Heterocyclic GABA Agonists. Synthesis and Crystal Structure of (*RS*)-5-(*N*-t-Butyloxycarbonylaminomethyl)-3-oxoisoxazolidine-2-carboxamide, a Derivative of Dihydromuscimol

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Reaction of the *O*- and *N*-protected (*RS*)-3-hydroxy-4-aminobutyric acid ester (4) with hydroxyurea under basic conditions unexpectedly yielded (*RS*)-5-(*N*-t-butyloxycarbonylaminomethyl)-3-oxoisoxazolidine-2-carboxamide (8), the structure of which has been confirmed by an *X*-ray analysis. Elimination of the cyanate ion, which could be trapped with dimethylamine, converted (8) into the corresponding 2-isoxazolin-3-ol derivative (7). Attempts to prepare the individual enantiomers of (8) were unsuccessful. The (*R*)-(−)-3-hydroxy-4-aminobutyric acid derivative (5) yielded racemic (8). The cyclization reactions of (5) and (4) are believed to involve elimination of toluene-4-sulphonate giving the corresponding α,β-unsaturated ester as an intermediate.

Certain heterocyclic analogues of the central inhibitory neurotransmitter γ-aminobutyric acid (GABA) including muscimol and (*RS*)-5-aminomethyl-2-isoxazolin-3-ol (dihydromuscimol) are more potent than GABA itself as agonists at the GABA receptors.[1] Whilst muscimol and dihydromuscimol are equipotent with respect to activation of GABA receptors in the mammalian central nervous system,[1] the latter is the more active GABA agonist on central neurones in certain invertebrates.[2] Since dihydromuscimol apparently is capable of adopting conformations, which almost perfectly mimic the ' receptor-active conformation(s) ' of GABA, this heterocyclic amino acid is a key compound in studies of the molecular pharmacology of GABA agonists.[3] Dihydromuscimol is, however, not a specific GABA agonist. It also interacts with the GABA transport mechanisms, although with low affinity.[4] Since these transport systems and the GABA receptors have different, and in the case of some GABA analogues opposite, stereoselectivity,[3,4] one of the enantiomers of dihydromuscimol might be a specific and very active model compound for studies of GABA receptor mechanisms. With these prospects in mind we have, unfortunately unsuccessfully, attempted to synthesize both enantiomers of dihydromuscimol. This synthetic work and the determination of the structure of a key intermediate is described in this paper.

