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Anticonvulsant Activity of 1-Alkyl-4-substituted 3,5-Pyrazolidinediones

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Abstract □ Methods were developed for the synthesis of 1-methyl-4-substituted 3,5-pyrazolidinediones. These compounds are related to phensuximide and diphenylhydantoin and were prepared as potential anticonvulsant agents. The reaction between substituted malonic esters and methylhydrazine in the presence of sodium methoxide was employed to prepare a series of 1-methyl-4,4-disubstituted 3,5-pyrazolidinediones. 1-Methyl-4-phenyl-3,5-pyrazolidinedione was prepared from diethyl phenylmalonate and methylhydrazine. 1,4-Diethyl-4-phenyl-3,5-pyrazolidinedione was obtained by the alkylation of 4-ethyl-4-phenyl-3,5-pyrazolidinedione with ethyl bromide in the presence of potassium *tert*-butoxide as the base. All compounds are novel and were characterized by elemental analysis and IR and PMR spectrometry. All products were evaluated by maximal electroshock seizure and pentylenetetrazol seizure threshold tests.

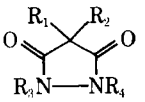
Keyphrases □ 1-Methyl-4,4-disubstituted 3,5-pyrazolidinediones —synthesis, evaluation of anticonvulsant activity □ 3,5-Pyrazolidinediones, 1-methyl-4,4-disubstituted—synthesis, evaluation of anticonvulsant activity □ Anticonvulsant activity—synthesis and evaluation of 1-methyl-4-substituted 3,5-pyrazolidinediones

It has been firmly established that an important pharmacophoric grouping among anticonvulsant agents is the imide group (1). Cyclic hydrazides, which may be represented by Structure I, have rarely been studied for their anticonvulsant properties. The two compounds (2, 3) of Structure I that were examined were found to be inactive; however, neither contains alkylated nitrogen atoms.

Cyclic imides and cyclic hydrazides have similar physical and chemical properties, and one might reasonably expect parallel pharmacological actions. The 3,5-pyrazolidinediones (I) are isomeric with the hydantoins, representing only a transposition of one CONR grouping. They represent the barbituric acids after removal of the urea carbonyl. The latter two observations were made more than 40 years ago (4).

DISCUSSION

In a program designed to synthesize molecular modifications of the imide grouping, the 3,5-pyrazolidinediones (I) were investigated. This report describes the preparation of a series of compounds in which R_3 = alkyl, R_4 = H, and R_1 and R_2 = a combination of H, alkyl, and aryl groups.



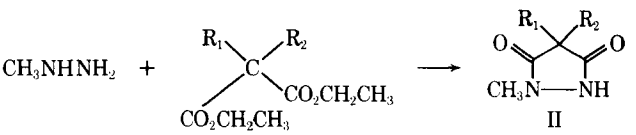
I

Although numerous 3,5-pyrazolidinediones containing aryl substituents on one or both nitrogens are known, the authors are unaware of *N*-monosubstituted compounds containing the simple methyl or ethyl substituents. The primary interest was in the *N*-methyl or *N*-ethyl compounds since the clinically useful succinimides and hydantoins containing *N*-substituents possess such alkyl groups. The synthesis of some *N*-*n*-hexyl-4-substituted 3,5-pyrazolidinediones was described previously (5).

The *N*-methyl-4-substituted 3,5-pyrazolidinediones (II) were obtained by the reaction of methylhydrazine with substituted diethyl malonates (Scheme I). Three distinct methods (A, B, and C) were developed because a given method was sometimes refractory with respect to the preparation of a specific compound. The details of each method are described in the *Experimental* section. The yields ranged from 16 to 74%. One product (II*g*) (R_1 = C_6H_5, R_2 = CH_3) was converted into its *N*-acetyl derivative (III) by treatment with acetyl chloride in pyridine.

