Synthesis and Anticonvulsant Activity of 3-Alkyl-3,4-dihydro-2(1*H*)-quinazolinones

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Previously we reported the potent anticonvulsant activity of 3-dimethylamino-3,4-dihydro-2(1*H*)-quinazolinone. In this report, a series of 3-alkyl-3,4-dihydro-2(1*H*)-quinazolinones was synthesized in three steps from isatoic anhydrides or an anthranilic acid. Structure/activity investigations revealed optimal activity for the 3-isopropyl and 3-cyclohexyl analogs. These compounds were effective against seizures induced by maximal electroshock.

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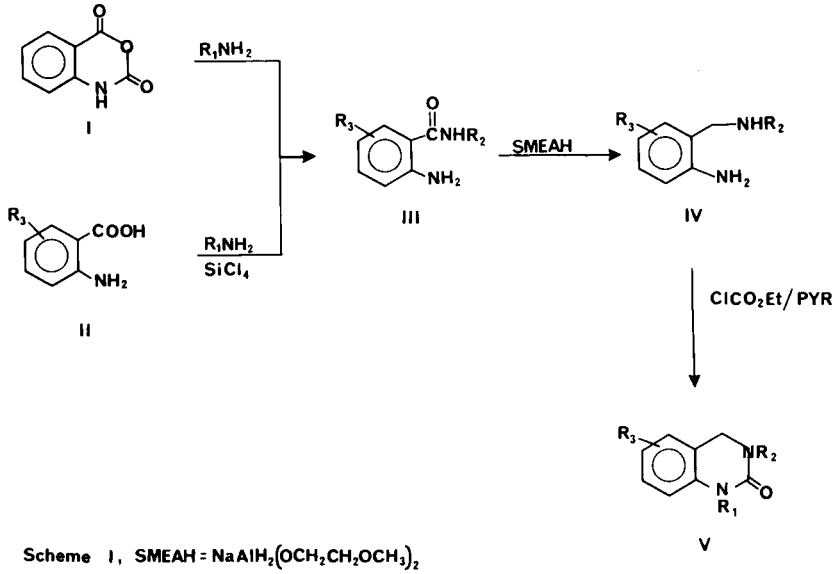
In an earlier paper [1] we reported the synthesis and anticonvulsant activity of a series of 3-amino-3,4-dihydro-2(1*H*)-quinazolinones. The 3-dimethylamino analog **V** [R_1, R_3 = H, R_2 = $N(CH_3)_2$] exhibited an MES ED_{50} of 24 mg/kg and a TD_{50} of 58 mg/kg. These promising results led us to consider quinazolinones **V** with R_2 = alkyl and cycloalkyl. Such compounds may be considered as isosteric [2] equivalents of the 3-amino-3,4-dihydro-2(1*H*)-quinazolinones. A literature survey showed that the only known quinazolinones **V** with 3-alkyl groups were the 3-methyl [3] and 3-ethyl [4] compounds. In this report, we are communicating the synthesis and anticonvulsant activity of a series of 3-alkyl-3,4-dihydro-2(1*H*)-quinazolinones **V**. Compound **Vh** is also included and differs from the other members in that it is 1,3-dialkylated.

A three step synthesis starting from isatoic anhydride (**I**) was utilized for the preparation of **Va-e**. The anthranilamides **III** obtained by reaction of isatoic anhydride with an amine were reduced with sodium bis(2-methoxyethoxy)-aluminum hydride (SMEAH) to the *o*-aminobenzylamines **IV**. Compounds **IV** were then cyclized to the quinazolinones **V** by means of ethyl chloroformate/pyridine [1] except that carbonyldiimidazole [5] was used to obtain **Va** (Scheme I). Because of the unavailability of aromatic ring methylated isatoic anhyrides, an alternate reaction for the first step of the synthesis was used for **Vf** and **Vg**. The requisite anthranilamides **IIIf-g** were obtained by condensing anthranilic acids **II** with aliphatic amines by means of silicon tetrachloride [6-8] (Scheme I). Compound **Vh** was synthesized *via* sodium hydride promoted alkylation of **Va** with *o*-fluorobenzyl chloride.

