Synthesis and Anticonvulsant Activity of 2-Aryl-3,4-dialkyltetrahydro-1,3,4-oxadiazines and 2-Aryl-3,4-dialkyltetrahydro-1,3,4-oxadiazin-5-ones

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Several 2-aryl-3,4-dialkyltetrahydro-1,3,4-oxadiazines have been synthesized from 2-(1,2-dialkylhydrazino)ethanol (**2**) and aromatic aldehydes. Also, three 2-aryl-3,4-dialkyltetrahydro-1,3,4-oxadiazin-5-ones were obtained from the reaction of 1,2-dialkylglycolylhydrazine (**5**) and aromatic aldehydes. These compounds exhibited activity in the maximal electroshock seizure test.

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The synthesis and testing of novel anticonvulsants has been a continuing goal in our laboratories [1]. This report describes the synthesis and anticonvulsant testing of several 2-aryl-3,4-dialkyltetrahydro-1,3,4-oxadiazines **3** and 2-aryl-3,4-dialkyltetrahydro-1,3,4-oxadiazin-5-ones **6**. Previously, Kalm [2] obtained variously substituted 5-methyl-6-phenyltetrahydro-1,3,4-oxadiazines having central nervous system depressant, anorectic, hypocholesteremic, and antiinflammatory activity by condensing *N*-amino-β-hydroxy-α-methylphenylethylamines with formaldehyde.

Synthesis of compounds **3** required three steps. Alkylation of 1,2-dialkylhydrazine with ethyl bromoacetate afforded ethyl 1,2-dialkylhydrazinoacetate (**1**). Reduction of **1** with lithium aluminum hydride gave the necessary hydrazinoethanols **2**. Heating equimolar mixtures of **2** and aromatic aldehydes in toluene solution in a Dean Stark apparatus with azeotropic removal of water produced **3** (Scheme I).

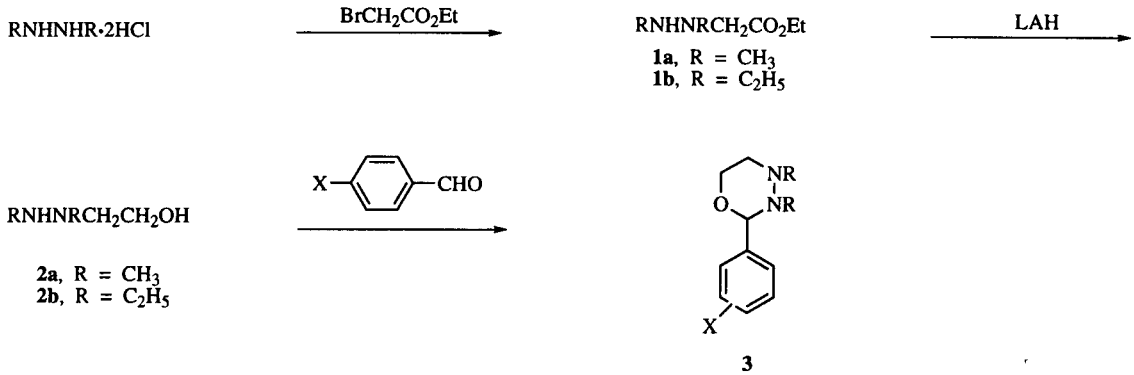
Acylation of 1,2-diethylhydrazine with benzyloxyacetyl chloride gave benzyloxyacetyl 1,2-diethylhydrazine (**4**). Debenzylation of **4** was achieved by catalytic hydrogenation using a palladium on carbon catalyst which produced 1,2-diethylglycolylhydrazine (**5**). Condensation of **5** with aromatic aldehydes (Dean Stark trap) afforded compounds **6** (Scheme II). This latter condensation was extremely slow unless *p*-toluenesulfonic acid was added to the reaction mixture.

