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

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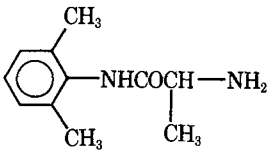
Abstract □ The synthesis, local anesthetic and antiarrhythmic properties, and CNS toxicity of 19 2-(2-alkylaminoalkylamido)pyrroles are described. Most of the compounds exhibited local anesthetic activity by the guinea pig wheal test, and four showed activity comparable to or greater than that of lidocaine. Most compounds also exhibited antiarrhythmic activity; five compounds had activity comparable to that of lidocaine, and one was more potent. All compounds exhibiting antiarrhythmic activity also were toxic to the central nervous system.

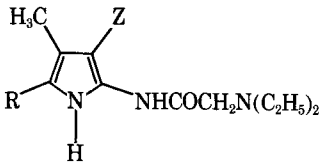
Keyphrases □ 2-(2-Alkylaminoalkylamido)pyrroles—synthesis and evaluation for local anesthetic and antiarrhythmic properties and CNS toxicity □ Antiarrhythmic agents—2-(2-alkylaminoalkylamido)pyrroles, synthesis and evaluation for activity □ Anesthetic activity—2-(2-alkylaminoalkylamido)pyrroles, synthesis and evaluation for local anesthetic activity

The success of lidocaine as a local anesthetic (1) and antiarrhythmic agent (2) has served as an impetus for the synthesis and pharmacological evaluation of numerous analogs and homologs of this drug. Modifications of the aminoacyl portion of this structure and the effects of these modifications on biological activity have been studied extensively (3–6).

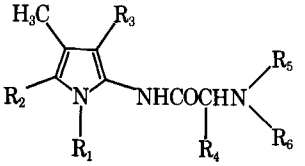
Branching of the aminoacyl chain in this structure has proven to be a successful structural modification for local anesthetic and antiarrhythmic properties. From these research endeavors, prilocaine (7), etidocaine (8), mepivacaine (9), and bupivacaine (9) have been introduced as local anesthetics. More recently, tocainide (I) was synthesized (4) and currently is in the third phase of clinical trials as an orally effective antiarrhythmic agent.



I



II: Z = CN
III: Z = $CONH_2$



IV

In previous work directed toward heterocyclic replacement of the benzenoid ring system in lidocaine, the synthesis and local anesthetic and antiarrhythmic properties of a series of 2-diethylaminoacetamido-3-cyano-4-methyl-5-substituted pyrroles (II) and a series of the corresponding 3-carbamyl analogs (III) were studied (10, 11). The results of these studies, together with the positive results obtained from branching of the aminoacyl chain in lidocaine, prompted the synthesis and pharmacological evaluation of the alkylaminoalkylamides (IV) of various substituted 2-aminopyrroles.

RESULTS AND DISCUSSION

Chemistry—The synthesis of the alkylaminoalkylamides (IV) of substituted 2-aminopyrroles is illustrated in Schemes I–III. All of the compounds possessing an asymmetric center were obtained as a racemic mixture, and no attempts were made to resolve the racemates.

Acylation of 2-amino-3-cyano-1,4,5-trimethylpyrrole (V) (12) in acetone, utilizing pyridine as a base, with 2-bromopropionyl chloride or chloroacetyl chloride gave the α-haloamide (VI*a* or VI*b*), respectively (Scheme I). The 2-(2-alkylaminopropionamido)-3-cyano-1,4,5-trimethylpyrroles (VII*a*–VII*f*) were obtained by displacement of the α-halogen in VI*a* with the appropriate primary or secondary amine. This displacement was accomplished by refluxing (2–3 hr) a solution of VI*a* in absolute ethanol with a four- to fivefold excess of the amine. 2-Diethylaminoacetamido-3-cyano-1,4,5-trimethylpyrrole (VII*g*) was obtained by reacting VI*b* with excess diethylamine by the same procedure.

In general, the free amines (VII*a*–VII*g*) were isolated by removal of the ethanol and excess unreacted amines *in vacuo*. The crude residues were dissolved in 10% HCl, the solutions were filtered, and the free amines (VII*a*–VII*g*) were extracted into chloroform after the aqueous solutions were made basic (pH 9–10) with potassium hydroxide. After the chloroform extracts were dried, the chloroform was removed *in vacuo*. The amine residues (VII*a*–VII*g*) were purified further by recrystallization (or reoiling) from cyclohexane or cyclohexane–benzene (4:1). These gummy semisolids or oils were used for hydrochloride salt formation without further purification.

The amine hydrochlorides (VIII*a*–VIII*g*) were prepared by treating an acetone solution of the free amines (VII*a*–VII*g*) with concentrated hydrochloric acid.

In the second series, 2-amino-3-cyano-4-methyl-5-substituted pyrroles (IX–XI) (13, 14) in acetone were acylated with 2-bromopropionyl chloride, utilizing pyridine as a base, to yield the corresponding α-halopropionamides (XII–XIV) (Scheme II). Nucleophilic displacement of the α-halogen with sodium azide in refluxing methanol gave the corresponding alkyl azides. Catalytic hydrogenation of the alkyl azides at 40–50 psi, utilizing 10% palladium-on-carbon as the catalyst and methanol–chloroform (100:3) as the solvent (15), gave the corresponding 2-(2-aminopropionamido)-3-cyano-4-methyl-5-substituted pyrrole hydrochlorides (XV–XVII).

