})	*f*(R_1)	*f*(R_2)	*f*(R_{34})	I1	I2	I3	I4	I5	I6
log P	1.000												
MR(R_1)	**0.743**	1.000											
MR(R_2)	**0.803**	**0.665**	1.000										
MR(R_{34})	**0.526**	0.057	0.024	1.000									
f(R_1)	**0.781**	**0.959**	**0.698**	0.086	1.000								
f(R_2)	**0.793**	**0.620**	**0.967**	0.045	**0.694**	1.000							
f(R_{34})	**0.522**	0.041	0.021	**0.997**	0.075	0.049	1.000						
I1	0.222	0.195	**0.406**	−0.247	0.278	**0.501**	−0.229	1.000					
I2	−0.256	−0.062	−0.235	−0.068	−0.316	−0.370	−0.079	−0.256	1.000				
I3	−0.201	−0.196	−0.327	0.233	−0.192	−0.250	0.234	**−0.452**	0.010	1.000			
I4	0.063	0.172	0.027	0.107	0.163	−0.004	0.048	−0.141	−0.036	−0.036	1.000		
I5	−0.100	−0.2146	−0.226	0.329	−0.232	−0.160	0.331	−0.388	−0.076	**0.804**	−0.127	1.000	
I6	0.077	0.016	0.011	0.250	−0.002	0.019	0.238	**−0.480**	−0.220	0.570	0.085	**0.709**	1.000

[a] Bold figures are significant at $P = 0.95$.

a consequence it is difficult to differentiate between steric and hydrophobic effects even though some of the resulting equations allow at least a suggestion as to which of the two may be the more important. Multiple correlations exist between log *P* and the molar refractivities over all positions of substitution which must be kept in mind when looking at the results:

$$\log P = 0.084(\pm 0.021)\mathrm{MR}(R_1) + 0.111(\pm 0.015)(\mathrm{MR}(R_2) + \mathrm{MR}(R_{34})) - 1.399(\pm 0.577) \quad (1)$$

$$n = 26 \quad r = 0.980 \quad r^2 = 0.960 \quad s = 0.386 \quad F = 274.4 \quad P = 100\%$$

$$\log P = + 0.100(\pm 0.011)(\mathrm{MR}(R_1) + \mathrm{MR}(R_2)) + 0.102(\pm 0.019)\mathrm{MR}(R_4) - 1.30(\pm 0.604) \quad (2)$$

$$n = 26 \quad r = 0.977 \quad r^2 = 0.954 \quad s = 0.410 \quad F = 241.0 \quad P = 100\%$$

An explanation for this behavior is that MR describes the polarizability as well as the size of the molecule, which coincides with the number of CH_2 groups. The reason two relationships between log *P* and molar refractivity are presented is that both of them are needed to estimate the values of log(1/HR75) and log(1/SR75), respectively, for hypothetical compounds which are optimal with respect to one of these activities (see Section 6, Discussion).

5. Results

The results of the in vitro investigations are summarized in Table 6. This table contains EC values of the measured parameters (SR75, F75, FRP125) as well as selectivity quotients (SelF = F75/SR75, SelFRP = FRP125/SR75). In addition, score points are listed for the decrease of the sinus rate and the selectivity versus the decrease in force of contraction. The sum of these two scores is listed in column 9, reflecting the compound's suitability as bradycardic agent. Finally, in Table 6 the score points for the selectivity versus the additional effect on functional refractory period are listed. Table 6, which ranks the compounds according to their total score, shows nine compounds with high scores for a selective decrease in sinus rate, effecting the force of contraction at higher concentrations only,

Table 6. Results of the in Vitro Investigations (Guinea Pig Atria)[a]

	parameters measured			select. quot		scores			
compd	SR75 2	F75 3	FRP125 4	SelF 5	SelFRP 6	Sc1 7	Sc2 8	SS 9	Sc3 10
22	0.40	75.1	1.14	167	2.85	6	0	6	2
24	0.44	23.1	0.73	52.5	1.66	6	0	6	3
19	0.52	56.1	0.63	108	1.21	6	0	6	3
15	0.88	16.3	0.48	18.5	0.55	6	−1	5	3
17	1.00	35.5	1.54	35.5	1.54	5	0	5	3
23	1.21	>215	1.87	>177	1.54	5	0	5	3
25	1.21	106	2.08	87.6	1.72	5	0	5	3
06	1.30	49.0	0.76	37.6	0.56	5	0	5	3
13	1.99	211	2.63	106	1.32	5	0	5	3
09	2.18	39.6	0.80	18.2	0.37	5	−1	4	4
01	3.00	104	1.00	35.0	0.33	4	0	4	4
16	3.07	−	0.82	#	0.27	4	0	4	4
05	0.87	3.07	0.44	3.53	0.51	6	−3	3	3
08	3.53	−	1.52	#	0.43	3	0	3	4
21	8.55	>215	4.30	>25	0.50	3	0	3	4
10	0.60	1.39	1.27	2.32	2.12	6	−4	2	2
18	1.90	3.65	1.45	1.92	0.76	5	−5	0	3
07	1.91	2.14	1.01	1.12	0.53	5	−5	0	3
14	10.9	−	111	#	10.2	2	−2	0	0
04	3.21	1.52	0.54	0.47	0.17	4	−6	−2	5
03	6.20	4.69	0.68	0.76	0.11	3	−6	−3	5
11	7.57	2.65	0.62	0.35	0.08	3	−6	−3	6
26	−	83.8	1.40	∼1	# #	0	−5	−5	6
02	−	−	122	∼1	∼1	0	−5	−5	3
12	***	17.5	0.84	***	***				
20	***	105	85	***	***				

[a] The compounds are ranked according to the total score (see below) for desired and undesired effects. Column 1 shows the number of the compound tested. Columns 2−4 show the EC values of the parameters measured, columns 5−6 the values of the selectivity quotients calculated. Score points are listed for the desired effect, SR75 (Sc1, column 7) and for the selectivity versus the undesired effect, F75 (Sc2, column 8). The sum of these two is listed in column 9 (SS), the main column, reflecting the compound's value in fulfilling the objectives mentioned above. Score points for the selectivity versus the additional effect FRP are listed in column 10. Except for compound **6,** all EC values (columns 2−4) are geometric means of two or three measurements, given in μM. For compound **6**, geometric means with 95% confidence limits calculated from nine measurements are given below. SR75, 1.30 (0.77−2.19) μM; F75, 49.0 (41−58) μM; FRP125, 0.76 (0.62−0.92) μM. −: effective concentration not reached. ***: parameter not measured. #: very high (estimated). # #: very low (estimated).

thus fulfilling the requirements for bradycardic agents. On the other hand, at the bottom of Table 6 compounds can be found with low scores for such a selective decrease in sinus rate. Such compounds, poorly suited as bradycardic agents, show pronounced selectivity for prolongation of the functional refractory period.

The results of the in vivo investigations with anesthetized rats are summarized in Table 7. ED values of the measured parameters (HR75, DAP125, RαT125) are listed as well as selectivity quotients (SelDAP = DAP125/HR75, SelRαT = RαT125/HR75). Furthermore score points are given for the desired effect on heart rate and for the selectivity against the undesired effect on diastolic blood pressure. The sum of these scores is listed in column 9, reflecting the compound's suitability as bradycardic agent in fulfilling the main in vivo objectives. The score points for the selectivity with regard to the additional effect (RαT-interval) are listed in column 10. In ranking the total scores, seven of 25 compounds can be selected, showing high scores for the decrease in heart rate without increase in blood pressure resulting in total scores of 4 and 5 (upper group). In contrast to the in vitro evaluation in guinea pig tissue, all compounds of the selected set show high scores for the prolongation of refractoriness (RαT-interval). It should be noted that in intact animals the decrease in heart rate contributes to the prolongation of RαT, whereas in isolated tissue the rate of stimulation is kept constant.