Results

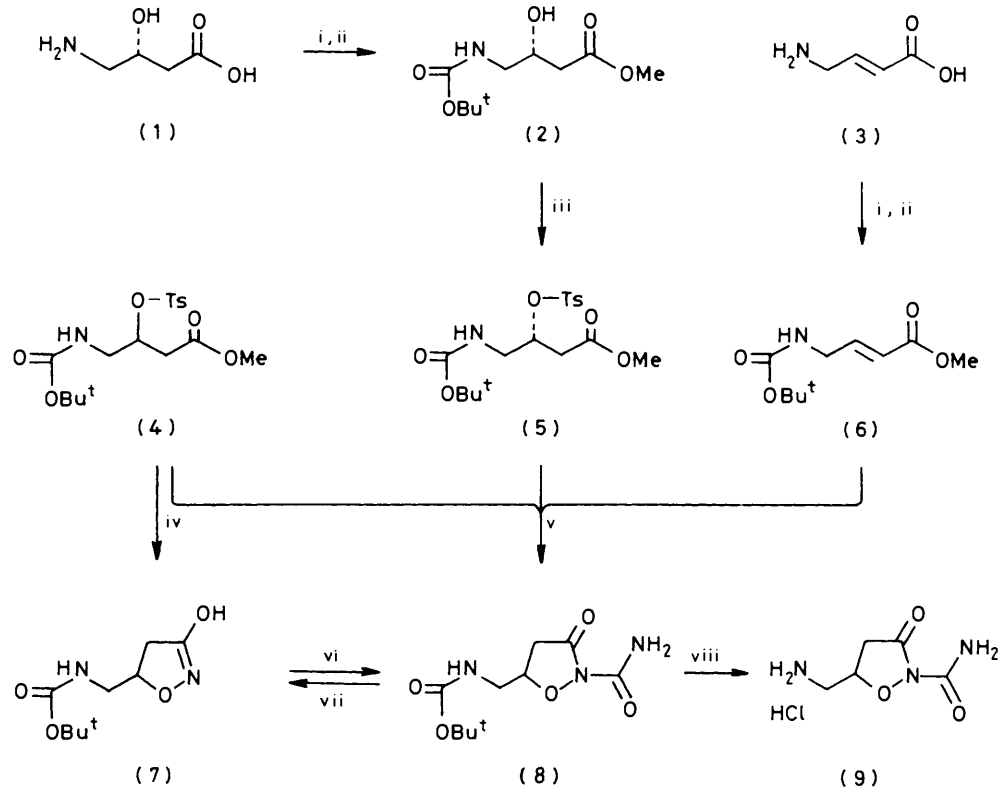
The synthesis of the 2-isoxazolin-3-ol derivative (7) (see Scheme) has previously been described.[5] The protected (*RS*)-3-hydroxy-4-aminobutyric acid derivative (4) was treated with hydroxyurea under basic conditions to give (7). A mechanism involving elimination of toluene-4-sulphonate from (4) followed by nucleophilic addition and subsequent cyclization between the α,β-unsaturated intermediate formed and the hydroxyurea anion was proposed.[5] Under slightly modified conditions for the reaction of (4) with hydroxyurea, *i.e.* use of potassium t-butoxide as a base instead of sodium methoxide and with a reaction temperature of 0—25 °C instead of 40 °C, we obtained the 3-oxoisoxazolidine-2-carboxamide derivative (8) (Scheme) as the major product. The 3-ol derivative (7) could be detected only as a minor product by t.l.c. By repeating the reported procedure [5] for the preparation of (7), the 2-carboxamide (8) actually could be detected by t.l.c. In a previous report [6] concerning the synthesis of 2-isoxazolin-3-ols from α,β-unsaturated esters, the proposed 2-carboxamide intermediates were assumed to be unstable, being converted into the 2-isoxazolin-3-ols by spontaneous elimination of cyanate. The 2-carboxamide (8) was obtained as a stable crystalline compound and when deprotected under anhydrous conditions gave the 2-carboxamide derivative (9) as a stable compound. In dilute aqueous sodium hydroxide (8) was spontaneously transformed into the corresponding 2-isoxazolin-3-ol derivative (7) by a reversible reaction; thus, acidification of the reaction mixture gave back (8). The 2-carboxamide (8) could also be prepared by treatment of (7) with potassium cyanate in methanol under weak acidic conditions. Treatment of (8) with aqueous base proceeded quantitatively to give (7), when the cyanate ion was trapped with a large excess of dimethylamine.

Treatment of the protected (*R*)-(−)-3-hydroxy-4-aminobutyric acid derivative (5) with hydroxyurea using the same modified reaction conditions as described for the conversion (4) ⟶ (8) correspondingly gave the 2-carboxamide (8). However, no significant optical rotation of (8) could be measured. With the same reaction conditions, the α,β-unsaturated ester (6) also gave the 2-carboxamide (8) as the only product. We therefore believe that the mechanisms of the cyclization reactions of (4) and (5) involves an elimination of the toluene-4-sulphonate group giving the α,β-unsaturated ester (6) as an intermediate. This is in agreement with what was previously proposed.[5]

The structure of (*RS*)-5-(*N*-t-butyloxycarbonylaminomethyl)-3-oxoisoxazolidine-2-carboxamide (8), crystallizing with half a mole of ethyl acetate, has been determined by an *X*-ray analysis.

The overall shape of the molecule of (8) is illustrated in Figure 1. The bond lengths, valency angles, and torsion angles are listed in Table 1.

The molecule of (8) contains an *intra*molecular NH · · · O bond between the carbamoyl group and the carbonyl O(2) atom of the isoxazolidin-3-on moiety, *cf.* Table 2 and Figure 1. The molecule is composed of two almost planar moieties: one consisting of the isoxazolidin-3-one moiety and the carbamoyl group, and a second formed by the atoms C(6), N(7), and the t-Boc group, except the methyl carbon atoms C(11) and C(12). The angle between the two planes is 89°. The conformation of the isoxazolidin-3-one ring is a distorted envelope. The C(5) atom is on the flap of the envelope and deviates 0.44 Å from the best plane formed by the four remaining atoms of the ring. All the remaining atoms of the molecule are on the opposite side of the plane in relation to C(5). The displacements from the plane are: O(1) = 0.011, N(2) = −0.018, C(3) = 0.017, C(4) = −0.010, C(5) = −0.44, C(6) = 0.15, O(2) = 0.08, C(14) = 0.21, N(15) = 0.23, and O(4) = 0.34 Å.



