Synthesis and Vasodepressor Screen of a Series of 2-(2-Alkylaminoalkylamido)-3-carbamyl-4-methyl-5-benzylpyrroles

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Received September 15, 1980, from the **Division of Medicinal Chemistry and the* ‡*Division of Pharmacology, College of Pharmacy, University of South Carolina, Columbia, SC 29208.* Accepted for publication November 19, 1980.

Abstract □ A series of 2-(2-alkylaminoalkylamido)-3-carbamyl-4-methyl-5-benzylpyrroles was synthesized and screened for vasoactivity. The compounds were administered intraperitoneally as a suspension to approximate the oral route of administration and intravenously when solubilization could be affected with suitable solvents. The most active compound following intravenous or intraperitoneal administration lowered blood pressure 73 and 35.5 mm Hg at doses of 4 mg/kg iv and 100 mg/kg ip, respectively. It also exhibited the longest duration of vasodepressor activity (25 min). Several other compounds exhibited vasodepressor activity following intraperitoneal administration. Several hydrochloride salts appeared to be more potent vasoactive agents than the corresponding bases.

Keyphrases □ Lidocaine analogs—synthesis, analysis of vasoactivity, intraperitoneal and intravenous administration □ Vasoactive agents—synthesis, analysis, intraperitoneal and intravenous administration, lidocaine analogs □ Synthesis and analysis—vasoactive agents, lidocaine analogs, intraperitoneal and intravenous administration □ Administration routes—effect on vasoactivity, lidocaine analogs, vasoactive agents

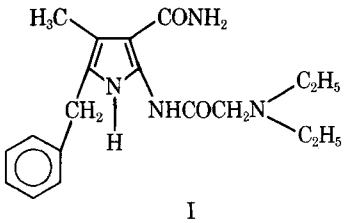
Several series of 2-aminopyrrole analogs of lidocaine recently were investigated as local anesthetic and antiarrhythmic agents (1–3). From one series, the hydrochloride salt of the benzylcarbamyl analog [2-(diethylaminoacetamide)-3-carbamyl-4-methyl-5-benzylpyrrole, I] was found to possess potent hypotensive activity following intravenous administration at doses of 2–4 mg/kg (4, 5). Compound I was more active than lidocaine with respect to antiarrhythmic activity, local anesthetic activity, and rectal temperature and respiratory depression.

Since I exerted its potent hypotensive property following intravenous administration, its structure was utilized as a basis for designing and synthesizing amine analogs that would have hypotensive activity following oral administration. Intraperitoneal administration was chosen to simulate oral activity since the drugs must cross biological membranes prior to exerting a hypotensive action.

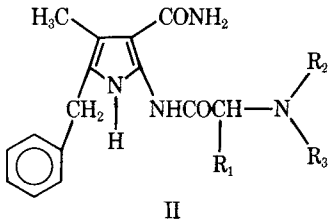
The present article reports the synthesis and vasoactivity of a series of 2-(alkylaminoalkylamido)-3-carbamyl-4-methyl-5-benzylpyrroles (II) following intraperitoneal and intravenous administration.

EXPERIMENTAL

Chemistry[1]—*2-[(N-Ethyl-N-2-hydroxyethyl)amino]acetamido-3-carbamyl-4-methyl-5-benzylpyrrole (IIa)*—The procedure given for the synthesis of IIa is representative of that used for IIb–IIh. A suspension of 2-chloroacetamido-3-carbamyl-4-methyl-5-benzylpyrrole (7.0 g, 0.023 mole) (1) in absolute ethanol (160 ml) and 2-(ethylamino)ethanol (10.2



I



II

g, 0.115 mole) was refluxed with stirring for 8 hr. The ethanol was removed *in vacuo* to yield an orange solid. The residue was suspended in water (350 ml), and the insoluble product was collected by filtration and dried.

The crude product (6.0 g, 73.1%) was recrystallized from ethanol–water (7:3) to yield off-white crystals, mp 182.5–183.5°; IR (KBr): 3480, 3315, 3180, 2960, 1660, 1630, 1570, 1380, and 720 cm^{-1}; NMR (dimethyl sulfoxide-d_6): δ 0.97 (t, 3H, CH_3 of ethyl), 2.07 (s, 3H, CH_3 at C_4), 2.40–2.70 (m, 4H, α methylenes of amino radical), 3.13 (s, 2H, $-COCH_2-$), 3.25 (s, 1H, $-CH_2OH$), 3.45 (q, 2H, methylene of $-CH_2OH$), 3.80 (s, 2H, benzylic methylene), 6.57 (s, 2H, $-CONH_2$), 7.07 (s, 5H, aromatic H), 10.60 (2, 1H, NH), and 11.54 (s, 1H, NH) ppm (Table I).

