

Structural and Molecular Modeling Studies of Quinazolinone Anticonvulsants

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Abstract

Studies of derivatives of the anticonvulsant methaqualone led to the discovery that unsaturation in the 2-substituent produced active, but less toxic compounds; accordingly, 2-arylethanone derivatives have been developed. The crystal structures of five 2-arylethanone derivatives of methaqualone were determined to probe structure–activity relationships. Although these compounds display different activities, the solid-state and calculated structures are similar: each compound is observed as the enamine tautomer containing an intramolecular hydrogen bond between the ethanone and the amine N atom and the molecular conformations are the same. These studies conclude that recognition of the anticonvulsants arises from specific binding of an *ortho* substituent on the N(3) phenyl substituent, rather than from binding of a particular conformation or tautomeric form adopted by the compound containing an *ortho* substituent, and that such recognition is characteristic of a broad range of anticonvulsant drugs. Crystal data: (1), 2-[2-oxo-2-(4-pyridyl)ethyl]-3-phenyl-4(3*H*)-quinazolinone, $C_{21}H_{15}N_3O_2$, $M_r = 341.37$, monoclinic, $P2_1$, $a = 12.1646$ (5), $b = 5.5988$ (2), $c = 12.389$ (2) Å, $\beta = 90.47$ (1)°, $V = 843.8$ (1) Å³, $Z = 2$, $D_x = 1.35$ g cm⁻³, $\lambda(\text{Cu } K\alpha) = 1.5418$ Å, $\mu = 7.31$ cm⁻¹, $T = 293$ K, $R = 0.039$, 1764 unique reflections; (2), 3-(2-chlorophenyl)-2-[2-oxo-2-(4-pyridyl)ethyl]-4(3*H*)-quinazolinone, $C_{21}H_{14}ClN_3O_2$, $M_r = 375.82$, monoclinic, $P2_1/a$, $a = 10.9354$ (6), $b = 14.502$ (1), $c = 13.019$ (1) Å, $\beta = 114.481$ (4)°, $V = 1879.0$ (2) Å³, $Z = 4$, $D_x = 1.33$ g cm⁻³, $\lambda(\text{Cu } K\alpha) = 1.5418$ Å, $\mu = 19.87$ cm⁻¹, $T = 293$ K, $R = 4.6\%$, 3550 unique reflections; (3), 3-(2-methylphenyl)-2-[2-oxo-2-(4-pyridyl)ethyl]-4(3*H*)-quinazolinone, $C_{22}H_{17}N_3O_2$, $M_r = 355.40$, monoclinic, $P2_1/c$, $a = 5.618$ (2), $b = 30.329$ (7), $c = 10.456$ (4) Å, $\beta = 98.21$ (2)°, $V = 1763.3$ (9) Å³, $Z = 4$, $D_x = 1.34$ g cm⁻³, $\lambda(\text{Mo } K\alpha) = 0.71069$ Å, $\mu = 0.95$ cm⁻¹, $T = 293$ K, $R = 5.8\%$, 3075 unique reflections; (4), 3-(4-chlorophenyl)-2-[2-oxo-2-(4-

pyridyl)ethyl]-4(3*H*)-quinazolinone, $C_{21}H_{14}ClN_3O_2$, $M_r = 375.82$, orthorhombic, $Pbca$, $a = 13.9347$ (7), $b = 9.6794$ (6), $c = 25.962$ (1) Å, $V = 3501.7$ (3) Å³, $Z = 8$, $D_x = 1.43$ g cm⁻³, $\lambda(\text{Cu } K\alpha) = 1.5418$ Å, $\mu = 21.32$ cm⁻¹, $T = 293$ K, $R = 6.9\%$, 3385 unique reflections; (5), 3-(2-methylphenyl)-2-(2-oxophenethyl)-4(3*H*)-quinazolinone, $C_{23}H_{18}N_2O_2$, $M_r = 354.41$, orthorhombic, $Pbca$, $a = 10.2078$ (4), $b = 10.237$ (1), $c = 35.676$ (3) Å, $V = 3728.0$ (5) Å³, $Z = 8$, $D_x = 1.26$ g cm⁻³, $\lambda(\text{Cu } K\alpha) = 1.5418$ Å, $\mu = 6.62$ cm⁻¹, $T = 293$ K, $R = 4.8\%$, 3532 unique reflections.

Introduction

Class II anticonvulsants are thought to act by enhancing physiological responses to the inhibitory neurotransmitter GABA (γ -aminobutyric acid) (Catterall, 1987) and representatives of this class of anticonvulsants, benzodiazepines and valproic acid, are prescribed to control acquired myoclonic seizures. The type of seizure treated by class II drugs is modeled by chemically inducing seizures through subcutaneously administered metrazole (scMET).

Methaqualone (6) is a moderately effective anticonvulsant in the scMET test with an effective dose (ED₅₀) of 33.5 mg kg⁻¹ (Wolfe, Rathman, Sleevi, Campbell & Greenwood, 1990) and has been the focus of development efforts to enhance activity and lessen toxicity. One study of methaqualone structure–activity relationships established that addition of a 2-arylethylene substituent changes the activity profile of the parent compound (von Boltze, Dell, Lehwald, Lorenz & Ruberg-Schwerr, 1963). Accordingly, a series of compounds has been prepared (Wolfe *et al.*, 1990; Rathman, Sleevi, Krafft & Wolfe, 1980; Wolfe & Rathman 1980), wherein the C(2) substituent is an arylethanone which allows for the formation of an intramolecular hydrogen bond as well as for imine–enamine tautomerization.

