ID_{50} values were determined by inverse prediction from a parallel line assay of regression lines through points between 10% and 90% inhibition. Doses were increased in approximately 1/2 log intervals (3-fold) with two to six animals tested at each dose. ID_{50} values were computed for each drug to its own control with use of both the common and separate slopes. Since there were no significant departures from parallelism at the 5% level, only the common slope estimates are shown in Table III. All of the drugs reported in Table III produced essentially complete blockage of the LTD_4-induced bronchoconstriction at 10 mg/kg iv.

Acknowledgment. We thank A. Dervinis, A. Blumenthal, S. Schwalm, M. Skrowronek, and L. O'Neill-Davis for technical assistance and the staff of the Analytical Chemistry Department of Wyeth for determination of spectral and analytical data.

Registry No. **4**, 91327-53-6; **5**, 91324-99-1; **6**, 101835-98-7; **7**, 101835-99-8; **8**, 101836-00-4; **9**, 101836-01-5; **10**, 101836-02-6; **11**, 101836-03-7; **12**, 101836-04-8; **13**, 40786-20-7; **14**, 57161-85-0; **15**, 91324-96-8; **16**, 101836-05-9; **17**, 101836-06-0; **18**, 101836-07-1; **19**, 91324-97-9; **20**, 101836-08-2; **21**, 101836-09-3; **22**, 101836-10-6; **23**, 72106-43-5; **24**, 38469-85-1; **25**, 37439-85-3; ethyl oxalyl chloride, 4755-77-5; 2-allyl-3-acetamidophenol, 37439-79-5; leukotriene D_4, 73836-78-9.

New Antiarrhythmic Agents. 2,2,5,5-Tetramethyl-3-pyrroline-3-carboxamides and 2,2,5,5-Tetramethylpyrrolidine-3-carboxamides

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N-(ω-Aminoalkyl)-2,2,5,5-tetramethyl-3-pyrroline- or -pyrrolidine-3-carboxamides were acylated on the primary amino group of the side chain by means of reactive acid derivatives (acid chlorides, activated esters, phthalic anhydrides, phthalimide, 2-alkyl-4*H*-3,1-benzoxazin-4-ones) or they were alkylated by forming the Schiff bases and subsequent sodium borohydride reduction. Other tetramethyl-3-pyrrolinecarboxamide compounds were synthesized by acylating the aminoalkyl compounds with 2,2,6,6-tetramethyl-3,5-dibromo-4-piperidinone in a reaction involving Favorskii rearrangement. Saturation of the double bond of some pyrroline derivatives furnished the pyrrolidinecarboxamides. The new compounds of each type were active against aconitine-induced arrhythmia and several of them had higher activity and better chemotherapeutic index than quinidine. A few selected examples from each type of the active new compounds showed strong activity against ouabain-induced arrhythmia; for comparison known drugs such as lidocaine, mexiletine, and tocainide were selected. The most potent compounds were oxidized to the paramagnetic nitroxides and the latter were reduced to the *N*-hydroxy derivatives; these products had no or only decreased antiarrhythmic effect.

Antiarrhythmic drugs in current use can reduce the occurrence of cardiac arrhythmias; however, the search for better agents preventing death in man due to myocardial infarction has remained an important task of drug research.[1-4] Although no universally effective antiarrhythmic agent exists,[5] certain criteria would characterize an ideal antiarrhythmic drug.[6] Such characteristics would be, for example: (a) efficacy against resistant ventricular arrhythmias, (b) minimal toxicity to the central nervous system, (c) high oral and intravenous absorption (better than 80% bioavailability), (d) long biologial half-life, lasting at least 8 h.

With these targets in mind we synthesized new compounds that are chemically close to those antiarrhythmic agents belonging to class I according to Vaughan Williams' classification,[7] e.g., quinidine, procainamide, mexiletine, and tocainide. This group is characterized by the presence of three structural units:[4] (a) an aromatic ring capable of intercalating between the alkyl chains of phospholipids, (b) an amino group undergoing ionization in the biological system at pH 8–9, (c) an interconnecting chain (between the aromatic ring and the amino group) bearing substituents capable of hydrogen bonding.

Chemistry. In the present work we describe the syntheses of compounds containing a strongly basic amino group, connected through chains of different length (–V–, –Y–, –W–) to functional aryl or heteroaryl groups. The amino compounds selected were the sterically hindered 2,2,5,5-tetramethyl-3-pyrroline-3-carboxamides (**1**) and 2,2,5,5-tetramethylpyrrolidine-3-carboxamides (**2**) containing an aminoalkyl side chain. 3,5-Dibromo-2,2,6,6-tetramethyl-4-piperidinone hydrobromide (**3**) was prepared in the known way[8] by the bromination of triacetonamide (2,2,6,6-tetramethyl-4-piperidinone). The reaction of **3** with diaminoalkanes gave, by Favorskii rearrangement, the *N*-(ω-aminoalkyl)-2,2,5,5-tetramethyl-3-pyrroline-3-carboxamides (**1a–g**) (method A). Catalytic hydrogenation (method B) of **1b** furnished *N*-(3-aminopropyl)-2,2,5,5-tetramethylpyrrolidine-3-carboxamide (**2**) (Scheme I).

The primary amino group of compounds **1a–g** were acylated with reactive acid derivatives, such as activated esters (**4**, **5**) or acid chlorides (**6**) (methods C, D) to obtain the diacyl derivatives **7a–o** and **8a–z**.

The alkylated derivatives **9a–s**, **10a–k**, and **11a–l** were synthesized by the reduction of the Schiff bases prepared from the amines **1a–g** with oxo compounds (**12**) (method E).

The dibromo ketone **3** was allowed to react with amino compounds (**13**) [commercially available aralkylamines, *N*-(α-aminoacyl)-2,6-xylidines[9] and 1-(2,6-dimethylphenoxy)-2-propanamine[10]] to yield products **14a–l** (method F).

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‡ Alkaloida, Tiszavasvári.

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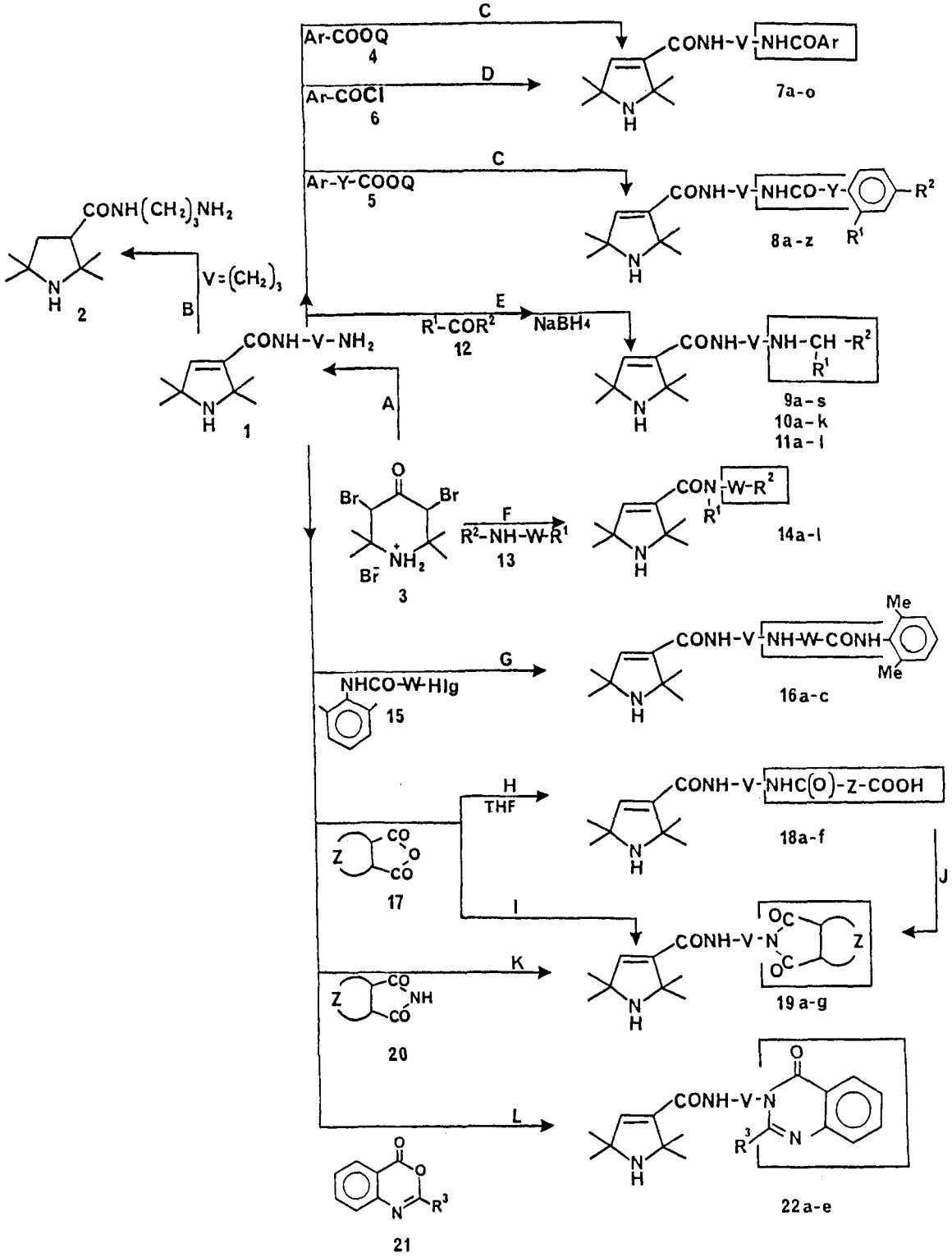
0022-2623/86/1829-1138$01.50/0

Scheme I[a]



[a] Method A: H_2O, TEA, K_2CO_3, 25 °C. Method B: 10% Pd-C, $CHCl_3$, 25 °C. Method C: EtOH, 25 °C, 5 h. Method D: benzene, ∇, 5 h. Method E: toluene, *p*-toluenesulfonic acid, ∇, 16 h. Method F: MeOH–H_2O (3:1), K_2CO_3, 25 °C. Method E: Et_2O–THF (2:1), 25 °C, 2 days. Method I: toluene, TEA, ∇, 8 h. Method J: toluene, TEA, ∇, 5 h. Method K: ∇. Method L: ∇.

Compounds **1a,b** were alkylated with *N*-(α-haloacyl)-2,6-xylidines[11] (**15**) to give derivatives **16a–c** (method G).

The hexahydro- and tetrahydrophthalamide acids **18a-d** and the phthalamide acids **18e-f** were prepared by the acylation of compounds **1a-c** with acid anhydrides (**17**) in tetrahydrofuran (THF), at room temperature (method H).

The phthalamide acids **18e,f** were cyclized in refluxing toluene in the presence of triethylamine to the phthalimide derivatives **19e,f** (method J). Imides were formed also when **1a,b** was refluxed for 3 h with an acid anhydride (**17**) in toluene, in the presence of triethylamine (method I). Another approach to the phthalimide derivatives **19f,g** consisted of the heating of the amines **1b,d** with phthalimide (**20**) (method K).

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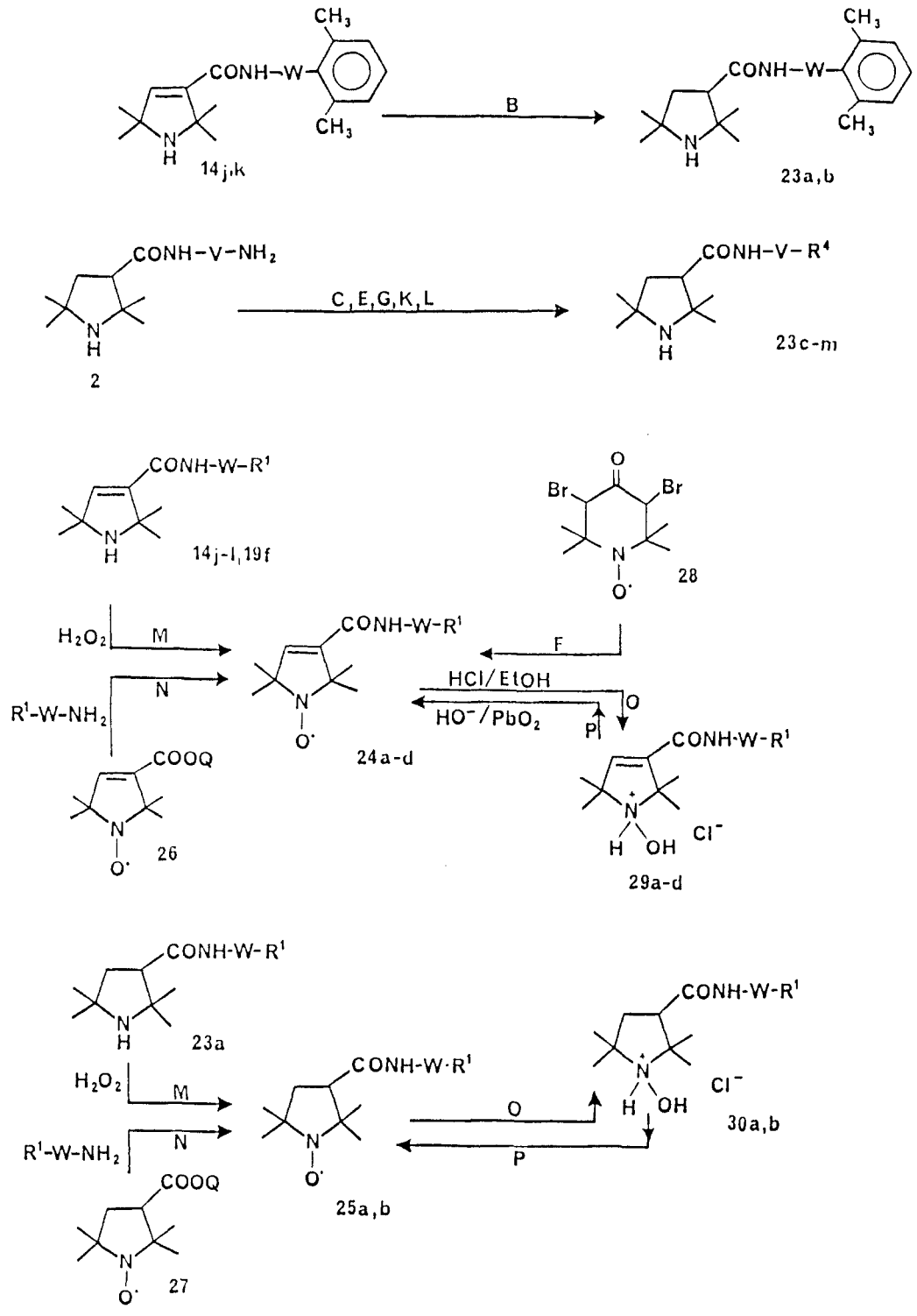
Scheme II[a,b]



[a] See corresponding footnotes (methods B, C, E, G, K, L) in Scheme I. [b] Method M: MeOH, EDTA-Na_2, $Na_2WO_4 \cdot 2HCl$, H_2O, 30% H_2O_2, 20 °C, 3 days. Method N: $CHCl_3$, N_2, ▽, 2 h. Method O: EtOH, HCl gas, 20 °C, 10 min. Method P: 5% K_2CO_3, $CHCl_3$, PbO_2.