The only *N*-ethyl compound prepared was 1,4-diethyl-4-phenyl-3,5-pyrazolidinedione. It was synthesized (Scheme II) by alkylating 4-ethyl-4-phenyl-3,5-pyrazolidinedione with ethyl bromide in the presence of potassium *tert*-butoxide as the base (Method D). This procedure proved unsuccessful as a general method for the preparation of other *N*-alkyl 3,5-pyrazolidinediones because it usually gave a complex mixture of *N*-alkyl, *N,O*-dialkyl, and *N,N*-dialkyl products. Such mixtures were not readily separated.

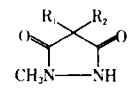
The single *N*-methyl-3,5-pyrazolidinedione containing one substituent at C-4 was 1-methyl-4-phenyl-3,5-pyrazolidinedione (II*f*). Support for the cyclic structure was obtained by dialkylation of the compound with excess methyl iodide in alcoholic potassium hydroxide and isolation of 1,2,4-trimethyl-4-phenyl-3,5-pyrazolidinedione (IV). The structure of the dialkylation product was established by an alternate synthesis from methyl sulfate and 4-methyl-4-phenyl-3,5-pyrazolidinedione (V). The latter was prepared, in turn, from diethyl methylphenylmalonate and anhydrous hydrazine (Scheme III). The TLC and IR spectra of the



II

Scheme I

Table I—1-Alkyl-4,4-disubstituted 3,5-Pyrazolidinediones



Compound	R_1	R_2	Method	Melting Point	Yield, %	Crystallization Solvent[a]	Formula	Analysis, % Calc.	Found
II*a*	CH_3	CH_3	A	115–117°	74	X	$C_6H_{10}N_2O_2$	C 50.69	50.83
								H 7.09	6.94
								N 19.71	19.74
II*b*	—$CH_2CH_2CH_2$—		A	89–91°	55	X	$C_7H_{10}N_2O_2$	C 54.54	54.52
								H 6.54	6.75
								N 18.17	18.21
II*c*	CH_3	C_2H_5	A	98–100°	16	Y	$C_7H_{12}N_2O_2$	C 53.83	53.73
								H 7.74	7.66
								N 17.94	18.04
II*d*	—$CH_2CH_2CH_2CH_2$—		A	107–109°	39	Y	$C_8H_{12}N_2O_2$	C 57.13	57.30
								H 7.19	7.07
								N 16.66	16.82
II*e*	C_2H_5	C_2H_5	A	108–110°	23	Y	$C_8H_{14}N_2O_2$	C 56.45	56.64
								H 8.29	8.36
								N 16.46	16.46
II*f*	C_6H_5	H	C	185–187°	68	—[b]	$C_{10}H_{10}N_2O_2$	C 63.15	63.07
								H 5.30	5.49
								N 14.73	14.68
II*g*	C_6H_5	CH_3	A	177–178.5°	69	Y	$C_{11}H_{12}N_2O_2$	C 64.69	64.65
								H 5.92	5.86
								N 13.72	13.62
II*h*	C_6H_5	C_2H_5	A	171–172°	62	Y	$C_{12}H_{14}N_2O_2$	C 66.04	66.23
								H 6.47	6.54
								N 12.84	12.86
II*i*	n-C_4H_9	n-C_4H_9	B	158–159°	59	Y	$C_{12}H_{22}N_2O_2$	C 63.69	63.55
								H 9.80	9.51
								N 12.38	12.39
II*j*	C_6H_5[c]	C_2H_5	D	136–138°	78	Z	$C_{13}H_{16}N_2O_2$	C 67.22	67.23
								H 6.94	6.92
								N 12.06	11.99

[a] X = cyclohexane–ethyl acetate, Y = hexane–ethyl acetate, and Z = cyclohexane–benzene. [b] Could not be recrystallized. [c] This compound contains an *N*-ethyl group in place of *N*-methyl.

product obtained in this way were identical with those of the dialkylation product.

Compound II*f* also reacted with 2 equivalents of acetyl chloride in pyridine and furnished the di-*O*-acetate (VI). The pyrazole structure is proposed since the IR spectrum of the product shows a single carbonyl band at 1780 cm^{-1}, reminiscent of an enol acetate group (6).

