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Structure of N-(β-Phenylpropionyl)glycine Ethyl Dithioester*

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Abstract. $C_{13}H_{17}NOS_2$, $M_r = 267.4$, monoclinic, $P2_1/c$, $a = 11.863$ (2), $b = 4.821$ (1), $c = 25.292$ (3) Å, $\beta = 90.61$ (1)°, $V = 1446.4$ Å³, $Z = 4$, $D_x = 1.228$ Mg m⁻³, $\lambda(Cu\,K\alpha_1) = 1.54056$ Å, $\mu(Mo\,K\alpha) = 0.34$ mm⁻¹, $F(000) = 568$, $T = 293$ K, final $R = 0.045_5$, $wR = 0.051$ for 2335 unique reflections. The glycinic N and thiol S atoms are in short non-bonded contact [2.901 (2) Å] as frequently observed in thioester derivatives of glycine and alanine. The $N-CH_2-C-S$(thiol) and $C-NH-CH_2-C$ torsion angles are -18.9 (3) and -75.4 (3)° respectively, and the dihedral angle between the phenyl ring and the amide group is 58.9°. A molecular-mechanics calculation indicates that this dihedral angle is 81.9° in the minimum-energy conformation.

Introduction. Joint crystallographic and spectroscopic studies on various N-acylglycine and N-acylalanine dithio- and thiolesters have elucidated some structure–spectra relationships in this series of compounds (Huber, Ozaki, Pliura, Storer & Carey, 1982; Huber, Carey, Hsi, Lee & Storer, 1984; Varughese, Storer & Carey, 1984; Angus, Carey, Lee, Storer & Varughese, 1985). These correlations are used to obtain detailed information on the acyl group structure in corresponding dithioacyl papain intermediates, using the dithioester group as a resonance Raman probe. Although the resonance Raman spectra of N-benzoylglycine ethyl dithioester and of its para-substituted analogues are reasonably well understood, some aspects of the spectra of the title compound (I) were puzzling (Lee, Storer & Carey, 1983) and prompted this X-ray study. In particular, ¹³C=S isotopic substitution of (I) gives a resonance Raman spectrum in CH_3CN/H_2O solution in which a peak that was expected (by comparison with the N-benzoyl

analogue) to occur near 1100 cm⁻¹ is apparently split into two peaks at 1079 and 1115 cm⁻¹. Very similar behavior is observed in the spectrum of the corresponding dithioacylpapain (Storer, Lee & Carey, 1983).

(I)
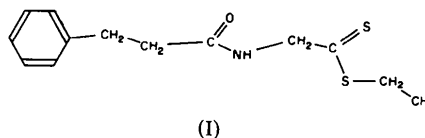
Experimental. Yellow lath-shaped crystals, grown by diffusion of hexane vapor into an ether solution of (I), were provided by Dr A. C. Storer; precession photographs indicated monoclinic symmetry, space group Pc or $P2_1/c$; specimen $0.20 \times 0.25 \times 0.40$ mm; Enraf–Nonius CAD-4F diffractometer; cell dimensions from refinement of θ angles of 25 carefully-centered reflections with $30 < \theta < 44°$ using Ni-filtered Cu $K\alpha$ radiation. Intensity measurements made with Zr-filtered Mo $K\alpha$ radiation; $\omega/2\theta$ scans with $\Delta\omega = 1.5(1.25 + 0.35\tan\theta)°$; three check reflections monitored after every 3000 s of X-ray exposure showed only random fluctuations; all 4184 independent reflections in the range $\theta \leq 30°$ were measured; index range h 0 to 16, k 0 to 6, l −35 to 35; 2335 reflections considered observed [$I \geq 1.50\sigma(I)$]. Lorentz–polarization corrections applied, but not absorption. Structure solved with *MULTAN*78 (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978). Intensity statistics indicated strongly that the structure was noncentrosymmetric, and therefore space group Pc was assumed for the structure solution step. However, the structure clearly conforms to $P2_1/c$ symmetry and has been refined in this space group. Non-H atoms refined first isotropically, subsequently anisotropically, all H atoms located on difference maps and refined isotropically, block-diagonal least squares, minimizing $\sum w(\Delta F)^2$.

