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Structural Analogues of Ibotenic Acid. Syntheses of 4-Methylhomoibotenic Acid and AMPA, Including the Crystal Structure of AMPA, Monohydrate

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(*RS*)-α-Amino-3-hydroxy-4-methylisoxazole-5-propionic acid (4-methylhomoibotenic acid) and (*RS*)-α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) were prepared from 4,5-dimethyl-3-methoxyisoxazole.

Crystals of the monohydrate of AMPA are triclinic, space group $P\bar{1}$, with cell dimensions $a = 9.900(6)$, $b = 7.152(3)$, $c = 7.327(6)$ Å, $\alpha = 68.67(4)$, $\beta = 102.73(9)$, $\gamma = 101.77(5)°$. The structure was solved by direct methods and refined by least-squares methods to a final R-value of 0.060. The 3-hydroxyisoxazole moiety is unionized in the crystal structure.

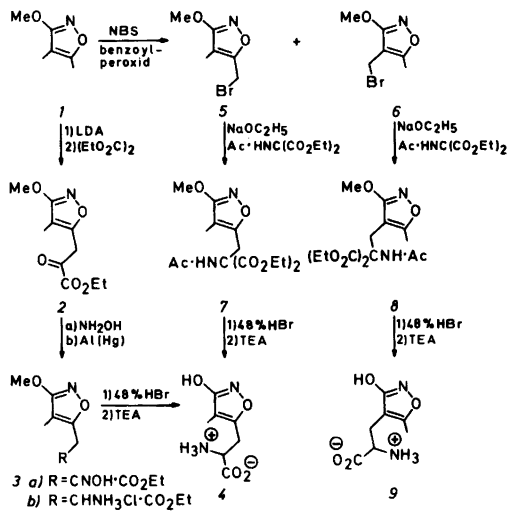
The identification of L-glutamic acid (glu) and L-aspartic acid (asp) as transmitters mediating synaptic excitation in the mammalian central nervous system would be facilitated by the discovery of compounds which are strong and specific agonists or antagonists of amino acid-induced synaptic excitation.

Ibotenic acid [(*RS*)-α-amino-3-hydroxyisoxazole-5-acetic acid], a structural analogue of glu isolated from *Amanita muscaria*,[1] has a powerful excitatory effect on central neurones.[2,3] However, this effect seems to be an asp more than a glu agonism.[4] In contrast to ibotenic acid, homoibotenic acid and 4-bromohomoibotenic acid were shown[5] to be specific glu-agonists.

These findings prompted us to synthesize (*RS*)-α-amino-3-hydroxy-4-methylisoxazole-5-propionic acid (4-methylhomoibotenic acid, *4*) and (*RS*)-α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA, *9*).

The 3-hydroxyisoxazole anion can be considered as a masked carboxylate group. In the X-ray crystallographic structure determinations of several 3-hydroxyisoxazoles, the compounds are found as 3-hydroxyisoxazole/amine zwitterions.[6–9] Because of the different acidities of 3-hydroxyisoxazoles and α-amino acid groups[10] the present compounds might be examples of unionized 3-hydroxyisoxazole moieties in surroundings with hydrogen bond-donor and -acceptor capabilities, and hence an X-ray crystallographic structure determination of AMPA, monohydrate was undertaken.

The syntheses of *4* and *9* are outlined in Scheme 1. The key step in the synthesis of *4* is the condensation of 3-methoxy-4,5-dimethylisoxazole (*1*) and diethyl



Scheme 1.

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oxalate, using the fact that *1* can be selectively lithiated in the 5-methylgroup.[11]

The resulting α-keto ester *2* was immediately converted into the oxime *3a*, as *2* was considered to be labile on the basis of preliminary purification experiments. The oxime *3a* was by reduction converted to the amino ester *3b*. Deprotection, followed by triethylamine (TEA) treatment gave the amino acid zwitterion *4*.

Treatment of *1* with *N*-bromosuccinimide (NBS) under free radical conditions was shown to give *5* and *6* in a three to seven ratio as shown by ^{1}H NMR spectroscopy using the intensities of the methyl signals in *5* (δ 1.85) and *6* (δ 2.35), respectively. Addition of NBS in quarter equivalents and complete consumption of the reagent before a new portion of the reagent is added is of vital importance for the synthesis of *5* and *6*; otherwise a complex mixture of di- and trihalogenated compounds was obtained. After reaction of the mixture of *5* and *6* with diethyl acetylaminomalonate the protected amino acids *7* and *8* could be separated by crystallization. The amino acids *4* and *9* were obtained by subsequent deprotection, decarboxylation and treatment with TEA.

