Synthesis of Substituted 2-Aminopyrrole Analogs of Lidocaine I

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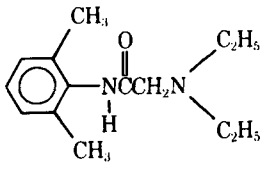
Abstract □ The synthesis, local anesthetic, and antiarrhythmic properties of nine 2-diethylaminoacetamido-3-cyano-4-methyl-5-substituted pyrroles are described. All compounds showed local anesthetic activity by the guinea pig wheal test and antiarrhythmic activity for chloroform-induced ventricular arrhythmias in mice.

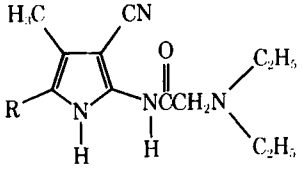
Keyphrases □ 2-Aminopyrrole analogs of lidocaine, various—synthesized, evaluated for local anesthetic activity in guinea pigs and antiarrhythmic activity in mice □ Structure–activity relationships—various 2-aminopyrrole analogs of lidocaine evaluated for local anesthetic activity in guinea pigs and antiarrhythmic activity in mice □ Lidocaine analogs—2-aminopyrroles synthesized

The use of lidocaine (I) as a local anesthetic is well documented. In recent years, lidocaine has also gained popularity for the treatment of ventricular arrhythmia. Due to its rapid metabolic rate (1), lidocaine is normally given by continuous intravenous administration in the treatment of ventricular arrhythmia. Plasma and tissue lidocaine levels fall rapidly (1) when intravenous administration is discontinued. The limited extent of plasma protein binding coupled with rapid metabolic transformations (2–4) accounts for the relatively short biological half-life.

Numerous analogs and homologs of lidocaine have been synthesized and evaluated. The major research thrust has been directed at modification of the aminoacyl portion of the lidocaine structure. The effect of these structural modifications on activity has been well established. The replacement of the benzenoid ring system in lidocaine by the heteroaromatic pyrrole ring system, however, has not been studied.



