pension was sonicated at 20 KHz for 30 s twice, and the sonicate was centrifuged at 10000g for 10 min. The supernatant solution was stored at -80 °C.

Enzyme Assay. The activity of 5-lipoxygenase was assayed by a modification of the procedure of Ochi et al.[25] The reaction mixture contained 50 mM potassium phosphate buffer (pH 7.4), 2 mM $CaCl_2$, 1 mM glutathione, 2 mM adenosine-5'-triphosphate, 200 μg of the enzyme, and the test compound (dissolved in 4 μL DMSO) in a final volume of 200 μL. Preincubation of enzyme with the test compound was performed at 30 °C for 5 min. Reaction was started by adding 16 μM [1-^{14}C]arachidonic acid (6.29 kBq/5 μL of ethanol), performed with shaking at 30 °C for 30 min, and terminated by adding 50 μL of 0.2 N citric acid. Arachidonic acid and its metabolites were extracted with 1.5 mL of ethyl acetate. The ethyl acetate layer (1 mL) was dried under a nitrogen gas stream and spotted on a silica gel plate. Thin-layer chromatography was carried out with a solvent system of diethyl ether–petroleum ether–acetic acid (85/15/0.1). Radioactivity on the plate was monitored with the use of a Packard radiochromatogram scanner. For quantitative determination of the enzyme activity, the silica gel zones corresponding to authentic 5-hydroxyeicosatetraenoic acid (5-HETE) were scraped into scintillation vials. Radioactivity was determined by a Packard liquid-scintillation counter. The enzyme activity was expressed in terms of the amount of 5-HETE synthesized for 30 min.

(25) Ochi, K.; Yoshimoto, T.; Yamamoto, S.; Taniguchi, K.; Miyamoto, T. *J. Biol. Chem.* **1983**, *258*, 5754.

Acknowledgment. We thank the following individuals for their useful comments and technical assistance: Dr. S. Ushiyama, F. Aizawa, K. Kobayashi, Y. Sato, T. Koga, N, Kasanuki, and F. Tabata.

Registry No. **7a**, 100480-35-1; **7b**, 100480-15-7; **7c**, 100480-16-8; **7d**, 100480-17-9; **7e**, 100480-19-1; **7f**, 100480-20-4; **4g**, 100480-21-5; **7h**, 100505-37-1; **7i**, 100480-24-8; **7j**, 100480-81-7; **7k**, 100480-40-8; **7l**, 100480-23-7; **15a**, 83857-82-3; **17a**, 100479-81-0; **17b**, 125714-62-7; **18**, 100479-96-7; **19**, 125714-63-8; **20a**, 125714-63-8; **20b**, 125714-64-9; **24**, 100480-05-5; **25**, 56539-25-4; **26**, 100480-67-9; **27a**, 950-99-2; **27b**, 79907-49-6; **27c**, 56305-04-5; EtCOCl, 79-03-8; PrCOCl, 141-75-3; BuCOCl, 638-29-9; $C_6H_{13}COCl$, 2528-61-2; $C_7H_{15}COCl$, 111-64-8; $C_{19}H_{39}COCl$, 40140-09-8; methyl succinyl chloride, 1490-25-1; *tert*-butylhydroquinone, 1948-33-0; 5,5'-bis(1,1-dimethylethyl)-2,2'-dithiobishydroquinone, 125714-65-0; 5,5'-bis(1,1-dimethylethyl)-2,2'-trithiobishydroquinone, 125714-66-1.

Supplementary Material Available: A table of hypolipidemic activity of 1,3-benzoxathioles along with compound **2** are available (1 page). Ordering information is given on any current masthead page.

Specific Bradycardic Agents. 1. Chemistry, Pharmacology, and Structure–Activity Relationships of Substituted Benzazepinones, a New Class of Compounds Exerting Antiischemic Properties

Manfred Reiffen,*[†] Wolfgang Eberlein,[†] Peter Müller,[†] Manfred Psiorz,[†] Klaus Noll,[†] Joachim Heider,[†] Christian Lillie,[‡] Walter Kobinger,[‡] and Peter Luger[§]

Department of Chemical Research, Ressort Chemische Forschung, Dr. Karl Thomae GmbH, Postfach 1755, D-7950 Biberach 1, West Germany, Department of Pharmacology, Ernst-Boehringer-Institut für Arzneimittelforschung, Dr. Beohringer-Gasse 5-11, A-1121 Wien, Austria, and Freie Universität Berlin, Institut für Kristallographie, Takustrasse 6, 1000 Berlin 33, West Germany. *Received June 21, 1989*

Structural modification of the calcium-antagonist verapamil (1) by replacement of the lipophilic α-isopropylacetonitrile moiety by various heterocyclic ring systems has led to a new class of cardiovascular compounds which are characterized by a specific bradycardic activity. These agents reduce heart rate without binding to classical calcium channels or β-adrenoceptors, interacting instead specifically with structures at the sino atrial node. Therefore they have also been termed sinus node inhibitors. The prototype falipamil (2) has been submitted to further optimization mainly by manipulation of the phthalimidine moiety. This has resulted in a second generation of specific bradycardic agents with increased potency and selectively and prolonged duration of action represented by the benzazepinone-derivative UL-FS 49 (4). Structure–activity relationships within this novel class of compounds have revealed a marked dependence of activity on the substitution pattern of the aromatic rings, the nature of the central nitrogen atom, and the length of the connecting alkyl chains. The crucial role of the benzazepinone ring for bradycardic activity can be best explained by its special impact on the overall molecular conformation.

Ischemic heart disease is characterized by an imbalance between myocardial substrate supply and demand. This imbalance may result in ischemic pain, myocardial dysfunction, or tissue necrosis. Heart rate is a major determinant of myocardial energy demand.[1] Thus, drug-induced bradycardia would be expected to reduce myocardial oxygen consumption.[2] In addition, bradycardia may increase blood flow to the subendocardial layers of the myocardium, which are predominantly perfused during diastole.[3,4] Two classes of pharmacological agents which are frequently used in the treatment of ischemic heart disease induce bradycardia. These include the β-adrenoceptor antagonists[5] and calcium channel blockers, the most prominent being verapamil and diltiazem.[6] However, most β-blockers and calcium channel blockers not only reduce heart rate but also reduce myocardial contractile force. In addition, the latter agents are capable of reducing the coronary perfusion pressure, which may result in a decrease in ischemic coronary flow and myocardial perfusion.

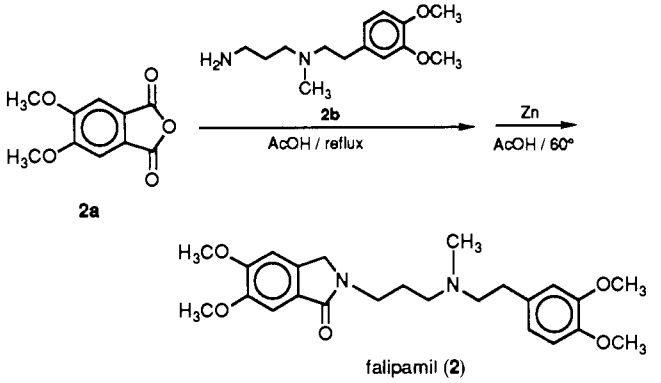
Because of these potential drawbacks of β-blockers and calcium channel blockers, a synthesis program was initiated aimed at compounds which selectively reduce heart rate

[†] Dr. Karl Thomae GmbH.
[‡] Ernst-Boehringer Institut für Arzneimittelforschung.
[§] Freie Universität Berlin, Institut für Kristallographie.

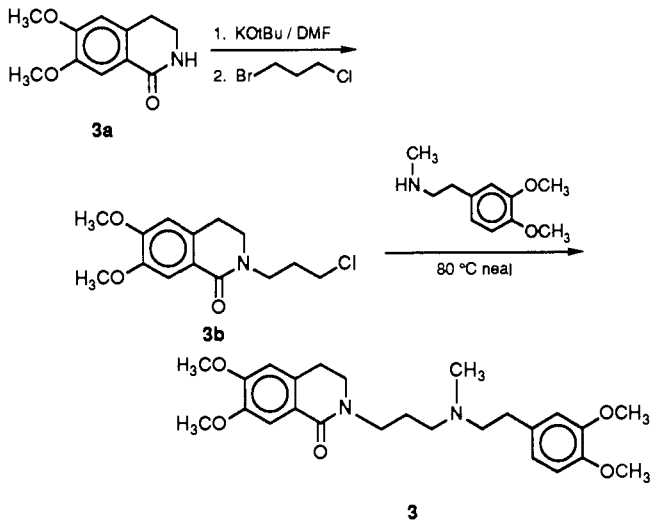
(1) Sonnenblick, E. H.; Ross, J., Jr.; Braunwald, E. *Am. J. Cardiol.* **1968**, *32*, 328.
(2) Braunwald, E. *Am. J. Cardiol.* **1976**, *27*, 416.
(3) Buckberg, G. D.; Fixler, D. E.; Archie, J. P.; Hoffman, J. I. E. *Circ. Res.* **1972**, *30*, 67.
(4) Buckberg, G. D.; Fixler, D. E.; Archie, J. P.; Henney, R. P.; Hoffman, J. I. E. *Cardiovasc. Res.* **1975**, *9*, 1.
(5) Connolly, M. E.; Kersting, F.; Dollery, C. T. *Prog. Cardiovasc. Dis.* **1976**, *19*, 203.
(6) McAllister, R. G. *Prog. Cardiovasc. Dis.* **1982**, *25*, 83.

