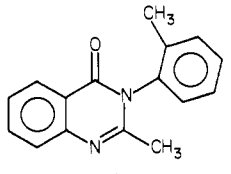
Synthesis of 3,4-Dihydro-4-oxoquinazoline Derivatives as Potential Anticonvulsants

Niteen A. Vaidya, C. H. Panos, A. Kite, W. Ben Iturrian, and C. DeWitt Blanton, Jr.*

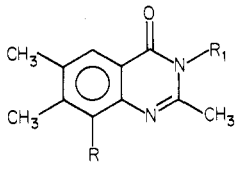
Departments of Medicinal Chemistry/Pharmacognosy and Pharmacology, College of Pharmacy, University of Georgia, Athens, Georgia 30602. *Received December 6, 1982*

Twenty-three substituted 3,4-dihydro-4-oxoquinazolines or 3,4-dihydro-4-oxoazaquinazolines have been synthesized utilizing 2-amino-3-cyano-4,5-dimethylfuran and methyl acrylate as precursors for synthesis of the required substituted anthranilates. Six additional azaquinazolones were synthesized from 2-aminonicotinic or 3-aminopicolinic acid for comparison studies. All compounds were evaluated in mice with the maximal electroshock (MES) seizure and pentylenetetrazol (sc Met) seizure threshold tests for potential anticonvulsant activity and in the rotorod test to evaluate neurotoxicity. Nine of the twenty-nine compounds in the series demonstrated anticonvulsant action. The azaquinazolones were found to possess the most significant activity.

Quinazoline derivatives have been found to be biologically versatile compounds having anticonvulsant, hypnotic, antimalarial, antipyretic, analgesic, antiinflammatory, diuretic, antihypertensive, antitubercular, bronchodilator, and other diverse activities.[1] One derivative, 3,4-dihydro-2-methyl-4-oxo-3-*o*-tolylquinazoline (methaqualone, **1**), has been examined extensively for its sedative–hypnotic



1



2

effects.[1,2] In addition, **1** is a potent anticonvulsant with demonstrated activity in the electroshock, the metrazol, and audiogenic seizures tests.[1,2] Since both the hypnotic and anticonvulsant actions of **1** are quite sensitive to structural alterations,[1,3] our recently developed procedure[4,5] for the synthesis of new, previously inaccessible, anthranilate derivatives led us to prepare a series of methaqualone analogues (**2**) with potential for anticonvulsant action and diminution of undersirable effects through alteration in absorption, distribution, or metabolic patterns.

Chemistry. Quinazolone derivatives (**2**) were prepared from methyl 3-cyano-4,5-dimethylanthranilate (**3**, Scheme I). The starting anthranilate **3** was synthesized from the Diels–Alder adduct[4] obtained with 2-amino-3-cyano-4,5-dimethylfuran[6] and methyl acrylate. Formation of the quinazolonecarboxylic acid (e.g., **2a**, Table I) from 2-acetamido-5,6-dimethyl-3-(methoxycarbonyl)benzoic acid (**4**) was reported[5] earlier. Compound **4** was obtained from the anthranilate when **3** was heated with acetic anhydride containing a few drops of sulfuric acid, and it was isolated as a solid after pouring the mixture onto ice. When **3** was refluxed with acetic anhydride alone, followed by dilution with water, the acetylated product **6** was obtained without nitrile hydrolysis. From this latter product (**6**) and an appropriate aromatic amine (**5**), thermal cyclization (method A) gave the cyano-substituted quinazolone derivative **2t** (Table I). Finally, The quinazolonecarboxylic acids (**2**, R = COOH) were esterified by the diazomethane[7] method or by the alcoholic acid method.[8] Pertinent physical and analytical data for all new compounds are tabulated in Table I.

The azaquinazolones (**8** and **9**) were synthesized by the standard procedure (methods A or B) from 2-aminonicotinic[9] or 3-aminopicolinic acid[9] and the appropriate arylamine (**5**). Pertinent physical and analytical data are tabulated in Table II.

