Synthesis of 1-Methyl- and 1-Ethoxycarbonyl-2-phenylcarbamoylpiperidazines as Potential Anticonvulsant Agents

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1-Methyl- and 1-ethoxycarbonyl-2-phenylcarbamoylpiperidazines were synthesized and examined for anticonvulsant activity in the maximal electroshock seizure and pentylenetetrazol seizure threshold tests. One synthetic pathway for the 1-methyl compounds involved the reaction between aryl isocyanates and 1-methylpiperidazine. A second procedure, of lesser utility, utilized selective lithium aluminum hydride reduction of 1-ethoxycarbonyl-2-phenylcarbamoylpiperidazines and gave the corresponding 1-methyl compounds. The 1-ethoxycarbonyl series was obtained from aryl isocyanates and 1-ethoxycarbonylpiperidazine. Several 1-methyl-2-phenylcarbamoylpiperidazines exhibited significant anticonvulsant activity.

J. Heterocyclic Chem., **18**, 293 (1981).

Previously, the synthesis and anticonvulsant activity of phenylcarbamoylpyrazolidines of Types I (1) and II (2) were described. Compounds of Type I were active in the

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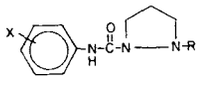


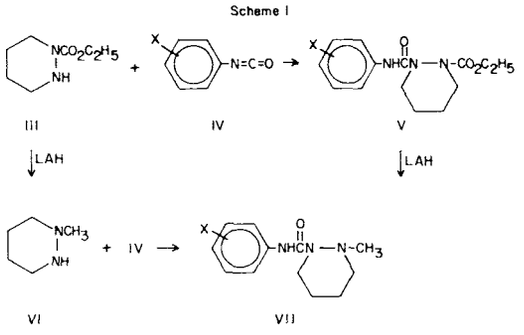
I, R = CH_3

II, R = C_6H_4Y

maximal electroshock seizure and pentylenetetrazol seizure threshold tests, whereas compounds of Type II were for the most part inactive.

These studies have now been extended by the preparation of compounds in which the heterocycle is six-membered, the phenylcarbamoylpiperidazines (V) and VII (Scheme I). Since II and V contain electron withdrawing

Scheme I



groups on *N*-1 and I and VII contain the electron releasing *N*-methyl substituent, additional information regarding structure-activity relationships could be expected by preparing both series V and VII. Secondly, series V could conceivably serve as the precursors for the corresponding

Table I

Physical Properties of 1-Ethoxycarbonyl-2-phenylcarbamoylpiperidazines

Compound No.	X	M.p. °C	Formula	Analysis, % Calcd./Found C	H	N
Va	H	122-123.5 (a)	$C_{14}H_{19}N_3O_3$			
Vb	*m*-Cl	130-132	$C_{14}H_{18}ClN_3O_3$	53.94	5.82	13.48
				54.02	5.86	13.59
Vc	*p*-Cl	124.5-126 (b)	$C_{14}H_{18}ClN_3O_3$	53.94	5.82	13.48
				54.09	5.90	13.58
Vd	*p*-CH_3	130-130.5 (c)	$C_{15}H_{21}N_3O_3$			
Ve	*p*-CH_3O	126-128 (d)	$C_{15}H_{21}N_3O_4$			
Vf	*p*C_2H_5O	133-136	$C_{16}H_{23}N_3O_4$	59.80	7.21	13.07
				59.99	7.40	13.18
Vg	*m*-CF_3	118-120.5	$C_{15}H_{18}F_3N_3O_3$	52.17	5.25	12.17
				52.16	5.36	12.24
Vh	3,4-Cl_2	139.5-142 (e)	$C_{14}H_{17}Cl_2N_3O_3$			

(a) Lit. m.p. 123-124°. (b) Lit. m.p. 133-134.5°. (c) Lit. m.p. 131.5-132.5°. (d) Lit. m.p. 128-130°. (e) Lit. m.p. 144-145.5°. All of these melting points are given in reference 6.

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N-methyl compounds VII. A report concerning the lithium aluminum hydride reduction of the urethan group to *N*-methyl in the presence of an amide has appeared (3).

Treatment of 1-carbethoxypiperidazine (III) (4,5) with aryl isocyanates readily afforded 1-ethoxycarbonyl-2-phenylcarbamoylpiperidazines (V) (Scheme I) (Table I). Subsequently, a patent (6) was found describing some of the adducts.