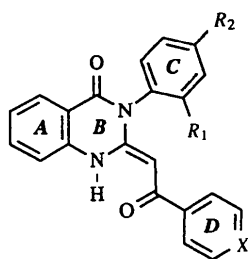
The site of action of methaqualone is unknown; the benzodiazepines are unique amongst anticonvulsants as they are known to bind to a saturable, specific receptor which is part of the GABA inhibitory neuropathway. However, both methaqualone (6) and piriqualone, a MET-active quinazolinone

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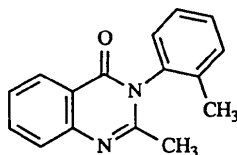
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similar to the [2-oxo-2-(4-pyridyl)-ethyl] compounds, have been reported to enhance *in vivo* binding of the anticonvulsant benzodiazepine, flunitrazepam, to the benzodiazepine receptor (Koe, Minor, Kondratas, Lebel & Koch, 1986). It is possible that other methaqualone derivatives, like the quinazolinone reported here, act similarly to enhance the *in vivo* binding of benzodiazepines, and that these anticonvulsants are interacting with the benzodiazepine/Cl⁻ ionophore/GABA receptor, although not, apparently, by binding directly to the benzodiazepine receptor itself.

We determined the crystal structures of five of these compounds [see (1)–(5)] to analyze the effects of various substituents on the pendant phenyl ring attached to N(3), the effects of different types of aryl rings in the ethanone side chain, and the tautomeric form. The compounds studied vary in activity and a correlation of structure and activity is sought; compounds (2) and (3) are active in the scMET test with ED₅₀ values of 30 mg kg⁻¹. Compound (2) shows a twofold increase in activity over methaqualone as a result of lower toxicity so that the protective index (ratio of toxic dose/effective dose) for (2) is 18 (Wolfe *et al.*, 1990). Compound (1) shows low activity with an ED₅₀ = 300 mg kg⁻¹ and compounds (4) and (5) show no activity, even at doses of 300 mg kg⁻¹ (Wolfe *et al.*, 1990).



- (1) $R_1 = \text{H}, R_2 = \text{H}, X = \text{N}$
 (2) $R_1 = \text{Cl}, R_2 = \text{H}, X = \text{N}$
 (3) $R_1 = \text{CH}_3, R_2 = \text{H}, X = \text{N}$
 (4) $R_1 = \text{H}, R_2 = \text{Cl}, X = \text{N}$
 (5) $R_1 = \text{Cl}, R_2 = \text{H}, X = \text{CH}$



(6)

Experimental

The samples were provided by Dr J. F. Wolfe of the Virginia Polytechnic Institute and State University. For all crystal structure determinations, the data were measured at room temperature on an Enraf-Nonius CAD-4F diffractometer and the unit-cell parameters and orientation angles were obtained by the method of least squares from the angular parameters of 25 individually centered reflections. The dif-

fracted intensities were collected by ω - 2θ scans; all intensities were corrected for Lorentz and polarization effects. Absorption corrections were applied to the data collected from crystals of compound (4) by using the program *DIFABS* (Walker & Stuart, 1983); the minimum correction was 0.688, the maximum was 1.376. The structures were solved by direct methods by using the program *MULTAN78* (Germain, Main & Woolfson, 1971). Refinement was based upon *F* values. Neutral-atom scattering factors and anomalous-dispersion corrections for the non-H atoms were taken from Cromer & Mann (1968) and for H atoms from Stewart, Davidson & Simpson (1965). For compound (1), the origin of the unit cell was defined by holding the y coordinate of atom N(1) invariant. For each structure, all the H atoms were identified in difference Fourier syntheses and were included in the model in idealized positions. In each structure, except that of compound (4), the coordinates of all the atoms, the anisotropic vibration parameters for the non-H atoms, and the isotropic vibration parameters of the H atoms were refined; each structure was refined in blocks with the non-H-atom parameters in one cycle and the H-atom parameters in the subsequent cycle. For structure (4), the isotropic vibration parameters for the H atoms [except for H(1)] were assigned values 120% of the attached non-H atoms and were not refined; subsequently, the coordinates of all the atoms, the anisotropic vibration parameters of the non-H atoms and the isotropic vibration parameter of H(1) were refined. The *XRAY76* (Stewart, Machin, Dickinson, Ammon, Heck & Flack, 1976) system of programs was used in the analysis except where mentioned above. A summary of the crystal data and structure refinements is given in Table 1. The atomic coordinates and equivalent isotropic vibration parameters for the non-H atoms of all five structures are given in Table 2. Selected bond distances, bond angles and the hydrogen-bond geometry are given in Table 3.*

Calculation methodology

The *MM2* (Allinger, 1977) molecular-mechanics force field and extensions to it, including specific treatment of hydrogen bonds, as provided in the *MACROMODEL* software package (Mohamadi, Richards, Guide, Liskamp, Caufield, Chang, Hendrickson & Still, 1990) was used to examine the stability of the intramolecular hydrogen bonds and the observed molecular conformations for com-

* Lists of structure factors, anisotropic thermal parameters, H-atom parameters, and additional bond lengths and bond angles have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 55876 (140 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: HH0630]