Biological Results

All of the compounds were tested in the Anticonvulsant Screening Project Test Systems,[10] described in the Experimental Section. Methaqualone was used as a reference compound. Nine of the twenty-nine compounds in the series demonstrated anticonvulsant action, as summarized in Table III.

Most of the methaqualone analogues were neither active nor neurotoxic. Substitution at the 6-, 7-, and 8-positions markedly decreased CNS action of quinazolones, although very active benzodiazepine and quinazoline analogues have been observed.[11] Activity in the MES seizure and sc Met seizure threshold tests and sedative actions are not universal properties of quinazolones, and the results with this series suggest that each of these CNS actions are differentially sensitive to structural alterations. Compounds **2h** and **2v** were devoid of anticonvulsant activity but were neurotoxic. The acid analogues (**2**, R = COOH) were devoid of significant anticonvulsant activity at doses including 600 mg/kg, although **2k** (R_1 = *p*-FC_6H_4) exhibited some protection in the sc Met test. Among the ester analogues (**2**, R = $COOCH_3$), sc Met activity was observed in the 3-aryl meta- and para-substituted derivatives, compounds **2j** (R_1 = *m*-FC_6H_4) and **21** (R_1 = *p*-FC_6H_4), respectively. The 3-aryl ortho-substituted derivative **2b** (R_1 = *o*-$CH_3C_6H_4$) was only active at 600 mg/kg. With this limited number of compounds, sc Met activity appears to

(1) (a) Amin, A. M; Mehta, D. R.; Samarth, S. S. *Prog. Drug Res.* **1970**, *14*, 218. (b) Armarego, W. L. F. In "Fused Pyrimidines", Part I; Brown, D. J., Ed.; Interscience: New York, 1967; p 509.
(2) Vida, J. A. "Anticonvulsants"; Academic Press, New York, 1977; pp 428, 432–450, and 471–472.
(3) Brown, S. S.; Goenechea, S. *Clin. Pharmacol. Ther.* **1973**, *14*, 314.
(4) Nixon, W. J., Jr.; Garland, J. J.; Blanton, C. D., Jr. *Synthesis* **1980**, 56.
(5) Vaidya, N. A.; Blanton, C. D., Jr. *J. Org. Chem.* **1982**, *47*, 1977.
(6) Gewald, K. *Chem. Ber.* **1966**, *99*, 1002.
(7) Prepared from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald). deBoer, T. J.; Bocker, H. J. In "Organic Syntheses"; Wiley: New York 1963; Collect Vol. IV, p 250.
(8) Harrison, H. R.; Haynes, W. M.; Arthur, P.; Eisenbraun, E. J. In "Reagents for Organic Synthesis"; Fieser, L. F.; Fieser, M., Eds.; Wiley: New York, 1967; Vol. 1, p 705.
(9) (a) Sucharda, E. *Ber. Dtsch. Chem. Ges.* **1925**, *58*, 1727. (b) Oakes, V.; Pascoe, R.; Rydon, H. N. *J. Chem. Soc.* **1956**, 1045. (c) Irwin, W. J.; Wibberly, D. G. *J. Chem. Soc.* **1965**, 4240.
(10) (a) Anticonvulsant Screening Project, Antiepileptic Drug Development Program, National Institutes of Health, *DHEW Publ (NIH) (U.S.)* **1978**, *NIH 78-1093*. (b) Swinyward, E. A.; Brown, W. C.; Goodman, L. S. *J. Pharmacol. Exp. Ther.* **1952**, *106*, 319. (c) Kornet, M. J.; Crider, A. M.; Magarian, E. O. *J. Med. Chem.* **1977**, *20*, 405. (d) Litchfield, J. T.; Wilcoxon, F. *J. Pharmacol. Exp. Ther.* **1949**, *96*, 99.
(11) Fatmi, A. A., Ph.D. Dissertation, University of Georgia, Athens, GA, 1981.