2-[(N-2-Hydroxyethyl-N-ethyl)amino]acetamido-3-carbamyl-4-methyl-5-benzylpyrrole Hydrochloride (IIIa)—The procedure given for the synthesis of IIIa is representative of that used for IIIb and IIIc and IIIe–IIIh. A stirred suspension of IIa (1.20 g, 0.0033 mole) in acetone (25 ml) was treated with 0.4 ml of concentrated hydrochloric acid. The resulting suspension was stirred for 30 min at ambient temperature, and the white precipitate was collected by filtration, washed with acetone (25 ml), and dried. The hydrochloride salt (1.1 g, 83.0%) was homogeneous on TLC, mp 175–177° dec.; IR (KBr): broad absorption between 3400 and 2600 (with absorptions at 3400, 3320, 3120, and 3000), 1680, 1640, 1610, 1550, 1480, 1380, and 960 cm^{-1} (Table I).

Solution Preparation—Compounds I, IIa–IIh, and IIIa–IIIh were prepared for intraperitoneal administration by suspending 50 mg/ml in 0.9% saline containing 0.5% polysorbate 80[2] and 0.5% acacia. Compound I was solubilized in 0.9% saline by adjusting the pH to 2.2 with 2 *N* HCl prior to intravenous injection. A solution of IIId (3.6 mg/ml) was prepared by adding 20 mg of IId to 5 ml of 20% dimethyl sulfoxide in saline and 0.5 ml of 10% sorbitol in saline, followed by adjustment of the pH to 2.0 with hydrochloric acid. Solubilization was effected after slight warming of the resulting solution. A solution of IIIh (4.0 mg/ml) was prepared using 20% dimethyl sulfoxide in saline.

Blood Pressure Determination—Male Sprague–Dawley (Spd: Sprague–Dawley, DS) rats, 300–400 g, were administered pentobarbital sodium (30 mg/kg) and urethan (950 mg/kg) intraperitoneally prior to surgery for blood pressure determination. After anesthetization, the animal was positioned on its back and the trachea, carotid artery, and jugular vein were exposed. The jugular vein was cannulated with polyethylene tubing[3]. The trachea was cannulated with a tracheal tube[4] as necessary and connected to a respirator[5] with 100% oxygen at 50 psi. The respirator was adjusted to deliver a respiratory rate of 60/min at an inspiratory pressure of 12–15 cm H_2O.

The carotid artery was cannulated with polyethylene tubing[3] containing 100 units of heparin/ml. Blood pressure was monitored *via* a pressure transducer[6], channel amplifier[7], and recorder[8]. Test compounds

[1] Melting points were determined on a Thomas-Hoover apparatus (capillary method) and are uncorrected. NMR spectra were determined on a Varian EM360A NMR spectrometer with tetramethylsilane as an internal standard. IR spectra were determined on a Beckman Acculab 4 spectrophotometer using the potassium bromide technique. Elemental analyses were performed by Atlantic Microlabs, Atlanta, Ga.

[2] Tween 80, ICI Americas, Wilmington, Del.
[3] PE-50 (0.58 mm i.d. × 0.97 mm o.d.), Clay Adams, Parsippany, N.J.
[4] 1.5. mm i.d. × 3.0 mm o.d., Foregger Co., Smithtown, N.J.
[5] Mark 7, Bird Corp., Palm Springs, Calif.
[6] Type P-1000B, Narco Bio-Systems, Houston, Tex.
[7] Type 7070, Narco Bio-Systems, Houston, Tex.
[8] Physiograph DMP-4A, Narco Bio-Systems, Houston, Tex.

0022-3549/81/0600-0699$01.00/0

Table I—Structural and Analytical Data for 2-(2-Alkylaminoalkylamido)-3-carbamyl-4-methyl-5-benzylpyrroles