i, MeOH/HCl; ii, di-t-butyl oxydiformate/TEA; iii, tosyl chloride/pyridine; iv, MeONa/MeOH–$NH_2CONHOH$; v, Me_3COK–$NH_2CONHOH$; vi, $KOCN/CH_3COO_3H$; vii, Me_2NH/H_2O; viii, $HCl/MeCO_2Et$

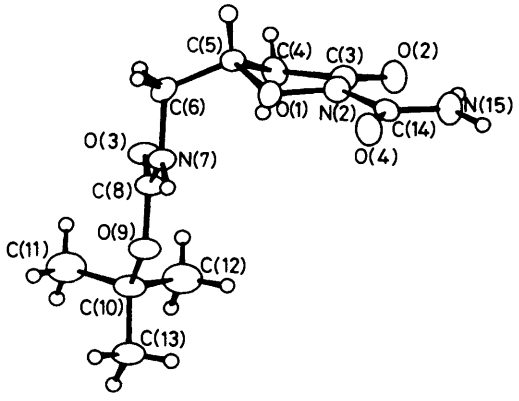


Figure 1. Perspective drawing of compound (8). The thermal ellipsoids for the non-hydrogen atoms correspond to 50% probability; hydrogen atoms are represented as spheres of arbitrary radius

The C(8)–O(3) bond is situated between two of the methyl groups [C(11) and C(12)] of the t-butoxy group. Accordingly, short contacts arise between the methyl groups C(11) and C(12) and the oxygen atom O(3), 3.021(6) and 3.039(6) Å, respectively.

The ethyl acetate molecule adopts the *trans-gauche* conformation, the torsion angle associated with $O\text{-}C_2H_5$ as central bond is 89° (see Figure 2).

The ethyl acetate molecules lie across centres of symmetry at $0,\frac{1}{2},0$ and $0,0,\frac{1}{2}$. Thus, the ethyl acetate molecules are situated at two alternative positions related by a centre of symmetry. All distances between the ethyl acetate and compound (8) molecules are greater than the sum of the respective van der Waals' radii, the shortest distance being between N(2) and O(3EA), 3.047(7) Å.

The crystal structure is stabilized by hydrogen bonds formed between compound (8) molecules related by a 2-fold screw axis, *i.e.* N(15)–H(152) · · · O(4) [II] and N(7)–H(71) · · · O(4) [III]. Thus, each molecule is hydrogen bonded to two adjacent molecules (see Figure 2). Hydrogen bond dimensions are given in Table 2. The shortest intermolecular distances between non-hydrogen atoms are from C(5) and C(6) to O(3) $[1\text{-}x,\bar{y},\bar{z}]$, 3.163(5) and 3.277(5) Å, respectively, and from C(4) to O(2) $[1\text{-}x,\text{-}1\text{-}y,\bar{z}]$, 3.388(5) Å.

Experimental

M.p.s, determined in capillary tubes, are corrected. Analyses were performed by Mr. G. Cornali, Microanalytical Laboratory, Leo Pharmaceutical Products, Denmark. I.r. and u.v. spectra were determined with Perkin-Elmer 247 and 402 spectrophotometers, respectively. Optical rotations were measured on a Perkin-Elmer polarimeter 141. ^1H N.m.r. spectra were recorded on a JEOL JMN-C-60HL instrument using $SiMe_4$ as an internal standard. Compounds dissolved in D_2O were referred to sodium 3-(trimethylsilyl)propanesulphonate. T.l.c. and column chromatography were accomplished by using silica gel F_{254} plates (Merck) and silica gel (Woelm 0.063—0.100 mm), respectively.

(R)-(−)-*Methyl N-t-Butyloxycarbonyl-3-hydroxy-4-aminobutanoate* (2).—A solution of (1) [7] (1.0 g, 8.4 mmol) in methanolic hydrogen chloride (30 ml, 5%) was refluxed for 24 h. The reaction mixture was evaporated under reduced pressure. To an ice-cooled solution of the residue in water (10 ml) triethylamine (2.9 g, 28 mmol) and a solution of di-t-butyl oxydiformate (2.5 g, 11.1 mmol) in dioxan (10 ml) were

Table 1. Molecular dimensions for compound (8). Estimated standard deviations are given in parentheses.

