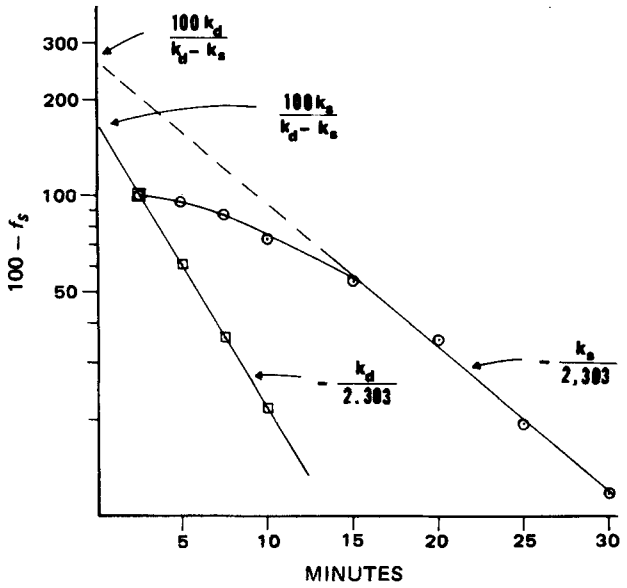

Figure 3—*Semilogarithmic plot of 100 minus cumulative percent dissolved (100 − f_s) versus time for Capsule F. Key: ○, actual values; and □, residual values.*

which can be derived by solving Eq. 7 to yield:

$$A_p = \frac{k_d A_0}{k_d - k_s}\,(e^{-k_s t} - e^{-k_d t}) \qquad \text{(Eq. 13)}$$

and substituting for A_p in Eq. 3. To estimate k_d accurately using Eq. 12, dissolution tests should be carried out automatically so that a sufficient number of early (dA_s/dt) points can be used in the plotting.

The values of DT_{exp} were in good agreement with those of DT_{calc} (Table II). These data confirm that the method proposed, in addition to its simplicity, is capable of reliably characterizing both dissolution and disintegration. In fact, if the percent dissolved–time data are well described by Eq. 10, the amount of drug in small particles at any given time (A_p) can be determined by employing Eq. 12, which permits the prediction of the disintegration time course. Such an approach is being investigated.

Previous models (5, 6) are in sharp disagreement with the present method, which assumes that dissolution occurs at a single rate constant throughout the dissolution test. In fact, the early data points that constitute the first dissolution phase according to previous models (5, 6) may not only represent dissolution but disintegration as well. By separating the disintegration component of these points from that of dissolution, a good estimate of the disintegration rate constant (k_d) may be obtained.

The described method provides a comprehensive, practical, and simple tool for the disintegration–dissolution analysis of dissolution rate data where familiar mathematics is employed. The good fit of the data obtained to the developed equation does not imply that drug dissolution and disintegration are first order in nature; it indicates that dissolution data for conventional tablets and capsules may be described by Eq. 10, in which case k_s and k_d can be estimated graphically.

REFERENCES

(1) J. G. Wagner, *J. Pharm. Sci.*, **58**, 1253 (1969).

(2) M. Gibaldi and S. Feldman, *ibid.*, **56**, 1238 (1967).

(3) F. Langenbucher, *J. Pharm. Pharmacol.*, **24**, 979 (1972).

(4) A. El-Yazigi, *Int. J. Pharm.*, **5**, 89 (1980).

(5) S. Kitazawa, I. Johno, Y. Ito, S. Teramura, and J. Okada, *J. Pharm. Pharmacol.*, **27**, 765 (1975).

(6) S. Kitazawa, I. Johno, T. Minouchi, and J. Okada, *ibid.*, **29**, 453 (1977).

(7) K. G. Nelson and L. Y. Wang, *J. Pharm. Sci.*, **66**, 1758 (1977).

(8) *Ibid.*, **67**, 86 (1978).

(9) A. J. Aguiar, J. E. Zelmir, and A. W. Kinkel, *ibid.*, **56**, 1243 (1967).

(10) M. Gibaldi and D. Perrier, "Pharmacokinetics," Dekker, New York, N.Y., 1974, pp. 270, 281.

Synthesis of Alkylaminoalkylamides of Substituted 2-Aminopyrroles as Potential Local Anesthetic and Antiarrhythmic Agents II: β-Amines

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Received September 9, 1980, from the **College of Pharmacy, University of South Carolina, Columbia, SC 29208*, and ‡*Astra Research Laboratory, Framingham, MA 01701.* Accepted for publication October 23, 1980. §Present address: Medical University of South Carolina, Charleston, SC 29403. ¶Present address: Bristol-Myers International Division, New York, NY 10022.

