step in this direction, an analog of huperzine A has been synthesized (Kozikowski *et al.*, 1990) in which the ethylidene group is replaced by a propylidene group. The resulting reduction of AChE inhibitory activity by two orders of magnitude is understandable in terms of increased steric bulk preventing the molecule from fitting into the active site. Surprisingly, removal of the methyl group from the same olefin function of huperzine A reduces the AChE inhibitory activity to an equal extent. This result may reflect an essential contribution of hydrophobic interactions of the methyl group with a nonpolar region of the active site in the binding of huperzine A. Further structural modifications of huperzine A aimed at a complete characterization of the active site of AChE as well as at the discovery of more potent AChE inhibitors are in progress. The atomic coordinates available from the present X-ray analysis should prove useful in this endeavor.

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Structures of *N*-Substituted 1,2-Oxazines. I. A Monocyclic Derivative, 2-(*tert*-Butylthio)-3-(3,6-dihydro-2*H*-1,2-oxazin-2-yl)acrylonitrile

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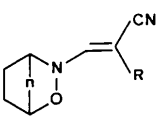
Abstract. $C_{11}H_{16}N_2OS$, $M_r = 224{\cdot}42$, monoclinic, $C2/c$, $a = 27{\cdot}791\ (3)$, $b = 9{\cdot}361\ (1)$, $c = 9{\cdot}606\ (1)$ Å, $\beta = 92{\cdot}97\ (1)°$, $V = 2495{\cdot}7\ (4)$ Å^3, $Z = 8$, $D_x = 1{\cdot}19$ g cm^{-3}, Cu $K\alpha$, $\lambda = 1{\cdot}5418$ Å, $\mu = 20{\cdot}6$ cm^{-1}, $F(000) = 960$, $T = 291$ K, $R = 0{\cdot}048$ for 1936 observed reflections. The configuration of the substituents on the double bond is *Z*. The ethylenic moiety is strongly conjugated with the N—O bond. A half-chair conformation with a large puckering around N—O [70·9 (8)°] is observed for the six-membered ring.

Introduction. A series of N-substituted bicyclic 1,2-oxazines (I) has been synthetized and their thermal isomerization in epoxy-epimines has been studied (Vaerman, 1989).



$n = 0$ to 3
R = CN or S-*t*Bu

(I)

With the aim to quantify the effects of the bridge length (n) and the substituent (R) of the olefin on the geometry, we have determined the X-ray structures of some of these 1,2-oxazines. In this first paper, we report the structure of the monocyclic derivative: 2-(*tert*-butylthio)-3-(3,6-dihydro-2*H*-1,2-oxazin-2-yl)-acrylonitrile ($n = 0$, R = S-*t*Bu).

Experimental. Crystal obtained by evaporation from a mixture 80:20 petroleum ether and ethyl acetate. D_m not measured. Parallelepiped crystal with dimensions $0{\cdot}22 \times 0{\cdot}20 \times 0{\cdot}11$ mm. Lattice parameters refined using 19 reflections in the range $5 \le 2\theta \le 50°$. Huber four-circle diffractometer, graphite-monochromatized Cu $K\alpha$ radiation. 2255 $hk \pm l$ independent reflections with $(\sin\theta)/\lambda \le 0{\cdot}60$ Å^{-1}; $0 \le h \le 33$, $0 \le k \le 11$, $-11 \le l \le 11$, 1936 with $I \ge 2{\cdot}5\sigma(I)$. Standard reflection $(\bar{1}1,\bar{1},0)$ checked every 50 reflections: no significant deviation. Structure solved by *SHELXS*86 (Sheldrick, 1985). H atoms from difference Fourier synthesis. Anisotropic least-squares refinement (*SHELX*76; Sheldrick, 1976)

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using F; H isotropic with common refined temperature factor. $w = 1/(\sigma^2 + 0{\cdot}00014F^2)$, $R = 0{\cdot}048$, $wR = 0{\cdot}049$ for 1936 observed reflections. Final maximum shift to e.s.d. = 0·04. $S = 3{\cdot}06$. Maximum and minimum heights in final difference Fourier synthesis = 0·20 and $-0{\cdot}36$ e Å^{-3}. Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV).