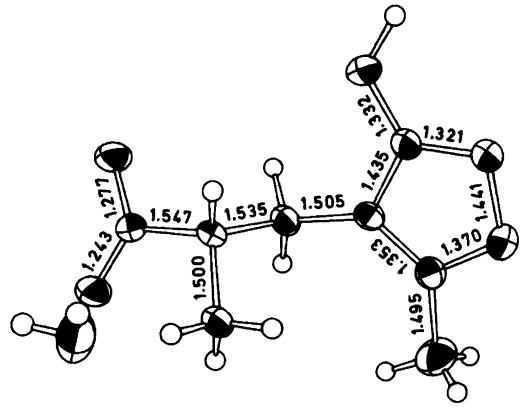
The structure determinations of the novel compounds *3a, b*, *4*, *7*, *8* and *9* were based on spectroscopic methods and elementary analyses.

The conformation and the molecular dimensions of AMPA, monohydrate as determined by the X-ray crystallographic investigation are shown in Fig. 1. AMPA crystallizes in a zwitterionic form with the hydroxy group of the isoxazole nucleus unionized. From the bond length values the unionized 3-hydroxyisoxazole group can be considered as a masked carboxylic acid group. The isoxazole ring is planar within the limits of experimental error. The exocyclic atoms O(2), C(6) and C(7), and the hydrogen atom H(821) are at distances ±0.017, ±0.020, ∓0.039 and ∓0.05 Å, respectively, from this plane. A list of selected torsion angles and selected *intra*-molecular distances is given in Table 1.

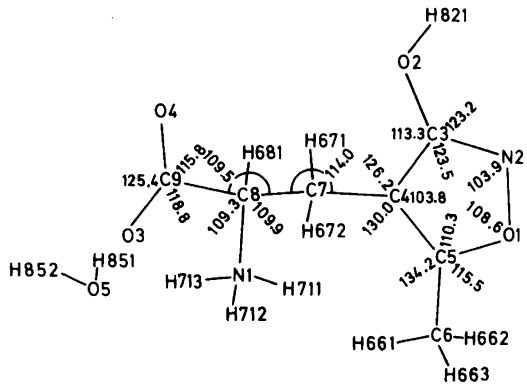
The packing of the molecules in the crystals is illustrated in Fig. 2. The dimensions of the hydrogen

Table 1.

Torsion angles (°)	
N(1)–C(8)–C(9)–O(3)	±14.4(4)
C(3)–C(4)–C(7)–C(8)	±77.1(3)
C(4)–C(7)–C(8)–C(9)	∓174.0(2)
C(4)–C(7)–C(8)–N(1)	±65.9(2)
C(7)–C(8)–C(9)–O(3)	∓106.1(3)
C(7)–C(8)–C(9)–O(4)	±70.5(3)
Intra-molecular distances (Å)	
N(2)···N(1)	4.892(4)
N(2)···O(3)	6.864(5)
N(2)···O(4)	6.277(6)
O(2)···N(1)	4.499(5)
O(2)···O(3)	5.796(5)
O(2)···O(4)	4.591(4)



a



b

Fig. 1. (a) Bond lengths (Å) between non-hydrogen atoms. E.s.d.'s are 0.003–0.005 Å. Thermal ellipsoids for non-hydrogen atoms are scaled to 50 % probability; hydrogen atoms are represented as spheres of arbitrary radius. Drawings were made by ORTEP II.[14] (b) The atomic numbering and bond angles (°) between non-hydrogen atoms. E.s.d.'s are 0.2°.