Table 1. *Crystallographic data for the quinazolinones*

	(1)	(2)	(3)	(4)	(5)
Crystal dimensions (mm)	0.09 × 0.12 × 0.17	0.10 × 0.25 × 0.25	0.20 × 0.27 × 0.40	0.08 × 0.36 × 0.45	0.20 × 0.20 × 0.30
θ range of reflections used for cell parameters (°)	41.0–56.7	34.3–43.7	16.0–23.2	43.8–68.5	39.9–48.1
hkl range for data	–14/14, –6/6, –15/15	0/13, –17/17, –14/14	0/6, 0/34, –12/12	0/16, 0/11, –30/0	0/12, 0/12, 0/42
θ_{\max} (°)	70	70	25	70	70
Total reflections	7282	8487	3572	3154	5262
R_{merge} (%)	3	4	2	4	3
Unique reflections	1764	3550	3075	3385	3532
Observed reflections [$I > 2.5\sigma(I)$]	1322	2411	1875	2511	2495
Total parameters refined	321	300	312	287	316
$w = 1/[\sigma^2(F) + kF^2]$, $k =$	0.0004	0.0004	0.00008	0.0004	0.0003
R	0.039	0.046	0.058	0.069	0.048
wR	0.043	0.056	0.051	0.084	0.066
S	1.00	1.01	1.00	1.09	1.00
$(\Delta/\sigma)_{\max}$	0.070	0.003	0.067	0.001	0.010
$\Delta\rho_{\max}$ (e Å ⁻³)	0.16	0.26	0.22	0.39	0.13
$\Delta\rho_{\min}$ (e Å ⁻³)	–0.16	–0.20	–0.20	–0.29	–0.12

Table 2. *Atomic fractional coordinates (× 10⁴) and equivalent isotropic vibrational parameters (Å² × 10²) for the non-H atoms*

B_{eq} is defined as one third of the trace of the B_{ij} matrix.