The selective lithium aluminum hydride reduction of V was explored (Scheme I). Although the 1-methyl products VIIb, VIIf and VIIh were obtained in purified form, this reaction routinely produced product mixtures which were for the most part difficult to separate. Side-products which were identified (NMR and mass spectral analysis) in some of the reaction mixtures included structures VIII, IX and X. Although reaction time was varied total selectivity was not achieved.

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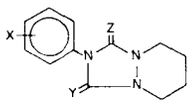

VIII: Z=O, Y=H_2
IX: Z=H_2, Y=H_2
X: Z=O, Y=O

The superior two-step procedure for the preparation of VII involved first the lithium aluminum hydride reduction of III which gave VI. 1-Methylpiperidazine (VI) then added readily to aryl isocyanates and produced 1-methyl-2-phenylcarbamoylpiperidazines (VII) (Scheme I) (Table II).

Compounds Va-Vh and VIIa-VIIi were tested in the maximal electroshock (MES) seizure and pentylenetetrazol (scMet) seizure threshold tests for anticonvulsant activity and neurotoxicity in male Carworth Farms No. 1 mice by reported procedures (1). In series V, all of the compounds were inactive at 300 mg./kg., except Ve which showed activity in both tests at this dose (0.5 hour). None of these compounds showed toxicity at the three doses tested (30, 100 and 300 mg./kg.). The inactivity displayed by this series of compounds is comparable to the Type II series, apparently indicating that the *N*-phenyl and *N*-ethoxycarbonyl substituents exert similar effects.

The results for series VII compounds are summarized in Table III. Noteworthy are compounds VIIc, VIIg and VIIi. Further testing of VIIi gave MES ED_{50} = 45 mg./kg. and TD_{50} = 144 mg./kg. Compounds VIIc, VIIe and VIIg exhibited scMet ED_{50} = 70, 103 and 44 mg./kg. and TD_{50} = 414, 340 and 154 mg./kg., respectively. The data for series I and VII indicate that anticonvulsant activity can be found among both the 5- and 6-membered ring compounds and that the best aromatic ring substituents are: *o*-CH_3; 2-Cl, 6-CH_3; and 2,6-$(CH_3)_2$.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The ir spectra were taken on a Perkin-Elmer 700 spectrophotometer as either liquid films or as potassium

Table II

Physical Properties of 1-Methyl-2-phenylcarbamoylpiperidazines

Compound No.	X	M.p. °C	Recrystallization Solvent	Method	Formula	Analysis, % Calcd./Found C	H	N
VIIa	H	95-97	cyclohexane	B	$C_{12}H_{17}N_3O$	65.73	7.81	19.16
						65.53	7.78	19.12
VIIb	*m*-Cl	90-92	ether-petroleum ether (a)	A	$C_{12}H_{16}N_3O$	56.81	6.36	16.56
						56.53	6.38	16.43
VIIc	*o*-CH_3	103.5-105	cyclohexane	B	$C_{13}H_{19}N_3O$	66.92	8.21	18.01
						66.70	8.06	18.22
VIId	*m*-CH_3	61.62.5	cyclohexane-petroleum ether (a)	B	$C_{13}H_{19}N_3O$	66.92	8.21	18.01
						66.79	8.40	18.24
VIIe	*p*-CH_3	101-103	hexane	B	$C_{13}H_{19}N_3O$	66.92	8.21	18.01
						66.80	8.35	17.88
VIIf	3,4-Cl_2	103-105	benzene-petroleum ether (a)	A	$C_{12}H_{15}Cl_2N_3O$	50.02	5.25	14.58
						50.29	5.44	14.69
VIIg	2-Cl,6-CH_3	65-67	(b)	B	$C_{13}H_{18}ClN_3O$	58.32	6.78	15.69
						58.17	6.97	15.46
VIIh	*p*-CH_3O	120-121.5	petroleum ether (a)	A	$C_{13}H_{19}N_3O_2$	62.63	7.68	16.85
						62.41	7.55	17.01
VIIi	2,6-$(CH_3)_2$	107-109	cyclohexane	B	$C_{14}H_{21}N_3O$	67.98	8.56	16.99
						68.13	8.46	16.93

(a) Fraction of b.p. 30-60°. (b) Purified by column chromatography on silica gel; eluted with benzene-ethyl acetate (4:1) followed by benzene-ethyl acetate (1:1).

