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2-Acetamido-*N*-benzyl-2-(methoxyamino)acetamides: functionalized amino acid anticonvulsants

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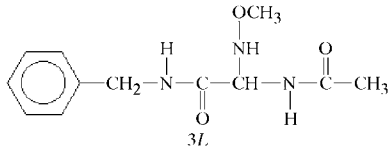
In the crystal structure of 2-acetamido-*N*-benzyl-2-(methoxyamino)acetamide (3*L*), $C_{12}H_{17}N_3O_3$, the 2-acetylaminoacetamide moiety has a linearly extended conformation, with an interplanar angle between the two amide groups of 157.3 (1)°. In 2-acetamido-*N*-benzyl-2-[methoxy(methyl)amino]acetamide (3*N*), $C_{13}H_{19}N_3O_3$, the planes of the two amide groups intersect at an angle of 126.4 (4)°, resulting in a chain that is slightly more bent. The replacement of the methoxyamino H atom of 3*L* with a methyl group to form 3*N* and concomitant loss of hydrogen bonding results in some positional/thermal disorder in the methoxy(methyl)amino group. In both structures, in addition to classical N—H···O hydrogen bonds, there are also weak non-standard C—H···O hydrogen bonds. The hydrogen bonds and packing interactions result in planar hydrophilic and hydrophobic areas perpendicular to the *c* axis in 3*L* and parallel to the *ab* plane in the *N*-methyl derivative. Stereochemical comparisons with phenytoin have identified two O atoms and a phenyl group as molecular features likely to be responsible for the anticonvulsant activities of these compounds.

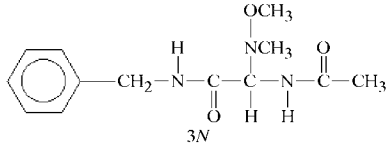
Comment

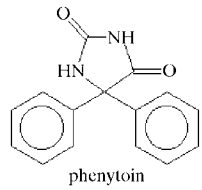
The title compounds, 2-(acetylamino)-*N*-benzyl-2-(methoxyamino)acetamide (3*L*) and its *N*-methyl derivative (3*N*), are members of a series of functionalized α-heteroatom-substituted non-naturally occurring amino acids synthesized and tested for anticonvulsant activity (Kohn *et al.*, 1991). These two compounds were the most potent of the group, demonstrating median effective dose values required to prevent maximal electroshock seizures in mice comparable to the well known antiepileptic drug phenytoin. We determined the crystal structures of 3*L* and 3*N* in order to investigate the stereochemical basis for their anticonvulsant properties.

‡ Deceased.

The structure of 3*L* is presented in Fig. 1. The asymmetric unit contains one molecule, with atoms C7–C13 extended







linearly, and with the two amide-group planes (atoms C7/N8/C9/C10/O14 and C10/N11/C12/C13/O18) intersecting at an angle of 157.3 (1)°. The C9—C10—N11—C12 torsion angle is −160.9 (2)°. The sp^3-hybridization of atom N15 is indicated by the sum of the bond angles at this atom (319.4°). Four standard hydrogen bonds, weak non-standard C—H···O hydrogen bonds (Table 1) and van der Waals interactions are the main contributors to the crystal packing. The molecules are packed in head-to-head and tail-to-tail fashions, creating distinct hydrophilic and hydrophobic regions running perpendicular to the *c* axis, as shown in Fig. 2. The 3*N* chain conformation (Fig. 3) is a little more curved, with an angle of 126.4 (4)° between the two planar amide groups (atoms C7/N8/C9/C10/

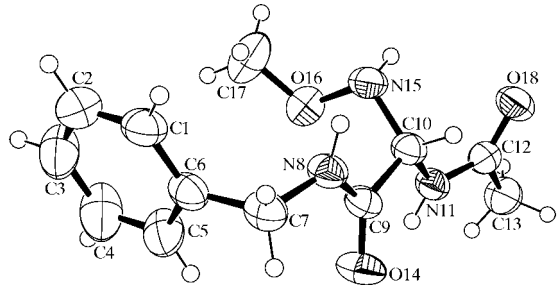


Figure 1
The molecular structure of 3*L*, showing 50% probability displacement ellipsoids.