	x	y	z	B_{eq}		x	y	z	B_{eq}
Compound (1)					Compound (3)				
N(1)	5727 (1)	3894 (0)	2355 (1)	397 (9)	N(1)	3836 (4)	722 (1)	3159 (2)	338 (12)
C(2)	6826 (1)	4179 (7)	2415 (1)	351 (9)	C(2)	4925 (6)	1117 (1)	3376 (3)	322 (14)
N(3)	7413 (1)	2696 (6)	3105 (1)	361 (8)	N(3)	3983 (4)	1467 (1)	2616 (2)	310 (12)
C(4)	6934 (2)	845 (7)	3708 (2)	365 (9)	C(4)	2065 (5)	1428 (1)	1585 (3)	335 (15)
O(5)	7487 (1)	–332 (6)	4339 (1)	485 (9)	O(5)	1454 (4)	1747 (1)	912 (2)	410 (11)
C(6)	5748 (2)	487 (7)	3530 (1)	353 (9)	C(6)	897 (6)	998 (1)	1468 (3)	331 (15)
C(7)	5208 (2)	–1393 (8)	4037 (2)	422 (11)	C(7)	–1186 (6)	934 (1)	577 (3)	433 (17)
C(8)	4091 (2)	–1680 (8)	3877 (2)	487 (13)	C(8)	–2304 (7)	531 (1)	503 (3)	512 (19)
C(9)	3515 (2)	–51 (9)	3238 (2)	497 (14)	C(9)	–1406 (7)	190 (1)	1319 (3)	558 (21)
C(10)	4032 (2)	1821 (8)	2741 (2)	472 (13)	C(10)	646 (6)	247 (1)	2204 (3)	436 (18)
C(11)	5174 (2)	2077 (7)	2873 (1)	366 (10)	C(11)	1789 (6)	653 (1)	2274 (3)	336 (15)
C(12)	7321 (1)	5916 (8)	1786 (2)	386 (10)	C(12)	6891 (5)	1163 (1)	4325 (3)	325 (14)
C(13)	6709 (2)	7371 (8)	1081 (2)	413 (11)	C(13)	7911 (5)	805 (1)	5076 (3)	319 (15)
O(14)	5666 (1)	7315 (6)	1008 (1)	538 (10)	O(14)	7222 (4)	411 (1)	4938 (2)	390 (11)
C(15)	7276 (2)	9120 (7)	359 (2)	400 (10)	C(15)	10011 (5)	907 (1)	6095 (3)	290 (13)
C(16)	6691 (2)	11078 (9)	–14 (2)	499 (14)	C(16)	12024 (6)	637 (1)	6261 (3)	367 (16)
C(17)	7194 (3)	12698 (10)	–675 (2)	654 (17)	C(17)	13901 (6)	755 (1)	7209 (3)	456 (18)
N(18)	8225 (3)	12508 (10)	–1007 (2)	772 (19)	N(18)	13916 (5)	1099 (1)	8002 (3)	489 (16)
C(19)	8783 (2)	10595 (12)	–668 (3)	713 (22)	C(19)	11943 (7)	1345 (1)	7843 (3)	461 (18)
C(20)	8350 (2)	8864 (9)	17 (2)	543 (15)	C(20)	9989 (6)	1267 (1)	6902 (3)	372 (15)
C(21)	8596 (1)	3013 (6)	3227 (1)	341 (9)	C(21)	4979 (5)	1908 (1)	2881 (3)	295 (14)
C(22)	8993 (2)	4833 (7)	3869 (2)	432 (11)	C(22)	6699 (6)	2055 (1)	2157 (3)	383 (16)
C(23)	10130 (2)	5082 (8)	3989 (2)	496 (13)	C(23)	7610 (7)	2477 (1)	2363 (3)	512 (20)
C(24)	10825 (2)	3521 (9)	3476 (2)	522 (14)	C(24)	6778 (8)	2739 (1)	3276 (4)	548 (21)
C(25)	10421 (2)	1727 (9)	2836 (2)	546 (15)	C(25)	5082 (7)	2590 (1)	3993 (3)	441 (18)
C(26)	9283 (2)	1460 (8)	2708 (2)	459 (12)	C(26)	4157 (6)	2165 (1)	3823 (3)	349 (15)
					C(27)	2378 (7)	2002 (1)	4661 (3)	579 (21)
Compound (2)					Compound (4)				
N(1)	3482 (2)	–523 (1)	5309 (2)	338 (8)	N(1)	7666 (2)	–614 (3)	6102 (1)	236 (10)
C(2)	4403 (2)	–36 (2)	6153 (2)	316 (9)	C(2)	6716 (2)	–619 (3)	6194 (1)	218 (11)
N(3)	4007 (2)	821 (1)	6389 (2)	313 (8)	N(3)	6162 (2)	341 (2)	5930 (1)	232 (9)
C(4)	2747 (2)	1225 (2)	5761 (2)	341 (10)	C(4)	6530 (2)	1273 (3)	5566 (1)	249 (11)
O(5)	2508 (2)	1993 (1)	6011 (2)	439 (8)	O(5)	6001 (1)	2063 (2)	5341 (1)	366 (10)
C(6)	1808 (2)	658 (2)	4853 (2)	332 (10)	C(6)	7568 (2)	1210 (3)	5483 (1)	244 (11)
C(7)	513 (2)	972 (2)	4191 (2)	404 (12)	C(7)	8009 (2)	2116 (3)	5138 (1)	307 (13)
C(8)	–369 (2)	432 (2)	3357 (2)	455 (13)	C(8)	8988 (2)	2094 (4)	5080 (1)	348 (15)
C(9)	20 (3)	–445 (2)	3167 (3)	471 (13)	C(9)	9539 (2)	1173 (3)	5370 (1)	322 (13)
C(10)	1290 (3)	–772 (2)	3802 (2)	425 (12)	C(10)	9114 (2)	269 (3)	5707 (1)	296 (13)
C(11)	2193 (2)	–218 (2)	4656 (2)	328 (10)	C(11)	8118 (2)	281 (3)	5767 (1)	235 (11)
C(12)	5678 (2)	–383 (2)	6774 (2)	334 (10)	C(12)	6327 (2)	–1585 (3)	6533 (1)	246 (11)
C(13)	6099 (2)	–1244 (2)	6541 (2)	347 (10)	C(13)	6898 (2)	–2602 (3)	6760 (1)	252 (11)
O(14)	5373 (2)	–1745 (1)	5726 (1)	423 (8)	O(14)	7801 (1)	–2689 (2)	6700 (1)	290 (9)
C(15)	7467 (2)	–1597 (2)	7294 (2)	362 (11)	C(15)	6447 (2)	–3714 (3)	7083 (1)	268 (12)
C(16)	8369 (3)	–1133 (2)	8214 (3)	519 (15)	C(16)	5466 (2)	–3978 (4)	7104 (1)	387 (15)
C(17)	9609 (3)	–1534 (2)	8846 (3)	610 (18)	C(17)	5138 (3)	–5075 (4)	7395 (2)	491 (19)
N(18)	9997 (2)	–2348 (2)	8639 (2)	544 (13)	N(18)	5698 (3)	–5935 (3)	7663 (1)	504 (17)
C(19)	9115 (3)	–2785 (2)	7761 (3)	532 (14)	C(19)	6631 (3)	–5658 (4)	7641 (1)	474 (18)
C(20)	7862 (2)	–2453 (2)	7068 (2)	423 (12)	C(20)	7034 (2)	–4603 (3)	7362 (1)	359 (15)
C(21)	4940 (2)	1320 (2)	7351 (2)	323 (10)	C(21)	5147 (2)	497 (3)	6043 (1)	235 (11)
C(22)	5854 (2)	1918 (2)	7223 (2)	419 (12)	C(22)	4483 (2)	–299 (3)	5782 (1)	312 (13)
C(23)	6801 (3)	2336 (2)	8164 (3)	502 (14)	C(23)	3509 (2)	–67 (4)	5864 (1)	352 (15)
C(24)	6830 (3)	2189 (2)	9212 (3)	509 (15)	C(24)	3229 (2)	951 (4)	6196 (1)	346 (14)
C(25)	5896 (3)	1606 (2)	9340 (2)	493 (14)	C(25)	3895 (2)	1754 (4)	6457 (1)	392 (16)
C(26)	4965 (2)	1167 (2)	8406 (2)	368 (11)	C(26)	4861 (2)	1507 (3)	6381 (1)	319 (13)
Cl(27)	3810 (1)	415 (1)	8554 (1)	553 (4)	Cl(27)	2011 (1)	1254 (1)	6293 (1)	651 (6)

Table 2 (cont.)

Compound (5)	x	y	z	B _{eq}	Compound (5)	x	y	z	B _{eq}
N(1)	7471 (2)	19 (2)	6485 (0)	461 (7)	O(14)	8047 (1)	1877 (2)	6015 (0)	563 (8)
C(2)	6272 (2)	29 (2)	6332 (1)	403 (8)	C(15)	6555 (2)	2476 (2)	5538 (1)	418 (8)
N(3)	5360 (1)	-865 (1)	6468 (0)	402 (7)	C(16)	5560 (2)	2089 (2)	5298 (1)	530 (11)
C(4)	5655 (2)	-1824 (2)	6733 (1)	426 (8)	C(17)	5316 (2)	2765 (3)	4969 (1)	631 (12)
O(5)	4838 (2)	-2637 (2)	6819 (0)	552 (7)	C(18)	6041 (3)	3839 (3)	4879 (1)	638 (13)
C(6)	6965 (2)	-1752 (2)	6899 (1)	430 (8)	C(19)	7014 (3)	4256 (2)	5116 (1)	637 (13)
C(7)	7333 (2)	-2602 (2)	7185 (1)	509 (10)	C(20)	7271 (2)	3577 (2)	5443 (1)	520 (10)
C(8)	8556 (3)	-2513 (3)	7342 (1)	581 (11)	C(21)	4051 (2)	-875 (2)	6309 (1)	403 (8)
C(9)	9427 (2)	-1577 (3)	7212 (1)	604 (12)	C(22)	3781 (2)	-1722 (2)	6019 (1)	504 (10)
C(10)	9091 (2)	-735 (2)	6931 (1)	549 (11)	C(23)	2543 (3)	-1753 (3)	5866 (1)	611 (13)
C(11)	7852 (2)	-820 (2)	6769 (1)	439 (9)	C(24)	1586 (3)	-931 (3)	6002 (1)	586 (12)
C(12)	5968 (2)	881 (2)	6042 (1)	436 (9)	C(25)	1874 (2)	-75 (3)	6288 (1)	561 (11)
C(13)	6907 (2)	1733 (2)	5885 (1)	439 (9)	C(26)	3110 (2)	-30 (2)	6452 (1)	490 (9)
					C(27)	3415 (4)	901 (4)	6767 (1)	769 (18)