The oxadiazines (Table I) were tested in the maximal electroshock seizure and pentylenetetrazole seizure threshold tests for anticonvulsant activity and neurotoxicity in mice by known procedures [3]. In the pentylenetetrazole test, only **6a** and **6c** showed activity at 300 mg/kg but were also toxic. In the maximal electroshock test, **3b**, **3d**, **3g** and **6a-c** exhibited activity at 100 mg/kg without toxicity. Additional testing in the rat (oral) at 50 mg/kg showed activity for **3b**, **3d**, **3g** and **6b** without toxicity. However, in a subsequent attempt to quantitate the activity of **3g**, this result could not be reproduced.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance (nmr) spectra were recorded on a Varian XL-400 spectrometer in chloroform-d, using 1% v/v tetramethylsilane (TMS) as the internal standard. Elemental analyses were performed by Kurt Eder, Geneva, Switzerland and Baron Consulting Company, Orange, Connecticut.

Scheme I



Scheme II

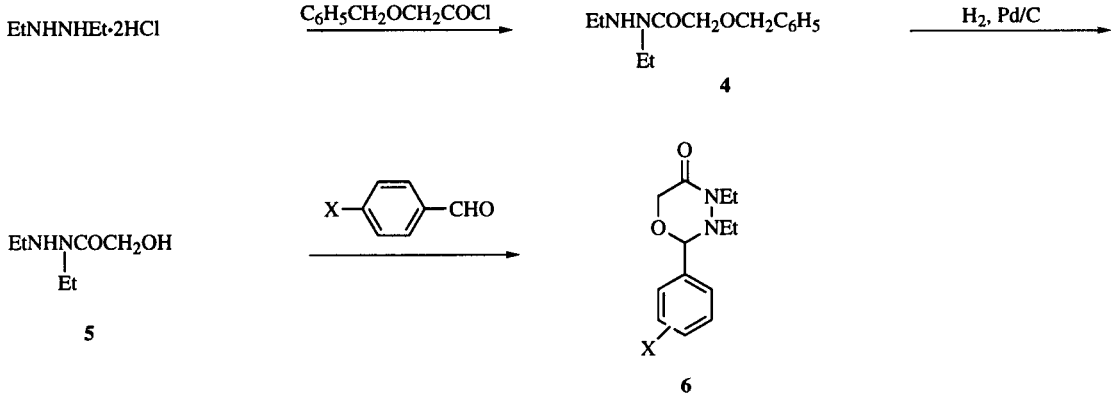


Table I

2-Aryl-3,4-dialkyl-1,3,4-oxadiazines

Compound	R	X	BP °C/ mmHg	^{1}H nmr, δ OCHN	Yield %	Analysis, % Calcd./Found C	H	N
3a	CH_3	*p*-CH_3	78/0.03	5.63	73	69.87 69.49	8.80 8.60	13.58 13.24
3b	CH_3	*m*-CF_3	67/0.03	5.68	82	55.38 54.99	5.81 5.79	10.76 10.56
3c	CH_3	*p*-NO_2	98-99 [a]	5.68	68	55.69 55.54	6.37 6.70	17.71 17.39
3d	C_2H_5	H	73/0.1	5.68	80	70.87 70.53	9.15 9.55	12.72 12.82
3e	C_2H_5	*p*-CH_3	77/0.04	5.66	77	71.76 71.94	9.46 9.15	11.95 11.59
3f	C_2H_5	*p*-Cl	108/0.05	5.63	80	61.29 60.95	7.52 7.71	11.00 10.96
3g	C_2H_5	*m*-CF_3	75/0.05	5.68	76	58.32 58.00	6.64 6.37	9.72 9.45
6a	C_2H_5	H	97/0.03	5.58	75	66.64 66.52	7.74 8.00	11.96 11.64
6b	C_2H_5	*p*-CH_3	110/0.2	5.55	69	67.72 67.76	8.12 8.17	11.28 11.17
6c	C_2H_5	*m*-CF_3	103/0.02	5.61	74	55.63 55.74	5.67 5.68	9.27 8.99

[a] Melting point, from hexane.