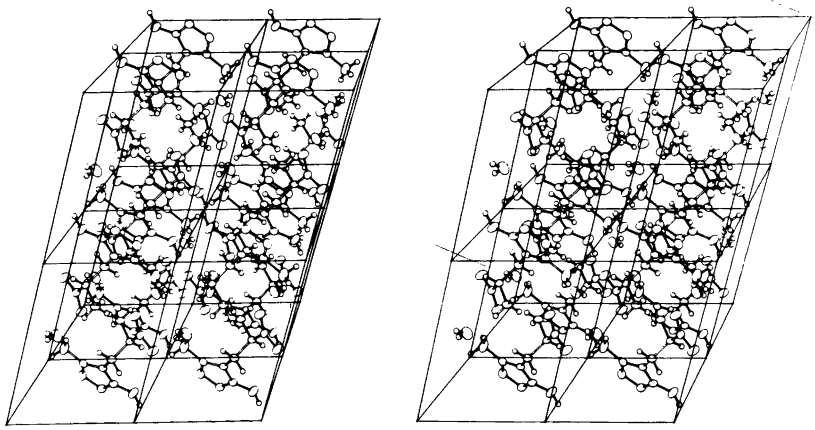


Fig. 2. Stereo diagram illustrating the molecular packing. The view is down *b*, with *a* ↑ and *c* →.

bonds are summarized in Table 2. All of the oxygen and nitrogen atoms in the structure except O(1) are involved in the formation of hydrogen bonds. The two AMPA molecules related by a centre of symmetry at $\frac{1}{2},\frac{1}{2},\frac{1}{2}$ are linked as dimers by two hydrogen bonds, N(1)–H(712)···O(3). Furthermore, the crystal structure is stabilized by hydrogen bonds between one AMPA molecule and two symmetry related AMPA molecules. Each water molecule is hydrogen bonded to three different AMPA molecules, two of which act as acceptors with the oxygen atoms O(4). All other *inter*-molecular constacts correspond to van der Waals' interactions.

EXPERIMENTAL

Melting points, determined in capillary tubes, are corrected. Elemental analyses were performed by Mr. P. Hansen, Chemical Laboratory II, University of Copenhagen. A Perkin-Elmer grating infrared spectrophotometer model 247, and a Varian T-60 (60 MHz) ^{1}H NMR instrument were used. ^{1}H NMR spectra were recorded by Mrs. M. Wehmeyer, Chemical Laboratory II, University of Copenhagen, using TMS as an internal standard, except for the compounds dissolved in D_2O where DSS was used. TLC and CC were accomplished by using silica gel F_{254} plates (Merck) and silica gel, 0.063–0.100 mm (Woelm), respectively,

The computations in connection with the X-ray crystallographic structure determination were performed on an IBM 3033 computer using MULTAN (1974 version,[12] *The X-Ray System* (1972 version)[13] and ORTEP II.[14] Numbers in parentheses in connection with cell dimensions and molecular dimensions are the estimated standard deviations of the last significant digits.

*Ethyl α-hydroxyimino-3-methoxy-4-methylisoxazole-5-propionate (*3a*).* To a solution of diisopropyl-

Table 2. Hydrogen bonds.
Symmetry code:
(i) *x*, *y*, *z*
(ii) 2−*x*,2−*y*,1−*z*
(iii) 1−*x*,1−*y*,1−*z*
(iv) 2−*x*,1−*y*,2−*z*
(v) *x*,*y*+1, *z*
(vi) 1−*x*,1−*y*,2−*z*

A–H···B	A–H (Å)	H···B (Å)	A···B (Å)	∠AHB (°)
N(1)–H(713)···O(5)^{i}	0.91(4)	1.94(4)	2.827(5)	165(3)
N(1)–H(711)···N(2)^{ii}	0.96(3)	2.04(4)	2.941(3)	156(4)
N(1)–H(712)···O(3)^{iii}	0.91(4)	2.07(4)	2.940(4)	159(4)
O(2)–H(821)···O(4)^{iv}	1.02(4)	1.59(4)	2.605(4)	174(5)
O(5)–H(851)···O(4)^{v}	0.89(4)	2.26(5)	3.139(4)	167(4)
O(5)–H(852)···O(4)^{vi}	0.78(5)	2.03(5)	2.810(4)	173(4)

amine (1.00 g; 10 mmol) in dry tetrahydrofuran (10 ml) kept under nitrogen at −70 °C was added butyl lithium (10 mmol) with stirring followed by a solution of *1*[15] (1.27 g; 10 mmol). This solution was added to a stirred, cooled (−70 °C) solution of diethyl oxalate (1.46 g; 10 mmol) in dry tetrahydrofuran (10 ml). After additional stirring at −70 °C for 1½ h hydrochloric acid (1 M; 30 ml) was added.

