Milton J. Kornet and George Shackleford

Division of Pharmaceutical Sciences, College of Pharmacy,
University of Kentucky, Lexington, Kentucky 40536-0082

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Microwave irradiation of 1(2*H*)-phthalazinone with benzyl halides and potassium carbonate in dimethylformamide afforded 2-benzyl-1(2*H*)phthalazinones in modest yields. These products were tested in mice and rats in maximal electroshock and pentylenetetrazole seizure models for anticonvulsant activity, and in the rotorod test for neurotoxicity. A majority of the compounds exhibited anticonvulsant protection. The *p*-aminobenzyl analog **1f** was the most active compound in the maximal electroshock assay; it's ED_{50} value was 19.46 mg/kg and the TD_{50} was 61.35 mg/kg. In the rat, the values were 3.71 mg/kg and >125 mg/kg, respectively.

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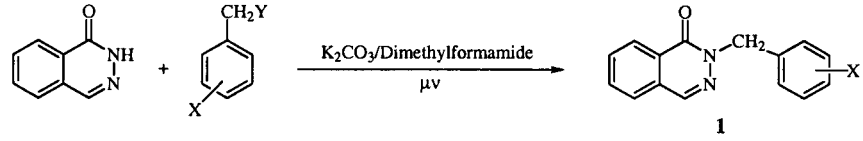
In our last report, which represents part of a continuing search for novel anticonvulsant agents, the synthesis and evaluation of a series of 3-benzyl-1,2,3-benzotriazin-4(3*H*)-ones [1] was described. Several analogs showed protection against seizures in mice and we have therefore extended this investigation to the preparation and testing of a series of isosteric 2-benzyl-1(2*H*)-phthalazinones (**1**). Many phthalazines exhibit biological activity and some are used as drugs [2]. A series of 2,4,8-trisubstituted 1(2*H*)-phthalazinones although atoxic were inactive in screening tests for cardiovascular, renal and central nervous system effects; inactivity was ascribed to the relative insolubility of the compounds [3].

Microwave irradiation of a mixture of 1(2*H*)-phthalazinone, benzyl halide (chloride or bromide), and potassium carbonate in dry dimethylformamide afforded 2-benzyl-1(2*H*)-phthalazinones **1a** in moderate yields (Scheme I) (Table I). An attempt to alkylate 1(2*H*)-phthalazinone with



Y = Cl, Br

1

X, see Table 1

Table 1

2-Benzyl-1(2*H*)-phthalazinones

Compound	X	MP °C	^{1}H NMR[a]	Yield, %	Analysis, % Calcd./Found C	H	N
1a	H	106.5-107.5 [b] [c]	H-4 8.18, CH_2 5.41	33			
1b	2-Cl	153-155 [d]	H-4 8.19, CH_2 5.56	57	66.55	4.10	10.35
					66.50	3.99	10.37
1c	2-F	116-116.5 [e]	H-4 8.17, CH_2 5.50	59	70.86	4.36	11.02
					70.99	4.15	11.10
1d	2-CH_3	147-147.5 [f]	H-4 8.17, CH_2 5.44	64	76.78	5.64	11.19
					76.60	5.74	11.34
1e	4-NO_2	187-188 [d]	H-4 8.18, CH_2 5.47	59	64.05	3.94	14.94
					63.90	4.02	14.63
1f	4-NH_2	172-173.5 [d]	H-4 8.13, CH_2 5.28	69	71.70	5.21	16.72
					71.59	5.46	16.74
1g	3,4-Cl	128 [g]	H-4 8.18, CH_2 5.34	40	59.04	3.30	9.18
					59.16	2.99	9.28
1h	2-Cl,6-F	194.5-195 [d]	H-4 8.08, CH_2 5.59	65	62.40	3.49	9.70
					62.14	3.49	9.83
1i	2,6-F	159.5-160 [h]	H-4 8.12, CH_2 5.52	62	66.18	3.70	10.29
					65.86	3.63	10.38
1j	3,4-F	107.5-108.5 [i]	H-4 8.17, CH_2 5.33	57	66.18	3.70	10.29
					66.00	3.51	10.40
1k	3,5-F	111.5-112 [j]	H-4 8.18, CH_2 5.36	53	66.18	3.70	10.29
					66.02	3.47	10.38

[a] All ^{1}H NMR signals are singlets. [b] Reference [4] reported mp 107°. [c] 70% Ethanol. [d] 95% Ethanol. [e] Hexane-toluene. [f] Hexane. [g] Ligroine (bp 66-75°)-toluene. [h] 50% Ethanol. [i] 75% Ethanol. [j] 60% Ethanol.