5.1. QSAR for the Sinus Rate. For the decrease in sinus rate of the isolated guinea pig right atria (SR75) (Table 6, column 2), eq 3 is obtained (see Figure 1):

$$\log(1/\mathrm{SR75}) = -0.0039(\pm 0.0015)(\mathrm{MR}(R_1) + \mathrm{MR}(R_2))^2 + 0.36(\pm 0.10)(\mathrm{MR}(R_1) + \mathrm{MR}(R_2)) - 0.0034(\pm 0.0019)(\mathrm{MR}(R_{34}))^2 + 0.17(\pm 0.07)\mathrm{MR}(R_{34}) - 9.61(\pm 2.56) \quad (3)$$

$$n = 21 \qquad r = 0.893 \qquad r^2 = 0.797 \qquad s = 0.191 \qquad F = 15.73 \qquad P = 100\%$$

In computing eq 3, compound **4** was omitted as an outlier (with **4** included, $r = 0.828$ and $s = 0.234$). Equation 3 shows an acceptable fit (see Figure 1) "explaining" 80% of the data variance. $\mathrm{MR}(R_{34})$ and $(\mathrm{MR}(R_{34}))^2$ in this equation can be replaced by $f(R_{34})$ and $f(R_{34})$,[2] respectively, without changing anything else ($r = 0.891$, $s = 0.193$, $F = 15.41$) while an analogous exchange regarding R_1 and R_2 is not possible. This may be interpreted to mean that steric interactions operate in positions R_1 and R_2 while, for position R_{34}, no conclusion is possible whether substituent effects are steric or hydrophobic. Optima exist for all positions such that $[(\mathrm{MR}(R_1) + \mathrm{MR}(R_2)]$ should be about 46 and $\mathrm{MR}(R_{34})$ about 25 [or $f(R_{34})$ about 3.3, respectively] for compounds with high potency. Closest to these values are compounds **22** and **24** which, in fact, show the highest potencies in this in vitro test. Equation 3 does not allow differentiation between bulk in positions R_1 and R_2. As will be shown in a forthcoming publication, this equation has true predictive power. To gain more

Table 7. Results of the in Vivo Investigations (Anesthetized Rat)[a]

	parameters measured			select. quot		scores			
compd	HR75 2	DAP125 3	RαT125 4	SelDAP 5	SelRαT 6	Sc1 7	Sc2 8	SS 9	Sc3 10
06	5.30	−	2.50	#	0.47	5	0	5	4
13	4.50	>36	0.53	>8	0.12	6	−1	5	5
17	5.70	>41	0.73	>7	0.13	5	−1	4	5
16	5.70	>41	0.73	>7	0.13	5	−1	4	5
15	5.70	>41	0.96	>7	0.17	5	−1	4	5
23	7.10	>46	0.94	>6	0.13	5	−1	4	5
03	11.0	−	5.5	#	0.50	4	0	4	3
18	9.30	>66	1.10	>7	0.12	4	−1	3	5
24	3.50	2.40	0.32	0.68	0.09	6	−3	3	6
12	25.0	>106	3.00	>4	0.12	3	−1	2	5
09	6.40	11.0	1.80	1.72	0.28	5	−3	2	4
22	4.90	1.50	0.58	0.31	0.12	6	−4	2	5
11	20.0	>61	12.0	>3	0.6	3	−2	1	3
08	12.0	10.00	2.10	0.80	0.18	4	−3	1	5
07	8.70	5.10	3.20	0.58	0.37	4	−3	1	4
25	5.90	2.20	0.70	0.37	0.12	5	−4	1	5
19	4.70	0.60	0.55	0.13	0.12	6	−5	1	5
04	4.60	0.57	0.61	0.12	0.13	6	−5	1	5
05	14.0	2.80	5.60	0.20	0.40	3	−4	−1	4
01	5.30	0.20	0.57	0.04	0.11	5	−6	−1	5
26	46.0	−	8.40	∼1	0.18	1	−3	−2	5
14	52.0	−	18.0	∼1	0.35	1	−3	−2	4
10	−	−	4.00	∼1	# #	0	−3	−3	6
02	***	***	***						
20	***	***	***						
21	***	***	***						

[a] The compounds are ranked according to the total score (see below) for desired and undesired effects. Column 1 shows the number of the compound tested. Columns 2−4 show the ED values of the parameters measured, columns 5−6 the values of the selectivity quotients calculated. Score points are listed for the desired effect, HR75 (Sc1, column 7) and for the selectivity versus the undesired effect, DAP125 (Sc2, column 8). The sum of these two is listed in column 9 (SS), the main column, reflecting the compound's value in fulfilling the objectives mentioned above. Score points for the selectivity versus the additional effect RαT-interval are listed in column 10. Except for compound **6**, all ED values (columns 2−4) are geometric means of two or three measurements, given in μmol/kg. For compound **6**, geometric means with 95% confidence limits calculated from 10 measurements are given below. HR75, 5.30 (4.68−6.00) μmol/kg; RαT125, 2.50 (2.04−3.08) μmol/kg. −: effective dose not reached. ***: parameter not measured. #: very high (estimated). # #: very low (estimated).

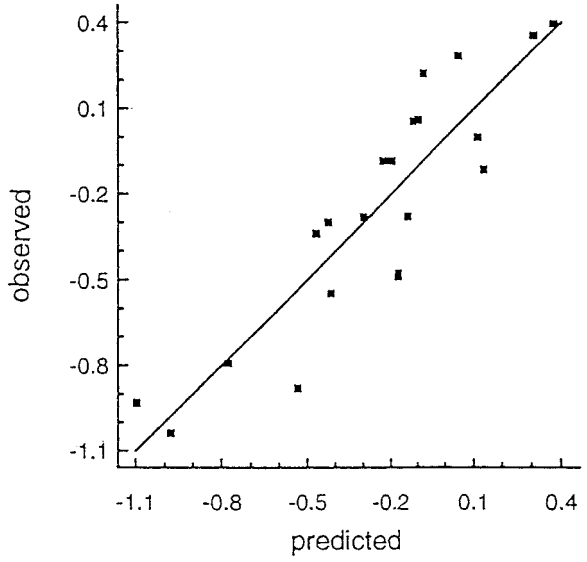


Figure 1. Plot of observed versus predicted values of log(1/SR75) (eq 3).

insight into the relative importance of bulk in the different positions, synthesis and testing of some additional compounds is under way. So far, measured values of log(1/SR75) agree very well with estimates from eq 3.

5.2. QSAR for the Force of Contraction. Bradycardic antianginal agents should exert their bradycardic activity without affecting contractility. For the influence on force of contraction (Table 6, column 3), the following relationship could be obtained:

$$\log(1/\mathrm{F75}) = -0.14(\pm 0.07)(\log P)^2 + 1.93(\pm 0.87)\log P - 7.15(\pm 2.49) \quad (4)$$

$$n = 20 \quad r = 0.802 \quad r^2 = 0.643 \quad s = 0.428 \quad F = 15.29 \quad P = 100\%$$

Compound **4** again appears as a severe outlier. If this compound is removed, the fit is greately improved:

$$\log(1/\mathrm{F75}) = -0.14(\pm 0.05)(\log P)^2 + 1.90(\pm 0.66)\log P - 7.20(\pm 1.90) \quad (5)$$

$$n = 19 \quad r = 0.883 \quad r^2 = 0.780 \quad s = 0.322 \quad F = 28.30 \quad P = 100\%$$

Equation 5 describes a parabolic relationship with the maximum at log $P \approx 7$. The presence of the $(\log P)^2$ term is mainly due to only one point (compound **20**) as can be seen from a plot of log(1/F75) against log P presented in Figure 2 (note also the deviating behavior of compound **4**). As this makes the parabola uncertain, compound **20** was also removed, leading to eq 6:

$$\log(1/\mathrm{F75}) = 0.41(\pm 0.08)\log P - 3.42(\pm 0.44) \quad (6)$$

$$n = 18 \quad r = 0.937 \quad r^2 = 0.877 \quad s = 0.240 \quad F = 114.4 \quad P = 100\%$$

Because of eq 1, log P in eq 6 can be replaced by molar refractivity terms; introducing two additional indicator

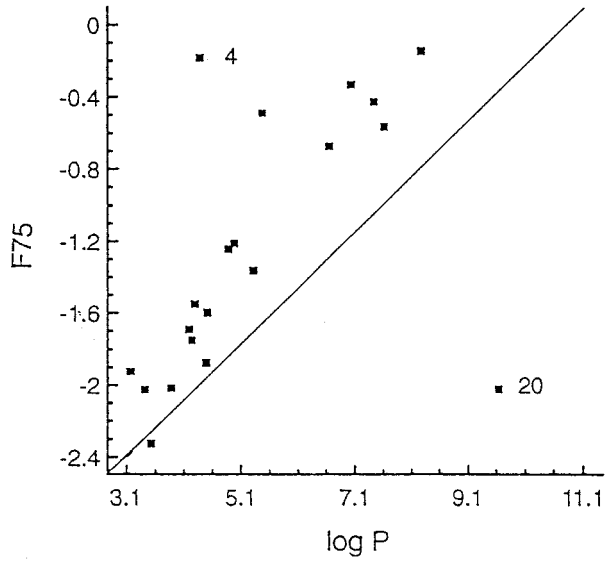


Figure 2. Plot of log(1/F75) against log *P*.

