M. J. Kornet*, T. Varia and W. Beaven

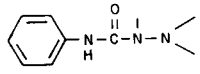
College of Pharmacy, University of Kentucky,
Lexington KY 40536

Received May 23, 1983

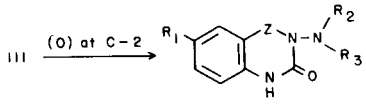
Several 3-amino-4(3*H*)-quinazolinones were prepared from *o*-aminobenzoylhydrazines and triethyl orthoformate or from isatoic anhydrides, hydrazines and triethyl orthoformate. *o*-Aminobenzoylhydrazine intermediates were obtained by reaction of isatoic anhydrides with hydrazines. Some of the aminoquinazolinones displayed anticonvulsant activity in mice.

*J. Heterocyclic Chem.*, **20**, 1553 (1983).

In recent years [1] we have prepared active anticonvulsants containing the following structural feature. A more



recent objective is to synthesize additional novel compounds which retain this pharmacophoric unit. One way to do this is to join N-2 to the ortho carbon of the phenyl ring by a one carbon bridge, *e.g.* structure IV. Investigation of

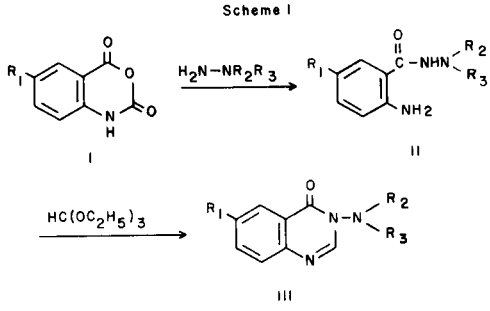


IV

Z: CO, $CH_2$

compounds resulting from such a tying back of the active group into the aromatic ring should provide additional information regarding structure-activity relationships. Although the aminoquinazolinones III do not possess the requisite pharmacophore, such compounds nevertheless may be metabolically transformed *in vivo* into IV. Another reason for our interest in III is that a member of this series of compounds, 3-dimethylamino-4(3*H*)-quinazolinone (IIIa) exhibited anticonvulsant activity [2]. Compounds III also show analgesic and antipyretic properties [3]. This report describes the synthesis and anticonvulsant activity of additional 3-amino-4-(3*H*)-quinazolinones III.

Scheme I



Two pathways were utilized to prepare compounds III. In Method A, the isatoic anhydride was reacted with a hydrazine to give 2-aminobenzoylhydrazines II (Table I) [4]. The reaction of isatoic anhydride with *t*-butylhydrazine hydrochloride gave three products. In addition to the expected IIb, 1-*t*-butyl-4-(*o*-carboxyphenyl)semicarbazide and 3-*t*-butylamino-2,4(1*H*,3*H*)-quinazolindione were isolated. Condensation of II with triethyl orthoformate afforded the desired compounds III. In a more direct route (Method B), the isatoic anhydride, hydrazine and triethyl orthoformate were heated together and produced III (Table II) (Scheme I).

Compounds IIIa-IIIk were tested in the maximal electroshock (MES) seizure and pentylenetetrazol(sc Met) seizure threshhold tests for anticonvulsant activity and neurotoxicity in male Carworth Farms No. 1 mice by reported procedures [5]. In the MES test, compounds IIIa, IIIb, IIIc, and IIIf exhibited activity at 300 mg/kg at 30 minutes and IIIa was active also at 4 hours. At this dose level, IIIa, IIIc, and IIId showed toxicity, whereas IIIb and IIIf showed no toxicity. Compound IIId was active at 100 mg/kg (30 minutes) with no toxicity. In the sc Met test, compounds IIIa, IIIc, and IIId were active at 300 mg/kg (30 minutes).

## EXPERIMENTAL

Melting points were determined on a Thomas-Hoover 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. Elemental analyses were performed by Baron Consulting Co., Orange, CT, and Micanal, Tucson, AZ.

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

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 (approximately 6-7 hours). The excess thionyl chloride was evaporated under reduced pressure. The solid residue was dissolved in 200 ml of ether and added dropwise to a stirred solution of 20.0 g (0.2 mole) of *N*-aminopiperidine in 200 ml 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 90% ethanol afforded 20.5 g (78%) of pale yellow crystals, mp 153-155°.

*Anal.* Calcd. for $C_{13}H_{17}N_3O_3$: C, 59.30; H, 6.51; N, 15.96. Found: C, 59.58; H, 6.37; N, 15.75.