The quinazolinones (Table I) were tested in the maximal electroshock (MES) seizure and pentylenetetrazol (sc Met) seizure threshold tests for anticonvulsant activity and neurotoxicity in mice by known methods [9]. In the MES test, compounds **Vc** and **Ve** showed activity at 100 mg/kg at 30 minutes with no toxicity. Compounds **Va**, **Vb**, **Vd** and **Vf** showed activity at 100 mg/kg at 30 minutes but were toxic



Scheme I, SMEAH = $NaAlH_2(OCH_2CH_2OCH_3)_2$

Table I
Physical Properties of 3,4-Dihydro-2(1*H*)-quinazolinones

Compound	R_1	R_2	R_3	Melting Point, °C	Yield %	Formula	Analysis, % Calcd./Found C	H	N
Va	H	CH_3	H	200-203 [a]	46	$C_9H_{10}N_2O$			
Vb	H	C_2H_5	H	146-147 [b]	61	$C_{10}H_{12}N_2O$			
Vc	H	$(CH_3)_2CH$	H	171.5-172 [c]	63	$C_{11}H_{14}N_2O$	69.45	7.42	14.72
							69.74	7.41	14.92
Vd	H	*c*-C_5H_9	H	156-158 [c]	75	$C_{13}H_{16}N_2O$	72.19	7.46	12.95
							72.25	7.33	12.93
Ve	H	*c*-C_6H_{11}	H	189-191 [c]	63	$C_{14}H_{18}N_2O$	73.01	7.88	12.16
							73.30	7.76	12.42
Vf	H	$CH_3(CH_2)_2$-	8-CH_3	111-112 [d]	59	$C_{12}H_{16}N_2O$	70.56	7.90	13.71
							70.66	8.18	13.80
Vg	H	*c*-C_6H_{11}	6-CH_3	193-195 [c]	61	$C_{15}H_{20}N_2O$	73.74	8.25	11.46
							73.84	8.49	11.53
Vh	*o*-$FC_6H_4CH_2$	CH_3	H	121-122 [e]	88	$C_{16}H_{15}FN_2O$	71.10	5.59	10.36
							71.15	5.32	10.57

[a] Reference [3] reported mp 198-202. [b] Reference [4] reported mp 146-148. [c] Aqueous ethanol. [d] Petroleum ether (bp 35-56°)-hexane. [e] Toluene-hexane.

at this dose. Compound **Vh** exhibited activity at 300 mg/kg (30 minutes, no toxicity). In the sc Met test, **Vb** and **Vf** were active at 100 mg/kg but also toxic. Compounds **Va, Vc, Vd, Ve,** and **Vh** were active at 300 mg/kg and with the exception of **Ve** also toxic.

The single inactive compound (300 mg/kg) in both tests was **Vg**. Compound **Vc** was submitted for Phase II testing and exhibited an MES ED_{50} value of 32 mg/kg, sc Met ED_{50} value of 72 mg/kg and TD_{50} value of 78 mg/kg. This compound, therefore, shows activity and toxicity comparable to that of the isosteric 3-dimethylamino-3,4-dihydro-2(1*H*)-quinazolinone [1].

EXPERIMENTAL

Melting points were determined on either a Thomas-Hoover or Fisher-Johns melting point apparatus and are uncorrected. The ir spectra were taken on a Perkin-Elmer 1430 spectrophotometer as liquid films or potassium bromide pellets. The nmr spectra were recorded on a Varian XL-200 spectrometer using tetramethylsilane as the internal reference. Mass spectra were obtained on an RMU-7 double focusing spectrometer by Hitachi/Perkin-Elmer. Elmental analyses were performed by Baron Consulting Co., Orange, CT.

N-Cyclopentylanthranilamide (**IIId**).

A solution of 9.37 g (0.11 mole) of cyclopentylamine in 15 ml of methylene chloride was added dropwise to 8.15 g (0.05 mole) of isatoic anhydride in 45 ml of methylene chloride with stirring (magnetic). After standing overnight, chloroform was added to attain solution. The organic phase was washed twice with 60 ml of 5% sodium carbonate solution. The aqueous phase was extracted with chloroform and the combined organic phase was dried (magnesium sulfate). The solvent was evaporated at reduced pressure and the solid residue was recrystallized from toluene and afforded 8.31 g (81%) of a white solid, mp 157-158°; ^{1}H nmr (deuteriochloroform): δ 1.3-2.25 (m, 8H), 4.2-4.5 (m, 1H), 4.8-6.3 (two broad s, 3H), 6.45-6.8 (m, 2H), 7.0-7.4 (m, 2H).

N-(*o*-Aminobenzyl)cyclopentylamine (**IVd**).

To a stirred mixture of 50 ml of 70% sodium bis(2-methoxyethoxy)aluminum hydride in toluene and 50 ml of toluene was added 4.5 g (0.022 mole) of **IIId** portionwise over a period of 15 minutes. The mixture was refluxed overnight, cooled to room temperature, and added dropwise to 80 ml of a stirred, cooled solution of 20% sodium hydroxide. The organic layer was separated and the aqueous layer was extracted twice with toluene. The combined toluene extract was dried (magnesium sulfate) and concentrated to 4.17 g of oily diamine which was used directly in the next step.

3-Cyclopentyl-3,4-dihydro-2(1*H*)-quinazolinone (**Vd**).

