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(–)-(*R*)-5,5-Dimethylmorpholinyl-2-acetic Acid Ethyl Ester Hydrochloride,† $C_{10}H_{20}NO_3^+.Cl^-$

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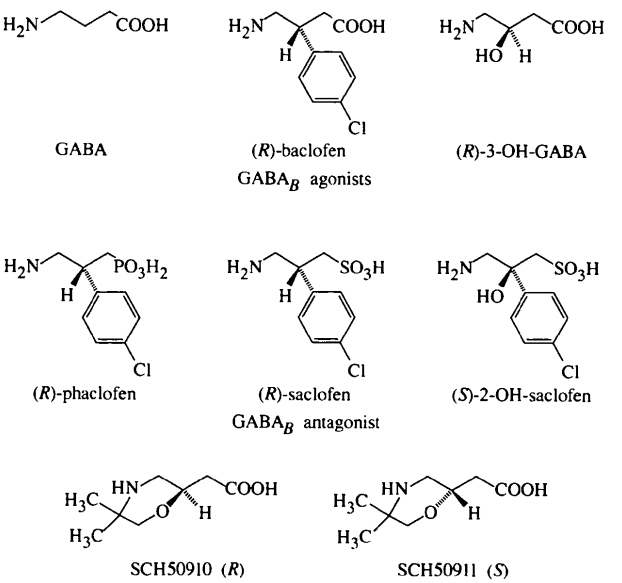
Abstract

One of the enantiomers of 5,5-dimethylmorpholinyl-2-acetic acid is observed to be a $GABA_B$ receptor antagonist. The absolute configuration of the inactive enantiomer is found to be the *R* configuration. The morpholine ring adopts a chair conformation with the acetic acid moiety in an equatorial position. In the crystal packing, hydrogen bonds are observed between the ammonium group and the chloride ions.

Comment

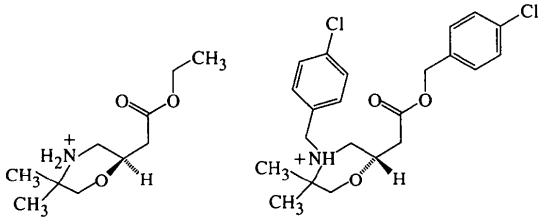
4-Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the mammalian central nervous system and operates through $GABA_A$ and $GABA_B$, and probably also $GABA_C$ receptors (Krujevic, 1974; Olsen & Venter, 1986; Barnard & Costa, 1989; Enna & Bowery, 1997). The present investigation was performed in order to obtain knowledge of the stereochemical requirements for the ligands to interact with the $GABA_B$ receptor recognition site. (*R*)-4-Amino-3-hydroxybutyric acid [(*R*)-3-OH-GABA] and (*R*)-baclofen are both $GABA_B$ receptor agonists (Falch *et al.*, 1986), showing that $GABA_B$ receptors are capable of accommodating the hydroxyl group of the first and the 4-chlorophenyl group of the second in different stereochemical orientations (see Scheme I). (*R*)-Phaclofen (Frydenvang *et al.*, 1994), (*R*)-saclofen (Carruthers *et al.*, 1995) and (*S*)-2-OH-saclofen (Prager, Schafer, Hamon & Massy-Westropp, 1995) are all $GABA_B$ receptor antagonists. The stereochemical orientations of the hydroxy groups of the $GABA_B$ receptor agonist, (*R*)-3-OH-GABA, and the $GABA_B$ receptor antagonist, (*S*)-2-OH-saclofen, are identical (see Scheme I). Recently, a series of morpholinyl-2-acetic acid analogues was synthesized and tested as $GABA_B$ receptor ligands, and one of these cyclized 3-oxygenated GABA analogues, namely, (+)-5,5-dimethylmorpholinyl-2-acetic acid (SCH50911), was shown to be a competitive $GABA_B$ receptor antagonist (Bolser *et al.*, 1995), while the (–)-enantiomer, SCH50910, was inactive. The absolute configuration of SCH50911 was established to be *S* by X-ray analysis of a derivative of SCH50911 containing bulky substituents (Blythin *et al.*, 1996) (see Scheme I). The stereochemical orientation of the oxygen function of SCH50911 is thus the opposite of the hydroxyl groups of (*R*)-3-OH-GABA and (*S*)-2-OH-saclofen.



Scheme I

† Alternative name: (*R*)-2-(ethoxycarbonylmethyl)-5,5-dimethylmorpholin-4-ium chloride.