Table I records relevant data for the series of 1-alkyl-4-substituted 3,5-pyrazolidinediones. The IR spectra (chloroform) exhibit two strong absorption bands in the ranges of 1668–1682 and 1732–1737 cm^{-1}, with the former band being the more intense. Table II contains the PMR data for these compounds.

PHARMACOLOGY

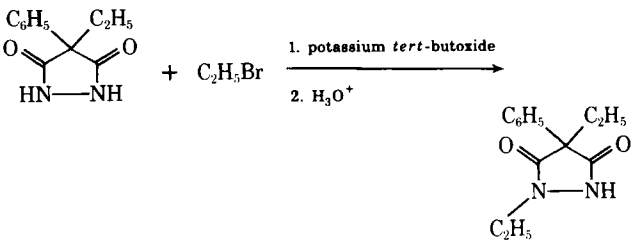
The anticonvulsant activity of each test compound was evaluated by maximal electroshock seizure and pentylenetetrazol seizure threshold tests (7) with modifications. Parallel procedures were performed using both the vehicle and drugs of proven anticonvulsant potency.

Diphenylhydantoin[1], phensuximide[2], or the experimental compounds were mixed with 0.5% methylcellulose, using five strokes of a Potter-Elvehjem homogenizer, and administered intraperitoneally. The concentration of each preparation was such that a volume of 0.1 ml was injected for every 10 g of body weight.

Fifteen male albino Swiss-Webster mice, weighing 20–27 g, were injected with each compound for each procedure[3]. A group of five animals was tested at 1, 2, or 3 hr following drug administration, each animal being used only once. In the maximal electroshock procedure, animals were stimulated with 60 v of 60-cycle alternating current for 0.3 sec, delivered through saline-wetted corneal electrodes. A variable transformer was used to regulate the applied voltage. The duration of the stimulus was kept constant by the inclusion of a relay in the circuit operated by a square wave stimulator[4]. Mice not demonstrating full tonic extension of both hindlimbs following stimulation were considered protected. In the pentylenetetrazol seizure threshold, test animals were injected with an aqueous solution of pentylenetetrazol[5] (85 mg/kg sc) and observed for 45 min. The absence of 3 continuous sec of clonic muscular activity was considered to indicate protection. For the duration of the test procedure, mice were kept individually in 1-liter glass beakers separated by opaque material.

An attempt was made to detect possible neurological toxicity of each compound prior to the pentylenetetrazol seizure test. Toxicity was considered present if the animal failed to climb to the top of a 1-liter beaker after being suspended from the rim by its forelimbs three times within 1 min.

Results of the anticonvulsant tests are shown in Tables III and IV. No compound displayed the marked protection obtained with diphenylhydantoin in the maximal electroshock procedure or with



Scheme II

[1] Dilantin, Parke, Davis & Co., Detroit, Mich.
[2] Prepared by the procedure described by C. A. Miller and L. M. Long, *J. Amer. Chem. Soc.*, 73, 4895(1951).
[3] Laboratory Supply, Inc., Indianapolis, IN 46241. Food and water were supplied *ad libitum*. All animals were allowed several days to recover from shipping stress before use.
[4] Grass S-4.
[5] Metrazol, Knoll Pharmaceutical, Whippany, NJ 07981