The organic phase was separated, and the aqueous phase was extracted with ether (2 × 15 ml). The combined organic phases were washed with water (2 × 10 ml), dried (Na_2SO_4) and evaporated. A solution of this crude oil, hydroxylammonium chloride (0.75 g; 10.8 mmol) and sodium acetate trihydrate (1.45 g; 10.8 mmol) in aqueous ethanol (50 %; 90 ml) was refluxed for 2 h. The reaction mixture was evaporated to *ca.* 30 ml and extracted with ether (2 × 30 ml). The combined ether phases were dried (Na_2SO_4), evaporated and CC of the residue [eluent: toluene containing ethyl acetate (50 %) and formic acid (1 %)] followed by recrystallization (ether−light petroleum) gave *3a* (0.71 g; 29 % based on *1*), m.p. 91.0−92.5 °C. Anal. $C_{10}H_{14}N_2O_5$: C, H, N. IR (KBr): 3450−2730 (s, several broad bands), 1750 (s), 1660 (m), 1630 (w), 1540 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 10.6−10.0 (1 H, broad signal), 7.70 (2 H, q, *J* 7.4 Hz), 3.95 (5 H, s), 1.85 (3 H, s), 1.35 (3 H, t, *J* 7.4 Hz).

*Ethyl (RS)-α-amino-3-methoxy-4-methylisoxazole-5-propionate hydrochloride (*3b*).* To a solution of *3a* (480 mg; 2 mmol) in ethanol−water (1:1; 15 ml) was added aluminium amalgam prepared by treatment of aluminium strips (700 mg; 26 mmol) with aqueous mercury(II) chloride (5 %; 120 ml) for 30 s followed by washing with ethanol. After stirring for 20 h the reaction mixture was filtered and concentrated to *ca.* 7 ml and extracted with ether (3 × 5 ml). The combined ether phases were dried (Na_2SO_4), evaporated, ethanolic hydrogen chloride added (5 ml, 3 mmol), evaporated and recrystallized (ethanol−ether) to give *3b* (390 mg; 74 %), m.p. 171.5−172.5 °C. Anal. $C_{10}H_{17}ClN_2O_4$: C, H, Cl, N. IR (KBr): 3650−2700 (s, broad signals), 1740 (s), 1535 (s) cm^{-1}. ^1H NMR (D_2O): δ 4.8 (*ca.* 3 H, s), 4.7−4.1 (3 H, m), 4.03 (3 H, s), 3.45 (2 H, d, *J* 6.0 Hz), 1.85 (3 H, s), 1.30 (3 H, t, 7.0 Hz).

*(RS)-α-Amino-3-hydroxy-4-methylisoxazole-5-propionic acid and (RS)-α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (*4 *and* 9*).* A solution of *3b* (200 mg; 0.8 mmol) in hydrobromic acid (48 %; 30 ml) was refluxed at 140 °C for 15 min. Evaporation followed by subsequent addition of water (3 ml) and a solution of TEA (81 mg; 0.8 mmol) in ethanol (3 ml) yielded *4* (110 mg; 67 %). In a similar manner, using *7* (1200 mg; 3.5 mmol) as the starting material, *4* (540 mg; 76 %) was obtained. *9* (190 mg; 57 %) was prepared in a similar manner using *8* (510 mg; 1.5 mmol) as the starting material.

4: M.p. 247.5−248.5 °C (decomp.). Anal. $C_7H_{10}N_2O_4$, H_2O: C, H, N. IR (KBr): 3650−2750 (s, broad signals), 1635 (s), 1600 (s), 1535 (s), 1510 (s) cm^{-1}. ^1H NMR (D_2O-CF_3COOD): δ 4.9 (*ca.* 6 H, s), 4.45 (1 H, t, *J* 6.0 Hz), 3.35 (2 H, d, *J* 6.0 Hz), 1.85 (3 H, s).

9: M.p. 240−250 °C (decomp.). Anal. $C_7H_{10}N_2O_4$,2 H_2O: C, H, N. IR (KBr): 3600−2500 (s, broad signals), 1660 (m), 1640 (s), 1580 (w), 1520 (s) cm^{-1}. ^1H NMR (D_2O-CF_3COOD): δ 4.9 (*ca.* 8 H, s), 4.35 (1 H, t, *J* 6.0 Hz), 3.05 (2 H, d, *J* 6.0 Hz), 2.30 (3 H, s).

