Synthesis of Substituted 2-Aminopyrrole Analogs of Lidocaine II

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Abstract □ The synthesis and local anesthetic and antiarrhythmic properties of eight substituted 2-diethylaminoacetamido-3-carbamyl-4-methylpyrroles are described. Three compounds showed significant local anesthetic activity by the guinea pig wheal test, and four showed antiarrhythmic activity against chloroform-induced ventricular arrhythmias in mice.

Keyphrases □ Lidocaine analogs—synthesis of 2-diethylaminoacetamido-3-carbamyl-4-methylpyrroles, local anesthetic activity, antiarrhythmic activity, structure–activity relationships □ Structure–activity relationships—lidocaine analogs, local anesthetic activity, antiarrhythmic activity □ Local anesthetic agents—lidocaine analogs, synthesis, structure–activity relationships □ Antiarrhythmic agents—lidocaine analogs, synthesis, structure–activity relationships

The synthesis and local anesthetic and antiarrhythmic properties of a series of substituted 2-diethylaminoacetamido-3-cyano-4-methylpyrrole (I) analogs of lidocaine (II) were reported previously (1). The biological activity exhibited by members of I prompted further research on heteroaromatic pyrrole analogs of II.

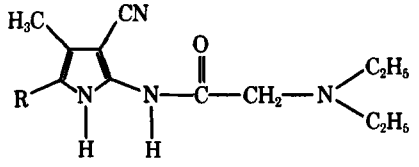
This report describes the synthesis and preliminary pharmacological evaluation for local anesthetic and antiarrhythmic activities of a series of substituted 2-diethylaminoacetamido-3-carbamyl-4-methylpyrroles (III).

DISCUSSION

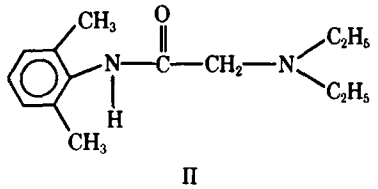
Chemistry—The utilization of substituted 2-amino-3-cyano-4-methylpyrroles (IV*a*–IV*h*) (2–4) as precursors to substituted 2-chloroacetamido-3-cyano-4-methylpyrroles (V*a*–V*h*) was reported previously (1). In the present work, V*a*–V*h* were utilized as intermediates in the synthesis of III (Scheme I).

Nitrile hydrolysis proceeded smoothly, by heating V*a*–V*h* in 85% phosphoric acid, to yield the corresponding substituted 2-chloroacetamido-3-carbamyl-4-methylpyrroles (VI*a*–VI*h*). The lower molecular weight analogs (V*a* and V*b*) and analogs possessing polar R groups (V*d* and V*g*) were hydrolyzed easily in 85% phosphoric acid at 120–125° for 5–10 min. The higher molecular weight analogs with nonpolar R groups (V*e*, V*f*, and V*h*) required more drastic conditions for hydrolysis. These conditions included more phosphoric acid, a temperature of 135–140°, and a total hydrolysis time of 10 min. With V*d*, the more drastic reaction conditions resulted in a decreased yield of VI*d*.

In general, the hydrolyzed compounds VI*a*–VI*h* were less soluble in organic solvents than their immediate precursors V*a*–V*h*. The decreased solubility can be explained, in part, by the increased potential for intramolecular hydrogen bonding. NMR and IR spectra were consistent with the assigned structures. Elemental analysis and TLC were used in determining chloroacetamide purity (Table I).