I



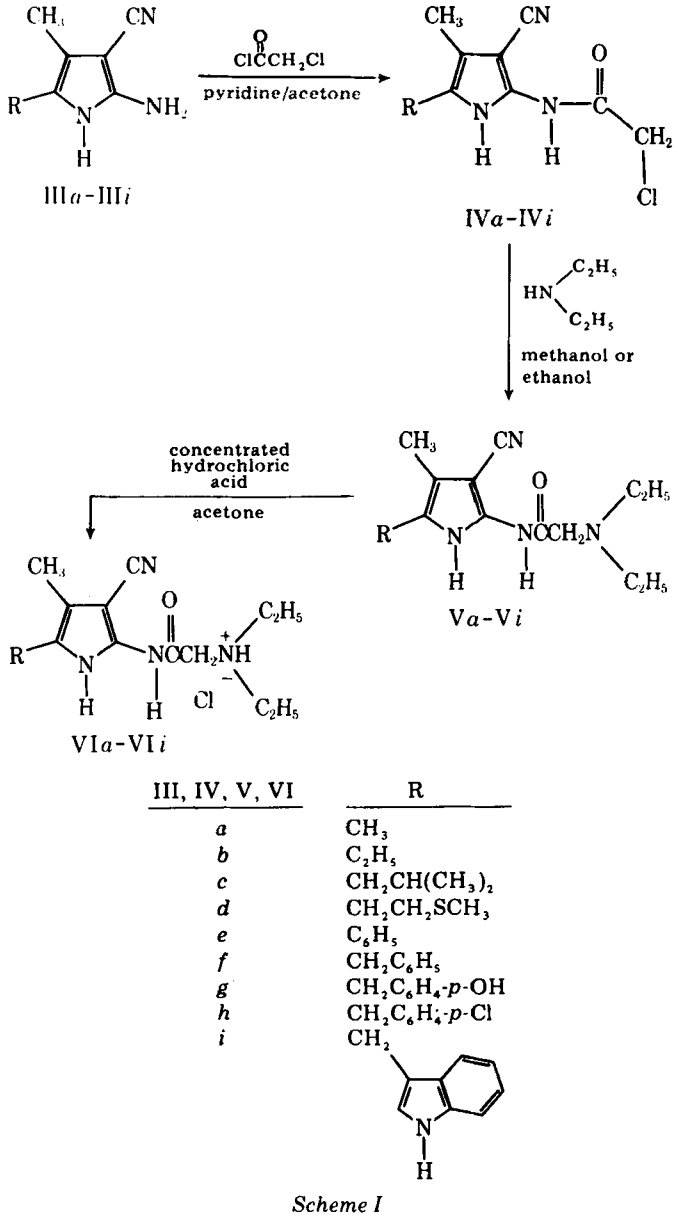
II

A series of 2-diethylaminoacetamido-3-cyano-4-methyl-5-substituted pyrrole (II) analogs of lidocaine was synthesized to compare the effects of this nuclear modification on both the local anesthetic and antiarrhythmic activities.

DISCUSSION

Chemistry—The synthesis of 2-amino-3-cyano-4-methyl-5-substituted pyrroles (III*a*–III*i*) (Scheme I) was reported previously (5–7). Comparatively few simple 2-aminopyrroles are known, and the majority of those are substituted with an electron-withdrawing group on the pyrrole ring (8). The nitrile at the 3-position of III*a*–III*i* stabilizes the 2-aminopyrroles from decomposition. The substituent at the 5-position corresponds to the R group of various α-amino acids utilized as precursors to III*a*–III*i*. The choice of these compounds as starting materials for the synthesis of the lidocaine analogs was made on the basis of their availability in good yields from commercially available L- or DL-α-amino acids.

The synthetic route to the 2-aminopyrrole analogs (II) of lidocaine parallels the original synthesis of lidocaine by Löfgren and Lundgvist (9). Acylation of III*a*–III*i* with chloroacetyl chloride in acetone with an equivalent amount of pyridine gave the corresponding 2-chloroacetamides (IV*a*–IV*i*) in excellent yields (Table I). These amides were high melting, stable, and relatively insoluble. The IR and NMR spectra were



III, IV, V, VI	R
a	CH_3
b	C_2H_5
c	$CH_2CH(CH_3)_2$
d	$CH_2CH_2SCH_3$
e	C_6H_5
f	$CH_2C_6H_5$
g	$CH_2C_6H_4$-*p*-OH
h	$CH_2C_6H_4$-*p*-Cl
i	CH_2

Scheme I

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Table I—Data for 2-Chloroacetamido-3-cyano-4-methyl-5-substituted Pyrroles

Compound	Yield, %	Melting Point	R_f[a]	Recrystallization Solvent	Formula	Analysis, %	Calc.	Found
IV*a*	90.0	240–241.5° dec.	0.57	Ethanol	$C_9H_{10}ClN_3O$	C	51.07	51.04
						H	4.76	4.76
						Cl	16.75	16.74
						N	19.85	19.89
IV*b*	94.2	208–209° dec.	0.56	Ethanol	$C_{10}H_{12}ClN_3O$	C	53.22	53.28
						H	5.36	5.39
						Cl	15.71	15.80
						N	18.62	18.61
IV*c*	94.1	160–161°	0.57	Ethanol	$C_{12}H_{16}ClN_3O$	C	56.80	56.85
						H	6.36	6.37
						Cl	13.97	13.93
						N	16.56	16.54
IV*d*	81.6	166–167°	0.46	Ethanol	$C_{11}H_{14}ClN_3OS$	C	48.61	48.67
						H	5.19	5.19
						Cl	13.05	13.03
						N	15.46	15.45
						S	11.80	11.77
IV*e*	95.6	246–247.5° dec.	0.55	Ethanol	$C_{14}H_{12}ClN_3O$	C	61.43	61.38
						H	4.42	4.46
						Cl	12.95	13.05
						N	15.35	15.32
IV*f*	100	183.5–184°	0.57	Ethanol–2-propanol–water	$C_{15}H_{14}ClN_3O$	C	62.61	62.62
						H	4.90	4.91
						Cl	12.32	12.38
						N	14.60	14.63
IV*g*	80	218–219° dec.	0.57	Ethanol–water	$C_{15}H_{14}ClN_3O_2$	C	59.31	59.21
						H	4.65	4.66
						Cl	11.67	11.66
						N	13.83	13.82
IV*h*	91.7	188–189°	0.58	Ethanol	$C_{15}H_{13}Cl_2N_3O$	C	55.92	55.96
						H	4.07	4.09
						Cl	22.01	22.14
						N	13.04	13.02
IV*i*	73.5	200–201° dec.	0.56	Ethanol–water	$C_{17}H_{15}ClN_4O$	C	62.48	62.55
						H	4.63	4.66
						Cl	10.85	10.75
						N	17.14	17.17

[a] Ethyl acetate.

