Synthesis of 1-Phenyl-2-(phenylcarbamoyl)pyrazolidines as Potential Anticonvulsant Agents

MILTON J. KORNET [x] **and R. JOYCE GARRETT**

Received July 10, 1978, from the *College of Pharmacy, University of Kentucky, Lexington, KY 40506.* Accepted for publication August 17, 1978.

Abstract □ Twelve 1-phenyl-2-(phenylcarbamoyl)pyrazolidines were synthesized from 1-arylpyrazolidines and aryl isocyanates. These adducts showed little anticonvulsant activity in the maximal electroshock seizure and pentylenetetrazol seizure assays.

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

The synthesis and evaluation of a series of 1-methyl-2-(phenylcarbamoyl)pyrazolidines (I) as anticonvulsant agents revealed good activity for at least three compounds (1). In the most active compounds, R_1 = Cl or CH_3 and R_2 = H or CH_3. To study compounds of this type further, the *N*-methyl group of the pyrazolidine ring was replaced by phenyl. Such a substitution changes the basicity of the molecule and is thereby expected to affect the absorption, distribution, and metabolism of the resultant compounds. This report describes the synthesis and anticonvulsant activity of such compounds, *i.e.*, the 1-phenyl-2-(phenylcarbamoyl)pyrazolidines (III*a*–III*l*, Table I).

DISCUSSION

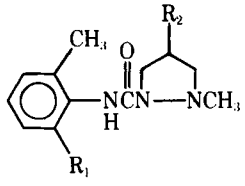
Chemistry—1-Phenylpyrazolidine has been prepared from trimethylene bromide and a large excess of the sodium salt of phenylhydrazine (2, 3). The latter reagent was obtained from sodium metal and phenylhydrazine. To avoid the tedious procedure employed to make the sodium salt of phenylhydrazine, a modified procedure was developed with sodium hydride as the base. Isolation of the sodium salt of phenylhydrazine also was eliminated; after its formation from phenylhydrazine and sodium hydride in benzene *in situ*, it was reacted directly with the dibromide. In this way, a much smaller excess of phenylhydrazine was required and 1-phenylpyrazolidine (II*a*) was obtained in an 86% yield. With a similar procedure, 1-*p*-(chlorophenyl)pyrazolidine (II*b*) (4) and 1-*p*-tolylpyrazolidine (II*c*) (5) were synthesized in moderate yields (Scheme I).

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

Compound	X	Y	Melting Point	Yield, %	Formula	Analysis, %	Calc.	Found
III*a*	H	H	116.5–118° [a]	52	$C_{16}H_{17}N_3O$	C	71.89	71.98
						H	6.41	6.50
						N	15.72	15.70
III*b*	*m*-Cl	H	121–123°	90	$C_{16}H_{16}ClN_3O$	C	63.63	63.77
						H	5.34	5.48
						N	13.92	13.85
III*c*	*p*-Cl	H	110–112°	58	$C_{16}H_{16}ClN_3O$	C	63.68	63.79
						H	5.34	5.46
						N	13.92	13.90
III*d*	*p*-F	H	109–111°	68	$C_{16}H_{16}FN_3O$	C	67.35	67.58
						H	5.65	5.59
						N	14.73	14.70
III*e*	*p*-CH_3O	H	117–118.5°	54	$C_{17}H_{19}N_3O_2$	C	68.67	68.41
						H	6.44	6.91
						N	14.13	13.95
III*f*	*p*-C_2H_5O	H	142–143°	42	$C_{18}H_{21}N_3O_2$	C	69.43	69.00
						H	6.80	6.24
						N	13.49	13.35
III*g*	*o*-CH_3	H	110–113°	50	$C_{17}H_{18}N_3O$	C	72.83	72.78
						H	6.47	6.81
						N	14.99	15.05
III*h*	*p*-CH_3	H	97–98°	38	$C_{17}H_{18}N_3O$	C	72.83	72.61
						H	6.47	6.61
						N	14.99	14.91
III*i*	2-Cl,6-CH_3	H	100–101°	32	$C_{17}H_{18}ClN_3O$	C	64.66	64.70
						H	5.74	5.83
						N	13.31	13.47
III*j*	2,6-$(CH_3)_2$	H	125–127°	29	$C_{18}H_{21}N_3O$	C	73.19	73.26
						H	7.17	7.05
						N	14.22	14.29
III*k*	H	Cl	130–133°	54	$C_{16}H_{16}ClN_3O$	C	63.68	63.82
						H	5.34	5.39
						N	13.92	14.01
III*l*	*m*-Cl	CH_3	89.5–91°	13	$C_{17}H_{18}ClN_3O$	C	64.66	64.68
						H	5.74	5.85
						N	13.31	13.32

[a] Lit. (3) mp 114°.

0022-3549/79/0300-0377$01.00/0



I

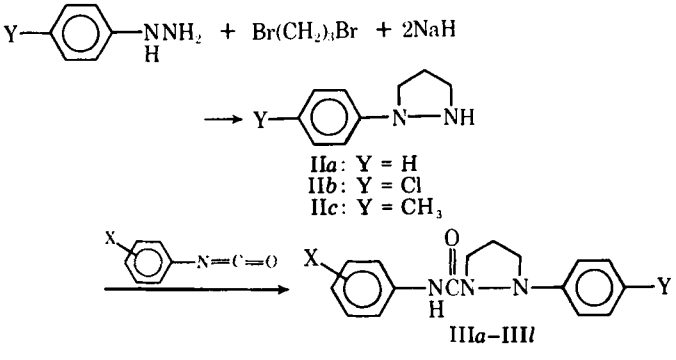
Reaction of these 1-arylpyrazolidines with aryl-substituted isocyanates occurred readily to give the adducts IIIa–IIIl. In most cases, these adducts were accompanied by the corresponding ureas derived from the starting isocyanates. The unwanted urea by-products were insoluble in benzene and could be removed by trituration of the crude reaction mixture followed by filtration. The physical properties of IIIa–IIIl are given in Table I.