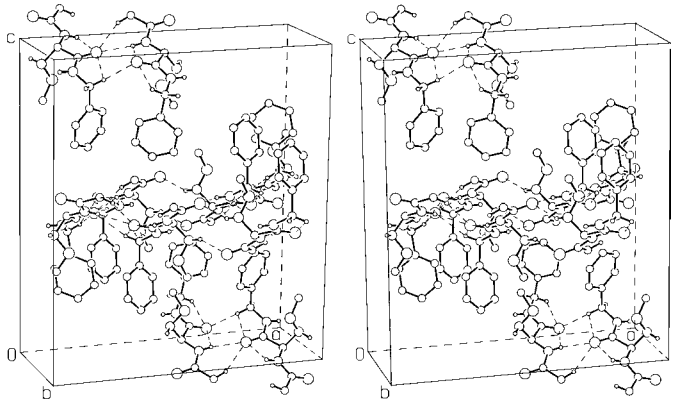


Figure 2
A stereodiagram of the molecular packing and hydrogen-bond scheme (dashed lines) in 3*L*. Atoms are drawn as circles of arbitrary radii.

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O14 and C10/N11/C12/C13/O18). The C9—C10—N11—C12 torsion angle is −128.5 (10)°. The replacement of the H atom at N15 in 3*L* with the methyl group in 3*N* results in a much weaker hydrogen-bonding scheme, with only two classical N—H···O interactions producing infinite molecular chains parallel to the *a* axis (see Table 2). Van der Waals forces and non-standard hydrogen bonds also contribute to the crystal packing, creating planar hydrophillic and hydrophobic areas parallel to the *ab* plane. The weaker hydrogen-bonding interactions are very probably responsible for abnormal displacement ellipsoids and mild disorder in the N15, O16, C17 and C18 positions, as well as high displacement parameters for some other atoms. Despite these problems, the overall conformational structure of the molecules in the solid state is undoubtedly established.

We have compared the structures of 3*L* (Fig. 4) and 3*N* (Fig. 5) with that of phenytoin (Camerman & Camerman, 1971), a chemically different clinically used anticonvulsant, in order to correlate pharmacological properties with stereochemical features. The structures were superposed by maximizing the fit of three atoms in each, *viz.* O14, O16 and C6 in 3*L*, and O14, O16 and C5 in 3*N*, with the two carbonyl O atoms and atom C15 (for 3*L*) or C19 (for 3*N*) in phenytoin. Atom O16 was chosen, rather than the second carbonyl O atom in 3*L* and 3*N*, because pharmacological evaluations have shown that a functionalized O atom located two atoms removed from the Cα atom is necessary for maximal activity in the series tested (Kohn *et al.*, 1991). To yield better phenyl-group fits, rotations of 80° about C7—N8 and 90° about C6—C7 were performed for 3*L*, and a single rotation of 65° about C6—C7 was performed for 3*N*. The superpositions show that the O atoms in each molecule can occupy similar positions in space (small movements of the methoxy O atoms in 3*L* and 3*N*, *via* C10—N15 bond rotation, would make the correspondences exact), and the hydrophobic phenyl groups can also occupy similar regions. Since these are the stereochemical determinants of phenytoin anticonvulsant activity (Camerman & Camerman, 1981), the results indicate that the similar activity of these compounds could be mediated through mechanisms similar to those of phenytoin.

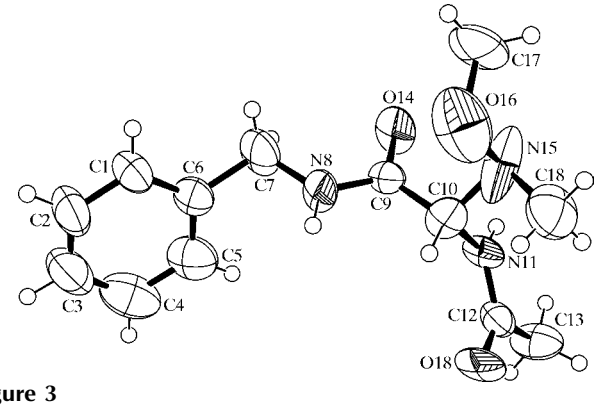

Figure 3
The molecular structure of 3*N*, showing 50% probability displacement ellipsoids.

