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An Eight-Membered N,N,S,S-Heterocyclic Compound: 4,7-Bis(4-chlorophenyl)-3,8-dihydro-1,2,5,6-dithiadiazocine

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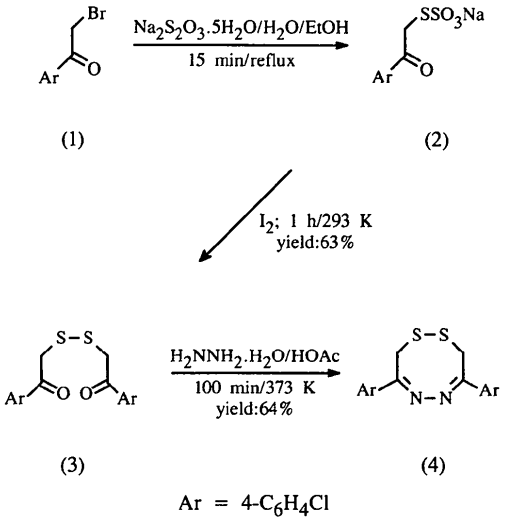
Abstract

The eight-membered ring in the title compound, $C_{16}H_{12}Cl_2N_2S_2$, adopts a non-planar conformation as expected, and the least-squares planes of the 4-substituted aromatic ring form a dihedral angle of 83.3 (2)° as a result of steric constraints. The molecular dimensions are of general interest for comparison with structural data of analogous compounds.

Comment

The experimental investigations were performed in order to develop efficient syntheses for substituted eight-membered heterocycles. The cyclization of 1,*n*-difunctional carbonyl compounds can be accomplished with hydrazine to give five- and six-membered N,N-heterocycles (Kost & Grandberg, 1966; Tišler & Stanovnik, 1968). In the same manner cyclization to form seven-membered N,N- and N,N,S-heterocycles (Lipp, Dallacker & Munnes, 1958; Sataty, 1970; Cuthbertson, Hardy & MacNicol, 1975) is also an effective synthetic route. The preparation of eight-membered N,N,S,S-heterocycles could be an interesting possibility.

With this in mind, 2-bromo-1-(4-chlorophenyl)ethan-1-one, (1), in ethanol was treated with sodium thiosulfate pentahydrate in water (reflux); the resulting Bunte salt, (2), (Distler, 1967) can be converted by treatment with iodine (Hiskey, Thomas & Kepler, 1964) to the corresponding bis(4-chlorophenacyl)disulfide, (3). The cyclizing condensation of this 1,6-difunctional intermediate can be achieved with hydrazine monohydrate in acetic acid and facilitates the efficient preparation of the target molecule, (4).



The constitution of the title compound can be deduced from ^1H and ^{13}C NMR ($CDCl_3$, 400 MHz) experiments. The *AB* signal (δ_A = 3.46, δ_B = 4.15 p.p.m.; J_{AB} = 12.8 Hz) is characteristic of the cyclic methylene groups being not equivalent. The Raman absorption for the S—S bond (ν = 512.9 cm^{-1}) is consistent with fundamental results (van Wart & Scheraga, 1976).

X-ray diffraction measurements were carried out to confirm these preliminary spectroscopic results and to determine the conformation of the target molecule in the solid phase.

The spectroscopic conclusions regarding the eight-membered ring are confirmed by the results of the X-ray analysis. The structure of the N,N,S,S-heterocycle is nearly regular, as demonstrated by the almost equivalent values for corresponding bond lengths S—C [1.835 (5), 1.829 (4) Å], C—C [1.510 (6), 1.496 (6) Å] and N—C [1.286 (6), 1.281 (5) Å].

The conformation of the eight-membered ring is determined by the spatial arrangement of the azine group. The electronic repulsion of the lone-pair electrons at the N atoms is reduced by distortion around the N—N bond; the value of 83.6 (5)° for the C—N—N—C torsion angle of the azine group is remarkable.

The bond angles at the S atoms are within the range of values for acyclic disulfanes (Jones, Bernal, Frey & Koetzle, 1974); there is also no significant difference in lengths for the S—S bond. The C—C—S—S torsion angles are 91.0 (3) and 89.5 (3)°; this orientation leads to minimum repulsion of the S-atom lone pairs.

On the other hand the structure of the C—S—S—C fragment agrees with the values for cyclic disulfanes (Capasso, Mattia & Mazzarella, 1977); the bond lengths, bond angles and the torsion angle are all nearly equivalent.