Compound	R_1	R_2	R_3	Recrystallization Yield, %	Recrystallization Solvent	Melting Point	Formula	Analysis, %	Calc.	Found
II*a*	H	C_2H_5	CH_2CH_2OH	73.1	Ethanol–water (7:3)	182.5–183.5°	$C_{19}H_{26}N_4O_3$	C	63.66	63.59
								H	7.31	7.35
								N	15.63	15.58
III*a*	Hydrochloride			83.0	—[a]	175–177° dec.	$C_{19}H_{27}ClN_4O_3$			
II*b*	H	H	n-C_4H_9	92.7	Toluene	213.0–214.5°	$C_{19}H_{26}N_4O_2$	C	66.64	66.53
								H	7.65	7.70
								N	16.36	16.32
III*b*	Hydrochloride			87.3	Water	228.5–229.5°	$C_{19}H_{27}ClN_4O_2$			
II*c*	H	H	$CH_2C_6H_5$	84.0	Ethanol	179.5–181.0°	$C_{22}H_{24}N_4O_2 \cdot 0.56H_2O$	C	68.35	68.35
								H	6.55	6.55
								N	14.49	14.47
III*c*	Hydrochloride			94.5	—[a]	230–232° dec.	$C_{22}H_{25}ClN_4O_2$			
II*d*[b]	CH_3	CH_3	$CH_2C_6H_5$	70.9	Methanol	155–157°	$C_{24}H_{28}N_4O_2$	C	71.26	71.04
								H	6.98	7.00
								N	13.85	13.80
III*d*[c]	Hydrochloride			—	—	—	$C_{24}H_{29}ClN_4O_2$			
II*e*[b]	CH_3	C_2H_5	C_2H_5	63.4	Ethanol–water (3:1)	167.0–169.0°	$C_{20}H_{28}N_4O_2$	C	67.39	67.26
								H	7.92	7.94
								N	15.72	15.68
III*e*	Hydrochloride			86.3	—[a]	204–205° dec.	$C_{20}H_{29}ClN_4O_2$			
II*f*	H	$-CH_2CH_2CH_2CH_2-$		92.6	Ethanol	243.5–244.5° dec.	$C_{19}H_{24}N_4O_2$	C	67.03	67.01
								H	7.11	7.15
								N	16.46	16.41
III*f*	Hydrochloride			88.9	Ethanol	233–234°	$C_{19}H_{25}ClN_4O_2$			
II*g*	H	$-CH_2CH_2-O-CH_2CH_2-$		98.2	Toluene	258.5–260.0°	$C_{19}H_{24}N_4O_3$	C	64.02	64.00
								H	6.79	6.79
								N	15.72	15.72
III*g*	Hydrochloride			87.3	—[a]	266.0–268° dec.	$C_{19}H_{25}ClN_4O_3$			
II*h*	H	$-CH_2CH_2-N(CH_3)-CH_2CH_2-$		92.0	Ethanol	249.0–251.0°	$C_{20}H_{27}N_5O_2$	C	65.01	64.88
								H	7.37	7.42
								N	18.95	18.88
III*h*	Dihydrochloride			87.3	—[a]	246–247.5° dec.	$C_{20}H_{29}Cl_2N_5O_2$			

[a] Homogeneous on TLC. [b] Racemic. [c] Salt prepared by the addition of concentrated hydrochloric acid to an equimolar amount of the free base (II*d*) suspended in water.

Table II—Blood Pressure Response[a] to Intraperitoneally Administered 2-(2-Alkylaminoalkylamido)-3-carbamyl-4-methyl-5-benzylpyrroles

Compound[b]	Dose, mg/kg	Blood Pressure Response: Onset[c], min	Maximum Change, mm Hg	Average Change, mm Hg	Duration[d], min	Average Duration, min
I	60	0	0		0	
II*a*	100	5	−15	−7.5	25	12.5
		0	0		0	
III*a*	100	0	0	−2.5	0	7.5
		5	−5		15	
II*b*	100	0	0		0	
		0	0		0	
III*b*	100	5	+17	+16	21	21.5
		5	+15		22	
II*c*	100	0	0		0	
		0	0		0	
III*c*	100	0	0		0	
		0	0		0	
II*d*	100	5	−32	−31	25	25
		5	−30		25	
III*d*	100	5	−29	−35.5	25	25
		5	−40		25	
II*e*	100	5	+12	+6	25	12.5
		0	0		0	
III*e*	100	5	−36	−22	20	15
		5	−8		10	
II*f*	100	5	−20	−6	25	17.5
		5	+8		10	
III*f*	100	5	+13	+10.5	25	17.5
		17	+8		10	
II*g*	100	5	−53	−21.6	25	21.7
		5	+10		15	
		5	−22		25	
III*g*	100	5	+40	+13.5	21	18.5
		5	−13		16	
II*h*	100	0	0	−5	0	3.5
		23	−10		7	
III*h*	100	0	0	−12.5	0	12.5
		5	−25		25	
Hydrazaline	5	5	−40	−75	25	25
		5	−75		25	
		5	−110		25	

[a] $n = 2$ or 3. [b] Compound I refers to the benzylcarbamyl analog of lidocaine previously reported (4) and examined (5). Compound II refers to the free base and III refers to the hydrochloride salt of the amine analogs of the benzylcarbamyl derivative. [c] Blood pressure analysis was started 5 min after the intraperitoneal administration of the compound to avoid vehicle artifacts. [d] Duration was defined as the time required for the blood pressure to return to within 95% of the predrug value.

