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tert-Butyl 3-[4-(2-Bromoethoxy)-3-chlorophenyl]-5-methylisoxazole-4-carboxylate

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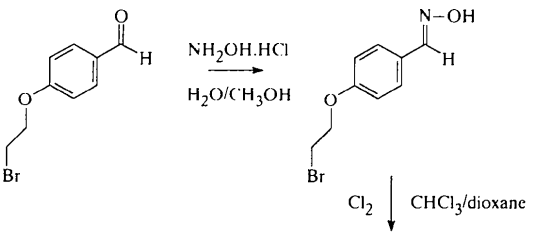
Abstract

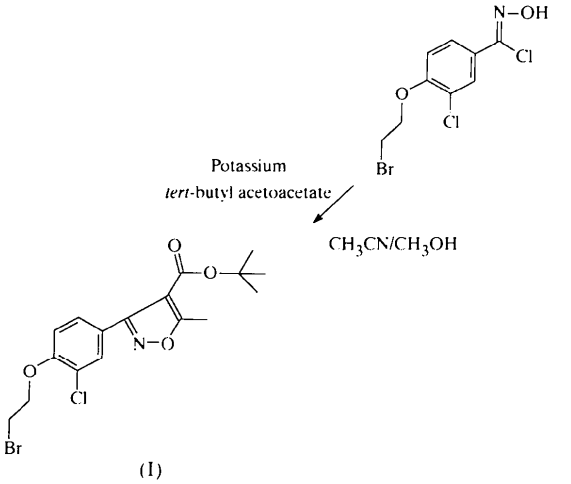
The title compound, $C_{17}H_{19}BrClNO_4$, has been prepared for the development of homogeneous immunoassays involving penicillins as tracers. An X-ray diffraction study has shown that the Cl atom is located *ortho* to the bromoethoxy group on the aromatic ring.

Comment

For the development of homogeneous immunoassays involving penicillins as tracers, carbenicillin, cefuroxime, cefotaxime and oxacillin conjugates to low molecular weight compounds (haptens) have been prepared (Kohl *et al.*, 1997). By a competition pathway, these conjugates are able to diminish the hydrolysis rate of nitrocephin, which is a coloured revelator of a specific enzyme and a class C β-lactamase. This interference is suppressed by antibody addition and restored when a free hapten is introduced into the medium (Kohl *et al.*, 1996).

A modulation of colour production by the hapten results in its determination. These reactions are only possible if the conjugate affinity for the specific enzyme (represented by the Michaelis enzymatic constant, K_m) is high (low K_m values) and their own hydrolysis rate (represented by the catalytic constant k_{cat}) is slow (Galleni & Frère, 1988). Oxacillin is the best β-lactamic antibiotic from this point of view. Unfortunately, oxacillins have no functional groups available for coupling and therefore cannot be conjugated if they are not functionalized.





(I)

It is for this purpose that the preparation of the title compound, (I), has been investigated. The following procedure has been carried out in three steps: (1) starting from 4-(2-bromoethoxy)benzaldehyde, preparation of the corresponding oxime by reaction with hydroxylamine in hydromethanolic medium buffered at pH 5; (2) oxime chlorination using gaseous chlorine in chloroform for the preparation of the chloroxime; (3) reaction of the chloroxime with one equivalent amount of *tert*-butyl acetoacetate potassium salt in the presence of acetonitrile/methanol. During the second step of this synthesis, the aromatic ring has been substituted by a Cl atom. This phenomenon has been confirmed by elemental analysis, by mass spectrometry and by proton nuclear magnetic resonance. However, with these techniques the position of the Cl atom on the aromatic ring cannot be located exactly. Consequently, it was decided to establish the position of the substitution by X-ray diffraction. The crystal structure determination has shown that the electrophilic substitution is in the position *ortho* to the bromoethoxy group. The achiral compound crystallizes in a polar space group and the absolute direction of the polar axis has been determined. The bond lengths and angles are within expected values. Steric interactions between the rings and the carboxylate group in

the title compound, (I), are less than in ethyl 3-(9-anthryl)-5-methyl-4-isoxazolecarboxylate, (II) (Mosher *et al.*, 1996), or in 2′-(*N*-methylamino)-2-methylpropyl-5-methyl-3-phenylisoxazole-4-carboxylate hydroiodide, (III) (Smith *et al.*, 1991). The torsion angles show indeed that (II) and (III) are more distorted from planarity than (I), where C9—C10—C13—O4 = −161.8 (4)° and C7—C6—C9—C10 = 21.9 (7)°. The corresponding angles are 78.2 (5) and 2.4 (3)° in (II), and 45.9 (7) and 23.2 (9)° in (III), respectively. The cohesion of the crystal is the result of van der Waals interactions. There are no hydrogen bonds involving O, N, Br or Cl atoms.

