Synthesis of Phenylurethans of a Pyrazolidinylcarbinol as Anticonvulsant Agents

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Eleven phenylurethans were prepared from 1,2-dimethyl-3-hydroxymethylpyrazolidine and various phenyl isocyanates. Anticonvulsant screening revealed that two of the phenylurethans exhibited moderate activity in the maximal electroshock seizure (MES) test in mice.

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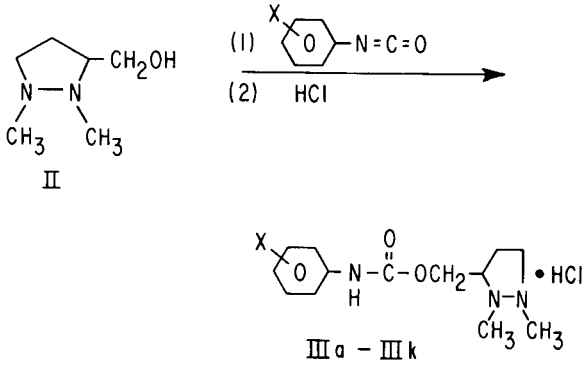
In the past several years the development of novel anticonvulsants in our laboratories has been a major goal (1-5). More recently, our attention has been focused on the synthesis of phenylurethans of pyrazolidine alcohols. The initial report described a series of phenylurethans of 1,2-dialkyl-4-pyrazolidinols (6). A low order of activity was observed for some of these compounds. Further studies on related urethans has been continued and this report is concerned with the synthesis and anticonvulsant activity of a new series of phenylurethans of 1,2-dimethyl-3-hydroxymethylpyrazolidine.

The necessary pyrazolidinylcarbinol, 1,2-dimethyl-3-hydroxymethylpyrazolidine (II), was synthesized in two steps from diethyl maleate and 1,2-dimethylhydrazine analogous to the method reported for the 1,2-diethyl analog (7). Alcohol II added readily to aryl substituted isocyanates and afforded the phenylurethans (IIIa-IIIk) (Scheme I). The latter compounds were uniformly isolated



Scheme I

as their hydrochloride salts and their physical properties are given in Table I.

Compounds IIIa-IIIk were tested in the maximal electroshook (MES) seizure and pentylenetetrazol (sc Met) seizure threshold tests for anticonvulsant activity and neurotoxicity in male Carworth Farms No. 1 mice by procedures described earlier (4). Except for IIIe, all of the compounds showed some degree of anticonvulsant activity (Table II) in one or both tests. Both the degree and uniformity of activity is greater in the MES test indicating potential efficacy in the treatment of major motor seizures of the grand mal type. Further evaluation in the MES assay of IIIj and IIIk showed ED_{50} = 63 (57-74) mg./kg. and TD_{50} = 155 (134-174) mg./kg. for the former and ED_{50} = 72 (65-81) mg./kg. and TD_{50} = 163 (155-173) mg./kg. for the latter. The anticonvulsant activity of this series of compounds is greater than that of the phenylurethans of the 4-pyrazolidinols previously reported (6).

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. Elemental analyses were performed by Dr. Kurt Eder, Geneva, Switzerland.

1,2-Dimethyl-5-ethoxycarbonyl-3-pyrazolidinone (I).

This compound was prepared in a manner analogous to that of the 1,2-diethyl compound (7) from 52.8 g. (0.88 mole) of 1,2-dimethylhydrazine and 152.5 g. (0.88 mole) of diethyl maleate in 144 ml. of absolute ethanol (reflux time of 25 hours). Distillation afforded 160 g. (97%) of colorless liquid, b.p. 110° (0.5 mm); ir (film): 5.75 (ester C=O), 5.91 μ (amide C=O).

Anal. Calcd. for $C_8H_{14}N_2O_3$: C, 51.60; H, 5.78; N, 15.04. Found: C, 51.76; H, 7.72; N, 15.13.

1,2-Dimethyl-3-hydroxymethylpyrazolidine (II).

This compound was prepared in a manner analogous to that of the 1,2-diethyl compound (7) from 158 g. (0.839 mole) of I and 47.0 g. (1.24 moles) of lithium aluminum hyride in 780 ml. of anhydrous ether. Workup and distillation gave 71.4 g. (65%) of a colorless liquid, b.p. 80-82° (9 mm); ir (film): 2.88-3.18 μ (broad OH).

Anal. Calcd. for $C_6H_{14}N_2O$: C, 55.35; H, 10.84; N, 21.52. Found:C, 55.46; H, 10.79; N, 21.53.