0022-2623/90/1833-1496$02.50/0

Scheme I



Scheme II



without affecting cardiac contractility or aortic blood pressure.[7-10] Among the various agents mentioned above, verapamil was chosen as a lead structure because it exerts a bradycardic component which is directly mediated via the sinus node. The hemodynamic profile of verapamil is characterized by a decrease of heart rate, blood pressure, and cardiac contractility.[11] Furthermore it exerts a marked effect on the cardiac excitation and conducting system, especially on the AV node.[12] Thus, our intention was to change the biological profile of verapamil in such a way that the negative chronotropic activity would become prominent while all other hemodynamic effects would be suppressed.

In an attempt to approach this problem, the structure of verapamil was modified mainly by replacement of the asymmetric α-isopropylacetonitrile moiety with various heterocyclic ring systems. In this paper, we report the synthesis and structure–activity relationships of novel five-, six-, and especially seven-membered-ring benzolactam derivatives of verapamil exerting specific bradycardic activity.

(7) Kobinger, W.; Lillie, C.; Pichler, L. *Naunyn Schmiedeberg's Arch. Pharmacol.* **1979**, *306*, 255.
(8) Kobinger, W.; Lillie, C.; Pichler, L. *Eur. J. Pharmacol.* **1979**, *58*, 141.
(9) Stähle, H.; Daniel, H.; Kobinger, W.; Lillie, C.; Pichler, L. *J. Med. Chem.* **1980**, *23*, 1217.
(10) Kobinger, W. Progress in Pharmacology; Gustav Fischer Verlag: New York, 1985; Vol. 5/3.
(11) Soward, A. L.; Vanhaleweyk, G. L.; Serruys, P. W. Drugs **1986**, *32*, 66.
(12) Traunecker, W. *Arzneim.-Forsch. (Drug Res.)* **1988**, *38*, 509.

Scheme III

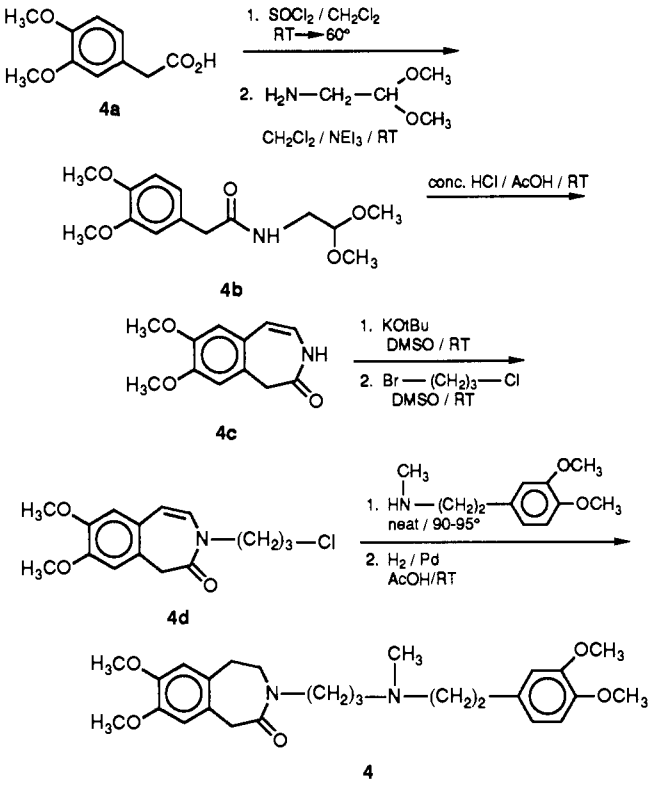
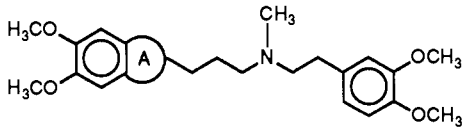
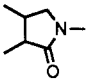
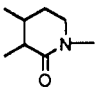
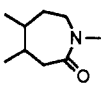
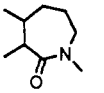


Table I. Chemical and Pharmacological Data of Five-, Six-, and Seven-Membered Ring Benzolactams



no.	formula	A	mp, °C	heart rate in cats: % decrease[b] at 1 mg/kg iv
2 (falipamil)	$C_{24}H_{32}N_2O_5 \cdot HCl$		170–2	-16
3	$C_{25}H_{34}N_2O_5 \cdot HCl$		178–9	-29
4 (UL-FS 49)	$C_{26}H_{36}N_2O_5 \cdot HCl$		168/188[a]	-56
5	$C_{26}H_{36}N_2O_5$		<30[a]	-8

[a] Two crystal modifications of the hydrochloride salt. [b] Values are the mean of three experiments with a standard deviation below ±30%.

Chemistry

The five-membered phthalimidine ring system of falipamil was easily obtained by ring opening of the corresponding phthalic anhydride **2a** with the diamine **2b** followed by zinc reduction in acetic acid according to Scheme I.

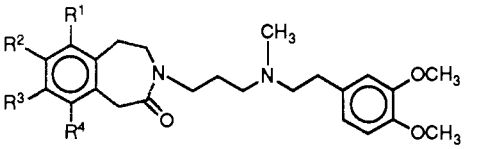
The six-membered ring-derivative **3** was obtained by alkylation of the corresponding isochinolinone **3a** with 1-bromo-3-chloropropane in the presence of potassium *tert*-butoxide followed by reaction of the intermediate chloro derivative **3b** with *N*-methylhomoveratrylamine according to Scheme II.

Table II. The Effects of Substances on Spontaneous Rate and Contractility in Isolated Guinea-Pig Atria and on K^+-Induced Contraction in Isolated Aortic Strips of Rabbits

substance	decrease in atrial rate: EC_{30}, μg/mL	atrial contractility: EC_{30}, μg/mL	aortic contracture: EC_{30}, μg/mL	ratio of EC_{30}[a]: atrial contractility/atrial rate	ratio of EC_{30}[a]: aortic contracture/atrial rate
4	0.0300 (0.0182–0.0435) [20]	108 (81.6–154.0) [16]	15.0 (10.29–19.58) [13]	3600	500
falipamil (2)	0.608 (0.4938–0.7494) [12]	93.6 (71.81–113.35) [10]	21.3 (8.53–36.30) [17]	154	35.0
verapamil (1)	0.0694 (0.0427–0.1859) [12]	0.0611 (0.0416–0.0818) [9]	0.0284 (0.0190–0.0365) [13]	0.880	0.409
nifedipine	0.11[b] [10]	0.0149 (0.0079–0.0221) [11]	0.00397 (0.00277–0.0049) [14]	0.135	0.036
diltiazem	0.14[c] [10]	2.73 (2.036–3.508) [13]	0.0741 (0.0568–0.0935) [11]	19.5	0.53

[a] EC_{30} = concentration which decreased the predrug value by 30%; in parentheses are the 95% confidence limits of the EC_{30}s; the number of experiments is in brackets. [b] Extrapolated, flat concentration–response curve up to 0.1 μg/mL (r = −0.64), with 0.3 μg/mL standstill in 2/2 preparations. [c] Flat curve up to 0.3 μg/mL (r = −0.65), with 1 μg/mL arrhythmias in 3/4 preparations.

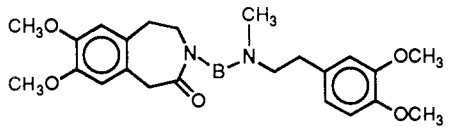
Table III. Chemical and Pharmacological Data of Benzazepinone Derivatives (Part A)



no.	formula	R^1	R^2	R^3	R^4	mp, °C	heart rate in rats % decrease[a] at 5 mg/kg iv
4	Table I	H	OCH_3	OCH_3	H	Table I	−56 ± 7
6	$C_{25}H_{32}N_2O_5$·HCl	H	OCH_2	-O-	H	210–2	−42
7	$C_{26}H_{34}N_2O_5$·HCl	H	OCH_2CH_2	-O-	H	208–10	−49
8	$C_{26}H_{36}N_2O_3$·2HCl	H	CH_3	CH_3	H	154–7	−49
9	$C_{24}H_{32}N_2O_5$	H	OH	OH	H	>40	−30
10	$C_{25}H_{34}N_2O_5$·HCl	H	OH	OCH_3	H	80–2	−47
11	$C_{25}H_{34}N_2O_4$·2HCl	H	H	OCH_3	H	121–2	−44
12	$C_{25}H_{34}N_2O_5$	H	OCH_3	OH	H	>30	−29
13	$C_{24}H_{34}N_2O_4$·HCl	H	OCH_3	H	H	149–51	−31
14	$C_{26}H_{36}N_2O_5$·HCl	OCH_3	H	H	OCH_3	73–6	−21
15	$C_{26}H_{36}N_2O_5$·HCl	H	H	OCH_3	OCH_3	131–3	−34
16	$C_{24}H_{32}N_2O_3$·HCl	H	H	H	H	160–2	−35
17	$C_{28}H_{40}N_2O_3$·HCl	CH_3	CH_3	CH_3	CH_3	177	−41

[a] Heart rate reduction in rats is given as means (n = 3); SE for 4 is based on n = 45.