Attempts to obtain crystals suitable for X-ray analysis of the unsubstituted 5,5-dimethylmorpholinyl-2-acetic acid were unsuccessful, but crystals were obtained of the hydrochloride of SCH50910 ethyl ester showing satisfactory diffraction characteristics. X-ray analysis of these crystals confirmed the recently reported absolute configuration of SCH50911 (Blythin *et al.*, 1996). The molecular structure of the title compound is shown in Fig. 1. The morpholine ring adopts a chair conformation with the acetic acid moiety in an equatorial position. Bond lengths and angles of the morpholine ring of the two compounds are similar (see Scheme II). Small changes are observed around the ammonium N atom, but only one bond length changes significantly, N4—C5 with a value of 1.517 (3) Å in the ethyl ester of SCH50910 and 1.546 (5) Å in the derivative of SCH50911, and this is probably due to the substitution at the N atom in the derivative of SCH50911 (Blythin *et al.*, 1996).



SCH50910 ethyl ester SCH50911 derivative

Scheme II

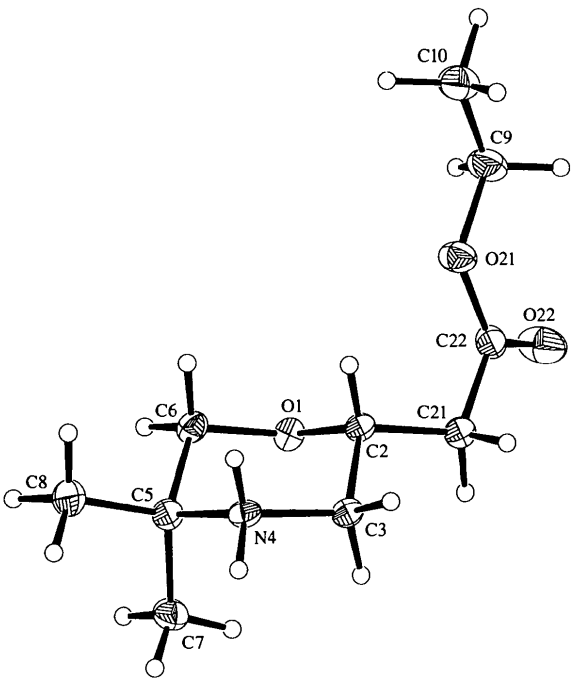


Fig. 1. The molecular structure (*ORTEPII*; Johnson, 1976) of SCH50910 ethyl ester with the atomic labelling. Displacement ellipsoids are shown for non-H atoms at the 50% probability level.

In the crystal packing, hydrogen bonds are observed between the ammonium group and the chloride ions. Each chloride ion accepts two hydrogen bonds (Table 2) from two different ammonium groups forming infinite chains along the *x* axis. The morpholine rings are located in the *yz* plane with the ethyl ester moiety along the *x* axis almost perpendicular to the ring plane. Ethyl ester groups are packed in one layer and the six-membered rings are located in a different layer, which also includes the chloride ions.

The molecular flexibility of the $GABA_B$ receptor antagonist SCH50911 is reduced due to the morpholine ring compared with that of the non-cyclized $GABA_B$ receptor agonists and antagonists. C22—C21—C2—C3—N4 defines the GABA backbone in SCH50910/SCH50911. The conformation of the GABA structure element of SCH50910/SCH50911 is extended, the two torsion angles C22—C21—C2—C3 and C21—C2—C3—N4 are approximately 180° (Table 1). The torsion angle C21—C2—C3—N4 is around 180° in the observed chair conformation and would be approximately ∓80° in the alternative chair conformation of the six-membered ring (acetic acid moiety in an axial position). The energy difference between these two chair conformations is around 25 kJ mol^{-1} with the torsion angle C22—C21—C2—C3 180° [calculation performed with the program *MacMimic/MM3*(92) (InStar Software, Lund, Sweden; Allinger, Yuh & Lii, 1989)]. The torsion angle C21—C2—C3—N4 of SCH50911 is therefore expected to be able to obtain two different values, 80 and 180°, while the other torsion angle, C22—C21—C2—C3, is able to obtain at least the three staggered conformations, 80, −80 and 180°. The compound SCH50911 is interesting for pharmacophore modelling of the $GABA_B$ receptor recognition site, but there is still a flexible part of the GABA backbone. An analogue with the flexibility of the acidic moiety restricted is required before a valuable pharmacophore model for the $GABA_B$ receptor can be made.

Experimental

Crystalline material was obtained from a solution of SCH50910 hydrochloride in ethanol followed by vapour diffusion of diethyl ether saturated with hydrogen chloride. During this process, the ethyl ester is formed. Single crystals of the ethyl ester of SCH50910 hydrochloride were obtained from a solution in chloroform followed by vapour diffusion of diethyl ether saturated with hydrogen chloride.