0022-2623/83/1826-1422$01.50/0

Scheme I

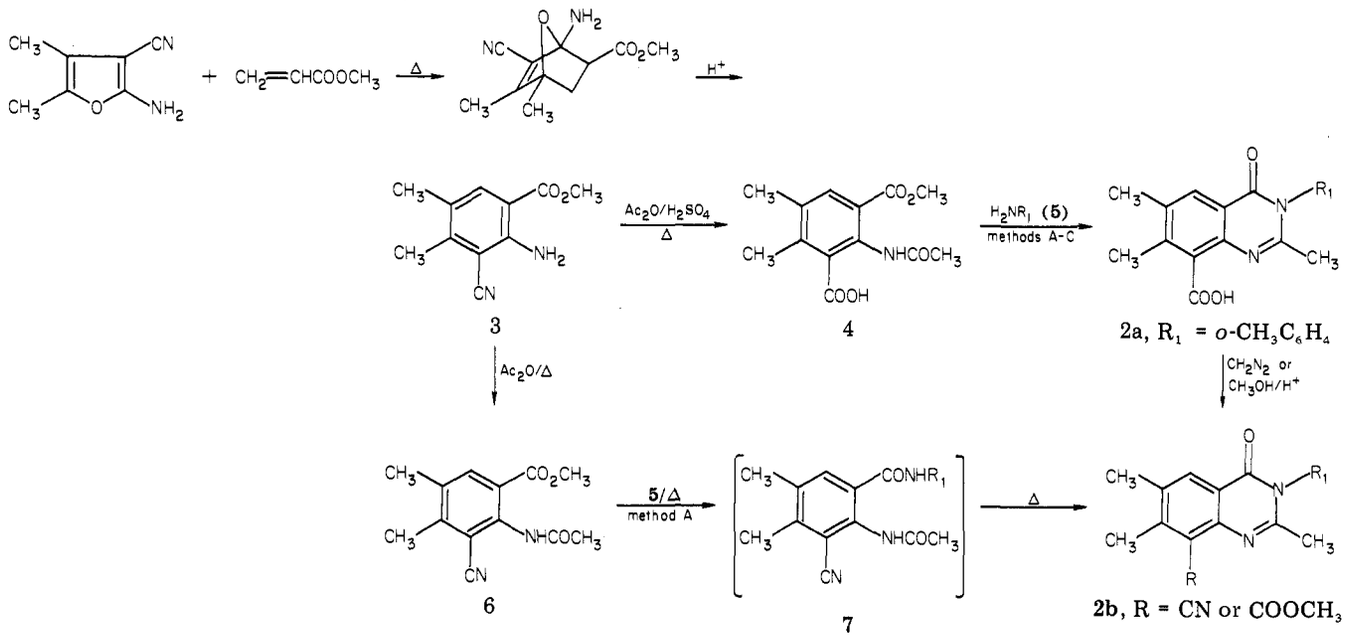
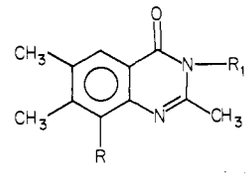