Bond lengths (Å)

O(1)–N(2)	1.413(4)	C(5)–C(6)	1.505(5)
N(2)–C(3)	1.390(4)	C(6)–N(7)	1.443(5)
C(3)–O(2)	1.213(5)	N(7)–C(8)	1.357(4)
C(3)–C(4)	1.493(5)	C(8)–O(3)	1.229(3)
C(4)–C(5)	1.511(5)	C(8)–O(9)	1.340(5)
C(5)–O(1)	1.476(4)	O(9)–C(10)	1.483(5)
N(2)–C(14)	1.405(4)	C(10)–C(11)	1.522(6)
N(15)–C(14)	1.312(5)	C(10)–C(12)	1.513(6)
C(14)–O(4)	1.235(4)	C(10)–C(13)	1.516(6)

Valency angles (°)

C(5)–O(1)–N(2)	104.3(2)	C(6)–C(5)–O(1)	107.0(2)
O(1)–N(2)–C(3)	112.6(2)	C(5)–C(6)–N(7)	114.7(3)
O(1)–N(2)–C(14)	115.5(2)	C(6)–N(7)–C(8)	123.1(2)
C(3)–N(2)–C(14)	130.3(3)	N(7)–C(8)–O(9)	109.7(2)
N(2)–C(14)–N(15)	114.7(2)	N(7)–C(8)–O(3)	124.0(3)
N(2)–C(14)–O(4)	118.7(3)	O(9)–C(8)–O(3)	126.3(3)
N(15)–C(14)–O(4)	126.6(3)	C(8)–O(9)–C(10)	121.3(2)
N(2)–C(3)–C(4)	106.2(3)	O(9)–C(10)–C(11)	109.6(3)
N(2)–C(3)–O(2)	123.8(3)	O(9)–C(10)–C(12)	110.0(3)
C(4)–C(3)–O(2)	130.0(3)	O(9)–C(10)–C(13)	102.1(2)
C(3)–C(4)–C(5)	104.0(3)	C(11)–C(10)–C(12)	113.0(3)
C(4)–C(5)–O(1)	104.1(3)	C(11)–C(10)–C(13)	110.8(4)
C(4)–C(5)–C(6)	117.2(3)	C(12)–C(10)–C(13)	110.8(4)

Torsion angles (°)

C(4)–C(5)–O(1)–N(2)	±29.1(3)	C(4)–C(5)–C(6)–N(7)	±57.7(3)
C(5)–O(1)–N(2)–C(3)	∓20.9(4)	C(5)–C(6)–N(7)–C(8)	∓102.0(3)
O(1)–N(2)–C(3)–C(4)	±3.4(4)	C(6)–N(7)–C(8)–O(9)	∓174.2(3)
N(2)–C(3)–C(4)–C(5)	±15.1(4)	N(7)–C(8)–O(9)–C(10)	±178.5(3)
C(3)–C(4)–C(5)–O(1)	∓27.1(4)	C(8)–O(9)–C(10)–C(13)	∓178.5(3)
O(2)–C(3)–N(2)–C(14)	∓10.5(6)	C(8)–O(9)–C(10)–C(12)	±63.9(4)
C(3)–N(2)–C(14)–N(15)	±12.8(6)	C(8)–O(9)–C(10)–C(11)	∓61.0(4)
O(1)–N(2)–C(14)–O(4)	∓3.5(5)	C(6)–N(7)–C(8)–O(3)	±6.6(5)
O(1)–C(5)–C(6)–N(7)	∓58.6(3)	C(10)–O(9)–C(8)–O(3)	∓2.4(5)

Table 2. Hydrogen-bond distances (Å) and angles (°) for compound (8). Estimated standard deviations are given in parentheses Symmetry code:

(i) x,y,z
(ii) $2-x, y-\frac{1}{2}, \frac{1}{2}-z$
(iii) $2-x, y+\frac{1}{2}, \frac{1}{2}-z$

A–H · · · B	A–H	H · · · B	A · · · B	∠AHB
N(15)–H(151) · · · O(2^{i})	0.85(3)	2.09(3)	2.744(4)	133(3)
N(15)–H(152) · · · O(4^{ii})	0.85(3)	2.13(4)	2.870(4)	146(3)
N(7)–H(71) · · · O(4^{iii})	0.85(3)	2.13(3)	2.919(4)	155(4)

added with stirring. Stirring was continued at 0 °C for 3 h. The solution was concentrated under reduced pressure to 15 ml and extracted with ethyl acetate (3 × 25 ml). The combined and dried ($MgSO_4$) ethyl acetate phases were evaporated under reduced pressure. Column chromatography [silica gel: 60 g; eluants: toluene containing ethyl acetate (50—70%)] gave (2) (1.6 g, 82%). An analytical sample was recrystallized (toluene–light petroleum) to give pure (2), m.p. 61.0—62.0 °C $[\alpha]_D^{20}$ +0.5° (*c* 7.2 in ethanol). The i.r. spectrum was very similar to that of (±)-(2) prepared as previously described.[5]

