drug levels were higher than blood levels; but in both compartments, camazepam concentrations were considerably lower than those found in rats 5 min after injection. The drug declined faster in the blood of mice than in that of rats, the apparent half-lives in the two species being 9 and 20 min, respectively, as calculated according to Gibaldi (4).

REFERENCES

(1) R. Ferrini, G. Miragoli, and B. Taccardi, *Arzneim.-Forsch.*, **24**, 2029 (1974).
(2) L. Merlo, V. Noseda, R. Ferrini, G. Miragoli, and G. Marchetti, *ibid.*, **24**, 1759 (1974).
(3) M. Bianchi, P. Ghirardi, and F. Ravaccia, *ibid.*, **24**, 2032 (1974).
(4) M. Gibaldi, *Ann. N.Y. Acad. Sci.*, **179**, 19 (1971).

ACKNOWLEDGMENTS

The authors thank Mr. G. Meroni for technical assistance.

Synthesis of 1-Methyl-2-phenylcarbamoylpyrazolidines as Potential Anticonvulsant Agents

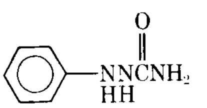
MILTON J. KORNET

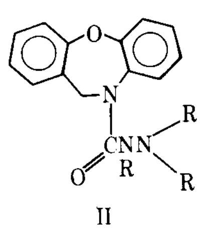
Received November 28, 1977, from the *Division of Medicinal Chemistry, College of Pharmacy, University of Kentucky, Lexington, KY 40506.* Accepted for publication January 13, 1978.

Abstract □ Lithium aluminum hydride reduction of 1,4-dimethyl-3-pyrazolidinone yielded 1,4-dimethylpyrazolidine. The latter compound and 1-methylpyrazolidine reacted with aryl isocyanates to produce 1-methyl-2-phenylcarbamoylpyrazolidines. Several of these adducts displayed significant anticonvulsant activity in the maximal electroshock seizure and pentylenetetrazol seizure threshold tests.

Keyphrases □ Pyrazolidines, various substituted—synthesized, evaluated for anticonvulsant activity in mice □ Anticonvulsant activity—various substituted pyrazolidines evaluated in mice □ Structure–activity relationships—various substituted pyrazolidines evaluated for anticonvulsant activity in mice

Antiepileptic agents containing the semicarbazide functionality have been investigated only rarely (1–3). 1-Phenylsemicarbazide (I) is devoid of protective activity in the maximal electroshock test at 300 mg/kg (4). However, several tricyclic semicarbazides (II), which possess good potency and a favorable therapeutic ratio, have been described (5).

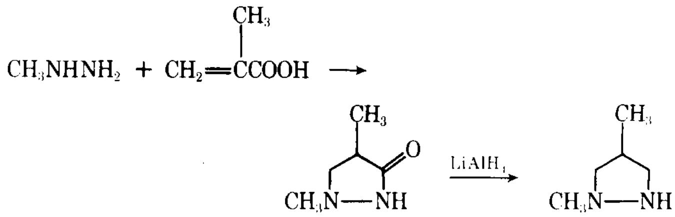

I


II

Interest in new anticonvulsant agents (6–8) as well as in pyrazolidine analogs of medicinals (9) prompted the synthesis and evaluation of a series of 1-methyl-2-phenylcarbamoylpyrazolidines (IV*a*–IV*w*).

DISCUSSION

Chemistry—The synthesis of the title compounds necessitated the preparation of the two pyrazolidine bases III*a* and III*b*. 1-Methylpyrazolidine (III*a*) was obtained by previously described methods (10). 1,4-Dimethylpyrazolidine (III*b*), a new base, resulted from the lithium aluminum hydride reduction of 1,4-dimethyl-3-pyrazolidinone. The latter precursor was prepared by condensing methylhydrazine with methacrylic acid (11) (Scheme I).

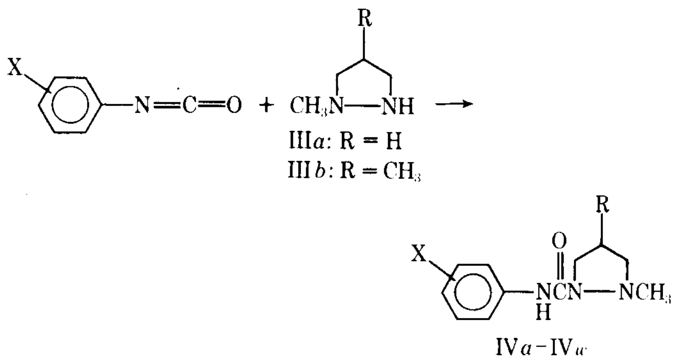

Scheme I

Addition of these pyrazolidines to aryl-substituted isocyanates occurred smoothly to give IV*a*–IV*w* (Scheme II). The physical properties of these adducts are given in Table I.