Table I. Quinazolone Derivatives



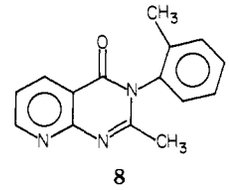
compd	R	R_1	mp, °C	yield, %	synth method	formula[a]
2a	COOH	o-$CH_3C_6H_4$	238-239	55[b]	A	$C_{19}H_{18}N_2O_3$
2b	CO_2CH_3	o-$CH_3C_6H_4$	182-184	63[b]	D	$C_{20}H_{20}N_2O_3$
2c	COOH	m-$CH_3C_6H_4$	267-269	40[b]	B	$C_{19}H_{18}N_2O_3$
2d	CO_2CH_3	m-$CH_3C_6H_4$	175-176	48[c]	D	$C_{20}H_{20}N_2O_3$
2e	COOH	p-$CH_3C_6H_4$	249-251	47[b]	B	$C_{19}H_{18}N_2O_3$
2f	CO_2CH_3	p-$CH_3C_6H_4$	159-160	70[c]	D	$C_{20}H_{20}N_2O_3$
2g	COOH	o-FC_6H_4	328-330	33[b]	B	$C_{18}H_{15}N_2O_3F$
2h	CO_2CH_3	o-FC_6H_4	115-117	48[d]	D	$C_{19}H_{17}N_2O_3F$
2i	COOH	m-FC_6H_4	298-300	33[e]	B	$C_{18}H_{15}N_2O_3F$
2j	CO_2CH_3	m-FC_6H_4	161-163	32[c]	E	$C_{19}H_{17}N_2O_3F$
2k	COOH	p-FC_6H_4	284-286	81[b]	A	$C_{18}H_{15}N_2O_3F$
2l	CO_2CH_3	p-FC_6H_4	237-239	71[d]	D	$C_{19}H_{17}N_2O_3F$
2m	CO_2H	C_6H_5	262-264	34[b]	B	$C_{18}H_{16}N_2O_3$
2n	CO_2CH_3	C_6H_5	191-192	77[c]	D	$C_{19}H_{18}N_2O_3$
2o	COOH	o-$CF_3C_6H_4$	304-306	41[e]	A	$C_{19}H_{15}N_2O_3F_3$
2p	CO_2CH_3	o-$CF_3C_6H_4$	225-227	43[b]	D	$C_{20}H_{17}N_2O_3F_3$
2q	COOH	o-$NO_2C_6H_4$	326-328	28[c]	A	$C_{18}N_{15}N_3O_5$
2r	CO_2CH_3	o-$NO_2C_6H_4$	131-133	54[c]	D	$C_{19}H_{17}N_3O_5$
2s	COOH	o-$CH_3OC_6H_4$	289-291.5	30[b]	A	$C_{19}H_{18}N_2O_4$
2t	CN	o-$CH_3C_6H_4$	232-233	51.9[b]	A	$C_{19}H_{17}N_3O$
2u	COOH	3,4,5-$(CH_3O)C_6H_2$	245-246	22.9[b]	A	$C_{21}H_{22}N_2O_6$
2v	COOH	α-C_5H_4N	276-278	51.5[c]	C	$C_{17}H_{15}N_3O_3$[f]
2w	$COOCH_3$	α-C_5H_4N	215-216	64.0[g]	D	$C_{18}H_{17}N_3O_3$

[a] All compounds gave satisfactory analyses for C, H, and N (±0.4%) unless otherwise noted. [b] Methanol. [c] Methylene chloride-petroleum ether (30-60 °C). [d] Ether-methanol. [e] Dimethylformamide-methanol. [f] C: calcd, 66.01; found, 65.04. [g] Benzene-petroleum ether (30-60 °C).

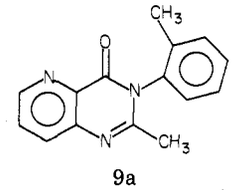
favor electron-withdrawing substituents, particularly when located in the para or meta position. Compound **21** also possessed some activity in the MES test.

When the aromatic group at the 3-position was an α-pyridyl moiety, an interesting shift in the activity pattern was observed by the incorporation of a third ring nitrogen atom into the molecule. Compound **2w** (R = $COOCH_3$; R_1 = α-pyridyl) was as active as methaqualone in the MES test but without neurotoxicity or sc Met activity. In contrast, compound **2v** (R = COOH; R_1 = α-pyridyl) was a convulsant accompanied by deaths at 300 mg/kg.

Several aza analogues of methaqualone (e.g., **8** and **9a**)

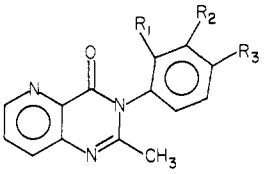


8



9a

Table II. Azaquinazolones



compd	R_1	R_2	R_3	mp, °C	yield, %	synth method	formula[a]
9a	CH_3	H	H	164.5-166[b]	49.9[c]	B[d]	$C_{15}H_{13}N_3O$
9b	Cl	H	Cl	255-257	40.0[c]	A	$C_{14}H_9Cl_2N_3O$
9c	CF_3	H	H	192-194	51[c]	B[d]	$C_{15}H_{10}F_3N_3O$
9d	H	CF_3	H	137-138	77[c]	B[d]	$C_{15}H_{10}F_3N_3O$
9e	H	H	CF_3	213-214.5	61[c]	B[d]	$C_{15}H_{10}F_3N_3O$

[a] All of the compounds in this table gave satisfactory analyses for C, H, N, and Cl (±0.4%). [b] Literature[12b] mp 166-168 °C. [c] Benzene-petroleum ether (30-60 °C). [d] Benzene was used as the solvent instead of toluene.