Acylation of 2-amino-3-cyano-4,5-dimethylpyrrole (IX) with 2-chloropropionyl chloride by the procedure described previously gave the 2-chloropropionamide (XVIII) in a 96.1% yield (Scheme III). Compound

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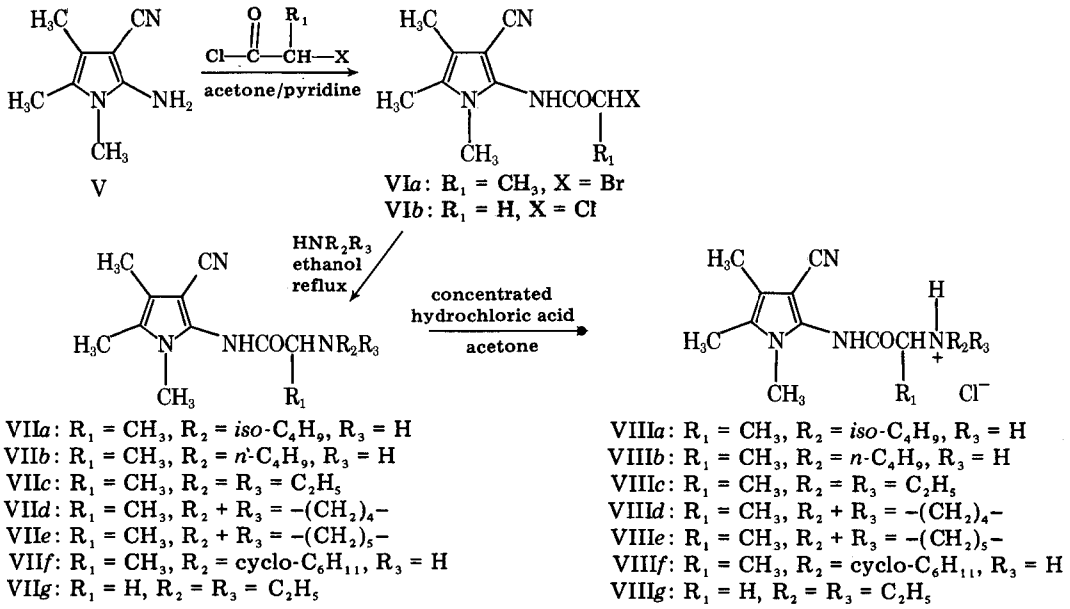


V

VIa: $R_1 = CH_3$, X = Br
VIb: R_1 = H, X = Cl

VIIa: $R_1 = CH_3$, $R_2 = iso\text{-}C_4H_9$, R_3 = H
VIIb: $R_1 = CH_3$, $R_2 = n\text{-}C_4H_9$, R_3 = H
VIIc: $R_1 = CH_3$, $R_2 = R_3 = C_2H_5$
VIId: $R_1 = CH_3$, $R_2 + R_3 = -(CH_2)_4-$
VIIe: $R_1 = CH_3$, $R_2 + R_3 = -(CH_2)_5-$
VIIf: $R_1 = CH_3$, R_2 = cyclo-C_6H_{11}, R_3 = H
VIIg: R_1 = H, $R_2 = R_3 = C_2H_5$

VIIIa: $R_1 = CH_3$, $R_2 = iso\text{-}C_4H_9$, R_3 = H
VIIIb: $R_1 = CH_3$, $R_2 = n\text{-}C_4H_9$, R_3 = H
VIIIc: $R_1 = CH_3$, $R_2 = R_3 = C_2H_5$
VIIId: $R_1 = CH_3$, $R_2 + R_3 = -(CH_2)_4-$
VIIIe: $R_1 = CH_3$, $R_2 + R_3 = -(CH_2)_5-$
VIIIf: $R_1 = CH_3$, R_2 = cyclo-C_6H_{11}, R_3 = H
VIIIg: R_1 = H, $R_2 = R_3 = C_2H_5$

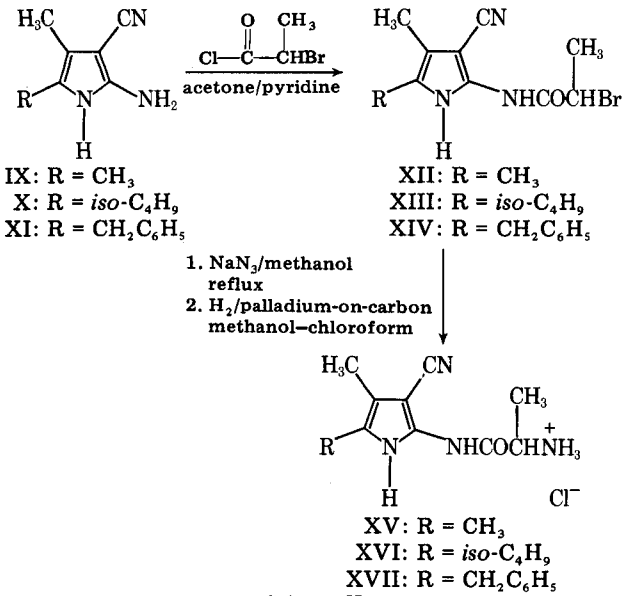
Scheme I

XVIII, the corresponding 2-bromopropionamide (XII), and 2-(2-bromopropionamido)-3-cyano-4-methyl-5-isobutylpyrrole (XIII) were utilized as precursors for the synthesis of a series of 2-(2-alkylaminopropionamido)-3-cyano-4-methyl-5-substituted pyrroles (XIX*a*–XIX*e* and XXI). The synthesis of these compounds and their conversion to the corresponding hydrochloride salts (XX*a*–XX*e* and XXII) were analogous to the procedure described in Scheme I.

