Synthesis of 3-Amino-3,4-dihydro-2(1*H*)-quinazolinones as Potential Anticonvulsants

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Thirteen 3-amino-3,4-dihydro-2(1*H*)-quinazolinones have been synthesized from ethyl chloroformate and *o*-aminobenzylhydrazines. The latter compounds were obtained from the metal hydride reduction of either *o*-aminobenzhydrazides or *o*-acylaniline hydrazones. All compounds were evaluated in mice in the maximal electroshock (MES) seizure and pentylenetetrazole (sc Met) seizure threshold tests for anticonvulsant activity and in the rotorod test to determine neurotoxicity. Five of the compounds showed activity in one or both tests at a dose of 300 mg/kg or lower. The most active compound is 3-dimethylamino-3,4-dihydro-2(1*H*)-quinazolinone.

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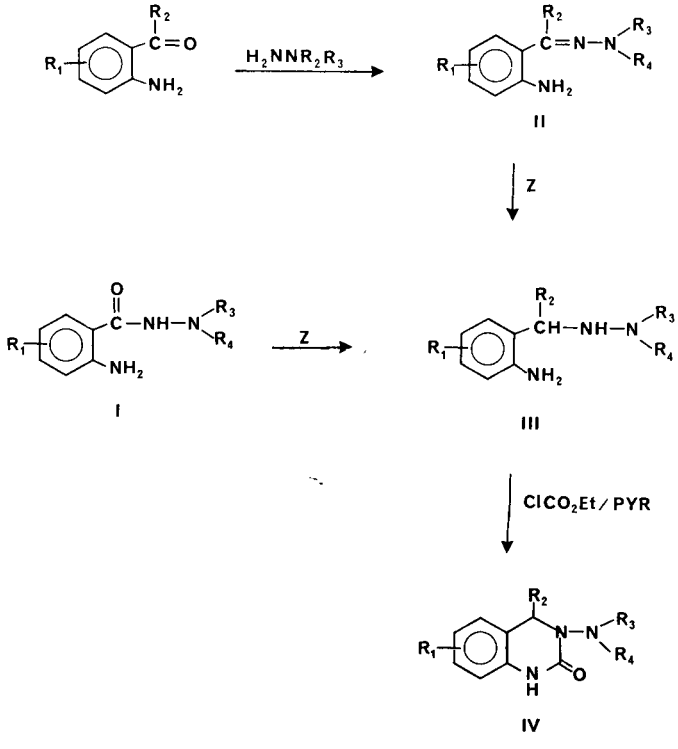
Anticonvulsant activity is associated with the ArNHCONRNR$_2$ pharmacophoric group [1]. Compounds in which N-2 is joined to the ortho position of th Ar ring by a carbonyl group have been reported [2] and several of these 3-amino-2,4(1*H*,3*H*)-quinazolinediones exhibited anticonvulsant activity. These encouraging results prompted additional related investigations. This report is concerned with the synthesis and anticonvulsant testing of a series of 3-amino-3,4-dihydro-2(1*H*)-quinazolinones. This series also contains the previously mentioned pharmacophore, however, N-2 is joined to the ortho position of the aromatic ring by a reduced one carbon bridge (CH$_2$ or CHR).

The pathways utilized to obtain the title compounds are summarized in Scheme I. The key intermediate *o*-aminobenzylhydrazines (III) were prepared in two ways. In Method A, *o*-aminobenzhydrazides (I) [2-3] were reduced by sodium bis(2-methoxyethoxy)aluminum hydride to III in high yield and purity as evidenced by tlc and mass spectral analysis. Normally, the reduction was carried out by refluxing the mixture overnight. Because of the possibility of dehalogenation [4] the reflux time was reduced to one hour for chlorine-containing I.

In Method B, intermediate III was produced by the sodium bis(2-methoxyethoxy)aluminum hydride reduction of *o*-acylaniline hydrazones (II). The latter compounds were accessible by heating 1,2-disubstituted hydrazines with *o*-acylanilines in the presence of molecular sieves. Other workers [5] obtained *N,N*-dimethylhydrazones of substituted acetophenones by heating the reactants in ethanol, however, in our hands the reaction with *o*-aminoacetophenone was very slow under these conditions. Intermediates II and III were used directly in a subsequent step without thorough purification.