Table IV. Chemical and Pharmacological Data of Side Chain B Derivatives

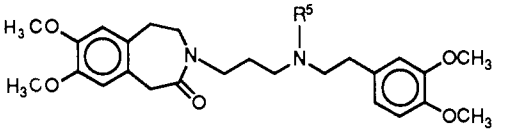


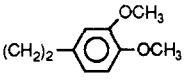
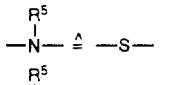
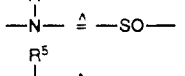
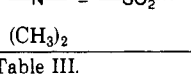
no.	mol formula	B	mp, °C	heart rate in rats % decrease[a] at 5 mg/kg iv
4	Table I	$-(CH_2)_3-$	Table I	−56 ± 7
18	$C_{27}H_{38}N_2O_5$·HCl	$-CH_2CH(CH_3)CH_2-$	99–101	−43
19	$C_{26}H_{38}N_2O_6$	$-CH_2CH(OH)CH_2-$	oil	−28
20	$C_{25}H_{34}N_2O_5$·HCl	$-CH_2CH_2-$	188–9	−13
21	$C_{27}H_{38}N_2O_5$·HCl	$-(CH_2)_4-$	192–4	−33

[a] See footnote *a* in Table III.

The synthesis of the seven-membered-ring derivative **4** starts from 3,4-dimethoxyphenylacetic acid as outlined in Scheme III and is a general example for the synthesis of other substituted benzazepinone derivatives contained in Tables III–VII. The crucial steps in this reaction sequence are the ring closure of the acetal **4b** to the benzazepinone **4c**[13,14] as well as the N-alkylation of the latter leading to the chloroalkyl intermediate **4d**. Hydroxy or alkoxy substituents are necessary to perform the electrophilic cyclization of **4b** in hydrochloric acid/acetic acid. In the case of alkyl groups (examples **9**, **15**, **18**) the ring closure could only be achieved in polyphosphorous acid. For the synthesis of **14** and **17** the corresponding *N*-(2-phenylethyl)-1-chloroacetamide was cyclized either by means of

Table V. Chemical and Pharmacological Data of N-Substituted Derivatives (Part C)

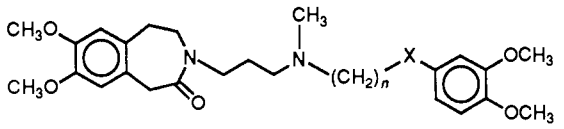


no.	formula	R^5	mp, °C	heart rate in rats % decrease[a] at 5 mg/kg iv
4	Table I	CH_3	Table I	−56 ± 7
22	$C_{25}H_{34}N_2O_5$·HCl	H	153–5	−66
23	$C_{28}H_{38}N_2O_5$·HCl	$CH_2CH{=}CH_2$	153–5	−65
24	$C_{28}H_{40}N_2O_5$·HCl	n-C_3H_7	<90	−56
25	$C_{35}H_{46}N_2O_7$		oil[b]	−28
26	$C_{27}H_{36}N_2O_6$	$COCH_3$	oil	−3
27	$C_{28}H_{38}N_2O_7$	CO_2Et	oil	−8
28	$C_{25}H_{33}NO_5S$		92–3	+1
29	$C_{25}H_{33}NO_6S$		91–4	−4
30	$C_{25}H_{33}NO_7S$		148–50	−1
31	$C_{27}H_{39}IN_2O_5$	$(CH_3)_2$	169–72	−9

[a] See footnote *a* in Table III.

(13) Holden, K. G.; Kaiser, C. EP-A-O. 007-070, 1979.
(14) Berger, J. G.; Chang, W. K.; Peters, M. EP-A-O. 285.919, 1988.

Table VI. Chemical and Pharmacological Data of Side Chain D Derivatives



no.	formula	n	X	mp, °C	heart rate in rats % decrease[a] at 5 mg/kg iv
4	Table I	2		Table I	−56 ± 7
32	$C_{24}H_{32}N_2O_5$	0		122–4	−17
33	$C_{25}H_{34}N_2O_5$	1		87–90	−26
34	$C_{27}H_{38}N_2O_5$·HCl	3		220–1	−55
35	$C_{28}H_{40}N_2O_5$·HCl	4		136–9	−46
36	$C_{29}H_{42}N_2O_5$·HCl	5		165–6	−36
37	$C_{26}H_{37}N_3O_5$	2	-NH-	<40	−39
38	$C_{26}H_{36}N_2O_5S$·HCl	2	-S-	205–10	−44
39	$C_{26}H_{36}N_2O_6$·HCl	2	-O-	213–6	−59
40	$C_{27}H_{39}N_3O_5$	3	-NH-	<40	−51
41	$C_{27}H_{38}N_2O_5S$·HCl	3	-S-	150–4	−47
42	$C_{27}H_{38}N_2O_6$·HCl	3	-O-	179–83	−63
43	$C_{28}H_{40}N_2O_6$·HCl	4	-O-	162–6	−37

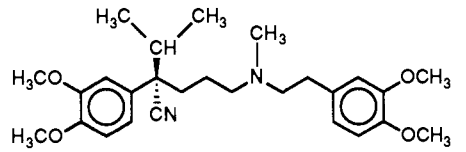
[a] See footnote *a* in Table III.

aluminum chloride or photochemically[15] to give the tetrahydrobenzazepinones. The double bond in the seven-membered ring is an important element for enhancing the reactivity as well as the selectivity of *N*- versus C-alkylation in the alkylation step leading to **4d**. Reaction of **4d** with *N*-methylhomoveratrylamine is usually effected without solvent at elevated temperatures followed by catalytic hydrogenation of the double bond in the seven-membered ring.

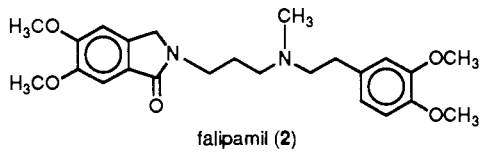
Pharmacological Results and Discussion

Most of the derivatives described in this study were evaluated for bradycardic activity in anesthetized rats. These compounds were tested under identical conditions, that is iv injection of 5 mg/kg to anesthetized rats. To avoid major pharmacokinetic influences, reduction of heart rate for each compound was measured 5 min after application, this being generally found to be the time at which maximum bradycardic activity occurred. Compounds with a slow onset of action leading to maximum activity of 20 min or more after application were therefore excluded from the study. A few derivatives were also tested in anesthetized cats. The in vitro effects of the substances on atrial rate and contractility were evaluated in isolated guinea pig atria. The effects on aortic contraction were studied in isolated aortic strips of rabbits.

The first major breakthrough toward a new lead structure was made by replacement of the α-isopropylacetonitrile moiety of verapamil by an N-substituted phthalimidine ring system. Compound **2**, later known as falipamil, turned out to be the prototype specific bradycardic agent.[16-18] This is reflected by its rather unique biological profile in comparison to verapamil: It reduces heart rate specifically, it is not a β-blocker,[19] it does not interfere with the cardiac conducting system at therapeutic doses,[23,24] and it is not a classical calcium channel blocker.[20-22] The specific bradycardic activity of falipamil and its benefit in myocardial ischemia has been shown in a number of animal models[24-33] and also in human studies.[34-41] En-



verapamil (**1**)



falipamil (**2**)

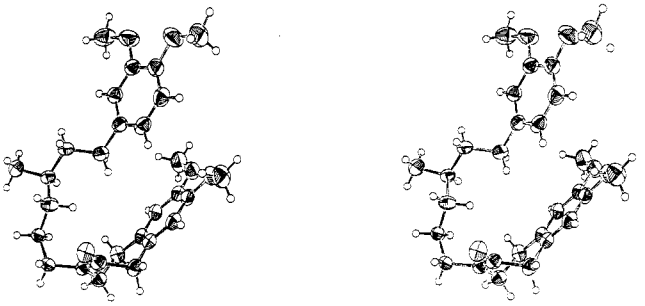


Figure 1. Molecular structure of 4·HCl·4H_2O in the crystal.

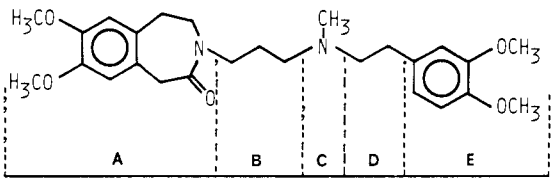


Figure 2. Substructures of 4.

(15) Okuno, Y.; Hemmi, K.; Yonemitsu, O. Chem. Pharm. Bull. **1972**, *20*, 1164.

(16) Eberlein, W.; Kutter, E.; Heider, J.; Austel, V.; Kadatz, R.; Diederen, W.; Kobinger, W.; Lillie, C. DE-A-2509797, 1975.

(17) Kobinger, W.; Lillie, C. *Eur. J. Pharmacol.* **1981**, *72*, 153.

(18) *Drugs Future* **1981**, *6*, 402. Update: *Ibid.* **1982**, *7*, 520; **1983**, *8*, 639; **1984**, *9*, 545; **1985**, *10*, 593; **1986**, *11*, 618; **1987**, *12*, 713.

(19) Lillie, C.; Kobinger, W. *J. Cardiovasc. Pharmacol.* **1983**, *5*, 1048.

(20) Lillie, C.; Kobinger, W. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1984**, *328*, 210.