Hydrolysis of the nitrile (11) in XVIII in 85% phosphoric acid at 100° gave 2-(2-chloropropionamido)-3-carbamyl-4,5-dimethylpyrrole (XXIII) in a 46% yield after purification. This intermediate was utilized as a common precursor for the synthesis of the 2-(2-alkylaminopropionamido)-3-carbamyl-4,5-dimethylpyrroles (XXIV*a*–XXIV*c*) (Scheme III). The general procedure described previously was utilized in their synthesis.

The corresponding hydrochloride salts (XXV*a*–XXV*c*) were prepared by the acetone–concentrated hydrochloric acid procedure. Compound XXV*c* precipitated from acetone as white crystals; however, upon exposure to the atmosphere, the hygroscopic salt could not be isolated as a solid. After repeated attempts, the free base (XXIV*c*) was characterized.

Data for the various 2-haloalkylamides, used as precursors in this study, are given in Table I. TLC and elemental analyses were used in determining the purity of these amides. The IR and NMR spectra were consistent with the assigned structures.



IX: R = CH_3
X: R = $iso\text{-}C_4H_9$
XI: R = $CH_2C_6H_5$

XII: R = CH_3
XIII: R = $iso\text{-}C_4H_9$
XIV: R = $CH_2C_6H_5$

XV: R = CH_3
XVI: R = $iso\text{-}C_4H_9$
XVII: R = $CH_2C_6H_5$

Scheme II

The yields, melting points, and purification data for the 2-(2-alkylaminoalkylamido)pyrroles are given in Table II. With the exception of XXIV*c*, these amines were characterized as their hydrochloride salts.

Data for the various 2-(2-alkylaminoalkylamido)pyrrole hydrochlorides are presented in Table III. The purity of these salts was determined by TLC and elemental analysis. The NMR and IR spectra were consistent with the assigned structures.

Pharmacology—*Local Anesthetic Activity*—Various degrees of activity were observed for all of the 2-(2-alkylaminoalkylamido)pyrrole hydrochlorides that contained the nitrile function at the 3-position (Table IV). Compounds XX*a* and XXII were comparable to lidocaine by the method employed for evaluation of local anesthetic activity. Compound XVI was slightly more active than lidocaine. The most potent compound in this series was VIII*f*, which had a duration of local anesthetic activity 1.67 times that of lidocaine when compared at a concentration of 0.125%.

Compounds XXV*a*–XXV*c*, which all possess a carbamyl function at the 3-position, were devoid of local anesthetic activity. The loss of activity may be the result of relatively low lipophilicity. Previous observations (10, 11) that pyrrole analogs of lidocaine with a 3-cyano substituent are more potent than the corresponding 3-carbamyl derivatives, except where substituents in the 5-position are large and very lipophilic, are consistent with this interpretation.

Antiarrhythmic Activity and Acute Central Nervous System (CNS) Toxicity—Both activities were determined in mice following subcutaneous administration of the target compounds. Respiratory arrest was induced by exposure to chloroform, and ventricular rates were measured from ECG recordings. Reduction of the incidence of ventricular tachycardia was interpreted as an antiarrhythmic effect. The presence of ataxia during the period between drug administration and exposure to chloroform was interpreted as a sign of acute CNS toxicity.

In general, the compounds listed in Table V evoked dose-dependent reductions in the incidence of tachycardia after chloroform treatment. Several compounds (VIII*a*, VIII*d*, VIII*e*, VIII*g*, and XX*b*) had a potency similar to that of lidocaine, and one compound (XVI) was more potent. Structure–activity analyses based on the limited chemical and biological information gave partially inconsistent results. While the pyrrolidinyl derivative VIII*d* with an N^1-methyl substituent had the lowest ED_{50} value for protection among VIII*a*–VIII*g*, the corresponding compound with an N^1-hydrogen substituent (XX*d*) had the highest ED_{50} value (together with XX*c*) among XX*a*–XX*e*. Conversely, while XX*b* was the most potent compound among XX*a*–XX*e*, the corresponding VIII*b* was not particularly potent but was very toxic. In general, pyrrole derivatives with an N^1-methyl substituent appear to be more potent and more toxic than those with an N^1-hydrogen substituent.

As with lidocaine, these compounds evoked acute CNS side effects at

Table I—Data for 2-Haloalkylamides of Substituted 2-Aminopyrroles

Compound	Yield, %	Melting Point	R_f[a]	Recrystallization Solvent	Formula	Analysis, %	Calc.	Found
VI*a*[b]	54.2	169–170° dec.	0.55	Ethanol	$C_{11}H_{14}BrN_3O$	C	46.49	47.85
						H	4.97	5.12
						Br	28.12	28.91
						N	14.79	15.17
VI*b*	55.4	173–173.5°	0.63	Methanol	$C_{10}H_{12}ClN_3O$	C	53.22	53.10
						H	5.36	5.41
						Cl	15.71	15.68
						N	18.62	18.58
XII	93.1	212–212.5°	0.65	Ethanol	$C_{10}H_{12}BrN_3O$	C	44.44	44.48
						H	4.47	4.48
						Br	29.60	29.52
						N	15.56	15.56
XIII[b]	69.3	120–121°	0.69	2-Propanol–water (2:1)	$C_{13}H_{18}BrN_3O$	C	50.01	51.49
						H	5.81	5.68
						Br	25.60	26.34
						N	13.46	13.86
XIV[b]	87.3	188.5–189°	0.71	Ethanol	$C_{16}H_{16}BrN_3O$	C	55.50	58.51
						H	4.66	4.99
						Br	23.08	23.56
						N	12.14	12.74
XVIII	96.1	190–191° dec.	0.63	Methanol	$C_{10}H_{12}ClN_3O$	C	53.22	53.26
						H	5.36	5.39
						Cl	15.71	15.68
						N	18.62	18.61
XXIII	46.0	166.5–167°	0.53	Methanol	$C_{10}H_{14}ClN_3O_2$	C	49.28	49.14
						H	5.79	5.83
						Cl	14.55	14.49
						N	17.24	17.16

[a] Ethyl acetate. [b] Repeated attempts to obtain correct elemental analyses for amides derived from 2-bromopropionyl chloride were unsuccessful. IR and NMR spectral data were consistent with the assigned structures, the products were homogeneous on TLC, and the products derived from the 2-bromopropionamides gave correct elemental analyses.