Table II—Data for 2-Diethylaminoacetamido-3-cyano-4-methyl-5-substituted Pyrroles

Compound	Yield, %	Melting Point	Reaction Solvent[a]	Recrystallization Solvent	Formula
V*a*	83.9	88–89°	Methanol	—[b]	$C_{13}H_{20}N_4O$
V*b*	98.0	84–85°	Ethanol	—[b]	$C_{14}H_{22}N_4O$
V*c*	95.8	86.5–87.5°	Ethanol	Methanol–water (4:1)	$C_{16}H_{26}N_4O$
V*d*	97.5	95–96°	Ethanol	Methanol–water (4:1)	$C_{15}H_{24}N_4OS$
V*e*	88.7	84.5–86°	Methanol	Methanol–water (4:1)	$C_{18}H_{22}N_4O$
V*f*	83.7	133–134°	Methanol	—[b]	$C_{19}H_{24}N_4O$
V*g*	64.7	149–150.5°	Methanol	—[b]	$C_{19}H_{24}N_4O_2$
V*h*	90.0	99–99.5°	Ethanol	Methanol–water (4:1)	$C_{19}H_{23}ClN_4O$
V*i*[c]	86.3	141–142.5°	Methanol	Methanol–water (4:1)	$C_{21}H_{25}N_5O$

[a] Absolute. [b] Free amine suitable for hydrochloride salt formation without recrystallization. [c] Calc. for: C, 69.40; H, 6.93; N, 19.27. Found: C, 69.45; H, 6.97; N, 19.22.

consistent with the assigned structures. The purity of the chloroacetamides was determined by TLC and elemental analysis (Table I).

The 2-diethylaminoacetamido-3-cyano-4-methyl-5-substituted pyrroles (V*a*–V*i*) were obtained by refluxing a suspension of the corresponding chloroacetamides (IV*a*–IV*i*) in absolute methanol or ethanol with excess diethylamine. During these reactions, solutions were achieved within 1–4 hr. The solvent and excess diethylamine were removed *in vacuo*, the amine residues were dissolved in 10% HCl, and the solutions were filtered to remove unreacted chloroacetamides. The amines were precipitated by the addition of 5% aqueous sodium hydroxide. Yields, melting points, and purification data are given in Table II.

All amine hydrochlorides, except VI*c* and VI*d*, were conveniently prepared by treating an acetone solution of the free amines with concentrated hydrochloric acid (Method A in *Experimental*). Compounds VI*c* and VI*d* were prepared in excellent yields by treating a solution of the amines in anhydrous ether with a saturated solution of hydrogen chloride in absolute ethanol (Method B in *Experimental*).

The IR spectra of the amine hydrochlorides (VI*a*–VI*h*) exhibited the expected N–H stretching absorption bands between 3400 and 3100 cm^{-1} and broad absorption in the 2800–2300-cm^{-1} region for the amine salts. The spectra contained intense, sharp absorption bands in the 2220–2210-cm^{-1} region for the nitrile and carbonyl absorption bands at 1630–1610 cm^{-1}. The NMR spectra of the amine hydrochlorides in dimethyl sulfate-d_6 contained a singlet at 1.84–2.12 ppm, integrating for three protons, which was assigned to the methyl group of the C-4 position. The protons of the diethylamino moiety appeared as a typical triplet and quartet for the methyl and methylene, respectively. The chemical shift for the triplet ranged from 1.16 to 1.30 ppm, and that for the quartet ranged from 3.10 to 3.28 ppm. The triplet and quartet integrated for three protons and two protons, respectively.