Table 3. Selected bond lengths, bond angles and intramolecular hydrogen-bond geometry for the quinazolines

Bond lengths (Å)	(1)	(2)	(3)	(4)	(5)
C(11)—N(1)	1.381 (3)	1.383 (3)	1.385 (4)	1.379 (4)	1.384 (3)
N(1)—C(2)	1.347 (2)	1.343 (3)	1.349 (4)	1.346 (4)	1.341 (2)
C(2)—C(12)	1.388 (5)	1.384 (3)	1.382 (4)	1.394 (4)	1.390 (3)
C(12)—C(13)	1.403 (4)	1.407 (3)	1.411 (4)	1.397 (4)	1.412 (3)
C(13)—O(14)	1.272 (2)	1.260 (3)	1.258 (4)	1.271 (3)	1.261 (2)
Bond angles (°)					
C(2)—N(1)—C(11)	123.3 (2)	124.3 (2)	124.0 (2)	124.3 (2)	124.0 (2)
N(1)—C(2)—N(3)	118.0 (2)	117.0 (2)	117.2 (2)	117.2 (2)	117.7 (2)
C(2)—N(3)—C(4)	123.7 (2)	124.3 (2)	124.1 (2)	124.0 (2)	123.6 (1)
C(2)—N(3)—C(21)	119.6 (2)	117.8 (2)	119.2 (2)	120.8 (2)	119.0 (1)
C(4)—N(3)—C(21)	116.6 (2)	117.9 (2)	116.7 (2)	115.1 (2)	117.2 (1)
C(2)—C(12)—C(13)	121.7 (2)	122.5 (2)	122.8 (3)	121.1 (2)	122.0 (2)
C(12)—C(13)—O(14)	123.7 (3)	123.1 (2)	124.9 (2)	124.0 (3)	123.7 (2)
C(12)—C(13)—C(15)	120.4 (2)	119.3 (2)	116.8 (2)	120.1 (2)	118.5 (2)
O(14)—C(13)—C(15)	115.9 (3)	117.6 (2)	118.2 (2)	115.8 (2)	117.8 (2)
Hydrogen-bond geometry					
N(1)—H(1)···O(14) (Å)	2.541 (3)	2.604 (3)	2.637 (3)	2.546 (3)	2.603 (2)
N(1)—H(1) (Å)	1.13 (5)	0.82 (3)	0.96 (3)	1.00 (4)	0.97 (2)
H(1)···O(14) (Å)	1.52 (5)	1.90 (3)	1.83 (3)	1.64 (4)	1.78 (2)
N(1)—H(1)···O(14) (°)	147 (3)	143 (2)	139 (2)	147 (3)	141 (2)

pounds (1) and (3) and the *p*-CH₃ derivative of compound (4). Usage-directed Monte Carlo searching of conformational space was used to examine 3000 conformers with tabulation of those conformers within 50 kJ mol⁻¹ of the lowest energy structure.

In addition, the barrier to rotation about the N(3)—phenyl bond was evaluated by rigid rotation of the phenyl ring in 20° intervals followed by minimization of the structure by holding the torsion angle that defines the phenyl-ring orientation fixed. At the heights of the barrier (torsion angles = 0 and 180° producing a coplanar arrangement of the phenyl ring and the quinazolinone) the *MM2* force field allowed unrealistic distortion of the *sp*² atoms in the phenyl ring, undoubtedly due to the omission of a π calculation in this calculation. Consequently, the calculations for the energy barrier were performed with all of the torsion angles in the phenyl ring constrained to assure planarity of the ring.

Ab initio molecular orbital calculations were performed using the *GAUSSIAN90* program (Frisch, Head-Gordon, Trucks, Foresman, Schlegel, Raghavachari, Robb, Binkley, Gonzalez, Defrees, Fox, Whiteside, Seeger, Melius, Baker, Martin, Kahn,

Stewart, Topiol & Pople, 1990) to search for differences between the active and inactive structures and to evaluate the relative stabilities of the two tautomeric forms of compounds (1) and (3). To reduce computer time, the structures were modeled with a CH₃ group in place of the pyridyl ring in position 15. All calculations were conventional closed-shell *ab initio* molecular orbital calculations wherein equilibrium values of geometrical parameters were obtained by minimizing the molecular energy. The geometry of each model structure was fully optimized using the STO-3G basis set and a stationary-point calculation was performed with the 3-21G basis set.