(21) Lillie, C.; Kobinger, W. *Arch. Pharmacol.* **1987**, *335*, 331.

(22) Lillie, C.; Kobinger, W. *Arch. Pharmacol.* **1987**, *335*, Suppl. R, 55.

(23) Brachmann, J.; Senges, J.; Hammann, H. D.; Anders, G.; Beck, L.; Braun, W.; Kübler, W. *Z. Kardiol.* **1979**, *68*, 635.

(24) Dämmgen, J. W.; Kadatz, R.; Diederen, W. *Arzneim.-Forsch. (Drug Res.)* **1981**, 31/I, 666.

(25) Gross, G. J.; Dämmgen, J. W. *J. Cardiovasc. Pharmacol.* **1987**, *10*, 123.

(26) Trach, V.; Dämmgen, J. W. *J. Mol. Cell. Cardiol.* **1986**, *18*, Suppl. 2, 60.

(27) Diederen, W.; Meel, J. C. A. van *J. Mol. Cell. Cardiol.* **1986**, *18*, Suppl. 2, 46.

(28) Gross, G. J.; Dämmgen, J. W. *J. Pharmacol. Exp. Ther.* **1986**, *238*, 422.

(29) Wenger, H. C.; Siegl, P. K. S. *J. Cardiovasc. Pharmacol.* **1987**, *9*, 246.

(30) Siegl, P. K. S.; Morgan, G. *Can. J. Physiol. Pharmacol.* **1987**, *65*, 146.

(31) Wenger, H. C.; Siegl, P. K. S. *J. Clin. Pharmacol.* **1985**, *25*, 466.

(32) Siegl, P. K. S.; Wenger, H. C.; Sweet, C. S. *J. Cardiovasc. Pharmacol.* **1984**, *6*, 565.

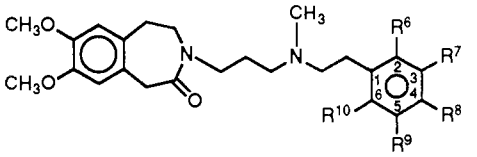
(33) Bush, L. R.; Sweet, C. S. *Clin. Res.* **1984**, *32*, 668A.

(34) Lēvy, S.; Mētge, M.; Hilaire, J.; Cointe, R.; Bru, P.; Eychenne, J. L.; Grerard, R. *Eur. Heart J.* **1987**, *8*, 1236.

(35) Tryba, M.; Zenz, M. *Arzneim.-Forsch. (Drug Res.)* **1987**, *37*, 1298.

(36) Jost, S.; Schulz, W.; Kober, G. *Arzneim.-Forsch. (Drug Res.)* **1985**, *35* (II), 1279.

Table VII. Chemical and Pharmacological Data of Phenyl Ring E Derivatives



no.	formula	R_6	R_7	R_8	R_9	R_{10}	mp, °C	heart rate in rats % decrease[a] at 5 mg/kg iv
4	Table I	H	OCH_3	OCH_3	H	H	Table I	−56 ± 7
44	$C_{24}H_{32}N_2O_3 \cdot 2HCl$	H	H	H	H	H	>165	−52
45	$C_{25}H_{34}N_2O_4 \cdot HCl$	H	H	OCH_3	H	H	175–7	−42
46	$C_{26}H_{37}N_3O_3 \cdot 2HCl$	H	H	$N(CH_3)_2$	H	H	193–6	−60
47	$C_{24}H_{31}N_2O_3Cl \cdot 2HCl$	H	H	Cl	H	H	148–51	−55
48	$C_{25}H_{34}N_2O_6S \cdot HCl$	H	H	OSO_2CH_3	H	H	173–6	−46
49	$C_{24}H_{31}N_3O_5 \cdot HCl$	H	H	NO_2	H	H	180–2	−41
50	$C_{24}H_{32}N_2O_4 \cdot HCl$	H	H	OH	H	H	109–12	−33
51	$C_{24}H_{33}N_3O_3$	H	H	NH_2	H	H	>40	−30
52	$C_{28}H_{40}N_2O_4$	H	H	OC_4H_9	H	H	67–9	−55
53	$C_{28}H_{40}N_2O_3 \cdot 2HCl$	H	H	t-C_4H_9	H	H	146–9	−58
54	$C_{31}H_{38}N_2O_4$	H	H	OCH_2Ph	H	H	100–2	−27
55	$C_{27}H_{38}N_2O_6 \cdot HCl$	H	OCH_3	OCH_3	OCH_3	H	153–5	−21
56	$C_{27}H_{38}N_2O_6 \cdot HCl$	OCH_3	H	OCH_3	H	OCH_3	65–70	−25
57	$C_{24}H_{30}N_2O_3Cl_2 \cdot 2HCl$	H	Cl	Cl	H	H	160–1	−47
58	$C_{24}H_{30}N_2O_3Cl_2 \cdot 2HCl$	Cl	H	H	H	Cl	145–7	−13

[a] See footnote *a* in Table III.

couraged by these results we tried to find compounds with a falipamil-like profile but with improved bradycardic potency as well as a more favorable kinetic profile, i.e. longer duration of action.

Among numerous structural modifications of the phthalimidine moiety, manipulation of the ring size turned out to be most suitable to obtain the desired overall pharmacological profile. According to Table I, there is a clear-cut increase of activity going from falipamil to the six-membered ring derivative **3**.[42–46] However, a further ring expansion to the seven-membered ring homologue **5** did not result in a concomitant increase in bradycardic activity. Surprisingly, however, the slightly modified symmetrical benzazepinon derivative **4** (UL-FS 49) turned out to be the most active compound among all the falipamil derivatives.[47] In addition to its high potency, which could be demonstrated in numerous animal models, **4** shows the highest degree of selectivity for heart-rate reduction with only minor influence on blood pressure and cardiac contractility.[48–53] Both potency and selectivity are most clearly demonstrated in in vitro experiments.[48] In isolated guinea pig atria (Table II), compound **4** is about 20 times as potent as a bradycardic agent than falipamil (EC_{30} atrial rate) and also exhibits a much higher degree of selectivity, as shown by the high ratios of EC_{30} values between atrial contractility, aortic contraction, and atrial rate, when compared with the standard reference compounds.

Conformational Aspects. Due to the long aliphatic chain connecting the benzazepinone system A with the aromatic moiety E (Figure 2), compounds of this type are expected to show a high degree of conformational flexibility. Surprisingly, however, semiempirical quantum mechanics (using the QCPE program PCILO[54]) as well as molecular mechanics calculations (using the QCPE program ECEPP[55]) with compound **4** have resulted in folded structures as the lowest energy conformations.[56]

In accordance with these theoretical calculations, compound **4** also adopts a rather unexpected U-shaped geometry in the crystalline state. X-ray analysis of the protonated orthorhombic tetrahydrate revealed that both phenyl rings are located in close proximity to each other with a distance of only about 3.5 Å (Figure 1).[57] A very similar U-shaped conformation has been found for the monoclinic water-free form (data not shown). This is in sharp contrast to falipamil, which has been shown to adopt an extended conformation in the crystalline state.[58] Thus, in terms of its conformational properties, benzazepinone

(37) Herzog, H.; Simon, H. *Herz-Kreislauf* **1983**, *7*, 354.
(38) Gülker, H. *Eur. Heart J.* **1987**, *8*, (Suppl. L), 141.
(39) Gilgrich, H. J.; Oberhoffer, M.; Witzke, J. *Eur. Heart J.* **1987**, *8*, (Suppl. L), 147.
(40) Hack, G.; Murday, H.; Mück, R.; Orellano, L.; Simon, H. J.; Börschsupan, I. *Thorac. Cardiovasc. Surg.* **1983**, *31* (I), 10.
(41) Hilaire, J.; Broustet, J. P.; Colle, J. P.; Theron, M. *Br. J. Clin. Pharmacol.* **1983**, *16*, 627.
(42) Eberlein, W.; Heider, J.; Austel, V.; Dämmgen, J. W.; Kadatz, R. DE-A-26 39 718, 1976.
(43) Gross, G. J.; Warltier, D. C.; Dämmgen, J. W. *J. Cardiovasc. Pharmacol.* **1985**, *7*, 929.
(44) Dämmgen, J. W.; Gross, G. J. *J. Cardiovasc. Pharmacol.* **1985**, *7*, 1048.
(45) Gross, G. J.; Dämmgen, J. W. *Eur. Heart J.* **1987**, *8* (Suppl. L), 69.
(46) Eberlein, W.; Austel, V.; Heider, J.; Dämmgen, J. W.; Kadatz, R.; Lillie, C.; Kobinger, W. DE-A-26 39 291, 1976.
(47) Reiffen, M.; Heider, J.; Hauel, N.; Austel, V.; Eberlein, W.; Kobinger, W.; Lillie, C.; Noll, K.; Pieper, H.; Krüger, G.; Keck, J. EP-A-0.065.229, 1982.
(48) Kobinger, W.; Lillie, C. *Eur. J. Pharmacol.* **1984**, *104*, 9.
(49) Krumpl, G.; Winkler, M.; Schneider, W.; Raberger, G. *Br. J. Pharmacol.* **1988**, *94*, 55.
(50) Lillie, C.; Kobinger, W. *J. Cardiovasc. Pharmacol.* **1986**, *8*, 791.
(51) Lillie, C.; Kobinger, W. *Naunyn-Schmiedebergs Arch. Pharmacol.* **1983**, *129*, Suppl. 324, R 33.
(52) *Drugs Future* **1985**, *10*, 639–641. Update: *Ibid.* **1986**, *11*, 718; **1987**, *12*, 825; **1988**, *13*, 804.
(53) Riley, D. C.; Gross, G. J.; Kampine, J. P.; Warltier, D. C. *Anesthesiology* **1987**, *67* (5), 707.
(54) Claverie, P.; et al. QCPE program PCILO, No. 220, 1971.
(55) Browman, M. J.; et al., resubmitted by Sheraga, H. A. QCPE-program ECEPP, No. 454, 1982.
(56) Müller, P. Dissertation, University of Ulm, 1986, FRG.
(57) Müller, P.; Reiffen, M.; Luger, P.; Prox, A. *Acta Crystallogr.* **1987**, AS *43*, C-49.
(58) Luger, P. Freie Universität Berlin, Inst. für Kristallographie, 1986.

derivative 4 constitutes a novel and rather unique type of structure, possibly reflecting its particular pharmacological properties.