The reaction of **1a-d** with 2-alkyl-4*H*-3,1-benzoxazin-4-ones (**21**) afforded the 2-alkyl-4(3*H*)-quinazolinone derivatives **22a–e** (method L).

Pyrrolidine derivatives **23a,b** were obtained by the catalytic hydrogenation of **14j,k** (method B). The conversions of **2** to **23c** (method C_4), **2** to **23d–i** (method E), **2** to **23j** (method G), **2** to **23k** (method K), and **2** to **23l,m** (method L) were also done (Scheme II).

The metabolic oxidation at secondary alicyclic nitrogens leads to the formation of hydroxylamines, which may then oxidize further to nitrones and then to nitroxide free radicals.[12] The 2,2,6,6-tetramethylpiperidine is metabolized enzymatically via a 1-hydroxy derivative to the stable nitroxide free radical 2,2,6,6-tetramethylpiperidinyl-1-oxyl.[13] So a possible way of conversion of tetramethylpyrroline and tetramethylpyrrolidine derivatives in the

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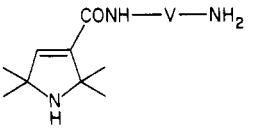
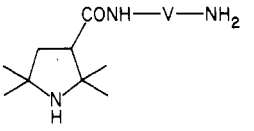
Table I. *N*-(ω-Aminoalkyl)-3-pyrroline(pyrrolidine)-3-carboxamides



1a-g

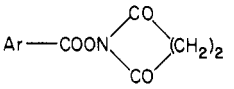


2

compd	V	method	yield, %	mp, °C	formula	anal.[a]
1a	CH_2CH_2	A_1	70	115–117	$C_{11}H_{21}N_3O$	C, H, N
1b	$CH_2CH_2CH_2$	A_1	70	87–88	$C_{12}H_{23}N_3O$	C, H, N
1c	$CH_2CH_2CH_2CH_2$	A_2	55	108–111	$C_{13}H_{25}N_3O$	C, H, N
1d	$CH_2CH(OH)CH_2$	A_2	68	83–85	$C_{12}H_{23}N_3O_2$	C, H, N
1e	$CH_2C(CH_3)_2CH_2$	A_3	79	108–110	$C_{14}H_{27}N_3O$	C, H, N
1f	$CH_2CH(CH_3)$	A_2	50	93–95	$C_{12}H_{23}N_3O$	C, H, N
1g	$CH_2C(CH_3)_2$	A_3	60	108–110	$C_{13}H_{25}N_3O$	C, H, N
2	$CH_2CH_2CH_2$	B	76	oil	$C_{12}H_{25}N_3O$	C, H, N

[a] All compounds were analyzed for C, H, and N. Elemental analyses were within ±0.3% of the theoretical values.

Table II. Intermediates for Table IV: *N*-Succinimide Active Esters

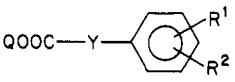


4a-e

compd	Ar	yield, %	mp, °C	formula	anal.[a]
4a	$C_6H_5CH_2$	97	112–114	$C_{12}H_{11}NO_4$	C, H, N
4b	$C_6H_5CH(OH)$	72	115–116	$C_{12}H_{11}NO_5$	C, H, N
4c	$4\text{-}HOC_6H_4CH_2$	98	133–134	$C_{12}H_{11}NO_5$	C, H, N
4d	2-thienyl	91	159–161	$C_9H_7NO_4S$	C, H, N
4e	2-thenyl	84	128–130	$C_{10}H_9NO_4S$	C, H, N

[a] All compounds were analyzed for C, H, and N. Elemental analyses were within ±0.3% of the theoretical values.

Table III. Intermediates for Table V: Active Esters



5a-n

compd	R^1	R^2	Y	Q[a]	yield, %	mp, °C	formula	anal.[b]
5a	H	H	CH_2O	Su	80	99–100	$C_{12}H_{11}NO_5$	C, H, N
5b	H	H	CH_2S	Su	78	97–98	$C_{12}H_{11}NO_4S$	C, H, N
5c	2-Cl	4-Cl	CH_2O	Su	98	85–86	$C_{12}H_9Cl_2NO_5$	C, H, N
5d	$2\text{-}CH_3$	4-Cl	CH_2O	Su	81	71–72	$C_{13}H_{12}ClNO_5$	C, H, N
5e	H	4-Cl	$C(CH_3)_2O$	Su	95	111–112	$C_{14}H_{14}ClNO_5$	C, H, N
5f	$2\text{-}CH_2CH{=}CH_2$	$4\text{-}CH_3$	CH_2O	Su	79	81–82	$C_{16}H_{17}NO_5$	C, H, N
5g	$2\text{-}OCH_3$	$4\text{-}CH_2CH_2CH_3$	CH_2O	Su	81	78–80	$C_{16}H_{19}NO_6$	C, H, N
5h	$2\text{-}OCH_3$	$4\text{-}CH_2CH{=}CH_2$	CH_2O	Su	95	98–99	$C_{16}H_{17}NO_6$	C, H, N
5i	$2\text{-}OCH_3$	$4\text{-}CH_2CH{=}CH_2$	CH_2O	PCP	74	108–110	$C_{18}H_{13}Cl_5O_4$	C, H, N
5j	$2\text{-}OCH_3$	$4\text{-}CH_2CH{=}CH_2$	CH_2O	COOEt	68	oil	$C_{15}H_{18}O_6$	C, H, N
5k	$2\text{-}OCH_3$	$4\text{-}CH_2CH{=}CH_2$	$CH(CH_3)O$	Su	84	85–86	$C_{17}H_{19}NO_6$	C, H, N
5l	$2\text{-}OCH_3$	$4\text{-}CH{=}CHCH_3$	CH_2O	Su	84	142–144	$C_{16}H_{17}NO_6$	C, H, N
5m	$2\text{-}OCH_3$	$4\text{-}CH{=}CHCH_3$	$CH(CH_3)O$	Su	94	115–116	$C_{17}H_{19}NO_6$	C, H, N
5n	$2\text{-}CH_3$	$6\text{-}CH_3$	$CH(CH_3)O$	Su	88	85–86	$C_{15}H_{17}NO_3$	C, H, N

[a] Su = *N*-succinyl, PCP = pentachlorophenyl. [b] The elemental analysis (C, H, and N) were within ±0.3% of the theoretical values.

living organism is their oxidation to the corresponding nitroxides.[14] It is also well known that the sterically hindered tetramethylpyrrolines, -pyrrolidines, and -piperidines can be oxidized by hydrogen peroxide to stable nitroxide free radicals.[15] The analysis of the electron spin resonance (ESR) spectra of paramagnetically labeled biomolecules/drugs is a powerful method for obtaining information about the immediate environment of the labeling.[16,17] Therefore our experiments included the oxidation of a few compounds belonging to types **14** and **19** to obtain 3-(aminocarbonyl)-2,2,5,5-tetramethyl-3-pyrrolinyl-1-oxy derivatives (**24**) (method M); the pyrrolidine derivative **23a** gave the *N*-oxyl compound **25a**. The succinimide ester of 1-oxy-2,2,5,5-tetramethyl-3-pyrroline-3-carboxylic acid (**26**)[18] was converted to **24b** and succinimide ester of the corresponding pyrrolidine derivative (**27**) to **25b**, by allowing these activated esters to react with glycylxylidide (**13**) (method N). The reaction of 3,5-dibromo-2,2,6,6-tetramethyl-4-oxopiperidyl-1-oxy

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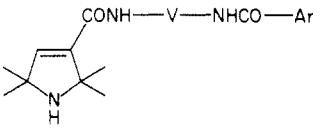
Table IV. *N*-[[(Arylcarbonyl)amino]alkyl]-2,2,5,5-tetramethyl-3-pyrroline-3-carboxamides

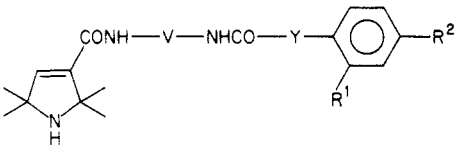


7a-o

compd	V	Ar	method[a]	yield, %	mp, °C	formula	anal.[b]
7a	$(CH_2)_2$	3,4-OCH_2O-C_6H_3	C_1	35	232–233	$C_{19}H_{25}N_3O_4 \cdot HCl$[c]	C, H, N, Cl
7b	$(CH_2)_3$	3,4-OCH_2O-C_6H_3	C_1	47	191–194	$C_{20}H_{27}N_3O_4 \cdot HCl$[d]	C, H, N, Cl
7c	$(CH_2)_3$	3,4,5-$(OCH_3)_3C_6H_2$	C_1	50	196–198	$C_{22}H_{33}N_3O_5 \cdot HCl$[d]	C, H, N, Cl
7d	$(CH_2)_2$	2-pyridyl	D	70	170–173	$C_{17}H_{24}N_4O_2 \cdot 2HCl$	C, H, N, Cl
7e	$(CH_2)_2$	2-thienyl	D	55	110–112	$C_{16}H_{23}N_3O_2S \cdot HCl$	C, H, N, Cl
7f	$(CH_2)_3$	2-thienyl	D	76	132–135	$C_{17}H_{25}N_3O_2S \cdot HCl$	C, H, N, Cl
7g	$(CH_2)_4$	2-thienyl	D	66	112–115	$C_{18}H_{27}N_3O_2S \cdot HCl$	C, H, N, Cl
7h	$CH_2CH(OH)CH_2$	2-thienyl	C_2	55	208–209	$C_{17}H_{25}N_3O_3S$	C, H, N
7i	$(CH_2)_3$	$C_6H_5CH_2$	C_3	45	125–126	$C_{20}H_{29}N_3O_2 \cdot HCl$[e]	C, H, N, Cl
7j	$(CH_2)_3$	4-$OHC_6H_4CH_2$	C_3	50	79–80	$C_{20}H_{29}N_3O_3 \cdot HCl$[e]	C, H, N, Cl
7k	$(CH_2)_2$	$C_6H_5CH(OH)$	C_3	63	205–206	$C_{19}H_{27}N_3O_3$	C, H, N
7l	$(CH_2)_3$	$C_6H_5CH(OH)$	C_3	55	145–147	$C_{20}H_{29}N_3O_3 \cdot C_4H_4O_4$[f]	C, H, N
7m	$(CH_2)_2$	2-thenyl	C_3	61	160–163	$C_{17}H_{25}N_3O_2S \cdot HCl$[d]	C, H, N, Cl
7n	$(CH_2)_3$	2-thenyl	C_3	55	228–230	$C_{18}H_{27}N_3O_2S \cdot HCl$[c]	C, H, N, Cl
7o	$CH_2CH(OH)CH_2$	2-thenyl	C_2	56	136–138	$C_{18}H_{27}N_3O_3S$	C, H, N

[a] See Experimental Section for general preparative procedures. [b] The analytical results were within ±0.3% of the theoretical values for all elements listed. [c] EtOH–ethanolic HCl. [d] Acetone–aniline hydrochloride. [e] Acetone–HCl gas. [f] Acetone–fumaric acid.

Table V. *N*-[[[[(Aryloxy- or -thio)alkyl]carbonyl]amino]alkyl]-2,2,5,5-tetramethyl-3-pyrroline-3-carboxamides



8a-z

compd[a]	V	Y	R^1	R^2	yield, %	mp, °C	formula	anal.[b]
8a	$(CH_2)_3$	CH_2O	H	H	68	92–99	$C_{20}H_{29}N_3O_3 \cdot HCl$[c]	C, H, N, Cl
8b	$(CH_2)_3$	CH_2S	H	H	56	107–108	$C_{20}H_{29}N_3O_2S \cdot HCl$[c]	C, H, N, Cl
8c	$(CH_2)_2$	CH_2O	Cl	Cl	39	223–226	$C_{19}H_{25}Cl_2N_3O_3 \cdot HCl$[c]	C, H, N, Cl
8d	$(CH_2)_3$	CH_2O	Cl	Cl	62	156–157	$C_{20}H_{27}Cl_2N_3O_3 \cdot HCl$[c]	C, H, N, Cl
8e	$(CH_2)_2$	CH_2O	CH_3	Cl	46	226 dec	$C_{20}H_{28}ClN_3O_3 \cdot HCl$[c]	C, H, N, Cl
8f	$(CH_2)_3$	CH_2O	CH_3	Cl	50	187–188	$C_{21}H_{30}ClN_3O_3 \cdot HCl$[c]	C, H, N, Cl
8g	$(CH_2)_2$	$C(CH_3)_2O$	H	Cl	69	179–181	$C_{21}H_{30}ClN_3O_3 \cdot HCl$[c]	C, H, N, Cl
8h	$(CH_2)_3$	$C(CH_3)_2O$	H	Cl	74	196–198	$C_{22}H_{32}ClN_3O_3 \cdot HCl$[c]	C, H, N, Cl
8i	$CH_2CH(OH)CH_2$	$C(CH_3)_2O$	H	Cl	61	211–215	$C_{22}H_{32}ClN_3O_4 \cdot HCl$[c]	C, H, N, Cl
8j	$(CH_2)_2$	CH_2O	$CH_2CH{=}CH_2$	CH_3	60	162–164	$C_{23}H_{33}N_3O_3 \cdot HCl$[d]	C, H, N, Cl
8k	$(CH_2)_3$	CH_2O	$CH_2CH{=}CH_2$	CH_3	55	134–136	$C_{24}H_{35}N_3O_3 \cdot HCl$[d]	C, H, N, Cl
8l	$(CH_2)_3$	CH_2O	OCH_3	$CH_2CH_2CH_3$	48	140–143	$C_{24}H_{37}N_3O_4 \cdot HCl$[d]	C, H, N, Cl
8m	$(CH_2)_2$	CH_2O	OCH_3	$CH_2CH{=}CH_2$	60	130–132	$C_{23}H_{33}N_3O_4 \cdot HCl$[d]	C, H, N, Cl
8n	$(CH_2)_3$	CH_2O	OCH_3	$CH_2CH{=}CH_2$	73	158–160	$C_{24}H_{35}N_3O_4 \cdot HCl$[d]	C, H, N, Cl
8o	$CH_2CH(OH)CH_2$	CH_2O	OCH_3	$CH_2CH{=}CH_2$	60	232–236	$C_{24}H_{35}N_3O_5 \cdot HCl$[c]	C, H, N, Cl
8p	$(CH_2)_2$	$CH(CH_3)O$	OCH_3	$CH_2CH{=}CH_2$	62	104–106	$C_{24}H_{35}N_3O_4 \cdot HCl$[d]	C, H, N, Cl
8q	$(CH_2)_3$	$CH(CH_3)O$	OCH_3	$CH_2CH{=}CH_2$	60	145–147	$C_{25}H_{37}N_3O_4 \cdot HCl$[c]	C, H, N, Cl
8r	$CH_2C(CH_3)_2CH_2$	CH_2O	OCH_3	$CH_2CH{=}CH_2$	63	116–118	$C_{26}H_{39}N_3O_4 \cdot HCl$[c]	C, H, N, Cl
8s	$(CH_2)_2$	CH_2O	OCH_3	$CH{=}CHCH_3$	60	161–163	$C_{23}H_{33}N_3O_4 \cdot HCl$[c]	C, H, N, Cl
8t	$(CH_2)_3$	CH_2O	OCH_3	$CH{=}CHCH_3$	75	132–134	$C_{24}H_{35}N_3O_4 \cdot HCl$[d]	C, H, N, Cl
8u	$CH_2CH(OH)CH_2$	CH_2O	OCH_3	$CH{=}CHCH_3$	60	77–78	$C_{24}H_{35}N_3O_5$	C, H, N
8v	$(CH_2)_3$	$CH(CH_3)O$	OCH_3	$CH{=}CHCH_3$	58	170–172	$C_{25}H_{37}N_3O_4 \cdot HCl$[c]	C, H, N, Cl
8z	$CH_2C(CH_3)_2CH_2$	CH_2O	OCH_3	$CH{=}CHCH_3$	49	106–107	$C_{26}H_{39}N_3O_4 \cdot HCl$[d]	C, H, N, Cl

