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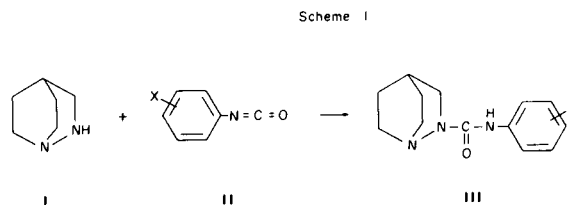
A number of aryl isocyanates were adducted to 1,2-diazabicyclo[2.2.2]octane and afforded 2-phenylcarbamoyl-1,2-diazabicyclo[2.2.2]octanes. Some of the products displayed anticonvulsant activity.

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In a continuing search for novel anticonvulsants, a series of 2-phenylcarbamoyl-1,2-diazabicyclo[2.2.2]octanes (III) has been prepared and examined for anticonvulsant activity. Previous studies (1,2) on related compounds have dealt with 1,2-diazamonocyclic bases and it was deemed worthwhile to extend this work to 1,2-diazabicyclic bases. Initially, 1,2-diazabicyclo[2.2.2]octane (I) was selected for study. This base, with its cage structure, would be expected to provide markedly different steric and basic properties in comparison with the monocyclic compounds.

The synthesis of 1,2-diazabicyclo[2.2.2]octane (I) (3) was accomplished in four steps from isonipecotic acid with only minor deviations from the reported procedures (4). Compound I reacted readily with aryl isocyanates (II) to produce III in good yields (Scheme I) (Table I).

Compounds IIIa-IIIj 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). None of the compounds showed activity in the



scMet test. In the MES test, compounds IIIId, IIIg and IIIi exhibited activity at 300 mg/kg at 30 minutes. Compounds IIIId and IIIi showed no toxicity at this dose whereas IIIg displayed some toxicity. The most active compound was IIIh. Its estimated ED₅₀ is between 100 and 200 mg/kg and its estimated TD₅₀ is 300 mg/kg.

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 bromide pellets. The nmr spectra were recorded on a Varian EM-360 or

Table I
Physical Properties of 2-Phenylcarbamoyl-1,2-diazabicyclo[2.2.2]octanes

Compounds	X	Melting Point, °C	Recrystallization Solvent (a)	Yield, %	Formula	Analysis, %		
						C	H	N
IIIa	H	163.5-166	B	76	C ₁₃ H ₁₇ N ₃ O	67.51	7.41	18.17
						67.74	7.56	18.08
IIIb	o-Cl	124-125.5	A	58	C ₁₃ H ₁₆ ClN ₃ O	58.76	6.07	15.81
						58.88	6.25	15.91
IIIc	o-F	90-91.5	A	65	C ₁₃ H ₁₆ FN ₃ O	62.64	6.47	16.86
						62.88	6.47	16.67
IIId	o-CH ₃	139-140	B	98	C ₁₄ H ₁₉ N ₃ O	68.54	7.81	17.13
						68.83	7.81	16.93
IIIe	m-CH ₃	132.5-134	B	90	C ₁₄ H ₁₉ N ₃ O	68.54	7.81	17.13
						68.74	7.87	17.12
IIIf	p-CH ₃	169-171	B	91	C ₁₄ H ₁₉ N ₃ O	68.54	7.81	17.13
						68.51	7.73	17.29
IIIg	p-CH ₃ O	115-116.5	B	98	C ₁₄ H ₁₉ N ₃ O ₂	64.35	7.33	16.08
						64.61	7.28	16.16
IIIh	2-Cl,6-CH ₃	121.5-123	B	89	C ₁₄ H ₁₈ ClN ₃ O	60.11	6.49	15.02
						60.12	6.52	15.31
IIIi	2,6-(CH ₃) ₂	167-168.5	B	90	C ₁₃ H ₂₁ N ₃ O	69.47	8.16	16.20
						69.25	8.27	16.02
IIIj	(b)	145-147	B	66	C ₁₇ H ₁₉ N ₃ O	72.57	6.81	14.93
						72.86	7.04	14.95

(a) A = cyclohexane, B = benzene-cyclohexane. (b) α -Naphthyl replaces phenyl.

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.

2-Phenylcarbamoyl-1,2-diazabicyclo[2.2.2]octanes (III).

Compound IIIg was prepared from 997 mg (6.69 mmoles) of *p*-methoxyphenyl isocyanate and 802 mg (7.15 mmoles) of 1,2-diazabicyclo[2.2.2]octane (I) (3,4) in 16 ml of dry benzene according to the procedure previously described (1). Workup gave 1.65 g (98%) of white crystalline product, mp 107-111°. Recrystallization from benzene-cyclohexane afforded analytically pure material, mp 115-116.5°.

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REFERENCES AND NOTES

- (1) M. J. Kornet, *J. Pharm. Sci.*, **67**, 1471 (1978).
- (2) M. J. Kornet and J. Chu, *J. Heterocyclic Chem.*, **18**, 293 (1981).
- (3) P. M. Carabateas, A. R. Surrey and L. S. Harris, *J. Med. Chem.*, **7**, 293 (1964).
- (4) E. E. Mikhлина, N. A. Komarova and M. V. Rubtsov, *Khim. Geterotsikl. Soedin.*, **2**, 259 (1966).