Structure–Activity Relationships of Benzazepinone Derivatives. In the following section a more detailed discussion of the structure–activity relationships in a series of benzazepinone derivatives is presented.[59-61] In this respect the contribution and significance of certain substructures of 4 in relation to the overall bradycardic activity, as indicated in Figure 2, has been evaluated. However, it should be noted that the characteristic seven-membered ring lactam with its special stereochemical features was retained in all these derivatives.

In a first set of compounds, the influence of the aryl substituents R^1–R^4 on the biological activity was studied, as shown in Table III. In this respect, electron-donating groups, with special emphasis on their substitution pattern, were the main subject of investigation. Replacement of both of the methoxy groups of 4 by a methylenedioxy or an ethylenedioxy moiety (compounds 6 and 7) or by alkyl substituents (compound 8) is well-tolerated without any major decline in bradycardic activity. The introduction of the polar catechol function (compound 9), however, results in a significantly lower activity. On the other hand, removal of only one of the methoxy groups has a different influence on activity, depending on whether the R^2 or the R^3 substituent is replaced. Thus, replacement of the methoxy group in the R^2 position by a hydroxy group or a hydrogen atom (compounds 10 and 11) has no major effect on activity, whereas substitution of the R^3 methoxy group by either a hydroxy group or a hydrogen atom (compounds 12 and 13) results in a significantly lower potency. These results indicate a different contribution of the two methoxy groups in the overall bradycardic activity. a Shift of the R^2 and R^3 methoxy groups into the R^1 or R^4 positions (compounds 14 and 15) strongly reduces the activity to a level which is comparable to that of the unsubstituted benzazepinone derivative 16, indicating a strong correlation between the substitution pattern and the bradycardic effect.

On the other hand, the highly substituted tetramethyl derivative 17 is almost as potent as dimethyl compound 8, indicating that the dependence on the substitution pattern is not due to sterical restrictions in the R^1 and R^4 position. Thus, these results indicate that high bradycardic potency depends strongly on the presence of electron-donating substituents in the R^3 or in the R^2 and R^3 position. All other substitution patterns investigated so far are less favorable for activity.

The side chain B was modified in two respects: introduction of substituents and variation of the chain length. As one can see from Table IV, introduction of an alkyl or hydroxyl group (compounds 18 and 19) to the middle carbon atom of the C_3-chain significantly reduces the bradycardic activity. On the other hand, shortening or extension of the alkyl chain to two or four carbon atoms (compounds 20 and 21, respectively) leads to a significant decline in bradycardic activity. In addition, the latter derivatives only have a short duration of action. Thus, an unsubstituted C_3-alkyl chain connecting the benzazepinone ring and the *N*-methyl group is optimal for bradycardic activity. Obviously, very small changes in this domain result in an unfavorable sterical orientation of the other parts of the molecule thus leading to a sharp decline of the overall activity.

The effects of substituents on the central nitrogen atom are shown in Table V. N-Demethylated compound 22, which as been shown to be one of the metabolites of compound 4 in a number of animal species,[62] as well as the *N*-allyl derivative (compound 23) are slightly more active than *N*-methyl compound 4. *N*-propyl compound 24 is equally active, whereas larger substituents such as aralkyl (compound 25) are not well-tolerated in this position. Acylation of the nitrogen atom (compounds 26 and 27) leads to a complete loss of activity. This result can be best interpreted on the basis that a basic nitrogen atom is an essential prerequisite for the interaction with the receptor. This hypothesis is further supported by the inactivity of sulfur derivatives 28–30, which lack the basic nitrogen atom. On the other hand, the permanently charged quaternary compound 31 is also devoid of activity, which can be rationalized on the basis of an inability to reach the possible intracellular site of action.[63-65] In summary, a basic nitrogen atom bearing a hydrogen or small, nonpolar, alkyl substituents is most favorable for bradycardic activity.

The alkyl chain D was investigated mainly in two respects: the influence of chain length and/or insertion of various heteroatoms into this chain. According to Table VI shortening of the alkyl chain to $n = 0$ or $n = 1$ (compounds 32 and 33) drastically reduces the bradycardic activity, probably because of the inability of the dimethoxyphenyl ring to reach its proper binding position at the receptor site. On the other hand, chain extension of up to five carbon atoms is well-tolerated, giving maximum activity at $n = 3$ (compound 34). An almost identical relation between activity and chain length is seen when heteroatoms such as nitrogen, sulfur, or oxygen are inserted into the α-position of the aromatic ring. In this series the nitrogen and sulfur derivatives are in the same potency range as the carbon analogues (compounds 34, 37, 38; 35, 40, 41) whereas phenol ethers 39 and 42 are somewhat more active than the corresponding all-carbon derivatives 34 and 35. Thus, a chain length of three or four gives rise to the most potent compounds, due to the ability to bring the dimethoxyphenyl moiety E into an optimal position for receptor interaction. Obviously, an overextension, beyond an optimum length (compounds 36 and 43), is unfavorable because of the increase in entropy. The importance of an appropriate folding of the connecting chain is further supported by the sharp decline in bradycardic activity of various cyclic derivatives which cannot adopt the "active conformation" because of their greater rigidity.[66] The insertion of oxygen atoms in combination with the "correct" chain length gives rise to the most potent derivatives obtained sor far (compounds 39 and 42).

In order to elucidate the structural prerequisites of the aromatic moiety E, the substituents R^6–R^{10} were varied mainly in terms of electronic properties, size, and substitution pattern, as indicated in Table VII. In a series of derivatives bearing 4-substituents with a wide range of electronic properties it could be shown that there is only a slight decline in activity when going from electron-do-

(59) Reiffen, M.; Heider, J.; Austel, V.; Hauel, N.; Kobinger, W.; Lillie, C. Ep-A-O.109 636, 1983.
(60) Reiffen, M.; Noll, K.; Heider, J.; Austel, V.; Hauel, N.; Kobinger, W.; Lillie, C. EP-A-O.161 599, 1985.
(61) Reiffen, M. 189th ACS National Meeting, Miami Beach, Florida, 1985.
(62) Roth, W., Dr. K. Thomae GmbH, unpublished results.
(63) Bogaert, P. P. van; Goethals, M. *Pfluegers Arch.* **1988**, *06*, 412.
(64) Bogaert, P. P. van; Goethals, M. International workshop at the Ernst-Boehringer-Institut Bender u. Co., 1986, 1.
(65) Bogaert, P. P. van; Goethals, M. *Eur. Heart J.* **1987**, *8*, 35.
(66) Psiorz, M.; Lillie, C.; Reiffen, M. IXth International Symposium on Medicinal Chemistry, Berlin (West), 1986.

nating functionality such as methoxy or dimethylamino (compounds **45** and **46**) through the unsubstituted compound **44** to electron-withdrawing groups such as chlorine, (methylsulfonyl)oxy or nitro (compounds **47**, **48**, and **49**). Only the polar hydroxy and amino derivaties (compounds **50** and **51**) show considerably lower activity. The size of substituents in the 4-position also has no major impact on bradycardic potency as indicated by the almost identical activity of the unsubstituted, *n*-butoxy, and even *tert*-butyl derivatives (compounds **44**, **52**, and **53**). There is, however, a bulk-tolerance limit in this region as demonstrated by the significantly lower activity of 4-benzyloxy compound **54**. In contrast to the great variability in the series of 4-substituted derivatives, the substitution pattern of higher functionalized derivatives is critical for bradycardic activity. Thus, the 4-methoxy and 3,4-dimethoxy derivatives (compounds **45** and **4**) are highly active, whereas the 3,4,5- or 2,4,6-trimethoxy congeners (compounds **55** and **56**) show only borderline activity. A similar difference in activity is seen bwtween the 3,4- and 2,6-dichloro derivatives (compounds **57** and **58**). In general, however, the activity is much less sensitive to change in this portion of the molecule than in the aromatic ring A. This result is important and suggests that future elaboration of analogues of **4** need not to be limited to specially substituted aromatic rings but might be extended to other systems such as aromatic heterocycles.

