Acta Cryst. (1996). C**52**, 3163–3165

5-(2-Naphthyl)thio-1-phenyltetrazole: Chemical Reactivity and Electronic Effects of Conjugation through Sulfur

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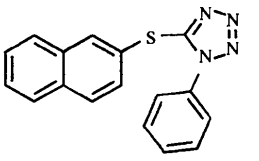
(*Received 10 June 1996; accepted 5 September 1996*)

Abstract

The title compound, $C_{17}H_{12}N_4S$, is a sulfide in which an aromatic naphthyl group is connected through the S atom to the electronegative 1-phenyltetrazole. Investigations of similar systems in which oxygen ethers of phenols or naphthols are connected to the very electronegative benzisothiazole 1,1-dioxide have found that the O atom of the central ether linkage has one long bond to the aryl group of the original phenol or naphthol and one short bond to the heterocyclic system. The C—O bond lengths show that the O atom is strongly conjugated to the heterocycle but not at all to the aryl ring. In the title compound with its thioether (sulfide) in place of an oxygen ether, the difference in the two central C—S bond lengths is very small and the S atom is only slightly conjugated with either of the two aromatic systems to which it is attached. These differences between the oxygen and sulfur ethers are reflected in their chemical reactivity.

Comment

The title compound (1) is a sulfide in which a naphthalene ring is bonded through the S atom to the strongly electronegative 1-phenyltetrazole system. The C—S bond lengths in the central thioether are very similar at 1.741 (9) and 1.780 (7) Å. This behaviour is very unlike that of oxygen ether analogues. In the latter systems (Brigas & Johnstone, 1996; Alves, Brigas & Johnstone, 1996), in which an aryl group is connected to a pseudosaccharyl system through an O atom, the C—O bonds of the central ether are very unequal, one being about 1.35 and the other 1.45 Å. In these oxygen ethers, the bond lengths indicate that the O atom is strongly conjugated to the nitrogen heterocycle but not at all to the aryl ring. In the title sulfur compound (1), the C—S bond lengths are very similar to those found (1.74 Å) in diaryl sulfides (Mitchell & Cross, 1958; Lide, 1993). Thus, although there is some electronic influence of the 1-phenyltetrazole in the sense that the C2—S1 bond in (1) is stretched slightly to 1.780 (7) Å, the effect is not as dramatic as in the case of the oxygen ethers. The C1—S1 bond is the same length as those found in simple diaryl sulfides and is not shortened as it is in the analogous oxygen ethers. By using a bond-length/bond-order relationship (Pauling, 1960; Bürgi & Dunitz, 1987), it can be shown that the C—S bonds in the title compound (1) have partial double-bond character of 12% (1.78 Å) and 29% (1.74 Å), respectively; the latter value is almost identical to those found in, say, di-*p*-tolylsulfide (Mitchell & Cross, 1958; Lide, 1993) for which the sulfide linkages have about 30% double-bond character. By comparison, in the oxygen ether analogues, the corresponding two C—O bonds have zero and 50% double-bond character. The relationship between bond order (n) and bond length (r) for sulfur compounds ($r_n = r_1 - 0.27 \times \ln n$) was derived from the following bond lengths: C—S (single bond, n = 1) = 1.81 Å (dimethyl sulfide, ethyl methyl sulfide; Lide, 1993), C—S (double bond, n = 2) = 1.61 Å (thioformaldehyde; Lide, 1993) and C—S (carbon monosulfide; triple bond, n = 3) = 1.54 Å (Bell, Ng & Suggitt, 1972).



(1)

The oxygen and sulfur analogues differ also in the central C—O—C and C—S—C bond angles. Whereas in aryl heterocyclic ethers this bond angle is close to 120° implying considerable sp^2 hybrid character at the O atom, in the corresponding sulfide (thioether) the bond angle is only 105° and is similar to those found for sulfur in simple diaryl sulfides.