A crystalline picrate derivative was prepared and recrystallized from absolute ethanol, m.p. 182.5-183.5.

Anal. Calcd. for $C_{12}H_{17}N_5O_8$: C, 40.12; H, 4.77; N, 19.49. Found: C, 40.06; H, 4.99; N, 19.60.

Hydrochlorides of Phenylurethans of 1,2-Dimethyl-3-hydroxymethylpyrazoline (IIIa-IIIk) (Table I).

A mixture of 6.53 g. (0.04 mole) of *p*-ethoxyphenyl isocyanate, 5.20 g. (0.04 mole) of II, and 50 ml. of dry toluene was refluxed for 18 hours. The mixture was cooled and extracted twice with 50 ml. of portions of 2*N*-hydrochloric acid. The combined acidic extract was washed with 50 ml. of benzene, filtered through a glass sintered funnel, and basified with solid sodium carbonate. The separated oil was extracted into methylene chloride and dried (magnesium sulfate). Evaporation of the solution under reduced pressure gave an oily residue.

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Table I

Physical Properties of Hydrochlorides of Phenylurethans of 1,2-Dimethyl-3-hydroxymethylpyrazolidine

Compound No.	X	M.p., °C	Yield, %	Formula	Analyses, % Calcd./Found C	H	N
IIIa	H	127-129.5	88	$C_{13}H_{20}ClN_3O_2$	54.63	7.05	14.70
					54.62	7.16	14.59
IIIb	*o*-Cl	119-121	84	$C_{13}H_{19}Cl_2N_3O_2$	48.76	5.98	13.12
					49.11	6.42	13.26
IIIc	*p*-Cl	178-179	43	$C_{13}H_{19}Cl_2N_3O_2$	48.76	5.98	13.12
					49.17	6.21	13.08
IIId	*p*-C_2H_5O	145-147	83	$C_{15}H_{24}ClN_3O_3$	54.62	7.33	12.74
					54.67	7.38	12.91
IIIe	*p*-CH_3O	166.5-168	80	$C_{14}H_{22}ClN_3O_3$	53.24	7.02	13.31
					53.31	6.97	13.40
IIIf	*o*-CH_3	144.5-145.5	82	$C_{14}H_{22}ClN_3O_2$	56.08	7.40	14.02
					56.32	7.42	14.14
IIIg	*p*-CH_3	149-151	81	$C_{14}H_{22}ClN_3O_2$	56.08	7.40	14.02
					56.00	7.24	13.96
IIIh	3,4-$(Cl)_2$	201-203	48	$C_{13}H_{18}Cl_3N_3O_2$	44.02	5.12	11.85
					44.44	5.29	11.85
IIIi	2,5-$(CH_3)_2$	204.5-206.5	82	$C_{15}H_{24}ClN_3O_2$	57.40	7.71	13.39
					57.30	7.79	13.39
IIIj	2,6-$(CH_3)_2$	168-169	86	$C_{15}H_{24}ClN_3O_2$	57.40	7.71	13.39
					57.71	7.18	13.36
IIIk	2-Cl,6-CH_3	153-155	64	$C_{14}H_{21}Cl_2N_3O_2$	50.31	6.33	12.57
					50.84	6.78	12.59

Table II

Anticonvulsant and Toxic Effects

Compound No.	MES Activity (a) 0.5 Hours	4 Hours	sc Met Activity (a) 0.5 Hours	4 Hours	Toxicity (a) 0.5 Hours	4 Hours
IIIa	+	b	−	−	+	−
IIIb	+	−	−	−	+	−
IIIc	+	−	−	b	+	+
IIId	+	−	+	−	+	−
IIIe	b	b	b	b	+	b
IIIf	+	b	b	b	+	b
IIIg	+	b	−	b	+	+
IIIh	+	+	+	−	+	−
IIIi	+	−	b	−	+	−
IIIj	++	b	b	b	++	b
IIIk	++	b	b	−	+	−

(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. (b) No activity or toxicity observed at 100 mg./kg.

The oily free base was dissolved in absolute ethanol and acidified to *p*H ~ 2-3 with 2*N* ethanolic hydrogen chloride. Evaporation under reduced pressure gave a viscous liquid which was treated with 50 ml. of absolute ethanol and again evaporated. Trituration of the residue with anhydrous ether produced a solid which was filtered. Recrystallization from absolute ethanol-ether gave 11.0 g. (83%) of IIId as white crystals, m.p. 145-147°; ir (potassium bromide): 5.90 μ (C=O).

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