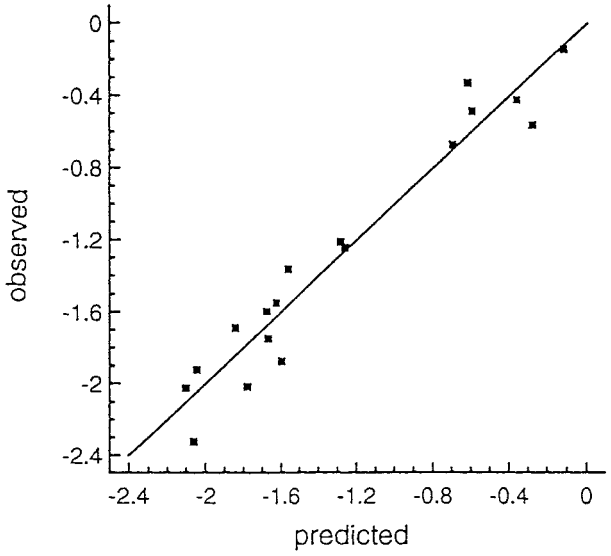


Figure 3. Plot of observed versus predicted values of log(1/F75) (eq 7).

variables will then lead to an improvement (see Figure 3):

$$\log(1/F75) = 0.033(\pm0.016)MR(R_1) + 0.062(\pm0.020)MR(R_2) + 0.041(\pm0.011)MR(R_{34}) - 0.23(\pm0.21)I6 - 0.31(\pm0.29)I2 - 4.10(\pm0.55) \quad (7)$$

$$n = 18 \quad r = 0.969 \quad r^2 = 0.938 \quad s = 0.165 \quad F = 36.54 \quad P = 100\%$$

I6 takes a value of 1 if branching or ring structures occur in R_1 or R_2, and I2 indicates unsaturation in the R_1 substituent. At what point the linear equations (6 and 7) turn into parabolic relationships cannot be answered with the data at hand unless the large impact of analogue **20** is taken for granted. There is no way to decide whether the causal relationship for F75 is with log *P* (eqs 5 and 6) or with substituent size (eq 7).

5.3. QSAR for Functional Refractory Period. As an additional effect, the prolongation of refractory period

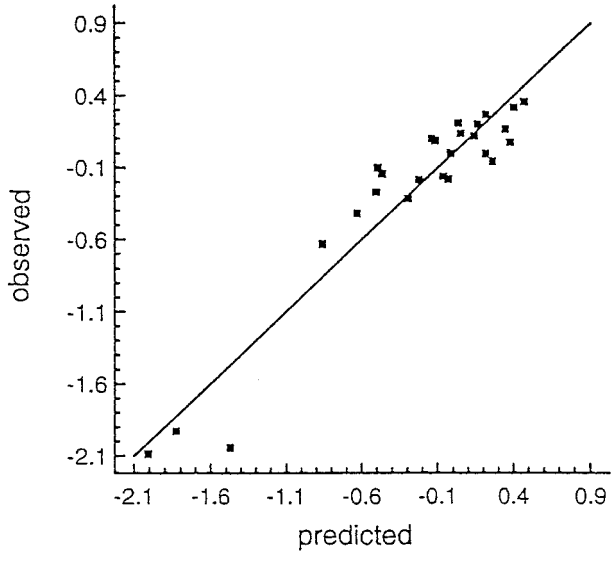


Figure 4. Plot of observed versus predicted values of log(1/FRP125) (eq 8).

(Table 6, column 4) was investigated. As can be seen in eq 8, the most important property is once again the hydrophobicity term log *P* (see Figure 4):

$$\log(1/FRP125) = -0.15(\pm0.02)(\log P)^2 + 1.69(\pm0.26)\log P - 0.41(\pm0.25)I3 - 4.34(\pm0.66) \quad (8)$$

$$n = 26 \quad r = 0.948 \quad r^2 = 0.899 \quad s = 0.220 \quad F = 64.85 \quad P = 100\%$$

Equation 8 provides a very good fit "explaining" 90% of the data variance *T*; if the small cluster of points in the low potency region is left out from the analysis, the model remains stable. Potency passes through an optimum with respect to log $P \approx 5.6$ and is decreased by branched substituents in R_2 (I3 = 1). Replacement of log *P* by MR terms in eq 8 leads to a severe loss of significance. Because of this and because very similar relationships with log *P* were observed for other classes of compounds possessing the bispidine structure,[20] it can be concluded that eq 8 in fact reflects hydrophobic interactions and not a hidden steric effect. Concerning the effects on FRP compound **6** with a log *P* value of 4.2 is about one log *P* unit away from the optimum. However as the parabola described by eq 8 has a wide shape, **6** still belongs to the group of the more active compounds.

5.4. QSAR for Heart Rate. As can be seen in eq 9, hydrophobicity plays an important role for the decrease in heart rate (Table 7, column 2; see Figure 5):

$$\log(1/HR75) = -0.08(\pm0.04)(\log P)^2 + 0.83(\pm0.40)\log P - 0.0035(\pm0.0014)MR(R_1)^2 + 0.14(\pm0.05)MR(R_1) - 4.27(\pm1.04) \quad (9)$$

$$n = 22 \quad r = 0.888 \quad r^2 = 0.789 \quad s = 0.150 \quad F = 15.86 \quad P = 100\%$$

Equation 9 could again be improved in two steps: (1) removing **14** as an outlier (see Figure 5); (2) introduction of an indicator variable I6, which takes a value of 1 if

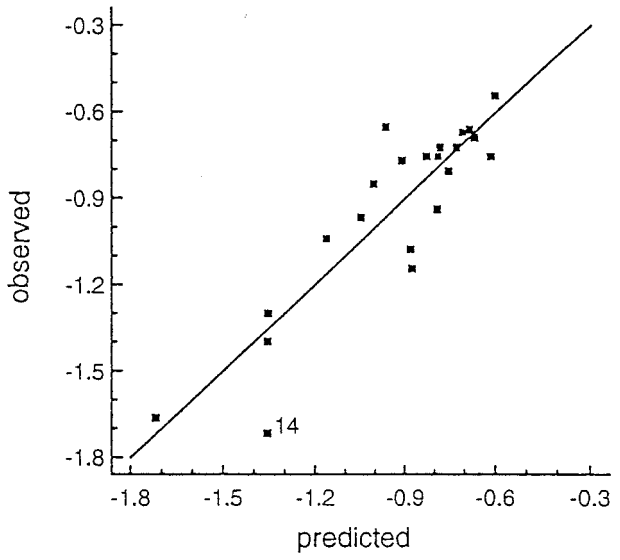


Figure 5. Plot of observed versus predicted values of log(1/HR75) (eq 9).

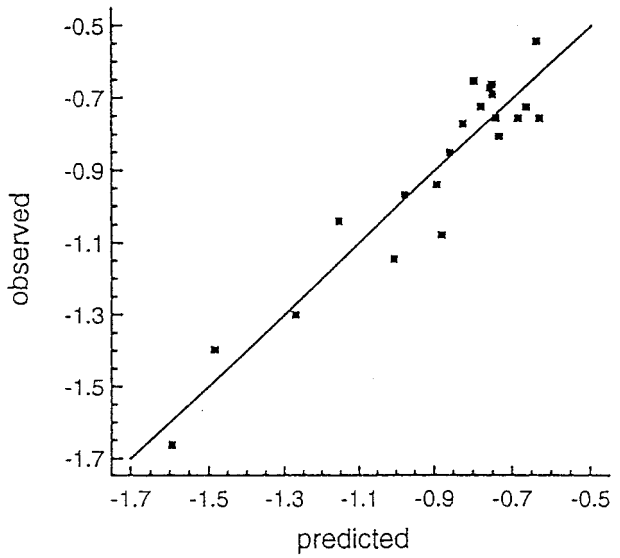


Figure 6. Plot of observed versus predicted values of log(1/HR75) (eq 10).

branching or ring structures occur in R_1 or R_2 (see Figure 6):

$$\log(1/\mathrm{HR75}) = -0.035(\pm 0.031)(\log P)^2 + 0.35(\pm 0.33)\log P - 0.0035(\pm 0.0011)\mathrm{MR}(R_1)^2 + 0.14(\pm 0.03)\mathrm{MR}(R_1) + 0.11(\pm 0.11)\mathrm{I6} - 3.03(\pm 0.86) \quad (10)$$

$$n = 21 \quad r = 0.945 \quad r^2 = 0.892 \quad s = 0.093 \quad F = 24.84 \quad P = 100\%$$

Equation 10 shows a good fit and "explains" 90% of the data variance. Optima exist with respect to hydrophobicity and the size of substituents in R_1. Strongly active compounds should have log P values of about 5 and $\mathrm{MR}(R_1)$ values close to about 20. In addition branching or ring structures in R_1 and/or R_2 exert a slight activity enhancing effect (I6). With respect to all these properties, **6** is optimal with $\mathrm{MR}(R_1) = 18.18$, log $P = 4.2$ and I6 = 1.