*Ethyl α-ethoxycarbonyl-α-acetylamino-3-methoxy-4-methylisoxazole-5-propionate and ethyl α-ethoxycarbonyl-α-acetylamino-3-methoxy-5-methylisoxazole-4-propionate (*7 *and* 8*).* A mixture of *1* (8.89 g; 70 mmol), tetrachloromethane (50 ml), NBS (a total of 12.45 g; 70 mmol) and benzoylperoxide (a total of 200 mg) was refluxed for 2 h. NBS and benzoylperoxide were added in quarter portions each half hour. After cooling to room temperature the reaction mixture was filtered and evaporated to give an oil, which was dissolved in ethanol (40 ml) and added to a solution of sodium (1.61 g; 70 mmol) and diethyl acetylaminomalonate (15.19 g; 70 mmol) in ethanol (100 ml). The reaction mixture was refluxed for 4 h, cooled to room temperature, filtered and evaporated. To the mixture was added water (100 ml), followed by extraction with methylene chloride (5 × 100 ml). The combined organic phases were dried ($MgSO_4$) and evaporated. Recrystallization from ether−light petroleum containing varying amounts of ethanol gave *7* (1.52 g; 6 %) and *8* (5.78 g; 25 %).

7: M.p. 145.5−146.0 °C. Anal. $C_{15}H_{22}N_2O_7$: C, H, N. IR (KBr): 3250 (m), 2980 (w, broad signal), 1745 (s), 1635 (s), 1530 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.8 (1 H, broad signal), 4.35 (4 H, q, *J* 7.2 Hz), 4.00 (3 H, s), 3.76 (2 H, s), 2.00 (3 H, s), 1.75 (3 H, s), 1.30 (6 H, t, *J* 7.2 Hz).

8: M.p. 96.0−97.0 °C. Anal. $C_{15}H_{22}N_2O_7$: C, H, N. IR (KBr): 3250 (m), 2980 (w, broad signal), 1745 (s), 1635 (s), 1525 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.7 (1 H, broad signal), 4.5−4.1 (4 H, m), 3.95 (3 H, s), 3.40 (2 H, s), 2.20 (3 H, s), 2.00 (3 H, s), 1.30 (6 H, t, *J* 7.0 Hz).

*Crystal data. (RS)-*α-Amino-3-hydroxy-5-methylisoxazole-4-propionic acid monohydrate, $C_7H_{10}N_2O_4.H_2O$,* M = 204.19. Triclinic, space group *P*1. $a = 9.900(6)$, $b = 7.152(3)$, $c = 7.327(6)$ Å, $\alpha = 68.67(4)$, $\beta = 102.73(9)$, $\gamma = 101.77(5)°$, $Z = 2$, $D_m = 1.48$, $D_x = 1.45$ gcm^{-3}. $\mu(MoK\alpha) = 1.29$ cm^{-1}. Cell dimensions were obtained from a least-

* Prepared according to Ref. 16.

Table 3. Atomic coordinates and thermal parameters (Å^2 $\times 10^2$). The temperature factors are of the form: $\exp[-2\pi^2(U_{11}h^2a^{*2}+U_{22}k^2b^{*2}+U_{33}l^2c^{*2}+2U_{12}hka^*b^*+2U_{13}hla^*c^*+2U_{23}klb^*c^*)]$ or $\exp[-2U_{iso}(2\sin\theta/\lambda)^2]$.