Discussion. The atomic parameters are given in Table 1. Fig. 1 is a stereoscopic view of the molecule (*PLUTO*: Motherwell & Clegg, 1978). Bond distances and angles are given in Table 2.*

The configuration of the double bond is *Z*, the S-*t*Bu group being on the same side as the oxazine O atom. The olefinic group and the N—O bond of the heterocycle are coplanar. The maximum deviation from the mean plane through the atoms O1, N2, C7, C8, C9, N10, S11 is only 0·025 (2) Å. As a consequence, the distance O1···S11 [3·080 (2) Å] is rather short; it is less than the sum of the van der Waals radii (O = 1·4, S = 1·85 Å) (Pauling, 1960). The angles N2—C7—C8 and C7—C8—S11 are significantly enlarged [131·6 (2) and 129·3 (2)°, respectively] in order to avoid a too close proximity of O and S atoms. The sum of the angles around N2 is 358·5 (2)° and this atom is 0·099 (2) Å from the plane through its three neighbours. This clearly indicates the sp^2 hybridization of the heterocyclic N atom.

All the above observations show that there is a large conjugation between the olefin and the N—O part of the ring. The delocalization of electrons is made obvious by some of the bond-length values. In Table 2, we compare the distances in O1—N2—C7=C8—(CN)(S*R*) with the expected values (Allen, Kennard, Watson, Brammer, Orpen & Taylor, 1987). This shows that the single bonds N2—C7, C8—C9 are significantly shorter and the multiple bonds C7=C8, C9≡N10 larger than the expected values. The N—O bond length needs some comment as it seems better to compare it with the values observed in other 1,2-oxazines. To our knowledge, only one monocyclic 1,2-oxazine with a planar N atom has been described: *p*-nitrophenyl tetrahydro-2*H*-1,2-oxazin-2-yl ketone (Johnson, Hodzi, Todd, de Meester & Chu, 1986). In this molecule, the N—O bond length of 1·417 (3) Å is similar to that observed here. In bridged heterocycles, a larger value is observed in all structures except one: 1·410 Å in *N*-formyl-3-oxa-2-azabicyclo[2.2.2]octane (Nelsen, Thompson-Colon, Kirste, Rosenhouse & Kaftory, 1987); but it is, for example, 1·431 Å in 6-hydroxymethyl-2-oxa-3-azabicyclo[2.2.2]oct-5-ene-2-yl phenyl ketone (Bodger & Patel, 1984). When the N atom is pyramidal – as it is in the majority of the reported structures – the bond length is still about

Table 1. *Atomic coordinates* ($\times 10^4$) *and equivalent isotropic temperature factors* (Å^2)

$B_{eq} = (8\pi^2/3)\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	B_{eq}
O1	1265 (1)	3331 (2)	8653 (2)	4·71 (3)
N2	1719 (1)	3560 (2)	8137 (2)	4·53 (4)
C3	2047 (1)	4298 (3)	9124 (3)	5·06 (5)
C4	2036 (1)	3574 (3)	10510 (3)	5·60 (6)
C5	1706 (1)	2605 (4)	10754 (3)	5·95 (6)
C6	1308 (1)	2261 (4)	9725 (3)	5·51 (6)
C7	1844 (1)	2885 (3)	7002 (2)	4·07 (4)
C8	1590 (1)	2002 (3)	6091 (2)	3·97 (4)
C9	1855 (1)	1494 (3)	4958 (3)	4·40 (4)
N10	2061 (1)	1086 (3)	4028 (3)	5·73 (5)
S11	998 (1)	1358 (1)	6165 (1)	4·44 (1)
C12	635 (1)	2649 (3)	5090 (3)	4·88 (5)
C13	808 (2)	2702 (5)	3596 (4)	7·81 (8)
C14	669 (1)	4120 (4)	5737 (5)	6·67 (7)
C15	121 (1)	2098 (5)	5128 (6)	8·06 (9)

Table 2. *Observed bond lengths* (Å) *and comparison with some expected values and bond angles* (°)