Abstract □ The synthesis, local anesthetic and antiarrhythmic properties, and CNS toxicity of 14 2-(3-alkylaminoalkylamido)-pyrroles are described. Most of the compounds exhibited local anesthetic activity by the guinea pig wheal test, with seven showing comparable or greater activity than lidocaine. Most compounds also exhibited antiarrhythmic activity; three compounds had more potent activity than lidocaine. All compounds exhibiting antiarrhythmic activity also were toxic to the CNS. However, two of the three compounds having greater activity than lidocaine possessed more desirable therapeutic indexes.

Keyphrases □ 2-(3-Alkylaminoalkylamido)pyrroles—synthesis, evaluated for local anesthetic activity in guinea pigs and for antiarrhythmic activity and CNS toxicity in mice □ Anesthetic activity, potential—2-(3-alkylaminoalkylamido)pyrroles synthesized and evaluated for activity in guinea pigs, structure–activity relationships □ Antiarrhythmic activity, potential—2-(3-alkylaminoalkylamido)pyrroles synthesized and evaluated for activity in mice, structure–activity relationships □ Structure–activity relationships—2-(3-alkylaminoalkylamido)pyrroles synthesized and evaluated for anesthetic activity and antiarrhythmic activity and CNS toxicity in guinea pigs and mice

Previous publications reported the synthesis and pharmacological evaluation of several series of 2-(2-alkylaminoalkylamido)pyrroles (I*a*) as potential local anesthetic and antiarrhythmic agents (1–3). Many of these compounds possessed significant activity (1–3), but most compounds with the desired activity were also toxic to the central nervous system (CNS).

Several series of antiarrhythmic agents derived from substituted anilines were reported recently (4–6). The β-amino analog (II*b*) of tocainide (II*a*) was more potent

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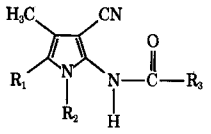


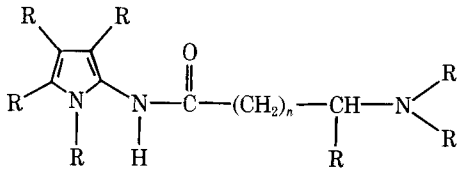
Table I—Data for Amides of Substituted 2-Aminopyrroles

Compound	R_1	R_2	R_3	Melting Point	R_f[a]	Recrystallization Solvent	Yield, %	Formula		Analysis, % Calc.	Found
IIIa	CH_3	CH_3	$CH{=}CHCH_3$	174.5–175.5°	0.46	Methanol	42.3	$C_{12}H_{15}N_3O \cdot 0.625\ CH_3OH$	C	63.90	63.87
									H	7.43	7.54
									N	17.71	17.77
IIIb	CH_3	CH_3	$CH_2CHBrCH_3$	134.5–135.5°	0.50	Benzene	82.8	$C_{12}H_{16}BrN_3O$	C	48.33	48.36
									H	5.41	5.41
									Br	26.80	26.76
									N	14.09	14.05
IIIc	CH_3	H	$CH_2CHBrCH_3$	141.5–142.5°	0.66	Methanol–water (4:1)	88.6	$C_{11}H_{14}BrN_3O$	C	46.49	46.68
									H	4.97	5.01
									Br	28.12	27.93
									N	14.79	14.83
IIId	CH_3	CH_3	CH_2CH_2Cl	181.5–182.5°	0.47	Ethanol	64.8	$C_{11}H_{14}ClN_3O$	C	55.12	55.06
									H	5.89	5.94
									Cl	14.79	14.69
									N	17.53	17.51
IIIe	CH_3	H	CH_2CH_2Cl	209–210° dec.	0.55	Ethanol	86.0	$C_{10}H_{12}ClN_3O$	C	53.22	53.27
									H	5.36	5.39
									Cl	15.71	15.66
									N	18.62	18.62
IIIf	C_2H_5	H	CH_2CH_2Cl	176–176.5°	0.54	Ethanol	88.0	$C_{11}H_{14}ClN_3O$	C	55.11	55.22
									H	5.89	5.96
									Cl	14.79	14.77
									N	17.53	17.55
IIIg	C_6H_5	H	CH_2CH_2Cl	221.5–222°	0.55	Ethanol	90.4	$C_{15}H_{14}ClN_3O$	C	62.61	62.68
									H	4.90	4.95
									Cl	12.32	12.29
									N	14.60	14.61
IIIh	$CH_2C_6H_5$	H	CH_2CH_2Cl	157–158°	0.54	Ethanol	92.8	$C_{16}H_{16}ClN_3O$	C	63.68	63.73
									H	5.35	5.38
									Cl	11.75	11.76
									N	13.92	13.93

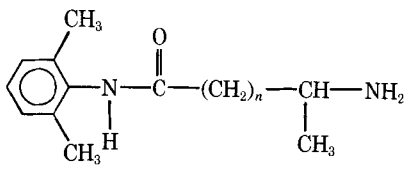
[a] Ethyl acetate.

and had a more favorable therapeutic ratio for CNS side-effects in animals than tocainide (6). Therefore, elongation of the intermediate chain between amide and amine functions might improve the pharmacological properties of aminoanilides related to lidocaine. The transfer of this method to a series of pyrrole analogs of lidocaine was considered a reasonable approach to enhance antiarrhythmic activity and to decrease CNS toxicity in this new class of antiarrhythmic agents.