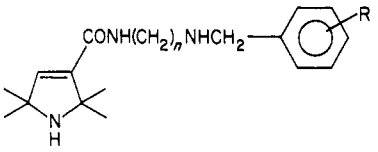
[a] All compounds were made by method C_4. [b] All compounds were analyzed (C, H, N, and halogens), and the values obtained were within ±0.3% of the theoretical values besides the following data. Calcd (found): **8d**, Cl, 22.88 (22.34); **8r**, Cl, 7.18 (7.56). [c] acetone–HCl gas. [d] EtOH–HCl gas.

(**28**)[19,20] (the 1-oxy derivative of the dibromo compound **3**) with glycylxylidide gave also **24a** by Favorskii rearrangement (method F) (Scheme II).

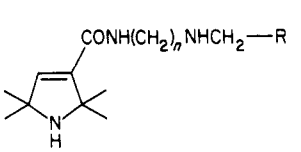
Treatment of the paramagnetic compounds **24a–d** and **25a,b** in ethyl alcohol saturated with hydrogen chloride furnished the hydrochlorides of the diamagnetic 1-hydroxy compounds **29a–d** and **30a,b** (method O). The base forms of the 1-hydroxy compounds **29** and **30** are instable; when exposed to air with stirring or when acted upon by lead(IV) oxide (PbO_2) even more rapidly and quantitatively, they undergo reoxidation to give the paramagnetic compounds **24** and **25** (method P). The new compounds in this work are summarized in Tables I–XII.

(19) Golding, B. T.; Ioannou, P. V.; O'Brien, M. M. *Synthesis* **1975**, 462.
(20) Alcock, N. W.; Golding, B. T.; Ioannou, P. V.; Sawyer, J. F. *Tetrahedron* **1977**, *33*, 2969.

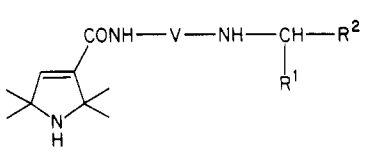
Table VI. *N*-[ω-[(Arylmethyl)amino]alkyl]-2,2,5,5-tetramethyl-3-pyrroline-3-carboxamides



9a-s, 10a-k



11a-h



11i-z

compd[a]	n	R	yield, %	mp, °C	formula	anal.[b]
9a	3	H	73	217–221	$C_{19}H_{29}N_3O{\cdot}2HCl$[e]	C, H, N, Cl
9b	2	4-Cl	80	255–257	$C_{18}H_{26}ClN_3O{\cdot}2C_7H_8O_3S$[d]	C, H, N, Cl
9c	3	4-CF_3	61	148–150	$C_{20}H_{28}F_3N_3O{\cdot}2HCl$[c]	C, H, N, Cl
9d	3	2-OCH_3	72	154–155	$C_{20}H_{31}N_3O_2{\cdot}2HCl$[e]	C, H, N, Cl
9e	2	2-OH	77	206–208	$C_{18}H_{27}N_3O_2{\cdot}2HCl$[f]	C, H, N, Cl
9f	3	2-OH	66	116–117	$C_{19}H_{29}N_3O_2$	C, H, N
9g	3	3-OH	40	243–244	$C_{19}H_{29}N_3O_2{\cdot}2HCl$[f]	C, H, N, Cl
9h	3	4-OH	40	165–169	$C_{19}H_{29}N_3O_2{\cdot}2HCl$[f]	C, H, N, Cl
9i	3	3-OC_6H_5	70	197–201	$C_{25}H_{33}N_3O_2{\cdot}2HCl$[e]	C, H, N, Cl
9j	3	4-OC_6H_5	84	182–185	$C_{25}H_{33}N_3O_2{\cdot}2HCl$[e]	C, H, N, Cl
9k	3	2-$OCH_2C_6H_5$	82	164–165	$C_{26}H_{35}N_3O_2{\cdot}2HCl$[e]	C, H, N, Cl
9l	3	3-$OCH_2C_6H_5$	71	210–211	$C_{26}H_{35}N_3O_2{\cdot}2HCl$[c]	C, H, N, Cl
9m	3	4-$OCH_2C_6H_5$	54	90–91	$C_{26}H_{35}N_3O_2{\cdot}2HCl$[e]	C, H, N, Cl
9n	3	2-$OCH_2CH{=}CH_2$	95	201–202	$C_{22}H_{33}N_3O_2{\cdot}2HCl$[c]	C, H, N, Cl
9o	3	3-$OCH_2CH{=}CH_2$	64	174–175	$C_{22}H_{33}N_3O_2{\cdot}2HCl$[c]	C, H, N, Cl
9p	3	4-$OCH_2CH{=}CH_2$	68	136–139	$C_{22}H_{33}N_3O_2{\cdot}2HCl$[f]	C, H, N, Cl
9q	3	2-OCH_2CONH_2	82	155–158	$C_{21}H_{32}N_4O_3{\cdot}2HCl$[f]	C, H, N, Cl
9r	2	4-$NHCOCH_3$	54	213–214	$C_{20}H_{30}N_4O_2{\cdot}2HCl$[f]	C, H, N, Cl
9s	3	4-$NHCOCH_3$	66	184–185	$C_{21}H_{32}N_4O_2{\cdot}2HCl$[f]	C, H, N, Cl
10a	3	2,4-$(OCH_3)_2$	83	201–202	$C_{21}H_{33}N_3O_3{\cdot}2HCl$[f]	C, H, N, Cl
10b	2	3,4-$(OCH_3)_2$	60	239–241	$C_{20}H_{31}N_3O_3{\cdot}2C_7H_8O_3S$[d]	C, H, N
10c	3	2-OH, 3-OCH_3	74	206–208	$C_{20}H_{31}N_3O_3{\cdot}2HCl$[f]	C, H, N, Cl
10d	3	3-OCH_3, 4-OH	66	159–162	$C_{20}H_{31}N_3O_3{\cdot}2HCl$[f]	C, H, N, Cl
10e	3	2-$OCH_2CH{=}CH_2$, 3-OCH_3	68	204–206	$C_{23}H_{35}N_3O_3{\cdot}2HCl$[f]	C, H, N, Cl
10f	3	3-OCH_3, 4-$OCH_2CH{=}CH_2$	57	154–155	$C_{23}H_{35}N_3O_3{\cdot}2HCl$[f]	C, H, N, Cl
10g	3	2-$OCH_2C_6H_5$, 3-OCH_3	67	197–198	$C_{27}H_{37}N_3O_3{\cdot}2HCl$[f]	C, H, N, Cl
10h	3	2-OCH_3, 4-$OCH_2C_6H_5$	43	201–202	$C_{27}H_{37}N_3O_3{\cdot}2HCl$[f]	C, H, N, Cl
10i	3	2-OCH_2CONEt_2, 3-OCH_3	78	184–185	$C_{26}H_{42}N_4O_4{\cdot}2HCl$[f]	C, H, N, Cl
10j	2	3,4,5-$(OCH_3)_3$	68	227–228	$C_{21}H_{33}N_3O_4{\cdot}2C_7H_8O_3S$[d]	C, H, N
10k	3	3,4,5-$(OCH_3)_3$	73	212–213	$C_{22}H_{35}N_3O_4{\cdot}2HCl$[e]	C, H, N, Cl
11a	3	2-pyrrolyl	69	197–198	$C_{17}H_{28}N_4O{\cdot}2HCl$[e]	C, H, N, Cl
11b	3	2-pyridyl	70	170–174	$C_{18}H_{28}N_4O{\cdot}3HCl$[e]	C, H, N, Cl
11c	3	4-pyridyl	41	178–180	$C_{18}H_{28}N_4O{\cdot}H_2O{\cdot}2C_7H_8O_3S$[d]	C, H, N
11d	3	2-furyl	62	220–222	$C_{17}H_{27}N_3O_2{\cdot}2HCl$[f]	C, H, N, Cl
11e	2	2-thienyl	70	228–229	$C_{16}H_{25}N_3OS{\cdot}2C_7H_8O_3S$[d]	C, H, N
11f	3	2-thienyl	65	230–231	$C_{17}H_{27}N_3OS{\cdot}2HCl$[c]	C, H, N, Cl
11g	3	3-thienyl	96	230–234	$C_{17}H_{27}N_3OS{\cdot}2HCl$[c]	C, H, N, Cl
11h	4	2-thienyl	49	>250	$C_{18}H_{29}N_3OS{\cdot}2HCl$[e]	C, H, N, Cl

	V	R^1	R^2	yield, %	mp, °C	formula	anal.[b]
11i	CH_2CH_2	CH_3	2-thienyl	68	214–216	$C_{17}H_{27}N_3OS{\cdot}2HCl$[e]	C, H, N, Cl
11j	$CH_2CH(CH_3)$	H	2-thienyl	68	145–149	$C_{17}H_{27}N_3OS{\cdot}2HCl$[c]	C, H, N, Cl
11k	$CH_2C(CH_3)_2$	H	2-thienyl	54	>250	$C_{18}H_{29}N_3OS{\cdot}2HCl$[c]	C, H, N, Cl
11l	$CH_2CH(OH)CH_2$	H	2-thienyl	80	208–211	$C_{17}H_{27}N_3O_2S{\cdot}2HCl$[c]	C, H, N, Cl

[a] All compounds were made by method E. [b] All compounds were analyzed (C, H, N, and halogens), and the values obtained were within ±0.4% of the theoretical values besides the following data. Calcd (found): **11j**, C, 51.77 (51.33). [c] Acetone–HCl gas. [d] Acetone–*p*-toluenesulfonic acid. [e] Ethanolic HCl. [f] EtOAc–HCl gas.

Pharmacology. Preliminary screening tests were carried out in aconitine-induced arrhythmia in anesthesized rats by methods of Baldini and Brambilla[21] and the second evaluation by Zetler and Strubelt.[22]

A group of selected active compounds were investigated in a ouabain-induced arrhythmia.[23]

Results and Discussion

On the basis of the antiarrhythmic biological tests, the compounds described above can be considered to belong to the group of class I agents; therefore, in determining the structure–activity relationships, we used quinidine, the classic representative of drugs with this type of action, as reference for comparison. In view of the chemical structural units present in our compounds, primarily due to similarities between the acid amide bonds and the aromatic rings, comparative tests of efficacy were also made with procainamide, mexiletine, and tocainide.

The data of pharmacological evaluations are summarized in Tables XIII and XIV.

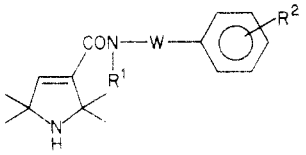
Comparison of the actions of the compounds containing pyrroline and pyrrolidine ring has shown that the efficacy and toxicity of the corresponding pyrroline/pyrrolidine pairs were different.

Of the *diacyl compounds*, the pyrroline derivative (e.g., **8n**) was effective, and the pyrrolidine compound (**23c**) had no antiarrhythmic activity.

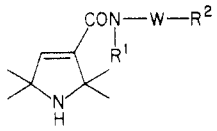
In the case of the *monoacyl derivatives*, the unsaturated compounds (e.g., **9c**) are less potent than the corresponding saturated compounds (e.g., **23e**), yet their therapeutical indices are identical since the latter compounds have

(21) Baldini, L.; Brambilla, G. *Farmaco, Ed. Sci.* **1964**, *19*, 556.
(22) Zetler, G.; Strubelt, O. *Arzneim.-Forsch.* **1980**, *30*, 1497.
(23) Sekiya, A.; Vaughan Williams, E. M. *Br. J. Pharmacol.* **1963**, *21*, 462.

Table VII. Miscellaneous *N*-Substituted 2,2,5,5-Tetramethyl-3-pyrroline-3-carboxamides



14a-h, j-m

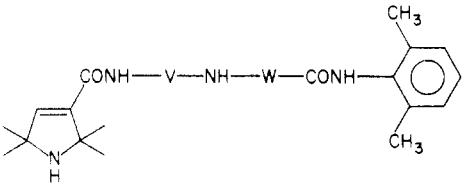


14i

compd[a]	R^1	W	R^2	yield, %	mp, °C	formula	anal.[b]
14a	H		2,6-$(CH_3)_2$	40	237–239	$C_{17}H_{24}N_2O$·HCl	C, H, N, Cl
14b	H	CH_2	H	68	188–189	$C_{16}H_{22}N_2O$·HCl	C, H, N, Cl
14c	CH_3	CH_2	H	62	225–226	$C_{17}H_{24}N_2O$·HCl	C, H, N, Cl
14d	H	CH_2	4-Cl	71	216–218	$C_{16}H_{21}ClN_2O$·HCl	C, H, N, Cl
14e	H	CH_2	4-OCH_3	69	214–216	$C_{17}H_{24}N_2O_2$·HCl	C, H, N, Cl
14f	H	$CH(CONH_2)$	H	93	220–223	$C_{17}H_{23}N_3O_2$·HCl	C, H, N, Cl
14g	H	CH(Ph)	H	97	245–247	$C_{22}H_{26}N_2O$·HCl	C, H, N, Cl
14h	H	CH_2CH_2	3,4-$(OCH_3)_2$	45	212–214	$C_{19}H_{28}N_2O_3$·HCl	C, H, N, Cl
14i	H	CH_2	4-pyridyl	68	198–200	$C_{15}H_{21}N_3O$·2HCl	C, H, N, Cl
14j	H	$CH(CH_3)CH_2O$	2,6-$(CH_3)_2$	82	218 dec.	$C_{20}H_{30}N_2O_2$·HCl	C, H, N, Cl
14k	H	CH_2CONH	2,6-$(CH_3)_2$	63	211–213	$C_{19}H_{27}N_3O_2$·HCl	C, H, N, Cl
14l	H	$CH(CH_3)CONH$	2,6-$(CH_3)_2$	59	187–188	$C_{20}H_{29}N_3O_2$	C, H, N
					168–169	$C_{20}H_{29}N_3O_2$·HCl	C, H, N, Cl
14m	H	$CH(C_6H_5)CONH$	2,6-$(CH_3)_2$	70	>250	$C_{25}H_{31}N_3O_2$	C, H, N
					242–243	$C_{25}H_{31}N_3O_2$·HCl	C, H, N, Cl

[a] All compounds were prepared by method F. [b] The analytical results were within ±0.3% of the theoretical values for all elements listed.