Summarizing the results, we can conclude that in the case of **4** activity is preferentially brought about by the benzazepinone system by, the protonated nitrogen atom of the side chain, as well as by the dimethoxyphenyl ring. These groups have to fulfill rather specific three-dimensional requirements in order to maintain a proper conformation for receptor interaction. The bradycardic activity is very sensitive to structural modifications in the benzazepinone ring. The same holds true for the three-carbon alkyl chain and the basic nitrogen atom, which is mandatory for biological activity. On the other hand, the aralkyl moiety exhibits sufficient variability for further structural manipulations. Due to its exceptional pharmacological profile, **4** has been selected for development as a second-generation specific bradycardic agent for the treatment of ischemic heart disease.[67-73] It is currently undergoing clinical trials.[74]

Experimental Section

Chemistry. Melting points were determined in open glass capillaries with a Büchi melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained on a Perkin-Elmer Model 298 spectrophotometer. Nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Bruker AM-400 with tetramethylsilane as internal standard. Mass spectra were measured on a MAT-CH5 mass spectrometer. Microanalyses were conducted by the Thomae Research Microanalysis Laboratory, Biberach, West Germany. Silica gel (Silica Woelm 32–63 μm) was used for chromatography.

2,3-Dihydro-5,6-dimethoxy-2-[3-[*N*-(3,4-dimethoxyphenethyl-2)methylamino]propyl]-1*H*-isoindolone Hydrochloride (Falipamil) (2·HCl). *N*-Methyl-*N*-(3,4-dimethoxyphenethyl-2)propylamine (**2b**), 126 g, 0.5 mol) was added at room temperature to a solution of 4,5-dimethoxyphthalic anhydride (**2a**), 104 g, 0.5 mol) in 1200 mL of glacial acetic acid. The mixture was then heated under reflux for 8 h. After cooling down to room temperature, zinc powder (100 g, 1.5 mol) was added in small portions (**caution**: evolution of foam upon addition of zinc powder to the reaction mixture). After completion of the addition, the mixture was heated under reflux for another 2 h. Unreacted zinc powder was removed by simple filtration and the solvent was evaporated in vacuo. The resulting residue was dissolved in water and extracted with ethyl acetate to remove neutral byproducts. The aqueous solution was then made alkaline by addition of 2 N NaOH and extracted with chloroform. The organic layer was separated, washed with water, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was dissolved in acetone and the hydrochloride was precipitated by careful addition of ethereal HCl. The precipitate was isolated by suction through a Büchner funnel to yield 75 g (32%) of **2** · HCl: mp 170–172 °C; IR (CH_2Cl_2) 2960, 2840, 2300 (br), 1680, 1620, 1518, 1502, 1465, 1307, 1222, 1028 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 12.40 (br s, 1 H, NH^+), 7.24 (s, 1 H), 6.95 (s, 1 H), 6.76 (m, 3 H), 4.44 (br d, 2 H), 3.94 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 3.71 (m, 2 H), 3.18 (m, 6 H), 2.84 (d, 3 H, NCH_3), 2.38 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 169.37 (s), 152.67 (s), 149.57 (s), 149.14 (s), 148.11 (s), 134.96 (s), 128.01 (s), 123.95 (s), 120.46 (d), 111.82 (d), 111.45 (d), 105.14 (d), 104.94 (d), 57.55 (t), 56.07 (q), 56.00 (q), 55.84 (q), 55.73 (q), 53.89 (t), 49.64 (t), 39.81 (q), 39.36 (t), 29.67 (t), 23.67 (t); mass spectrum, *m*/*z* (relative intensity) 428 (M^+, 3), 277 (100), 234 (70), 206 (28), 151 (14), 84 (23), 58 (70).

2-(3-Chloropropyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisochinolinone (3b). Potassium *tert*-butoxide (61.7 g, 0.55 mol) was added at room temperature to a solution of 6,7-dimethoxy-1,2,3,4-tetrahydroisochinolinone (**3a**, 103 g, 0.5 mol) in 720 mL of DMF. After 1 h of stirring, the mixture was cooled to 15 °C. The suspension was sucked through a Büchner funnel and the wet, solid residue was added to 500 mL of 1-bromo-3-chloropropane within 10 min under vigorous stirring during which time the temperature rose to 60–65 °C. After completion of the addition, the reaction mixture was stirred for 1 h at room temperature and then poured onto ice water. The organic layer was separated, washed with water, dried over Na_2SO_4, and evaporated in vacuo. The residue was crystallized from acetone to yield 92 g (65%) of **3b**: mp 92–95 °C (ethyl acetate); IR (CH_2Cl_2) 2940, 2840, 1645, 1605, 1510, 1483, 1341, 1212, 1100, 1018 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.58 (s, 14), 6.65 (s, 1 H), 3.92 (s, 6 H), 3.69 (t, 2 H), 3.65 (t, 2 H), 3.60 (t, 2 H), 2.95 (t, 2 H), 2.16 (p), 2 H); ^{13}C NMR ($CDCl_3$) δ 164.50 (s), 151.67 (s), 147.85 (s), 131.47 (s), 121.75 (s), 110.28 (d), 109.15 (d), 55.85 (q), 49.96 (t), 45.25 (t), 42.42 (t), 30.79 (t), 27.65 (t); mass spectrum, *m*/*z* (relative intensity) 283/285 (M^+, 39/13) 248 (100), 220 (50), 150 (18).

6,7-Dimethoxy-2-[3-[*N*-(3,4-dimethoxyphenethyl-2)-methylamino]propyl]-1,2,3,4-tetrahydroisochinolinone (3). *N*-methyl-2-(3,4-dimethoxyphenyl)ethylamine (129 g, 0.66 mol) was added within 10 min to a solution of **3b** (70 g, 0.25 mol) in 300 mL of acetone and the mixture was then heated under reflux for 2 h. The mixture was cooled in an ice bath to crystallize the hydrochloride of the unreacted *N*-methyl-2-(3,4-dimethoxyphenyl)ethylamine. This hydrochloride was removed by filtration and the filtrate was evaporated in vacuo. The residue was dissolved in diluted hydrochloric acid, extracted with toluene, then made alkaline by addition of concentrated ammonia, and extracted with chloroform. The chloroform solution was washed several times with 3% acetic acid to remove starting amine and was evaporated in vacuo. The residue was dissolved in acetone and the hydrochloride was precipitated by carefully adding ethereal HCl. The precipitate was isolated by suction through a Büchner funnel to yield 73 g (62%) of **3**·HCl: mp 178–179 °C; IR (CH_2Cl_2) 2960, 2840, 2300 (br), 1645, 1608, 1516, 1485, 1342, 1240, 1027 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 12.35 (br s, 1 H, NH^+), 7.51 (s, 1 H), 6.77 (m, 3 H), 6.66 (s, 1 H), 3.91 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 3.86

(67) Dämmgen, J. W.; Lamping; K. A.; Gross, G. J. *J. Cardiovasc. Pharmacol.* **1985**, *7*, 71.
(68) Guth, B. D.; Heusch, G.; Seitelberger, R.; Matsuzaki, M.; Ross, J. *Eur. Heart J.* **1987**, 8 (Suppl. L), 61.
(69) Guth, B. D.; Heusch, G.; Seitelberger, R.; Ross, J. *Circulation* **1987**, *75* (3), 661.
(70) Krumpl, G.; Schneider, W.; Raberger, G. *Naunyn-Schmiedebergs Arch. Pharmacol.* **1986**, *334*, 540.
(71) Krumpl, G.; Schneider, W.; Mayer, N.; Raberger, G. *Z. Kardiol.* **1986**, *75* (Suppl. 1), Abstr. P124.
(72) Krumpl, G.; Mayer, N.; Beck, A. *Naunyn-Schmiedebergs Arch. Pharmacol.* **1986**, *219*, 332.
(73) Raberger, G.; Krumpl, G.; Schneider, W. *Int. J. Cardiol.* **1987**, 14, 343.
(74) Franke, H.; Su, C. A. P. F.; Schumacher, K.; Seiberling, M. *Eur. Heart J.* **1987**, 8 (Suppl. L), 91.

(s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.65 (m, 4 H), 3.20 (m, 6 H), 2.98 (m, 2 H), 2.86 (d, 3 H, NCH_3), 2.31 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 164.83 (s), 151.78 (s), 148.97 (s), 147.93 (s), 147.66 (s), 131.76 (s), 127.99 (s), 120.96 (s), 120.36 (d), 111.73 (d), 111.31 (d), 109.98 (d), 109.21 (d), 57.26 (t), 55.73 (q), 55.71 (q), 55.71 (q), 55.59 (q), 53.90 (t), 46.05 (t), 43.99 (t), 39.65 (q), 29.59 (t), 27.37 (t), 22.91 (t); mass spectrum, m/z (relative intensity) 442 (M^+, 2), 291 (100), 248 (60), 246 (38), 220 (14), 151 (9), 58 (23).

***N*-(2,2-Dimethoxyethyl)-3,4-dimethoxyphenylacetamide (4b).** Thionyl chloride (60 mL, 0.82 mol) was added over a period of 30 min at room temperature to a suspension of 3,4-dimethoxyphenylacetic acid (54.9 g, 0.28 mol) in 60 mL of dichloromethane. The mixture was heated under reflux for 1 h, evaporated, and distilled at 125–130 °C (1 Torr) to yield 48.5 g (81%) of the corresponding acid chloride. This was added as a solution in 110 mL of dichloromethane to a solution of aminoacetaldehyde dimethyl acetal (23.7 g, 0.23 mol) and triethylamine (22.9 g, 0.23 mol) in 220 mL of dichloromethane under permanent cooling so that the temperature did not exceed 10–15 °C. After 1 h for stirring at room temperature, the mixture was extracted with water and evaporated in vacuo to yield 60.8 g (96%) of **4b**: mp 67–69 °C; IR (CH_2Cl_2) 3430, 2940, 2835, 1670, 1510, 1460, 1230, 1130, 1022 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.78 (m, 3 H), 5.71 (br s, 1 H), 4.31 (t, 1 H), 3.87 (s, 6 H), 3.50 (s, 2 H), 3.36 (d, 2 H), 3.30 (s, 6 H).