I



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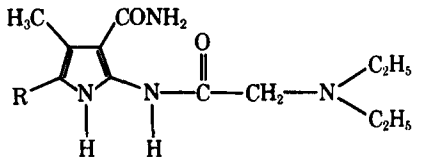
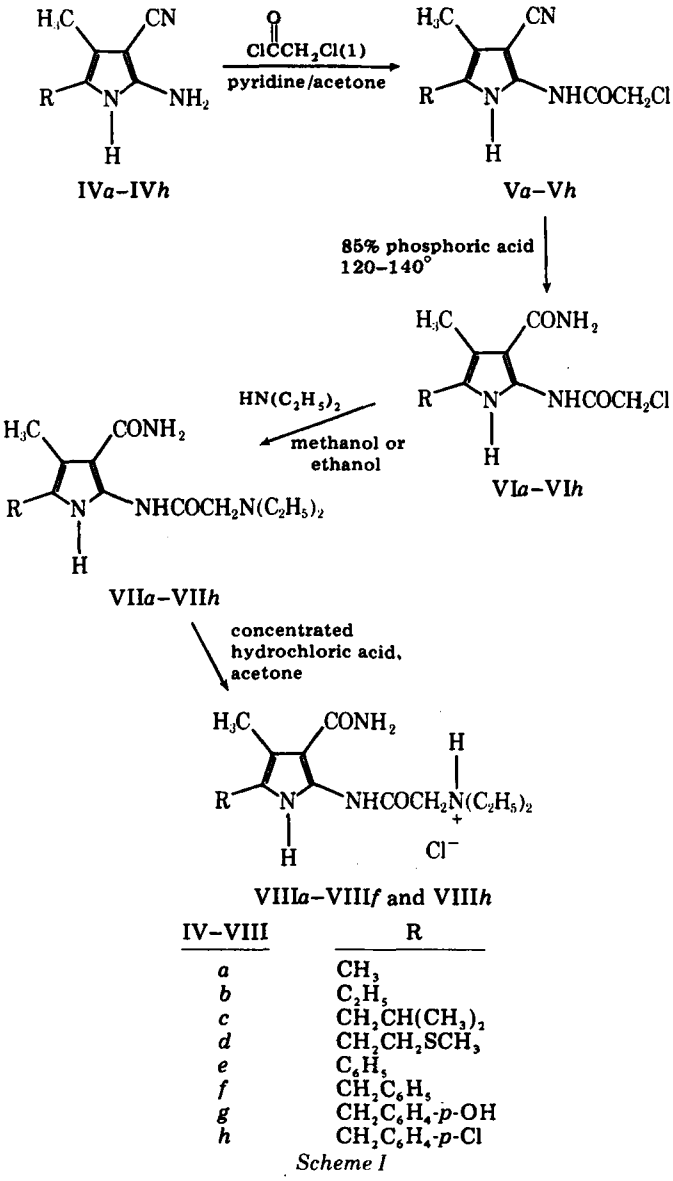


III

The substituted 2-diethylaminoacetamido-3-carbamyl-4-methylpyrroles (VII*a*–VII*h*) were obtained by refluxing a suspension of the corresponding chloroacetamide (VI*a*–VI*h*) in methanol or ethanol with



IV–VIII	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

Scheme I

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Table I—Substituted 2-Chloroacetamido-3-carbamyl-4-methylpyrroles

Compound	Yield, %	Melting Point	R_f[a]	Recrystallization Solvent	Formula	Analysis, %	Calc.	Found
VI*a*	96.9	210–211° dec.	0.46	Methanol	$C_9H_{12}ClN_3O_2$	C	47.06	47.10
						H	5.27	5.29
						Cl	15.44	15.36
						N	18.30	18.26
VI*b*	81.3	195–196° dec.	0.47	Ethanol	$C_{10}H_{14}ClN_3O_2$	C	49.28	49.33
						H	5.79	5.82
						Cl	14.55	14.61
						N	17.24	17.22
VI*c*	89.6	210–211° dec.	0.35	Ethanol	$C_{12}H_{18}ClN_3O$	C	53.04	52.99
						H	6.68	6.71
						Cl	13.05	13.04
						N	15.46	15.44
VI*d*	73.0	195.5–196° dec.	0.41	Ethanol	$C_{11}H_{16}ClN_3O_2S$	C	45.59	45.75
						H	5.57	5.67
						Cl	12.24	12.06
						N	14.50	14.43
						S	11.07	11.20
VI*e*	89.7	215–216° dec.	0.47	Ethanol	$C_{14}H_{14}ClN_3O_2$	C	57.64	57.72
						H	4.84	4.88
						Cl	12.16	12.07
						N	14.40	14.34
VI*f*	95.3	224.5–225° dec.	0.42	Ethanol–2-propanol–toluene	$C_{15}H_{16}ClN_3O_2$	C	58.92	58.96
						H	5.28	5.31
						Cl	11.60	11.65
						N	13.74	13.75
VI*g*	84.4	231–232° dec.	0.36	Methanol–ethanol–benzene	$C_{15}H_{16}ClN_3O_3$	C	55.99	55.84
						H	5.01	5.09
						Cl	11.02	11.01
						N	13.06	12.99
VI*h*	88.1	209.5–210.5° dec.	0.41	Ethanol	$C_{15}H_{15}Cl_2N_3O_2$	C	52.95	52.92
						H	4.44	4.44
						Cl	20.84	20.74
						N	12.35	12.37