(R)-(−)-*Methyl* N-*t*-*Butyloxycarbonyl*-3-(*toluene*-4-*sulphonyloxy*)-4-*aminobutanoate* (5).—To a solution of (2) (1.6 g, 6.9 mmol) in pyridine (15 ml) was added toluene-4-sulphonyl chloride (2.3 g, 12.0 mmol). After 5 days at room temperature, the reaction mixture was evaporated under reduced pressure and the residue taken up in water (10 ml) and extracted with chloroform (3 × 30 ml). The combined and dried ($MgSO_4$) chloroform phases were evaporated under reduced pressure. Column chromatography [silica gel (60 g); eluants, toluene containing ethyl acetate (30—40%)] gave (5) (1.7 g, 65%). An analytical sample was recrystallized (toluene–light petroleum) to give pure (5), m.p. 65.0—66.0 °C; $[\alpha]_D^{20}$ −4.9° (*c* 3.9 in ethanol). The i.r. spectrum was very similar to that of (±)-(5) prepared as previously described.[5]

Methyl trans-N-*t*-*Butyloxycarbonyl*-4-*aminobut*-2-*enoate* (6).—Compound (6) was prepared as described above for (2) using (3) (12.0 g, 0.12 mol). An analytical sample of (6) was prepared by ball-tube distillation at 0.1 mmHg (oven temperature 175 °C), $\nu_{max.}$ (film) 3 350m, 3 000m, 1 700s, 1 520m, 1 280s, and 1 170s cm^{-1}; δ ($CDCl_3$) 7.1—6.7 (1 H, a double t, *J* 16.5 and 6.0 Hz), 6.1—5.7 (1 H, d, *J* 16.5 Hz), 4.9br (1 H, s), 3.8 (2 H, m), 3.73 (3 H, s), and 1.50 (9 H, s) (Found: C, 55.7; H, 7.95; N, 6.6. $C_{10}H_{17}NO_4$ requires C, 55.80; H, 7.96; N, 6.51%).

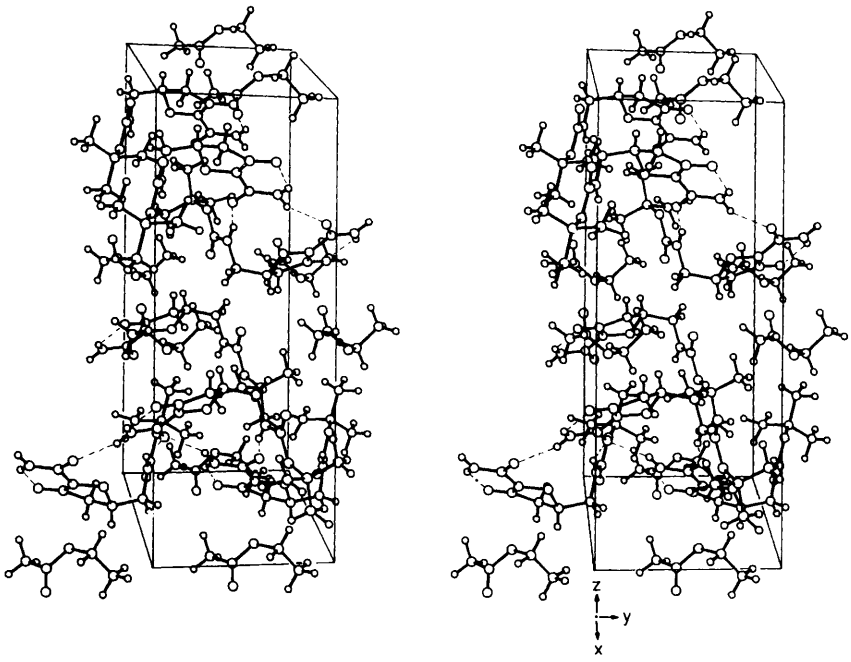


Figure 2. Stereoview of the molecular packing of compound (8)·½$C_4H_8O_2$. For clarity only one of the two alternative positions (related by a centre of symmetry) for the ethyl acetate molecules is shown. Hydrogen bonds are shown as broken lines