3-picolyl chloride hydrochloride and excess potassium carbonate failed. Compound **1a** was previously made by others [4] by decarboxylation of the corresponding 4-carboxylic acid. Compound **1f** was obtained by the catalytic reduction of the nitrobenzylphthalazinone **1e**. A comparison of the chemical shift difference for the methylene protons singlet in the benzylbenzotriazepinones [1] and the benzylphthalazinones (among 2-benzyl, 2-chlorobenzyl and 2-methylbenzyl compounds) shows a fairly constant value of 0.22-0.23 with the benzylbenzotriazepinones displaying the more downfield chemical shift values.

The anticonvulsant activity of all of the compounds in Table I except **1e** against maximal electroshock and subcutaneous pentylenetetrazol induced seizures was determined [5-7]. Compounds **1a, 1c,** and **1d** were active in the subcutaneous pentylenetrazol test at a dose of 100 mg/kg at 0.5 hour, while **1f** and **1i** were active at 30 mg/kg at 0.5 hour. Compound **1f** at 100 mg/kg also showed protection at 4 hours. Compounds **1a, 1c, 1f** and **1i** were active in the maximal electroshock test at 30 mg/kg at 0.5 hour, whereas **1b** was active at 100 mg/kg at 0.5 hour. Compound **1f** also showed activity at 100 mg/kg at 4 hours.

Quantification of anticonvulsant activity was carried out for **1a, 1c** and **1f**. Compound **1a** exhibited (in rat) maximal electroshock ED_{50} of 10.80 mg/kg, pentylenetetrazol ED_{50} >150 mg/kg and TD_{50} >300 mg/kg. Compound **1c** (in mice) has a maximal electroshock ED_{50} of 33.99 mg/kg, pentylenetetrazol ED_{50} of 47.95 and TD_{50} of 296.21 mg/kg. The most active compound **1f** displayed maximal electroshock ED_{50} equal to 19.46 mg/kg, pentylenetetrazol ED_{50} equal to 60.51 mg/kg, and TD_{50} equal to 61.35 mg/kg in mice, whereas the values were 3.71 mg/kg, >250 mg/kg and >125 mg/kg, respectively, in the rat.

EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Nuclear magnetic resonance (nmr) spectra were recorded on a Varian VXR-300 MHz spectrometer in chloroform-d, using 1% v/v tetramethylsilane as the internal standard. Microwave irradiation was conducted in a commercial Samsung MW5351G 800 watt microwave oven at full power. Elemental analyses were performed by Baron Consulting Company, Orange, Connecticut.

2-Benzyl-1(2*H*)-phthalazinones **1a-1k.**

The preparation of **1d** is representative of the alkylation method.

2-(2-Methylbenzyl)-1(2*H*)-phthalazinone (**1d**).

A mixture of 1.46 g (0.01 mole) of 1-(2*H*)-phthalazinone, 1.41 g (0.01 mole) of 2-methylbenzyl chloride and 1.67 g (0.0121 mole) of potassium carbonate in 15 ml of dry dimethylformamide was irradiated six times for 1.5 minutes (intermediate time 3 minutes). The mixture was cooled for 20 minutes and poured into 125 ml of water. The resulting white precipitate was filtered and dried. Recrystallization from hexane afforded 1.59 g (63%) of a fluffy white solid, mp 147-147.5°.

For benzyl bromides, seven irradiations for one minute (intermediate time 3 minutes) were used.

3-(4-Aminobenzyl)-1(2*H*)-phthalazinone (**1f**).

A mixture of 810 mg (2.88 mmoles) of **1e**, 150 mg of 5% palladium on carbon catalyst, 75 ml of ethyl acetate and 75 ml of absolute ethanol was hydrogenated in a Parr pressure reaction apparatus at an initial hydrogen pressure of 50 psi. After 3.5 hours the reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was recrystallized from 95% ethanol and produced 500 mg (69%) of a pale yellow solid, mp 164.5-165.5°.

A subsequent reduction of 3.16 g of **1e** with 345 mg of 10% Pd/C in 225 ml of ethyl acetate for 7.5 hours gave 2.23 g (79%) of **1f**, mp 165-167°.

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