Results

As is shown in Figs. 1 and 2, the structures for the five quinazolines are similar: in each structure, the enamine tautomer is observed and a strong intramolecular hydrogen bond is found between the amino group of the heterocyclic ring and the carbonyl O atom of the ethanone (see Table 3). The enamine form was also found in a ¹H NMR study of the solution state (Wolfe *et al.*, 1990; Rathman *et al.*, 1980; Wolfe & Rathman, 1980). The hydrogen bond determines the orientation of the ethanone fragment relative to the quinazolinone and produces an extended planar region made up of ring A, ring B, and atoms O(5), C(12), C(13) and O(14). The least-squares planes calculated for these atoms [N(1)—O(14)] have standard deviations of less than 0.07 Å. The position of the terminal pyridyl or phenyl ring on the ethanone side chain is not fixed by the hydrogen bond, and varies over a wide range. In each structure, the pendant phenyl ring attached to N(3) (ring C) is approximately perpendicular to the quinazolinone backbone.

The molecular-mechanics search of conformational space for three compounds which differ in the substitution pattern in ring C, (1), (3) and the *p*-CH₃ derivative of (4), found a predominance of low-energy conformers which have an intramolecular hydrogen bond and an orientation for ring C similar

to that found in the crystals. These low-energy, hydrogen-bonded structures predominate over other conformations by a factor of 2.5 to 1. Each search also revealed an alternative family of conformations in which the hydrogen bond is broken; the steric energy of each alternative conformation is approximately 18.0 kJ mol^{-1} higher than the hydrogen-bonded structure. This difference in energy is a result of the stabilization gained from forming the hydrogen bond. The energy required to break the hydrogen bond could easily be gained through interaction with a recognition site that could bind to either or both of the N(1)H group and the carbonyl group [O(14)] freed by breaking the intramolecular bond. Upon interaction with a recognition site, the conformation depicted in the 'open' structure in Fig. 3 could participate in three hydrogen bonds, in contrast to the intramolecular hydrogen-bonded structure which could form only one recognition-site hydrogen bond, and could, therefore, bind with greater affinity. This alternative for the conformation

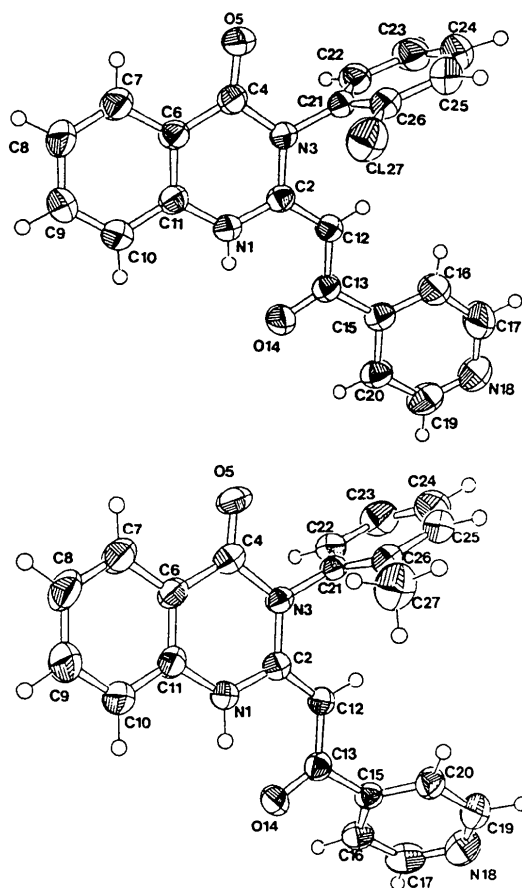


Fig. 1. The molecular conformations of the active quinazolinone derivatives: (2) (top) and (3) (bottom). The diagram was drawn with the plotting program *ORTEP* (Johnson, 1976) with thermal ellipsoids at the 50% probability level except for H atoms.

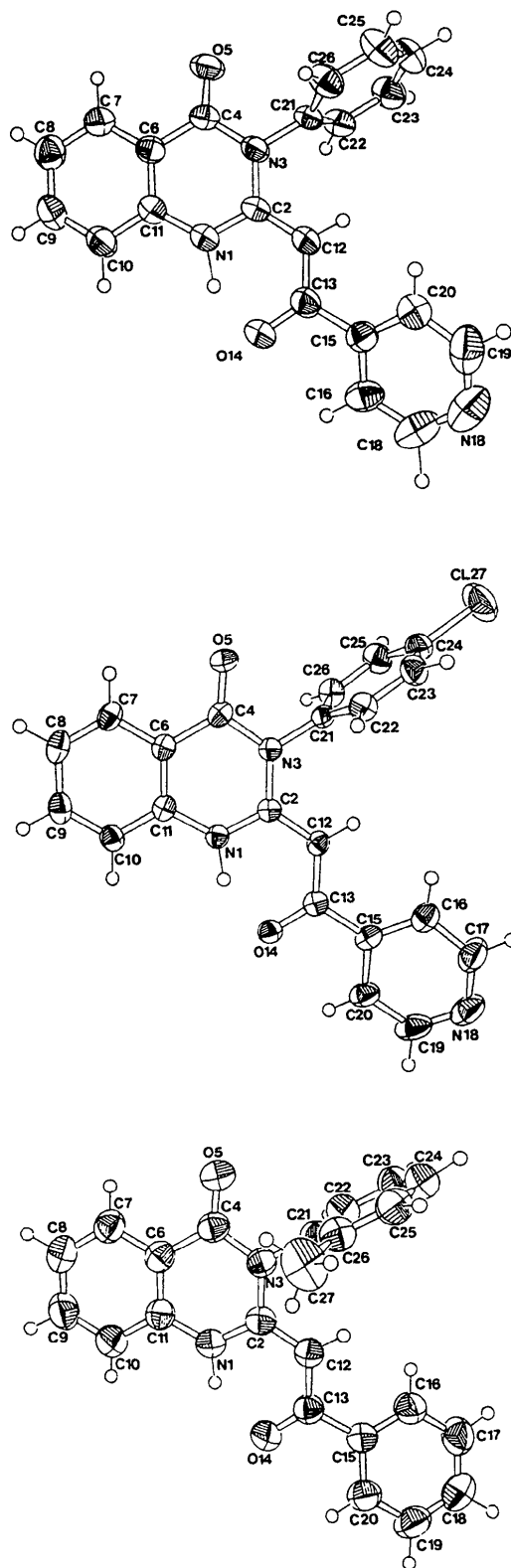


Fig. 2. The molecular conformations of the three inactive quinazolinone derivatives: (1) (top), (4) (middle) and (5) (bottom). The diagram was drawn as in Fig. 1.