Table III. Anticonvulsant Activity of Selected Quinazolones in Mice

compd	MES ED_{50}, mg/kg	sc Met ED_{50}, mg/kg	TD_{50},[a] mg/kg
2b	*b*	600[c]	*b*
2h	*b*	*b*	280
2j	*b*	430	540
2k	*b*	440	*b*
2l	600	440	*b*
2v	*b*	*b*	*b*, *d*
2w	52[h]	*b*	*b*
8	X[e] (300)	40 (26-62)[f,g]	137 (126-147)[h]
9a	52 (48-55)[h]	16.5 (12-20)[h]	40 (36-43)
9b	X (30)	X (5)	1
9c	X (100)	100[i]	100[h]
9d	*b*	*b*	50
9e	X (300)	90[i]	170
methaqualone	52 (48-56)[h]	33.5 (28-40)[h]	55 (47-65)[h]

[a] Median neurotoxic dose in the rotorod test (0.5 h). [b] Inactive at all doses, including 600 mg/kg. [c] Estimated graphically. [d] 4 out of 4 mice died at 600 mg/kg; wild running and tonic extension convulsion at 300 mg/kg. [e] Activity observed at the dose indicated in parentheses, but mice showed neurotoxicity. [f] Determined at time of peak effect (1 h). [g] 95% confidence limits calculated by the Litchfield-Wilcoxon method.[10d] [h] Determined at time of peak effect (0.5 h). [i] Determined at 4 h.

have been reported[12] to possess anticonvulsant activity. Compounds 8 and **9a** were resynthesized for use in comparison studies with other azaquinazolones. In addition, several new aza analogues related to **9a** were synthesized for preliminary evaluation (Table II).

Compound 8 has activity in the sc Met test comparable to methaqualone, but unlike methaqualone, activity of compound 8 in the MES test only occurs at anesthetic doses. Compound **9a** is active in both anticonvulsant tests, being slightly more potent in the sc Met test than methaqualone but also more toxic. Compound **9a** was inactive against the bicuculline, picrotoxin, and strychnine tests, which are additional chemically induced seizure models used in the Antiepileptic Drug Development (ADD) Program.[10] Methaqualone is a very active antistrychnine agent. Compound **9b** was the most potent neurotoxic agent in the series, with a prominent excitatory phase preceding a general anesthesia, which lasts for days. The lethal dose (LD_{50}) is 65 mg/kg.

Compounds **9c** and **9e** were active in all three tests, but the protection in the sc Met persisted after the neurotoxic effect disappears. Like compound **9b**, **9c** has excitatory effects preceding anesthesia. Compound **9d** was a respiratory depressant without anticonvulsant action.

The data suggest that a broad range of CNS activity was favored by the incorporation of the additional ring nitrogen in the classical methaqualone structure. Studies on the selective anticonvulsant activity of **2w**, 8, and **9a–e** as leads are suggested.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Melting points over 250 °C were determined on Mel-Temp capillary melting point apparatus. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA, and results were within ±0.4% of the calculated values unless otherwise noted. Satisfactory IR (Perkin-Elmer 467 grating spectrophotometer, KBr) and NMR (60-MHz Hitachi Perkin-Elmer R20A high-resolution spectrometer, Me_4Si as internal reference) spectra were obtained for all new compounds.