Table III—Blood Pressure Response to Intravenously Administered 2-(2-Alkylaminoalkylamido)-3-carbamyl-4-methyl-5-benzylpyrroles

Compound	Dose, mg/kg	Blood Pressure Response[a] Average Change, mm Hg	Average Duration[b], min	n
Ic	4	−54.3	7.5	5
III*d*	4	−73	30.0	3
III*h*	4	−43.5	2.25	2

[a] Blood pressure recording was started immediately after the intravenous administration of the compound. [b] Duration was defined as the time required for the blood pressure to return within 95% of the predrug value. [c] Compound I is the benzylcarbamyl analog of lidocaine previously reported (4) and examined (5).

and the vehicle control were administered either intravenously through the jugular cannula or intraperitoneally. Saline (0.1 ml) was used to flush the cannula following each injection of the test compound or vehicle control solution.

Since the average vehicular vasodepressor response lasted 3–4 min following intraperitoneal administration, the maximal response and duration were recorded for each compound between 5 and 30 min. The blood pressure duration response was defined as the time required for the blood pressure to return to within 95% of the predrug value. Data collection of blood pressure activity for the intravenous studies began with the injection of the compound and lasted for 30 min.

RESULTS

The blood pressure effects of the derivatives of the benzylcarbamyl analog of lidocaine following intraperitoneal administration (60 or 100 mg/kg) appear in Table II. Compounds II*a*–II*h* represent the free base forms, and III*a*–III*h* represent the corresponding hydrochloride salt forms. The most potent agents exhibiting vasodepressor activity were II*d* and III*d*. Compound II*d* lowered the blood pressure an average of 31 mm Hg with a duration of 25 min. Compound III*d* was slightly more active, depressing the blood pressure 35.5 mm Hg with a similar duration (25 min). Other compounds exhibiting vasodepressor activity were III*e* and II*g*, lowering the blood pressure 22 and 21.6 mm Hg with a duration of 15 and 21.7 min, respectively. For comparison, hydralazine, 5 mg/kg, lowered blood pressure 75 mm Hg with a duration of 25 min.

Two compounds (III*b* and III*f*) appeared to exhibit a vasopressor effect, elevating the blood pressure 16 and 10.5 mm Hg with durations of action of 21.5 and 17.5 min, respectively. The remaining compounds in Table II were inactive with respect to vasoactivity or produced inconsistent blood pressure effects.

One of the more potent vasodepressor compounds (III*d*) and one of the more variable compounds (III*h*) from Table II were administered intravenously (Table III) to compare hypotensive activity as a function of administration route. Both III*d* and III*h* exhibited a greater vasodepressor activity when administered intravenously. Compound III*d* was the most active, lowering blood pressure 73 mm Hg with a duration of 30 min.

DISCUSSION

The present series of amine derivatives of the benzylcarbamyl analog of lidocaine was synthesized to obtain vasodepressor activity following intraperitoneal administration. The derivatives exhibited variable blood pressure effects (Table II). The vasodepressor response obtained following intraperitoneal administration indicates that the compounds can cross biological membranes prior to exerting a hypotensive action. Although the amine derivatives exerted vasodepressor activity, the most active (II*d* and III*d*) appeared to be only one-fortieth as active as hydralazine administered under similar experimental conditions. Comparison of Tables II and III indicates that intravenous administration of III*d* and III*h* produced a greater vasodepressor response than intraperitoneal administration. The decreased activity may be explained by reduced solubility, decreased absorption, or increased metabolism.

The lack of solubility of the compounds as one explanation was supported by the fact that among the active compounds (compounds *d*, *e*, and *h*) the salt was more active than the base in producing vasodepression. The compounds may not have been absorbed well into the blood following intraperitoneal administration since they were not very soluble in common solvents. An alternative explanation may be that the compounds were metabolized at an increased rate following intraperitoneal administration due to first-pass phenomena (6).

In the original series of 2-aminopyrrole analogs of lidocaine (1, 2), the benzylcarbamyl analog was the most potent vasodepressor agent (4). This fact established the structural requirements of the carbamyl function at position 3 and the benzyl group at position 5 of the pyrrole ring for maximal vasodepressor activity. Comparison of the compounds from a structure–activity relationship in the present series indicates that the secondary amines were devoid of vasodepressor activity. The most potent vasodepressors (compounds *d* and *e*) were substituted alpha to the tertiary amino functional group. From the limited data available, it appears that a benzyl substitution on the amino group enhances vasodepressor activity.

The activity of II*d* and III*d* represents an improvement over the parent compound (I), which does not appear to exert hypotensive activity following intraperitoneal administration. Additional structural modifications will be necessary to improve hypotensive activity following intraperitoneal (or oral) administration.

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ACKNOWLEDGMENTS

Supported in part by Dean Julian H. Fincher of the College of Pharmacy and by University Research and Productive Scholarship Grants 11010-E122 and 11010-E121 awarded to J. W. Kosh and J. W. Sowell, respectively, from the University of South Carolina.

The authors are grateful for the technical assistance of Robert Friedman and Rusty Boland and for the excellent typing assistance of Mrs. Sheila B. Lilly.