of the drugs should be considered in the design of new or constrained analogues. The 'open' structures (see Fig. 3) differ from the hydrogen-bonded structures in that they provide two hydrogen-bond acceptors on opposite edges of the molecule and the orientation of ring *C* deviates more from the less perpendicular orientation. The *N*-phenyl ring (*C*) in the *ortho*-substituted compound is closest to a perpendicular orientation, as might be expected from steric considerations.

Investigation of the barrier to rotation about the N(3)—C(21) bond found that rotation through the planar conformation that placed the *o*-methyl group proximal to the carbonyl O atom [O(5)] required 80 kJ mol^{-1} and rotation through the planar conformation that placed the *o*-methyl group proximal to C(12) required 83 kJ mol^{-1} . For these calculations the bonding of the phenyl-ring atoms was constrained to reflect the planar geometry of a π system. In the calculations, the high-energy conformations of the planar transition states are produced by distortion of the planarity of the bonding around N(3) and thus the planarity of the *B* ring; when the torsion angle C(4)—N(3)—C(21)—C(26) is 0° , the sum of bond angles around N(3) is 356.0° , when the angle is 180° [which orients the *o*-methyl group toward C(12)], the sum of bond angles is 351.0° .

Because of a lack of appropriate parameters for the imine tautomer, *ab initio* calculations were used to evaluate the stability of the two tautomeric forms (enamine or imine) of both an active compound (3) and an inactive compound (1). [In the calculations,

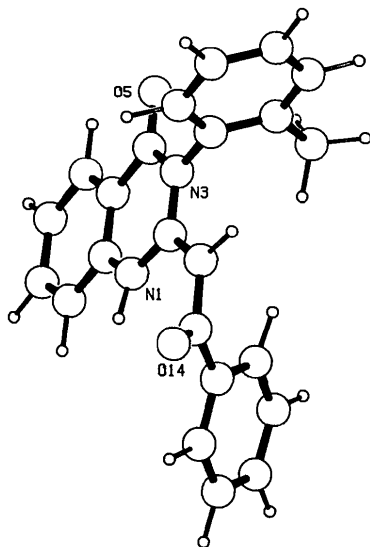


Fig. 3. The 'open' conformation of compound (3), formed by breaking the intramolecular hydrogen bond between N(1) and O(14). This conformation offers three hydrogen-bonding sites to a potential recognition interaction. The diagram was drawn with the plotting program *PLUTO* (Motherwell, 1979).

compounds (1) and (3) were modeled by replacing the pyridyl ring with a CH_3 group.] The results of the calculations were consistent with ^1H NMR studies (Wolfe *et al.*, 1990) and showed that the enamine tautomer is more stable and that tautomer stability is unaffected by substituents on ring *C*.

Discussion

The structure–activity data for this series of meth-aqualone derivatives indicate that the pyridyl ring in the arylethanone side chain is important for activity and that compounds with *ortho* substituents in the N(3) phenyl ring (*C*) are active while compounds with no substitutions on ring *C* are weakly active and *para*-substituted compounds are inactive, presumably due to steric restriction at the position of the *para* substituent in the anticonvulsant recognition site. We undertook crystal structure determinations and computations of molecular properties to determine what effects these different substituent patterns had on the molecular conformations, the preferred tautomer, and the inter- and intramolecular interactions.

We found, by examining the lack of conformational differences among the active and inactive compounds (see Fig. 4), the accessibility of the perpendicular orientation of ring *C* in each compound and the similarity of the electronic structures as demonstrated by *ab initio* calculations, that the effectiveness and low toxicity of the *ortho*-substituted compounds can best be explained by hypothesizing that *recognition arises from specific binding of the ortho group*, rather than from binding of a conformation or particular tautomer adopted by the compound containing an *ortho* substituent. The structure–activity relationship (SAR) data for these compounds indicate that the type of substituent in the *ortho* position has little effect on activity; therefore, the recognition is probably hydrophobic or steric in nature and may function by contributing to

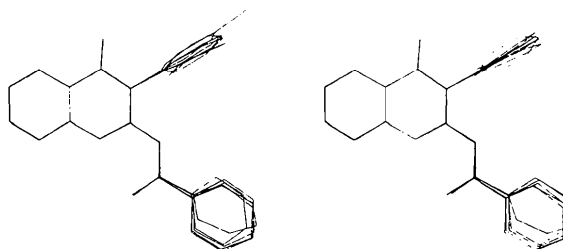


Fig. 4. A stereoscopic diagram of the superposition of all five observed conformations for compounds (1)–(5) showing the similarity of the molecular conformations. The superposition was calculated by a least-squares fit of the quinazolinone atoms by using the program *PROFIT* (Smith, 1983) and plotted with the program *PLUTO* (Motherwell, 1979). The molecular orientations are the same as in Figs. 1 and 2.

an accurate positioning of the strong hydrogen-bonding and π -stacking interactions in the recognition site.