Table VIII. {[[(Pyrrolinylcarbonyl)amino]alkyl]amino}acyl Anilides

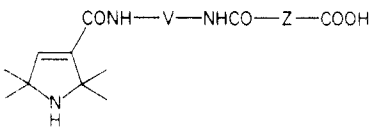


16a-c

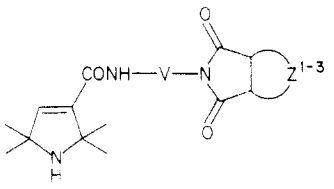
compd	V	W	method	yield, %	mp, °C	formula	anal.[a]
16a	$(CH_2)_3$	CH_2	G	58	168–169	$C_{22}H_{34}N_4O_2$·2HCl	C, H, N, Cl
16b	$(CH_2)_2$	$CH(CH_3)$	G	60	216–220	$C_{22}H_{34}N_4O_2$·2HCl	C, H, N, Cl
16c	$(CH_2)_3$	$CH(CH_3)$	G	85	171–173	$C_{23}H_{36}N_4O_2$·2HCl	C, H, N, Cl

[a] The elemental analysis (C, H, N, and Cl) for all compounds were within ±0.4% of the theoretical values.

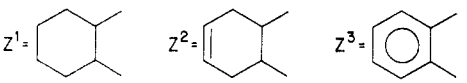
Table IX. *N*-[ω-(Acylamino)alkyl]-Substituted Phthalamide Acids and Phthalimides



18a-f



19a-g



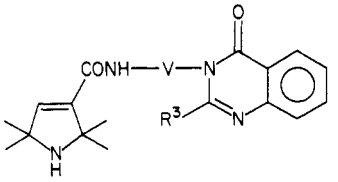
compd	V	Z	method	yield, %	mp, °C	formula	anal.[a]
18a	CH_2CH_2	Z^1	H	90	135–136	$C_{19}H_{31}N_3O_4$	C, H, N
18b	$CH_2CH_2CH_2$	Z^1	H	94	136–138	$C_{20}H_{33}N_3O_4$	C, H, N
18c	CH_2CH_2	Z^2	H	93	186–188	$C_{19}H_{29}N_3O_4$	C, H, N
18d	$CH_2CH_2CH_2$	Z^2	H	94	88–90	$C_{20}H_{31}N_3O_4$	C, H, N
18e	CH_2CH_2	Z^3	H	86	182–184	$C_{19}H_{25}N_3O_4$	C, H, N
18f	$CH_2CH_2CH_2$	Z^3	H	93	127–128	$C_{20}H_{27}N_3O_4$	C, H, N
19a	CH_2CH_2	Z^1	I	78	176–180	$C_{19}H_{29}N_3O_3$·HCl	C, H, N, Cl
19b	$CH_2CH_2CH_2$	Z^1	I	89	180–182	$C_{20}H_{31}N_3O_3$·HCl	C, H, N, Cl
19c	CH_2CH_2	Z^2	I	86	185–188	$C_{19}H_{27}N_3O_3$·HCl	C, H, N, Cl
19d	$CH_2CH_2CH_2$	Z^2	I	88	108–110	$C_{20}H_{29}N_3O_3$·HCl	C, H, N, Cl
19e	CH_2CH_2	Z^3	I	92	>230	$C_{19}H_{23}N_3O_3$·HCl	C, H, N, Cl
			J	45			C, H, N, Cl
19f	$CH_2CH_2CH_2$	Z^3	I	60	250 dec	$C_{20}H_{25}N_3O_3$·HCl	
			J	40			
			K	80			
19g	$CH_2CH(OH)CH_2$	Z^3	K	70	241–242	$C_{20}H_{25}N_3O_4$·HCl	C, H, N, Cl

[a] The elemental analysis (C, H, N, and Cl) were within ±0.4% of the theoretical values.

higher toxicity. Compounds **9n** and the corresponding saturated derivative **23f** have the same potency.

Among the *2-thienyl derivatives*, the unsaturated compound **11f** has about the same efficacy as the saturated

Table X. 2-Alkyl-3-[[[(2,2,5,5-tetramethyl-3-pyrrolin-3-yl)carbonyl]amino]alkyl]-4(3*H*)-quinazolinones

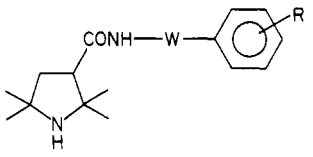


22a-e

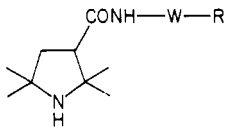
compd	V	R^3	method	yield, %	mp, °C	formula	anal.[a]
22a	CH_2CH_2	CH_3	L	70	218–220	$C_{20}H_{26}N_4O_2 \cdot 2HCl$	C, H, N, Cl
22b	$CH_2CH_2CH_2$	CH_3	L	53	193–194	$C_{21}H_{28}N_4O_2 \cdot 2HCl$	C, H, N, Cl
22c	CH_2CH_2	CH_2CH_3	L	61	218–221	$C_{21}H_{28}N_4O_2 \cdot HCl$	C, H, N, Cl
22d	$CH_2CH_2CH_2$	CH_2CH_3	L	66	213–215	$C_{22}H_{30}N_4O_2 \cdot 2HCl$	C, H, N, Cl
22e	$CH_2CH(OH)CH_2$	CH_3	L	70	201–202	$C_{21}H_{28}N_4O_2 \cdot 2HCl$	C, H, N, Cl

[a] The elemental analysis (C, H, N, and Cl) were within ±0.3% of the theoretical values.

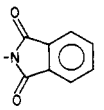
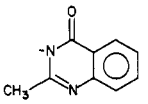
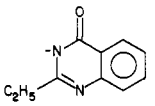
Table XI. Miscellaneous N-Substituted 2,2,5,5-Tetramethyl-3-pyrrolidine-3-carboxamides



23a-g, j



23h, i, k-m

compd	W	R	method	yield, %	mp, °C	formula	anal.[a]
23a	$CH(CH_3)CH_2O$	2,6-$(CH_3)_2$	B	78	216–218	$C_{20}H_{32}N_2O_2 \cdot HCl$[b]	C, H, N, Cl
23b	CH_2CONH	2,6-$(CH_3)_2$	B	86	215–217	$C_{19}H_{29}N_3O_2 \cdot HCl$[b]	C, H, N, Cl
23c	$(CH_2)_3NHCOCH_2O$	2-OCH_3,4-$CH_2CH{=}CH_2$	C_4	62	105–107	$C_{24}H_{37}N_3O_4 \cdot HCl$[b]	C, H, N, Cl
23d	$(CH_2)_3NHCH_2$	2-Cl	E	69	150–155	$C_{19}H_{30}ClN_3O \cdot 2HCl$[b]	C, H, N, Cl
23e	$(CH_2)_3NHCH_2$	4-CF_3	E	76	>250	$C_{20}H_{30}F_3N_3O \cdot 2HCl$[b]	C, H, N, Cl
23f	$(CH_2)_3NHCH_2$	2-$OCH_2CH{=}CH_2$	E	95	201–202	$C_{22}H_{35}N_3O_2 \cdot 2HCl$[c]	C, H, N, Cl
23g	$(CH_2)_3NHCH_2$	2-$OCH_2C_6H_5$	E	82	164–165	$C_{26}H_{37}N_3O_2 \cdot 2HCl$[c]	C, H, N, Cl
23h	$(CH_2)_3NHCH_2$	2-thienyl	E	57	140–143	$C_{17}H_{29}N_3OS \cdot 2HCl$[c]	C, H, N, Cl
23i	$(CH_2)_3NHCH_2$	3-thienyl	E	48	160–162	$C_{17}H_{29}N_3OS \cdot 2HCl$[b]	C, H, N, Cl
23j	$(CH_2)_3NHCH(CH_3)CONH$	2,6-$(CH_3)_2$	G	45	147–150	$C_{23}H_{38}N_4O_2 \cdot 2HCl$[c]	C, H, N, Cl
23k	$CH_2CH_2CH_2$		K	50	144–147	$C_{20}H_{27}N_3O_3 \cdot HCl$[d]	C, H, N, Cl
23l	$CH_2CH_2CH_2$		L	90	125–128	$C_{21}H_{30}N_4O_2 \cdot 2HCl$[d]	C, H, N, Cl
23m	$CH_2CH_2CH_2$		L	50	170–175	$C_{22}H_{32}N_4O_2 \cdot 2HCl$[d]	C, H, N, Cl

[a] The analytical results were within ±0.4% of the theoretical values for all elements listed. [b] Acetone–HCl gas. [c] EtOAc–HCl gas. [d] Ethanolic HCl.

product **23h**, the therapeutical index (TI) (12.3) of the former being only slightly better (10.2) than that of the latter. However, comparison of the *3-thienyl* derivative **11g**) has shown 90% protective action compared to 70% of the *2-thienyl* derivative (**11f**), but the former is more toxic.

The unsaturated (**9k**) and saturated (**23g**) *2-(benzyloxy)phenyl derivatives* possess identical activity (100%); as the unsaturated compound is less toxic, its therapeutic index is better (**9k**, LD_{50} = 9.0 mg/kg, TI = 14.3; **23g**, LD_{50} = 13.0 mg/kg, TI = 25.0).

In the *phthalimide derivatives*, a higher dose of the saturated compound **23k** than of the unsaturated analogue **19f** is required to attain 100% protective action; thus, the therapeutic index of **19f** is much better.

Saturation of the double bond in the *xylyl ether derivative* (**23a**) increased the potency; however, this was accompanied by a still greater increase of toxicity; hence, the unsaturated analogue (**14j**) has a better therapeutic index (**14j**, LD_{50} = 11.0 mg/kg, TI = 11.8; **23a**, LD_{50} = 2.0 mg/kg, TI = 5.1).

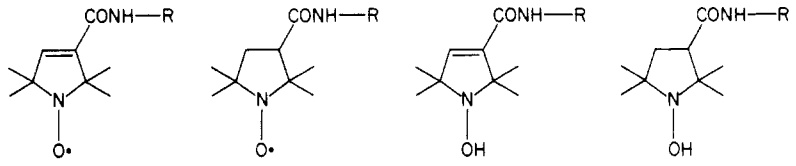
In the *xylidide derivatives*, comparison of the pair **14k** and **23b** has shown higher relative activity and better therapeutic index for the saturated compound (**23b**) than for the unsaturated one (**14k**).

Of the *2-methylquinazolinone derivatives*, the therapeutic index of the unsaturated compound **22b**, giving 100% protection, is more favorable than that of quinidine, but the corresponding saturated derivative **23l** has only a fraction (30%) of the activity.

Comparison of the *2-ethylquinazolinones* revealed 100% efficacy in both types (**22d** and **23m**); the unsaturated derivative acts in a lower dose, but it is more toxic; hence, the therapeutic indices are nearly identical.

Summing up the results, the pyrrolinecarboxamide compounds have, in general, more favorable action than

Table XII. 1-Oxyl and 1-Hydroxy Derivatives of Substituted 3-Pyrroline(pyrrolidine)-3-carboxamides



24a-d 25a, b 29a-d 30a, b

compd	R	method	yield, %	mp, °C	formula	anal.[a]
24a	$CH(CH_3)CH_2OC_6H_3$-2,6-$(CH_3)_2$	F, M	60, 52	109–110	$C_{20}H_{29}N_2O_3$	C, H, N
24b	$CH_2CONHC_6H_3$-2,6-$(CH_3)_2$	M, N, P	50, 48, 90	172–174	$C_{19}H_{26}N_3O_3$	C, H, N
24c	$CH(CH_3)CONHC_6H_3$-2,6-$(CH_3)_2$	M	55	200–201	$C_{20}H_{28}N_3O_3$	C, H, N
24d	$CH_2CH_2CH_2N$-phthalyl	M	63	157–158	$C_{20}H_{24}N_3O_4$	C, H, N
25a	$CH(CH_3)CH_2OC_6H_3$-2,6-$(CH_3)_2$	M, P	52, 90	152–153	$C_{20}H_{31}N_2O_3$	C, H, N
25b	$CH_2CONHC_6H_3$-2,6-$(CH_3)_2$	M, N	55, 42	184–186	$C_{19}H_{28}N_3O_3$	C, H, N
29a	$CH(CH_3)CH_2OC_6H_3$-2,6-$(CH_3)_2$	O	82	151–153	$C_{20}H_{30}N_2O_3$·HCl	C, H, N, Cl
29b	$CH_2CONHC_6H_3$-2,6-$(CH_3)_2$	O	86	163–164	$C_{19}H_{27}N_3O_3$·HCl	C, H, N, Cl
29c	$CH(CH_3)CONHC_6H_3$-2,6-$(CH_3)_2$	O	84	139–141	$C_{20}H_{29}N_3O_3$·HCl	C, H, N, Cl
29d	$CH_2CH_2CH_2N$-phthalyl	O	92	154–157	$C_{20}H_{25}N_3O_4$·HCl	C, H, N, Cl
30a	$CH(CH_3)CH_2OC_6H_3$-2,6-$(CH_3)_2$	O	88	151–152	$C_{20}H_{32}N_2O_3$·HCl	C, H, N, Cl
30b	$CH_2CONHC_6H_3$-2,6-$(CH_3)_2$	O	84	126–128	$C_{19}H_{29}N_3O_3$·HCl	C, H, N, Cl

[a] The analytical results were within ±0.4% of the theoretical values for all elements listed.

the pyrrolidinecarboxamide derivatives.

Investigation of the *role of the length of the connecting chains in the diacyl derivatives* has shown that the increasing of the number of members in this chain [–V–; $(CH_2)_n$, n = 2–4] results in increased toxicity of the compounds (**7e–g**).