The neighbouring imino groups and aryl groups are nearly coplanar [dihedral angles: 4.9 (3), 3.1 (2)°], which permits optimum conjugation. Further indications for the presence of a conjugative interaction are the N—C bond lengths 1.281 (5)–1.286 (6) Å; there is a significant shortening with respect to the corresponding single bonds.

Steric repulsion of the cyclic methylene groups is avoided by the preferred spatial arrangement and the *endo* position of one H atom. Steric interaction of the *exo*-faced position of the other H atom with the *ortho*-position of the aryl groups seems to be relatively unimportant. Another feature of interest is the geometry of the C—S—S—C fragment, which has a torsion angle of −59.7 (2)°.

The most interesting structural features are the values for the single S—S [2.027 (2) Å)] and N—N [1.386 (5) Å] bonds.

The regular structure of the eight-membered ring is further illustrated by values consistent with typical bond angles S—S—C [102.5 (2), 103.0 (2)°] and S—C—C [108.0 (3), 109.2 (3)°]. A pseudo-twofold axis runs along the midpoint of the S—S and N—N bonds.

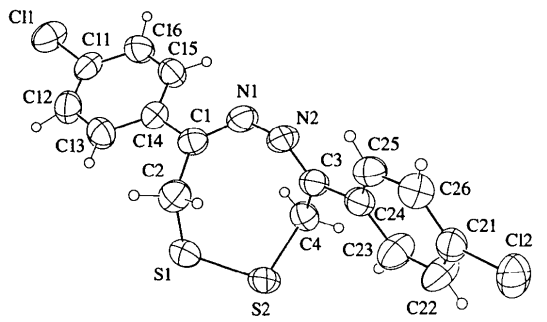


Fig. 1. View of the title compound showing the labelling of all non-H atoms. Displacement ellipsoids are shown at the 50% probability level. H atoms are drawn as circles of arbitrary radius.

Experimental

4,7-Bis(4-chlorophenyl)-3,8-dihydro-1,2,5,6-dithiadiazocine, (4), was prepared by cyclization of bis(4-chlorophenacyl)disulfide, (3), with hydrazine monohydrate in 2-propanol/acetic acid (reflux) or acetic acid (373 K); the cyclization product was purified by recrystallization from ethyl acetate (m.p. 441 K).

Crystal data

$C_{16}H_{12}Cl_2N_2S_2$
M_r = 367.30
Monoclinic
$P2_1/c$
a = 9.826 (2) Å
b = 17.899 (4) Å
c = 10.307 (2) Å
β = 115.56 (3)°
V = 1635.3 (6) Å^3
Z = 4
D_x = 1.492 Mg m^{-3}
D_m not determined
Mo $K\alpha$ radiation
λ = 0.71069 Å
Cell parameters from 50 reflections
θ = 7.3–13.3°
μ = 0.648 mm^{-1}
T = 291 (1) K
Plate
0.54 × 0.26 × 0.13 mm
Colourless

Data collection

Siemens *R3m/V* diffractometer
ω–2θ scans
Absorption correction: none
3630 measured reflections
2867 independent reflections
1840 reflections with $I > 2\sigma(I)$
R_{int} = 0.0339
θ_{max} = 25.05°
$h = -1 \rightarrow 11$
$k = -1 \rightarrow 21$
$l = -12 \rightarrow 11$
6 standard reflections
every 300 reflections
frequency: 300 min
intensity decay: <6%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.063
$wR(F^2)$ = 0.177
S = 0.988
2867 reflections
247 parameters
All H-atom parameters refined
$w = 1/[\sigma^2(F_o^2) + (0.1116P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ <0.001
$\Delta\rho_{max}$ = 0.458 e Å^{-3}
$\Delta\rho_{min}$ = −0.403 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

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

S1—C2	1.835 (5)	N1—N2	1.386 (5)
S1—S2	2.027 (2)	N2—C3	1.281 (5)
S2—C4	1.829 (4)	C1—C2	1.510 (6)
N1—C1	1.286 (6)	C3—C4	1.496 (6)
C2—S1—S2	103.0 (2)	N1—C1—C2	123.6 (4)
C4—S2—S1	102.5 (2)	C1—C2—S1	108.0 (3)
C1—N1—N2	120.5 (4)	N2—C3—C4	124.0 (4)
C3—N2—N1	120.8 (4)	C3—C4—S2	109.2 (3)
C2—S1—S2—C4	−59.7 (2)	S2—S1—C2—C1	91.0 (3)
C1—N1—N2—C3	83.6 (5)	N1—N2—C3—C4	−6.5 (6)
N2—N1—C1—C2	−8.3 (6)	N2—C3—C4—S2	−98.0 (5)
N1—C1—C2—S1	−96.9 (5)	S1—S2—C4—C3	89.5 (3)

The structure was solved by direct methods and successive difference Fourier syntheses. Refinement was by full-matrix least-squares methods. All H atoms were found from difference Fourier syntheses and refined with independent isotropic displacement parameters.