(RS)-5-(N-*t-Butyloxycarbonylaminomethyl*)-3-*oxoisoxazolidine*-2-*carboxamide* (8).—*From* (4). To a stirred solution of potassium t-butoxide (2.47 g, 22 mmol) in methanol (50 ml) was added hydroxyurea (0.84 g, 11 mmol). The mixture was cooled in ice and then an ice-cooled solution of (4) [5] (3.9 g, 10 mmol) in methanol (20 ml) added. After 3 h at 0 °C and then 24 h at room temperature, the reaction mixture was adjusted to pH 3 with hydrochloric acid (1 M) and then evaporated under reduced pressure. The residue was taken up in water (50 ml) and extracted with ethyl acetate (3 × 75 ml). The combined and dried ($MgSO_4$) ethyl acetate phases were evaporated under reduced pressure and the residue subjected to column chromatography [silica gel (150 g); eluant, ethyl acetate containing acetic acid (2%)] followed by recrystallization (ethyl acetate–light petroleum) gave (8) (0.96 g, 37%), m.p. 123.0—124.0 °C; $\nu_{max.}$ (KBr) 3 400s, 2 950w, 1 740s, 1 700s, 1 590m, 1 520m, 1 280s, and 1 250s cm^{-1}; $\lambda_{max.}$ 234 nm (log ε 3.58); δ ($CDCl_3$) 7.0—6.3 (2 H, m), 5.4 (1 H, m), 4.8 (1 H, m), 3.57 (2 H, t), 3.01 (2 H, d), and 1.50 (9 H, s) (Found: C, 47.55; H, 7.0; N, 13.7. $C_{10}H_{17}N_3O_5 \cdot \frac{1}{2}CH_3CO_2C_2H_5$ requires C, 47.52; H, 6.98; N, 13.68%).

From (5). Compound (8) was synthesized from (5) (1.2 g, 2.9 mmol) as described above using potassium t-butoxide (0.65 g, 5.8 mmol) and hydroxyurea (0.24 g, 3.2 mmol). Recrystallization (ethyl acetate–light petroleum) gave (8) (0.36 g, 45%), m.p. 122.0—123.0 °C; $[\alpha]_D^{20}$ 0° (*c* 5.0 in ethanol). The i.r. spectrum was identical with that of (8) described above.

From (6). Compound (8) was synthesized from (6) (4.3 g, 20.0 mmol) as described above using potassium t-butoxide (4.9 g, 44 mmol) and hydroxyurea (1.7 g, 22 mmol). Recrystallization (ethyl acetate–light petroleum) gave (8) (2.45 g, 47%), m.p. 123.0—124.0 °C. The i.r. spectrum was identical with that of (8) described above.

From (7). To a solution of (7) [5] (33 mg, 0.15 mmol) in methanol (1 ml) potassium cyanate (15 mg, 0.18 mmol) and acetic acid to pH 4 were added with stirring. Stirring was continued at room temperature for 2 h after which the solution was evaporated under reduced pressure and the residue taken up in water (5 ml) and extracted with ethyl acetate (3 × 5 ml). The combined and dried (Na_2SO_4) ethyl acetate phases were evaporated under reduced pressure and the residue recrystallized (ethyl–light petroleum) to give (8) (30 mg, 76%), m.p. 122.5—123.5 °C. The i.r. spectrum was identical with that of (8) described above.

(RS)-5-(N-*t-Butyloxycarbonylaminomethyl*)-2-*isoxazolin*-3-*ol* (7).—*From* (4). Compound (7) was synthesized from (4) (16.1 g, 41.6 mmol) as previously described [5] using sodium (2.1 g, 91.6 mmol) and hydroxyurea (3.2 g, 41.6 mmol).