Crystal data

$C_{10}H_{20}NO_3^+.Cl^-$ Cu $K\alpha$ radiation
M_r = 237.72 λ = 1.54180 Å

Orthorhombic
$P2_12_12_1$
a = 7.393 (1) Å
b = 8.827 (2) Å
c = 19.907 (3) Å
V = 1299.1 (4) Å^3
Z = 4
D_x = 1.215 Mg m^{-3}
D_m not measured

Cell parameters from 20 reflections
θ = 38.61–44.26°
μ = 2.536 mm^{-1}
T = 122 (2) K
Plate
0.32 × 0.32 × 0.04 mm
Colourless

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scan mode
Absorption correction: Gaussian (*ABSORB*; De Titta, 1985)
T_{min} = 0.364, T_{max} = 0.900
4373 measured reflections
2667 independent reflections

2606 reflections with $I>2\sigma(I)$
R_{int} = 0.0134
θ_{max} = 74.93°
$h = -9 \rightarrow 9$
$k = -10 \rightarrow 11$
$l = -24 \rightarrow 24$
5 standard reflections
every 600 reflections
frequency: 166 min
intensity decay: 5.7%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.027
$wR(F^2)$ = 0.076
S = 1.082
2667 reflections
196 parameters
Only coordinates of H atoms refined
$w = 1/[\sigma^2(F_o^2) + (0.0516P)^2 + 0.2231P]$
where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{max}$ = −0.001
$\Delta\rho_{max}$ = 0.238 e Å^{-3}
$\Delta\rho_{min}$ = −0.237 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)
Absolute configuration: Flack (1983)
Flack parameter = 0.00 (1)

Table 1. *Selected geometric parameters (Å, °)*

C2—O1	1.429 (2)	C5—C7	1.527 (2)
C2—C3	1.519 (2)	C21—C2	1.515 (2)
O1—C6	1.431 (2)	C22—C21	1.510 (2)
C3—N4	1.497 (2)	O21—C22	1.333 (2)
N4—C5	1.517 (2)	O22—C22	1.202 (2)
C5—C8	1.525 (2)	O21—C9	1.456 (2)
C5—C6	1.526 (2)	C9—C10	1.508 (3)
C2—O1—C6	111.0 (1)	C8—C5—C7	111.6 (1)
O1—C2—C21	107.6 (1)	C6—C5—C7	112.4 (1)
O1—C2—C3	110.2 (1)	O1—C6—C5	111.7 (1)
C21—C2—C3	109.8 (1)	C22—C21—C2	115.3 (1)
N4—C3—C2	109.3 (1)	O22—C22—O21	124.2 (2)
C3—N4—C5	114.1 (1)	O22—C22—C21	123.4 (2)
N4—C5—C8	106.8 (1)	O21—C22—C21	112.3 (1)
N4—C5—C6	106.2 (1)	C22—O21—C9	116.4 (1)
C8—C5—C6	110.6 (1)	O21—C9—C10	107.1 (2)
N4—C5—C7	109.0 (1)		
C21—C2—O1—C6	−178.4 (1)	C8—C5—C6—O1	172.7 (1)
C3—C2—O1—C6	61.9 (2)	C7—C5—C6—O1	−61.9 (2)
O1—C2—C3—N4	−55.3 (2)	C22—C21—C2—O1	71.9 (2)
C21—C2—C3—N4	−173.6 (1)	C22—C21—C2—C3	−168.2 (1)
C2—C3—N4—C5	53.1 (2)	O22—C22—C21—C2	−147.9 (2)
C3—N4—C5—C8	−170.9 (1)	O21—C22—C21—C2	34.7 (2)
C3—N4—C5—C6	−52.9 (2)	C9—O21—C22—O22	0.1 (2)
C3—N4—C5—C7	68.4 (2)	C9—O21—C22—C21	177.4 (1)
C2—O1—C6—C5	−64.4 (2)	C22—O21—C9—C10	−169.2 (2)
N4—C5—C6—O1	57.2 (2)		

Table 2. *Hydrogen-bonding geometry (Å, °)*

D—H···A	D—H	H···A	D···A	D—H···A
N4—H41···Cl1	0.92 (3)	2.21 (3)	3.117 (1)	165 (2)
N4—H42···Cl1^i	0.92 (3)	2.17 (3)	3.084 (1)	174 (2)

Symmetry code: (i) $\frac{1}{2}+x, \frac{3}{2}-y, 1-z$.

The chloride ion was located using the heavy-atom method (*SHELXS*86; Sheldrick, 1990) and the other non-H atoms were located using difference electron-density maps. H atoms were located in subsequent difference electron-density maps. The absolute configuration was determined using the method described by Flack (1983) [x = 0.00 (1)] and it confirmed the published determination of the absolute configuration of SCH50911 (Blythin *et al.*, 1996). The residual density is observed close to the position of the chloride ion (within 1 Å). Neutral atomic scattering factors have been applied.

Data reduction: *DREADD* (Blessing, 1987, 1989). Program(s) used to solve structure: *SHELXS*86. Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *ORTEP*II (Johnson, 1976).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1104). Services for accessing these data are described at the back of the journal.