The methylene, alpha to the carbonyl, appeared as a singlet, integrating for two protons, at 3.89–4.20 ppm. The NH proton of the salt appeared as a broad singlet at 10.0–10.8 ppm. The NH protons of the amide and the pyrrole ring appeared as two broad singlets at 11.15–11.90 ppm.

Table III—Data for 2-Diethylaminoacetamido-3-cyano-4-methyl-5-substituted Pyrrole Hydrochlorides

Compound	Method	Yield, %	Recrystallization Solvent	R_f[a]	Melting Point	Formula	Analysis, %	Calc.	Found
VI*a*	A	84.7	Methanol–acetone	0.52	237.5–239° dec.	$C_{13}H_{21}ClN_4O$	C	54.82	54.77
							H	7.43	7.45
							Cl	12.45	12.54
							N	19.67	19.66
VI*b*	A	96.2	—[b]	0.48	221–222° dec.	$C_{14}N_{23}ClN_4O$	C	56.27	56.26
							H	7.76	7.76
							Cl	11.87	11.88
							N	18.75	18.74
VI*c*	B	94.5	Acetone–ether	0.50	156.5–157°	$C_{16}H_{27}ClN_4O$	C	58.79	58.68
							H	8.33	8.35
							Cl	10.85	10.85
							N	17.14	17.13
VI*d*	B	89.3	Acetone–ether	0.48	133–133.5°	$C_{15}H_{25}ClN_4OS$	C	52.23	52.18
							H	7.31	7.34
							Cl	10.28	10.24
							N	16.25	16.22
VI*e*	A	55.6[c]	Acetone–ether	0.51	199–201° dec.	$C_{18}H_{23}ClN_4O$	C	62.33	62.20
							H	6.68	6.72
							Cl	10.22	10.14
							N	16.15	16.12
VI*f*	A	51.5[c]	Methanol–acetone	0.56	221–222° dec.	$C_{19}H_{25}ClN_4O$	C	63.23	63.27
							H	6.98	6.98
							Cl	9.83	9.80
							N	15.53	15.54
VI*g*	A	46.7[c]	Ethanol–acetone	0.50	74–76°	$C_{19}H_{25}ClN_4O_2 \cdot H_2O$	C	57.78	57.78
							H	6.89	6.89
							Cl	8.98	8.99
							N	14.19	14.18
VI*h*	A	37.4[c]	—[b]	0.49	229–231° dec.	$C_{19}H_{24}Cl_2N_4O$	C	57.72	57.75
							H	6.12	6.12
							Cl	17.94	17.93
							N	14.17	14.17
VI*i*[d]	A and B	—	—	—	Oil	—		—	—

[a] Ethyl acetate. [b] Salt obtained was analytically pure. [c] Near quantitative yields obtained upon concentration of mother liquor. [d] Hydrochloride salt was a red oil, which would not solidify with several techniques employed. Elemental analysis was determined on the free base (V*i*).

Miscellaneous absorptions for the various members were consistent with their structures. The purity of the amine hydrochlorides (VI*a*–VI*h*) was determined by TLC and elemental analysis (Table III).

Pharmacology—*Antiarrhythmic Activity*—Cardiac rates of less than 200 beats/min were used as an index of protection from arrhythmia at 70 mg/kg. Compounds VI*a*, VI*b*, and VI*d*–VI*g* (Table IV) all showed activity at this dosage. The most active agent (VI*f*) was only slightly less potent than lidocaine.

Local Anesthetic Activity—All lidocaine analogs (VI*a*–VI*i*) possessed varying degrees of local anesthetic action (Table V). Compound VI*h* appeared to have the least activity while VI*e* and VI*f* were the most active. The latter compounds were more active than lidocaine at all three solution concentrations.

EXPERIMENTAL[1]

Chemistry—*2-Chloroacetamido-3-cyano-4,5-dimethylpyrrole (IVa)*—The procedure for the synthesis of IV*a* is given as representative for IV*b*–IV*i*. A solution of 2-amino-3-cyano-4,5-dimethylpyrrole (III*a*) (20.3 g, 0.15 mole) (5) in 300 ml of absolute acetone with pyridine (12.0 g, 0.15 mole) was prepared in a 500-ml erlenmeyer flask equipped with a drying tube. This solution was stirred in an acetone–ice bath for 10 min, followed by the dropwise addition of chloroacetyl chloride (17.4 g, 0.18 mole). The solution was stirred in the acetone–ice bath for 10 min and then at room temperature for 20 min. The reaction mixture was poured over 400 g of crushed ice.