Table II—Data for Substituted 2-(2-Alkylaminoalkylamido)pyrroles

Compound	Precursor	Yield, %	Reaction Solvent[a]	Recrystallization Solvent[b]	Melting Point	Formula
VII*a*	VI*a*	90.4	Ethanol	Cyclohexane	110.5–111.5°	$C_{15}H_{24}N_4O$
VII*b*	VI*a*	—[c]	Ethanol	Cyclohexane–benzene (5:1)	Oil	$C_{15}H_{24}N_4O$
VII*c*	VI*a*	—[c]	Ethanol	Cyclohexane	Oil	$C_{15}H_{24}N_4O$
VII*d*	VI*a*	—[c]	Ethanol	Cyclohexane	Oil	$C_{15}H_{22}N_4O$
VII*e*	VI*a*	—[c]	Ethanol	Cyclohexane–benzene (4:1)	Oil	$C_{16}H_{24}N_4O$
VII*f*	VI*a*	—[c]	Ethanol	Cyclohexane–benzene (4:1)	Oil	$C_{17}H_{26}N_4O$
VII*g*	VI*b*	62.6	Ethanol	—[d]	Oil	$C_{14}H_{22}N_4O$
XIX*a*	XII	53.4	*n*-Propanol	Methanol–water (4:1)	118.5–120°	$C_{14}H_{22}N_4O$
XIX*b*	XII	42.0	*n*-Propanol	Cyclohexane	160–161°	$C_{14}H_{22}N_4O$
XIX*c*	XII	34.0	Ethanol	Methanol–water (4:1)	91.5–93°	$C_{14}H_{22}N_4O$
XIX*d*	XII	56.9	Ethanol	Cyclohexane–benzene (1:1)	125–127°	$C_{14}H_{20}N_4O$
XIX*e*	XVIII	68.8	Methanol	—[d]	120–121°	$C_{14}H_{20}N_4O_2$
XXI	XIII	75.0	*n*-Propanol	Methanol–water (4:1)	87–88°	$C_{18}H_{28}N_4O$
XXIV*a*	XXIII	36.0	Ethanol	Methanol–water (9:1)	168.5–169.5°	$C_{12}H_{22}N_4O_2$
XXIV*b*	XXIII	52.7	Methanol	—[d]	234–235°	$C_{14}H_{22}N_4O_3$
XXIV*c*[e]	XXIII	10.2	Methanol	2-Propanol–water (1:2)	185.5–186.5°	$C_{14}H_{24}N_4O_2$

[a] Absolute. [b] The oils were dissolved in boiling recrystallization solvent(s), treated with activated charcoal, filtered, and collected as oils after cooling. [c] Yields were not determined for the free base. [d] Free amine suitable for hydrochloride salt formation without recrystallization. [e] *Anal.*—Calc. for XXIV*c*: C, 59.97; H, 8.63; N, 19.99. Found: C, 59.80; H, 8.65; N, 19.91.

doses that were not significantly different from those required for efficacy. While VIII*g* appeared to have some separation between protection and ataxia, there was no significant difference between the ED_{50} value for ataxia and the acute LD_{50} value determined in the same group of mice.

EXPERIMENTAL

Chemistry[1]—*2-(2-Bromopropionamido)-3-cyano-4,5-dimethylpyrrole (XII)*—The procedure for the synthesis of XII is representative of that for VI*a*, VI*b*, XIII, XIV, and XVIII. A solution of 2-amino-3-cyano-4,5-dimethylpyrrole (IX) (27.0 g, 0.2 mole) (13) in pyridine (17.4 g, 0.22 mole) and 200 ml of acetone was stirred in an ice bath as 2-bromopropionyl chloride (37.7 g, 0.22 mole) was added dropwise. After the addition was complete, the thick slurry was stirred at room temperature for 20 min. The slurry was poured over 500 g of crushed ice, the resulting suspension was stirred until the ice had melted, and the crude product was collected by filtration.

The amide was resuspended in 300 ml of distilled water, and the insoluble product was collected by filtration and was air dried. One gram of the pale-yellow product (50.3 g, 93.1%) was recrystallized from 40 ml of absolute ethanol to yield yellow needles (homogeneous on TLC; in ethyl acetate, R_f 0.65), mp 212–212.5°; IR (KBr): 3360, 3260, 3160, 3100, 3020, 2910–2700 (broad), 2210, 1670, 1620, 1510, 1470, 1440, 1360, 1230, 1210, 1170, and 700 cm^{-1}; NMR (dimethyl sulfoxide-d_6): δ 1.73 (d, 3H, $CHBrCH_3$), 1.94 (s, 3H, CH_3 at C-4), 2.04 (s, 3H, CH_3 at C-5), 4.72 (q, 1H, $CHBrCH_3$), 10.78 (s, 1H, NH), and 11.25 (s, 1H, NH) ppm. Table I gives the results of the elemental analyses.