In the final step, intermediates III were cyclocondensed with ethyl chloroformate in pyridine to yield IV. Physical and analytical data are recorded in Table I.

The pathway to IVl differed from Scheme I as follows: 3-methoxy-2-nitrobenzaldehyde was converted to the hydrazone, followed by stepwise reduction of the nitro group (H_2, Pd/C) [3] and the hydrazone [NaAlH$_2$(OCH$_2$CH$_2$OCH$_3$)$_2$], and cyclization of the resultant *o*-aminobenzylhydrazine with ethyl chloroformate.



Scheme I, Z = NaAlH$_2$(OCH$_2$CH$_2$OCH$_3$)$_2$

Compounds IVa-IVm were examined in the maximal electroshock (MES) seizure and pentylenetetrazole (sc Met) seizure threshold tests for anticonvulsant activity and neurotoxicity in male Carworth Farms No. 1 mice by reported procedures [6]. In the MES test, compound IVa showed activity at 30 mg/kg at 30 minutes with no toxicity. Compounds IVd and IVg were active at 100 mg/kg (30

Table I

Physical Properties of 3-Amino-3,4-dihydro-2(1*H*)-quinazolinones

Compound	R_1	R_2	R_3	R_4	Melting Point	Yield, %	Method	Formula	Analysis, % Calcd./Found C	H	N
IVa	H	H	CH_3	CH_3	170-171 [a]	36	A	$C_{10}H_{13}N_3O$	62.81	6.85	21.97
									62.52	7.09	21.69
IVb	H	H	$(CH_2)_5$		194-196 [b]	19	A	$C_{13}H_{17}N_3O$	67.51	7.41	18.17
									67.79	7.27	18.40
IVc	H	H	$O(CH_2CH_2)_2$		242-244 [c]	46	A	$C_{12}H_{15}N_3O_2$	61.79	6.48	18.01
									61.95	6.72	17.84
IVd	6-Cl	H	CH_3	CH_3	171-173 [d]	33	A	$C_{10}H_{12}ClN_3O$	53.22	5.36	18.62
									52.98	5.60	18.40
IVe	6-Cl	H	$(CH_2)_5$		204-207 [d]	42	A	$C_{13}H_{16}ClN_3O$	58.76	6.07	15.81
									59.02	6.20	15.61
IVf	6-Cl	H	$O(CH_2CH_2)_2$		258-260 [e]	36	A	$C_{12}H_{14}ClN_3O_2$	53.84	5.27	15.70
									53.59	5.49	15.89
IVg	$6\text{-}CH_3$	H	CH_3	CH_3	175.5-177 [a]	31	A	$C_{11}H_{15}N_3O$	63.37	7.37	20.47
									64.43	7.71	20.20
IVh	$6\text{-}CH_3$	H	$(CH_2)_5$		185-187 [f]	40	A	$C_{14}H_{19}N_3O$	68.54	7.81	17.13
									68.32	8.01	17.32
IVi	H	CH_3	$(CH_2)_5$		191-193 [e]	64	B	$C_{14}H_{19}N_3O$	68.54	7.81	17.13
									68.82	7.99	17.28
IVj	H	CH_3	$O(CH_2CH_2)_2$		228-229 [b]	57	B	$C_{13}H_{17}N_3O_2$	63.14	6.93	16.99
									63.30	7.14	16.67
IVk	H	CH_3	$(CH_2)_6$		185-187 [e]	39	B	$C_{15}H_{21}N_3O$	69.47	8.16	16.20
									69.69	8.41	15.97
IVl	$8\text{-}OCH_3$	H	$(CH_2)_5$		164-165.5 [a]	15	B	$C_{14}H_{19}N_3O_2$	64.35	7.33	16.08
									64.45	7.29	16.10
IVm	H	C_6H_5	$(CH_2)_5$		192-194.5 [e]	31	B	$C_{19}H_{21}N_3O$	74.24	6.89	13.67
									74.30	7.02	13.42

[a] Toluene. [b] 95% Ethanol. [c] Ethanol-toluene. [d] Cyclohexane-toluene. [e] Isopropyl alcohol. [f] 80% Ethanol.

minutes, no toxicity) whereas IVb and IVc exhibited activity at 300 mg/kg (30 minutes, no toxicity). In the sc MET test, IVa and IVd were active at 100 mg/kg and IVg at 300 mg/kg (toxicity evident for all three at the same doses). Compound IVa exhibited an MES ED_{50} value of 24 mg/kg, sc Met ED_{50} value of 25 mg/kg and TD_{50} value of 58 mg/kg. For comparison, the corresponding values for methaqualone, a quinazoline derivative, are 52, 35.5 and 55 [7].