Biological Activity—All phenylcarbamoylpyrazolidines were tested for anticonvulsant activity and neurotoxicity by the methods described under *Experimental* (Table II). Of the 22 compounds tested, 19 exhibited some anticonvulsant activity. The *p*-bromo derivatives IV*b* and IV*p* were uniformly inactive.

Compounds IV*m*, IV*n*, and IV*v* showed the best activity against maximal electroshock. They all possess a 2,6-substitution pattern in the aromatic ring reminiscent of the local anesthetic–antiarrhythmic drug lidocaine, which can temporarily arrest *grand mal* as well as certain other epileptic seizures (12). However, the short time of peak effect (0.5 hr) for IV*m*, IV*n*, and IV*v* probably indicates a short duration of action and may limit their usefulness (5).

Compounds IV*e*, IV*i*, and IV*m* showed significant activity in the pentylenetetrazol test at 0.5 hr but were devoid of activity at 4 hr.


Scheme II

0022-3549/ 78/ 1000-1471$01.00/ 0

Table I—Physical Properties of 1-Methyl-2-phenylcarbamoylpyrazolidines

Compound	R	X	Melting Point	Yield, %	Recrystallization Solvent[a]	Formula	Analysis, %	
							Calc.	Found
IV*a*	H	H	71–73°	40	C	$C_{11}H_{15}N_3O$	C 64.38	64.32
							H 7.37	7.62
							N 20.47	20.67
IV*b*	H	*p*-Br	121–123°	56	A	$C_{11}H_{14}BrN_3O$	C 46.49	46.44
							H 4.97	5.14
							N 14.79	14.55
IV*c*	H	*m*-Cl	105–107°	65	A	$C_{11}H_{14}ClN_3O$	C 55.12	55.38
							H 5.89	6.06
							N 17.53	17.22
IV*d*	H	*p*-Cl	110–112°	62	A	$C_{11}H_{14}ClN_3O$	C 55.12	55.01
							H 5.89	5.94
							N 17.53	17.27
IV*e*	H	*p*-F	84–85°	82	A	$C_{11}H_{14}FN_3O$	C 59.18	59.33
							H 6.32	6.36
							N 18.82	18.85
IV*f*	H	*p*-CH_3O	72.5–73.5°	48	A	$C_{12}H_{17}N_3O_2$	C 61.26	60.89
							H 7.28	7.43
							N 17.86	17.73
IV*g*	H	*m*-CH_3	91–93°	71	A	$C_{12}H_{17}N_3O$	C 65.73	65.73
							H 7.81	7.74
							N 19.16	19.13
IV*h*	H	*p*-CH_3	87–89°	60	B	$C_{12}H_{17}N_3O$	C 65.73	65.81
							H 7.81	7.89
							N 19.16	18.87
IV*i*	H	*m*-NO_2	101.5–103.5°	60	E	$C_{11}H_{14}N_4O_3$	C 52.79	52.91
							H 5.64	5.85
							N 22.39	22.38
IV*j*	H	*p*-NO_2	112–113°	41	C	$C_{11}H_{14}N_4O_3$	C 52.79	53.16
							H 5.64	5.52
							N 22.39	22.65
IV*k*	H	*m*-CF_3	85.5–86.5°	57	A	$C_{12}H_{14}F_3N_3O$	C 52.75	52.92
							H 5.16	5.18
							N 15.38	15.32
IV*l*	H	3,4-Cl_2	94–95°	79	A	$C_{11}H_{13}Cl_2N_3O$	C 48.19	48.28
							H 4.78	4.88
							N 15.33	15.33
IV*m*	H	2-Cl, 6-CH_3	92–93°	71	A	$C_{12}H_{16}ClN_3O$	C 56.80	56.89
							H 6.36	6.59
							N 16.56	16.26
IV*n*	H	2,6-$(CH_3)_2$	110–112°	60	A	$C_{13}H_{19}N_3O$	C 66.92	67.01
							H 8.21	8.47
							N 18.01	17.87
IV*o*	CH_3	H	70–71°	58	A	$C_{12}H_{17}N_3O$	C 65.73	65.69
							H 7.81	7.72
							N 19.16	19.08
IV*p*	CH_3	*p*-Br	101–102°	66	A	$C_{12}H_{16}BrN_3O$	C 48.34	48.28
							H 5.41	5.54
							N 14.09	14.21
IV*q*	CH_3	*p*-Cl	99–101°	72	A	$C_{12}H_{16}ClN_3O$	C 56.80	56.94
							H 6.36	6.45
							N 16.56	16.71
IV*r*	CH_3	*p*-CH_3O	107–109°	60	A	$C_{13}H_{19}N_3O_2$	C 62.63	62.74
							H 7.68	7.84
							N 16.85	16.74
IV*s*	CH_3	*m*-CH_3	79–80°	94	A	$C_{13}H_{19}N_3O$	C 66.92	67.12
							H 8.21	8.31
							N 18.01	17.97
IV*t*	CH_3	*p*-CH_3	67–68°	46	A	$C_{13}H_{19}N_3O$	C 66.92	66.99
							H 8.21	8.25
							N 18.01	17.96
IV*u*	CH_3	*p*-NO_2	126–127°	64	D	$C_{12}H_{16}N_4O_3$	C 54.54	54.61
							H 6.10	6.23
							N 21.20	21.31
IV*v*	CH_3	2-Cl, 6-CH_3	72–73°	43	A	$C_{13}H_{18}ClN_3O$	C 58.31	58.34
							H 6.78	6.93
							N 15.69	15.88
IV*w*	CH_3	2,6-$(CH_3)_2$	113–115°	65	A	$C_{14}H_{21}N_3O$	C 67.98	68.14
							H 8.56	8.54
							N 16.99	17.16