*2-(2-Pyrrolidinopropionamido)-3-cyano-4,5-dimethylpyrrole (XIX*d*)*—The procedure for the synthesis of XIX*d* is representative of

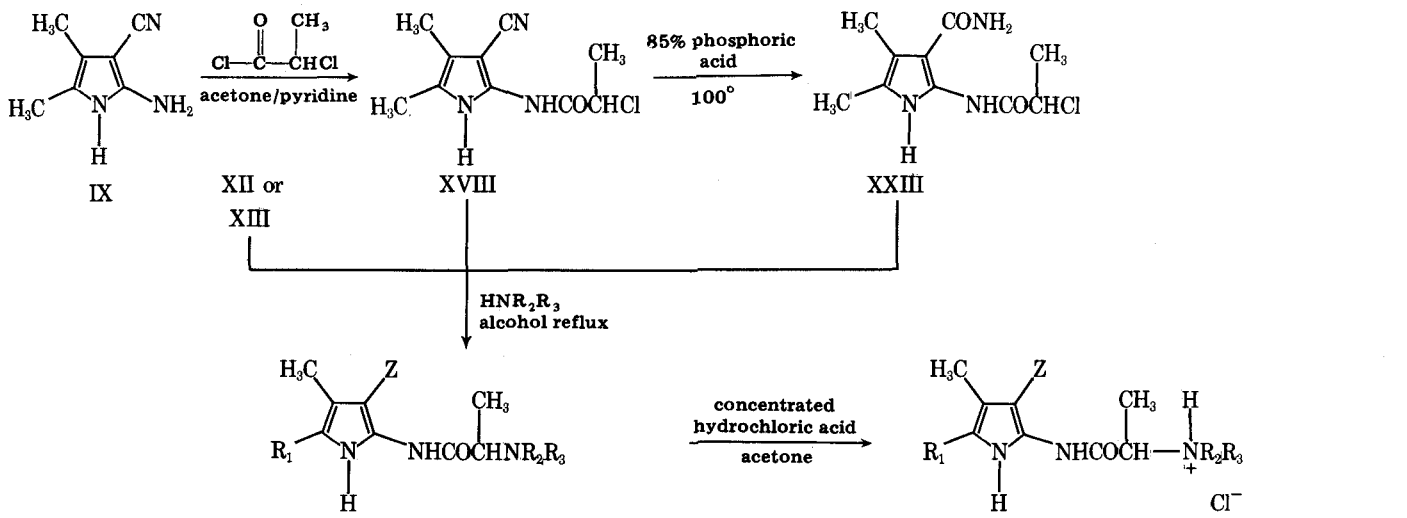
[1] All IR spectral data were determined on a Beckman Acculab-4 spectrophotometer using the potassium bromide technique. NMR spectra were determined on a Hitachi Perkin-Elmer R24 high-resolution spectrophotometer with tetramethylsilane as the internal reference. The reported melting points were obtained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

Table III—Data for Substituted 2-(2-Alkylaminoalkylamido)pyrrole Hydrochlorides

Compound	Yield, %	Melting Point	R_f	Recrystallization Solvent	Formula	Analysis, %	Calc.	Found
VIII*a*	85.0	226–227° dec.	0.32[a]	Water	$C_{15}H_{25}ClN_4O$	C	57.59	57.58
						H	8.06	8.08
						Cl	11.33	11.33
						N	17.91	17.89
VIII*b*	79.9[b]	231.5–232°	0.23[a]	—[c]	$C_{15}H_{25}ClN_4O$	C	57.59	57.40
						H	8.06	8.08
						Cl	11.33	11.28
						N	17.91	17.85
VIII*c*	55.6[b]	244.5–245°	0.62[d]	—[c]	$C_{15}H_{25}ClN_4O$	C	57.59	57.46
						H	8.06	8.07
						Cl	11.33	11.32
						N	17.91	17.86
VIII*d*	66.8[b]	243.5–244.5°	0.56[d]	—[c]	$C_{15}H_{23}ClN_4O \cdot 1.0\ H_2O$	C	54.78	54.71
						H	7.66	7.66
						Cl	10.78	10.74
						N	17.04	17.00
VIII*e*	82.1[b]	215.5–216.5°	0.51[a]	2-Propanol–hexanes (1:3)	$C_{16}H_{25}ClN_4O$	C	59.15	58.95
						H	7.76	7.80
						Cl	10.91	10.82
						N	17.25	17.18
VIII*f*	63.9[b]	253.5–254.5°	0.29[a]	—[c]	$C_{17}H_{27}ClN_4O$	C	60.25	60.25
						H	8.04	8.07
						Cl	10.46	10.36
						N	16.53	16.43
VIII*g*	81.5	187–187.5°	0.35[a]	Methanol–acetone (1:9)	$C_{14}H_{23}ClN_4O$	C	56.27	56.44
						H	7.76	7.84
						Cl	11.87	11.82
						N	18.75	18.74
XV	35.0[b]	272–275° dec.	0.56[d]	—[e]	$C_{10}H_{15}ClN_4O \cdot 0.55\ H_2O$	C	47.54	47.53
						H	6.42	6.42
						Cl	14.04	14.02
						N	22.18	22.18
XVI	59.7[b]	250° dec.	0.57[d]	—[f]	$C_{13}H_{21}ClN_4O \cdot 1.3\ H_2O$	C	50.66	50.64
						H	7.72	7.74
						Cl	11.50	11.48
						N	18.18	18.16
XVII	35.6[b]	255–256° dec.	0.59[d]	Water	$C_{16}H_{19}ClN_4O$	C	60.28	60.35
						H	6.01	6.08
						Cl	11.12	11.08
						N	17.58	17.52
XX*a*	99.0	195–196° dec.	0.52[a]	—[c]	$C_{14}H_{23}ClN_4O \cdot 1.0\ H_2O$	C	53.07	52.90
						H	7.95	8.00
						Cl	11.19	11.19
						N	17.68	17.60
XX*b*	67.0	246–246.5°	0.59[a]	—[c]	$C_{14}H_{23}ClN_4O$	C	56.27	56.33
						H	7.76	7.76
						Cl	11.87	11.78
						N	18.75	18.80
XX*c*	95.0	245.5–246.5°	0.55[a]	—[c]	$C_{14}H_{23}ClN_4O$	C	56.27	56.07
						H	7.76	7.79
						Cl	11.87	11.80
						N	18.75	18.70
XX*d*	93.7	265.5–267°	0.41[a]	—[c]	$C_{14}H_{21}ClN_4O$	C	56.65	56.56
						H	7.13	7.16
						Cl	11.95	11.89
						N	18.88	18.81
XX*e*	81.8	252–253°	0.50[a]	—[c]	$C_{14}H_{21}ClN_4O_2$	C	53.75	53.72
						H	6.77	6.76
						Cl	11.34	11.29
						N	17.91	17.85
XXII	76.4	120–123°	0.65[a]	2-Propanol–ethyl acetate–hexane (1:1:3)	$C_{18}H_{29}ClN_4O \cdot 0.75\ H_2O$	C	59.00	59.02
						H	8.39	8.44
						Cl	9.68	9.68
						N	15.29	15.29
XXV*a*	49.0	213–214°	0.52[g]	2-Propanol–acetone (1:5)	$C_{14}H_{23}ClN_4O_2$	C	53.41	53.58
						H	7.36	7.32
						Cl	11.26	11.39
						N	17.80	17.88
XXV*b*	92.1	242–244°	0.32[a]	Methanol–acetone (1:3.75)	$C_{14}H_{23}ClN_4O_3$	C	50.83	50.80
						H	7.01	7.03
						Cl	10.72	10.68
						N	16.94	16.91
XXV*c*[h]	—	—	—	—	—	—	—	—