Table III

Anticonvulsant and Toxic Effects

Compound No.	MES Activity (a) 0.5 hour	4 hours	sc Met Activity (a) 0.5 hour	4 hours	Toxicity (a) 0.4 hour	4 hours
VIIa	+	–	–	–	–	–
VIIb	–	–	+	–	–	–
VIIc	–	–	+ + +	–	+	–
VIId	+	–	+	–	+	–
VIIe	–	–	+	–	+	–
VIIf	–	–	–	–	–	–
VIIg	+ + +	–	+	–	+	–
VIIh	–	–	+	–	–	–
VIIi	+ +	–	+ +	–	+	–

(a) Activity and toxicity at 30, 100, and 300 mg./kg. are represented by + + +, + +, and +, respectively; – denotes no activity or toxicity observed at 300 mg./kg.

bromide pellets. Nmr spectra were recorded on a Varian EM-360 or T-60 spectrometer, using tetramethylsilane as the internal reference. Mass spectra were obtained on a RMU-7 double focusing spectrometer by Hitachi/Perkin Elmer. Elemental analyses were performed by Micro-Analysis, Inc., Wilmington, Delaware, and Dr. Kurt Eder, Geneva, Switzerland.

1-Methylpiperidazine (VI).

A solution of 13.0 g. (0.082 mole) of 1-ethoxycarbonylpiperidazine (4,5) (III) in 15 ml. of anhydrous ether was added to 15.6 g. (0.41 mole) of lithium aluminum hydride in 110 ml. of anhydrous ether at room temperature over a period of 2 hours. The mixture was refluxed for an additional 16 hours and decomposed with 40% aqueous potassium hydroxide (70 ml.) with cooling by a brine and ice cooling mixture. The ether layer was decanted and the inorganic sludge was washed several times with ether. The combined ethereal solution was dried (magnesium sulfate) and distilled through a one foot column packed with glass helices. After removal of the ether, the column was removed and the residue was distilled through a Claisen head and afforded 10.6 g. of a colorless liquid, b.p. 90-134° (estimated b.p. is 120-121°). This product was used directly for the preparation of VII (Method B). Nmr and mass spectral analysis showed contamination by the oxidation product, 1-methyl-1,4,5,6-tetrahydropyridazine.

1-Methyl-2-phenylcarbamoylpiperidazines (VII).

Method A.

A solution of 1.56 g. (5.20 mmoles) of Vb in 20 ml. of tetrahydrofuran and 40 ml. of anhydrous ether was added to 0.737 g. (19.4 mmoles) of lithium aluminum hydride in 50 ml. of anhydrous ether at room temperature over a period of 20 minutes. An additional 5 ml. of tetrahydrofuran and 25 ml. of ether was added and the mixture was refluxed for 4 hours and 50 minutes. The cooled mixture was treated with 2 ml. of 1*N* sodium hydroxide and 1 ml. of water and stirred for 5 minutes. Next, 50 ml. of ether was added and stirring was continued for an additional 5 minutes. The ether layer was separated and the inorganics were extracted three times with 70 ml. portions of ether. The combined ethereal solution was washed with 30 ml. of water and dried (magnesium sulfate). Evaporation of the solvent gave 1.1 g. of residue. Purification by repeated recrystallization from ether-petroleum ether (30-60° fraction) gave analytically pure VIIb, m.p. 90-92°. This method gave poor yields.

Method B.

Compound VIIe was prepared from 1.25 g. (12.5 mmoles) of 1-methylpiperidazine (VI) (as obtained above) and 1.18 g. (8.90 mmoles) of *p*-tolyl isocyanate in 25 ml. of dry benzene according to the procedure previously described (1). Workup gave 1.6 g. of crude product. Recrystallization from hexane produced white crystalline adduct, m.p. 101-103°. This method gave 50-60% yields.

1-Ethoxycarbonyl-2-phenylcarbamoylpiperidazines (Va-Vh) (Table I).

A solution of 1.89 g. (0.0153 mole) of phenyl isocyanate in 12 ml. of dry benzene was treated with 2.42 g. (0.153 mole) of IV (heat evolved). The mixture was refluxed for 2 hours and cooled. Evaporation of the solvent afforded a white solid which was triturated with petroleum ether (30-60° fraction) and filtered. Recrystallization from 95% ethanol gave 2.95 g. (70%) of colorless Va, m.p. 122-123.5°. The other adducts were obtained in yields of 55-83%.

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