As an extension of the 2-(2-alkylaminoalkylamido)-pyrrole (Ia) research, the synthesis and pharmacological evaluation of 14 2-(3-alkylaminoalkylamido)pyrroles (Ib) are presented. Compounds with a more acceptable therapeutic index than those previously reported are being sought.



Ia: $n = 0$
Ib: $n = 1$



IIa: $n = 0$
IIb: $n = 1$

RESULTS AND DISCUSSION

Chemistry—Acylation of various substituted 2-amino-3-cyanopyrroles (7–10) with 3-bromobutyryl chloride (11), *trans*-2-butenoyl chloride, or 3-chloropropionyl chloride in acetone, utilizing pyridine as a base, gave the requisite amide (IIIa–IIIh) precursors to the 2-(3-alkylaminoalkylamido)pyrroles (Ib) (Table I). The purity of these amides was determined by elemental analyses and TLC. IR and NMR spectra were consistent with the assigned structures.

The various substituted 2-(3-alkylaminoalkylamido)-3-cyanopyrroles (IVa–IVl) (Table II) were obtained either by Michael addition of a primary or secondary amine to the 2-butenamide (IIIa) or by nucleophilic displacement of the halogen of the β-haloamides (IIIb–IIIh) by the appropriate primary or secondary amine. For both methods, the products were obtained after refluxing (6–12 hr) the requisite amide (IIIa–IIIh) in ethanol or 2-propanol with a four- to fivefold excess of amine.

The crude products were isolated by removal of the alcohol and excess unreacted amines *in vacuo*. The residues were dissolved in 5–10% HCl and filtered, and the aqueous filtrates were made alkaline (pH 9–10) with 10% NaOH. The solid products (IVe, IVf, IVi, IVj, and IVl) were collected and purified further by recrystallization from methanol–water (4:1). The amines that oiled or gummed upon addition of alkali were extracted into chloroform, and the chloroform was removed *in vacuo* after drying. The residues were dissolved in an appropriate boiling solvent, treated with charcoal, and collected as oils or gums upon cooling.

The 2-(3-alkylaminoalkylamido)-3-carbamylpyrroles (IVm and IVn) were obtained by hydrolysis of the nitrile in IVi and IVj, respectively, in 85% phosphoric acid at 125–130° for 5 min. The free amines were precipitated by alkalinization of the cold dilute phosphoric acid solutions with 20% NaOH.

Percent yields, melting points, and purification data for the 2-(3-alkylaminoalkylamido)pyrroles (IVa–IVn) are given in Table II. These amines were characterized as their corresponding hydrochloride salts.

The 2-(3-alkylaminoalkylamido)pyrrole hydrochlorides (Va–Vf and Vh–Vn) were prepared by treating an acetone solution or suspension of the corresponding free bases with a slight excess of concentrated hydrochloric acid. In the case of IVg, the hydrochloride salt (Vg) precipi-

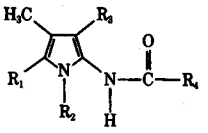


Table II—Data for Alkylaminoalkylamides of Substituted 2-Aminopyrroles and Corresponding Hydrochloride Salts