From (8). To a suspension of (8) (3.0 g, 11.6 mmol) in water (100 ml) was added a solution of dimethylamine in ethanol (8 ml, 30%). Aqueous hydrochloric acid (4 M) was added to pH = 8, and the mixture was stirred for 24 h. The mixture was concentrated under reduced pressure to 50 ml, and the pH adjusted to 4 with aqueous hydrochloric acid (4 M); it was then extracted with ethyl acetate (3 × 100 ml). The combined and dried (Na_2SO_4) ethyl acetate phases were evaporated under reduced pressure and the residue subjected to column chromatography [silica gel (70 g); eluant, ethyl acetate containing acetic acid (2%)] and recrystallization to give (7) (1.5 g, 60%), m.p. 89.0—90.0 °C. The i.r. spectrum was identical with that of (7) previously described.[5]

(RS)-5-*Aminomethyl*-3-*oxoisoxazolidine*-2-*carboxamide Hydrochloride* (9).—To a solution of hydrogen chloride in ethyl acetate (4 ml; 2.9 M) was added a solution of (8) (0.8 g, 3.1 mmol) in ethyl acetate (10 ml); compound (9) (0.45 g, 75%) crystallized from the mixture at room temperature. Recrystallization (methanol) gave pure (9), m.p. 182—183.0 °C; $\nu_{max.}$ (KBr) 3 500—2 600m (several bands), 1 755s, 1 740s, 1 700s, 1 290s, and 1 270s cm^{-1}; $\lambda_{max.}$ (MeOH) 239 nm (log ε 3.61); δ (D_2O) 4.9 (1 H, m), 3.6—2.7 (4 H, m) (Found: C, 30.6; H, 5.35; Cl 17.95; N, 21.4. $C_5H_{10}ClN_3O_3$ requires C, 30.70; H, 5.15; Cl, 18.12; N, 21.49%).

X-*Ray Crystallographic Analysis of* (RS)-5-(N-*t-Butyloxycarbonylaminomethyl*)-3-*oxoisoxazolidine*-2-*carboxamide* [(8)·½$C_4H_8O_2$].—Crystal data are as follows: $C_{10}H_{17}N_3O_5 \cdot \frac{1}{2}C_4H_8O_2$,

Table 3. Positional and thermal (Å²) parameters for the non-hydrogen atoms of compound (8)·½ ethyl acetate. Estimated standard deviations are given in parentheses

Atom	x	y	z	B_{eq}
O(1)	0.861 7(3)	−0.239 6(3)	0.143 6(1)	1.44
N(2)	0.820 2(3)	−0.399 8(3)	0.141 8(1)	1.42
C(3)	0.664 8(4)	−0.430 4(4)	0.096 4(2)	1.68
C(4)	0.600 8(4)	−0.278 6(4)	0.062 3(2)	1.78
C(5)	0.748 9(4)	−0.176 7(4)	0.079 2(1)	1.62
C(6)	0.729 5(4)	−0.004 5(4)	0.089 5(1)	1.62
N(7)	0.669 8(3)	0.031 2(3)	0.141 1(1)	1.41
C(8)	0.514 4(4)	0.072 0(4)	0.128 0(2)	1.58
O(9)	0.498 0(3)	0.112 4(3)	0.185 0(1)	1.80
C(10)	0.340 9(4)	0.166 1(5)	0.185 3(2)	2.37
C(11)	0.287 8(5)	0.314 1(6)	0.143 3(2)	3.85
C(12)	0.218 2(5)	0.035 3(6)	0.162 0(2)	3.53
C(13)	0.382 6(5)	0.201 7(5)	0.258 7(2)	3.09
C(14)	0.925 0(4)	−0.492 0(4)	0.194 2(1)	1.41
N(15)	0.880 9(3)	−0.638 8(4)	0.193 3(1)	1.76
O(2)	0.600 6(3)	−0.557 9(3)	0.089 6(1)	2.18
O(3)	0.406 8(2)	0.069 3(3)	0.072 0(1)	1.86
O(4)	1.047 2(3)	−0.430 5(3)	0.235 3(1)	1.74
C(1EA)	0.815 5(13)	−0.643 1(13)	−0.019 7(6)	4.55
C(2EA)	0.961 6(10)	−0.554 3(10)	−0.004 0(4)	3.30
O(3EA)	0.958 1(6)	−0.435 2(5)	0.033 7(2)	6.54
C(4EA)	1.128 8(10)	−0.339 4(12)	0.060 2(5)	3.57
C(5EA)	1.110 4(10)	−0.223 3(12)	0.009 5(4)	3.48

$B_{eq} = \frac{8}{3}\pi^2\Sigma_i\Sigma_j U_{ij}a_i^*a_j^*\mathbf{a}_i\mathbf{a}_j$.