It is tempting to interpret the parabolic relationship with log P in eq 10 as transport effect. One must, however, be aware of the relationship between the molar refractivity of substituents and log P (eq 1). The steric effect of R_1 seems to be outstanding and of high importance.

5.5. QSAR for the Diastolic Arterial Pressure. In addition to a decrease in contractility, an increase of the diastolic blood pressure (DAP125) also is an undesired side effect. The data for increase in diastolic blood pressure (Table 7, column 3) do not admit a Hansch analysis to be performed. However, the compounds can be divided into two classes according to their potency: class 1 (active class), DAP125 ≤ 11; class 2 (inactive class), DAP125 > 11.

The distribution of compounds can now be investigated by discriminant analysis leading to the following discriminant function

$$w = -1.64 \log P + 0.18\mathrm{MR}(R_1) + 2.02f(R_{34}) + 2.29\mathrm{I1} \quad (11)$$

with the class means

$$w\ (\text{mean, class 1}) = 3.13$$

$$w\ (\text{mean, class 2}) = 1.16$$

The indicator variable I1 takes a value of 1 for saturated and unbranched substituents in R_2 equal to or greater than *n*-butyl. The two classes are fairly well distinguished from each other by the discriminant function (11) (all terms significant at $P > 98\%$) which correctly reclassifies 9 out of the 10 compounds in class 1 (90%) and 11 out of the 13 compounds in class 2 (84.6%) (total: 20 out of 23 compounds = 87%). A comparison of the results from eq 11 with the class mean values shows that the chances of a compound to be classified as inactive with respect to an increase of diastolic blood pressure increase with overall hydrophobicity. In addition the hydrophobicity of R_{34} and the size of R_1 should not become too large. Equation 11 is difficult to interpret but seems to reflect some complex interplay between steric and hydrophobic properties of substituents. The important point is that **6** falls into the property space for inactivity with respect to the undesired increase of diastolic blood pressure.

5.6. QSAR for the RαT-Interval. Focusing on in vivo effects on refractoriness (RαT-interval, Table 7, column 4), eq 12 is obtained after removing compound **14** which again behaves as an outlier (see Figure 7):

$$\log(1/\mathrm{R\alpha T125}) = -0.0034(\pm 0.0014)(\mathrm{MR}(R_1) + \mathrm{MR}(R_2))^2 + 0.30(\pm 0.12)(\mathrm{MR}(R_1) + \mathrm{MR}(R_2)) - 0.0023(\pm 0.0012)\mathrm{MR}(R_{34})^2 + 0.096(\pm 0.053)\mathrm{MR}(R_{34}) + 0.39(\pm 0.28)\mathrm{I5} - 0.08(\pm 0.10)f(R_2)^*\mathrm{I4} - 7.39(\pm 2.93) \quad (12)$$

$$n = 22 \quad r = 0.901 \quad r^2 = 0.812 \quad s = 0.194 \quad F = 10.79 \quad P = 99.99\%$$

Equation 12 shows an only moderate but yet acceptable fit considering the type of data involved "explaining" 81% of data variance. As was the case with eq 3, molar

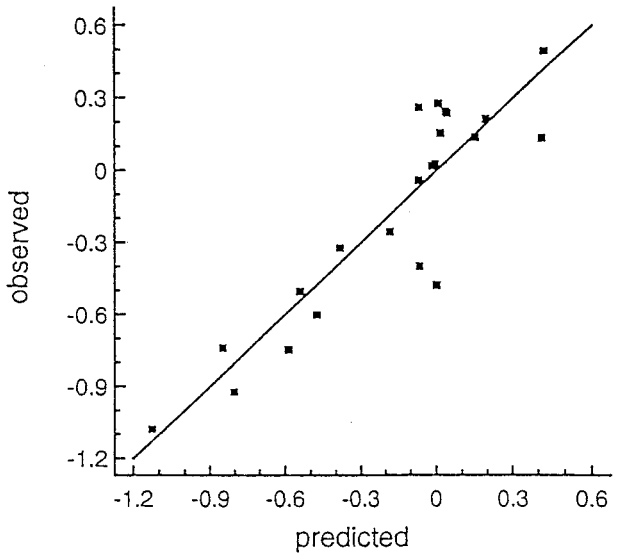


Figure 7. Plot of observed versus predicted values of log(1/RαT125) (eq 12).

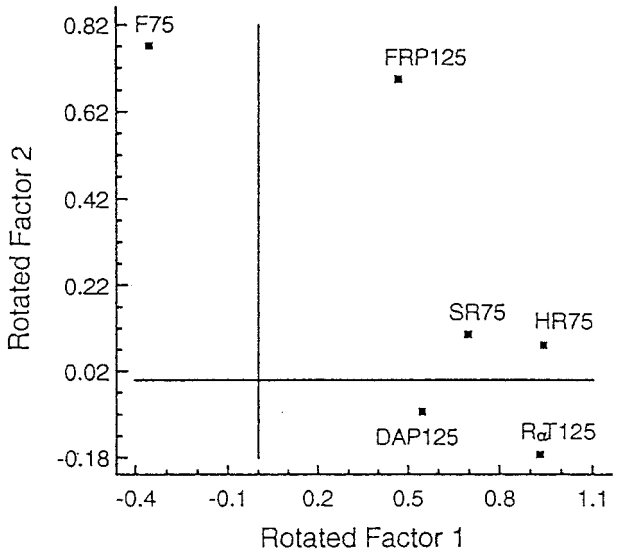


Figure 8. Plot of factor weights after VARIMAX rotation.

refractivity in eq 12 can be replaced by *f* values for R_{34} ($r = 0.902$, $s = 0.194$, $F = 10.90$) but not for R_1 and R_2. This may again be taken as an indication that steric effects operate in R_1 and R_2 while no preference between hydrophobic and steric effects can be made with respect to R_{34}. Thus, eq 12 indicates an optimum of substituent bulk for positions R_1 and R_2 and an optimum in bulk or/and hydrophobicity for R_{34}. In eq 12 a positive effect of branching in R_1 and R_2 is reflected by I5 [I5 = 0 (no branch) and I5 = 1 (branch in R_1 and/or R_2)]. The cross product term in eq 12, though statistically significant, is of doubtful validity and difficult to interpret. I4 indicates the occurrence of a ring in R_{34} and the cross product seems to indicate that, if such a ring is present, a slight decrease of potency appears with hydrophobicity of R_2. If this term is removed from eq 12, nothing else changes; only the statistics become, of course, a little poorer with $r = 0.836$, $s = 0.246$, and $F = 10.75$. With respect to the increase of the RαT-interval, **6** is placed among compounds with high potency in the anesthetized rat model.

5.7. QSAR for Selectivities. To investigate the internal relationship of the different tests, a factor analysis was performed resulting in three significant factors with eigenvalues $\lambda 1 = 2.89$, $\lambda 2 = 1.13$, and $\lambda 3 = 0.51$ and extracted variances of 63.7%, 25.0%, and 11.3%, respectively. As the first two factors account for 89% of the variance, it is possible to plot the data in the space spanned by these factors as shown in Figure 8 (VARIMAX rotation). Tests characterizing the heart's automaticity, sinus rate, and heart rate, are clustered together, which points to a common mechanism of action. For the in vitro model the parameters of refractoriness, FRP125, and of force of contraction, F75, are clearly separated from each other as well as from the sinus rate. This indicates that systematic differences between these parameters exist and that it should be possible to design selective compounds with respect to these properties. This finding is in full accordance with the in vitro score board (Table 6) where selective bradycardic compounds without decrease in contractility are found at the top of the list (high scores in column 9) and compounds selectively prolonging the refractory period are found at the end (low scores in column 9 and high scores in column 10).

In vivo the parameter of refractoriness, the RαT-interval, is located in the same area as the heart rate. Again this agrees with the in vivo score board (Table 7), where the compounds representing bradycardic agents without increase in diastolic blood pressure additionally show prolongation of refractoriness. The diastolic blood pressure seems to be close to the heart rate and RαT-interval, so that selectivity might not follow any simple pattern of properties. However, the communality of DAP125 is very low (0.5), so that this variable is only poorly represented in common factor space and its position in Figure 8 does permit only limited conclusions.