After the ice had melted, the crude product was collected by filtration, resuspended in cold 95% methanol, filtered, and air dried. Two grams of the pale-yellow product (28.6 g, 90.0%) was recrystallized twice from absolute ethanol to yield white needle-shaped crystals (homogeneous on TLC, ethyl acetate, R_f 0.57), mp 240–241.5° dec.; IR (KBr): 3345, 3300, 3280, 3180, 2230, 1675, 1635, 1480, 1335, 1250, 1220, 755, 730, 680, and 640 cm^{-1}; NMR ((dimethyl sulfate-d_6): δ 1.85 (s, 3H, CH_3 at C_4), 1.95 (s, 3H, CH_3 at C_5), 4.12 (s, 2H, CH_2), 10.41 (broad s, 1H, NH of amide at C_2 or N_1H), and 10.95 (broad s, 1H, N_1H or NH of amide at C_2) ppm. (See Table I for analyses.)

2-Diethylaminoacetamido-3-cyano-4,5-dimethylpyrrole (Va)—The procedure for the synthesis of V*a* is given as representative for V*b*–V*i*.

[1] IR spectral data were determined on a Beckman IR-20A grating spectrophotometer using the potassium bromide technique. NMR spectra were determined on a Hitachi Perkin-Elmer R24 high-resolution spectrometer with tetramethylsilane as the internal reference. Melting points were obtained using a Thomas-Hoover capillary apparatus and are uncorrected. Carbon, hydrogen, chlorine, and nitrogen values were obtained from analyses performed by Atlantic Microlab, Inc., Atlanta, Ga. TLC was performed using Eastman Chromatogram sheets, type 6060 (silica gel), and the plates were developed in an iodine chamber.

Table IV—Antiarrhythmic Activity of 2-Aminopyrrole Analogs of Lidocaine[a]

Compound	40 mg/kg	70 mg/kg	100 mg/kg
Lidocaine	242 ± 13	141 ± 23	116 ± 6
VI*a*	206 ± 16	182 ± 14	140 ± 12
VI*b*	198 ± 19	186 ± 3	148 ± 18
VI*c*	196 ± 10	202 ± 6	186 ± 13
VI*d*	219 ± 8	175 ± 12	167 ± 13
VI*e*	249 ± 15	162 ± 7	140 ± 5
VI*f*	193 ± 16	153 ± 5	147 ± 7
VI*g*	220 ± 6	200 ± 7	183 ± 14
VI*h*	227 ± 4	233 ± 10	211 ± 12
VI*i*	278 ± 14	243 ± 8	197 ± 9
Control	351 ± 8	—	—

[a] Data represent arrhythmias induced in mice by exposure to chloroform vapor (n = 6).

Table V—Local Anesthetic Activity of 2-Aminopyrrole Analogs of Lidocaine[a]

Compound	1%	0.5%	0.2%
VI*a*	72	27	10
VI*b*	45	25	6
VI*c*	63	32	7
VI*d*	41	13	—
VI*e*	72	60	20
VI*f*	72	72	50
VI*g*	72	19	14
VI*h*	25	8	—
VI*i*	50	17	8
Lidocaine	68	41	17
0.9% NaCl	0	0	0

[a] Data represent the number of pricks failing to elicit a response following intradermal injection in guinea pigs (n = 2).

A suspension of IV*a* (21.2 g, 0.10 mole) in 300 ml of absolute methanol and diethylamine (36.6 g, 0.5 mole) was refluxed, with stirring, until complete solution was achieved (1–4 hr). The deep-orange-colored solution was refluxed for an additional 1 hr, the solvent and excess diethylamine were removed *in vacuo*, and the residue was dissolved in 100 ml of 10% HCl.

The acidic solution was filtered, 400 g of ice was added, and the amine was precipitated by the addition of 5% aqueous sodium hydroxide. The product was collected by filtration, washed with water, and air dried. The light-tan product (20.8 g, 83.9%), mp 88–89°, was suitable for formation of the hydrochloride salt. (See Table II for analogs.)