Compound	R_1	R_2	R_3	R_4	Precursor	Melting Point	R_f	Recrystallization Solvent[a]	Yield[b], %	Formula	Analysis, %	Calc.	Found
IV*a*	CH_3	CH_3	CN	$CH_2CH(CH_3)N$	III*a*	Gum	—	Cyclohexane	—	$C_{16}H_{24}N_4O$		—	—
V*a*	Hydrochloride				IV*a*	222–223°	0.28[c]	—[d]	50.0	$C_{16}H_{25}ClN_4O$	C	59.15	58.90
											H	7.76	7.75
											Cl	10.91	10.83
											N	17.25	17.16
IV*b*	CH_3	CH_3	CN	$CH_2CH(CH_3)N$ (cyclic)	III*b*	Gum	—	Cyclohexane	—	$C_{17}H_{26}N_4O$		—	—
V*b*	Hydrochloride				IV*b*	209.5–210.5° dec.	0.53[c]	—[d]	73.8	$C_{17}H_{27}ClN_4O$	C	60.25	60.36
											H	8.04	8.07
											Cl	10.46	10.42
											N	16.53	16.49
IV*c*	CH_3	CH_3	CN	$CH_2CH(CH_3)N(H)$-*n*-C_4H_9	III*b*	Gum	—	Cyclohexane–benzene (6:1)	—	$C_{16}H_{26}N_4O$		—	—
V*c*	Hydrochloride				IV*c*	208.5–209.5° dec.	0.36[c]	—[d]	74.0	$C_{16}H_{27}ClN_4O \cdot 0.4\ H_2O$	C	57.52	57.44
											H	8.39	8.33
											Cl	10.61	10.57
											N	16.77	16.75
IV*d*	CH_3	CH_3	CN	$CH_2CH(CH_3)N(H)$-*iso*-C_4H_9	III*a*	Gum	—	Cyclohexane	—	$C_{16}H_{26}N_4O$		—	—
V*d*	Hydrochloride				IV*d*	194–194.5° dec.	0.06[e]	Water	53.5	$C_{16}H_{27}ClN_4O$	C	58.79	58.57
											H	8.33	8.38
											Cl	10.85	10.81
											N	17.14	17.08
IV*e*	CH_3	H	CN	$CH_2CH(CH_3)N$ (cyclic)	III*c*	168–169°	0.47[e]	Methanol–water (4:1)	83.3	$C_{15}H_{22}N_4O$		—	—
V*e*	Hydrochloride				IV*e*	94.0–95.5°	0.24[e]	—[d]	89.2	$C_{15}H_{23}ClN_4O \cdot 1.0\ H_2O$	C	54.78	54.80
											H	7.66	7.66
											Cl	10.78	10.80
											N	17.04	17.04
IV*f*	CH_3	H	CN	$CH_2CH(CH_3)N(C_2H_5)_2$	III*c*	156.5–158°	0.47[e]	Methanol–water (4:1)	32.0	$C_{15}H_{24}N_4O$		—	—
V*f*	Hydrochloride				IV*f*	120–121°	0.53[e]	2-Propanol–acetone (1:10)	72.0	$C_{15}H_{25}ClN_4O \cdot 0.54\ H_2O$	C	55.84	55.84
											H	8.15	8.18
											Cl	10.99	11.01
											N	17.37	17.35
IV*g*[f]	CH_3	H	CN	$CH_2CH(CH_3)N(H)$-*n*-C_4H_9	III*c*	—	—	—	—	$C_{15}H_{24}N_4O$		—	—
V*g*	Hydrochloride				IV*g*	180.5–181.5°	0.26[e]	Water	65.0	$C_{15}H_{25}ClN_4O \cdot 1.83\ H_2O$	C	52.09	52.09
											H	7.29	7.40
											Cl	10.25	10.22
											N	16.20	16.21
IV*h*	CH_3	CH_3	CN	$CH_2CH_2N(C_2H_5)_2$	III*d*	Gum	—	Cyclohexane	—	$C_{15}H_{24}N_4O$		—	—
V*h*	Hydrochloride				IV*h*	169–171.5° dec.	0.38[c]	—[d]	65.0	$C_{15}H_{25}ClN_4O$	C	57.59	57.36
											H	8.06	8.09
											Cl	11.33	11.27
											N	17.91	17.83
IV*i*	CH_3	H	CN	$CH_2CH_2N(C_2H_5)_2$	III*e*	126.5–127°	—	Methanol–water (4:1)	93.5	$C_{14}H_{22}N_4O$		—	—
V*i*	Hydrochloride				IV*i*	183.5–184.5°	0.18[e]	—[d]	94.1	$C_{14}H_{23}ClN_4O \cdot 1.0\ H_2O$	C	53.07	53.14
											H	7.95	7.95
											Cl	11.19	11.17
											N	17.68	17.69
IV*j*	C_2H_5	H	CN	$CH_2CH_2N(C_2H_5)_2$	III*f*	122.5–123.5°	—	Methanol–water (4:1)	84.5	$C_{15}H_{24}N_4O$		—	—
V*j*	Hydrochloride				IV*j*	80–85° (hydrate) (151.5–152.5°)	0.23[e]	—[d]	88.3	$C_{15}H_{25}ClN_4O \cdot 1.0\ H_2O$	C	54.45	54.47
											H	8.23	8.25
											Cl	10.72	10.75
											N	16.93	16.93
IV*k*	C_6H_5	H	CN	$CH_2CH_2N(C_2H_5)_2$	III*g*	Oil	—	Methanol–water (1:1)	43.3	$C_{19}H_{24}N_4O$		—	—
V*k*	Hydrochloride				IV*k*	140.5–141.5°	0.21[e]	Methanol–acetone (1:10)	64.7	$C_{19}H_{25}ClN_4O \cdot 0.1\ H_2O$	C	62.92	63.02
											H	7.00	7.08
											Cl	9.78	10.01
											N	15.45	15.22
IV*l*	$CH_2C_6H_5$	H	CN	$CH_2CH_2N(C_2H_5)_2$	III*h*	120–121°	—	Methanol–water (4:1)	96.6	$C_{20}H_{26}N_4O$		—	—
V*l*	Hydrochloride				IV*l*	168–169°	0.21[b]	—[d]	93.1	$C_{20}H_{27}ClN_4O \cdot 1.0\ H_2O$	C	61.13	61.17
											H	7.44	7.45
											Cl	9.02	9.04
											N	14.26	14.28
IV*m*	CH_3	H	$CONH_2$	$CH_2CH_2N(C_2H_5)_2$	IV*i*	145–146°	—	Methanol–water (1:2)	71.3	$C_{14}H_{24}N_4O_2$		—	—
V*m*	Hydrochloride				IV*m*	213–214° dec.	0.07[b]	2-Propanol	83.1	$C_{14}H_{25}ClN_4O_2$	C	53.07	52.98
											H	7.95	8.02
											Cl	11.19	11.21
											N	17.68	17.69
IV*n*	C_2H_5	H	$CONH_2$	$CH_2CH_2N(C_2H_5)_2$	IV*j*	126–126.5°	—	Methanol–water (7:3)	85.1	$C_{15}H_{26}N_4O$		—	—
V*n*	Hydrochloride				IV*n*	194–195°	0.07[b]	—[d]	88.9	$C_{15}H_{27}ClN_4O$	C	54.45	54.51
											H	8.23	8.26
											Cl	10.72	10.75
											N	16.93	16.94