[a] A = cyclohexane, B = hexane–cyclohexane, C = benzene–petroleum ether, D = benzene, and E = benzene–cyclohexane.

EXPERIMENTAL[1]

1,4-Dimethylpyrazolidine (III*b*)[2]—This compound was prepared by the lithium aluminum hydride reduction of 1,4-dimethyl-3-pyrazolidinone (11) in tetrahydrofuran by the same procedure utilized for the preparation of 1-methylpyrazolidine (10). The colorless liquid, bp 128–131°, was obtained in 39% yield; NMR ($CDCl_3$): δ 1.17 (d, 3, C-CH_3),

[1] Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. IR spectra were taken on a Perkin-Elmer 700 spectrophotometer as either liquid films or potassium bromide pellets. NMR spectra were recorded on a Varian A-60A spectrometer, using tetramethylsilane as the internal reference. Elemental analyses were performed by PCR Inc., Gainesville, Fla., and Dr. Kurt Eder, Geneva, Switzerland.

[2] This experiment was carried out by W. J. Layton.

Table II—Anticonvulsant Effect

Compound	MES Activity[a] 0.5 hr	MES Activity[a] 4 hr	MES ED_{50}	sc Met Activity[a] 0.5 hr	sc Met Activity[a] 4 hr	sc Met ED_{50}	TD_{50}[b]
IV*a*	+	−	153 (144–163)	+	−	ND[c]	ND
IV*b*	−	−	ND	−	−	ND	ND
IV*c*	−	−	ND	+	−	ND	ND
IV*d*	−	−	ND	+	+	ND	ND
IV*e*	+	−	ND	++	−	ND	ND
IV*f*	+	−	ND	−	−	ND	ND
IV*g*	−	−	ND	+	−	ND	ND
IV*h*	−	−	ND	−	−	ND	ND
IV*i*	−	−	ND	++	−	181 (155–226)	ND
IV*j*	ND	ND	ND	ND	ND	ND	ND
IV*k*	−	−	ND	+	−	ND	ND
IV*l*	−	+	ND	−	−	ND	ND
IV*m*	++	+	55.7 (48.1–75.3)[d]	++	—[e]	ND	148 (134–166)[d]
IV*n*	++	−	48.8 (39.7–61.6)[d]	+	−	ND	150 (142–159)[d]
IV*o*	+	−	ND	+	−	ND	ND
IV*p*	−	−	ND	−	−	ND	ND
IV*q*	+	+	ND	−	+	ND	ND
IV*r*	+	−	ND	−	−	ND	ND
IV*s*	+	−	ND	+	+	ND	ND
IV*t*	+	−	ND	+	−	ND	ND
IV*u*	−	−	ND	+	−	ND	ND
IV*v*	++	−	62.2 (60.8–63.9)[d]	+	−	ND	174 (159–197)[d]
IV*w*	+	−	88.0 (75.5–99.3)[d]	−	−	ND	207 (177–245)[d]
Ethotoin			85.5 (72.0–92.2)			35.4 (19.0–56.1)	171 (144–250)

[a] +++, ++, and + signify activity at 30, 100, and 300 mg/kg, respectively; − denotes no activity observed at 300 mg/kg. [b] TD_{50} = median toxic dose in the rotorod test. [c] ND = not determined. [d] Determined at time of peak effect (0.5 hr). [e] No activity observed at 100 mg/kg.

