Synthesis of 3-Amino-2,4(1*H*,3*H*)-quinazolinediones for Testing as Anticonvulsants

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Received March 22, 1984

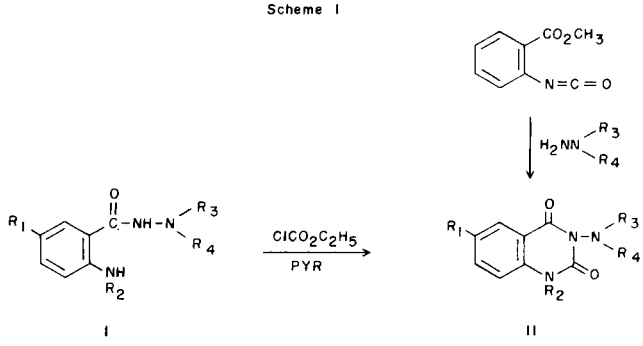
A number of 3-amino-2,4(1*H*,3*H*)-quinazolinediones were synthesized from *o*-aminobenzoylhydrazines and ethyl chloroformate in pyridine or from 2-methoxycarbonylphenyl isocyanate and 1,1-disubstituted hydrazines. Four of the ten compounds screened exhibited anticonvulsant activity in mice.

J. Heterocyclic Chem., **21**, 1533 (1984).

Several reports [1] have emanated from these laboratories concerning the synthesis and anticonvulsant testing of 4-phenylsemicarbazide analogs. A number of these compounds possess excellent anticonvulsant activity comparable to currently marketed antiepileptic drugs. This report concerns the synthesis and anticonvulsant activity of 3-amino-2,4(1*H*,3*H*)-quinazolinediones (II). As noted elsewhere [2], compounds II may be regarded as cyclic modifications of 4-phenylsemicarbazides. Two patents [3-4] dealing with II have recently appeared, but the physical properties of the compounds are not readily accessible.

Two methods were used to prepare II, depending on the availability of starting materials. In method A, *o*-aminobenzoylhydrazines (I) were reacted with ethyl chloroformate in dry pyridine and afforded II in moderate yields (Scheme I). The intermediates I were obtained from the reaction of isatoic anhydrides with hydrazines [2]. Initial experiments to cyclize I to II utilized urea (Dowtherm solvent) as the C-2 carbonyl source. This approach, although partially successful, was abandoned in favor of the chloroformate/pyridine procedure which gave cleaner products. In method B, compounds II (R_1 = H) were synthesized from 2-methoxycarbonylphenyl isocyanate [5] and 1,1-disubstituted hydrazines in toluene (Scheme I). Both methods were conveniently followed by tlc and indicated the prior formation of an uncharacterized intermediate which led to the cyclized products II.

Scheme I



Compounds IIa-IIj were examined in the maximal electroshock (MES) seizure and pentylenetetrazole (sc Met)

Table I

Physical Properties of 2-Aminobenzoyl Hydrazines

Compounds [a]	R_1	R_2	R_3	R_4	Melting Point	Yield %	Formula	Analysis, % Calcd./Found C	H	N
Ia	H	H	$O(CH_2CH_2)_2$		204-205 [b]	88	$C_{11}H_{15}N_3O_2$	59.71 60.00	6.83 7.09	18.99 19.21
Ib	CH_3	H	CH_3	CH_3	164.5-167 [c]	98	$C_{10}H_{15}N_3O$	62.15 61.89	7.82 8.01	21.74 21.50
Ic	NO_2	H	CH_3	CH_3	267-269 [b]	75	$C_9H_{12}N_4O_3$	48.21 48.41	5.39 5.69	24.99 24.77
Id	H	CH_3	CH_3	CH_3	117-119 [c]	43	$C_{10}H_{15}N_3O$	62.15 61.99	7.82 8.01	21.74 21.49
Ie	Cl	H	$(CH_2)_5$		208-210.5 [d]	74	$C_{12}H_{16}ClN_3O$	56.81 57.09	6.36 6.49	16.56 16.52
If	Cl	H	$O(CH_2CH_2)_2$		227.5-229.5 [e]	73	$C_{11}H_{14}ClN_3O_2$	51.67 51.80	5.52 5.80	16.43 16.20