Methyl 2-Acetamido-3-cyano-4,5-dimethylbenzoate (6). To a 50-mL round-bottomed flask equipped with a reflux condenser were added 7.8 g (38 mmol) of methyl 3-cyano-4,5-dimethylanthranilate (3)[4] and 18 mL of acetic anhydride. The flask was heated on a free flame for 1 h. The mixture was cooled and poured onto ice. After standing at room temperature for a brief period, a solid was collected by filtration, washed several times with water, and air-dried. The product was recrystallized from MeOH to give 9.0 g (95.7%) of 6: mp 165-167 °C; IR (KBr) 3230, 3040, 2240, 1735, 1680 cm^{-1}; NMR ($CDCl_3$) δ 9.4 (s, 1 H), 7.95 (s, 1 H), 3.9 (s, 3 H), 2.60 (s, 3 H), 2.45 (s, 3 H), 2.30 (s, 3 H). Anal. ($C_{13}H_{14}N_2O_3$) C, H, N.

Method A. 2,6,7-Trimethyl-3-*o*-tolyl-3,4-dihydro-4-oxoquinazoline-8-carboxylic Acid (2a). In a 50-mL round-bottomed flask equipped with a reflux condenser were placed 18.09 g (68 mmol) of 2-acetamido-3-carbomethoxy-5,6-dimethylbenzoic acid (4)[4] and *o*-toluidine (7.2 mL, *d* 1.004, 68.4 mmol). The mixture was heated in a free flame for 5 min with the reflux condenser in place and for 5 min with the reflux condenser removed. After the mixture was cooled to room temperature, anhydrous Et_2O was added to precipitate a white solid. The product was recrystallized from MeOH to give 12.0 g (54.9%) of 2a: mp 238-239 °C; IR (KBr) 3400, 1720, 1680, 1600 cm^{-1}; NMR ($CDCl_3$, Me_2SO-d_6) δ 9.2 (s, 1 H, exchanged by D_2O), 7.95 (s, 1 H), 7.25–7.45 (m, 4 H), 2.45 (br s, 6 H), 2.15 (s, 3 H), 2.10 (s, 3 H). Anal. ($C_{19}N_{18}N_2O_3$) C, H, N. (See Table I for other method A examples.)

Method B. 2,6,7-Trimetyl-3-*m*-tolyl-3,4-dihydro-4-oxoquinazoline-8-carboxylic Acid (2c). In a 250-mL round-bottomed flask equipped with a magnetic stirrer, reflux condenser, and heating mantle were added 5.2 g (0.02 mol) of 4,[4] 2.2 mL of toluidine, 1.0 g of phosphorus oxychloride,[13] and 100 mL of

(12) (a) Kretzchmar, E.; Barth, H.; Goldhahn, H.; Carstens, E. East German Patent 49610, 1966; *Chem. Abstr.* **1967**, *66*, 28795z. (b) Preuss, F. R.; Hoffmann, E. *Dtsch. Apoth.-Ztg.* **1976**, *116*, 893.

(13) Grimmel, H. W.; Guenther, A.; Morgan, J. F. *J. Am. Chem. Soc.* **1946**, *68*, 542. The original procedure utilized phosphorus trichloride.

toluene. The mixture was refluxed for 4 h and cooled to room temperature. The solvent was removed in vacuo, and Et_2O was added to precipitate a white solid. The product was recrystallized from MeOH to give 2.5 g (40%)[14] of **2c**: mp 267–269 °C; IR (KBr) 3450, 1715, 1685, 1610 cm^{-1}; NMR ($CDCl_3$, Me_2SO-d_6) δ 8.40 (s, 1 H), 7.15–7.50 (m, 4 H), 2.80 (s, 3 H), 2.60 (s, 3 H), 2.50 (s, 3 H), 2.45 (s, 3 H). Anal. ($C_{19}H_{18}N_2O_3$) C, H, N. (See Table I for other method B examples.)

Method C. 2,6,7-Trimethyl-3-(*o*-nitrophenyl)-3,4-dihydro-4-oxoquinazoline-8-carboxylic Acid (2r). In a 250-mL round-bottomed flask were placed 2.65 g (0.01 mol) of **4**,[4] 1.38 g (0.01 mol) of *o*-nitroaniline, and 35 mL of diphenyl ether. The mixture was heated at 230–240 °C for 2 h in the open flask. The reaction mixture was cooled and petroleum ether (50–110 °C) was added to precipitate a solid. The product was recrystallized from CH_2Cl_2/petroleum ether to give 1.0 g (28.3%) of **2r**: mp 326–328 °C; IR (KBr) 3450, 1715, 1685, 1615, 1600 cm^{-1}; NMR ($CDCl_3$, Me_2SO-d_6, TFA) δ 8.55 (s, 1 H), 7.70–8.40 (m, 4 H), 2.80 (s, 3 H), 2.75 (s, 3 H), 2.55 (s, 3 H). Anal. ($C_{18}H_{15}N_3O_5$) C, H, N.