7,8-Dimethoxy-1,3-dihydro-2*H*-benzazepin-2-one (4c). Glacial acetic acid (300 mL) was added to a solution of **4b** (60 g, 0.21 mol) in 300 mL of concentrated hydrochloric acid and the reaction mixture was kept at room temperature for 17 h. When the mixture was poured on 1 kg of crushed ice, the product precipitated and was filtered off. After drying at 70 °C, 35.0 g (75%) of **4c** were obtained: mp 235–237 °C; IR (KBr) 3180, 3065, 2930, 2840, 1668, 1633, 1515, 1359, 1270, 1118, 1065 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.43 (d, 1 H, NA), 6.88 (s, 1 H), 6.85 (s, 1 H), 6.27 (d, 1 H) 6.19 (dd, 1 H), 3.78 (s, 3 H), 3.75 (s, 3 H), 3.30 (s, 2 H); ^{13}C NMR (DMSO-d_6) δ 168.61 (s), 149.10 (s), 147.57 (s), 127.13 (s), 124.16 (d), 123.35 (s), 114.27 (d), 112.00 (d), 110.28 (d), 55.57 (q), 55.53 (q), 42.57 (t); mass spectrum, m/z (relative intensity) 219 (M^+, 100), 176 (28), 133 (18).

7,8-Dimethoxy-3-(3-chloropropyl)-1,3-dihydro-2*H*-3-benzazepin-2-one (4d). Potassium *tert*-butoxide (20.2 g, 0.18 mol) was added to a suspension of **4c** (32.9 g, 0.15 mol) in 220 mL of dimethyl sulfoxide. After stirring at room temperature for 30 min, this mixture was slowly added to a solution of 1-bromo-3-chloropropane (19 mL, 0.18 mol) in 75 mL of dimethyl sulfoxide within 20 min. After 30 min at room temperature, the reaction mixture was poured on 1 L of iced water. When the product had crystallized completely, it was isolated by filtration and recrystallized from acetone/water (1:6) to yield 38.9 g (87%) of **4d**: mp 101–103 °C; IR (CH_2Cl_2) 2940, 2840, 1660, 1610, 1510, 1402, 1235, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.80 (s, 1 H), 6.75 (s, 1 H), 6.45 (d, 1 H), 6.23 (d, 1 H), 3.91 (s, 3 H) 3.89 (s, 3 H), 3.72 (t, 2 H), 3.45 (s, 2 H), 3.45 (t, 2 H), 2.00 (p, 2 H); ^{13}C NMR ($CDCl_3$) δ 167.57 (s), 149.88 (s), 148.00 (s), 128.41 (d), 126.15 (s), 124.61 (s), 116.94 (d), 111.16 (d), 109.49 (d), 55.86 (q), 55.84 (q), 45.62 (t), 43.04 (t), 42.04 (t), 31.31 (t); mass spectrum, m/z (relative intensity) 295/297 (M^+, 100/32), 260 (25), 192 (31), 177 (33), 161 (33).

7,8-Dimethoxy-3-[3-[[2-(3,4-dimethoxyphenyl)ethyl]-methylamino]propyl]-1,3,4,5-tetrahydro-2*H*-benzazepin-2-one Hydrochloride (UL-FS 49) (4·HCl). Compound **4d** (35.5 g, 0.12 mol) was mixed with *N*-methyl-2-(3,4-dimethoxyphenyl)ethylamine (70.3 g, 0.36 mol) and heated to 90–95 °C for 2 h. After cooling to room temperature, 140 mL of water and 400 mL of ethyl acetate were added to the solidified mixture and stirred vigourously for 1 h. The organic layer was separated and washed several times with 3% acetic acid to remove the starting amine. The solvent was removed under reduced pressure. The resulting residue was dissolved in 400 mL of acetic acid and hydrogenated over 2 g of palladium/charcoal under a pressure of 5 bar at room temperature for 10 h. The catalyst was filtered off, and the solution was evaporated in vacuo. The residue was dissolved in 400 mL of dichloromethane and washed with potassium carbonate solution. The organic layer was dried over magnesium sulfate and evaporated. The residue was dissolved in acetone and the hydrochloride was precipitated by addition of ethereal hydrochloric acid to give 52.7 g (89%) of 4·HCl: mp 188 °C/168 °C (the hydrochloride crystallizes in two forms); IR (CH_2Cl_2) 2940, 2840, 2300 (br), 1652, 1610, 1518, 1460, 1222, 1102 cm^{-1}; ^1H NMR (CD_3OD) 6.91 (d, 1 H), 6.88 (d, 1 H), 6.79 (dd, 1 H), 6.72 (s, 1 H), 6.67 (s, 1 H), 3.87 (t, 2 H), 3.86 (s, 1 H), 3.83 (s, 3 H), 3.79 (s, 3 H), 3.77 (s, 3 H), 3.75 (s, 3 H), 3.52 (t, 2 H), 3.30 (t, 2 H), 3.10 (t, 2 H), 3.09 (t, 2 H), 2.90 (s, 3 H), 2.89 (t, 2 H), 2.06 (p, 2 H); ^{13}C NMR (CD_3OD) 173.03 (s), 149.27 (s), 148.23 (s), 148.03 (s), 147.18 (s), 128.08 (s), 127.34 (s), 122.91 (s), 120.53 (d), 113.78 (d), 113.50 (d), 111.87 (d), 111.54 (d), 57.83 (t), 55.95 (q), 55.85 (q), 55.85 (q), 55.81 (q), 53, 77 (t), 46.76 (t), 43.85 (t), 42.29 (t), 40.15 (q), 32.05 (t), 29.72 (t), 23.85 (t); mass spectrum, m/z (relative intensity) 456 (M^+, 5), 305 (100), 262 (77), 206 (19), 151 (13), 58 (27).

According to the synthesis of 4 starting from **4a** the benzazepinones in Tables III–VII were synthesized. Deviations from this synthetic sequence were carried out by using procedures described in the literature, as mentioned above.

Pharmacology. Experiments with Anesthetized Rats.[7] 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 artificial respiration was performed. The heart rate was recorded continuously on an ink-writing polygraph by means of an instantaneous beat to beat recording tachograph triggered by the electrocardiogram (ECG). Test substances were injected via the jugular vein. The heart rate was evaluated 2, 5, and 20 min after injection of the test substance.

Experiments in anesthetized cats were performed as described earlier.[17]

Experiments with Isolated Guinea Pig Atria.[48] 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 an 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 Isolated Aortic Strips of the Rabbit.[48] Addition of 40 mM KCl and 1.8 mM $CaCl_2$ increased the tension of isolated aortic strips from a resting value of 1.5 g to 2.03 ± 0.136 g (n = 74), whereby a plateau was reached after 30–45 min. Addition of the drug decreased the tension in a concentration-dependent manner. From the concentration–response curve the concentration was calculated which relaxed the contracture by 30%.

Single-Crystal X-ray Analysis.[57] Crystals of 4·HCl·$4H_2O$ were grown from a warm 2-propanol solution. Precise lattice parameters (from 28 high-order reflections) and three dimensional intensity data were measured on a stoe-diffractometer using Ni-filtered CuKα radiation (λ = 1.5418 Å). A single crystal with dimensions 0.35 × 0.40 × 0.45 mm was used to collect the intensity data of 3884 reflections ($\theta \leq 64°$; h, k, l all $\geq \theta$) by using the $\omega - 2\theta$ scan technique. An intensity decrease of less than 10% at the end of the measurement, monitored via two check reflections, was rescaled. A total of 542 reflections with $I < 2\sigma(I)$ were considered unobserved. The intensity data set was corrected for Lorentz and polarization effects and for the anomalous dispersion of chlorine, but not for absorption.

Crystal Data.[57] Molecular formula $C_{26}H_{36}N_2O_5 \cdot HCl \cdot 4H_2O$ (M_r = 565.1), space group *Pbca*, unit cell a = 40.364 (4) Å, b = 8.405 (1) Å, c = 17.779 (2) Å, orthorhombic, Z = 8, δ_x = 1.245 g cm^{-3}, δ_{exp} = 1.24 g cm^{-3}, μ(CuKα) = 15.55 cm^{-1}, V = 6031.7 $Å^3$. Phase determination was made with direct methods (program MULTAN,[75] version 1977) refinement with the corresponding least-squares

(75) Main, P.; Lessinger, L.; Woolfson, M. M.; Germain, G.; Declerq, J.-P. *MULTAN 77, a system of computer programs for the automatic solution of crystal structures from X-ray diffraction data*; Universities of York, England, and Louvain, Belgium, 1977.

programs of the XRAY76 program system.[76] All hydrogens were located from difference syntheses. After convergence R values of $R = 4.2\%$ and $R_w = 5.6\%$ were obtained. A weighting scheme was used that made $w\Delta F$ almost independent from F and sin θ. No significant peaks or holes were seen in final difference Fourier map.