[a] Ethyl acetate.

excess diethylamine. During the reactions, solutions were achieved within 0.5–3 hr. An exception was observed for the synthesis of VII*h*; a solution was not achieved after refluxing for 9 hr. In general, the solutions were refluxed for an additional hour, the solvent and excess diethylamine were removed *in vacuo*, and the residues were dissolved in 10% HCl. Unreacted chloroacetamides were removed by filtration, and the amines were precipitated by the addition of 5% aqueous NaOH. Yields, melting points, and purification data are given in Table II.

All amine hydrochlorides were prepared by treating an acetone solution of the free amine (VII*a*–VII*e*) or an acetone suspension of the free amine (VII*f* and VII*h*) with concentrated hydrochloric acid. Compound VIII*g* separated from acetone as a red oil when this procedure was employed for salt formation. IR spectra of the amine hydrochlorides (VIII*a*–VIII*f* and VIII*h*) exhibited typical N–H stretching absorption bands between 3500 and 3100 cm^{-1} and broad absorption in the 3100–2600-cm^{-1} region for the amine salts. Two intense carbonyl absorption bands at 1690–1680 and 1645–1640 cm^{-1} were observed for each compound.

NMR spectra of the amine hydrochlorides in dimethyl sulfoxide-d_6 exhibited a typical triplet and quartet for the methyl and methylene of the diethylamino group, respectively. Chemical shifts for the triplet ranged from 1.15 to 1.20 ppm, and those for the quartet ranged from 3.10 to 3.15 ppm. The triplet and quartet integrated for three protons and two protons, respectively. A singlet in the 2.00–2.15-ppm region, integrating for three protons, was assigned to the methyl group at the C-4 position. In the 4.05–4.15-ppm region, the spectra exhibited a singlet, integrating for two protons, which was assigned to the methylene located alpha to the carbonyl. A broad singlet at 6.55–6.85 ppm, integrating for two protons, was assigned to the carbamyl function protons.

The salt NH proton was observed as a broad singlet, integrating for one proton, in the 9.8–10.5-ppm region. Two additional broad singlets, one in the 10.7–11.0-ppm region and the other in the 10.95–11.0-ppm region, were assigned to the amide and pyrrole ring NH protons. Miscellaneous absorptions for the various hydrochloride salts were consistent with their structure. The purity of VIII*a*–VIII*f* and VIII*h* was determined by elemental analysis and TLC (Table III).

Pharmacology—*Antiarrhythmic Activity*—Cardiac rates less than the mean rate of 200 beats/min were used as an index of protection from arrhythmia at 70 mg/kg. Compounds VIII*a*, VIII*b*, VIII*d*, and VIII*e* (Table IV) showed activity at this dosage. Compounds VIII*c* and VIII*f* also may be effective if the standard error of the mean is considered.

Local Anesthetic Activity—Compounds VIII*c* and VIII*e*–VIII*g* possessed local anesthetic activity at all three solution concentrations whereas the remaining compounds possessed weak activity only at the highest solution concentration. Compounds VIII*e* and VIII*f* were the most active, having activity comparable to that of lidocaine (Table V).

EXPERIMENTAL[1]

Chemistry—*2-Chloroacetamido-3-carbamyl-4,5-dimethylpyrrole (VI*a*)*—The procedure for the synthesis of VI*a* is given as representative for VI*b*–VI*h*. A suspension of 2-chloroacetamido-3-cyano-4,5-dimethylpyrrole (V*a*) (15.0 g, 0.07 mole) (1) in 100 ml of 85% phosphoric acid was stirred at room temperature for 5 min. The vessel was placed into an oil bath preheated to 120° and stirred vigorously for 10 min. During this time, solution was achieved, and some of the product precipitated on the stirring solution surface. The vessel was removed from the oil bath and cooled to room temperature. The resulting semisolid was diluted with 300 ml of water and stirred for 10 min.