Method D. 2,6,7-Trimethyl-3-*o*-tolyl-3,4-dihydro-4-oxo-8-carbomethoxyquinazoline (2b). In a 250-mL Erlenmeyer flask was placed 3.2 g (10 mmol) of acid **2a** dissolved in 125 mL of chloroform. To this solution was added a methanolic ethereal solution of diazomethane[7] (15 mmol). The mixture was stirred at room temperature for 1 h and concentrated. The crude solid was recrystallized from MeOH–H_2O to give 2.1 g (62.5%) of **2b**: mp 182–184 °C; IR (KBr) 3040, 1730, 1680, 1590 cm^{-1}; NMR ($CDCl_3$) δ 8.1 (s, 1 H), 4.0 (s, 3 H), 2.40 (2 s, 6 H), 2.10 (2 s, 6 H). Anal. ($C_{20}H_{20}NO_3$) C, H, N.

Method E. 2,6,7-Trimethyl-3-*m*-tolyl-3,4-dihydro-4-oxo-8-carbomethoxyquinazoline (2j). In a 250-mL round-bottom flask equipped with a Soxhlet extractor charged with 3 g of 3Å molecular sieves[8] in a cellulose extraction thimble were placed 3.0 g of **2i**, 100 mL of absolute MeOH, and 1 mL of H_2SO_4. The mixture was refluxed for 15 h, cooled, and treated with 1.0 g of anhydrous Na_2CO_3. The solid material was filtered off, and the solution was concentrated. The colorless solid product was recrystallized from CH_2Cl_2–petroleum ether (30–60 °C) to give 1.25 g (32%) of **2j**: mp 161–163 °C; IR (KBr) 2900, 1720, 1660, 1590 cm^{-1}; NMR ($CDCl_3$) δ 7.90 (s, 1 H), 6.9–7.75 (m, 4 H), 3.95 (s, 3 H), 2.40 (s, 3 H), 2.30 (s, 3 H), 2.20 (s, 3 H). Anal. ($C_{19}H_{17}N_2O_3F_1$) C, H, N.

Pharmacological Testing. All compounds were suspended in 30% polyethylene glycol 400 and injected intraperitoneally in a volume of 0.01 mL/g of body weight into 20-g male CF1 mice (obtained from Charles River Breeding Laboratories). Anticonvulsant activity was tested by the Antiepileptic Drug Development (ADD) Program administered by the Epilepsy Section (National Institutes of Health, Bethesda, MD) using the Anticonvulsant Screening Project Test Systems.[10] Compounds were tested for four dosage levels (30, 100, 300, and 600 mg/kg) at 30 min and at 4 h with the maximal electroshock (MES) seizure and pentylenetetrazol (sc Met) seizure threshold test for anticonvulsant activity and the rotorod test to evaluate acute neurotoxicity. Four animals were injected with each dose. Any positive anticonvulsant activity was assessed by four additional observations. The same anticonvulsant methods were also conducted in our laboratory for selected compounds in the series to estimate relative anticonvulsant potency. The screening results from the two laboratories were found to be directly comparable, so the results were combined, and an estimate of the ED_{50} and TD_{50} was made with a graphic method.[10d]

Those compounds showing the anticonvulsant activity not accompanied by neurotoxicity were subjected to additional ADD testing to verify the ED_{50} and TD_{50} values and to establish confidence limits as calculated by the method of Litchfield and Wilcoxon.[10d]