Acknowledgment. We thank Sigwart Bombe, Wolfgang Fuchs, Herbert Fischbach, Günther Baisch, Horst Schweizer, and Inge Woblistin for their able technical assistance, and we are grateful to Prof. Axel Prox and his staff for the analytical and spectral data.

Registry No. **1**, 52-53-9; **2**, 60987-07-7; **2** free base, 77862-92-1; **2a**, 4821-94-7; **2b**, 55982-99-5; **3**, 66510-56-3; **3** free base, 95092-22-1; **3a**, 493-49-2; **3b**, 66510-55-2; **4**, 91940-87-3; 4 free base, 85175-67-3; **4**·HCl·4H_2O, 125846-52-8; **4a**, 93-40-3; **4b**, 73954-34-4; **4c**, 73942-87-7; **4d**, 85175-59-3; **5**, 95092-29-8; **6**, 85175-74-2; **6** free base, 96254-81-8; **7**, 125846-53-9; **7** free base, 125846-54-0; **8**, 85176-65-4; **8** free base, 96255-00-4; **9**, 85176-71-2; **10**, 85176-75-6; **10** free base, 96254-98-7; **11**, 85175-83-3; 11 free base, 96254-82-9; **12**, 85176-76-7; **13**, 125877-11-4; **13** free base, 125846-55-1; 14, 85176-93-8; 14 free base, 96255-02-6; **15**, 85176-96-1; **15** free base, 96255-04-8; **16**, 92460-20-3; **16** free base, 92460-21-4; **17**, 125846-56-2; **17** free base, 125846-57-3; **18**, 85176-89-2; **19**, 96255-01-5; **20**, 85176-51-8; **20** free base, 85176-63-2; **21**, 96254-96-5; **21** free base, 85176-27-8; **22**, 96254-88-5; **22** free base, 85176-31-4; **23**, 85175-76-4; **23** free base, 85176-33-6; **24**, 96254-90-9; **24** free base, 85176-34-7; **25**, 96254-91-0; **26**, 125846-58-4; **27**, 85176-56-3; **28**, 85176-57-4; **29**, 125846-59-5; **30**, 125846-60-8; **31**, 125846-61-9; **32**, 125846-62-0; **33**, 125846-63-1; **34**, 125846-64-2; **34** free base, 92460-18-9; **35**, 91940-90-8; **35** free base, 125846-65-3; **36**, 125846-66-4; **36** free base, 92460-25-8; **37**, 96255-12-8; **38**, 102247-08-5; **38** free base, 125846-67-5; **39**, 102226-78-8; **39** free base, 102247-13-2; **40**, 102247-16-5; **41**, 102247-09-6; 41 free base, 102247-17-6; **42**, 102226-88-0; **42** free base, 102246-76-4; **43**, 125846-68-6; **43** free base, 102246-78-6; 44, 125846-69-7; **44**, 92452-46-5; **45**, 92452-47-6; **45** free base, 85175-69-5; **46**, 85177-13-5; **46** free base, 85177-06-6; **478**, 96255-10-6; **47** free base, 85177-03-3; **48**, 96255-08-2; **48** free base, 125846-70-0; **49**, 125846-71-1; **49** free base, 85176-52-9; **50**, 85176-99-4; **50** free base, 85177-05-5; **51**, 96255-09-3; **52**, 85175-81-1; **53**, 85176-81-4; **53** free base, 85176-79-0; **54**, 96254-99-8; **55**, 125846-72-2; **55** free base, 96255-20-8; **56**, 96255-05-9; **56** free base, 85176-82-5; **57**, 96254-57-8; **57** free base, 85176-60-9; **58**, 96254-95-4; **58** free base, 85176-58-5; $BrCH_2CH(CH_3)CH_2Cl$, 96254-94-3; $BrCH_2CH(OH)CH_2Cl$, 6974-77-2; $Br(CH_2)_2Cl$, 4540-44-7; $Br(CH_2)_4Cl$, 107-04-0; 3,4-$(MeO)_2C_6H_3(CH_2)_2SHO$, 6940-78-9; 3,4-$(MeO)_2C_6H_3(CH_2)_2SO_2H$, 125846-73-3; 3,4-$(MeO)_2C_6H_3(CH_2)_3NHMe$, 125877-12-5; 3,4-$(MeO)_2C_6H_3(CH_2)_4NHMe$, 57010-78-3; 3,4-$(MeO)_2C_6H_3(CH_2)_5NHMe$, 104205-43-8; 3,4-$(MeO)_2C_6H_3NH(CH_2)_2NHMe$, 92460-23-6; 3,4-$(MeO)_2C_6H_3S(CH_2)_2NHMe$, 125846-74-4; 3,4-$(MeO)_2C_6H_3O(CH_2)_2NHMe$, 125846-75-5; 3,4-$(MeO)_2C_6H_3NH(CH_2)_3NHMe$, 125846-76-6; 3,4-$(MeO)_2C_6H_3S(CH_2)_3NHMe$, 125846-77-7; 3,4-$(MeO)_2C_6H_3O(CH_2)_3NHMe$, 125846-78-8; 3,4-$(MeO)_2C_6H_3O(CH_2)_4NHMe$, 102246-77-5; $MeNH(CH_2)_2Ph$, 102246-79-7; *p*-$MeOC_6H_4(CH_2)_2NHMe$, 589-08-2; *p*-$Me_2NC_6H_4(CH_2)_2NHMe$, 4091-50-3; *p*-$ClC_6H_4(CH_2)_2NHMe$, 125846-79-9; *p*-$MeNH(CH_2)_2C_6H_4OSO_2Me$, 38171-31-2; *p*-$O_2NC_6H_4(CH_2)_2NHMe$, 125846-80-2; *p*-$HOC_6H_4(CH_2)_2NHMe$, 85176-37-0; *p*-$H_2NC_6H_4(CH_2)_2NHMe$, 370-98-9; *p*-$BuOC_6H_4(CH_2)_2NHMe$, 32862-32-9; *p*-*t*-$BuC_6H_4(CH_2)_2NHMe$, 55384-06-0; *p*-$PhCH_2OC_6H_4(CH_2)_2NHMe$, 85176-80-3; 3,4,5-$(MeO)_3C_6H_2(CH_2)_2NHMe$, 38961-21-6; 2,4,6-$(MeO)_3C_6H_2(CH_2)_2NHMe$, 4838-96-4; 3,4-$(Cl)_2C_6H_3(CH_2)_2NHMe$, 85176-83-6; 2,6-$(Cl)_2C_6H_3(CH_2)_2NHMe$, 52516-06-0; 3,4-$(Me)_2C_6H_3CH_2CO_2H$, 85176-59-6; 3,4-$(HO)_2C_6H_3CH_2CO_2H$, 17283-16-8; 3-(MeO)-4-(HO)$C_6H_3CH_2CO_2H$, 102-32-9; *m*-$MeOC_6H_4CH_2CO_2H$, 306-08-1; 3-(HO)-4-(MeO)$C_6H_3CH_2CO_2H$, 1798-09-0; *p*-$MeOC_6H_4CH_2CO_2H$, 1131-94-8; 2,5-$(MeO)_2C_6H_3CH_2CO_2H$, 104-01-8; 2,3-$(MeO)_2C_6H_3CH_2CO_2H$, 1758-25-4; $PhCH_2CO_2H$, 90-53-9; 1-bromo-3-chloropropane, 103-82-2; *N*-methyl-2-(3,4-dimethoxyphenyl)ethylamine, 109-70-6; aminoacetaldehyde dimethyl acetal, 3490-06-0; 2-(3,4-dimethoxyphenyl)ethylamine, 22483-09-6; *N*-allyl-2-(3,4-dimethoxyphenyl)ethylamine, 120-20-7; *N*-propyl-2-(3,4-dimethoxyphenyl)ethylamine, 125846-81-3; *N*-[2-(3,4-dimethoxyphenyl)ethyl]-2-(3,4-dimethoxyphenyl)ethylamine, 83722-62-7; *N*-acetyl-2-(3,4-dimethoxyphenyl)ethylamine, 24997-88-4; *N*-carbethoxy-2-(3,4-dimethoxyphenyl)ethylamine, 6275-29-2; 3,4-dimethoxy-1-(2-ethylthio)benzene, 17889-63-3; *N*-dimethyl-2-(3,4-dimethoxyphenyl)ethylamine, 62978-83-0; 1-(methylamino)-3,4-dimethoxybenzene, 3490-05-9; *N*-methyl-3,4-dimethoxybenzenemethylamine, 35162-34-6; benzodioxole-5-acetic acid, 63-64-9; 1,4-benzodioxan-6-acetic acid, 2861-28-1; 2,3,4,5-tetramethylphenylacetic acid, 17253-11-1; 3,4-dimethoxyphenylacetic acid chloride, 53546-73-9, 10313-60-7.

Supplementary Material Available: X-ray data including coordinates, anistotropic temperature factors, distances, and angles for compound 4·HCl·4H_2O (5 pages); observed and calculated structure factors (23 pages). Ordering information is given on any current masthead page.

(76) Stewart, J. M.; Machin, P. A.; Ammon, H. L.; Dickerson, C. W.; Heck, H.; Flack, H. "The X-ray system-version of March 1976", Technical Report TR-466; Computer Science Center, University of Maryland: College Park, MD. 1976.