[a] The oils and gums were dissolved in boiling recrystallization solvent(s), treated with activated charcoal, filtered, and collected as oils or gums after cooling. [b] Where yields were not reported for free amine, the yield for salt was based on the haloamide or crotonamide precursor. [c] Acetone. [d] Hydrochloride salt obtained was analytically pure. [e] Ethyl acetate. [f] Hydrochloride was formed during workup procedure; therefore, free base was not isolated.

tated upon addition of 5% HCl to the crude residue remaining after removal of the reaction solvent and excess *n*-butylamine *in vacuo*.

Data for the hydrochloride salts (V*a*–V*n*) are given in Table II. These compounds were characterized on the basis of elemental analyses, TLC, and IR and NMR spectral data.

The β-haloamides and final products possessing an asymmetric center were obtained as racemic mixtures in this work.

Pharmacology—*Local Anesthetic Activity*—Activity was observed for all compounds evaluated at a solution concentration of 0.50%. Noticeable differentiation in local anesthetic activity was observed at 0.25%. At that concentration, V*a*–V*d* were more potent than lidocaine, V*k*, V*l*, and V*n* were comparable in potency, and all remaining compounds were less potent.

Further evaluation of V*a*–V*d* at a 0.125% solution concentration demonstrated their superiority over lidocaine under these test conditions. The durations of local anesthetic activity were 1.67, 1.42, 2.67, and 1.75 times longer than that of lidocaine (Table III).

Local anesthetic data previously reported (3) and the present results strongly support the introduction of a methyl group on the pyrrole nitrogen to augment local anesthetic activity. This finding applies for the 2-(2-alkylaminoalkylamido)pyrroles (I*a*) and the 2-(3-alkylaminoalkylamido)pyrroles (I*b*). The present work shows that the I*b* compounds are substantially more potent local anesthetics than their corresponding α-amine homologs (I*a*).

Antiarrhythmic Activity and CNS Toxicity—Antiarrhythmic activity, measured as protection against chloroform-induced ventricular tachycardia, and acute CNS toxicity, measured as drug-induced ataxia, were determined in mice as previously described (3). The results are listed as ED_{50} values, together with 95% Fieller limits and therapeutic indexes, in Table IV. All compounds tested, except V*g*, had antiarrhythmic activity; V*a*, V*c*, and V*d* were more potent than lidocaine, V*b* was equipotent, and the rest were less potent. Paralleling the findings on local anesthetic activity, the derivatives with a methyl substituent on the pyrrole nitrogen were more potent than those with a hydrogen substituent. More importantly, therapeutic indexes were also increased by the introduction of an *N*-methyl substituent. A comparison with previously published α-alkylaminoalkylamidopyrroles showed the β-derivatives to have higher potencies (except V*e*) and higher therapeutic indexes (except in hydrogen-substituted pyrroles). The extension of the intermediate chain, leading from α-amines to β-amines, again improved the therapeutic properties of a class of antiarrhythmic agents.

EXPERIMENTAL[1]

2-(2-Butenamido)-3-cyano-1,4,5-trimethylpyrrole (III*a*)—A solution of 2-amino-3-cyano-1,4,5-trimethylpyrrole (22.3 g, 0.15 mole) (10) in 150 ml of acetone with pyridine (13.1 g, 0.16 mole) was prepared in a 500-ml round-bottom flask equipped with a drying tube. This solution was stirred in an ice bath for 10 min, followed by the dropwise addition of *trans*-2-butenoyl chloride (18.8 g, 0.18 mole). The solution was stirred in the ice bath for 10 min and then for another 15 min after the ice bath was removed. The reaction mixture was brought to reflux and allowed to cool to room temperature, and then the dark solution was poured over crushed ice (500 g).