[a] Ethyl acetate. [b] Percent yield is based on the α-haloamide percursor. [c] The salt obtained was analytically pure. [d] Acetone. [e] The crystals were washed with boiling ethyl acetate and then with boiling 2-propanol. [f] The crystals were washed with boiling ethyl acetate. [g] 2-Propanol. [h] The hydrochloride salt obtained was deliquescent; therefore, elemental analysis was performed with the free base (XXIV*c*).

that of VII*a*–VII*g*, XIX*a*–XIX*e*, XXI, and XXIV*a*–XXIV*c*. A solution of XII (20.25 g, 0.075 mole) in 100 ml of absolute ethanol was stirred while pyrrolidine (21.3 g, 0.30 mole) was added. The mixture was refluxed with stirring for 6.5 hr, during which time the suspension changed to a clear brown solution. The solvent and excess amine were removed *in vacuo*, and the residue was dissolved in 100 ml of 10% HCl. The solution was



XIX*a*: $R_1 = CH_3$, $R_2 = iso\text{-}C_4H_9$, $R_3 = H$, Z = CN
XIX*b*: $R_1 = CH_3$, $R_2 = n\text{-}C_4H_9$, $R_3 = H$, Z = CN
XIX*c*: $R_1 = CH_3$, $R_2 = R_3 = C_2H_5$, Z = CN
XIX*d*: $R_1 = CH_3$, $R_2 + R_3 = -(CH_2)_4-$, Z = CN
XIX*e*: $R_1 = CH_3$, $R_2 + R_3 = -(CH_2)_2O(CH_2)_2-$, Z = CN
XXI: $R_1 = iso\text{-}C_4H_9$, $R_2 + R_3 = -(CH_2)_5-$, Z = CN
XXIV*a*: $R_1 = CH_3$, $R_2 + R_3 = -(CH_2)_4-$, Z = $CONH_2$
XXIV*b*: $R_1 = CH_3$, $R_2 + R_3 = -(CH_2)_2O(CH_2)_2-$, Z = $CONH_2$
XXIV*c*: $R_1 = CH_3$, $R_2 = R_3 = C_2H_5$, Z = $CONH_2$

XX*a*: $R_1 = CH_3$, $R_2 = iso\text{-}C_4H_9$, $R_3 = H$, Z = CN
XX*b*: $R_1 = CH_3$, $R_2 = n\text{-}C_4H_9$, $R_3 = H$, Z = CN
XX*c*: $R_1 = CH_3$, $R_2 = R_3 = C_2H_5$, Z = CN
XX*d*: $R_1 = CH_3$, $R_2 + R_3 = -(CH_2)_4-$, Z = CN
XX*e*: $R_1 = CH_3$, $R_2 + R_3 = -(CH_2)_2O(CH_2)_2-$, Z = CN
XXII: $R_1 = iso\text{-}C_4H_9$, $R_2 + R_3 = -(CH_2)_5-$, Z = CN
XXV*a*: $R_1 = CH_3$, $R_2 + R_3 = -(CH_2)_4-$, Z = $CONH_2$
XXV*b*: $R_1 = CH_3$, $R_2 + R_3 = -(CH_2)_2O(CH_2)_2-$, Z = $CONH_2$
XXV*c*: $R_1 = CH_3$, $R_2 = R_3 = C_2H_5$, Z = $CONH_2$

Scheme III

filtered, and the acidic filtrate was poured over 200 g of ice and alkalinized (pH 9) with 10% NaOH. A tan, gummy solid formed, which was extracted with three 40-ml portions of chloroform.