Table I

Physical Properties of 2-Aminobenzoylhydrazines

| Compounds | $R_1$ | $R_2$ | $R_3$ | Melting Point | Yield, % | Recrystallization Solvent | Formula | Analysis, % Calcd./Found C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|
| IIa | H | $CH_3$ | $CH_3$ | 143-144 [a] | 51 | Toluene | $C_9H_{13}N_3O$ | 60.32 | 7.31 | 23.45 |
| | | | | | | | | 60.05 | 7.52 | 23.20 |
| IIb | H | H | $C(CH_3)_3$ | 166-167 | 26 [b] | 95% Ethanol | $C_{11}H_{17}N_3O$ | 63.74 | 8.27 | 20.27 |
| | | | | | | | | 63.67 | 8.30 | 19.99 |
| IIc | H | $-CH_2(CH_2)_3CH_2-$ | | 168.5-169 | 46 | Toluene-ethanol | $C_{12}H_{17}N_3O$ | 65.73 | 7.81 | 19.16 |
| | | | | | | | | 65.45 | 8.06 | 18.93 |
| IIf | Cl | $CH_3$ | $CH_3$ | 159.5-161.5 | 79 | Toluene | $C_9H_{12}ClN_3O$ | 50.59 | 5.66 | 19.67 |
| | | | | | | | | 50.81 | 5.90 | 19.29 |
| IIk [c] | $CH_3$ | $-CH_2(CH_2)_3CH_2-$ | | 215-217 | 94 | 80% Ethanol | $C_{13}H_{19}N_3O$ | 66.92 | 8.21 | 18.01 |
| | | | | | | | | 67.19 | 8.32 | 17.89 |

[a] U. Bahr, H. Wieden, H.-A. Rinkler and G. Nischk, *Makromol. Chem.*, **161**, 1 (1972) reported mp 128°. [b] Obtained along with two side-products (see Experimental). [c] Obtained by catalytic reduction of the corresponding nitro compound.

Table II

Physical Properties of 3-Amino-4(3*H*)-quinazolinones

| Compounds [a] | $R_1$ | $R_2$ | $R_3$ | Melting Point | Yield, % | Recrystallization Solvent [b] | Formula | Analysis, % Calcd./Found C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|
| IIIa | H | $CH_3$ | $CH_3$ | 68.5-69 [c] | 85 | A | $C_{10}H_{11}N_3O$ | | | |
| IIIb | H | H | $C(CH_3)_3$ | 104.5-105 | 53 | B | $C_{12}H_{15}N_3O$ | 66.34 | 6.96 | 19.34 |
| | | | | | | | | 66.17 | 6.70 | 19.33 |
| IIIc | H | $-CH_2(CH_2)_3CH_2-$ | | 71-72 | 96 | A | $C_{13}H_{15}N_3O$ | 68.10 | 6.59 | 18.33 |
| | | | | | | | | 67.79 | 6.87 | 18.43 |
| IIId | H | $-CH_2CH_2OCH_2CH_2-$ | | 124.5-125 [d] | 71 | B | $C_{12}H_{13}N_3O_2$ | | | |
| IIIe | H | H | $C_6H_5$ | 166-167 [e] | 59 | C | $C_{14}H_{11}N_3O$ | | | |
| IIIf | Cl | $CH_3$ | $CH_3$ | 102-102.5 | 87 | B | $C_{10}H_{10}ClN_3O$ | 53.70 | 4.51 | 18.79 |
| | | | | | | | | 53.62 | 4.45 | 18.78 |
| IIIg | Cl | $-CH_2(CH_2)_3CH_2-$ | | 189-190 | 52 | B | $C_{13}H_{14}ClN_3O$ | 59.21 | 5.35 | 15.93 |
| | | | | | | | | 59.12 | 5.37 | 15.85 |
| IIIh | Cl | $-CH_2(CH_2)_4CH_2-$ | | 147.5-148.5 | 37 | D | $C_{14}H_{16}ClN_3O$ | 60.54 | 5.81 | 15.13 |
| | | | | | | | | 60.27 | 5.81 | 14.86 |
| IIIi | Cl | $-CH_2CH_2OCH_2CH_2-$ | | 187-188.5 | 55 | B | $C_{12}H_{12}ClN_3O_2$ | 54.25 | 4.55 | 15.82 |
| | | | | | | | | 53.99 | 4.24 | 16.10 |
| IIIj | Cl | H | $CH_2C_6H_5$ | 166.5-167 | 42 | E | $C_{15}H_{12}ClN_3O$ | 63.05 | 4.23 | 14.71 |
| | | | | | | | | 62.94 | 4.19 | 14.88 |
| IIIk | $CH_3$ | $-CH_2(CH_2)_3CH_2-$ | | 110-112 | 32 | F | $C_{14}H_{17}N_3O$ | 69.11 | 7.04 | 17.27 |
| | | | | | | | | 68.89 | 6.89 | 17.54 |

