

Milton J. Kornet

Division of Medicinal Chemistry and Pharmaceutics, College of Pharmacy,
University of Kentucky, Lexington, Kentucky 40536-0082

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Several 3-benzyl-1,2,3-benzotriazin-4(3H)-ones **1** were prepared by alkylation of 1,2,3-benzotriazin-4(3H)-one with benzyl halides in dimethylformamide in a microwave oven in moderate yields. Accompanying **1** were minor amounts of products believed to be the *O*-alkylated derivatives. Support for 3-benylation is shown by an alternate synthesis of **1a** from *o*-amino-*N*-benzylbenzamide by nitrous acid cyclization. The title compounds were evaluated in mice and rats in maximal electroshock (MES) and pentylenetetrazole (scMet) seizure models for anticonvulsant activity, and in the rotorod test for neurotoxicity. They were generally non-toxic. The 3-benzyl analog was the most active (maximal electroshock) compound; its maximal electroshock ED₅₀ value was 93 mg/kg (mouse).

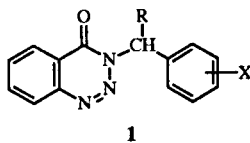
J. Heterocyclic Chem., **34**, 1391 (1997).

Anticonvulsant activity has been found in numerous quinazolines [1-6] synthesized in our laboratories. Since quinazolin-4(3H)-ones and 1,2,3-benzotriazin-4(3H)-ones are isosteric and because others [7-9] have reported that 3-substituted-1,2,3-benzotriazin-4(3H)-ones **1** possess central nervous system activity other than anticonvulsant activity, it was deemed worthwhile to prepare a series of 3-benzyl-1,2,3-benzotriazin-4(3H)-ones **1** and evaluate their anticonvulsant activity and neurotoxicity.

The microwave accelerated alkylation of NH acidic heterocycles on a solid support (silica or alumina) [10] or in dry media [11] occurs rapidly and in high yields.

However, we elected to effect alkylation in solution. Thus, microwave irradiation (~ 5 minutes) of a mixture of 1,2,3-benzotriazin-4(3H)-one, benzyl chloride, and potassium carbonate in dry dimethylformamide afforded the desired 3-*N*-benzyl product **1a** in 71% yield (Scheme 1). Other analogs **1b-1g** were obtained in a similar manner, Table I. The alkylation product was accompanied by a minor amount of a second component assumed to be the corresponding *O*-alkylation derivative [12]. Compound **1a** [9] was independently prepared by treatment of *o*-amino-*N*-benzylbenzamide **2a** [13] with nitrous acid at 0°. A comparison of the nmr spectra showed that

Table 1
3-Benzyl-1,2,3-benzotriazin-4(3H)-ones

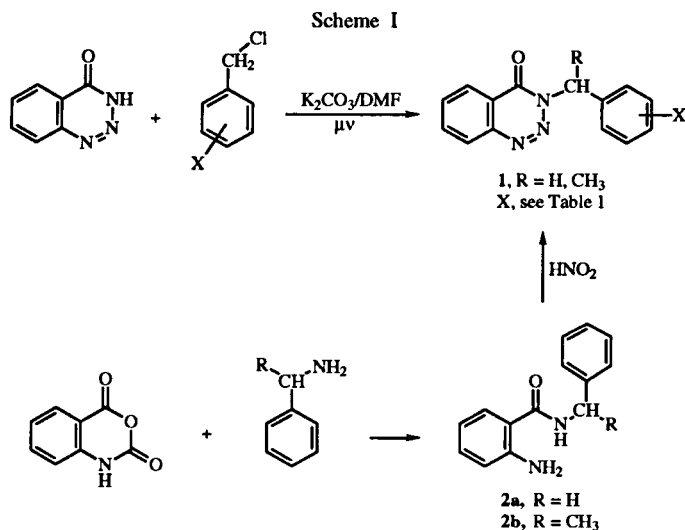


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Compound	R	X	MP °C	¹ H NMR, CHN [a]	Yield %	Analysis, % Calcd./Found		
						C	H	N
1a	H	H	116.5-118 [b]	5.64 (s)	71	71.70	5.21	16.72
1b	H	2-CH ₃	114-115.5	5.66 (s)	55	71.37	5.55	16.90
1c	H	2-Cl	120-121	5.79 (s)	71	61.89	3.71	15.46
1d	H	4-Cl	130-131 [c]	5.60 (s)	52	61.89	3.71	15.46
1e	H	4-CH ₃ O	120-121	5.57 (s)	63	61.64	3.93	15.69
1f	H	2,3-Cl ₂	132-133	5.79 (s)	67	67.41	4.90	15.72
1g	H	2,5-(CH ₃) ₂	135-135.5	5.63 (s)	69	67.09	5.09	15.90
1h [d]	CH ₃	H	75-76	6.45 (q)	75	54.93	2.96	13.72
						54.82	3.07	13.98
						72.43	5.70	15.84
						72.22	5.96	16.11
						71.70	5.21	16.72
						71.42	5.46	17.00

[a] s = singlet, q = quartet. [b] Reference [13] reported mp 115°. [c] Purified by chromatography on silica gel 60, EM Reagents; elution with toluene-ethyl acetate (6:1). [d] Obtained by nitrous acid cyclization of **2b**.

the alkylation product was identical to the product obtained by nitrous acid cyclization. Nitrous acid cyclization was also utilized to prepare **1h** which contains an α -methylbenzyl group at the 3-position of 1,2,3-benzotriazinone (Scheme I).