2.80 (s, 3, NCH_3), and 1.60–3.47 (m, 6, NH and remaining ring H) ppm. Storage under a nitrogen atmosphere is necessary to avoid oxidation to 1,4-dimethyl-2-pyrazoline.

Anal.—Calc. for $C_5H_{12}N_2$: C, 59.96; H, 12.08; N, 27.97. Found: C, 59.74; H, 12.28; N, 27.83.

1-Methyl-2-phenylcarbamoylpyrazolidines (IV*a*–IV*w*)—A typical reaction is described, that for the preparation of 1-methyl-2-*p*-chlorophenylcarbamoylpyrazolidine (IV*d*). Table I lists the physical and analytical data.

To a solution of 2.58 g (0.030 mole) of 1-methylpyrazolidine (10) in 15 ml of dry benzene was added dropwise a solution of 4.12 g (0.0268 mole) of *p*-chlorophenyl isocyanate in 10 ml of dry benzene with magnetic stirring. The resulting mixture was refluxed for 3 hr, cooled, diluted with 25 ml of benzene, and extracted with 50 ml of 5% hydrochloric acid. The acidic extract was washed with 40 ml of ether and made basic by the addition of solid sodium carbonate (carbon dioxide evolution).

The aqueous solution was extracted twice with 40-ml portions of ether and dried (magnesium sulfate). Evaporation of the ether resulted in a crystalline residue. Recrystallization from cyclohexane afforded 3.95 g (62%) of colorless crystals, mp 110–112°; IR (KBr): 1662 (C=O) and 3325 (NH) cm^{-1}; NMR ($CDCl_3$): δ 2.57 (s, 3, NCH_3), 1.67–4.20 (m, 6, aliphatic ring H), 7.4 (m, 4, ArH), and 8.57 (broad s, 1, CONH) ppm.

Pharmacological Testing—All compounds were tested for anticonvulsant activity[3]. The compounds were evaluated using the Anticonvulsant Screening Project Test Systems (13, 14). Three tests were performed: MES (maximal electroshock seizure test), sc Met (subcutaneous pentylenetetrazol seizure threshold test), and the rotorod test to evaluate neurotoxicity. The ED_{50} and TD_{50} values and their confidence limits were determined by probit analysis. Additional details concerning the pharmacological testing were reported recently (7). All tests were performed on male Carworth Farms No. 1 mice.

[3] By the Antiepileptic Drug Development Program administered by the Section on Epilepsy, National Institutes of Health, Bethesda, MD 20014.

REFERENCES

(1) W. J. Close and M. A. Spielman, in "Medicinal Chemistry," vol. 5, W. H. Hartung, Ed., Wiley, New York, N.Y., 1961, p. 48.

(2) A. Spinks and W. S. Waring, in "Progress in Medicinal Chemistry," vol. 3, G. P. Ellis and G. B. West, Eds., Butterworths, Washington, D.C., 1963, p. 261.

(3) J. Mercier, in "Anticonvulsant Drugs," vol. 1, J. Mercier, Sect. Ed., Pergamon, Elmsford, N.Y., 1973, chap. 6.

(4) H. H. Merritt and T. J. Putnam, *Epilepsia,* **3,** 51 (1945).

(5) W. E. Coyne and J. W. Cusic, *J. Med. Chem.,* **11,** 1158 (1968).

(6) M. J. Kornet, J. H. Thorstenson, and W. C. Lubawy, *J. Pharm. Sci.,* **63,** 1090 (1974).

(7) M. J. Kornet, A. M. Crider, and E. O. Magarian, *J. Med. Chem.,* **20,** 405 (1977).

(8) *Ibid.,* **20,** 1210 (1977).

(9) M. J. Kornet and H. S. I. Tan, *J. Pharm. Sci.,* **61,** 235 (1972).

(10) M. J. Kornet, *ibid.,* **56,** 963 (1967).

(11) W. S. Wadsworth, Jr., *J. Org. Chem.,* **31,** 1704 (1966).

(12) J. Mercier, in "Anticonvulsant Drugs," vol. 1, J. Mercier, Sect. Ed., Pergamon, Elmsford, N.Y., 1973, p. 228.

(13) Anticonvulsant Screening Project, Antiepileptic Drug Development Program, National Institutes of Health, DHEW Publication No. (NIH) 76-1093, Bethesda, MD 20014.

(14) E. A. Swinyard, W. C. Brown, and L. S. Goodman, *J. Pharmacol. Exp. Ther.,* **106,** 319 (1952).

ACKNOWLEDGMENTS

The author is indebted to Mr. Gill D. Gladding, Antiepileptic Drug Development Program, National Institutes of Health, for providing the anticonvulsant activity data. He is also grateful to Mr. James Swencki for technical assistance.