Table II—PMR Data of Substituted 3,5-Pyrazolidinediones

Compound	1-Methyl	2-NH	Other Substituents
II*a*[a]	3.28	9.40	1.36 (s) (4,4-dimethyl)
II*b*[a]	3.28	9.50	2.46 (m) (4,4-$CH_2CH_2CH_2$)
II*c*[a]	3.25	9.72	1.34 (s) (4-methyl), 0.89 (t), 1.80 (q) (4-ethyl)
II*d*[a]	3.21	9.42	1.96 (broad s) (4,4-$CH_2CH_2CH_2CH_2CH_2$—)
II*e*[a]	3.22	8.93	0.83 (t), 1.77 (q) (4,4-diethyl)
II*f*[b]	3.24	8.80	7.0–8.1 (m) (4-aromatic H), 8.80 (s) (3- or 5-OH)
II*g*[a]	3.26	7.68	1.75 (s) (4-methyl), 7.35–7.75 (m) (4-phenyl)
II*h*[a]	3.23	8.42	0.96 (t), 2.19 (q) (4-ethyl), 7.26–7.7 (m) (4-phenyl)
II*i*[a]	3.37	10.01	0.90 (t), 1.10–2.20 (m) (4,4-di-*n*-butyl)
II*j*[a]	—	9.0	0.98 (t), 2.25 (q) (4-ethyl), 7.5 (m) (4-phenyl), 1.25 (t), 3.37 (q) (1-ethyl)

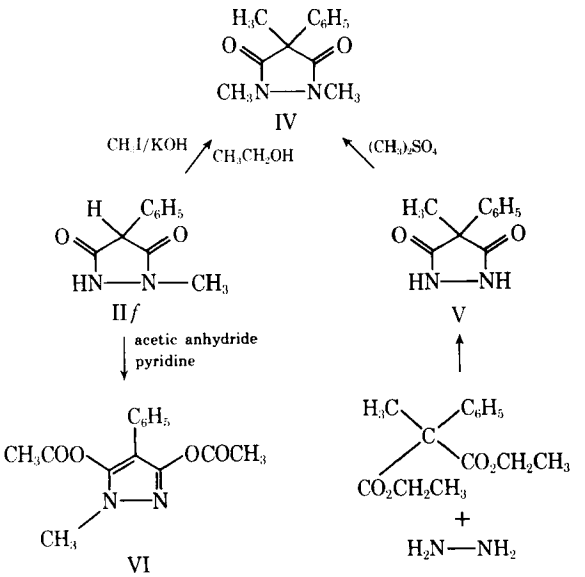
[a] Chemical shift given in δ units; multiplicity is reported as: s = singlet, t = triplet, and q = quartet. Spectra were determined in $CDCl_3$ with tetramethylsilane as internal reference. [b] Spectrum recorded in dimethyl sulfoxide-d_6 with tetramethylsilane as the internal reference.

phensuximide in the pentylenetetrazol test. Only sporadic protection against pentylenetetrazol-induced seizures was observed with several of the more lipid-soluble compounds. At the doses employed, no neurological toxicity was observable with any preparation tested.

EXPERIMENTAL[6]

3,5-Pyrazolidinediones—*Method A*—A solution of 0.04 mole of the substituted diethyl malonate, 15 ml of anhydrous methylhydrazine, and 5.5 g (0.102 mole) of sodium methoxide in 150 ml of anhydrous methanol was refluxed with stirring for approximately 70 hr. The solution was concentrated *in vacuo*, the gummy residue was treated cautiously with 30 ml of 18% hydrochloric acid, and the resulting solution was refluxed for 1 hr. The solution was neutralized to pH ~6 with 40% aqueous sodium hydroxide and concentrated *in vacuo* to one-half of its original volume. The resulting crystalline solid was filtered, dried, and recrystallized.

Method B—A solution of 0.05 mole of the substituted diethyl malonate and 0.07 mole of methylhydrazine in 200 ml of absolute ethanol containing 0.11 mole of sodium was heated in an autoclave at 80° for 20 hr. The temperature was raised to 135° and heating was continued for another 6 hr. The solution was cooled and evaporated to dryness, and the residue was dissolved in water and extracted twice with ether. Acidification of the aqueous solution with 20% aqueous hydrochloric acid afforded a solid which was filtered, dried, and recrystallized.