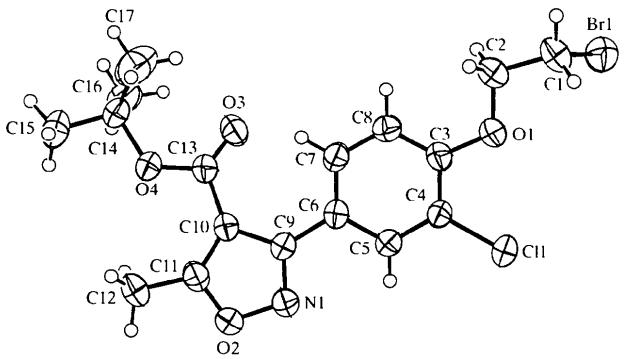


Fig. 1. Molecular structure with atom-labelling scheme. Displacement ellipsoids are shown at the 50% probability level; H atoms are drawn as small circles of an arbitrary radius.

Experimental

The title compound was synthesized by Kohl *et al.* (1996) at the Laboratory of Analytical Chemistry (Institute of Pharmacy, Liège). Crystals were obtained by slow evaporation from a toluene (15% volume) and petroleum ether (b.p. 373–413 K) (85%) solution at room temperature.

Crystal data

$C_{17}H_{19}BrClNO_4$
M_r = 416.69
Monoclinic
$P2_1$
a = 9.5664 (12) Å
b = 7.0768 (9) Å
c = 14.2175 (10) Å
β = 108.137 (7)°
V = 914.69 (18) Å^3
Z = 2
D_x = 1.513 Mg m^{-3}
D_m not measured
Cu $K\alpha$ radiation
λ = 1.54180 Å
Cell parameters from 35 reflections
θ = 27.48–36.78°
μ = 4.585 mm^{-1}
T = 293 (2) K
Prismatic
0.53 × 0.29 × 0.27 mm
Colourless

Data collection

Stoe–Siemens AED four-circle diffractometer
ω scan
Absorption correction: semi-empirical, ψ scan (*EMPIR*; Stoe & Cie, 1987*c*)
T_{min} = 0.152, T_{max} = 0.290
1871 measured reflections
1799 independent reflections
1503 reflections with $I > 2\sigma(I)$
R_{int} = 0.0308
θ_{max} = 68.03°
$h = -11 \rightarrow 10$
$k = -8 \rightarrow 0$
$l = 0 \rightarrow 17$
2 standard reflections
frequency: 60 min
intensity decay: 2.6%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.032
$wR(F^2)$ = 0.090
S = 0.942
1799 reflections
222 parameters
H atoms riding
$w = 1/[\sigma^2(F_o^2) + (0.0737P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.345 e Å^{-3}
$\Delta\rho_{min}$ = −0.303 e Å^{-3}
Extinction correction: *SHELXL*97 (Sheldrick, 1997)
Extinction coefficient: 0.0114 (9)
Scattering factors from *International Tables for Crystallography* (Vol. C)
Absolute structure: Flack (1983)
Flack parameter = 0.01 (3)

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

C6—C9	1.478 (5)	C11—O2	1.331 (5)
C9—N1	1.312 (5)	C13—O3	1.197 (5)
C9—C10	1.441 (5)	C13—O4	1.341 (5)
C10—C11	1.359 (5)	N1—O2	1.416 (4)
C10—C13	1.476 (5)		
N1—C9—C10	111.0 (3)	C10—C11—C12	134.7 (4)
N1—C9—C6	117.0 (3)	O3—C13—O4	125.2 (4)
C10—C9—C6	131.9 (3)	O3—C13—C10	124.9 (4)
C11—C10—C9	104.0 (3)	O4—C13—C10	109.9 (3)
C11—C10—C13	126.3 (3)	C9—N1—O2	105.5 (3)
C9—C10—C13	129.5 (3)	C11—O2—N1	109.4 (3)
O2—C11—C10	110.2 (3)	C13—O4—C14	121.0 (3)
O2—C11—C12	115.1 (3)		
C7—C6—C9—C10	21.9 (7)	C9—C10—C13—O4	−161.8 (4)
C6—C9—C10—C13	8.8 (8)	C10—C13—O4—C14	179.2 (4)

H atoms were included in calculated positions and allowed to ride on their parent atoms with isotropic displacement parameters fixed at $1.2U_{eq}$ of the parent atoms ($1.5U_{eq}$ for the methyl H atoms).