Ethyl 1,2-Diethylhydrazinoacetate (**1b**).

A solution of 41.7 g (0.25 mole) of ethyl bromoacetate in 42 ml of benzene was added in one hour dropwise with stirring (magnetic) and cooling (25-30°) to 44g (0.5 mole) of 1,2-diethylhydrazine [4] in 125 ml of dry benzene. The mixture was refluxed on a steam bath for 2 hours and stored in a refrigerator overnight. The benzene layer was decanted and the precipitate was washed twice with benzene and the solvents were evaporated under reduced pressure. The residue was distilled and afforded 4.5 g (70%) of colorless oil, bp 94° (22 mm Hg); ^{1}H nmr (deuteriochloroform): δ 1.04 (t, 3H, $NCCH_3$), 1.10 (t, 3H, $NCCH_3$), 1.28 (t, 3H, $OCCH_3$), 2.71-2.94 (m, 4H, NCH_2), 3.12 (s, 1H, NH), 3.52 (s, 2H, $CH_2C{=}O$), 4.18 (q, 2H, OCH_2).

Anal. Calcd. for $C_8H_{18}N_2O_2$: C, 55.15; H, 10.41; N, 16.08. Found: C, 55.36; H, 10.43; N, 16.01.

A picrate was made, mp 104-105° (absolute ethanol).

Anal. Calcd. for $C_{14}H_{21}N_5O_9$: C, 41.69; H, 5.25; N, 17.36. Found: C, 41.83; H, 5.33; N, 17.59.

2-(1,2-Diethylhydrazino)ethanol (**2b**).

A solution of 20.2 g (0.116 mole) of **1b** in 75 ml of anhydrous ether was added dropwise to 4.39 g (0.116 mole) of lithium aluminum hydride in 175 ml of ether and the mixture was refluxed for 12 hours. The complex was decomposed with 40% aqueous potassium hydroxide (cooling), the ether decanted and the salts extracted three times with ether. The combined ether solution was dried over magnesium sulfate, filtered and the solvent was distilled at atmospheric pressure. The remaining residue was distilled and gave 12.0 g (78%) of a colorless liquid, bp 81° (13 mm); ^{1}H nmr (deuteriochloroform): δ 1.08 (t, 3H, $NCCH_3$), 1.09 (t, 3H, $NCCH_3$), 2.64 (t, 2H, NCH_2), 2.69 (q, 2H, NCH_2), 2.84 (q, 2H, NCH_2), 3.81 (t, 2H, OCH_2).

Anal. Calcd. for $C_6H_{16}N_2O$: C, 54.51; H, 12.20. Found: C, 54.54; H, 12.20.

A picrate was prepared, mp 81.5-82.5 (absolute ethanol).

Anal. Calcd. for $C_{12}H_{19}N_5O_8$: C, 39.89; H, 5.30; N, 19.38. Found: C, 39.95; H, 5.21; N, 19.35.

Ethyl 1,2-Dimethylhydrazinoacetate (**1a**).

To a mixture of 20.0 g (0.15 mole) of 1,2-dimethylhydrazine

dihydrochloride and 37.8 g (0.45 mole) of sodium bicarbonate in 41 ml of dimethylformamide and 150 ml of toluene was added dropwise 25.1 g (0.15 mole) of ethyl bromoacetate over 1 hour. The stirred (magnetic) mixture was heated at 80-90° for 9 hours (carbon dioxide evolution). Water (35 ml) was added and the toluene layer was separated and washed with 50 ml of saturated sodium chloride solution. The combined salt-saturated aqueous phase was extracted four times with 50 ml portions of toluene, and the combined toluene extracts were dried over magnesium sulfate. After removal of the toluene under reduced pressure, the residue was distilled and gave 9.04 g (41%) of colorless liquid, bp 76-78° (14 mm); ^{1}H nmr (deuteriochloroform): δ 1.29 (t, 3H, C-CH_3), 2.56 (s, 3H, NCH_3), 2.63 (s, 3H, NCH_3), 2.84 (s, 1H, NH), 3.48 (s, 2H, NCH_2), 4.19 (q, 2H, OCH_2).