Scheme III

Method C—A solution of 9.7 g (0.041 mole) of diethyl phenylmalonate and 16 ml of anhydrous methylhydrazine in 150 ml of anhydrous methanol was refluxed for 24 hr. The mixture was evaporated *in vacuo* and the oily residue was treated with 40 ml of 18% aqueous hydrochloric acid. After refluxing for 2 hr, the mixture was cooled and neutralized with aqueous sodium hydroxide to pH ~3. The solid which precipitated was filtered and washed with hot ethyl acetate. The product amounted to 5.1 g.

Method D—A mixture of 1.0 g (4.9 mmoles) of 4-ethyl-4-phenyl-3,5-pyrazolidinedione and 554 mg (4.9 mmoles) of potassium *tert*-butoxide in 50 ml of dry 1,2-dimethoxyethane was stirred vigorously under nitrogen at 45° for 1 hr. After cooling, the mixture was treated with a solution of 535 mg (4.9 mmoles) of ethyl bromide in 2 ml of 1,2-dimethoxyethane. The resulting mixture was heated at 40–50° for 16 hr. An additional 100 mg of ethyl bromide was added and the heating was continued overnight. The solution was evaporated to dryness and the semisolid residue was treated with 20 ml of 10% hydrochloric acid and 95 ml of ethanol. The mixture was refluxed for 6 hr. Cooling afforded 900 mg of the product as white needles.

4-Methyl-4-phenyl-3,5-pyrazolidinedione (V)—A mixture of 10.0 g (0.40 mole) of diethyl methylphenylmalonate and 15 ml of anhydrous hydrazine was refluxed with stirring for 64 hr. The excess hydrazine was removed by distillation at atmospheric pressure and the oily residue was dissolved in water and acidified with 5% hydrochloric acid. Upon attempted extraction of the aqueous phase with chloroform, the product precipitated from solution. The solid was filtered and dried to give 3.7 g (48%) of material, mp 196.5–199°. Recrystallization from ethyl acetate afforded the pure product, mp 198.5–200°; IR (KBr): 1738 and 1660 cm^{-1}.

Anal.—Calc. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.84; H, 5.27; N, 14.61.

Table III—Maximal Electroshock Seizure Test

Compound	Dose, mg/kg	Number of Animals Protected 1 hr	2 hr	3 hr
II*a*	500	0/5	0/5	0/5
II*b*	500	0/5	0/5	0/5
II*c*	500	0/5	0/5	0/5
II*d*	500	0/5	0/5	0/5
II*e*	500	0/5	0/5	0/5
II*f*	500	0/5	0/5	0/5
II*g*	500	0/5	0/5	0/5
II*h*	500	0/5	0/5	0/5
II*i*	500	0/5	0/5	0/5
II*j*	500	0/5	0/5	0/5
III	500	1/5	1/5	—
Diphenylhydantoin	25	5/5	5/5	5/5
Methylcellulose, 0.5%	—	0/5	0/5	0/5

[6] Melting points were determined with a Thomas-Hoover melting-point apparatus and are uncorrected. The structures of the compounds were confirmed by their IR and NMR spectra. IR spectra were obtained on a Beckman IR-8 spectrophotometer. NMR spectra were determined on a Varian A-60A spectrometer, using tetramethylsilane as the internal reference. Microanalyses were performed by Dr. Kurt Eder, Geneva, Switzerland, and PCR, Inc., Gainesville, Fla.

Table IV—Pentylenetetrazol Seizure Threshold Tests

Compound	Dose, mg/kg	Number of Animals Protected		
		1 hr	2 hr	3 hr
II*a*	500	0/5	0/5	0/5
II*b*	500	1/5	0/5	0/5
II*c*	500	0/5	0/5	0/5
II*d*	500	0/5	1/5	0/5
II*e*	500	2/5	2/5	1/5
II*f*	500	0/5	1/5	2/5
II*g*	500	3/5	0/5	1/5
II*h*	500	0/5	1/5	1/5
II*i*	500	1/5	1/5	1/5
II*j*	300[a]	2/5	0/5	0/5
III	500	0/5	0/5	0/5
Phensuximide	200	5/5	4/5	3/5
Methylcellulose, 0.5%	—	0/5	0/5	0/5

[a] Dosage reduced due to small quantity of compound available.

