and the residue (142 mg) was purified using flash chromatography (12) (silica gel, ether, then ether–acetone, 1:1). A total of 24 mg of VI was obtained, mp 109–110° (*iso*-propyl ether); IR (KBr) ν_{max} 1690, 1615, 1590, and 1490 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 8.75 (1H, dd, J = 1.5, 4.5 Hz, C-2 H), 8.06 (1H, dd, J = 1.5, 8.5 Hz, C-4 H), 7.35 (1H, dd, J = 4.2, 8.5 Hz, C-3 H), 7.29 (1H, d, J = 2.7 Hz, C-7 H), 7.07 (1H, d, J = 2.7 Hz, C-5 H), 4.72 (1H, ddq, J = 6.0, 6.0, 6.0 Hz, C-1′ H), 3.90 (3H, s OCH_3), 2.6, and 1.8 (3H and 1H, m, C-3′ H, C-2′ H), 1.03 (3H, d, J = 6.0 Hz, CH_3); mass spectrum M^+ at m/z 256 (18%), 228 (18%), 213 (21%), 200 (81%), 187 (52%), 186 (51%), 159 (100%); ^{13}C-NMR data (Table I); TLC, solvent B, R_f 0.22[12].

Anal.—Calc. for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.32; H, 6.40; N, 10.86.

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Synthesis and Anticonvulsant Activity of Some 2-Methyl-3-phenylcarbamoyl-2,3-diazabicyclo-[2.2.1]heptanes

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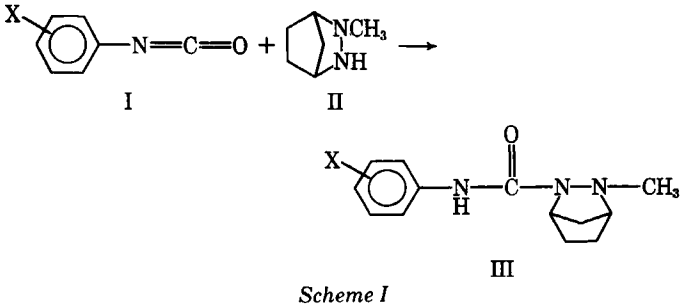
Abstract □ A series of 2-methyl-3-phenylcarbamoyl-2,3-diazabicyclo[2.2.1]heptanes were obtained by treating aryl isocyanates with 2-methyl-2,3-diazabicyclo[2.2.1]heptane. The compounds showed only minimal anticonvulsant activity.

Keyphrases □ 2-Methyl-3-phenylcarbamoyl-2,3-diazabicyclo[2.2.1]-heptanes—synthesis and anticonvulsant activity □ Anticonvulsants—synthesis of some 2-methyl-3-phenylcarbamoyl-2,3-diazabicyclo[2.2.1]-heptanes

A previous report (1) describes the synthesis and anticonvulsant activity of a series of 1-methyl-2-phenylcarbamoylpiperidazines. Four members of this series showed significant activity. The present report describes the synthesis and anticonvulsant activity of a series of 2-methyl-3-phenylcarbamoyl-2,3-diazabicyclo[2.2.1]heptanes (III). The series of III, with their cage structure, would be expected to provide different steric and basic properties in comparison with the monocyclic compounds (1).

BACKGROUND

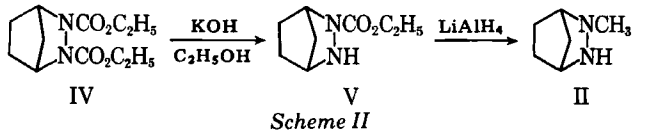
The synthesis of 2-methyl-2,3-diazabicyclo[2.2.1]heptane (II) was accomplished in two steps from 2,3-dicarboethoxy-2,3-diazabicyclo[2.2.1]heptane (IV) (2). Partial saponification of IV gave 2-carboethoxy-2,3-diazabicyclo[2.2.1]heptane (V), which underwent reduction with lithium aluminum hydride to afford the base, II (Scheme I). Compound II reacted with aryl isocyanates (I) to produce III in good yields (Scheme II; Table I).



Scheme I

Compounds III*a–j* were tested in the maximal electroshock seizure and subcutaneous pentylenetetrazol seizure threshold tests for anticonvulsant activity and in the rotorod test for neurotoxicity in male mice[1] by reported procedures (3). None of the compounds showed activity in either test at 100 mg/kg.