The crude product was collected by filtration, washed with water, and air dried. One gram of the pale-yellow product (15.6 g, 96.9%) was recrystallized twice from absolute methanol to yield yellow needle-shaped crystals (homogeneous on TLC, ethyl acetate, R_f 0.46), mp 210–211° dec.; IR (KBr): 3520, 3350, 3160, 1680, 1645, 1600, 1570, 1460, 1445, 1400, 1385, 1280, 1215, 790, 735, and 625 cm^{-1}; NMR (dimethyl sulfoxide-d_6): δ 1.95 (s, 6H, $-CH_3$ at C_4 and C_5), 4.20 (s, 2H, $-CH_2-$), 6.42 (broad s, 2H, $-CONH_2$ at C_3), 10.72 (broad s, 1H, NH of amide at C_2 or N_1H), and 10.89 (broad s, 1H, N_1H or NH of amide at C_2) ppm. (See Table I for analyses.)

*2-Diethylaminoacetamido-3-carbamyl-4,5-dimethylpyrrole (VII*a*)*—The procedure for the synthesis of VII*a* is given as representative for VII*b*–VII*h*. A suspension of VI*a* (9.2 g, 0.04 mole) in 125 ml of methanol

[1] IR spectral data were determined on a Beckman IR-20A grating spectrophotometer using the potassium bromide techniques. NMR spectra were determined on a Hitachi Perkin-Elmer R24 high-resolution spectrophotometer 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 analysis performed by Atlantic Microlab, Inc., Atlanta, Ga. TLC was performed using Eastman chromatogram sheets, type 6060 (silica gel), and the sheets were developed in an iodine chamber.

Table II—Substituted 2-Diethylaminoacetamido-3-carbamyl-4-methylpyrroles

Compound	Yield, %	Melting Point	Reaction Solvent[a]	Recrystallization Solvent	Formula
VII*a*	98.9	160.5–162°	Methanol	Methanol–water (4:1)	$C_{13}H_{22}N_4O_2$
VII*b*	90.2	164–166°	Ethanol	Methanol–water (4:1)	$C_{14}H_{24}N_4O_2$
VII*c*	74.6	116.5–117°	Ethanol	Methanol–water (4:1)	$C_{16}H_{28}N_4O_2$
VII*d*	93.4	130.5–131.5°	Ethanol	Methanol–water (4:1)	$C_{15}H_{26}N_4O_2S$
VII*e*	96.2	60–62°	Methanol	Methanol–water (4:1)	$C_{18}H_{24}N_4O_2$
VII*f*	59.2	202–204°	Methanol	—[b]	$C_{19}H_{26}N_4O_2$
VII*g*[c]	81.7	161–163°[d]	Methanol	Methanol–water (4:1)	$C_{19}H_{26}N_4O_3$
VII*h*	89.0	218–219.5°	Ethanol	—[d]	$C_{19}H_{25}ClN_4O_2$

[a] Absolute. [b] Crude product washed with cold acetone. [c] Calc. for: C, 63.67; H, 7.31; N, 15.63. Found: C, 63.40; H, 7.39; N, 15.73. [d] Crude product was boiled with 100 ml of methanol and filtered while hot. The insoluble amine was suitable for hydrochloride salt formation.

Table III—Substituted 2-Diethylaminoacetamido-3-carbamyl-4-methylpyrrole Hydrochlorides

Compound	Yield, %	Recrystallization Solvent	R_f[a]	Melting Point	Formula	Analysis, %	Calc.	Found
VIII*a*	97.3	Methanol–acetone	0.40	244–245° dec.	$C_{13}H_{23}ClN_4O_2$	C	51.56	51.32
						H	7.66	7.66
						Cl	11.71	11.55
						N	18.50	18.44
VIII*b*	94.7	—[b]	0.39	241.5–242.5° dec.	$C_{14}H_{25}ClN_4O_2$	C	53.07	53.10
						H	7.95	7.99
						Cl	11.19	11.22
						N	17.68	17.67
VIII*c*	82.6	—[b]	0.37	225.5–226.5° dec.	$C_{16}H_{29}ClN_4O_2$	C	55.72	55.62
						H	8.48	8.52
						Cl	10.28	10.18
						N	16.25	16.23
VIII*d*	84.9	—[b]	0.36	224–225° dec.	$C_{15}H_{27}ClN_4O_2S$	C	49.64	49.66
						H	7.50	7.50
						Cl	9.77	9.72
						N	15.44	15.47
						S	8.84	8.81
VIII*e*	79.9	Methanol–acetone–chloroform	0.44	260.5–261° dec.	$C_{18}H_{25}ClN_4O_2$	C	59.25	59.05
						H	6.91	6.94
						Cl	9.72	9.65
						N	15.36	15.32
VIII*f*	83.3	Methanol–acetone	0.44	247.5–248° dec.	$C_{19}H_{27}ClN_4O_2$	C	60.22	60.27
						H	7.18	7.22
						Cl	9.36	9.35
						N	14.79	14.84
VIII*g*[c]	—	—	—	Oil	—	—	—	—
VIII*h*	83.6	Ethanol	0.42	226–226.5° dec.	$C_{19}H_{26}Cl_2N_4O_2$	C	55.21	55.27
						H	6.34	6.40
						Cl	17.16	17.20
						N	13.56	13.57