Compounds **1a-1h** were tested in the maximal electroshock seizure and pentylenetetrazole seizure threshold tests for anticonvulsant activity and neurotoxicity in mice according to methods previously described [4]. Compounds **1c**, **1d** and **1e** were inactive in both tests up to the highest tested dose (all doses in mg/kg) of 300. Compounds **1b**, **1f** and **1h** were active in the maximal electroshock test at 300; all three were inactive in the scMet test and **1h** also showed toxicity at this dose. Compound **1g** was active against maximal electroshock at 100 but also toxic at 100. Compound **1a** exhibited maximal electroshock activity at 100 and polyethylenetetrazole activity at 300 with no toxicity up to 300. Further quantitative testing of **1a** indicated a maximal electroshock ED₅₀ of 93 and a pentylenetetrazole ED₅₀ of 140; TD₅₀ >500. Compound **1f** showed a maximal electroshock ED₅₀ of 295 and TD₅₀ >500. Additionally, both **1a** and **1f** were maximal electroshock active in the rat (oral) at 30 with no toxicity.

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.

3-Benzyl-1,2,3-benzotriazin-4(3H)-ones **1a-1g**.

The preparation of **1a** is representative of the alkylation procedure.

3-Benzyl-1,2,3-benzotriazin-4(3H)-one (**1a**).

A 250 ml Erlenmeyer flask containing a mixture of 1.47 g (0.01 mole) of 1,2,3-benzotriazin-4(3H)-one, 1.27 g (0.01 mole) of benzyl chloride, 1.67 g (0.0121 mole) of potassium carbonate and 15 ml of dimethylformamide (dried over molecular sieves) was irradiated four times for 2, 1, 1, and 1.5 minutes (intermediate time 3 minutes). The oven also contained 300 ml of diethylene glycol equally divided in two Erlenmeyer flasks to absorb excess radiation. After cooling, the mixture was poured into 125 ml of water and the precipitate was filtered, washed with water and dried. Recrystallization from aqueous ethanol gave 1.69 g (71%) of pale yellow needles, mp 116.5-118° (lit [13] mp 115°); ¹H nmr (deuteriochloroform): δ 5.64 (s, 2H, NCH₂), 7.27-8.37 (m, 9H, ArH).

o-Amino-*N*-benzylbenzamide (**2a**).

A solution of 2.25 g (0.021 mole) of benzylamine in 4 ml of dimethylformamide was added to a stirred solution of 3.26 g (0.020 mole) of isatoic anhydride in 10 ml of dimethylformamide maintained at 45-50°. Stirring and heating were continued for 3 hours. The cooled mixture was poured into water (100 ml), basified to pH 9 with 50% sodium hydroxide, filtered and washed well with water. The dried grey-colored solid amounted to 4.12 g (91%), mp 123.5-124.5° (lit [13] mp 120-122°).

3-Benzyl-1,2,3-benzotriazepin-4(3H)-one (**1a**).

By Nitrous Acid Cyclization of **2a**.

A solution of 0.822 g (0.0119 mole) of sodium nitrite in 4 ml of water was added dropwise over 15 minutes to a stirred suspension of 2.26 g (0.01 mole) of **2a** in 17 ml of 2*N* hydrochloric acid at 0°. The cooling bath was removed and the mixture was stirred at room temperature for 4 hours. The cream-colored precipitate was filtered and washed with water. Recrystallization from aqueous ethanol (charcoal) afforded 1.69 g (71%) of white crystals, mp 117-118° (lit [13] mp 115°). The nmr was identical to the product **1a** obtained by alkylation described above.

o-Amino-*N*-(1-phenylethyl)benzamide (**2b**).

This compound was prepared by a method similar to that used for **2a** from 3.26 g (0.02 mole) of isatoic anhydride and 2.54 g (0.021 mole) of 1-phenylethylamine in 14 ml of dimethylformamide. Workup gave 4.1 g (85%) of a grey solid, mp 113-113.5; ¹H nmr (deuteriochloroform): δ 1.57 (d, 3H, CH₃), 4.70-5.70 (m, 3H, CH and NH₂), 6.18-6.38 (broad d, 1H, CONH), 6.59-6.70 (m, 2H, ArH), 7.15-7.42 (m, 7H, ArH).

3-(1-Phenylethyl)-1,2,3-benzotriazin-4(3H)-one (**1h**).

This compound was obtained by a diazotization procedure similar to that used for **1a** from 1.5 g (6.25 mmole) of **2b** suspended in 10.6 ml of 2*N* hydrochloric acid and a solution of 0.514 g (7.45 mmoles) of sodium nitrite in 2.5 ml of water at 0°. Workup and recrystallization from aqueous ethanol (charcoal) produced 1.17 g (75%) of a white solid (2 crops), mp 75-76°; ¹H nmr (deuteriochloroform): δ 2.04 (d, 3H, CH₃), 6.45 (q, 1H, CH), 7.23-8.38 (m, 9H, ArH).

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