After the ice had melted, the crude product was collected by filtration, suspended in distilled water, filtered, and dried. The gray product (13.8 g, 42.3%) was recrystallized twice from absolute methanol to yield light-tan crystals (homogeneous on TLC; in ethyl acetate, R_f 0.46), mp 174.5–175.5° dec.; IR (KBr): 3420, 3050, 2980, 2920, 2220, 1675, 1645, 1540, 1195, 960, 935, 830, and 680 cm^{-1}; NMR (dimethyl sulfoxide-d_6): δ 1.9 (d, 3H, CH_3 of CO–C=C–CH_3), 2.00 (s, 3H, CH_3 at C-4), 2.09 (s, 3H, CH_3 at C-5), 3.33 (s, 3H, CH_3 at N-1), 5.8–6.3 (complex m, 1H, CH of CO–CH=C–C), 6.5–7.1 (complex m, 1H, CH of CO–C=CH–C), and 9.7–10.1 (broad s, 1H, NH of amide) ppm. Table I gives the results of the elemental analyses.

2-(3-Bromobutyramido)-3-cyano-4,5-dimethylpyrrole (III*c*)—The procedure for III*c* is given as a general method of synthesis of III*b*–III*h*. A solution of 2-amino-3-cyano-4,5-dimethylpyrrole (40.5 g, 0.30 mole) (7) in pyridine (26.1 g, 0.33 mole) and 300 ml of acetone was stirred in an ice bath while 3-bromobutyryl chloride (61.2 g, 0.33 mole) (11) was added dropwise. After the addition was complete, the dark-brown solution was stirred at room temperature for an additional 20 min; it then was poured over 400 g of ice. The resulting suspension was stirred until the ice had melted, and the crude product was collected by filtration.

The product was resuspended in 300 ml of distilled water, collected by filtration, and air dried. One gram of the crude amide (75.5 g, 88.6%) was recrystallized from 25 ml of methanol–water (4:1) to yield a white powder (homogeneous on TLC; in ethyl acetate, R_f 0.66), mp 141.5–142.5°; IR (KBr): 3420, 3160, 3100, 3020, 2900, 2205, 1650, 1610, 1500, 1480, 1450, 1320, 1230, 1210, 1000, and 670 cm^{-1}; NMR (dimethyl sulfoxide-d_6): δ 1.70 (d, 3H, CHBrCH_3), 1.90 (s, 3H, CH_3 at C-4), 2.02 (s, 3H, CH_3 at C-5), 2.92 (d, 2H, $COCH_2$), 4.50 (q, 1H, C*H*BrCH$_3$), 10.52 (s, 1H, NH), and 11.17 (s, 1H, NH). Table I gives the results of the elemental analyses.

Method A: 2-(3-Pyrrolidinobutyramido)-3-cyano-1,4,5-trimethylpyrrole Hydrochloride (V*a*)—The procedure for the synthesis of V*a* was also used for V*d*. A suspension of III*a* (8.7 g, 0.04 mole) in 80 ml of absolute 2-propanol with pyrrolidine (11.4 g, 0.16 mole) was refluxed, with continuous stirring, for 12 hr to give a clear brown solution. The solvent and excess pyrrolidine were removed *in vacuo*, and the gummy residue was dissolved in 50 ml of warm 10% HCl. The acidic solution was filtered, 200 g of ice was added, and the product was suspended in the solution by the addition of 10% aqueous potassium hydroxide. The alkaline aqueous suspension (pH 9–10) was extracted with two 150-ml

Table III—Local Anesthetic Activity of 2-(3-Alkylaminoalkylamido)pyrrole Hydrochlorides as Determined by the Guinea Pig Wheal Test [a]

Compound	Solution Concentration 0.50%	0.25%	0.125%
Lidocaine	100 (36)	100 (31)	100 (12)
V*a*	100 (36)	110 (34)	167 (20)
V*b*	100 (36)	112 (35)	142 (17)
V*c*	100 (36)	116 (36)	267 (32)
V*d*	100 (36)	116 (36)	175 (21)
V*e*	67 (24)	52 (16)	—
V*f*	61 (22)	13 (4)	—
V*g*	86 (31)	55 (17)	—
V*h*	94 (34)	77 (24)	—
V*i*	47 (17)	29 (9)	—
V*j*	89 (32)	52 (16)	—
V*k*	100 (36)	106 (33)	—
V*l*	100 (36)	103 (32)	—
V*m*	61 (22)	58 (18)	—
V*n*	100 (36)	100 (31)	—
Sodium chloride	0 (00)	—	—

[a] Values given are percent protection; the numbers in parentheses represent the number of pinpricks failing to elicit a response (skin twitch or cry) from the wheal resulting from intradermal injection of 0.25 ml of the test compound in preshaven guinea pig backs (n = 2).