The differences in behaviour of the oxygen and sulfur compounds is reflected in their reactivity. Aryl tetrazolyl or aryl pseudosaccharyl ethers can be cleaved catalytically (Brigas & Johnstone, 1990, 1994) but the reactions are highly specific, the ether O atom suffering *ipso* displacement at its aryl connection with no reaction at its connection with the heterocyclic group. In contrast, catalytic *ipso* displacement of sulfur in thioethers such as the title compound is fairly non-specific and both ends of the sulfide system are attacked simultaneously. Thus, treatment of the title thio ether (1) with trimethylphosphite in an Arbuzov reaction in the presence of nickel gives a 54% yield of one product (2-naphthylthiomethane) resulting from nucleophilic attack at the tetrazolyl-ring end of the sulfide and 10% of another product (dimethyl 2-naphthylphosphinate) resulting from nucleophilic attack at the other, naphthyl-ring end. These results will be reported fully elsewhere. The X-ray results are important in indicating the reasons for this difference in behaviour between the oxygen and sulfur ethers.

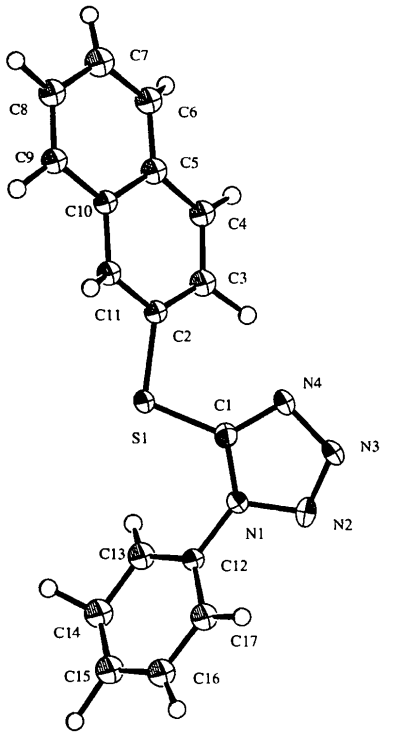


Fig. 1. Perspective drawing of the title compound with displacement ellipsoids drawn at 50% probability level.

Experimental

To a solution of naphthalene-2-thiol (2.7 g; 17 mmol) in dry *N,N*-dimethylformamide (DMF, 35 ml) under nitrogen at room temperature potassium *tert*-butoxide (2.0 g; 18 mmol) was added with stirring. After 30 min, the base had all dissolved, at which stage 5-chloro-1-phenyltetrazole (3.0 g; 17 mmol) was added and stirring was continued for a further 2 h. The reaction mixture was poured into a large excess of ice water to give a solid that was filtered off and dried in air at room temperature overnight. Recrystallization from ethanol afforded the title compound as colourless prisms (4.0 g; 79% yield; m.p. 397–400 K). Analysis found C 67.2, H 4.0, N 18.6%; $C_{17}H_{12}N_4S$ requires C 67.1, H 4.0, N 18.1%. ^{1}H NMR ($CDCl_3$): δ 8.05 (1 H, *s*, ArH), 7.72–7.59 (4 H, *m*, ArH), 7.74–7.59 (7 H, *m*, ArH). ν_{max} (Nujol): 2855, 1595, 1459, 1377, 817 and 769 cm^{-1}. MS: *m/z* 304 (M^+). A sample of 5-(2-naphthyl)thio-1-phenyltetrazole (1.0 g; 3.3 mmol) in trimethylphosphite (3 ml) was stirred for 30 min at 313 K to give a clear viscous solution, to which anhydrous nickel chloride (0.43 g; 3.3 mmol) was added. The initial blue solution was heated under reflux for 2 h to produce a yellowish green solid. At this stage, the excess of trimethylphosphite was removed under vacuum and, to the residual syrup was added dilute HCl (3 *M*; 20 ml) and diethyl ether (20 ml). After workup in the usual way, the organic residue from the diethyl ether layer was purified by chromatography on silica gel, eluting with hexane/dichloromethane, 10:90 *v/v*) to give dimethyl 2-naphthylphosphonate (80 mg; 10% yield; m.p. 325–327 K), *m/z* 236 (M^+) and 2-naphthylthiomethane (310 mg; 54% yield) as a colourless oil, *m/z* 174 (M^+).