[a] Compounds IIIa, b, c, f and k were prepared by Method A, all others by Method B. [b] A = cyclohexane, B = isopropyl alcohol, C = ethanol-isopropyl alcohol (1:1), D = 95% ethanol, E = isopropyl alcohol-ethyl acetate, F = cyclohexane-petroleum ether (bp 30-60°). [c] Reported [2] mp 68.2-69.2°. [d] Reported [3] mp 125-127°. [e] Z. Csuros, R. Soos, I. Bitter and J. Polinkas, *Acta Chem.* (Budapest), **69**, 361 (1971) reported mp 168-170°.

1-(5-Methyl-2-aminobenzoyl)-2,2-pentamethylenehydrazine (IIk).

A mixture of 6.5 g (0.05 mole) of 1-(5-methyl-2-nitrobenzoyl)-2,2-pentamethylenehydrazine and 0.5 g of 5% Pd/C catalyst in 400 ml of 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 white solid was recrystallized from 80% ethanol and gave 5.5 g (94%) of IIk (Table I).

A mixture of 16.3 g (0.1 mole) of isatoic anhydride, 13.7 g (0.12 mole) of *t*-butylhydrazine hydrochloride, 30.0 g (0.30 mole) of triethylamine and 200 ml of dry pyridine was refluxed under nitrogen for 15 hours. The pyridine was evaporated under reduced pressure and the residue was azeotroped with toluene several times to completely remove the last traces of pyridine. The residue was partioned between 50 ml of water and 75 ml of methylene chloride and undissolved solid was filtered on a glass-sintered funnel. The solid was washed with 75 ml of methylene chloride and dried. Recrystallization from aqueous ethanol gave 2.44 g of 1-*t*-butyl-4-(*o*-carboxyphenyl)semicarbazide as a white solid, mp 199-201°.

*Anal.* Calcd. for $C_{12}H_{17}N_3O_3$: C, 57.36; H, 6.82; N, 16.72. Found: C, 57.10; H, 6.89; N, 16.51.

The filtrate from the above experiment was separated and the organic layer was washed with 5% sodium bicarbonate solution (3 × 25 ml) and dried (magnesium sulfate). Evaporation and recrystallization of the residue from toluene-ethanol gave 5.47 g (26%) of IIb, mp 166-167° (Table I).

The filtrate from the above recrystallization was evaporated to dryness and dissolved in methylene chloride. The solution was extracted with 5% hydrochloric acid (2 × 15 ml), dried (magnesium sulfate) and evaporated. Recrystallization of the residue from aqueous ethanol afforded 1.0 g of 3-*t*-butylamino-2,4-(1*H*,3*H*)-quinazolindione as white crystals, mp 203-204°.

*Anal.* Calcd. for $C_{12}H_{15}N_3O_2$: C, 61.79; H, 6.48; N, 18.01. Found: C, 61.91; H, 6.51; N, 17.82.

3-Amino-4(3*H*)-quinazolinones (III).

Method A.

A mixture of 2-aminobenzoyl hydrazine (0.014 mole) and triethyl orthoformate (0.015 mole) was refluxed under nitrogen for 2 hours. Cooling afforded white crystals. Recrystallization gave the expected products IIIa, b, c, f and k (Table II).

Method B.

The hydrazine (0.03 mole) was added through the top of a condenser to a mixture of isatoic anhydride (0.03 mole) and triethyl orthoformate (0.03 mole). The resulting mixture was refluxed for 2 ¼ hours under a nitrogen atmosphere. Cooling and evaporation gave a solid residue which was recrystallized and gave products IIId, e, g, h, i and j (Table II).

Acknowledgement.

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

## REFERENCES AND NOTES

[1] M. J. Kornet and J. Y-R. Chu, *J. Pharm. Sci.*, in press and references cited therein.

[2] F. K. Kirchner and A. W. Zalay, U. S. 3,217,005 (1965); *Chem. Abstr.*, **64**, 3570 (1966).

[3] H. Herlinger, S. Petersen, E. Tietze, F. Hoffmeister, and W. Wirth, Belgian Patent 614,243 (1962); *Chem. Abstr.*, **61**, 4585 (1963).

[4] "Isatoic Anhydride", Sherwin Williams Chemicals, Technical Bulletin 112, The Sherwin Williams Co., Chemicals Division, Cleveland, Ohio 44101, 1977, p 22.

[5] M. J. Kornet, *J. Pharm. Sci.*, **67**, 1471 (1978).