The combined chloroform extracts were washed with two 50-ml portions of saturated aqueous sodium chloride solution, and the chloroform was removed *in vacuo*. The residue was recrystallized from 60 ml of methanol–water (2:5), yielding a brown, granular solid (11.50 g, 56.9%). The crude product was recrystallized twice from 200 ml of benzene–cyclohexane (1:1), yielding a tan solid (8.2 g, 42%). This solid was suitable for hydrochloride salt formation (homogeneous on TLC; in ethyl acetate, R_f 0.48), mp 125–127°. The data for the analogs are given in Table II.

2-(2-Pyrrolidinopropionamido)-3-cyano-4,5-dimethylpyrrole Hydrochloride (*XX*d)—The procedure given for the synthesis of XX*d* is representative of that of VIII*a*–VIII*g*, XX*a*–XX*e*, XXII, and XXV*a*–XXV*c*. The free amine (XIX*d*) (8.2 g, 0.032 mole) was dissolved in 150 ml of warm acetone and filtered, and the filtrate was treated with 3.0 ml of concentrated hydrochloric acid. The sealed flask then was placed in the freezer at −30° for 2.5 hr to yield a white powder. The salt (8.9 g, 93.7%) was collected, washed with acetone, and air dried (homogeneous on TLC; in ethyl acetate, R_f 0.41), mp 265.5–267°; IR (KBr): 3300–2800 (broad), with peaks at 3140, 3030, 2940, 2800, 2660, 2200, 1690, 1610, 1575, 1540, 1460, 1300, 1255, 1190, 1120, 1085, 1060, 1040, 950, 910, 860, and 690 cm^{-1}; NMR (dimethyl sulfoxide-d_6): δ 1.56 (d, 3H, $COCHCH_3$), 2.00 (broad m, 4H, β-carbons on pyrrolidine), 1.95 (s, 3H, CH_3 at C-4), 2.05 (s, 3H, CH_3 at C-5), 3.31 (m, 4H, α-carbons on pyrrolidine), 4.25 (q, 1H, COCH), 11.35 (s, 2H, NH), and 11.55 (s, 1H, NH) ppm. Table III presents the results of the elemental analyses.

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

Compound	Solution Concentration 1%	0.50%	0.25%
Lidocaine	100 (36)	100 (36)	100 (31)
VIII*a*	94 (34)	89 (32)	71 (22)
VIII*b*	100 (36)	69 (25)	68 (21)
VIII*c*	64 (23)	50 (18)	36 (11)
VIII*d*	89 (32)	58 (21)	61 (19)
VIII*e*	100 (36)	47 (17)	55 (17)
VIII*f* [b]	100 (36)	100 (36)	116 (36)
VIII*g*	92 (33)	36 (13)	26 (08)
XV	86 (31)	75 (27)	45 (14)
XVI	100 (36)	100 (36)	110 (34)
XVII	100 (36)	94 (34)	77 (24)
XX*a*	100 (36)	89 (32)	94 (29)
XX*b*	100 (36)	92 (33)	48 (15)
XX*c*	100 (36)	89 (32)	36 (11)
XX*d*	33 (12)	—	—
XX*e*	97 (35)	72 (26)	22 (07)
XXII	100 (36)	97 (35)	97 (30)
XXV*a*	3 (01)	—	—
XXV*b*	0 (00)	—	—
XXV*c*	3 (01)	—	—
Sodium chloride	0 (00)	—	—

[a] Values given are percent protection; the numbers in parentheses represent a sum of the number of pinpricks failing to elicit a response (skin twitch or cry) following intradermal injection of 0.25 ml of the test compound in preshaven guinea pig backs (n = 2). [b] At a concentration of 0.125%, lidocaine protected against 12 pricks (100%) and VIII*f* protected against 20 pricks (167%).

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

Compound	ED_{50}[c], mg/kg (95% Fieller Limits) Protection	Ataxia
VIII*a*	67 (47–118)	<25
VIII*b*	—[d]	21 (10–39)
VIII*c*	127 (74–217)[e]	126 (84–283)
VIII*d*	28 (14–62)	10 (5–19)
VIII*e*	71 (42–120)	39 (17–60)
VIII*f*	—[f]	25 (7–41)
VIII*g*	86 (24–302)	155 (84–284)
XV	—[g]	—[g]
XVI	26 (18–37)	27 (18–35)
XVII	—[h]	—[h]
XX*a*	111 (59–208)[e]	129 (83–509)
XX*b*	40 (21–59)	35 (21–52)
XX*c*	256 (176–319)	251 (168–307)
XX*d*	252 (168–307)	252 (168–307)
XX*e*	159 (73–351)[e]	79 (13–139)
XXII	—[i]	—[i]
XXV*a*	330 (170–641)	159 (87–327)
Quinidine	72 (61–83)	—[k]
Lidocaine	48 (44–53)	45 (40–50)

[a] Protection against chloroform-induced tachycardia. [b] Observed prior to exposure to chloroform. [c] Subcutaneous administration. [d] At 36 mg/kg, 20% were protected; at the next higher dose of 100 mg/kg, 90% died before chloroform exposure. [e] Approximate 95% Fieller limits. [f] At 50 mg/kg, 40% were protected; at 100 mg/kg, 100% died before chloroform exposure. [g] At 200 mg/kg, 22% were protected, 22% were ataxic, and 10% were dead. [h] At 35 mg/kg, no protection or ataxia was observed. Higher doses were not soluble. [i] At 398 mg/kg, no protection or ataxia was observed. [k] No ataxia occurred at 200 mg/kg.