When the effect of this chain length in the diacyl derivatives is evaluated, advantage is seen if section Y, in the vicinity of the aromatic ring, is longer and contains an electron-rich group, for instance, the protective action of **7i** (Ar = $PhCH_2$) is 60%, this value is 100% for **8a** (ArY = $PhOCH_2$), the 2-thienyl derivative **7f** is noneffective, and the **7n** 2-thenyl compound has 80% protective efficacy.

In the *(aryloxy)alkylene carboxamides*, higher activity is found if the intermediary connecting chain is propylene instead of ethylene; e.g., **8j** [V = $(CH_2)_2$] and **8k** [V = $(CH_2)_2$] can exert 30% and 80% protective action, respectively. This value for **8p** and **8q** is 70% and 100%, but the compound containing the longer chain (**8q**) can produce the same effect in a much lower dose (1.0 mg/kg for **8q** and 2.0 mg/kg for **8p**); thus, it has a better therapeutic index. The same applies to the pairs **8m** and **8n** as well as **8s** and **8t**.

Of the *monoacyl derivatives*, compound **10j** with an ethylene chain gave only 20% protection; in **10k** the presence of a trimethylene chain increased this to 90%. Reversed protective efficacies were found in the 2-hydroxyphenyl-substituted compounds: 70% for **9f** [$(CH_2)_3$] and 100% for **9e** [$(CH_2)_2$]; thus, the therapeutic indices are 30.0 (**9e**) and 5.9 (**9f**). A study of the effect of the number of chain members on the activity of the *thienyl derivatives* showed rather low protection (30%) for the compound with an ethylene chain [**11e**, $(CH_2)_2$], a higher value (70%) for a trimethylene chain [**11f**, $(CH_2)_3$], and full protection (100%) when the chain was tetramethylene [**11h**, $(CH_2)_4$], and with a 2-hydroxypropyl chain [**11l**, $CH_2CH(OH)CH_2$] the protective action was 90%.

As an example of compounds of types **14** and **16**, **14a**, affords 70% protection, but it is toxic (LD_{50} = 6.0 mg/kg); hence, the therapeutic index is poor (2.8). The derivatives containing glycyl or alanyl units ensure 100% protection with good therapeutic indices; examples are **14k** (TI = 22.1), **16a** (TI = 20.0), **16c** (TI = 19.9), and **14j** (TI = 11.8).

In the case of the *phthalimido compounds*, the presence of an ethylene, trimethylene, or 2-hydroxypropyl chain (**19e**, **19f**, and **19g**) does not give rise to a marked difference in activity.

The protective action of the *2-methyl-* and *2-ethyl-4(3H)-quinazolinone derivatives* containing ethylene and 2-hydroxypropyl chains (**22a** and **22e**) does not attain 100% (the values are 40% and 60%). The 2-methyl derivative having a trimethylene chain and giving 100% protection (**22b**) has a therapeutic index (6.9) nearly identical with that (7.6) of the 2-ethyl compound **22d**.

To summarize a comparison of the therapeutic values of the compounds as a function of the length of the intermediary chains points to the better efficacy of the derivatives containing a trimethylene chain.

Of the *diacyl derivatives* (**8**), the halo- and methyl-substituted compounds (**8c-i**) are noneffective. The 2-allyl-4-methyl-substituted products [**8j**, V = $(CH_2)_2$; **8k**, V = $(CH_2)_3$] have 30% and 80% protective action. The 2-methoxy-4-*n*-propyl derivative **8l**, ensuring 100% protection, has a less favorable therapeutic index (4.1) than the 2-methoxy-4-allyl (**8n**) and 2-methoxy-4-propenyl (**8t**) compounds (13.6).

Comparison of the *monoacyl derivatives* has revealed that the potency of the nonsubstituted phenyl compound **9a** (90% protection) is higher than that of the 4-chlorophenyl (**9b**), 4-(trifluoromethyl)phenyl (**9c**), 4-(acetylamino)phenyl (**9r** and **9s**), 3,4-dimethoxyphenyl (**10b**), and 3,4,5-trimethoxyphenyl (**10j**) derivatives. The protection afforded by the 2-, 3-, and 4-(benzyloxy)phenyl compounds **9k**, **9l**, and **9m** is 100%, 100%, and 80%, respectively, but the LD_{50} values are 9.0, 7.0, and 20.1 mg/kg, thus giving the therapeutical indices 14.3, 9.4, and 14.9, respectively. Of the 2- and 4-substituted derivatives, the former compound is preferred, though the therapeutic indices are the same, because of its 100% protective action.

Also the 2-substituted derivative has the most favorable action among the 2-, 3-, and 4-(allyloxy)phenyl derivatives (**9n**, **9o**, and **9p**). Of the compounds containing a heteroring, only the thienyl derivatives were active; the best therapeutic index (12.3) was found for **11f**.

The *paramagnetic analogues* (**24**, **25**) of the active compounds are insoluble in water; thus owing to uncertainties in the dosing, it is difficult to evaluate the efficacies. Yet, a study of the *salts of the N-hydroxy compounds* (**29**, **30**) has shown their activity, though it is lower than that of the nonoxidized compounds.

The activities of a selected group of compounds exhibited in ouabain-induced arrhythmia (Table XIV) show that each type of 2,2,5,5-tetramethylpyrroline(or pyrrolidine)-3-carboxamide derivatives described in this paper

has antiarrhythmic activity comparable with a group of therapeutically used antiarrhythmic drugs belonging to class I.

In our opinion, further detailed investigations of the most potent compounds, which best fulfill the four conditions mentioned in the introduction, may lead after favorable clinical tests to an extension of the range of agents useful as antiarrhythmic drugs.

Experimental Section

The syntheses of the compounds are described by way of typical examples; the methods are denoted in the same way as in Schemes I and II. The structural and molecular formulas and physical properties of the compounds are summarized in Tables I–XII. Melting points (uncorrected) were determined on a Boetius micro melting point apparatus. Elemental analyses (C, H, N) were obtained on a Heraeus micro U/E apparatus or (S, Hal) determined titrimetrically by Schöniger's method. The IR (Specord 75) and ^1H NMR spectra (Perkin-Elmer R 12) of the compounds were in each case consistent with the assigned structures.

Method A. General Procedure for Synthesis of *N*-[(2,2,5,5-Tetramethyl-3-pyrrolin-3-yl)carbonyl]diaminoalkanes (1a–g). (A_1) 2,2,6,6-Tetramethyl-3,5-dibromo-4-piperidone hydrobromide (**3**) (0.1 mol) was added, during about 1 h, to a solution of the diaminoalkane (0.4 mol) in water (500 mL) or (A_2) the hydrobromide **3** (0.1 mol) was added to a solution of the diaminoalkane (0.1 mol) and triethylamine (TEA) (0.3 mol) in water (500 mL) or (A_3) compound **3** (0.1 mol) was added to an aqueous solution (500 mL) of the diaminoalkane (0.1 mol) and potassium carbonate (0.3 mol).

The reaction mixture was stirred for 3 h at room temperature and then saturated with K_2CO_3 (200 g). The solution was extracted with $CHCl_3$ (3 × 100 mL), and the extract was washed with saturated brine, dried ($MgSO_4$), filtered, and concentrated. The excess amine (methods A_1 and A_2) was removed under reduced pressure, and the remaining solidifying oil was dissolved in ether (150 mL). Next day the crystalline product was filtered off, washed with ether, and dried.

Physical constants of the products are given in Table I.

These products (**1a–g**) were used in all the synthetic methods shown in Scheme I, except method F.

Method B. General Procedure for Catalytic Hydrogenolysis (2, 23a,b). A solution of the appropriate pyrrolinecarboxamide derivative (**1b** or **14j,k**) (10 mmol) in $CHCl_3$ (50 mL) was hydrogenated at room temperature over 10% Pd–C at atmospheric pressure until the reaction appeared complete by TLC. The reaction mixture was filtered, the filtrate evaporated to dryness in vacuo, and the residue (**2**, Table I) used without purification in further reactions (Scheme II) or acidified and purified as the hydrochloride salt by recrystallization (**23a,b**; Table XI).

General Procedure for Synthesis of Aryl- and (Aryloxy)alkyl Carboxylic Acid Activated Esters (4a–e, 5a–n). The carboxylic acid (0.1 mol) was suspended in dry ethyl acetate (200 mL), *N*-hydroxysuccinimide (0.1 mol) was added, and the mixture was cooled to 0 °C. In nitrogen atmosphere and with stirring, *N*,*N*′-dicyclohexylcarbodiimide (0.1 mol) in dry ethyl acetate (100 mL) was added dropwise. Cooling was stopped and the mixture allowed to stand overnight. 1,3-Dicyclohexylurea (DCU) that separated was filtered off, the filtrate was evaporated, and the residue was suspended in ether (50 mL). The product was filtered off, washed with ether, and dried.

Tables II and III show the structural and molecular formulas and the yields and physical constants of the compounds.

Method C. General Procedure for Synthesis of *N*-[[(Arylcarbonyl)amino]alkyl]-2,2,5,5-tetramethyl-3-pyrroline-3-carboxamides (7a–o) and *N*-[[[[(Aryloxy or -thio)alkyl]carbonyl]amino]alkyl]-2,2,5,5-tetramethyl-3-pyrroline-3-carboxamides (8a–z). (C_1) The activated ester **4** (10 mmol) and the amine **1a,b** (10 mmol) were dissolved in EtOH (10 mL), and the mixture was stirred at room temperature for 5 h. The solvent was evaporated, and the residue was mixed with water (30 mL) and extracted with $CHCl_3$ (3 × 50 mL). The extract was washed with saturated brine, dried ($MgSO_4$), filtered, and concentrated. The hydrochlorides of the residual crude bases (**7a–c**) were prepared as follows (*c*–*f*, see also footnotes of Table IV):

(*c*) The base **7a** was dissolved in EtOH (15 mL), and the solution was acidified to pH 3 with EtOH saturated with HCl, and the solution was diluted with Et_2O until crystallization had started. The resulting hydrochloride was filtered off, dried, and recrystallized from a mixture of EtOH and Et_2O.

(*d*) The base **7b,c** was dissolved in acetone (50 mL) and an equivalent amount of aniline hydrochloride, dissolved in acetone (30 mL), was added. The mixture was refrigerated overnight, then the hydrochloride of the product was filtered off, washed with Et_2O, dried, and recrystallized from EtOH–Et_2O.

(C_2) A solution of the activated ester (**4d,e**) (10 mmol) in tetrahydrofuran (THF) (50 mL) was added to a THF solution (10 mL) of the amine **1d** (10 mmol) and the mixture was refluxed for 3 h. The bases **7h,o** that separated were isolated by filtration and recrystallized from EtOH–Et_2O.

(C_3) A solution of the amine **1a,b** (10 mmol) and the activated ester **4** (10 mmol) in dry $CHCl_3$ (100 mL) was refluxed for 4 h. The solution was cooled to ambient temperature, washed with 5% $NaHCO_3$ and then with saturated NaCl solution, dried ($MgSO_4$), filtered, and evaporated. Of the crude bases, **7k** was recrystallized from acetone (40 mL); the others were converted into salts as follows.

(*e*) A solution of **7i,j** in acetone (10 mL) was acidified to pH 3 by the introduction of HCl gas; the salt that separated on dilution with Et_2O and cooling was filtered off and recrystallized from EtOH–Et_2O.

(*f*) A solution of base **7l** in acetone (20 mL) was mixed with an acetone solution (20 mL) of fumaric acid. The fumarate of the product was filtered off after cooling, dissolved in 1:1 EtOH–Me_2CO (40 mL), and obtained in recrystallized form on the addition of Et_2O. The hydrochlorides of bases **7m** and **7n** were prepared as described under (c) and (d), respectively.

(C_4) The activated esters of the (aryloxy)alkyl carboxylic acids (**5a–n**) (20 mmol) and the appropriate amine (**1a–g, 2b**) (20 mmol) were refluxed in dry $CHCl_3$ (200 mL) for 3 h while nitrogen was passed through the mixture. The solution was cooled, washed with saturated NaCl solution, dried ($MgSO_4$), filtered, and evaporated to dryness. The residual crude base (**8a–z**) was dissolved in an appropriate solvent [(c) acetone (100 mL) or (d) ethanol (30 mL)], and the solution was acidified to pH 3 by means of HCl gas. The hydrochloride was filtered off, washed with ether, dried, and recrystallized from EtOH–Et_2O.

Structural and molecular formulas of **7a–o**, percentage yields, methods of preparation, and physical constants are summarized in Table IV; those for **8a–z** are listed in Table V. The data of the pyrrolidine derivative (**23c**) obtained from the amine **2b** are given in Table XI.

Method D. General Procedure for Synthesis of Compounds 7d–g Using Acid Chlorides. The acid chloride **6** (4-pyridinecarboxylic acid chloride or 2-thiophenecarboxylic acid chloride) (10 mmol) was dissolved in dry benzene (50 mL) and added to a solution of amine **1a–c** (10 mmol) in dry benzene, with stirring and refluxing; moisture was excluded by applying $CaCl_2$ tubes. The mixture was refluxed for 5 h and allowed to cool to room temperature. The hydrochloride of the product was filtered off, washed with ether, dried, and recrystallized from EtOH–Et_2O. Physical properties of the products are listed in Table IV.