For a QSAR analysis selectivity indices were defined as follows:

$$\log \text{SelF} = \log(\text{F75}/\text{SR75})$$

$$\log \text{SelDAP} = \log(\text{DAP125}/\text{HR75})$$

As to be expected, when eqs 3 and 7 are compared, a relationship with substituent molar refractivity exists for log SelF (see Figure 9):

$$\log \text{SelF} = -0.010(\pm 0.007)\text{MR}(\text{R}_1)^2 + 0.37(\pm 0.33)\text{MR}(\text{R}_1) - 0.0043(\pm 0.002)\text{MR}(\text{R}_{34})^2 + 0.17(\pm 0.10)\ \text{MR}(\text{R}_{34}) + 0.43(\pm 0.40)\text{I2} - 3.03(\pm 4.28) \quad (13)$$

$$n = 16 \qquad r = 0.975 \qquad r^2 = 0.950 \qquad s = 0.194 \qquad F = 38.30 \qquad P = 100\%$$

Again, molar refractivity for R_{34} can be replaced by the corresponding *f* values ($r = 0.972$, $s = 0.203$, $F = 35.02$) while this is not possible for position R_1. This result once more may be taken to be indicative of steric interactions in this position. Equation 13 provides a good fit accounting for 95% of the data variance. Selectivity passes through a maximum with respect to

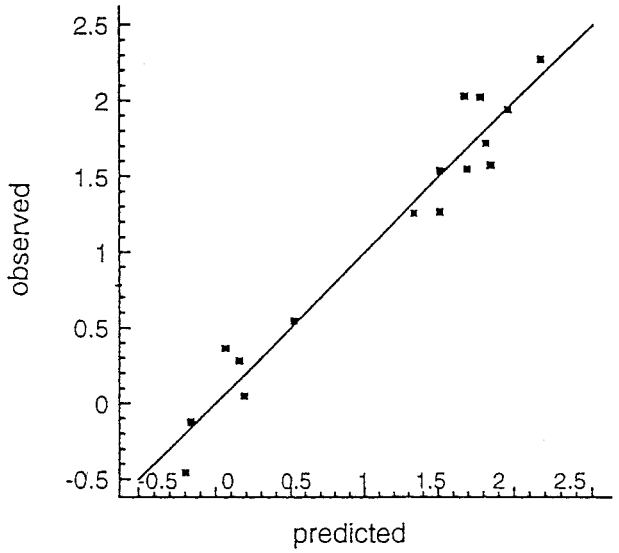


Figure 9. Plot of observed versus predicted values of log SelF (eq 13).

the size of substituents in R_1 (at $MR(R_1) \approx 18$) and with respect to size (at $MR(R_{34}) \approx 20$) or hydrophobicity in R_{34} (at $f(R_{34}) \approx 2.6$), respectively, and is enhanced by unsaturated substituents in R_1 (I2 = 1). The optimal size of substituents in R_{34} is close to the corresponding value found for SR75 (see eq 3), and the optimum for R_1 is compatible with the optimum found in this equation for the sum of molar refractivities in R_1 and R_2. Those compounds with high potency will also have a high selectivity potential. **6** has ideal selectivity properties with $MR(R_1) = 18.2$ and $MR(R_{34}) = 18.6$ or $f(R_{34}) = 2.40$, respectively. The molar refractivity terms in eq 13 can be replaced by a simple log *P* term with only a moderate loss in the goodness of fit:

$$\log \text{SelF} = -0.44(\pm 0.15) \log P + 0.56(\pm 0.57)\text{I2} + 3.37(\pm 0.85) \quad (14)$$

$$n = 16 \qquad r = 0.906 \qquad r^2 = 0.821 \qquad s = 0.368 \qquad F = 29.89 \qquad P = 100\%$$

Because of the relationships between log *P* and MR, it is again not possible to arrive at a clear decision whether hydrophobicity (transport?) or steric factors are of primary importance. For log SelDAP no meaningful relationship with either Hansch or discriminant analysis could be obtained. This is not surprising in the light of the results from factor analysis discussed above.

6. Discussion

Summarizing the scoring of test results from the in vitro models (guinea pig atria) and in vivo model (anesthetized rat), five representatives (**6**, **13**, **15**, **17**, and **23**) of compounds under investigation show high scores for the bradycardic activity and high selectivity with regard to force of contraction and diastolic arterial pressure. Furthermore, these five compounds additionally have prolonging effects on refractoriness. With respect to the performed in vitro/in vivo tests, within the series of synthesized 3,7,9,9-tetraalkyl-3,7-diazabicyclo[3.3.1]nonanes, **6** (tedisamil) in fact proved to be one of the most active derivatives selected for further in depth pharmacological evaluation. For the investigated potencies and selectivities, the results from QSAR yield a consistent picture with an overall satisfactory goodness of fit. In a few equations the number of terms is a little high, compared with the number of measurements, but the ratios are still acceptable, and in all cases simpler equations with less terms also exist. As expected for the type of structural variation involved, pharmacological properties primarily depend on substituent size and/or hydrophobicity with some additional influence by branching and/or unsaturation while electronic effects could not be detected.

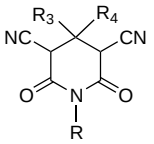
The QSARs obtained allow the potencies to be estimated from physicochemical parameters of substituents. Unfortunately, it is not possible to ascertain the role of log *P* or to relate log *P* terms with certain processes such as transport or membrane interactions because of the relationships between log *P* and MR_x (see eqs 1 and 2). The only exception is eq 8 where all evidence points to hydrophobic interactions. To clarify this situation, it would be necessary to break the correlations between log *P* and MR which could have been done only by synthesizing and testing additional compounds. However, the objective of the present investigation was only to prove whether **6** was the optimal choice out of the available variations.

To answer the question whether there might be more active derivatives than **6**, the highest possible value of log(1/SR75) and log(1/HR75) were computed from eqs 3 and 10. These values refer to hypothetical compounds having optimal values of MR and log *P*. These compounds will be referred to in the following as SR75opt and HR75opt, respectively. For SR75opt substituent size was defined according to the maxima of the MR terms in eq 3 ($MR(R_1) + MR(R_2) = 46$, and $MR(R_{34}) = 25$). Analogously, log $P = 5$ and $MR(R_1) = 20$ were defined for HR75opt from eq 10 which then leads to $(MR(R_2) + MR(R_{34})) = 43$ because of eq 1; this sum was divided into $MR(R_2) = 18$ and $MR(R_{34}) = 25$ (optimal value for $MR(R_{34})$). To be able to make an estimate of the value of log(1/HR75) for the hypothetical compound SR75opt, molar refractivities were derived from eq 2. The highest possible values estimated in this way are in comparison with the values of **6**:

	log(1/HR75)	log(1/SR75)
HR75opt	−0.64	0.67
SR75opt	−0.68	1.04
6 (calcd)	−0.68	0.44
6 (obsd)	−0.72	−0.11

There is one compound in the series, **24**, which has a value of log(1/HR75) = −0.54 which is slightly higher than that of HR75opt; the calculated value is −0.63, and the difference is well within the error of biological measurement. As was already pointed out, **6** is for all practical purposes optimal with respect to the decrease of heart rate in vivo while for the decrease of sinus rate in vitro somewhat more active compounds are possible. If now log(1/F75) and log SelF are computed from eqs 6 and 14 for HR75opt and SR75opt and the resulting

Table 8. Synthesized Dicyanoglutarimides of Formula **C** (R = H)



compd	R_3	R_4	% yield	mp, °C	lit. mp, °C	formula	analysis[g]	remarks
C1[a]	CH_3	CH_3	41	220−221	216−217	$C_9H_9N_3O_2$	C,H,N	
C2[b]	C_2H_5	C_2H_5	78	225	200	$C_{11}H_{13}N_3O_2$	C,H,N	
C3[c]	*n*-C_3H_7	*n*-C_3H_7	81	230−235	220−225	$C_{13}H_{17}N_3O_2$	C,H,N	
C4	*n*-C_4H_9	*n*-C_4H_9	90	201−205		$C_{15}H_{21}N_3O_2$	C,H,N	·0.3H_2O
C5	−$(CH_2)_3$−		46	198−200		$C_{10}H_9N_3O_2$	C,H,N	
C6[a]	−$(CH_2)_4$−		75	182−183	179−180	$C_{11}H_{11}N_3O_2$	C,H,N	
C7[d]	−$(CH_2)_5$−		84	215−222	211−212	$C_{12}H_{13}N_3O_2$	C,H,N	
C8[e]	CH_3	C_2H_5	55	180	193	$C_{10}H_{11}N_3O_2$	C,H,N	
C9[f]	CH_3	*n*-C_3H_7	33	190−192	201−202	$C_{11}H_{13}N_3O_2$	C,H,N	
C10	C_2H_5	*n*-C_4H_9	54	221−222		$C_{13}H_{17}N_3O_2$	C,H,N	