Atom	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
N(1)	.6483(2)	.7681(3)	.5666(3)	2.11(11)	2.92(12)	3.18(11)	0.78(9)	0.47(9)	−0.36(10)
N(2)	1.1479(2)	.8636(3)	.5391(3)	2.39(11)	3.23(12)	2.94(11)	0.55(9)	0.42(9)	−0.47(9)
O(1)	1.0720(2)	.9062(3)	.3398(3)	3.20(10)	3.71(11)	2.69(9)	0.44(8)	1.00(7)	−0.62(8)
O(2)	1.0887(2)	.6490(3)	.8461(3)	2.95(11)	5.36(13)	2.55(10)	0.15(9)	−0.01(8)	0.47(9)
O(3)	.4876(2)	.4229(3)	.7335(3)	2.22(10)	4.88(13)	3.44(10)	0.08(8)	−0.03(8)	−0.23(9)
O(4)	.6602(2)	.2827(3)	.9668(3)	2.98(11)	4.25(12)	3.35(10)	0.34(9)	0.14(8)	0.70(9)
O(5)	.5339(3)	.9418(4)	.7786(3)	4.92(13)	4.83(14)	4.27(12)	0.47(11)	2.19(11)	−1.02(11)
C(3)	1.0598(2)	.7286(4)	.6492(4)	2.14(12)	2.78(13)	2.83(12)	0.66(10)	0.43(9)	−0.32(10)
C(4)	.9293(2)	.6758(4)	.5357(3)	2.24(12)	2.62(12)	2.67(12)	1.09(10)	0.36(9)	−0.61(10)
C(5)	.9430(3)	.7914(4)	.3463(4)	2.66(13)	3.27(13)	2.78(12)	0.85(10)	0.66(10)	−0.93(10)
C(6)	.8498(4)	.8194(6)	.1504(5)	5.09(20)	5.83(22)	2.83(15)	0.15(17)	0.05(13)	−1.36(15)
C(7)	.8094(3)	.5228(4)	.6165(4)	2.14(12)	2.79(13)	3.06(13)	0.58(10)	0.46(10)	−0.71(11)
C(8)	.7217(2)	.5985(4)	.7172(3)	1.72(11)	2.84(13)	2.24(11)	0.57(9)	0.06(9)	−0.65(10)
C(9)	.6121(3)	.4228(4)	.8137(3)	2.39(13)	3.27(14)	2.08(11)	0.44(10)	0.19(9)	−0.62(10)

Atom	x	y	z	U_{iso}	Atom	x	y	z	U_{iso}
H(661)	.884(5)	.774(7)	.070(7)	8.5(15)	H(711)	.715(4)	.875(6)	.503(5)	5.1(9)
H(662)	.760(4)	.731(6)	.166(5)	5.7(10)	H(712)	.588(4)	.724(5)	.473(5)	5.0(10)
H(663)	.846(5)	.955(8)	.089(7)	9.2(16)	H(713)	.596(4)	.817(5)	.623(5)	4.5(9)
H(671)	.847(3)	.398(5)	.724(4)	3.3(7)	H(821)	1.186(5)	.684(7)	.919(6)	7.9(13)
H(672)	.745(3)	.478(4)	.512(4)	3.5(8)	H(851)	.583(4)	1.030(6)	.837(6)	5.1(10)
H(681)	.783(3)	.656(4)	.816(4)	1.9(6)	H(852)	.485(5)	.876(7)	.857(7)	7.4(14)

squares refinement of the 2θ values of 35 automatically centered reflections.

Data collection. The crystal ($0.5\times0.2\times0.2$ mm) was sealed in a Lindemann capillary. Intensity data were measured on a Nonius CAD-3 diffractometer using graphite-monochromated Mo$K\alpha$ ($\lambda=0.71069$ Å) radiation. The ω scan technique was employed. Of the 1681 independent reflections measured in the range $3.5\leq\theta\leq25.0°$, 1394 had net intensities $>3.0\sigma(I)$, where $\sigma(I)$ is the standard deviation from counting statistics. These were regarded as observed reflections and were used in the refinement procedure. Lorentz and polarization corrections were applied, but no absorption corrections were made.

Structure solution and refinements. The structure was solved using the MULTAN system,[12] which revealed the complete non-hydrogen atom skeleton of the AMPA molecule. The position of the oxygen atom of the water molecule was obtained from a difference electron density map. After initial least-squares refinements the 12 hydrogen atoms were located in a difference electron density map (>0.4 e Å^{-3}). In subsequent full-matrix least-squares calculations an overall scale factor, atomic coordinates, anisotropic thermal parameters of the non-hydrogen atoms and isotropic thermal parameters of the hydrogen atoms were refined. The quantity minimized was $\Sigma w(|F_o|-|F_c|)^2$, where $w=1.0+[(F_o-5.0)/3.5]^2$. The final R-value is 0.060 ($R_w=0.074$).

Table 3 lists the final atomic coordinates and thermal parameters. The final set of structure factors listed with the observed data is available by request. The X-ray atomic scattering factors for O, N and C were taken from Cromer and Mann[17] and for H those of Stewart, Davidson and Simpson[18] were used.

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