Method E. General Procedure for Synthesis of *N*-(2,2,5,5-Tetramethyl-3-pyrrolin-3-yl(pyrrolidin-3-yl))-carbonyl]-*N*′-aralkyldiaminoalkanes (9a–s, 10a–k, 11a–l, 23d–i). Equivalent amounts (20 mmol) of the amine **1a–g, 2b** and the oxo compound **12** were refluxed in toluene (100 mL) in the presence of a catalytic amount of *p*-toluenesulfonic acid, in a flask equipped with a Dean–Stark water separator. After the separation of the calculated amount of water (about 16 h), the mixture was cooled to ambient temperature and filtered, and the filtrate was concentrated under reduced pressure (water pump). The remaining crude Schiff base was added to a suspension of $NaBH_4$ (25 mmol) in EtOH (100 mL) which had been cooled to 0 °C, then the mixture was refluxed for 1 h. It was diluted with water (50 mL) and evaporated in vacuum to 70 mL, and the oily aqueous residue was extracted with $CHCl_3$ (3 × 50 mL). The extract was dried ($MgSO_4$), filtered, and concentrated. The crude base **9f** was recrystallized from a mixture of acetone and Et_2O;

Table XIII. Antiarrhythmic Activity and Acute Toxicity of Compounds in the Aconitine Rat Test

	incidence of arrhythmias[a]		secondary evaluation			
compd	dose, mg/kg iv	no. positive cases/no. cases tested	ED_{150}[b] mg/kg iv	LD_{50},[c] mg/kg iv	TI[d]	rel potency (quinidine = 1)
7a	4.0	2/10		95 (92–100)		
7b	4.0	4/10		76 (69–72)		
7c	4.0	5/10	12.3 (10.2–14.7)	119 (104–138)	9.7	0.97
7d	4.0	2/10		88 (85–93)		
7e	4.0	3/10		93 (77–114)		
7f	4.0	4/10		48 (41–57)		
7g	4.0	6/10		37 (33–41)		
7h	4.0	7/10	6.7 (5.6–7.8)	65 (59–72)	9.7	1.77
7i	4.0	6/10		54 (45–66)		
7j	NT[e]					
7k	4.0	0/10		85 (76–95)		
7l	4.0	1/10		52 (46–58)		
7m	4.0	2/10		86 (66–112)		
7n	4.0	8/10	3.1 (2.6–3.6)	71 (59–86)	22.9	3.8
7o	NT[e]					
8a	4.0	10/10	2.6 (2.1–2.9)	49 (40–61)	18.8	4.6
8b	4.0	7/10	6.9 (5.9–8.1)	38 (35–43)	5.5	1.7
8c	4.0	4/10		37 (31–45)		
8d	4.0	5/10		20 (17–22)		
8e	4.0	2/10		36 (29–44)		
8f	4.0	3/10		30 (25–35)		
8g	4.0	0/10		47 (40–56)		
8h	4.0	0/10		46 (38–55)		
8i	4.0	0/10		69 (59–82)		
8j	2.0	3/10		19 (15–23)		
8k	2.0	8/10	2.4 (1.9–2.9)	14 (13–16)	5.8	4.9
8l	4.0	10/10	2.9 (2.5–3.2)	12 (10–15)	4.1	4.1
8m	4.0	7/10	6.3 (5.2–7.6)	11 (8.4–16)	1.7	1.9
8n	4.0	10/10	1.4 (1.1–1.9)	19 (12–28)	13.6	8.5
8o	NT[e]					
8p	2.0	7/10	2.8 (2.2–3.4)	9.3 (8.2–9.8)	3.3	4.3
8q	1.0	10/10	0.80 (0.70–0.93)	7.6 (6.1–9.3)	9.5	14.9
8r	NT[e]					
8s	4.0	7/10	4.1 (3.4–5.0)	18 (14–22)	4.4	2.9
8t	4.0	7/10	2.2 (1.9–2.6)	30 (28–33)	13.6	5.4
8u	NT[e]					
8v	4.0	7/10	2.7 (2.4–3.0)	14 (11–17)	5.2	4.4
8z	4.0	6/10	3.9 (3.1–4.9)	31 (22–43)	7.9	3.1
9a	4.0	9/10	3.6 (3.1–4.2)	26 (19–35)	7.2	3.3
9b	4.0	5/10	5.4 (4.1–7.1)	82 (55–119)	15.2	2.2
9c	4.0	7/10	4.8 (4.1–5.5)	65 (57–73)	13.5	2.5
9d	4.0	10/10	1.6 (1.3–1.9)	7.9 (7.4–8.4)	4.9	7.4
9e	4.0	10/10	1.0 (0.81–1.3)	30 (27–33)	30.0	11.9
9f	4.0	7/10	4.7 (3.9–5.4)	28 (24–34)	5.9	2.5
9g	4.0	4/10	8.5 (7.3–9.8)	13 (10–17)	1.5	1.4
9h	4.0	4/10		17 (12–23)		
9i	2.0	10/10	0.96 (0.84–1.1)	11 (8.8–13)	11.5	12.4
9j	4.0	10/10	1.3 (1.1–1.6)	23 (19–26)	17.7	9.2
9k	2.0	10/10	0.60 (0.50–0.71)	9.0 (7.2–11)	14.3	19.8
9l	2.0	10/10	0.74 (0.68–0.82)	7.0 (5.8–8.5)	9.4	16.1
9m	2.0	8/10	1.3 (1.2–1.5)	20 (16–25)	14.9	9.2
9n	2.0	10/10	1.9 (1.4–2.6)	18 (16–21)	9.5	6.3
9o	2.0	7/10	2.7 (2.5–2.9)	34 (27–43)	12.6	4.4
9p	4.0	6/10	2.9 (2.6–3.4)	28 (21–38)	9.7	4.1
9q	2.0	1/10		10 (8.3–13)		
9r	4.0	2/10		25 (17–35)		
9s	4.0	2/10		23 (18–29)		
10a	4.0	9/10	1.7 (1.5–1.9)	16 (13–19)	9.4	7.0
10b	4.0	2/10		61 (48–78)		
10c	4.0	10/10	3.4 (2.4–4.7)	26 (24–29)	7.6	3.5
10d	2.0	10/10	0.47 (0.41–0.55)	8.7 (6.9–10.9)	18.5	25.3
10e	4.0	10/10	1.7 (1.3–2.2)	15 (12–18)	8.8	7.0
10f	4.0	10/10	2.2 (1.7–2.7)	21 (17–26)	9.5	5.4
10g	4.0	10/10	0.21 (0.19–0.24)	6.2 (5.7–6.8)	29.5	56.7
10h	4.0	10/10	0.69 (0.63–0.77)	13 (11–15)	18.8	17.2
10i	1.0	1/10		2.1 (1.6–2.7)		
10j	4.0	2/10		56 (46–67)		
10k	4.0	9/10	3.8 (3.3–4.4)	22 (18–26)	5.8	3.1
11a	4.0	4/10		20 (15–28)		
11b	4.0	0/10		102 (88–116)		
11c	4.0	0/10		94 (89–99)		
11d	4.0	0/10		34 (26–37)		
11e	4.0	3/10		123 (111–135)		

Table XIII (Continued)

	incidence of arrhythmias[a]		secondary evaluation			
compd	dose, mg/kg iv	no. positive cases/no. cases tested	ED_{150}[b] mg/kg iv	LD_{50},[c] mg/kg iv	TI[d]	rel potency (quinidine = 1)
11f	4.0	7/10	5.3 (4.6–6.1)	65 (60–68)	12.3	2.2
11g	4.0	9/10	5.5 (4.6–6.6)	28 (24–33)	5.1	2.2
11h	4.0	10/10	4.7 (3.6–6.2)	28 (23–35)	5.9	2.5
11i	4.0	2/10		53 (46–62)		
11j	4.0	4/10		68 (59–79)		
11k	4.0	1/10		49 (47–52)		
11l	4.0	8/10	7.6 (6.4–8.8)	49 (44–55)	6.4	1.6
14a	1.0	7/10	2.1 (1.8–2.5)	6.0 (5.5–6.6)	2.9	5.7
14b	4.0	3/10		34 (26–45)		
14c	4.0	1/10		51 (45–57)		
14d	4.0	0/10		49 (38–64)		
14e	4.0	0/10		66 (59–74)		
14f	4.0	2/10		75 (67–83)		
14g	4.0	5/10		63 (56–70)		
14h	4.0	0/10		123 (112–134)		
14i	4.0	0/10		132 (119–147)		
14j	0.5	10/10	0.93 (0.84–1.0)	11 (9.4–13)	11.8	12.8
14k	4.0	10/10	2.4 (2.0–2.9)	53 (46–62)	22.1	4.9
14l	4.0	10/10	1.9 (1.6–2.3)	15 (13–18)	7.9	6.3
14m	2.0	10/10	0.78 (0.62–0.98)	7.6 (6.1–9.5)	9.7	15.3
16a	1.0	10/10	0.37 (0.31–0.45)	7.4 (5.6–9.6)	20.0	32.2
16b	4.0	4/10		39 (33–46)		
16c	4.0	10/10	1.3 (1.1–1.5)	26 (23–29)	19.9	9.1
18a	4.0	0/10		1131 (1067–1197)		
18b	4.0	0/10		753 (673–845)		
18c	4.0	0/10		1514 (1402–1642)		
18d	4.0	0/10		344 (319–373)		
18e	4.0	0/10		357 (321–378)		
18f	4.0	0/10		419 (403–438)		
19a	4.0	0/10		128 (98–166)		
19b	4.0	0/10		106 (104–108)		
19c	4.0	0/10		182 (153–216)		
19d	4.0	2/10		113 (99–129)		
19e	4.0	7/10	7.9 (6.2–10.2)	55 (53.57)	6.9	1.5
19f	2.0	10/10	2.6 (2.0–3.3)	23 (18–28)	8.8	4.6
19g	4.0	10/10	3.0 (2.6–3.6)	28 (26–30)	9.3	3.9
22a	4.0	4/10		92 (76–111)		
22b	4.0	10/10	4.5 (3.6–5.7)	31 (22–45)	6.9	2.6
22c	4.0	10/10	10.5 (7.1–15.4)	48 (41–54)	4.6	1.1
22d	2.0	10/10	1.7 (1.4–1.9)	13 (10–17)	7.6	7.0
22e	4.0	4/10		73 (63–83)		
23a	0.5	10/10	0.39 (0.33–0.45)	2.0 (1.5–2.5)	5.1	30.5
23b	4.0	10/10	0.84 (0.69–1.0)	40 (34–47)	47.6	14.2
23c	4.0	0/10		38 (32–45)		
23d	4.0	7/10	2.4 (2.0–2.8)	31 (27–36)	12.9	4.9
23e	4.0	9/10	2.9 (2.6–3.4)	39 (31–50)	13.4	4.1
23f	2.0	10/10	2.1 (1.6–2.8)	13 (11–17)	6.2	5.7
23g	1.0	10/10	0.52 (0.46–0.58)	13 (11–17)	25.0	22.9
23h	4.0	10/10	4.2 (3.5–4.9)	43 (36–52)	10.2	2.8
23i	4.0	7/10	13.2 (10.4–16.8)	19 (15–24)	1.4	0.9
23j	4.0	10/10	2.3 (2.1–2.5)	39 (33–46)	16.9	5.1
23k	4.0	10/10	4.5 (3.7–5.5)	22 (17–28)	4.9	2.6
23	4.0	3/10		53 (49–57)		
23m	4.0	10/10	2.7 (2.4–3.0)	22 (18–26)	8.1	4.4
24a	8.0	0/10		54 (47–61)		
24b	4.0	0/10		136 (126–147)		
24c	4.0	0/10		165 (127–214)		
24d	4.0	0/10		187 (159–221)		
25a	4.0	6/10	9.2 (6.8–12.4)	21 (18–24)	2.3	1.3
25b	4.0	0/10		>200		

[a] The preliminary test method is described in the Experimental Section; 10 rats were used for each compound. [b] Effective dose (and 95% confidence ranges) against aconitine-induced arrhythmia in anesthetized rats. The duration of the aconitine infusion (5 μg/kg per min) was 6.12 min in the saline-pretreated controls. ED_{150} corresponds with an infusion time of 9.18 min. [c] LD_{50} was determined by the method of Litchfield and Wilcoxon.[24] [d] Therapeutic index ratio of LD_{50} in mice iv and ED_{150} in aconitine rat test iv (iv = intravenous administration). [e] NT = not tested.

the other bases were converted into salts in the following ways: (*c*) the base was dissolved in acetone (100 mL), and the solution was acidified with HCl gas to pH 3, and the salt was filtered off, washed with 1:1 acetone–ether mixture, and recrystallized from EtOH–Et_2O; (*f*) HCl gas was passed into an ethyl acetate solution (50 mL) of the base, followed by crystallization as before; (*e*) a solution of the base in EtOH (10 mL) was acidified by adding EtOH saturated with HCl, followed by the usual workup; (*d*) an acetone solution (50 mL) of the base was mixed with a solution of the equivalent amount of *p*-toluenesulfonic acid in acetone (20 mL), the mixture was cooled, and the *p*-toluenesulfonate of the product was filtered off, washed with Et_2O, and dried. The physical constants of the products are listed in Tables VI and XI (*c–f* correspond to footnotes in these Tables).

Table XIV. Preventive Effects of Some New 2,2,5,5-Tetramethyl-3-pyrroline(pyrrolidine)-3-carboxamide Derivatives, Lidocaine, Mexiletine, Tocainide, and Quinidine against Ouabain Arrhythmia in Anesthetized Guinea Pigs

compd	dose, mg/kg iv	n^a	amount of ouabain needed for production of ventricular arrhythmias (μg/kg ± SE)		
			extrasystole	ventricular fibrillation	cardiac arrest
control		30	145.6 ± 8.1	225.1 ± 12.3	264.9 ± 13.3
8n	2.0	5	226.6 ± 4.1[d]	353.6 ± 32.3[b]	398.8 ± 31.9[b]
8t	2.0	5	201.1 ± 4.4	250.9 ± 13.7	284.7 ± 9.5
9n	1.0	10	224.3 ± 21.3[b]	280.2 ± 29.1	306.1 ± 30.7
14j	1.0	5	253.4 ± 32.4[b]	316.6 ± 19.3[b]	347.6 ± 14.2[b]
14k	2.0	10	214.2 ± 8.9[d]	284.2 ± 14.2	331.4 ± 13.8[b]
14l	2.0	15	208.9 ± 6.1[d]	325.3 ± 9.3[d]	361.0 ± 9.5[d]
19f	2.0	10	236.9 ± 17.2[d]	345.5 ± 16.6[d]	382.5 ± 14.7[d]
22d	1.0	5	211.5 ± 13.9[b]	298.2 ± 16.4	316.0 ± 17.1
23b	2.0	10	196.9 ± 5.6[c]	290.9 ± 14.5[b]	319.9 ± 14.1
lidocaine	4.0	5	200.1 ± 8.9[b]	247.7 ± 10.2	270.2 ± 11.3
mexiletine	4.0	5	185.5 ± 9.7	245.9 ± 5.5	286.1 ± 13.0
tocainide	4.0	10	236.0 ± 12.4[d]	358.1 ± 18.7[d]	392.8 ± 30.2[c]
quinidine	2.0	10	195.4 ± 11.9[b]	291.1 ± 14.7[b]	313.9 ± 14.2

[a] n = the number of guinea pigs. Statistical significance of the difference from control. [b] $P < 0.05$. [c] $P < 0.01$. [d] < 0.001.

Method F. General Procedure for Synthesis of N-Substituted 2,2,5,5-Tetramethyl-3-pyrroline-3-carboxamides (14). The amine **13** (30 mmol) was dissolved in a 3:1 mixture of MeOH and H_2O (120 mL), and K_2CO_3 (30 mmol) was added, followed by the addition, at room temperature and with stirring, of 3,5-dibromo-2,2,6,6-tetramethyl-4-piperidinone hydrobromide (**3**) (30 mmol); the rate of addition was adjusted according to the rate of dissolution of **3**. Stirring was continued for 3 h more and then the mixture was diluted with 10% K_2CO_3 solution (100 mL) and extracted with $CHCl_3$ (3 × 50 mL). The organic phase was washed with saturated NaCl solution, dried ($MgSO_4$), and filtered and the solvent evaporated. The residue was dissolved in EtOH (15 mL), saturated with HCl, and diluted with Et_2O. The hydrochloride (**14a–m**) was filtered off and recrystallized from EtOH by diluting the solution with Et_2O. The constants of the products are given in Table VII. Compound **24a** was obtained from **28** and 1-(2,6-dimethylphenoxy)-2-propanamine in a Favorskii reaction (Table XII).