[a] Ethyl acetate. [b] Salt obtained was analytically pure. [c] Salt obtained was a red oil; therefore, elemental analysis was determined on the free base (VII*g*).

and diethylamine (30 g, 0.4 mole) was refluxed, with stirring, until complete solution was achieved (0.5–3 hr). Then the solution was refluxed for an additional 1 hr, the excess diethylamine and solvent were removed *in vacuo*, and the residue was dissolved in 100 ml of 10% HCl.

The solution was filtered and poured over 300 g of crushed ice. The amine was precipitated by the addition of 5% aqueous NaOH. The solid was collected by filtration, washed with distilled water, and air dried. The crude product (9.09 g, 98.9%) was recrystallized from methanol–water (4:1) to yield fine off-white crystals (mp 160.5–162°), which were suitable for hydrochloride salt formation. (See Table II for analogs.)

Table IV—Antiarrhythmic Activity of Substituted 2-Diethylaminoacetamido-3-carbamyl-4-methylpyrrole Hydrochlorides[a]

Compound	40 mg/kg	70 mg/kg	100 mg/kg
Lidocaine	242 ± 13	141 ± 23	116 ± 6
VIII*a*	236 ± 12	182 ± 8	158 ± 9
VIII*b*	232 ± 6	175 ± 5	133 ± 5
VIII*c*	196 ± 10	202 ± 6	187 ± 13
VIII*d*	218 ± 11	193 ± 13	217 ± 5
VIII*e*	244 ± 8	174 ± 10	157 ± 6
VIII*f*	208 ± 13	203 ± 12	200 ± 8
VIII*g*	255 ± 11	214 ± 8	211 ± 3
VIII*h*	248 ± 4	217 ± 17	214 ± 8
Control	351 ± 8	—	—

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

2-Diethylaminoacetamido-3-carbamyl-4,5-dimethylpyrrole Hydrochloride (*VIII*a)—The procedure for the synthesis of VIII*a* is given as representative for VIII*b*–VIII*f* and VIII*h*. A stirred solution of VII*a* (10.0 g, 0.03 mole) in 225 ml of acetone was treated with 4 ml of concentrated hydrochloric acid. After stirring for 5 min at room temperature, the vessel was sealed and placed in a freezer for 2 hr. The salt was collected by filtration, washed with 50 ml of cold acetone, and air dried.

The crude product (10.8 g, 97.3%) was recrystallized from methanol–

Table V—Local Anesthetic Activity of Substituted 2-Diethylaminoacetamido-3-carbamyl-4-methylpyrrole Hydrochlorides[a]

Compound	Concentration, % 1	0.5	0.2
VIII*a*	19	—	—
VIII*b*	19	—	—
VIII*c*	26	25	7
VIII*d*	5	—	—
VIII*e*	70	53	16
VIII*f*	70	59	16
VIII*g*	72	33	10
VIII*h*	20	—	—
Lidocaine	68	41	17
0.9% NaCl	0	0	0

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

acetone to yield light-tan crystals (homogeneous on TLC, ethyl acetate, R_f 0.40), mp 244–245° dec.; IR (KBr): 3420, 3340, broad absorption from 3200 to 2600, 1675, 1635, 1600, 1570, 1545, 1470, 1435, 1380, 1370, 1355, 1270, 1240, 1155, 955, 805, and 630 cm^{-1}; NMR (dimethyl sulfoxide-d_6): δ 1.19 (t, 6H, $-CH_3$ of diethylamino), 2.08 (s, 6H, $-CH_3$ at C_4 and C_5), 3.14 (q, 4H, methylenes of diethylamino), 4.05 (broad s, 2H, $COCH_2$), 6.55 (broad s, 2H, $CONH_2$), 9.90–10.50 (broad s, 1H, N^+H), 10.70 (broad s, 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 III for analyses.)