[a] Guareshi, I.; Grande, E. Synthese von Glutar- und Trimethylenderivaten. *Chem. Zbl.* **1899** (II), 439−440. [b] Peano, E. Einige Derivate des Diäthylketons. γ,γ-Diäthyl-β-β′-dicyan-α-α′-dioxypyridin. *Chem. Zbl.* **1901** (I), 582. [c] Guareshi, I. Synthese von Pyridin- und Trimethylenpyrrolverbindungen. *Chem. Zbl.* **1901** (I), 577−579. [d] Guareshi, I. Einige neue Derivate der Cyclohexanone. *Chem. Zbl.* **1911** (II), 361−362. [e] Guareshi, I.; Grande, E. Über ein Hydroäthyldicyanmethyldioxypyridin. *Chem. Zbl.* **1898** (II), 544−545. [f] Minozzi, A. Sintesi di nuovi derivati glutarici e trimetilenici. *Gazz. Chim. Ital.* **1900**, 30 (I), 265−278. [g] Compounds gave satisfactory analyses within ±0.4% of theoretical calculations unless otherwise stated.

values compared with those for **6**, the following picture is revealed:

	log(1/F75)	log SelF
HR75opt	−1.37	1.17
SR75opt	−0.96	0.73
6 (calcd)	−1.70	1.53
6 (obsd)	−1.62	1.58

Thus, with respect to the undesired effect on contractility, **6** is clearly better than HR75opt and SR75opt. The already mentioned compound **24** is slightly better than **6** with respect to log(1/HR75) and also with respect to log(1/SR75) (=0.36) as well as log SelF (=1.72) and about equiactive with respect to the prolongation of the refractory period and could thus be regarded as a possible alternative. However, **24** shows a higher decrease of the force of contraction (log(1/F75) = −1.36). Therefore, if the whole profile is considered with a higher weight attributed to the decrease of heart rate in vivo compared to sinus rate in vitro, **6** clearly is the best candidate within the space spanned by the type of substituent variations investigated. In addition **6** does not influence the diastolic arterial pressure. Also from the QSAR point of view for the type of substituents used and with a view to the spanned substituent space with regard to physiochemical variations, compound **6** (tedisamil) proved to be the optimal selection with respect to activity and pharmacological profile.

Comparing bradycardic action with prolongation of refractoriness in the in vitro and the in vivo models, different selectivities were observed. Besides the differences in heart rate control, this may be due to the mechanism of action of these compounds, demonstrated for **6** in voltage clamp experiments.[21,22] It was shown that **6** blocks a potassium outward current involved in ventricular repolarization of the rats more pronouncedly than in guinea pig hearts. So the differences between in vitro and in vivo selectivity may be due to species differences combined with the compound's mechanism of action. In further pharmacological investigations it could be shown that **6** (tedisamil) possesses clear-cut antiischemic properties in vitro (isolated rat heart model with ligation of the coronary artery[23]) and in vivo (angina pectoris model with conscious dogs[24]). This profile of activity could be confirmed in clinical investigations demonstrating the favorable hemodynamic and antiischemic effects in patients with ischemic heart disease.[25,26]

Experimental Section

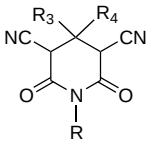
General Methods. Melting points were measured in a capillary melting point apparatus (HWS-SG 2000) and are uncorrected. Nuclear magnetic resonance (^{13}C NMR) spectra were collected in the pulsed Fourier-transformation mode, either on a Bruker HX90R or Bruker AM400 or Bruker ARX500 NMR spectrometer and were consistent with the proposed structures. Chemical shifts are referred to TMS. Where elemental analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

Determination of log P_{HPLC} Values. The applied technique was analogous to a method described by Kraak.[27] Bondapak Phenyl was used as stationary phase. The mobile phase consisted of a methanol/phosphate-buffer (0.005 M; pH 4; 60/40 vol %) containing 0.1% sodium dodecyl sulfate and 0.1 M $NaClO_4$. $Na_2Cr_2O_7$ was used as a nonretardent compound. The temperature was kept at 23.0 ± 0.5 °C. A UV detector running at 205 nm was used for detection. log P_{HPLC} values were determined as described by Kraak with linear regression via a calibration curve which was prepared from 28 compounds with known log $P_{octanol}$ values.

Chemistry. Dinitriles of the formula **C** as starting materials were synthesized according to a previously described method.[9] The compounds of the formulas **D**−**G** were synthesized according to the following general procedures. The physical properties of these derivatives and the starting dinitriles of formula **C** are summarized in Tables 1 and 8−12.

General Description of the Procedure To Synthesize 2,4,6,8-Tetraoxo-3,7-diazabicyclo[3.3.1]nonanes of Formula D and E. The dinitrile (20 g) of formula **C** (see Tables 8 and 9) were heated to between 120 and 140 °C while stirring in 100 mL of an acidic medium, the composition of which is given in Tables 10 and 11, until they are completely dissolved. After 10−15 min, the entire mixture is poured into ice water. The precipitated tetraoxo compound of formula **D** or **E** is filtered off by suction and, if required, is recrystallized, preferably from ethanol, and finally is dried.

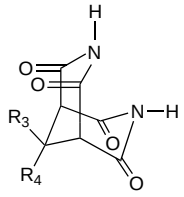
Table 9. Synthesized Dicyanoglutarimides of Formula C (R = R_1)



compd	R_1	R_3	R_4	% yield	mp, °C	formula	analysis[a]
C11	*n*-C_4H_9	CH_3	CH_3	56	85−87	$C_{13}H_{17}N_3O_2$	C,H,N
C12	*i*-C_4H_9	*n*-C_3H_7	*n*-C_3H_7	55	111	$C_{17}H_{25}N_3O_2$	C,H,N
C13	CHM	*n*-C_4H_9	*n*-C_4H_9	60	110	$C_{22}H_{33}N_3O_2$	C,H,N
C14	*n*-C_6H_{13}	C_2H_5	C_2H_5	68	64	$C_{17}H_{25}N_3O_2$	C,H,N
C15	*i*-C_4H_9	−$(CH_2)_5$−		66	119−121	$C_{16}H_{21}N_3O_2$	C,H,N

[a] Compounds gave satisfactory analyses within ±0.4% of theoretical calculations unless otherwise stated.

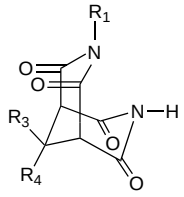
Table 10. Synthesized Unsubstituted 2,4,6,8-Tetraoxo-3,7-diazabicyclo[3.3.1]nonanes of Formula **D**



compd	R_3	R_4	used acid	% yield	mp, °C	lit. mp, °C	formula	analysis[c]	remarks
D1[a]	CH_3	CH_3	60% H_2SO_4	50	>350	>360	$C_9H_{10}N_2O_4$	C,H,N	
D2	C_2H_5	C_2H_5	60% H_2SO_4	61	230		$C_{11}H_{14}N_2O_4$	C,H,N	
D3	*n*-C_3H_7	*n*-C_3H_7	60% H_2SO_4	70	239		$C_{13}H_{18}N_2O_4$	C,H,N	
D4	*n*-C_4H_9	*n*-C_4H_9	60% H_2SO_4	45	195−199		$C_{15}H_{22}N_2O_4$	C,H,N	
D5	−$(CH_2)_3$−		60% H_2SO_4	70	>350		$C_{10}H_{10}N_2O_4$	C,H,N	·0.2H_2O
D6	−$(CH_2)_4$−		60% H_2SO_4	81	>350		$C_{11}H_{12}N_2O_4$	C,H,N	
D7[a]	−$(CH_2)_5$−		60% H_2SO_4	40	310	>370	$C_{12}H_{14}N_2O_4$	C,H,N	·0.2H_2O
D8[a]	CH_3	C_2H_5	H_2SO_4/H_3PO_4 (1:1)	84	324−326	329−331	$C_{10}H_{12}N_2O_4$	C,H,N	
D9[b]	CH_3	*n*-C_3H_7	H_2SO_4/H_3PO_4 (1:1)	65	291−295	278−280	$C_{11}H_{14}N_2O_4$	C,H,N	·0.3H_2O
D10	C_2H_5	*n*-C_4H_9	70 H_2SO_4	65	174−177		$C_{13}H_{18}N_2O_4$	C,H,N	

[a] Thorpe, J. F.; Wood, A. S. The Formation and Reaction of Imino-compounds. Part XVIII. The Condensation of Cyclohexanones with Cyanoacetamide Involving the Displacement of an Alkyl Group. *J. Chem. Soc.* **1913**, 1586. [b] Reference 10: Handley, G. J.; Nelson, E. R.; Samers, T. C. Compounds Derived from β-Substituted Glutaric Acids: Glutarimides, Glutaramic acids, 1,5-Pentane diols. *Austr. J. Chem.* **1960**, *13*, 129−144. [c] Compounds gave satisfactory analyses within ±0.4% of theoretical calculations unless otherwise stated.