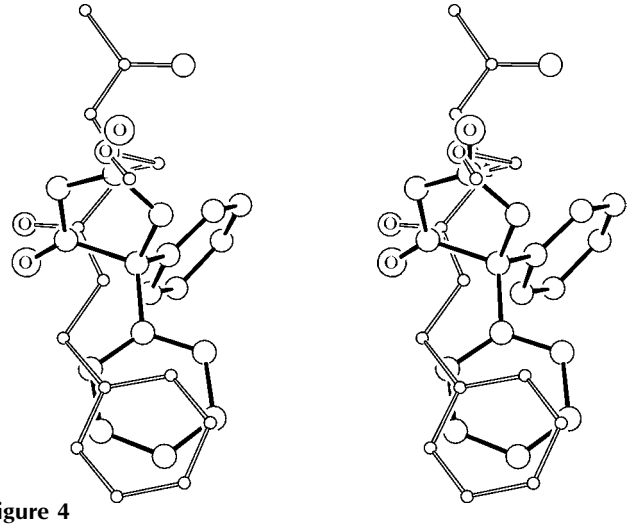

Figure 4
Superposition of 3*L* and phenytoin (large circles, solid bonds).

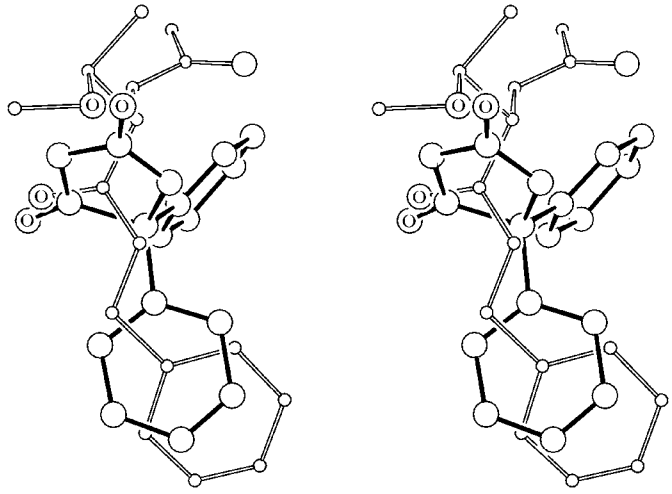

Figure 5
Superposition of 3*N* and phenytoin (large circles, solid bonds).

Experimental

Compounds 3*N* and 3*L* were supplied by Dr H. Kohn (Kohn *et al.*, 1991). After extensive crystallization experiments, crystals of 3*L* were obtained by slow evaporation from a 1:1 benzene–chloroform solution at 278 K. The crystals took the form of small colorless needles, generally of low quality. Crystals of 3*N* were obtained by slow evaporation from a 1:1 chloroform–toluene mixture and were of poor quality. Additional crystallization trials to produce better crystals were unsuccessful.

Compound 3*L*

Crystal data

$C_{12}H_{17}N_3O_3$
M_r = 251.29
Orthorhombic, *Pbcn*
a = 17.998 (5) Å
b = 7.112 (3) Å
c = 20.390 (6) Å
V = 2610.0 (15) Å^3
Z = 8
D_x = 1.279 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 32 reflections
θ = 19–44°
μ = 0.77 mm^{-1}
T = 294 (2) K
Needle, colorless
0.47 × 0.11 × 0.07 mm

Data collection

Picker FACS-1 four-circle diffractometer
$\theta/2\theta$ scan
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.900, T_{max} = 0.944
2225 measured reflections
2225 independent reflections
1655 reflections with $I > 2\sigma(I)$
θ_{max} = 65.0°
$h = 0 \rightarrow 21$
$k = 0 \rightarrow 8$
$l = 0 \rightarrow 23$
3 standard reflections
every 100 reflections
intensity decay: 1.9%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.062
$wR(F^2)$ = 0.146
S = 1.00
2225 reflections
172 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0284P)^2 + 2.7803P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.21 e Å^{-3}
$\Delta\rho_{min}$ = −0.16 e Å^{-3}
Extinction correction: *SHELXL97*
Extinction coefficient: 0.0045 (3)

Table 1
Hydrogen-bond geometry (Å, °) for 3*L*.

D—H···A	D—H	H···A	D···A	D—H···A
N8—H8···O18^{i}	0.86	2.53	3.212 (3)	137
N11—H11···O14	0.86	2.40	2.687 (3)	100
N11—H11···O14^{ii}	0.86	2.37	3.163 (3)	153
N15—H15···O18^{iii}	0.90 (3)	2.39 (3)	3.221 (4)	153 (3)
C7—H7*A*···O16^{iv}	0.97	2.47	3.399 (4)	161
C7—H7*B*···O14^{v}	0.97	2.48	3.359 (4)	151
C13—H13*A*···O14^{ii}	0.96	2.38	3.290 (4)	157

Symmetry codes: (i) $-x+1, -y, -z+1$; (ii) $-x+\frac{1}{2}, y-\frac{1}{2}, z$; (iii) $-x+1, -y-1, -z+1$; (iv) $x, y+1, z$; (v) $-x+\frac{1}{2}, y+\frac{1}{2}, z$.