Method G. General Procedure for Synthesis of Compounds 16. The *N*-(α-haloacyl)-2,6-xylidine (**15**) (12 mmol) was dissolved in dry dimethylformamide (DMF) (50 mL) and a DMF solution (20 mL) of **1a** or **1b** (12 mmol) and K_2CO_3 (2 g) was added. The mixture was maintained at 60 °C for 3 h. The solvent was then evaporated, the residue dissolved in $CHCl_3$ (100 mL), and the solution washed with saturated NaCl, dried ($MgSO_4$), filtered, and evaporated. The crude product was dissolved in ethyl acetate (50 mL) and acidified with HCl to pH 3. The salt was recrystallized from EtOH–Et_2O. The constants of the products (**16a–c**) are shown in Table VIII.

Method H. General Procedure for Synthesis of *N*-[(2,2,5,5-Tetramethyl-3-pyrroline-3-carboxamido)alkyl]-tetrahydro- and -hexahydrophthalamide Acids (18a–f). Compound **1a** or **1b** (10 mmol) and the appropriate anhydride (**17**) (10 mmol) were stirred in a 2:1 mixture of Et_2O and THF (75 mL) at room temperature for 2 days. The product that separated was filtered off, washed with Et_2O, dried, and recrystallized from EtOAc–$CHCl_3$ (1:1). Properties of the products are summarized in Table IX.

Method I. General Procedure for Synthesis of *N*-[(2,2,5,5-Tetramethyl-3-pyrroline-3-carboxamido)alkyl]-tetrahydro- and -hexahydrophthalimides (19a–f). A solution of **1a** or **1b** (15 mmol) and the anhydride (**17**) (15 mmol) in toluene (100 mL) was mixed with triethylamine (TEA) (4 mL) and the mixture was boiled for 8 h under a Dean–Stark water trap. After evaporation of the solvent, the residue was dissolved in EtOH (10 mL) and acidified with HCl in EtOH to pH 3. The hydrochloride of the product (**19a–f**) that separated on cooling was filtered off and recrystallized from EtOH–EtOAc (1:1). Constants are given in Table IX.

Method J. General Procedure for Synthesis of Phthalimide Derivatives (19e,f) from Phthalamide Acids (18e,f). Dissolution in toluene (50 mL) of compound **18e** or **18f** (10 mmol) prepared by method H and refluxing of the solution with TEA (2 mL) for 5 h gave, on evaporation to dryness, the crude base **19e** or **19f**. A solution of the base in EtOH was acidified with HCl in EtOH to pH 3, the mixture was cooled, and the crystalline salts were filtered off, washed with Et_2O–EtOH (10:1), and dried. Recrystallization from EtOH–EtOAc (1:1) gave the pure products; their properties (Table IX) were the same as those of the products prepared by method I; however, the yields were lower.

Method K. General Procedure for Synthesis of Phthalimide Derivatives (19f, 19g, 23k) from Phthalimide (20). The derivatives **19f, 19g,** and **23k** were obtained by heating equivalent amounts (10 mmol, each) of the amine (**1b**, **1d**, or **2**) and phthalimide (**20**), without any solvent, until the evolution of ammonia had ceased (about 30 min). After cooling, the melt was dissolved in EtOH (15 mL) and adjusted to pH 3 by means of HCl in EtOH. The crude product (**19f, 19g, 23k**) was recrystallized from EtOH-EtOAc (1:1). The physical constants of **19f** were the same as those of the products prepared by methods I and J (Table IX), but the yields were higher. Properties of the *pyrrolidine derivative* **23k** are given in Table XI.

Method L. General Procedure for Synthesis of 2-Alkyl-*N*-[[(2,2,5,5-tetramethyl-3-pyrrolin-3-yl(or pyrrolidin-3-yl))carbamoyl]alkyl]-4(3*H*)-quinazolinone Derivatives (22a–e, 23l,m). The 2-alkyl-4*H*-3,1-benzoxazin-4-one (**21**) (10 mmol) was allowed to react with **1a,b,d** or **2** (10 mmol) under the conditions of method K. Similar workup of the reaction mixture gave **22a–e** and **23l,m**; for the data of these products, see Tables X and XI.

Method M. General Procedure for Synthesis of 1-Oxypyrroline and 1-Oxypyrrolidine Derivatives (24 and 25). The nitroxide compounds of types **24** and **25** were synthesized from **14j,k,l, 19f,** and **23a,b** by preparing MeOH solutions (20 mL) of these compounds (10 mmol) and adding catalysts (EDTA–Na_2 and sodium tungstate, 0.10 g each), water (2 mL), and 30% H_2O_2 (10 mL). The mixture was then allowed to stand for 3 days at room temperature and diluted with water, the alcohol was evaporated, and the residue was extracted with $CHCl_3$ (3 × 20 mL). The extract was washed with saturated NaCl solution, dried ($MgSO_4$), and filtered and the solvent evaporated. The residual oil was taken up in Et_2O and refrigerated to give crystalline products. The crude bases (**24a–d, 25a,b**) were dissolved in $CHCl_3$ (5 mL) and diluted with Et_2O to start crystallization. The recrystallized product was recovered from the cold solution by filtration and dried. Data of the products are shown in Table XII.

Method N. General Procedure for Synthesis of Compounds 24b and 25b from the Paramagnetic Carboxyl Acid Activated Esters (26, 27). The succinimide ester of the 1-oxy-2,2,5,5-tetramethyl-3-pyrroline(or pyrrolidine)-3-carboxylic acid (**26** or **27**) (10 mmol) was refluxed for 2 h with the appropriate amine (**13**) (10 mmol) in dry $CHCl_3$ (50 mL), in a nitrogen atmosphere and with stirring. After cooling, the solution was washed successively with 5% sulfuric acid (10 mL), 10% Na_2CO_3 (10 mL), and saturated NaCl solution, dried ($MgSO_4$), filtered, and evaporated. The residue was dissolved in a small amount of $CHCl_3$ and diluted with Et_2O to obtain the crystalline products. Physical

constants of **24b** and **25b** were in agreement with those of the products prepared by method M, but the yields were lower (cf. Table XII).

Method O. General Procedure for Synthesis of *N*-Hydroxypyrroline(or pyrrolidine) Derivatives (29, 30) from Their Paramagnetic *N*-Oxyl Derivatives (24, 25). The paramagnetic compounds of types **24** and **25** (10 mmol) were dissolved in EtOH (10 mL) saturated with HCl gas, and after 10 min the solutions were diluted with Et_2O to start crystallization. The crystalline hydrochlorides of **29** and **30** that separated on refrigeration were filtered off, washed with Et_2O, and dried. Pure compounds were obtained by dissolving the products in a small amount of EtOH and dilution with Et_2O. Data of the products are listed in Table XII.

Method P. General Procedure for Synthesis of the Paramagnetic Compounds (24b and 25a) from the *N*-Hydroxy Derivatives (29b, 30a). An aqueous solution (5 mL) of the *N*-hydroxy derivative hydrochloride (**29b, 30a**) (5 mmol) was diluted with 5% K_2CO_3 solution (10 mL). It was extracted with $CHCl_3$ (2 × 15 mL), dried ($MgSO_4$), and filtered. The chloroform solution was exposed to air with stirring, whereupon it slowly became yellow, characteristic of the paramagnetic *N*-oxyl compound. The rate of oxidation was higher in the presence of PbO_2 (1 g); the solution was stirred for 30 min at room temperature, filtered, concentrated to about 5 mL, and diluted with Et_2O. The crystalline *N*-oxyl derivative (**24b, 25a**) that deposited on cooling was filtered off, washed with Et_2O, and dried. The physical constants of the product were identical with those of the products obtained by methods M and N. Properties of the compounds are given in Table XII.

Antiarrhythmic Activity and Acute Toxicity. Aconitine-Induced Arrhythmia. Preliminary screening tests of the compounds were performed in aconitine-induced arrhythmias in anesthetized rats.[21] Polymorph ventricular arrhythmias were induced by 30 μg/kg (0.1 mL/100 g of body weight) of aconitine solution given into the femoral vein of Wistar rats of both sexes, with urethane.

Antiarrhythmic activities of the test compounds were compared in most cases in intravenous (iv) doses of 4.0 mg/kg, except when the toxicity of the compound prohibited the administration of such a dose. The test materials were injected into the femoral vein in constant volume (0.1 mL/100 g of body weight) 5 min before the administration of aconitine. The lead II ECG was continuously recorded on a Hellige Multiscriptor for 30 min.

Animals that had normal sinus rhythms for 30 min following the administration of aconitine were considered protected.

Compounds active in the preliminary screening test were further tested according to the Zetler and Strubelt[22] experimental arrhythmic model.

These experiments were performed in anesthetized rats (180–240 g). At least three doses were used for each compound, and controls were treated with saline. The compounds were dissolved in saline and given in constant volume into the femoral vein. The iv infusion of aconitine (5 μg/kg per min, 0.1 mL/min) was started 5 min after the pretreatment and run until the first series of ventricular extrasystoles appeared 6.17 ± 0.27 min in the animals pretreated with saline. The ED_{150} corresponds with an infusion time of 9.12 min.

The results were expressed as regression lines that permitted the interpolation of the compound dose that would increase the aconitine dose producing ventricular arrhythmia by 50% (ED_{150}).

Ouabain-Induced Arrhythmia. Female and male adult guinea pigs, weighing 300–400 g, were anesthetized with urethane (1.6 g/kg ip) and given ouabain into the right jugular vein by slow infusion (0.1 mL/min for 30 s every 90 s of a 80 μg/mL ouabain solution in NaCl 0.9%), until the animals died. The progress of the ouabain intoxication was followed by recording the electrocardiogram every 90 s. The compounds were given iv 5 min before the ouabain infusion was started.

The average doses of ouabain inducing (a) ventricular extrasystoles, (b) ventricular fibrillation, and (c) death were compared to those of the control group.

Acute Toxicity. LD_{50} was determined from the 7-day mortality in CFLP mice (18–22 g) of both sexes. The LD_{50} values were calculated according to the method of Litchfield and Wilcoxon.[24]