Biological Activity—Compounds IIIa–IIIl were examined in the maximal electroshock seizure and pentylenetetrazol seizure threshold tests for anticonvulsant activity and neurotoxicity in mice by reported procedures (1). With one exception, all compounds were devoid of anticonvulsant activity at the highest dose tested (300 mg/kg). Compound IIIh showed activity in the pentylenetetrazol seizure test at 300 mg/kg (0.5 hr). None of the compounds showed toxicity at the three doses tested (30, 100, and 300 mg/kg).

This study indicates that replacement of *N*-methyl by phenyl in I results in a loss of anticonvulsant activity. Solubility tests in 5% HCl revealed that the *N*-methyl series of compounds (I) (1) is soluble whereas the *N*-phenyl series (IIIa–IIIl) is insoluble. Perhaps the inactivity of IIIa–IIIl results from a failure in absorption caused by poor solubility.

EXPERIMENTAL[1]

1-Phenylpyrazolidine (IIa)—To a stirred suspension of 40.42 g (0.960 mole) of a 57% mineral oil dispersion of sodium hydride in 500 ml of dry benzene, protected by a nitrogen atmosphere, was added dropwise a solution of 64.8 g (0.60 mole) of phenylhydrazine in 100 ml of dry benzene. The reaction mixture was warmed on an oil bath until hydrogen evolution (monitored by mercury bubbler) occurred. After 30 min, gas evolution had slowed; then 40.40 g (0.20 mole) of 1,3-dibromopropane was added in one portion to the reaction mixture, which had been cooled to room temperature. Upon heating, hydrogen was evolved over 1.5 hr.



Scheme I

The mixture was then refluxed for 1.5 hr. A second portion of 40.40 g (0.20 mole) of 1,3-dibromopropane was added dropwise to the refluxing reaction mixture, and refluxing was continued overnight (17–18 hr). After cooling, the reaction mixture was washed twice with 100-ml portions of water, and the benzene layer was dried (magnesium sulfate). After removal of the benzene under reduced pressure, the residue separated into two distinct layers. The top mineral oil layer was separated off. The lower product layer was distilled and afforded 50.6 g (86%) of liquid, bp 81–86°/0.25 mm [lit. (3) bp 160°/20 mm]; IR (film): 3300 (NH) cm^{-1}.

1-*p*-(Chlorophenyl)pyrazolidine (IIb) (4)—This compound was obtained from 11.8 g (0.083 mole) of *p*-chlorophenylhydrazine, 12.93 g (0.064 mole) of 1,3-dibromopropane, and 6.48 g (0.154 mole) of a 57% mineral oil dispersion of sodium hydride according to the same procedure used for the preparation of IIa. Distillation gave 6.03 g (52%) of product, bp 110–115°/0.25 mm; IR (film): 3295 (NH) cm^{-1}.

1-*p*-Tolylpyrazolidine (IIc) (5)—This compound was prepared from 12.5 g (0.102 mole) of *p*-tolylhydrazine, 15.9 g (0.0786 mole) of 1,3-dibromopropane, and 8.0 g (0.190 mole) of a 57% mineral oil dispersion of sodium hydride according to the same procedure used for the synthesis of IIa. Distillation afforded 6.42 g (50%) of the pyrazolidine, bp 94°/0.15 mm; IR (film): 3300 (NH) cm^{-1}.

1-Phenyl-2-(phenylcarbamoyl)pyrazolidines (III)—A typical reaction is described, that for the preparation of 1-phenyl-2-*p*-tolylcarbamoylpyrazolidine (IIIh). A mixture of 4.56 g (0.0308 mole) of IIa, 3.72 g (0.028 mole) of *p*-tolyl isocyanate, and 40 ml of dry toluene was refluxed for 6 hr. The mixture was cooled, and the solvent was evaporated under reduced pressure.

The remaining thick oily residue was triturated with petroleum ether and produced 8.0 g of solid crude product. The latter was triturated with benzene and filtered. Evaporation of the benzene solution gave a product uncontaminated with the urea by-product. Recrystallization from 95% ethanol gave 3.0 g (38%) of analytically pure material, mp 97–98°; IR (KBr): 1650 (C=O) and 3260 (NH) cm^{-1}; NMR ($CDCl_3$): δ 2.23 (s, 3, CH_3), 1.67–4.5 (m, 6, aliphatic ring H), 6.68–7.57 (m, 9, ArH), and 7.95 (broad s, 1, CONH) ppm.

[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 with tetramethylsilane as the internal reference. Elemental analyses were performed by Dr. Kurt Eder, Geneva, Switzerland.

REFERENCES

(1) M. J. Kornet, *J. Pharm. Sci.*, **67**, 1471 (1978).

(2) A. Michaelis, *Justus Liebigs Ann. Chem.*, **252**, 266 (1871).

(3) A. Michaelis and O. Lampe, *ibid.*, **274**, 316 (1893).

(4) G. A. Golubeva, Y. N. Portnov, A. N. Kost, and L. A. Sviridova, *Khim. Geterotsikl. Soedin.*, **7**(1), 118 (1971).

(5) H. Gysling and H. J. Peterli, U.S. pat. 2,936,290 (1960); through *Chem. Abstr.*, **54**, P24804f (1960).

ACKNOWLEDGMENTS

The authors are indebted to Mr. Gill D. Gladding, ADD Program, National Institutes of Health, for providing the anticonvulsant activity data and to Mrs. Kelly Filo for technical assistance in the syntheses.