Crystal data

$C_{17}H_{12}N_4S$
M_r = 304.369
Orthorhombic
$Pca2_1$
a = 11.911 (9) Å
b = 15.794 (8) Å
c = 7.468 (14) Å
V = 1404 (2) Å^3
Z = 4
D_x = 1.439 Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 19 reflections
θ = 3.46–6.20°
μ = 0.2205 mm^{-1}
T = 153 K
Prism
0.25 × 0.20 × 0.10 mm
Colourless

Data collection

Rigaku AFC-6*S* diffractometer
$\omega/2\theta$ scans
Absorption correction: none
1460 measured reflections
1459 independent reflections
902 observed reflections [$I > 3\sigma(I)$]
R_{int} = 0.015

θ_{max} = 24.97°
h = 0 → 14
k = 0 → 19
l = 0 → 9
3 standard reflections monitored every 150 reflections
intensity variation: ±15% (due to icing of crystal)

Refinement

Refinement on F
R = 0.0594
wR = 0.0632
S = 1.746
897 reflections
118 parameters
H atoms from $\Delta\rho$ synthesis, then riding model
$w = 4F_o^2/\sigma^2(F_o^2)$

$(\Delta/\sigma)_{max}$ = 0.06
$\Delta\rho_{max}$ = 0.38 e Å^{-3}
$\Delta\rho_{min}$ = −0.32 e Å^{-3}
Extinction correction: none
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)
Absolute configuration: not determined

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2)*

$U_{eq} = (1/3)\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	U_{eq}/U_{iso} †
S1	0.4827 (2)	0.1608 (1)	0.0720	0.0316 (1)
N1	0.3949 (5)	0.3141 (4)	0.151 (1)	0.0270 (2)
N2	0.2997 (6)	0.3499 (4)	0.221 (1)	0.0371 (2)
N3	0.2299 (6)	0.2880 (4)	0.251 (1)	0.0365 (2)
N4	0.2761 (5)	0.2113 (4)	0.205 (1)	0.0310 (2)
C1	0.3781 (7)	0.2303 (5)	0.142 (1)	0.0286 (2)
C2	0.4146 (6)	0.0610 (4)	0.049 (2)	0.020 (2)
C3	0.3088 (7)	0.0523 (5)	−0.036 (2)	0.027 (2)
C4	0.2689 (7)	−0.0274 (4)	−0.072 (1)	0.026 (2)
C5	0.3322 (7)	−0.1001 (5)	−0.035 (2)	0.026 (2)
C6	0.2983 (7)	−0.1831 (5)	−0.077 (1)	0.028 (2)
C7	0.3643 (8)	−0.2512 (5)	−0.045 (2)	0.034 (2)
C8	0.4697 (7)	−0.2407 (5)	0.033 (1)	0.028 (2)
C9	0.5081 (6)	−0.1622 (5)	0.079 (2)	0.026 (2)
C10	0.4407 (6)	−0.0898 (4)	0.047 (1)	0.022 (2)
C11	0.4778 (6)	−0.0076 (5)	0.090 (1)	0.023 (2)
C12	0.4890 (6)	0.3664 (4)	0.107 (1)	0.019 (2)
C13	0.5466 (7)	0.3514 (5)	−0.048 (1)	0.029 (2)
C14	0.6383 (8)	0.4041 (5)	−0.092 (1)	0.032 (2)
C15	0.6681 (7)	0.4678 (5)	0.023 (1)	0.032 (2)
C16	0.6100 (7)	0.4824 (5)	0.176 (1)	0.031 (2)
C17	0.5191 (7)	0.4303 (5)	0.221 (1)	0.029 (2)

† Atoms C1–C17 were refined isotropically.