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Registry No. **1a**, 93799-56-5; **1b**, 93799-49-6; **1c**, 93969-01-8; **1d**, 93799-52-1; **1e**, 102131-23-7; **1f**, 93969-00-7; **1g**, 93969-02-9; **2**, 93799-58-7; **3**, 19971-12-1; **4** (Ar = 3,4-$OCH_2OC_6H_3$), 102132-54-7; **4** (Ar = 3,4,5-$(OCH_3)_3C_6H_2$), 69705-20-0; **4a**, 23776-85-4; **4b**, 93799-43-0; **4c**, 73158-83-5; **4d**, 83039-60-5; **4e**, 93799-48-5; **5** (Ar = C_6H_5, Y = CH_2, Q = H), 103-82-2; **5** (Ar = C_6H_5, Y = CH(OH), Q = H), 90-64-2; **5** (Ar = 2-thienyl, Y = –, Q = H), 527-72-0; **5** (Ar = 4-HOC_6H_4, Y = CH_2, Q = H), 156-38-7; **5** (Ar = 2-thienyl, Y = CH_2, Q = H), 1918-77-0; **5** (Ar = C_6H_5, Y = CH_2O, Q = H), 122-59-8; **5** (Ar = C_6H_5, Y = CH_2S, Q = H), 103-04-8; **5** (Ar = 2,4-$Cl_2C_6H_3$, Y = CH_2O, Q = H), 94-75-7; **5** (Ar = 2-CH_3-4-ClC_6H_3, Y = CH_2O, Q = H), 94-74-6; **5** (Ar = 4-ClC_6H_4, Y = $C(CH_3)_2O$, Q = H), 882-09-7; **5** (Ar = 2-$CH_2CH{=}CH_2$-4-$CH_3C_6H_3$, Y = CH_2O, Q = H), 102131-24-8; **5** (Ar = 2-CH_3O-4-$CH_2CH_2CH_3C_6H_3$, Y = CH_2O, Q = H), 88425-71-2; **5** (Ar = 2-CH_3O-4-$CH_2CH{=}CH_2C_6H_3$, Y = CH_2O, Q = H), 6331-61-9; **5** (Ar = 2-CH_3O-4-$CH_2CH{=}CH_2C_6H_3$, Y = $CH(CH_3)O$, Q = H), 63857-97-6; **5** (Ar = 2-CH_3O-4-$CH{=}CHCH_3C_6H_3$, Y = CH_2O, Q = H), 7510-46-5; **5** (Ar = 2-CH_3O-4-$CH{=}CHCH_3C_6H_3$, Y = $CH(CH_3)O$, Q = H, 63857-98-7; **5** (Ar = 2,6-$(CH_3)_2C_6H_3$, Y = $CH(CH_3)O$, Q = H), 23359-47-9; **5a**, 38678-58-9; **5b**, 93799-47-4; **5c**, 93799-60-1; **5d**, 93799-61-2; **5e**, 40249-24-9; **5f**, 93799-46-3; **5g**, 102131-25-9; **5h**, 93799-44-1; **5i**, 93799-59-8; **5j**, 102131-26-0; **5k**, 102131-27-1; **5l**, 93799-45-2; **5m**, 93799-63-4; **5n**, 93799-62-3; **7a**, 102131-28-2; **7a**·HCl, 93823-58-6; **7b**, 102131-29-3; **7b**·HCl, 102131-37-3; **7c**, 93799-19-0; **7c**·HCl, 93844-06-5; **7d**, 102131-30-6; **7d**·2HCl, 93823-70-2; **7e**, 102131-31-7; **7e**·HCl, 93823-71-3; **7f**, 102131-32-8; **7f**·HCl, 93823-72-4; **7g**, 102131-33-9; **7g**·HCl, 93823-74-6; **7h**, 93823-73-5; **7i**, 102131-34-0; **7i**·HCl, 93823-59-7; **7j**, 102131-35-1; **7j**·HCl, 93823-60-0; **7k**, 93823-61-1; **7l**, 93823-62-2; **7l**·$C_4H_4O_4$, 93823-63-3; **7m**, 102131-36-2; **7m**·HCl, 93823-75-7; **7n**, 93799-24-7; **7n**·HCl, 93823-76-8; **7o**, 93823-77-9; **8a**, 102131-38-4; **8a**·HCl, 93823-64-4; **8b**, 93799-23-6; **8b**·HCl, 93823-69-9; **8c**, 102131-39-5; **8c**·HCl, 93823-83-7; **8d**, 102131-40-8; **8d**·HCl, 93823-84-8; **8e**, 102131-41-9; **8e**·HCl, 93823-85-9; **8f**, 102131-42-0; **8f**·HCl, 93823-86-0; **8g**, 102131-43-1; **8g**·HCl, 93823-80-4; **8h**, 102131-44-2; **8h**·HCl, 93823-81-5; **8i**, 102131-45-3; **8i**·HCl, 93823-82-6; **8j**, 93799-57-6; **8j**·HCl, 93823-67-7; **8k**, 93799-22-5; **8k**·HCl, 93823-68-8; **8l**, 102131-46-4; **8l**·HCl, 102131-54-4; **8m**, 102131-47-5; **8m**·HCl, 102131-55-5; **8n**, 93799-21-4; **8n**·HCl, 93823-66-6; **8o**, 102131-48-6; **8o**·HCl, 102131-56-6; **8p**, 102131-49-7; **8p**·HCl, 93823-87-1; **8q**, 102131-50-0; **8q**·HCl, 93823-88-2; **8r**, 102131-51-1; **8r**·HCl, 102150-76-5; **8s**, 93799-25-8; **8s**·HCl, 93823-78-0; **8t**, 93799-20-3; **8t**·HCl, 93823-65-5; **8u**, 102131-52-2; **8v**, 93799-26-9; **8v**·HCl, 93823-79-1; **8z**, 102131-53-3; **8z**·HCl, 102150-77-6; **9a**, 93799-28-1; **9a**·2HCl, 93798-81-3; **9b**, 93823-89-3; **9b**·$2C_7H_8O_3S$, 93823-90-6; **9c**, 102131-58-8; **9c**·2HCl, 93798-95-9; **9d**, 102131-59-9; **9d**·2HCl, 102131-89-5; **9e**, 102131-60-2; **9e**·2HCl, 102131-90-8; **9f**, 102131-61-3; **9g**, 102131-62-4; **9g**·2HCl, 102131-91-9; **9h**, 102131-63-5; **9h**·2HCl, 102131-92-0; **9i**, 102131-64-6; **9i**·2HCl, 102131-93-1; **9j**, 102131-65-7; **9j**·2HCl, 102131-94-2; **9k**, 102131-66-8; **9k**·2HCl, 102131-95-3; **9l**, 102131-67-9; **9l**·2HCl, 102131-96-4; **9m**, 102131-68-0; **9m**·2HCl, 102131-97-5; **9n**, 102131-69-1; **9n**·2HCl, 102131-98-6; **9o**, 102131-70-4; **9o**·2HCl, 102131-99-7; **9p**, 102131-71-5; **9p**·2HCl, 102132-00-3; **9q**, 102131-72-6; **9q**·2HCl, 102132-01-4; **9r**, 102131-73-7; **9r**·2HCl, 93823-91-7; **9s**, 93799-29-2; **9s**·2HCl, 93798-82-4; **10a**, 102131-74-8; **10a**·2HCl, 102132-02-5; **10b**, 93823-92-8; **10b**·$2C_7H_8O_3S$, 93823-93-9; **10c**, 102131-75-9; **10c**·2HCl, 102132-03-6; **10d**, 102131-76-0; **10d**·2HCl, 102132-04-7; **10e**, 102131-77-1; **10e**·2HCl, 102132-05-8; **10f**, 102131-78-2; **10f**·2HCl, 102132-06-9; **10g**, 102131-79-3; **10g**·2HCl, 102132-07-0; **10h**, 102131-80-6; **10h**·2HCl, 102132-08-1; **10i**, 102131-81-7; **10i**·2HCl, 102132-09-2; **10j**, 93823-94-0; **10j**·$2C_7H_8O_3S$, 93823-95-1; **10k**, 102131-82-8; **10k**·2HCl, 93798-83-5; **11a**, 93799-51-0; **11a**·2HCl, 93798-89-1; **11b**, 102131-83-9; **11b**·3HCl, 93798-84-6; **11c**, 102131-84-0; **11c**·$2C_7H_8O_3S$, 102132-10-5; **11d**, 102131-85-1; **11d**·2HCl, 93798-87-9; **11e**, 93799-27-0; **11e**·$2C_7H_8O_3S$, 93823-96-2; **11f**, 93799-30-5; **11f**·2HCl, 93798-88-0; **11g**, 93799-33-8; **11g**·2HCl, 93798-97-1; **11h**, 102131-86-2; **11h**·2HCl, 93798-93-7; **11i**, 102131-87-3; **11i**·2HCl, 93798-80-2; **11j**, 102150-78-7; **11j**·2HCl,

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93798-91-5; **11k**, 102131-88-4; **11k**·2HCl, 93798-92-6; **11l**, 93799-54-3; **11l**·2HCl, 93798-90-4; **12** (R^1 = C_6H_5, R^2 = H), 100-52-7; **12** (R^1 = 4-ClC_6H_4, R^2 = H), 104-88-1; **12** (R^1 = 4-$CF_3C_6H_4$, R^2 = H), 455-19-6; **12** (R^1 = 2-$CH_3OC_6H_4$, R^2 = H), 133-02-4; **12** (R^1 = 2-HOC_6H_4, R^2 = H), 90-02-8; **12** (R^1 = 3-HOC_6H_4, R^2 = H), 100-83-4; **12** (R^1 = 4-HOC_6H_4, R^2 = H), 123-08-0; **12** (R^1 = 3-$C_6H_5OC_6H_4$, R^2 = H), 39515-51-0; **12** (R^1 = 4-$C_6H_5OC_6H_4$, R^2 = H), 67-36-7; **12** (R^1 = 2-$C_6H_5CH_2OC_6H_4$, R^2 = H), 5896-17-3; **12** (R^1 = 3-$C_6H_5CH_2OC_6H_4$, R^2 = H), 1700-37-4; **12** (R^1 = 4-$C_6H_5CH_2OC_6H_4$, R^2 = H), 4397-53-9; **12** (R^1 = 2-CH_2=$CHCH_2OC_6H_4$, R^2 = H), 28752-82-1; **12** (R^1 = 3-CH_2=$CHCH_2OC_6H_4$, R^2 = H), 40359-32-8; **12** (R^1 = 4-CH_2=$CHCH_2OC_6H_4$, R^2 = H), 40663-68-1; **12** (R^1 = 2-$H_2NCOCH_2OC_6H_4$, R^2 = H), 24590-06-5; **12** (R^1 = 4-$CH_3CONHC_6H_4$, R^2 = H), 122-85-0; **12** (R^1 = 2,4-$(OCH_3)_2C_6H_3$, R^2 = H), 613-45-6; **12** (R^1 = 3,4-$(OCH_3)_2C_6H_3$, R^2 = H), 120-14-9; **12** (R^1 = 2-HO-3-$CH_3OC_6H_3$, R^2 = H), 148-53-8; **12** (R^1 = 3-OCH_3-4-OHC_6H_3, R^2 = H), 121-33-5; **12** (R^1 = 2-CH_2=$CHCH_2O$-3-$CH_3OC_6H_3$, R^2 = H), 23343-06-8; **12** (R^1 = 3-CH_3O-4-CH_2=$CHCH_2OC_6H_3$, R^2 = H), 22280-95-1; **12** (R^1 = 2-$C_6H_5CH_2O$-3-$CH_3OC_6H_3$, R^2 = H), 2011-06-5; **12** (R^1 = 2-CH_3O-4-$C_6H_5CH_2OC_6H_3$, R^2 = H), 58026-14-5; **12** (R^1 = 2-Et_2NCOCH_2O-3-$CH_3OC_6H_3$, R^2 = H), 102131-57-7; **12** (R^1 = 3,4,5-$(CH_3O)_3C_6H_2$, R^2 = H), 86-81-7; **12** (R^1 = 2-pyrrolyl, R^2 = H), 1003-29-8; **12** (R^1 = 2-pyridyl, R^2 = H), 1121-60-4; **12** (R^1 = 4-pyridyl, R^2 = H), 872-85-5; **12** (R^1 = 2-furyl, R^2 = H), 98-01-1; **12** (R^1 = 2-thienyl, R^2 = H), 98-03-3; **12** (R^1 = 2-ClC_6H_4, R^2 = H), 89-98-5; **12** (R^1 = 3-thienyl, R^2 = H), 498-62-4; **12** (R^1 = CH_3, R^2 = 2-thienyl), 88-15-3; **13a**, 87-62-7; **13b**, 100-46-9; **13c**, 103-67-3; **13d**, 104-86-9; **13e**, 2393-23-9; **13f**, 700-63-0; **13g**, 91-00-9; **13h**, 120-20-7; **13i**, 3731-53-1; **13j**, 31828-71-4; **13k**, 18865-38-8; **13l**, 41708-72-9; **13m**, 102089-62-3; **14a**, 93969-05-2; **14a**·HCl, 93969-11-0; **14b**, 102132-11-6; **14b**·HCl, 93968-90-2; **14c**, 102132-12-7; **14c**·HCl, 93968-93-5; **14d**, 102132-13-8; **14d**·HCl, 93968-91-3; **14e**, 93968-92-4; **14e**·HCl, 97813-47-3; **14f**, 93968-94-6; **14f**·HCl, 93969-07-4; **14g**, 93968-95-7; **14g**·HCl, 93969-08-5; **14h**, 102132-14-9; **14h**·HCl, 93968-96-8; **14i**, 102132-15-0; **14i**·2HCl, 93968-97-9; **14j**, 93968-89-9; **14j**·HCl, 93969-09-6; **14k**, 93969-03-0; **14k**·HCl, 94528-65-1; **14l**, 93969-04-1; **14l**·HCl, 97799-75-2; **14m**, 102132-16-1; **14m**·HCl, 102132-17-2; **16a**, 102132-18-3; **16a**·2HCl, 102132-21-8; **16b**, 102132-19-4; **16b**·2HCl, 102132-22-9; **16c**, 102132-20-7; **16c**·2HCl, 102132-23-0; **17** (Z = Z^1), 85-42-7; **17** (Z = Z^2), 85-43-8; **17** (Z = Z^3), 85-44-9; **18a**, 93799-07-6; **18b**, 93799-08-7; **18c**, 93799-09-8; **18d**, 93799-10-1; **18e**, 93799-11-2; **18f**, 93799-12-3; **19a**, 102132-24-1; **19a**·HCl, 93798-99-3; **19b**, 102132-25-2; **19b**·HCl, 93799-00-9; **19c**, 102132-26-3; **19c**·HCl, 93799-01-0; **19d**, 93799-35-0; **19d**·HCl, 93799-02-1; **19e**, 93799-36-1; **19e**·HCl, 93799-03-2; **19f**, 93799-37-2; **19f**·HCl, 93799-04-3; **19g**, 93799-38-3; **19g**·HCl, 93799-05-4; **21** (R^3 = Me), 525-76-8; **21** (R^3 = Et), 2916-09-8; **22a**, 102132-27-4; **22a**·2HCl, 93799-13-4; **22b**, 93799-39-4; **22b**·2HCl, 93799-14-5; **22c**, 93799-40-7; **22c**·HCl, 93799-15-6; **22d**, 93799-41-8; **22d**·2HCl, 93799-16-7; **22e**, 102132-28-5; **22e**·2HCl, 93799-18-9; **23a**, 93969-06-3; **23a**·HCl, 93968-98-0; **23b**, 102132-29-6; **23b**·HCl, 102132-36-5; **23c**, 102132-30-9; **23c**·HCl, 102132-37-6; **23d**, 102132-31-0; **23d**·2HCl, 102132-38-7; **23e**, 93799-32-7; **23e**·2HCl, 93798-96-0; **23f**, 102132-32-1; **23f**·2HCl, 102132-39-8; **23g**, 102132-33-2; **23g**·2HCl, 102132-40-1; **23h**, 93799-31-6; **23h**·2HCl, 93798-94-8; **23i**, 93799-34-9; **23i**·2HCl, 93798-98-2; **23j**, 102132-34-3; **23**·2HCl, 102132-41-2; **23k**, 93844-07-6; **23k**·HCl, 93799-06-5; **23l**, 102132-35-4; **23l**·2HCl, 93823-97-3; **23m**, 93799-42-9; **23m**·2HCl, 93799-17-8; **24a**, 102132-42-3; **24b**, 102132-43-4; **24c**, 102132-44-5; **24d**, 102132-45-6; **25a**, 102132-46-7; **25b**, 102132-47-8; **26**, 37558-29-5; **27**, 58537-73-8; **28**, 31084-42-1; **29a**, 102132-48-9; **29b**, 102132-49-0; **29c**, 102132-50-3; **29d**, 102132-51-4; **30a**, 102132-52-5; **30b**, 102132-53-6; $H_2NCH_2CH_2NH_2$, 107-15-3; $H_2NCH_2CH_2C$-H_2NH_2, 109-76-2; $H_2NCH_2CH_2CH_2CH_2NH_2$, 110-60-1; H_2NC-$H_2CH(OH)CH_2NH_2$, 616-29-5; $H_2NCH_2C(CH_3)_2CH_2NH_2$, 7328-91-8; $H_2NCH_2CH(CH_3)NH_2$, 78-90-0; $H_2NCH_2C(CH_3)_2NH_2$, 811-93-8; PCPOH, 87-86-5; EtOCOOH, 541-41-3; 4-pyridinecarbonyl chloride, 14254-57-0; 2-thiophenecarbonyl chloride, 5271-67-0; phtalimide, 85-41-6.

Pepstatin Analogues as Novel Renin Inhibitors

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Pepstatin analogues corresponding to the general formula A-X-Y-Sta-Ala-Sta-R were synthesized in solution phase. Various changes in the nature of the A, X, and Y groups were made to improve the inhibitory potency against human plasma renin activity. The results were interpreted by use of the active-site model based on the sequence of human angiotensinogen. The *tert*-butyloxycarbonyl group and the isovaleryl group were found to be the most effective acyl groups (A). The analogues having a Phe residue in place of Val[1] (X) and His or an amino acid with an aliphatic side chain such as norleucine or norvaline in the Y position showed the highest inhibition of human plasma renin activity with IC_{50} values of about 10^{-8} M. Esterification or amidification of the carboxyl group of the C-terminal statine did not change the inhibitory potency. The selectivity for rat, dog, pig, and monkey plasma renin of the most interesting compounds was studied.

Renin is an aspartyl proteinase that cleaves the circulating protein angiotensinogen releasing angiotensin I. This decapeptide is in turn the substrate for the converting enzyme, a zinc metallocarboxydipeptidase, which generates the pressor octapeptide angiotensin II. Blockage of the liberation of angiotensin II by inhibition of the converting enzyme (ACE) has led to the development of powerful antihypertensive agents such as captopril[1,2] and enalapril maleate.[3] Substances inhibiting the preceding step, i.e., cleavage of angiotensinogen by renin should also play an important role in the control of hypertension.[4]

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