Anticonvulsant activity in the MES test is defined as abolition of the hindlimbs tonic extensor component of the maximal electroshock seizure elicited in mice with a 60-Hz alternating current of 50 mA delivered for 0.2 s via corneal electrodes. The failure to observe even a threshold seizure (a single episode of clonic spasm of 5-s duration) following the subcutaneous administration of the convulsant dose 99% for pentylenetetrazol is considered anticonvulsant activity in the sc Met test.[10b] The complete details of ADD test systems are available.[10a,c]

Methaqualone was used as the reference compound in this study since it has activity in several different anticonvulsant tests, and the compounds we synthesized are methaqualone analogues. The common anticonvulsant phenytoin has a reported ED_{50} of 9.5 mg/kg in the MES portion of this test system but it is not active in the sc Met test.[10a] Ethosuximide's sc Met ED_{50} is reported as 130 mg/kg, but over 1000 mg/kg is required in the MES test. The TD_{50} for these two compounds are 65.5 and 441 mg/kg, respectively.[10a]

Acknowledgment. This research was supported in part by the National Institute of Neurological and Communicative Disorders and Stroke (Grant NS 16988). The authors are indebted to Gill Gladding and the Antiepileptic Drug Development Program, National Institutes of Health, for providing pharmacological data.

Registry No. **2a**, 86542-61-2; **2b**, 86542-62-3; **2c**, 86542-63-4; **2d**, 86542-64-5; **2e**, 81045-04-7; **2f**, 86542-65-6; **2g**, 86542-66-7; **2h**, 86542-67-8; **2i**, 81045-05-8; **2j**, 86542-68-9; **2k**, 81045-06-9; **2l**, 81045-12-7; **2m**, 86542-69-0; **2n**, 86542-70-3; **2o**, 86542-71-4; **2p**, 86542-72-5; **2q**, 86542-73-6; **2r**, 86542-74-7; **2s**, 86542-75-8; **2t**, 86542-76-9; **2u**, 86542-77-0; **2v**, 86542-78-1; **2w**, 86542-79-2; **3**, 73318-14-6; **4**, 73318-18-0; **5** (R_1 = *o*-$CH_3C_6H_4$), 95-53-4; **5** (R_1 = *m*-$CH_3C_6H_4$), 108-44-1; **5** (R_1 = *p*-$CH_3C_6H_4$), 106-49-0; **5** (R_1 = *o*-FC_6H_4), 348-54-9; **5** (R_1 = *m*-FC_6H_4), 372-19-0; **5** (R_1 = *p*-FC_6H_4), 371-40-4; **5** (R_1 = C_6H_5), 62-53-3; **5** (R_1 = *o*-$CF_3C_6H_4$), 88-17-5; **5** (R_1 = *o*-$NO_2C_6H_4$), 88-74-4; **5** (R_1 = *o*-$CH_3OC_6H_4$), 90-04-0; **5** (R_1 = 3,4,5-$(CH_3O)C_6H_2$), 24313-88-0; **5** (R_1 = α-C_5H_4N), 504-29-0; **6**, 86549-49-7; **9b**, 60770-78-7; **9c**, 86542-80-5; **9d**, 86542-81-6; **9e**, 86542-82-7; 2,4-dichloroaniline, 554-00-7; α,α,α-trifluoro-*m*-toluidine, 98-16-8; α,α,α-trifluoro-*p*-toluidine, 455-14-1; 3-aminopicolinic acid, 1462-86-8; 8-carbomethoxy-2,5,6-trimethyl-4*H*-3,1-benzoxazin-4-one, 81045-03-6.

Supplementary Material Available: Full anticonvulsant and toxicity screening data for the 29 compounds submitted to the National Institute of Health's Antiepileptic Drug Development (ADD) Program protocol (2 pages). Ordering information is given on any current masthead page.

(14) Yields can be increased dramatically when acid **4** was allowed to react for 3 h with phosphorus oxychloride in refluxing toluene, thus forming 8-carbomethoxy-2,5,6-trimethyl-4*H*-3,1-benzoxazin-4-one.[5] Removal of the solvent and treatment of the brown mass for 2 h with amine in refluxing toluene gave, upon standard workup, an improved yield of **2c**, 82.3%. Similarly, the yield of **2i** was raised from 33 to 55%.