2-(1,2-Dimethylhydrazino)ethanol (**2a**).

This compound was prepared from 9.04 g (0.0619 mole) of **1a** and 4.0 g (0.106 mole) of lithium aluminum hydride in 110 ml of anhydrous ether similar to the method used for **2b**. After workup, the residue was distilled and afforded 4.5 g (70%) of a colorless oil, bp 72° (15 mm); ^{1}H nmr (deuteriochloroform): δ 2.50 (s, 3H, NCH_3), 2.59 (s, 3H, NCH_3), 2.64 (t, 2H, NCH_2), 3.81 (t, 2H,OCH_2).

1,2-Diethylglycolylhydrazine (**5**).

To a mixture of 10.5 g (0.065 mole) of 1,2-diethylhydrazine dihydrochloride in 50 ml of dry pyridine was added dropwise 12.0 g (0.065 mole) of benzyloxyacetyl chloride with intermittent cooling. The mixture was stirred at room temperature for 30 minutes, heated at 60-70° for 2.5 hours, poured into 300 ml of water and extracted twice with toluene (100 ml, 60 ml). The toluene layer was washed with 40 ml of 5% sodium carbonate solution and the aqueous phase was backwashed with toluene (20 ml). The combined toluene extracts were dried (magnesium sulfate) and evaporated under reduced pressure. The residue was freed from pyridine by repeated evaporations with toluene leaving 11.6 g of **4** as a pale yellow oil.

A solution of the above oil in 100 ml of glacial acetic acid was treated with 800 mg of 10% palladium on carbon catalyst and the mixture was hydrogenated in a Parr apparatus for 6.5 hours. The catalyst was filtered and the filtrate was evaporated under reduced pressure. Toluene was added and the evaporation was repeated. The residue was covered with a mixture of ether and tetrahydrofuran (80:20) and neutralized with solid sodium carbonate. The separated solvent layer was dried (magnesium sulfate), filtered and evaporated under reduced pressure. The residue was distilled and gave 4.52 g (48%) of a colorless oil, bp 68° (0.2 mm); ^{1}H nmr (deuteriochloroform): δ 1.07 (t, 3H, CH_3), 1.17 (t, 3H, CH_3), 2.80-2.95 (m, 2H, NCH_2), 3.21-3.55 (broad s, 1H, NH), 3.56-3.78 (q, 3H, NCH_2, OH), 4.31 (s, 2H, OCH_2).

Anal. Calcd. for $C_6H_{14}N_2O_2$: C, 49.30; H, 9.65; N, 19.16. Found: C, 49.58; H, 9.99; N, 18.83.

General Procedure for the Synthesis of 2-Aryl-3,4-dialkyl-1,3,4-oxadiazines **3a-g** and **6a-c**.

An equimolar mixture (0.010-0.013 mole) of the aromatic aldehyde and dialkylhydrazinoethanol or dialkylglycolylhydrazine was heated under reflux in toluene (25-40 ml) with azeotropic removal of the water formed using a Dean-Stark trap. The reflux was continued until the theoretical quantity of water was collected. For compounds **3d** and **6a-c**, 100 mg of *p*-toluenesulfonic acid hydrate was also added to the reaction mixture. After heating, the acid was removed by washing the toluene solution with 5% aqueous sodium carbonate. The toluene solution was dried over magnesium sulfate and evaporated under reduced pressure. The remaining residue was then distilled (see Table I for physical properties).

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REFERENCES AND NOTES

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