Pharmacology—*Antiarrhythmic Activity*—With the method of Lawson (5), fibrillations were induced in 20–30-g male mice by exposure to chloroform vapor until respiration ceased. The heart was exposed, and the cardiac rate was determined with a binocular microscope. Mice with cardiac rates >200 beats/min were considered unprotected (Table IV).

Local Anesthetic Activity—The guinea pig wheal method of Bülbring and Wajda (6) 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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Comparative Pharmacokinetics of Coumarin Anticoagulants XLI: Effect of Phenobarbital on Systemic Availability of Orally Administered Dicumarol in Rats

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Abstract □ The purpose of this investigation was to determine the effect of phenobarbital on the systemic availability of orally administered dicumarol in rats. Adult male Sprague–Dawley rats, matched for dicumarol free fraction in serum, received either phenobarbital sodium, 75 mg/kg, or saline solution, orally or intravenously, daily for 7 days. On Day 6, they also received ^{14}C-dicumarol, 2 mg/kg iv, and unlabeled dicumarol, 50 mg/kg po, in aqueous suspension. Venous blood samples were obtained serially over 32 hr through an indwelling cannula. Systemic dicumarol availability was determined from the dose-normalized ratio of areas under the plasma concentration–time curves. Phenobarbital treatment almost doubled the total clearance of dicumarol and the intrinsic clearance of free dicumarol, with no significant difference between the inductive effects of oral and intravenous doses of phenobarbital. Systemic dicumarol availability in control rats (mean ± *SD*) was 84 ± 8% (n = 10) and 84 ± 10% (n = 6) in the oral and intravenous phenobarbital studies, respectively. The systemic dicumarol availability in phenobarbital-treated rats was appreciably lower: 48 ± 7% (n = 10) and 61 ± 12% (n = 6) for orally and intravenously treated animals, respectively. The effect of oral phenobarbital on systemic dicumarol availability was more pronounced than that of intravenous phenobarbital ($p < 0.025$). The apparent first-order absorption rate constants for the fraction of the dose available systemically were similar for control and treated animals. There was a positive correlation between systemic dicumarol availability and total dicumarol clearance in control animals ($p < 0.001$). Proper matching of control and treated animals is, therefore, important for this type of study. The rat appears to be a good model for investigating the mechanism of the inhibitory effect of phenobarbital on dicumarol absorption observed previously in humans.

Keyphrases □ Phenobarbital—effect on systemic availability of oral dicumarol, comparison of oral and intravenous doses □ Bioavailability—dicumarol in rats, effect of oral and intravenous phenobarbital □ Dicumarol—bioavailability, effect of oral and intravenous phenobarbital □ Anticoagulants—dicumarol, effect of oral and intravenous phenobarbital on systemic availability

The bioavailability of orally administered dicumarol in humans is reduced by pretreatment of the subjects with an orally administered barbiturate (1). Similar effects have been observed with respect to two other poorly water-soluble drugs, griseofulvin and diethylstilbestrol. The bioavailability of orally administered griseofulvin in humans is reduced by pretreatment with orally administered phenobarbital (2). Such a reduction in griseofulvin bioavailability has also been observed in rats (3). Pretreatment with phenobarbital has been reported to decrease diethylstilbestrol absorption from the rat intestine (4).

Little is known about the mechanism of the barbiturate effect on drug absorption. A study was designed to determine the effect of orally and intravenously administered phenobarbital on GI absorption of dicumarol in rats. The results of this investigation have bearing not only on the specific interaction under study but also on the design of studies to determine the bioavailability of drugs that are subject to enzyme induction and that exhibit pronounced interindividual differences in pharmacokinetic characteristics.

EXPERIMENTAL

The studies were carried out on adult male Sprague–Dawley rats weighing 250–375 g. Groups of animals were screened for plasma free fraction values of dicumarol, using serum obtained from ~5 ml of blood withdrawn from the tail artery under light ether anesthesia. The free fraction determinations were performed in duplicate by dialyzing, to

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