M = 303.32, Monoclinic, a = 8.963(8), b = 8.532(6), c = 21.62(2) Å, β = 112.35(6)°, U = 1 529 Å³, D_m (flotation) = 1.31 g cm⁻³. D_c = 1.318 g cm⁻³, Z = 4. Space group $P2_1/c$ (No. 14), μ(Mo-K_α) = 1.14 cm⁻¹.

The colourless prismatic crystals used for the X-ray examination were crystallized from a mixed solution of ethanol–ethyl acetate–light petroleum (1 : 1 : 2).

A single crystal of the size 0.45 × 0.25 × 0.08 mm was used for the determination of the unit cell parameters and for the collection of intensity data. The measurements were performed at 96 K with a Picker FACS-1 diffractometer using graphite monochromated (Mo-K_α) radiation (λ = 0.71069). A modified Enraf-Nonius low-temperature device was used to cool the crystal, and the temperature was kept constant within 0.5 K during the experiment. The general techniques employed are as previously described.[8] Of the 2 696 independent reflections measured in the range $2.4 \leqslant 2\theta \leqslant 50.0°$, 1 619 had net intensities greater than 5.0σ (I), where σ (I) is the estimated standard deviation of an intensity as calculated from counting statistics. These were regarded as observed reflections and used in the refinement procedure.

The structure was solved by direct methods with the MULTAN program [9] and refined by the least-squares method minimizing $\Sigma w(|F_o| - k|F_c|)^2$.[10] The positions of the hydrogen atoms of the molecule of (8) were obtained from a difference map. The hydrogen atoms of the ethyl acetate molecule were inserted in chemically reasonable positions, C–H = 1.0 Å.

In subsequent full-matrix least-squares calculations an overall scale factor, atomic co-ordinates for all atoms, except those of the hydrogen atoms of the ethyl acetate molecule, and anisotropic thermal parameters for the non-hydrogen atoms were refined. The thermal parameters for the hydrogen atoms were fixed at isotropic values corresponding to those of the atoms to which they are bonded. Two general positions with half occupancy are possible for the ethyl acetate molecule. The carbon and hydrogen atoms were constrained to have the occupancy 0.5, while the two oxygen atoms were treated as one oxygen atom, O(3EA), with an occupancy of 1.0. The weights used in the final cycles of refinement were given by $w = x \cdot y$, x = 1 for $\sin\theta \geqslant 0.30$, else $x = \sin\theta/0.30$, y = 1 for $F_o \leqslant 13.0$, else $y = 13.0/F_o$. On the last cycle of least-squares refinement the values of maximum and average shift/error were 0.8 and 0.1, respectively. The final R value is 0.55 and R_w = 0.066 for 1 619 unique reflections.

Table 4. Positional parameters for the hydrogen atoms * of compound (8). Estimated standard deviations are given in parentheses.

Atom	x	y	z
H(4A)	0.522(4)	−0.233(4)	0.081(2)
H(4B)	0.554(4)	−0.289(4)	0.014(2)
H(5)	0.797(4)	−0.188(4)	0.046(2)
H(6A)	0.827(4)	0.054(4)	0.098(2)
H(6B)	0.662(4)	0.042(4)	0.049(2)
H(7)	0.731(4)	0.033(4)	0.182(2)
H(11A)	0.384(6)	0.395(6)	0.166(2)
H(11B)	0.265(6)	0.294(6)	0.096(2)
H(11C)	0.202(6)	0.354(6)	0.154(2)
H(12A)	0.189(5)	0.012(5)	0.115(2)
H(12B)	0.254(5)	−0.072(5)	0.185(2)
H(12C)	0.130(6)	0.077(5)	0.171(2)
H(13A)	0.414(5)	0.103(5)	0.280(2)
H(13B)	0.466(5)	0.282(5)	0.272(2)
H(13C)	0.288(5)	0.255(5)	0.267(2)
H(15A)	0.793(4)	−0.672(4)	0.163(2)
H(15B)	0.932(4)	−0.699(4)	0.226(2)

* The hydrogen atoms have numbers corresponding to those of their parent carbon (nitrogen) atoms.

Table 3 lists the final positional and thermal parameters of the non-hydrogen atoms. Table 4 lists the final positional parameters of hydrogen atoms of the molecule of (8). Lists of structure factors and anisotropic thermal parameters of the non-hydrogen atoms have been deposited as a Supplementary publication [SUP. No. 23593 (9 pp.)].*

The X-ray atomic scattering factors used were those of Cromer and Mann [11] for O, N, and C, and of Stewart, Davidson and Simpson [12] for H.

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