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 700 spectrophotometer as either liquid films or potassium bromide pellets. The nmr spectra were recorded on a Varian EM-360 spectrometer using tetramethylsilane as the internal reference. Mass spectra were obtained on an RMU-7 double focusing spectrometer by Hitachi/Perkin-Elmer. Elemental analyses were performed by Baron Consulting Co., Orange, CT, and Micanal, Tucson, AZ.

3-Amino-3,4-dihydro-2(1*H*)-quinazolinones (IV).

Method A.

To a mixture of 55 ml (0.20 mole) of 70% sodium bis(2-methoxyethoxy) aluminum hydride in toluene and 60 ml of dry toluene was added 8.0 g (0.045 mole) of 1-(*o*-aminobenzoyl)-2,2-dimethylhydrazine [3] protionwise over a period of 25 minutes (exothermic reaction with hydrogen evolution). The resulting mixture was refluxed overnight and cooled to room temperature. The mixture was added dropwise to 84 ml of a stirred, cooled solution of 20% sodium hydroxide. The organic layer was separated and the aqueous layer was washed two times with 40 ml portions of toluene. The combined toluene extract was dried (magnesium sulfate) and concentrated to yield 7.6 g of crude 1-(*o*-aminobenzyl)-2,2-dimethylhydrazine as a yellow oil.

The reflux period was reduced to exactly one hour for compounds containing chlorine substituents.

To a stirred and ice-bath cooled solution of 7.6 g (0.045 mole) of the above oil in 38 ml of dry pyridine was added dropwise 5.61 g (0.0518 mole) of ethyl chloroformate. The mixture was stored in a refrigerator (4°), overnight and then refluxed overnight (nitrogen atmosphere). After pouring into 100 ml of water, the mixture was extracted three times with 40 ml portions of methylene chloride and dried (magnesium sulfate). Concentration yielded a residue which was azeotroped with toluene three times (50 ml portions) to remove pyridine. The solid residue was recrystallized from toluene (charcaol) and afforded 3.07 g (36%) of IVa, mp 163-172°. A second recrystallization gave the analytical sample, mp 170-171°; nmr (deuteriochloroform): δ 2.77 (s, 6H), 4.43 (s, 2H), 6.25-7.33 (m, 4H), and 8.66 (s, 1H) (Table I).

Method B.

To a 100 ml flask equipped with a 1.8 × 15.5 cm column (filled with 1/16 inch Linde 3A molecular sieve pellets) surmounted by a reflux con-

denser were added 6.8 g (0.05 mole) of *o*-aminoacetophenone and 20 g (0.20 mole) of 1-aminopiperidine. The mixture was refluxed in an oil bath for 44 hours. The excess aminopiperidine was removed under reduced pressure leaving 11.6 g of IIi as white crystals.

The above solid (11.6 g) was reduced with a mixture of 50 ml (0.18 mole) of 70% sodium bis(2-methoxyethoxy)aluminum hydride in toluene and 50 ml of dry toluene as described (*vide ante*). Workup afforded 11.1 g of crude IIIi as a yellow oily residue.

The above yellow oil (11.1 g) dissolved in 38 ml of dry pyridine was treated with 6.24 g (0.057 mole) of ethyl chloroformate as described above. Workup followed by recrystallization from isopropyl alcohol gave 7.9 g (64%) of IVi as white crystals, mp 191-193°; nmr (deuteriochloroform): δ 0.89-2.03 (m, 9H), 3.23 (broad s, 4H), 4.59 (q, 1H), 6.27-7.33 (m, 4H), and 8.51 (s, 1H).

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