1,2,4-Trimethyl-4-phenyl-3,5-pyrazolidinedione (IV)—*Method A*—To a solution of 1.0 g (5.25 mmoles) of II*f* in 80 ml of 95% ethanol was added 30 ml of 0.5 *M* ethanolic potassium hydroxide followed by 4.0 g (28 mmoles) of methyl iodide. The mixture was stirred at room temperature for 6 hr and then refluxed gently overnight. The solution was neutral to pHydrion paper. Evaporation afforded a residue which was triturated with chloroform and filtered. The filtrate was evaporated to dryness and gave 880 mg of red oil whose TLC [silica gel, ethyl acetate–acetone (4:1)] indicated one intense spot (R_f 0.48) along with three other components. Column chromatography [60 g of silica gel, elution with ethyl acetate–hexane (1:1)] afforded 620 mg (53%) of an oil; IR ($CHCl_3$): 1730 and 1675 cm^{-1}; NMR ($CDCl_3$): δ 1.75 (s, 3, CH_3—C), 3.35 (s, 6, CH_3N), and 7.45–7.75 (m, 5, ArH). The compound could not be induced to crystallize.

Method B—A mixture of 1.0 g (5.3 mmoles) of V and 4.5 g (36 mmoles) of dimethyl sulfate was heated at 140° for 4 hr. The dark-brown liquid was cooled and cautiously hydrolyzed with saturated aqueous sodium carbonate solution overnight. After dilution with 10 ml of water, the mixture was extracted thoroughly with chloroform. The chloroform extract was dried and concentrated to afford 720 mg (62%) of an oil, which was subsequently evaporatively distilled twice *in vacuo* (0.2 mm) at a bath temperature of 80°. The colorless oil so obtained was identical in its spectral and TLC properties with the oil described in *Method A*.

Anal.—Calc. for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.79; H, 6.78; N, 12.68.

3,5-Diacetoxy-1-methyl-4-phenylpyrazole (VI)—To a solution of 1.0 g (5.25 mmoles) of II*f* in 15 ml of dry pyridine was added dropwise 840 mg (10.7 mmoles) of acetyl chloride at room temperature. The mixture was stirred for 10 min and filtered, and the filtrate was diluted with water and extracted with chloroform. The chloroform phase was washed with 5% hydrochloric acid several times, dried, and concentrated to afford 1.0 g (70%) of white solid. Recrystallization from hexane–ethyl acetate gave pure material, mp 122.5–124°; IR ($CHCl_3$): 1780 cm^{-1}; NMR ($CDCl_3$): δ 2.24 (s, 3, CH_3CO), 2.30 (s, 3, CH_3CO), 3.65 (s, 3, CH_3N), and 7.40 (s, 5, ArH); mass spectrum: *m/e* 274 (M^+); UV (ethanol): 237 nm (log ϵ 4.08).

Anal.—Calc. for $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.45; H, 5.20; N, 10.29.

2-Acetyl-1,4-dimethyl-4-phenyl-3,5-pyrazolidinedione (III)—To a solution of 2.6 g (12.7 mmoles) of II*g* in 20 ml of dry pyridine was added 1.0 g of acetyl chloride at ice bath temperature. The solution was stirred with ice bath cooling for 20 min and then allowed to warm to room temperature over 2.5 hr. The mixture was poured onto 100 g of crushed ice and afforded 1.7 g (54%) of a white solid, mp 91–93.5°. Recrystallization from hexane–ethyl acetate gave pure material, mp 91–93°; IR ($CHCl_3$): 1770 and 1715 cm^{-1}; NMR ($CDCl_3$): δ 1.80 (s, 3, CH_3—C), 2.63 (s, 3, CH_3CON), 3.61 (s, 3, CH_3N), and 7.70 (s, 5, ArH).

Anal.—Calc. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.29; H, 5.83; N, 11.54.

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