Table 11. Synthesized Monoalkylated 2,4,6,8-Tetraoxo-3,7-diazabicyclo[3.3.1]nonanes of Formula **E**



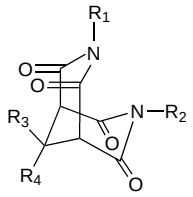
compd	R_1	R_3	R_4	used acid	% yield	mp, °C	formula	analysis[a]
E1	*n*-C_4H_9	CH_3	CH_3	H_2SO_4/H_3PO_4 (1:1)	56	175−178	$C_{13}H_{18}N_2O_4$	C,H,N
E2	*i*-C_4H_9	*n*-C_3H_7	*n*-C_3H_7	H_2SO_4/H_3PO_4 (1:1)	85	149−153	$C_{17}H_{26}N_2O_4$	C,H,N
E3	CHM	*n*-C_4H_9	*n*-C_4H_9	60 % H_2SO_4	86	140	$C_{22}H_{34}N_2O_4$	C,H,N
E4	*n*-C_6H_{13}	C_2H_5	C_2H_5	H_2SO_4/H_3PO_4 (1:1)	91	102−103	$C_{17}H_{26}N_2O_4$	C,H,N
E5	*i*-C_4H_9	−$(CH_2)_5$−		H_2SO_4/H_3PO_4 (1:1)	80	182	$C_{16}H_{22}N_2O_4$	C,H,N

[a] Compounds gave satisfactory analyses within ±0.4% of theoretical calculations unless otherwise stated.

The compounds of formula **D** (derivatives **D1**−**D10**) and **E** (derivatives **E1**−**E5**) which are obtained in this manner are listed in Tables 10 and 11.

General Description of the Procedure to Synthesize Alkylated 2,4,6,8-Tetraoxo-3,7-diazabicyclo[3.3.1]nonanes of Formula F. A mixture of 0.1 mol of the tetraoxo compound of formula **D** or **E** in 200 mL of absolute dimethyl formamide is heated to a temperature of between 60 °C and 70 °C. Then 0.125 mol (0.25 mol for dialkylation, respectively) of sodium hydride (or potassium carbonate, see Table 12) are added portion by portion, and the mixture is then boiled under reflux for about 1 h. After cooling, a solution of the alkylating agent in absolute dimethylformamide is added. In the case of monoalkylation, a solution of 0.15 mol of the respective alkylating agent in 50 mL of dimethylformamide is added dropwise. In the case of dialkylation, 0.3 mol of alkylating agent is used. The resulting mixture is refluxed for 3 h. Thereafter most of the solvent is distilled off under vacuum. Dichloromethane is added to the residue, and the mixture is washed with a 20% sodium hydroxide solution. The aqueous phase is again extracted with dichloromethane. The organic phases are combined, washed several times with water, and dried ($MgSO_4$). After distilling off the solvent, the remaining residue is recrystallized from a mixture of ether and hexane.

Table 12. Synthesized Dialkylated 2,4,6,8-Tetraoxo-3,7-diazabicyclo[3.3.1]nonanes of Formula **F**



compd	R_1	R_2	R_3	R_4	RX	base[a]	% yield	mp, °C	analysis[b]	remarks
F1	*n*-C_4H_9	*n*-C_4H_9	CH_3	CH_3	Br	C	61	97	C,H,N	
F2	CH_3	CH_3	CH_3	CH_3	J	H	82	273−278	C,H,N	
F3	CHM	CHM	CH_3	C_2H_5	Br	H	45	112−115	C,H,N	
F4	*n*-C_4H_9	*n*-C_4H_9	CH_3	C_2H_5	Br	H	81	82	C,H,N	
F5	*n*-C_6H_{13}	*n*-C_6H_{13}	$-(CH_2)_4-$		Br	H	30	70	C,H,N	
F6	CPM	CPM	$-(CH_2)_4-$		Cl	C	58	160−161	C,H,N	
F7	*n*-C_4H_9	*n*-C_4H_9	*n*-C_4H_9	*n*-C_4H_9	Br	H	85	73−75	C,H,N	
F8	*n*-C_3H_7	*n*-C_3H_7	C_2H_5	C_2H_5	Br	H	59	94	C,H,N	
F9	*i*-C_3H_7	*i*-C_3H_7	*n*-C_3H_7	*n*-C_3H_7	Br	H	30	153−154	C,H,N	
F10	*n*-C_6H_{13}	*n*-C_6H_{13}	C_2H_5	*n*-C_4H_9	Br	H	38	oil	C,H,N	
F11	CHM	CHM	$-(CH_2)_5-$		Br	H	43	140	C,H,N	
F12	CH_3	*n*-C_6H_{13}	C_2H_5	C_2H_5	J	H	31	100−101	C,H,N	·0.2H_2O
F13	*i*-C_3H_7	*i*-C_3H_7	CH_3	*n*-C_3H_7	Br	H	47	103	C,H,N	
F14	*i*-C_3H_7	*i*-C_3H_7	CH_3	CH_3	Br	H	68	118−120	C,H,N	
F15	*n*-C_4H_9	CHM	CH_3	CH_3	Br	H	64	100	C,H,N	
F16	*i*-C_4H_9	*n*-C_4H_9	CH_3	CH_3	Br	H	81	80	C,H,N	
F17	*i*-C_3H_7	*i*-C_4H_9	$-(CH_2)_5-$		Br	H	30	101	C,H,N	
F18	*i*-C_3H_7	CHM	*n*-C_4H_9	*n*-C_4H_9	Br	H	48	85	C,H,N	·0.2H_2O
F19	*n*-C_4H_9	*n*-C_4H_9	$-(CH_2)_3-$		Br	H	49	110	C,H,N	·0.5H_2O
F20	*n*-$C_{10}H_{24}$	*n*-$C_{10}H_{24}$	CH_3	CH_3	Br	H	56	63	C,H,N	
F21	allyl	allyl	CH_3	CH_3	Br	H	59	128−130	C,H,N	
F22	butenyl	butenyl	$-(CH_2)_5-$		Br	C	54	120	C,H,N	
F23	butenyl	butenyl	CH_3	CH_3	Br	C	76	91	C,H,N	
F24	butenyl	*i*-C_4H_9	*n*-C_3H_7	*n*-C_3H_7	Br	H	38	oil	C,H,N	
F25	butenyl	*n*-C_4H_9	CH_3	CH_3	Br	H	66	80−83	C,H,N	

[a] H = sodium hydride. C = potassium carbonate. [b] Compounds gave satisfactory analyses within ±0.4% of theoretical calculations unless otherwise stated.

According to this procedure the compounds of formula **F** (derivatives **F1**−**F25**), listed in Table 12, have been synthesized.

General Description of the Reduction of Alkylated 2,4,6,8-Tetraoxo-3,7-diazabicyclo[3.3.1]nonanes of Formula F to Bispidines of Formula G. A mixture of 0.1 mol of lithium aluminum hydride in 100 mL of THF/toluene (70:30) is heated at 80 °C. Subsequently, 0.025 mol of the tetraoxo compounds of formula **F** in 100 mL of a mixture of THF/toluene (70:30) is added dropwise at an oil bath temperature of 80 °C. The reaction mixture is kept at a temperature of 120 °C for 2−4 h. The reaction mixture is then hydrolyzed under basic conditions. The reaction mixture is then extracted with dichloromethane, and the organic phase is dried ($MgSO_4$). The dried organic phase is concentrated by evaporation, and the residue is subjected to fractional distillation under reduced pressure in a system provided with a bulb-tube fractionating column. Tetraoxo compounds of formula **F** with unsaturated alkenyl side chains are reduced in an analogous manner as described above by using sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al, Aldrich) as reducing agent in toluene.

By proceeding in this manner, the bispidine derivatives of formula **G** (compounds **1**−**25**), listed in Table 1, have been obtained. As indicated, the elementary analysis has been performed with the free base, respectively, the mentioned salts.

Pharmacology. Isolated Right and Left Guinea Pig Atria. The animals (female, 250−300 g) were killed by a blow on the head and bled from the carotid arteries. The hearts were quickly excised, and the atria (right and left) were dissected from the hearts in oxygenated buffer solution. The atria were attached to preparation holders and suspended individually in glass tissue chambers filled with buffer solution, continuously oxygenated and kept at 35 °C. The left atrial preparations were additionally provided with bipolar platinum stimulation electrodes. Right atria exert spontaneous activity; left atria were electrically paced at 2 Hz with rectangular pulses of 1 ms duration. Isometric contractions were recorded by means of force transducers and the signals fed into a computer for evaluation. For each compound, cumulative concentration response curves (maximum of five concentrations) were recorded. Effective concentrations (EC_{75} and EC_{125}), defined as drug concentrations inducing a decrease/increase of a parameter by 25% of the predrug value, were calculated as geometric mean of the individual EC values.