The hypothesis of recognition of an *ortho* substituent is supported by a study of methaqualone by Mannschreck, Koller, Stühler, Davies & Traber (1984) who found that the barrier to rotation about the N(3)-phenyl bond was high enough to prevent interconversion of the two enantiomers at room temperature and that the enantiomers differed in activity. The authors achieved partial resolution of the two enantiomers (70% optical purity) and found that the (-) enantiomer has 35% greater anticonvulsant activity, which suggests that the *ortho* substituent is *recognized* in one particular orientation relative to the quinazolinone. The measured ΔG^\ddagger for the racemization of the methaqualone enantiomers was 131.6 (4) kJ mol⁻¹ which is much higher than the barrier calculated in this study using the MM2 force field of *ca* 80 kJ mol⁻¹, a difference which highlights the limitations of a molecular-mechanics calculation which omits treatment of the π system. Unfortunately, Mannschreck *et al.* (1984) did not identify the absolute configuration of the more active enantiomer and energy calculations are insensitive to chirality; therefore, the precise position of the *ortho* substituent relative to the quinazolinone is unknown. The structure of the active enantiomer will be a subject of further study and should be the basis for design of restricted analogues to probe the preferred *ortho* orientation. Such information could have importance to the development of several types of anticonvulsants because, as shown below, the presence of an *ortho*-substituted phenyl ring is common in anticonvulsants.

Structure-activity studies of anticonvulsant drugs are hampered by the lack of information regarding the mechanism of action and the target site(s) for the drugs. Even without this information, surveys of several chemical classes of anticonvulsants reveal structural themes for these drugs. One theme is described in the *common structural model for central nervous system drugs* outlined by Lloyd & Andrews (1986) which requires a hydrophobic ring which is oriented perpendicular to the plane defined by a hydrogen bond to an N atom. Features that are more specific to anticonvulsants are becoming evident with increased development and study of active compounds. Early work identified the importance of hydrophobic groups and electron-donating regions (Camerman & Camerman, 1980) and a mutually perpendicular orientation of a single hydrophobic group and the electron pair (Coddling, Lee & Richardson, 1984). Recently, systematic investigation of sets of similar compounds, including phenylpiperidinopyridazines (Coddling, Duke, Aha, Palmer, McClurg & Szkaradzinska, 1990), 4-amino-*N*-

phenylbenzamides (Duke & Coddling, 1992), benzodiazepines (Hamor & Martin, 1983; Popp, 1977; Sternbach, Sancilio & Blount, 1974) and the quinazolinone compounds reported herein, emphasize four common features: (i) that the molecular conformations of active and inactive compounds are similar, yet (ii) the presence of *ortho* substituents on a phenyl ring results in an increase in activity, (iii) a *para* substituent on the same ring results in a decrease in activity, and (iv) the chemical properties of the group in the *ortho* position are not directly related to the activity of the compound. Given that the *ortho* substituent determines the molecular conformation, we suggest a *common aspect of anticonvulsant binding sites is a steric recognition site for an ortho-substituted phenyl ring*. The steric recognition of an *ortho* substituent may orient the critical binding region of these molecules which contains electron-donating regions.

In summary, we propose that the activity of the anticonvulsants reported herein arises from recognition of an *ortho*-substituted phenyl ring in a perpendicular orientation to the quinazolinone ring and that an 'open' conformation without the observed intramolecular hydrogen bond may contribute to high affinity binding. In addition, we propose that recognition of the *ortho*-substituted phenyl ring is common in anticonvulsant activity. The existence of enantiomers of methaqualone will allow further definition of the preferred orientation of the *ortho* substituent and the development of more effective anticonvulsants.

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A Lattice-Dynamical Calculation of Atomic Displacement Parameters in Oxahydrocarbons

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Abstract

A lattice-dynamical calculation of atomic displacement parameters for oxahydrocarbons has been carried out using empirical atom–atom potential functions and estimates of the atomic charge from the literature and considering Coulombic interactions. The Born–von Kármán formalism in terms of molecular translations and rotations has been used. The performances of the different parameter sets are assessed by comparison with experimental data.

Introduction

Lattice-dynamical calculations of atomic displacement parameters in hydrocarbon crystals, made using semiempirical atom–atom potential functions (Pertsin & Kitaigorodski, 1987), have been carried out for many years with considerable success using either rigid-molecule models (Filippini, Gramaccioli, Simonetta & Suffritti, 1973) or, more recently, allowing for molecular flexibility (Bonadeo & Burgos, 1982; Gramaccioli & Filippini, 1983, 1985; Filippini & Gramaccioli, 1986, 1989; Filippini, 1990). Also,

the calculated infrared and Raman frequencies, phonon dispersion curves and thermodynamical quantities are in very good agreement with experiment. An interesting extension of the method to silicates has also been proposed recently (Pilati, Bianchi & Gramaccioli, 1990).

Very little work has been performed on heteroatom molecules, mainly because in this case the semiempirical potential parameter sets are scarcer and have not been thoroughly tested. Moreover, for these compounds, the different electronegativities of the constituent atoms give rise to non-negligible multipolar electrostatic moments, which must be accounted for by the use of an appropriate Coulombic potential model.

In an attempt to extend the range of applicability of the available semiempirical force fields, we have previously applied the method to azahydrocarbons (Criado, 1990) and chloro- and fluorohydrocarbons (Muñoz & Criado, 1992). In both cases, the use of 6-exp potential functions for van der Waals forces and an atomic point-charge model to account for electrostatic forces proved to be fruitful. In the present work, we consider oxahydrocarbons. Closely