	This work	Allen *et al.* (1987)	
O1—N2	1·397 (2)	C_2—N—O—C (N planar)	1·397
N2—C7	1·321 (3)	C=C—N—C^*_2 (N planar)	1·355
C7=C8	1·373 (3)	C^*_2—C=CH—C*	1·326
C8—C9	1·426 (3)	C*—C≡N	1·470
C9≡N10	1·151 (3)	C*—C≡N	1·136
C8—S11	1·757 (2)	C=C—S—C*	1·751
C3—N2	1·456 (3)	C6—O1	1·437 (3)
C4—C3	1·496 (4)	C5—C4	1·320 (5)
C6—C5	1·479 (5)	C12—S11	1·853 (3)
C13—C12	1·538 (4)	C14—C12	1·511 (4)
C15—C12	1·523 (4)		
C6—O1—N2	108·5 (2)	C3—N2—O1	112·9 (2)
C7—N2—O1	120·1 (2)	C7—N2—C3	125·5 (2)
C4—C3—N2	108·9 (2)	C5—C4—C3	121·0 (3)
C6—C5—C4	122·2 (3)	C5—C6—O1	111·1 (3)
C8—C7—N2	131·6 (2)	C9—C8—C7	114·8 (2)
S11—C8—C7	129·3 (2)	S11—C8—C9	115·9 (2)
N10—C9—C8	178·8 (3)	C12—S11—C8	103·8 (1)
C13—C12—S11	110·7 (2)	C14—C12—S11	110·1 (2)
C14—C12—C13	109·7 (3)	C15—C12—S11	104·5 (2)
C15—C12—C13	111·9 (3)	C15—C12—C14	109·7 (3)

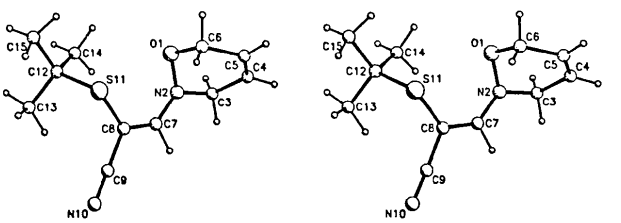

Fig. 1. Stereoscopic view of the molecule.

* Lists of structure factors, anisotropic thermal parameters, H-atom parameters and torsion angles have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 53476 (15 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

0·045 Å longer as a consequence of the rehybridization. These comparisons show that because of the electronic delocalization the N—O bond is short in the molecule discussed here. In fact, it is the shortest ever reported for 1,2-oxazines (Allen *et al.*, 1979) (Cambridge Structural Database, version 3.40).

Because of the 4,5 double bond, the six-membered heterocycle adopts a half-chair conformation. The endocyclic torsion angles −70·9 (8), 49·0 (8), −11·1 (8), −4·8 (8), −14·6 (8) and 50·1 (8)° indicate a large puckering [70·9 (8)°] at the N—O bond. The O atom is displaced by 0·64 (1) Å from the mean plane through the five other atoms. Large puckering has already been reported in chair conformations of perhydro-1,2-oxazines where the torsions around N—O are in the range 65–75° (Holzapfel, Kruger & Van Dijk, 1987).

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Structure of (±)-Aminoglutethimide

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Abstract. (±)-3-(4-Aminophenyl)-3-ethyl-2,6-piperidinedione, $C_{13}H_{16}N_2O_2$, $M_r = 232·3$, monoclinic, $P2_1/n$, $a = 16·895$ (2), $b = 8·519$ (1), $c = 8·762$ (1) Å, $\beta = 95·71$ (1)°, $V = 1254·9$ (2) Å^3, $Z = 4$, $D_x = 1·23$ g cm^{-3}, λ(Mo $K\alpha$) = 0·71069 Å, $\mu = 0·785$ cm^{-1}, $F(000) = 496$, $T = 294$ K, $R = 0·064$ for all 3676 reflections. The molecule is L shaped with the *p*-aminophenyl and the piperidinedione groups forming the vertical arm and the base, respectively. The polar imide half of the piperidinedione group is in front of the L for the active + enantiomer and at the back for the less-active − enantiomer. The structure is very similar to that of phenobarbital. Intermolecular interactions include one strong and one weak hydrogen bond and an apparent interaction between one of the amino H atoms with the π cloud of the phenyl ring.

Introduction. Aminoglutethimide (AG) is a non-steroidal aromatase inhibitor that has been used clinically for the treatment of breast cancer in post-menopausal women (Santen, Worgul, Samojlik, Boucher, Lipton & Harvey, 1982; Shaw, Nicholls & Smith, 1988). Structure–activity studies of AG and other non-steroidal aromatase inhibitors are complicated by the large variation in the structures of active compounds (Banting *et al.*, 1988). AG (Elipten CIBA) was initially introduced as an anticonvulsant but later withdrawn because of adrenal toxicity (Camacho, Brough, Cash & Wilroy, 1966). It is

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