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1-(1-Cyanocyclohexyl)-1-hydroxy-3-phenylurea

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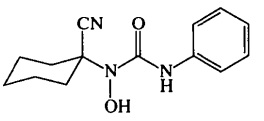
Abstract

In the crystals of the title compound, $C_{14}H_{17}N_3O_2$, there are two molecules (*A* and *B*) in the asymmetric unit. The conformation of the hydroxamic acid moiety, O=C—N—O, is antiperiplanar for both molecules. The phenyl substituent is in a synperiplanar conformation, with O=C—N—C torsion angles of 1.8 (2) and 2.1 (2)° for *A* and *B*, respectively. The corresponding torsion angles of the cyclohexyl substituents are −32.0 (2) and −30.8 (2)°, respectively. The cyclohexyl ring adopts a chair conformation in both molecules, with the hydroxamic acid moiety in an equatorial position and the cyano group in an axial position. The plane of the phenyl group is twisted with respect to the central urea plane [38.71 (7) and 43.08 (7)° for molecules *A* and *B*, respectively]. No other significant differences in bond lengths, angles or torsion angles between molecules *A* and *B* are observed. The crystal packing shows that the *A* and *B* molecules are interconnected by hydrogen bonds, OH···O and NH···N, in the direction of the *a* axis.

Comment

The title compound, (I), was first synthesized by Zinner & Krüger (1975) in a reaction between the corresponding hydroxylaminocarbonitrile and phenylisocyanate. It was observed that this type of substituted hydroxamic acid gives a positive Fe^{III} colour test only by using a non-aqueous Fe^{III} chloride solution (Krüger & Zinner, 1978). The conformation of a hydroxamic acid with very bulky substituents is expected to influence the ability of the compound to form a coloured complex with Fe^{III}. Limited flexibility might prevent the molecule from adopting the *sp* (synperiplanar) conformation of O=C—N—O, which is most favourable to complex formation (Larsen, 1988). X-ray structure determination of the title compound was carried out in order to establish the conformation of the hydroxamic acid moiety in the crystalline state of the compound.



(I)

There are two molecules of the title compound (*A* and *B*) in the asymmetric unit (Fig. 1). The conformations of the *A* and *B* molecules are very similar (see Table 1). The only conspicuous conformational deviation observed is in the twist of the phenyl ring with respect to the central urea moiety, the dihedral angles between the corresponding least-squares planes being 38.71 (7) and 43.08 (7)° for molecules *A* and *B*, respectively. The urea moiety is nearly planar with a maximum deviation from the least-squares plane through O2, C8, N1 and N3 of 0.017 (1) Å in both molecules. The hydroxyl O atom O1 is not included in this plane, the deviations being 0.429 (2) and 0.441 (2) Å in molecules *A* and *B*, respectively. This means that the N1 atom has a high degree of pyramidalization, which is also reflected in the distances of the N1 atoms from the planes defined by C1, C8 and O1 [0.371 (1) and 0.365 (1) Å for molecules *A* and *B*, respectively]. The other N atom (N3) has a completely planar configuration in both molecules.

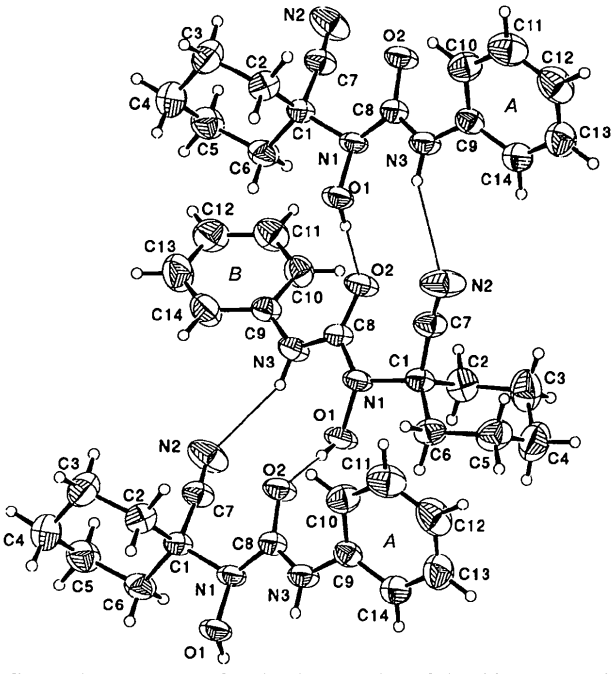


Fig. 1. The structures of molecules *A* and *B* of the title compound, which are linked together by hydrogen bonds (thin lines). The atom-labelling scheme is shown; displacement ellipsoids are drawn at the 50% probability level for non-H atoms.