Anesthetized rat. The animals (Wistar, male, 280−360 g) were anesthetized with urethane (1.25 g/kg ip) and provided with an endotracheal tube to facilitate spontaneous respiration. Arterial blood pressure was measured in the left femoral artery via a saline-filled tube catheter connected to a Statham pressure transducer. The electrocardiogram (ECG) was recorded with needle electrodes inserted subcutanously. The signals were fed into a computer and analyzed every 30 s by means of an evaluation software. The compounds were administered by continuous infusion at a volume of 0.1 mL/min using a tube catheter placed in the left femoral vein. At 10-min intervals, the drug concentration was increased by a factor of 10 without changing the infusion volume (3 doses). Effective doses (ED_{75} and ED_{125}), defined as drug doses inducing a decrease/increase of a parameter by 25 of the predrug value, were calculated as geometric mean of the individual ED values.

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Supporting Information Available: Tables containing ^{13}C NMR spectral data (4 pages) and elemental analyses (14 pages). Ordering information is given on any current masthead page.

References

(1) Kobinger, W. Specific Bradycardic Agents, A New Approach to Therapy in Angina Pectoris? *Prog. Pharmacol.* **1985**, *5/4*, 89−100.

(2) Mannich, C.; Mohs, P. Über Derivate eines aus zwei Piperidinringen kondensierte bicyclischen Systems. (Derivatives of a Condensed Ring System of Two Piperidine Rings.) *Chem. Ber.* **1930**, *63*, 506−512.

(3) (a) Böhme, H. Die Behandlung von Herzrhythmusstörungen mit Sparteinsulfat. (Treatment of Cardiac Arrhythmias with Sparteine Sulfate.) *Z. Gesamte Inn. Med.* **1964**, *19*, 883−889. (b) Raschack, M. Wirkungen von Spartein und Sparteinderivaten auf Herz und Kreislauf. (Effect of Sparteine and Sparteine Derivatives on the Cardiovascular System.) *Arzneim.-Forschung* **1974**, *24*, 753−759. (c) Wick, E.; Bell, U.; Dengler, H. J. Die Wirkung von Sparteinsulfat auf mechanisch ausgelöste Extrasystolen beim Menschen. (Effect of Sparteine Sulfate on Mechanically Produced Extrasystole in Humans.) *Med. Welt* **1971**, *22*, 303−304.

(4) (a) For instance: Smith, G. S.; Thompson, M. D.; Berlin, K. D.; Holt, E. M.; Scherlag, B. J.; Petterson, E.; Lazarra, R. A Study on the Synthesis and Antiarrhythmic Properties of Selected 3,7-Diheterobicyclo(3.3.1)nonanes with Substituents at the 2,4-Positions and at the 9-Position. *Eur. J. Med. Chem.* **1990**, *25*, 1-8. (b) Zhang, Z.-H.; Follmer, C. H.; Sarma, J. S. M.; Chen, F.; Singh, B. N. Effect of Ambasilide, a New Class III Agent, on Plateau Currents in Isolated Guinea Pig Ventricular Myocytes: Block of Delayed Outward Potassium Current. *J. Parmacol. Exp. Ther.* **1992,** *263*, 40−48.

(5) (a) Zefirov, N. S.; Palyulin, V. A. Conformational Analysis of Bicyclo[3.3.1]nonanes and Their Hetero analogs. *Top. Stereochem.* **1991**, *20*, 171−230. (b) Jeyaraman, R.; Avila, S. Chemistry of 3-Azabicyclo[3.3.1]nonanes, *Chem. Rev.* **1981**, *81*, 149−174.

(6) Schön, U.; Hachmeister, B.; Kehrbach, W.; Kühl, U. G.; Buschmann, G. Diazabicyclo[3.3.1]nonanes. German Patent DE 3 234 697, 1982; *Chem. Abstr.* **1984**, *101*, 55089v.

(7) (a) Blicke, F. F. The Mannich Reaction. *Org. React.* **1942**, *1*, 303−341. (b) Mannich, C.; Veit, F. Über Derivate des Bispidins. (Derivatives of Bispidine.) *Chem. Ber.* **1935**, *68B*, 506−512. (c) Reichert, B. *Die Mannich Reaktion* (*The Mannich Reaction*); Springer-Verlag: Berlin, 1959.

(8) Bohlmann, F.; Ottawa, N.; Keller, R. Aufbau des Tetrahydrochinolizons und des "Bispidins". (Contribution to the Synthesis of Cytisine; Structure of Tetrahydroquinolizone and "Bispidine".) *Annalen* **1954**, *587*, 162−176.

(9) McElvain, S. M.; Clemens, D. H. β-Methyl-β-phenyl-α,α'-dicyanoglutarimide. *Organic Syntheses;* Wiley: New York, 1963; Collect. Vol. IV, pp 62−663.

(10) Handley, G. J.; Nelson, E. R.; Somers, T. C. Compounds Derived from β-Substituted Glutaric Acids: Glutarimides, Glutaramic Acids, 1,5-Pentane diols. *Austr. J. Chem.* **1960,** *13*, 129−144.

(11) McElvain, S. M.; Clemens, D. H. Piperidine Derivatives XXX. 1,4-Dialkylarylpiperidines. *J. Am. Chem. Soc.* **1958**, *80*, 3915−3923.

(12) The rat ECG differs from other species, particularly in heart rate and configuration. The onset of ventricular depolarization shows no Q deflection, and the T-wave declines slowly. So in the rat ECG, the duration of ventricular depolarisation is described by the RαT-interval, beginning at the onset of R, ending at the apex of T. As the QT in other species, in the rat RαT-interval estimates the duration of ventricular depolarisation.

(13) Budden, R.; Buschmann, G.; Kühl, U. G. The Rat Electrocardiogram in Acute Pharmacology and Toxicology. In *The Rat Electrocardiogram in Pharmacology and Toxicology*; Budden, R., Detweiler, D. K., Zbinden, G., Eds.; Pergamon Press: Oxford, 1981; pp 41−81.

(14) Danesi, R.; del Tacca, M.; Soldani, G. Measurement of the S alpha T segment as the most reliable ECG parameter for the assessment of adriamycin.induced cardiotoxicity in the rat. *J. Pharmacol. Meth.* **1985**, *16*, 251−259.

(15) Multiple regression analysis from STATGRAPHICS version 5.0 (see ref 17).

(16) (a) Dove, S. Program VADIA (b) For details of this method, see, e.g., Franke, R. *Theoretical Drug Design Methods*; Elsevier: Amsterdam, 1984; pp 222−241.

(17) STATGRAPHICS 5.0, STSC Inc., 2155 East Jefferson St, Rockville, MD 20582.

(18) Hansch, C.; Leo, A. *Substituent Constants for Correlation Analysis in Chemistry and Biology*; J. Wiley & Sons: New York, 1979.

(19) Rekker, R. F.; Mannhold, R. *Calculation of Drug Lipophilicity*; VCH: Weinheim, 1992.

(20) Schön, U.; Antel, J.; Brückner, R.; Messinger, J.; Franke, R.; Gruska, A. Unpublished results.

(21) Dukes, I. D.; Morad, M. Tedisamil Modulates Outward K−Channels in Rat and Guinea Pig Ventricular Myocytes. *Circulation* **1989**, *80*, Suppl. II, 517.

(22) Dukes, I. D.; Cleemann, L.; Morad, M. Tedisamil Blocks the Transient and Delayed Rectifier K−Currents in Mammalian Cardiac and Glial Cells. *J. Pharmacol. Exp. Ther.* **1990**, *254*, 560−569.

(23) Duchosal, F.: Opie, L. H. Potential Beneficial Effects of Potassium Channel Blockade by Tedisamil in Isolated Perfused Working Heart with Coronary Ligation. *Cardiovasc. Drugs Ther.* **1992**, *6* (Suppl.1), 329−336.

(24) Grohs, J. G.; Fischer, G.; Raberger, G. Cardiac and Hemodynamic Effects of the Selective Bradycardic Agent KC 8857 During Exercise-Induced Myocardial Ischemia. *Eur. J. Pharmacol.* **1989**, *161*, 53−60.

(25) Mitrovic, V.; Oehm, E.; Liebrich, A.; Thormann, J.; Schlepper, M. Hemodynamic and Antiischemic Effects of Tedisamil in Humans. Cardiovasc. *Drugs Ther.* **1992**, *6* (Suppl. 1), 353−360.

(26) Mitrovic, V.; Oehm, E.; Strasser, R.; Schlepper, M.; Pitschner, H. F. Hemodynamic, Antiischemic and Neurohumoral Effects of the New Potassium Channel Blocking Agent Tedisamil in Patients with Coronary Artery Disease. *Z. Kardiol.* **1996**, *85*, 961−972.

(27) Kraak, J. C.; van Rooij, H. H.; Thus, J. L. G. Reversed-phase Ion-pair Systems for the Prediction of *n*-Octanol−Water Partition Coefficients of Basic Compounds by High-performance Liquid Chromatography. *J. Chromatogr.* **1986**, *352*, 455−463.

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