Table IV—Antiarrhythmic [a] and CNS Toxic [b] Effects in Mice

Compound	ED_{50}[c], mg/kg (95% Fieller Limits) Protection	Ataxia	Therapeutic Index
Lidocaine	48 (44–53)	45 (40–50)	0.94
V*a*	9 (4–29)	8 (5–11)	0.89
V*b*	39 (20–60)	107 (67–298)	2.74
V*c*	33 (24–39)	129 (91–282)	3.91
V*d*	24 (15–41)	131 (44–386)[d]	5.46
V*e*	330 (183–900)	125 (85–240)	0.38
V*f*	164 (86–301)	134 (83–202)	0.82
V*g*[e]	—	—	—
V*h*	145 (74–1168)	470 (356–737)	3.24
V*i*	345 (220–569)	159 (71–238)	0.46
V*j*	159 (116–226)	169 (101–212)	1.06
V*k*	125 (86–153)	78 (36–108)	0.62
V*l*	142 (53–379)[d,f]	253 (158–620)	1.78
V*m*	304 (190–411)	302 (186–400)	0.99
V*n*	316 (261–427)	292 (252–358)	0.92

[a] Protection against chloroform-induced tachycardia. [b] Observed prior to exposure to chloroform. [c] Subcutaneous administration. [d] Approximate 95% Fieller limits. [e] Lack of water solubility prevented determination. [f] Tremor, ED_{50} <20 mg/kg.

[1] All IR spectral data were determined on a Beckman Acculab-4 spectrophotometer using the potassium bromide technique. NMR spectra were determined on a Hitachi Perkin-Elmer R24 high-resolution spectrophotometer with tetramethylsilane as the internal reference. The reported melting points were obtained using a Thomas-Hoover capillary apparatus and are uncorrected. The reported analyses of carbon, hydrogen, chlorine, and nitrogen were obtained from Atlantic Microlab, Atlanta, Ga. TLC was performed using Eastman Chromatogram sheets (type 6060, silica gel); the sheets were developed in an iodine chamber.

portions of chloroform, and the organic solution then was extracted with 300 ml of saturated sodium chloride solution. The chloroform was removed *in vacuo*, and the residue was dissolved in 200 ml of boiling cyclohexane, treated with activated charcoal, and immediately filtered while hot.

After cooling to room temperature, a gummy residue was collected from the bottom of the flask by decantation. This residue was dissolved in 100 ml of acetone, 4 ml of concentrated hydrochloric acid was added, and the mixture was placed in the freezer. After 24 hr, fine gray crystals (6.5 g, 50%) were collected (homogeneous on TLC; in acetone, R_f 0.28), mp 222–223° dec.; IR (KBr): 3130, 3020, 2575, 2485, 2210, 1690, 1550, 1530, 1440, 1175, 1150, 975, and 710 cm^{-1}; NMR (dimethyl sulfoxide-d_6): δ 1.39 [d, 3H, CH_3 of $-CO-C-C(CH_3)-N^+$], 1.6–2.0 (complex m, 4H, β-methylenes of pyrrolidino), 1.99 (s, 3H, CH_3 at C-4), 2.05 (s, 3H, CH_3 at C-5), 2.7–3.1 [complex m, CH, α-methylenes of pyrrolidino and methylene of $CO-CH_2-C(C)-N^+$], 3.26 (s, 3H, CH_3 at N-1), 3.6–4.0 [complex m, 1H, methine of $-CO-C-CH(C)-N^+$], 10.5 (s, 1H, NH of amide or ^+NH), and 11.1–11.6 (broad s, 1H, ^+NH or NH of amide) ppm. Table II gives the results of the elemental analysis.

Method B: 2-(3-Pyrrolidinobutyramido)-3-cyano-4,5-dimethylpyrrole (IV*e*)—The procedure for IV*e* is given as a general method of synthesis of IV*b*, IV*c*, and IV*e*–IV*l*. A solution of 2-(3-bromobutyramido)-3-cyano-4,5-dimethylpyrrole (III*c*) (20.0 g, 0.07 mole) in 150 ml of *n*-propanol was stirred while pyrrolidine (29.9 ml, 0.42 mole) was added. The solution was refluxed with stirring for 8 hr, and then the solvent and excess amine were removed *in vacuo*. The residue was dissolved in 300 ml of 5% HCl, and the solution was filtered. The acidic filtrate was poured over 200 g of ice and made alkaline with 10% NaOH (pH 10), and the tan precipitate was collected by filtration. The crude product was recrystallized from 280 ml of methanol–water (4:1), yielding white crystals (16.0 g, 83.3%) which were collected and dried. The crystals were suitable for hydrochloride salt formation (homogeneous on TLC; in ethyl acetate, R_f 0.47), mp 168–169°. The data for the analogs are given in Table II.