2-Diethylaminoacetamido-3-cyano-4-methyl-5-substituted Pyrrole Hydrochlorides (VIa–VIh)—Method A, as illustrated for 2-diethylaminoacetamido-3-cyano-4,5-dimethylpyrrole hydrochloride (VI*a*), is representative for the synthesis of VI*b* and VI*e*–VI*h*. To a solution of the free amine (V*a*) (9.9 g, 0.04 mole) in 150 ml of cold absolute acetone, 8 ml of concentrated hydrochloric acid (dissolved in 15 ml of acetone) was added. After 3 min of stirring, a heavy white precipitate formed. The white powder was collected, washed with acetone, and air dried.

Four grams of the crude product (9.6 g, 84.2%) was recrystallized from methanol–acetone to yield white flakes (homogeneous on TLC, ethyl acetate, R_f 0.52), mp 237.5–239° dec.; IR (KBr): broad absorption between 3300 and 2500 (with peaks at 3140, 3050, 2960, 2840, 2800, 2790, and 2690), 2220, 1695, 1610, 1565, 1470, 1430, 1420, 1340, 1300, 1280, 1265, 1215, 960, 740, 715, and 690 cm^{-1}; NMR (dimethyl sulfate-d_6): δ 1.19 (t, 6H, CH_3's of diethylamine), 1.84 (s, 3H, CH_3 at C_4), 1.95 (s, 3H, CH_3 at C_5), 3.10 (q, 4H, CH_2's of diethylamine), 3.89 (s, 2H, $COCH_2$), 10.10–10.70 (broad s, 1H, N^+H), 11.18 (broad s, 1H, NH of amide at C_2 or N_1H), and 11.30 (broad s, 1H, N_1H or NH of amide at C_2) ppm. (See Table III for analyses.)

2 - Diethylaminoacetamido - 3 - cyano-4-methyl-5-isobutylpyrrole Hydrochloride (VIc)—Method B was used for the synthesis of VI*c* and VI*d*. For VI*c*, a solution of V*c* (7.8 g, 0.027 mole) in 150 ml of anhydrous ether was treated with 4 ml of absolute ethanol, which had been saturated with hydrogen chloride gas. After 15 min in the freezer, the solvents were decanted from the gummy residue. The residue was triturated with 40 ml of anhydrous acetone, the acetone solution was diluted with 40 ml of anhydrous ether, and the powder was collected by filtration and dried over phosphorus pentoxide.

The white powder (8.3 g, 94.5%) was analytically pure (homogeneous on TLC, ethyl acetate, R_f 0.50), mp 156.5–157°; IR (KBr): 3400, 3120, 3020, 2960, broad absorption between 2800 and 2300, 2215, 1700, 1610, 1560, 1460, 1270, 1210, 980, and 960 cm^{-1}; NMR (dimethyl sulfate-d_6): δ 0.82 (d, 6H, gem dimethyls of isobutyl), 0.8–1.2 (m, 1H, methine of isobutyl), 1.28 (t, 6H, CH_3's of diethylamino), 1.95 (s, 3H, CH_3 at C_4), 2.3 (d, 2H, methylene of isobutyl at C_5), 3.28 (q, 4H, methylenes of diethylamino), 4.15 (s, 2H, $COCH_2$), 10.5–11.0 (broad s, 1H, N^+H), and 11.47 (s, 2H, N_1H and NH of amide at C_2) ppm. (See Table III for analyses.)

Pharmacology—*Antiarrhythmic Activity*—With the method of Lawson (10), fibrillations were induced in 20–30-g male mice by exposure to chloroform vapor until respiration ceased. The heart was then exposed, and the cardiac rate was determined with the aid of a binocular microscope. Mice with cardiac rates in excess of 200 beats/min were considered unprotected (Table IV).

Local Anesthetic Activity—The guinea pig wheal method of Bülbring and Wajda (11) 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 aqueous 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 1 hr. Local anesthesia was present if the pinprick did not elicit a skin twitch. The number of pinpricks that failed to elicit a response was then recorded at each time interval (Table V).

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