[a] Obtained from the reaction of an isatoic anhydride with a hydrazine, except for Ib; the latter was prepared by catalytic hydrogenation of the corresponding nitro compound, see Exptl. [b] Aqueous dimethylformamide. [c] Toluene. [d] Toluene followed by 95% ethanol. [e] 95% Ethanol.

Table II

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

Compounds	R_1	R_2	R_3	R_4	Melting Point	Yield, %	Method	Formula	Analysis, % Calcd./Found C	H	N
IIa	H	H	CH_3	CH_3	240-241 [a]	72	B	$C_{10}H_{11}N_3O_2$	58.53 58.41	5.40 5.66	20.48 20.22
IIb	H	H	-(CH$_2$)$_5$-		261-262 [a]	76	B	$C_{13}H_{15}N_3O_2$	63.66 63.40	6.16 6.39	17.13 16.97
IIc	H	H	O(CH$_2$CH$_2$)$_2$		289-291 [a]	58	B	$C_{12}H_{13}N_3O_3$	58.29 58.50	5.30 5.49	16.99 16.72
IId	CH_3	H	CH_3	CH_3	227-228.5 [b]	21	A	$C_{11}H_{13}N_3O_2$	60.26 59.99	5.98 6.13	19.17 18.92
IIe	CH_3	H	-(CH$_2$)$_5$-		280-281.5 [c]	69	A	$C_{14}H_{17}N_3O_2$	64.85 64.60	6.61 6.86	16.20 16.58
IIf	H	CH_3	CH_3	CH_3	157-159 [d]	35	A	$C_{11}H_{13}N_3O_2$	60.26 59.99	5.98 6.14	19.17 19.03
IIg	Cl	H	CH_3	CH_3	261-263 [e]	42	A	$C_{10}H_{10}ClN_3O_2$	50.12 49.92	4.21 4.50	17.53 17.39
IIh	Cl	H	-(CH$_2$)$_5$-		292-294 [f]	38	A	$C_{13}H_{14}ClN_3O_2$	55.82 55.67	5.05 5.29	15.02 14.89
IIi	Cl	H	O(CH$_2$CH$_2$)$_2$		324-326 [g]	49	A	$C_{12}H_{12}ClN_3O_3$	51.17 51.12	4.29 4.49	14.92 14.78
IIj	H	H	H	$C(CH_3)_3$	203-204 [h]			$C_{12}H_{15}N_3O_2$			

[a] Absolute ethanol. [b] Toluene followed by 95% ethanol. [c] 95% ethanol. [d] Purified by column chromatography on silica gel followed by recrystallization from toluene-hexane. [e] 80% ethanol. [f] 90% ethanol. [g] Dimethylformamide. [h] See reference [2].

seizure threshold tests for anticonvulsant activity and neurotoxicity in male Carworth Farms No. 1 mice by reported procedures [6]. In the MES test, compounds IIa and IIj exhibited activity at 100 mg/kg at 30 minutes with no toxicity. Compound IIe (30 minutes) and IIg (4 hours) showed activity at 300 mg/kg, but the latter showed toxicity. In the sc Met test, compounds IIa and IIj were active at 300 mg/kg (30 minutes), however, toxicity was also evident. Compound IIa was further evaluated and its ED_{50} values in mg/kg were determined to be: 39 (MES), 98 (sc Met) and 113 (toxicity).

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 a RMU-7 double focusing spectrometer by Hitachi/Perkin Elmer. Elemented analyses were performed by Baron Consulting Co., Orange, CT, and Micanal, Tucson, AZ.