In the maximal electroshock seizure test, compounds III*a*, *d*, *g*, *i*, and *j* exhibited activity at 300 mg/kg at 30 min. Compounds III*a* and *i* showed no toxicity at this dose level, whereas III*d*, *g*, and *j* displayed some toxicity. Two compounds were active in the subcutaneous pentylenetetrazol seizure test at 300 mg/kg. Compound III*j* was active at 30 min; compound III*b* showed activity at 4 hr with no toxicity. Apparently, the introduction



Scheme II

[1] Carworth Farms No. 1 mice.

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Table I—Physical Properties of 2-Methyl-3-phenylcarbamoyl-2,3-diazabicyclo[2.2.1]heptanes

Compound	X	Melting Point	Yield, %	Recrystallization Solvent[a]	Formula		Analysis, % Calc.	Found
						C	67.51	67.65
IIIa	H	84–86	73	B	$C_{13}H_{17}N_3O$	H	7.41	7.23
						N	18.17	18.43
						C	58.76	58.76
IIIb	p-Cl	125–126.5	67	B	$C_{13}H_{16}ClN_3O$	H	6.07	5.95
						N	15.81	15.54
						C	62.64	62.67
IIIc	p-F	95.5–97	72	A	$C_{13}H_{16}FN_3O$	H	6.47	6.56
						N	16.86	16.83
						C	68.54	68.71
IIId	o-CH_3	81.5–83.5	57	C	$C_{14}H_{19}N_3O$	H	7.81	7.77
						N	17.13	17.21
						C	68.54	68.61
IIIe	m-CH_3	88–88.5	75	D	$C_{14}H_{19}N_3O$	H	7.81	7.73
						N	17.13	17.13
						C	68.54	68.72
IIIf	p-CH_3	123.5–125	56	B	$C_{14}H_{19}N_3O$	H	7.81	7.89
						N	17.13	17.34
						C	64.35	64.65
IIIg	p-CH_3O	95.5–97	82	B	$C_{14}H_{19}N_3O_2$	H	7.33	7.24
						N	16.08	16.08
						C	52.02	52.20
IIIh	3,4-Cl_2	113–115	67	B	$C_{13}H_{15}Cl_2N_3O$	H	5.04	5.01
						N	14.00	14.28
						C	60.11	60.09
IIIi	2-Cl,6-CH_3	92–94	77	B	$C_{14}H_{18}ClN_3O$	H	6.49	6.56
						N	15.02	14.98
						C	69.47	69.65
IIIj	2,6-$(CH_3)_2$	131.5–132.5	64	A	$C_{15}H_{21}N_3O$	H	8.16	8.12
						N	16.20	16.43

[a] A, cyclohexane; B, benzene–cyclohexane; C, cyclohexane–ether; D, ether.

of a methylene bridge into the 1,2-diazacyclohexane ring (1) leads to compounds with reduced anticonvulsant activity.

EXPERIMENTAL[2]

2-Carboethoxy-2,3-diazabicyclo[2.2.1]heptane (V)—This compound was prepared by saponification of 2,3-dicarboethoxy-2,3-diazabicyclo[2.2.1]heptane (IV) (2) according to the methods (4, 5) used in the preparation of 1-ethoxycarbonylpiperidazine. It was obtained as a colorless oil in 50% yield, bp 116–120° (1.3 mm). The NMR showed contamination by the starting material, and a satisfactory carbon analysis could not be obtained. Since the purity of this compound was ~95%, it was used directly in the next step.

2-Methyl-2,3-diazabicyclo[2.2.1]heptane (II)—This compound (6) was obtained from the lithium aluminum hydride reduction of V according to the same procedure (1) used for the preparation of 1-methylpiperidazine. It distilled as a colorless oil in 78% yield, bp 151–153°. This base was used directly in the preparation of III.

[2] 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. 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, Del., and Dr. Kurt Eder, Geneva, Switzerland. All compounds exhibited PMR and mass spectra consistent with the structures shown.

2-Methyl-3-phenylcarbamoyl-2,3-diazabicyclo-[2.2.1]heptanes (III)—Compound IIIj was prepared from 2.0 g (0.0178 mole) of 2-methyl-2,3-diazabicyclo[2.2.1]heptane (II) and 2.38 g (0.0162 mole) of 2,6-dimethylphenyl isocyanate (I) in 35 ml of dry benzene according to the procedure previously described (3). Workup gave 2.7 g (64%) of white solid, mp 130–132°. Recrystallization from cyclohexane afforded analytically pure material, mp 131.5–132.5°.

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