2-(2-Aminopropionamido)-3-cyano-4-methyl-5-isobutylpyrrole Hydrochloride (XVI)—The procedure for the synthesis of XVI is representative of that of XV and XVII and conforms to the method of Secrist and Loque (15).

A mixture of 2-(2-bromopropionamido)-3-cyano-4-methyl-5-isobutylpyrrole (XIII) (9.37 g, 0.03 mole) and sodium azide (2.0 g, 0.0309 mole) in absolute methanol (100 ml) was refluxed with stirring for 1.5 hr. The solution was transferred to a Parr bottle, chloroform (3.0 ml) and 10% palladium-on-carbon (1.0 g) were added, and the mixture was hydrogenated at 46 psi for 3.5 hr. (The progress of the hydrogenation was monitored by the disappearance of the azide band at 2040 cm^{-1} in the IR spectrum.) The mixture was acidified and filtered, and the filtrate was reduced *in vacuo* to yield a tan solid.

This solid was treated with 100 ml of 10% HCl and warmed gently, and the insoluble salt was collected and air dried. Treatment of the solid with boiling ethyl acetate (100 ml) gave a white powder (5.1 g, 59.7%) (homogeneous on TLC; in acetone, R_f 0.57; in methanol, R_f 0.54), mp 250° dec.; IR (KBr): 3380, 3270, 2960, 2220, 1685, 1620, 1590, 1505, 1475, 1245, 1215, and 685 cm^{-1}; NMR (dimethyl sulfoxide-d_6): δ 0.82 (d, 6H, J = 6.0 Hz, *gem*-dimethyls of isobutyl), 1.3–2.0 (m, 1H, methine of isobutyl), 1.50 [d, 3H, J = 7.2 Hz, $CH(\overset{+}{N}H_3)CH_3$], 1.95 (s, 3H, methyl at C-4), 2.31 [d, 2H, J = 6.0 Hz, $CH_2CH(CH_3)_2$], 4.06 [q, 1H, J = 7.2 Hz, $CH(\overset{+}{N}H_3)CH_3$], 9.01 (broad s, 4H, $\overset{+}{N}H_3$ and CONH), and 11.32 (broad s, 1H, N_1H) ppm. Table III shows the results of the elemental analyses.

Pharmacology—*Local Anesthetic Activity*—The guinea pig wheal method of Bulbring and Wajda (16) was used to determine the activity. The back of the guinea pig was shaved 1 day prior to the test, and 0.25 ml of the drug solution was administered intradermally at two sites along the midline. The resulting wheals were tested by pricking the area six times with a pin at 5-min intervals for 30 min. Local anesthesia was present if the pinprick did not elicit a skin twitch. The number of pinpricks that failed to elicit a response then was recorded at each interval and compared to that of lidocaine at the same percentage concentration (Table IV).

Antiarrhythmic Activity and CNS Toxicity—Antiarrhythmic activity was assessed by a modification of the method by Lawson (17). Groups of 10 female mice (Charles River, CD 1), 18–24 g, were injected subcutaneously with the drug solution delivered in a volume of 0.1 ml/10 g of body weight. After 20 min, the mice were placed one at a time in an atmosphere of chloroform. Each mouse was removed when respiratory arrest occurred (~35–45 sec later) and was pinned to a cork board with dissecting needles, which also served as electrodes.

Previous experience with this procedure indicated that fibrillation was not the most prevalent arrhythmia and that a one-lead ECG was inadequate to resolve the rapid ECG events that occur after respiratory arrest in chloroform (18). Consequently, after a thoracotomy was performed, three ECGs were recorded from each mouse until 90 sec from the time it had been placed in the chloroform. Leads I and II were obtained *via* the needle electrodes, and an epicardial ECG was obtained from a wick electrode placed on the exposed surface of the right ventricle. All ECGs were displayed on a multichannel seven-pen recorder as well as on a storage oscilloscope.

Ventricular rates (beats per minute) were measured directly from the clearest ECG by counting ventricular depolarizations for several seconds and extrapolating them to beats per minute (bpm). A mouse was assumed to have a tachycardia if the 30–40-sec ECG recording contained at least 5 sec in which the ventricular rate exceeded 520 bpm or 2 sec in which the rate exceeded 600 bpm. Conversely, a mouse was protected from the arrhythmogenic effects of chloroform if these criteria were not fulfilled. Antiarrhythmic efficacy was based on the percentage of mice protected at each dose. Doses were varied by at least 0.15 log unit in an up–down fashion; the intent was to achieve a dose–response curve in which the doses evoked a low, medium, and high incidence of protection. Doses were increased until either the limits of water solubility were reached or lethal effects precluded higher doses. Thereafter, the ED_{50} value for protection was calculated according to the logit χ^2 method of Berkson (19).

Acute CNS toxicity was assessed during the 20-min period prior to chloroform exposure. Any mouse that displayed a staggered gait, splayed limbs, or hypertonia was assumed to have acute CNS toxicity in the form of ataxia. In general, doses were increased until at least eight animals displayed these symptoms. The ED_{50} value for ataxia was also calculated according to the method of Berkson (19).

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ACKNOWLEDGMENTS

Adapted in part from theses submitted by M. E. Derrick and P. F. Mubarak to the University of South Carolina in partial fulfillment of the Master of Science degree requirements.

Supported by Astra Pharmaceutical Products.

The authors thank Ms. K. Landry and D. Charron for technical assistance.