1-(5-Methyl-2-nitrobenzoyl)-2,2-dimethylhydrazine.

A mixture of 18.1 g (0.1 mole) of 5-methyl-2-nitrobenzoic acid and 35.7 g (0.3 mole) of thionyl chloride was refluxed until gas evolution ceased (7-8 hours). The excess thionyl chloride was evaporated under reduced pressure and the solid residue was dissolved in 200 ml of ether and added dropwise to a stirred solution of 12.6 g (0.21 mole) of 1,1-dimethylhydrazine in 200 ml of ether cooled by an ice-water bath. Stirring was continued overnight at room temperature. The ether was evaporated and the residue was triturated with water and filtered. Recrystallization from 95% ethanol afforded 13.1 g (59%) of ivory colored crystals, mp 132-134°. A second recrystallization gave the analytical sample, mp 133.5-134.5°.

Anal. Calcd. for $C_{10}H_{13}N_3O_3$: C, 53.81; H, 5.87; N, 18.82. Found: C, 53.60; H, 6.02; N, 18.61.

1-(5-Methyl-2-aminobenzoyl)-2,2-dimethylhydrazine (Ib).

A mixture of 7.2 g (0.032 mole) of 1-(5-methyl-2-nitrobenzoyl)-2,2-dimethylhydrazine and 0.5 g of 5% Pd/C catalyst in 240 ml of absolute ethanol was hydrogenated at low pressure on a Parr hydrogenator. After hydrogen uptake was completed, the catalyst was filtered and the solvent was distilled at reduced pressure. The dried product weighed 6.1 g (98%) and melted at 163.5-166.5°. The analytical sample was obtained by recrystallization from toluene, mp 164.5-167° (Table I).

1-(5-Chloro-2-aminobenzoyl)-2,2-pentamethylenehydrazine (Ie).

A solution of 20.0 g (0.20 mole) of *N*-aminopiperidine in 20 ml of methylene chloride was added dropwise to a suspension of 19.7 g (0.10 mole) of 5-chloroisatoic anhydride in 100 ml of methylene chloride while shaking the mixture manually. After gas evolution had slowed, the mixture was refluxed in an oil bath for 4 hours and cooled. The white solid was filtered, and washed with a small amount of the same solvent. Recrystallization from toluene gave 18.9 g (74%) of product, mp 201-203.5°. A second recrystallization from 95% ethanol produced a purer product, mp 208-210.5° (Table I).

3-Amino-2,4(1*H*,3*H*)-quinazolinediones (II). Method A.

To a magnetically stirred mixture of 4.66 g (0.02 mole) of 1-(5-methyl-2-aminobenzoyl)-2,2-pentamethylenehydrazine [2] in 50 ml of dry pyridine was added dropwise 2.5 g (0.023 mole) of ethyl chloroformate. The mixture was stirred overnight at room temperature and refluxed for 20 hours under a nitrogen atmosphere. The mixture was poured into water, extracted three times with methylene chloride and dried (magnesium

sulfate). Evaporation of the solvent gave a solid which was recrystallized from 95% ethanol (charcoal) and yielded 3.55 g (69%) of white crystals, mp 280-281.5° (Table II).

Method B.

To a solution of 8.85 g (0.05 mole) of 2-methoxycarbonylphenyl isocyanate [5] in 35 ml of dry toluene was added a solution of 11.0 g (0.11 mole) of *N*-aminopiperidine in 10 ml of dry toluene. The reaction is exothermic. After completing the addition, the mixture was refluxed in an oil bath for 4 days. Cooling produced a precipitate which was filtered and recrystallized from 95% ethanol and gave 9.31 g (76%) of product, mp 261-262° (Table II).

Acknowledgement.

The authors are grateful to the Antiepileptic Drug Development Program, National Institutes of Health, for providing the anticonvulsant activity and toxicity data.

REFERENCES AND NOTES

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