2-(3-Pyrrolidinobutyramido)-3-cyano-4,5-dimethylpyrrole Hydrochloride (V*e*)—The procedure for V*e* is given as a general method of synthesis of V*b*, V*c*, and V*e*–V*n*. A solution of the free amine (IV*e*) (8.0 g, 0.03 mole) in 100 ml of acetone was filtered, and the filtrate was treated with 3.0 ml of concentrated hydrochloric acid. The sealed flask was placed in the freezer for 1 hr, yielding white crystals; these crystals were collected by filtration, washed with acetone, and dried. The crystals (8.3 g, 89.2%) were analytically pure (homogeneous on TLC; in ethyl acetate, R_f 0.24), mp 94–95.5° dec.; IR (KBr): 3510, 3400, 3225, 3030, 2980, 2640, 2600, 2210, 1670, 1620, 1460, 1330, 1230, 1180, 1080, and 760 cm^{-1}; NMR (dimethyl sulfoxide-d_6): δ 1.40 (d, 3H, $CHCH_3$), 1.95 (s, 3H, CH_3 at C-4), 2.05 (s, 3H, CH_3 at C-5), 2.00 (broad m, 4H, β-carbons on pyrrolidine), 2.95 (d, 2H, $COCH_2$), 3.50 (m, 1H, $COCH_2CH$), 2.80–3.80 (broad m, 4H, α-carbons on pyrrolidine), 10.80 (s, 1H, NH), and 11.35 (s, 2H, NH). Table II lists the results of the elemental analyses.

Method C: 2-(3-Diethylaminopropionamido)-3-carbamyl-4,5-dimethylpyrrole (IV*m*)—The procedure for IV*m* was also used for IV*n*. A solution of 2-(3-diethylaminopropionamido)-3-cyano-4,5-dimethylpyrrole (IV*i*) (13.12 g, 0.05 mole) in 85% H_3PO_4 (30 ml) was heated with stirring at 127–129° for 5 min. The contents of the vessel were cooled, crushed ice (200 g) was added, and the pH was adjusted to 10 by the addition of a saturated sodium hydroxide solution. The product was collected, resuspended in distilled water (300 ml), collected by filtration, and dried. The crude amine (10.0 g, 71.3%) was recrystallized from methanol–water (1:2) to yield off-white crystals (9.0 g, 90%), which were suitable for hydrochloride salt formation. [See Table II for analog and *Method B* for hydrochloride salt (V*m*) formation.]

Pharmacology—*Local Anesthetic Activity*—The guinea pig wheal method of Bulbring and Wajda (12) was employed in determining activity. The methodology was described previously (1–3).

Antiarrhythmic Activity and CNS Toxicity—A modification of the method of Lawson (13) was employed in assessing the antiarrhythmic activity and acute CNS toxicity. The methodology was described previously (3). Briefly, the mice were exposed to chloroform following subcutaneous injection of the target compounds. After respiratory arrest was evoked, a thoracotomy was performed; multilead ECGs were recorded for ~45 sec. If the ventricular rate was <520 beats per minute during this period, it was presumed that ventricular tachycardia had been prevented and the mouse was considered "protected." Symptoms of ataxia were monitored during the 20-min period between injection of the target compound and exposure to chloroform.

REFERENCES

(1) R. W. Johnson, T. H. Keenan, J. W. Kosh, and J. W. Sowell, Sr., *J. Pharm. Sci.*, **68**, 317 (1979).

(2) *Ibid.*, **68**, 955 (1979).

(3) J. W. Sowell, Sr., A. J. Block, M. E. Derrick, J. J. Freeman, J. W. Kosh, R. J. Mattson, P. F. Mubarak, and P. A. Tenthorey, *J. Pharm. Sci.*, **70**, 135 (1981).

(4) E. W. Byrnes, P. D. McMaster, E. R. Smith, M. R. Blair, R. N. Boyes, B. R. Duce, H. S. Feldman, G. H. Kronberg, B. H. Takman, and P. A. Tenthorey, *J. Med. Chem.*, **22**, 1171 (1979).

(5) P. D. McMaster, E. W. Byrnes, H. S. Feldman, B. H. Takman, and P. A. Tenthorey, *ibid.*, **22**, 1177 (1979).

(6) P. A. Tenthorey, R. L. DiRubio, H. S. Feldman, B. H. Takman, E. W. Byrnes, and P. D. McMaster, *ibid.*, **22**, 1182 (1979).

(7) R. Gewald, *Z. Chem.*, **1**, 349 (1961).

(8) V. I. Shvedov, M. V. Mezentseva, and A. N. Grinev, *Khimiya Geterotsikl. Soedin.*, **9**, 1219 (1975); through *Chem. Abstr.*, **84**, 59299 (1976).

(9) R. W. Johnson, R. J. Mattson, and J. W. Sowell, Sr., *J. Heterocycl. Chem.*, **14**, 383 (1977).

(10) R. J. Mattson and J. W. Sowell, Sr., *Synthesis*, **1979**, 217.

(11) D. M. Hall and E. E. Turner, *J. Chem. Soc.*, **1948**, 1909.

(12) E. Bulbring and I. Wajda, *J. Pharmacol. Exp. Ther.*, **85**, 78 (1945).

(13) J. W. Lawson, *ibid.*, **160**, 22 (1968).

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