Compound 3*N*

Crystal data

$C_{13}H_{19}N_3O_3$
M_r = 265.31
Triclinic, $P\overline{1}$
a = 4.859 (2) Å
b = 10.587 (3) Å
c = 14.168 (4) Å
α = 86.84 (2)°
β = 80.66 (3)°
γ = 80.28 (3)°
V = 708.6 (4) Å^3
Z = 2
D_x = 1.244 Mg m^{-3}
Cu $K\alpha$ radiation
Cell parameters from 32 reflections
θ = 23–45°
μ = 0.74 mm^{-1}
T = 294 (2) K
Needle, colorless
0.42 × 0.09 × 0.08 mm

Data collection

Picker FACS-1 four-circle diffractometer
$\theta/2\theta$ scan
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.930, T_{max} = 0.934
1338 measured reflections
1145 independent reflections
737 reflections with $I > 2\sigma(I)$
R_{int} = 0.085
θ_{max} = 45.0°
$h = -4 \rightarrow 0$
$k = -9 \rightarrow 9$
$l = -12 \rightarrow 12$
3 standard reflections
every 100 reflections
intensity decay: 2.7%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.102
$wR(F^2)$ = 0.250
S = 1.12
1145 reflections
174 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0768P)^2 + 2.5323P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.53 e Å^{-3}
$\Delta\rho_{min}$ = −0.30 e Å^{-3}

Table 2
Hydrogen-bond geometry (Å, °) for (3*N*).

D—H···A	D—H	H···A	D···A	D—H···A
N8—H8···O14^{v}	0.86	2.05	2.901 (10)	172
N11—H11···O18^{vi}	0.86	2.11	2.950 (9)	165
C10—H10···O14^{v}	0.98	2.59	3.428 (11)	144
C10—H10···O18	0.98	2.47	2.823 (12)	101
C13—H13*B*···O18^{vi}	0.96	2.46	3.331 (12)	151

Symmetry codes: (v) $x+1, y, z$; (vi) $x-1, y, z$.

All H atoms for both compounds, except for atom H15 on N15 in 3*L*, could be located in difference maps and were subsequently allowed for as riding atoms. For 3*L*, one overall isotropic displacement parameter was refined for methyl H atoms and another for the remaining H atoms [U_{iso}(H) = 0.116 (7) and 0.079 (4) Å^2, respectively]. For 3*N*, the corresponding values are 0.123 (16) and 0.099 (15) Å^2. The range of C—H distances is 0.93–0.98 Å, and the amide N—H distances are 0.86 Å. The N15—H15 bond length in 3*L* is 0.90 (3) Å.

For both compounds, data collection: *Picker Operating Manual* (Picker, 1967); cell refinement: *Picker Operating Manual*; data reduction: *DATRDN: The X-ray System* (Stewart, 1976); structure solution: *SHELXS97* (Sheldrick, 1997); structure refinement: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997); software used to prepare material for publication: *SHELXL97*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FG1843). Services for accessing these data are described at the back of the journal.

References

Camerman, A. & Camerman, N. (1971). *Acta Cryst.* B**27**, 2205–2211.
Camerman, A. & Camerman, N. (1981). *Acta Cryst.* B**37**, 1677–1679.
Farrugia, L. J. (1997). *J. Appl. Cryst.* **30**, 565.
Kohn, H., Sawhney, K. N., LeGall, P., Robertson, D. W. & Leander, J. D. (1991). *J. Med. Chem.* **34**, 2444–2452.
North, A. C. T., Phillips, D. C. & Mathews, F. S. (1968). *Acta Cryst.* A**24**, 351–359.
Picker (1967). *Picker Operating Manual*. Picker, Cleveland, Ohio, USA.
Sheldrick, G. M. (1997). *SHELXS97* and *SHELXL97*. University of Göttingen, Germany.
Stewart, J. M. (1976). *DATRDN: The X-ray System*. Technical Report TR-446 of the Computer Science Center, University of Maryland, College Park, Maryland, USA.