Data collection: *R3m/V* software. Cell refinement: *R3m/V* software. Data reduction: *R3m/V* software. Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1990). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *SHELXTL-Plus* (Sheldrick, 1991). Software used to prepare material for publication: *SHELXL*93, *PARST*95 (Nardelli, 1995).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: NA1282). Services for accessing these data are described at the back of the journal.

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Two 1,5-Disubstituted Proline Esters

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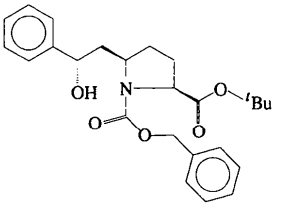
Abstract

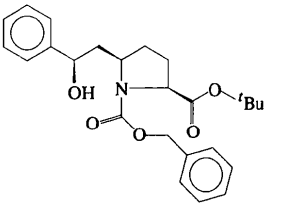
The absolute configurations of two diastereoisomers, (2*S*,5*R*)-*cis*-1-benzyloxycarbonyl-5-[(2*S*)-hydroxy-2-phenylethyl]-2-proline *tert*-butyl ester (PTBEA, $C_{25}H_{31}NO_5$) and (2*S*,5*R*)-*cis*-1-benzyloxycarbonyl-5-[(2*R*)-hydroxy-2-phenylethyl]-2-proline *tert*-butyl ester (PTBEB, $C_{25}H_{31}NO_5$), have been established by X-ray analysis. Partial disorder of the two methylene groups of the proline ring was observed in the structure of PTBEA. In both structures, the crystal packing is controlled by an O—H···O hydrogen bond between the hydroxyl and carbonyl groups of the benzyloxycarbonyl moiety.

Comment

The structural studies of PTBEA and PTBEB were undertaken in order to establish the absolute configuration adopted by the hydroxy-substituted C atom in both compounds, the absolute configurations of the two other asymmetric centres (C2 and C5) being already known. Single crystals of PTBEA and PTBEB were obtained by a new synthetic route proposed by Chiesa, Manzoni & Scolastico (1996). The procedure uses (2*S*)-pyroglutamic acid as starting material and requires, in an intermediate step, a Lewis acid-promoted allylation at position 5, yielding products with an observed *cis* selectivity, as confirmed also by the present X-ray studies of the title diastereoisomers. The target of the synthesis proposed by the cited authors was to obtain 2,5-disubstituted pyrrolidine derivatives with a hydroxyethyl or hydroxypropyl group at the 5 position, these derivatives being suitable precursors of conformationally restricted peptidomimetics (Colombo *et al.*, 1994, 1995). The latter compounds are the object of increasing interest as potential new bioactive molecules, providing valuable information on the conformation of the mimicked peptide in its complex with the receptor (Robl *et al.*, 1994; Williams *et al.*, 1993; Gleason & Johnson, 1993).



PTBEA



PTBEB

The numbering schemes adopted in the present analysis for compounds PTBEA and PTBEB are shown in Figs. 1 and 2, respectively. The structure of PTBEA was found to be affected by disorder of the C10 and C11 atoms of the proline ring. In both structures, the *cis* conformation is confirmed by the values assumed by the torsion angles C8—C9—C10—C11 [145.3 (2)° for PTBEB, and 91.8 (4) and 146.6 (2)°, respectively, for groups *A* and *B* of PTBEA] and C10—C11—C12—C13 [−85.3 (2)° for PTBEB, and −142.6 (3) and −84.9 (3)° for groups *A* and *B* of PTBEA]. The proline rings of the two molecules show a twisted conformation, with a torsion angle C9—C10—C11—C12 of −37.8 (2)° for PTBEB and of 41.5 (5) and −44.0 (3)°, respectively, for groups *A* and *B* of PTBEA. The crystal packing of both structures is characterized by O5—HO5···O1 intermolecular hydrogen bonding between the hydroxyl group and the carbonyl group of the benzyloxycarbonyl moiety [molecule at $(2-x, \frac{1}{2}-y, 1-z)$ for PTBEA and at $(1-x, \frac{1}{2}+y, -z)$ for PTBEB], with O···O separations of 2.763 (2) and 2.787 (2) Å in PTBEA and PTBEB, respectively.