Data collection: *DIF*4 (Stoe & Cie, 1987*a*). Cell refinement: *DIF*4. Data reduction: *REDU*4 (Stoe & Cie, 1987*b*). Program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1990). Program(s) used to refine structure: *SHELXL*97. Molecular graphics: *ORTEP*III (Burnett & Johnson, 1996). Software used to prepare material for publication: *SHELXL*97.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: LN1061). Services for accessing these data are described at the back of the journal.

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1-(β-D-Ribofuranosyl)-6-propylcytosine

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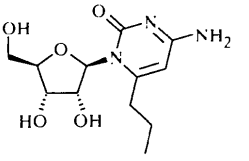
Abstract

The conformation of the title compound, $C_{12}H_{19}N_3O_5$, in the solid state is *syn*, and the ribose ring is close to the ^4E envelope conformation. The propyl side chain is planar and almost coplanar with the cytosine ring, the deviation between the two being 4.4 (2)°. Hence the overall structure consists essentially of two planes perpendicular [86.2 (2)°] to each other, the plane of the sugar moiety and that of the 6-propylcytosine.

Comment

Most pyrimidine nucleosides exist predominantly in the *anti* conformation about the glycosyl bond, partly due to a stabilizing C6—H···O5′ intramolecular hydrogen bond and partly to repulsive interaction between the C2 carbonyl atom and the furanose ring. However, pyrimidine nucleosides with a bulky C6 substituent are often constrained to the *syn* conformation due to steric hindrance between the sugar ring and the C6 substituent, one early reported example being the naturally occurring orotidine (6-carboxyuridine) (Hruska, 1971). Pyrimidine nucleosides and nucleotides constrained in the *syn* conformation by a C6-substituent are of interest both as (*a*) potential antimetabolites, *e.g.* 6-thiocarboxamide-UMP, a structural analogue of orotidine-5′-phosphate (OMP), is a potent inhibitor of OMP decarboxylase (Cody & Kalman, 1985), and (*b*) model compounds to determine whether the parent non-substituted nucleoside (or nucleotide) is involved in a given enzymatic reaction in the *syn* and/or *anti* conformation, *e.g.* several 6-substituted uridines are reasonable substrates for uridine phosphorylase (Krajewska & Shugar, 1982; Felczak *et al.*, 1996), pointing to involvement of the *syn* conformation of uridine as an intermediate in the reaction. This led to determination of the structures of a variety of 6-substituted uracil nucleoside analogues (Felczak *et al.*, 1996, and references cited), and the solid-state structure of one cytosine nucleoside analogue, 1-(β-D-arabinofuranosyl)-6-methylcytosine (Yamaguchi *et al.*, 1992). We here describe the crystal structure of another such compound, 6-propylcytidine, (I).



(I)

An *ORTEP* (Johnson, 1976) representation of the molecule with atomic labelling scheme is shown in Fig. 1. The conformation about the glycosyl bond is *syn* [C2—N1—C1′—O4′, χ = 73.9 (4)°], which is the one frequently favoured when there is a bulky C6 substituent, despite the resulting repulsion between the C2 carbonyl and the sugar moiety. The closest intramolecular contacts of O2, apart from O2···C1′ [2.695 (3) Å], are O2···C2′ and O2···H2′ [2.777 (3) Å and 2.39 Å] and somewhat longer to C3′, H3′ and O4′ [3.050 (3), 2.50 and 3.002 (3) Å, respectively].

The furanose ring is in the unusual C4′-*endo* envelope conformation with C4′ displaced to the same side as C5′ from the plane through the other four atoms by −0.577 (6) Å. However, with the O4′—C1′—C2′—C3′ torsion angle being −3.5 (2)° rather than zero, there is also a slight puckering at C3′, making the conformation strictly speaking $_4T^3$. The puckering of the ring, calculated from the torsion angles (Altona & Sundaralingam, 1972), is P = 50.7°. A trend towards the C3′-*endo* is observed for pyrimidines locked in the *syn* conformation (Saenger, 1984). In C6-substituted uridines in the *syn* conformation, C4′-*exo* and C2′-*endo* have also been observed (Cody & Kalman, 1985). The orientation around the exocyclic C4′—C5′ bond is *ap* (*gauche*, *trans*) with C3′—C4′—C5′—O5′ (γ) = −173.7 (6)° and there is no C5′ hydroxyl intramolecular hydrogen bond.