To a stirred and ice-bath cooled solution of 4.17 g (0.0219 mole) of the above oily diamine in 20 ml of dry pyridine was added dropwise 2.73 g (0.0252 mole) of ethyl chloroformate. The mixture was stirred overnight at room temperature and then refluxed for 24 hours (nitrogen atmosphere). The reaction mixture was poured into 100 ml of ice-water and gave a yellow solid which was filtered and washed well with water. Recrystallization from aqueous ethanol afforded 3.56 g (75%) of golden cyrstals, mp 156-158°; ^{1}H nmr (deuteriochloroform): δ 1.54-1.98 (m, 8H), 4.32 (s, 2H), 4.86-5.04 (m, 1H), 6.74-7.22 (m, 4H), 8.50-8.76 (m, 1H).

2-Amino-3-methyl-*N*-propylbenzamide (**IIIf**).

A solution of 4.54 g (0.03 mole) of 2-amino-3-methylbenzoic acid, 2.13 g (0.036 mole) of propylamine and 80 ml of pyridine was cooled in an ice-water bath. Silicon tetrachloride (6.1 g, 0.036 mole) was added dropwise with stirring (magnetic) over 30 minutes under nitrogen. After stirring at room temperature for 2 hours, the mixture was refluxed for 6.25 hours. The mixture was

poured onto ice with stirring and evaporated *in vacuo* to remove the pyridine as a pyridine-water azeotrope. Water was added and the mixture was evaporated *in vacuo* a second time. The residue (hydrochloride salt of the product) was basified with aqueous sodium carbonate solution and extracted three times with ether in a separatory funnel. Care was exercised to exclude the heavier silica particles each time. The combined ether extracts were dried (magnesium sulfate) and evaporated yielding 3.76 g (65%) of product, mp 99-101°; ^{1}H nmr (deuteriochloroform): δ 0.90-1.1 (t, 3H), 1.45-1.76 (m, 2H), 2.17 (t, 3H), 3.38 (q, 2H), 5.0-5.89 (broad s, 2H), 5.90-6.27 (broad s, 1H), 6.60 (t, 1H), 7.03-7.32 (dd, 2H). Because filtration of silica is avoided, this procedure is simpler than the one previously reported [8].

2-Amino-5-methyl-*N*-cyclohexylbenzamide (**IIIg**).

This compound was prepared similarly to **IIIf** from 4.54 g (0.03 mole) of 5-methylanthranilic acid, 2.98 g (0.03 mole) of cyclohexylamine, 6.1 g (0.036 mole) of silicon tetrachloride in 82 ml of pyridine. Workup afforded 2.52 g (36%) of white solid, mp 205-206°; ^{1}H nmr (deuteriochloroform): δ 1.08-2.08 (m, 10H), 2.23 (s, 3H), 3.82-4.01 (m, 1H), 4.8-5.6 (broad s, 2H), 5.7-6.1 (d, 1H), 6.60 (d, 1H), 7.01 (d, 1H), 7.08 (s, 1H).

1-(*o*-Fluorobenzyl)-3-methyl-3,4-dihydro-2(1*H*)-quinazolinone (**Vh**).

To a stirred mixture of 0.50 g (0.0031 mole) of **Va**, 0.20 g of sodium hydride (60% in mineral oil) and 4.0 ml of dry dimethyl sulfoxide was added dropwise 0.493 g (0.00341 mole) of *o*-fluorobenzyl chloride. The mixture was stirred for twenty hours at room temperature. Dilution with ice-water produced a pale yellow precipitate which was filtered. Recrystallization from aqueous ethanol gave 0.74 g (88%) of product, mp 118.5-121.5°. The analytical sample was obtained from toluene-hexane, mp 121-122°; ^{1}H nmr (deuteriochloroform): δ 3.09 (s, 3H), 4.45 (s, 2H), 5.17 (s, 2H), 6.65 (d, 1H), 6.84-7.34 (m, 7H).

3-Methyl-3,4-dihydro-2(1*H*)-quinazolinone (**Va**).

To a solution of 2.77 g (0.0204 mole) of 2-amino-*N*-methylbenzylamine [3] in 25 ml of tetrahydrofuran was added 4.12 g (0.0255 mole) of carbonyldiimidazole. The mixture was stirred at room temperature for one hour, refluxed for 19 hours, and poured into 200 ml of water. The precipitate was filtered, dried and after recrystallization from ethyl acetate afforded 1.52 g (46%) of product, mp 200-203° [lit [3] mp 198-202°]; ^{1}H nmr (deuteriochloroform): δ 3.04 (s, 3H), 4.44 (s, 2H), 6.73-7.20 (m, 4H), 8.55 (s, 1H).

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