Table 2. *Selected geometric parameters (Å, °)*

S1—C1	1.741 (9)	C2—C3	1.42 (1)
S1—C2	1.780 (7)	C2—C11	1.36 (1)
N1—N2	1.371 (9)	C3—C4	1.37 (1)
N1—C1	1.341 (9)	C4—C5	1.40 (1)
N2—N3	1.303 (9)	C5—C10	1.44 (1)
N3—N4	1.375 (8)	C10—C11	1.41 (1)
N4—C1	1.34 (1)		
C1—S1—C2	105.2 (4)	S1—C1—N1	122.1 (6)
N2—N1—C1	107.6 (6)	S1—C1—N4	127.9 (6)
C1—N1—C12	132.5 (7)	S1—C2—C3	122.3 (6)
N1—N2—N3	106.5 (6)	S1—C2—C11	115.7 (6)
N2—N3—N4	111.3 (6)	C3—C2—C11	121.1 (7)
N3—N4—C1	104.7 (6)		
S1—C1—N1—N2	−176.2 (7)	N1—C1—S1—C2	−171.0 (8)
S1—C1—N1—C12	2 (2)	N3—N2—N1—C12	−178.6 (8)
S1—C1—N4—N3	176.3 (8)	C1—S1—C2—C3	45 (1)
S1—C2—C3—C4	170.9 (9)	C1—S1—C2—C11	−146.0 (8)
S1—C2—C11—C10	−168.9 (8)	C7—C8—C9—C10	0 (2)

The rather low precision found for the molecular geometry parameters reflects limited crystal quality and the low fraction of data which could therefore be considered significant.

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1988). Cell refinement: *MSC/AFC Diffractometer Control Software*. Data reduction: *TEXSAN PROCESS* (Molecular Structure Corporation, 1993). Program(s) used to refine structure: *TEXSAN LS*. Software used to prepare material for publication: *TEXSAN FINISH*.

The authors thank the Eschenmoser Trust (UK) and JNICT (Portugal) for financial support (JACA) and Mr James V. Barkley for expert technical assistance.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: BM1096). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Acta Cryst. (1996). C**52**, 3165–3167

(3*S*,5*S*,1′*S*)-3-Benzyl-5-[1′-(*tert*-butoxycarbonylamino)-2′-phenylethyl]-4,5-dihydrofuran-2(3*H*)-one

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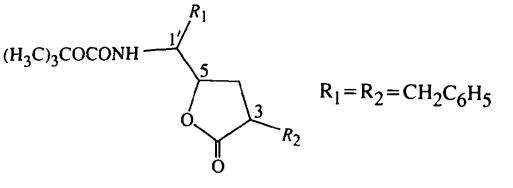
(*Received 12 February 1996; accepted 19 July 1996*)

Abstract

The crystal structure of the title lactone, $C_{24}H_{29}NO_4$, contains three chiral centres which are in the *S* configuration. The dihydrofuranone ring takes an envelope conformation.

Comment

Potent synthetic inhibitors of many aspartic proteases such as pepsin, renin, HIV-1 protease or candida protease have been described [for a review see Davies (1990)]. The design of the majority of protease inhibitors is now based on the replacement of a cleaved amide bond in a short substrate peptide by a non-hydrolysable hydroxyethylene isostere [—CH(OH)CH_2—] which resembles the tetrahedral intermediate formed during hydrolysis of a peptide (Greenlee, 1990).



(1)

Butyrolactones are crucial synthones for hydroxyethylene isostere synthesis. They contain three chiral centres at C3, C5 and C1′; the one at C1′ is derived from a natural amino acid of *S* configuration. Recently, we have prepared all four possible diastereoisomers of lactone (1) and transformed them in several series of protease inhibitors in order to study structure–activity relationships (Litera, 1995). The stereochemistry of all of the lactones was determined by ^1H and ^{13}C NMR spectroscopy after the necessary chemical transformations had been made. To confirm the structure of the lactone from which the best inhibitors were derived, we crystallized it from cyclohexane solution by slow evaporation of the solvent. The molecular structure of the resulting lactone together with the atom-