Weighting scheme of the form $w^{1/2} = 25 \cdot 0/|F_o|$ if $|F_o| > 25 \cdot 0$, $w = 1$ otherwise; this scheme chosen to make $\langle w(\Delta F)^2 \rangle$ reasonably independent of $|F_o|$ and of $\sin^2\theta$. Scattering factors for S, O, N, C and H and a correction for the real part of anomalous scattering for the S curve were taken from *International Tables for X-ray Crystallography* (1974). Final $(\Delta/\sigma)_{max}$ was $0 \cdot 5_4$ (for an H parameter) and $(\Delta/\sigma)_{mean}$ was $0 \cdot 06_5$; $R(F)$ $= 0 \cdot 045_5$ and $wR(F^2) = 0 \cdot 051$ for all observed reflections. No residual density over $0 \cdot 20\,e\,Å^{-3}$ on final difference map. Crystallographic calculations, unless otherwise specified, were performed with the NRC set of crystallographic programs (Ahmed, Hall, Pippy & Huber, 1973). The *MGTLS* program (Schomaker & Trueblood, 1968) was used for the thermal vibration analysis. Molecular-mechanics calculations employed a version modified by D. C. Rohrer of the *MM2* program (Allinger & Yuh, 1981).

Table 1. *Fractional coordinates and their e.s.d.'s (all × 10⁴) and equivalent isotropic temperature factors* (Å²)

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

	x	y	z	B_{eq}
S(1)	1780 (1)	−1747 (2)	3265 (1)	5·8
S(2)	1896 (1)	430 (2)	2172 (1)	8·0
O	4586 (2)	598 (3)	3298 (1)	5·7
N	4059 (2)	−3716 (4)	3095 (1)	4·7
C(1)	−138 (3)	12 (10)	3714 (1)	8·9
C(2)	494 (2)	244 (7)	3207 (1)	6·4
C(3)	2403 (2)	−1347 (5)	2665 (1)	4·6
C(4)	3502 (2)	−2880 (6)	2611 (1)	5·3
C(5)	4609 (2)	−1883 (5)	3400 (1)	4·5
C(6)	5235 (2)	−3048 (5)	3871 (1)	5·5
C(7)	6197 (3)	−1298 (6)	4057 (1)	6·8
C(8)	6841 (2)	−2505 (6)	4518 (1)	5·3
C(9)	7661 (3)	−4444 (7)	4440 (1)	6·8
C(10)	8271 (3)	−5534 (9)	4852 (1)	8·9
C(11)	8056 (3)	−4726 (9)	5351 (1)	8·7
C(12)	7245 (3)	−2898 (10)	5448 (1)	9·1
C(13)	6627 (3)	−1750 (9)	5028 (1)	8·2

Table 2. *Bond lengths (Å) and bond angles (°) with e.s.d.'s in parentheses*

S(1)–C(2)	1·807 (3)	C(6)–C(7)	1·492 (4)
S(1)–C(3)	1·704 (2)	C(7)–C(8)	1·504 (4)
S(2)–C(3)	1·624 (3)	C(8)–C(9)	1·365 (4)
O–C(5)	1·224 (3)	C(8)–C(13)	1·367 (4)
N–C(4)	1·443 (3)	C(9)–C(10)	1·367 (5)
N–C(5)	1·338 (3)	C(10)–C(11)	1·347 (5)
C(1)–C(2)	1·496 (5)	C(11)–C(12)	1·330 (6)
C(3)–C(4)	1·507 (4)	C(12)–C(13)	1·399 (5)
C(5)–C(6)	1·505 (4)		

C(2)–S(1)–C(3)	104·0 (1)	C(5)–C(6)–C(7)	114·1 (2)
C(4)–N–C(5)	121·4 (2)	C(6)–C(7)–C(8)	114·0 (3)
S(1)–C(2)–C(1)	108·8 (2)	C(7)–C(8)–C(9)	120·7 (3)
S(1)–C(3)–S(2)	125·7 (2)	C(7)–C(8)–C(13)	122·1 (3)
S(1)–C(3)–C(4)	114·2 (2)	C(9)–C(8)–C(13)	117·2 (3)
S(2)–C(3)–C(4)	120·2 (2)	C(8)–C(9)–C(10)	121·8 (3)
N–C(4)–C(3)	116·6 (2)	C(9)–C(10)–C(11)	119·9 (4)
O–C(5)–N	121·0 (2)	C(10)–C(11)–C(12)	120·6 (4)
O–C(5)–C(6)	122·7 (2)	C(11)–C(12)–C(13)	119·7 (4)
N–C(5)–C(6)	116·3 (2)	C(12)–C(13)–C(8)	120·7 (3)

Discussion. Final atomic parameters are given in Table 1* and the molecule is shown in Fig. 1. Bond lengths and bond angles are listed in Table 2. As observed in six of the eight dithio- and thiolester compounds already reported (Huber *et al.*, 1982; Huber *et al.*, 1984; Varughese *et al.*, 1984; Angus *et al.*, 1985; Varughese, Angus, Carey, Lee & Storer, 1986), the molecule adopts a '*B*' conformation, *i.e.* with a small N—C—C—S(thiol) torsion angle (and correspondingly short N···S distance) and with the ester and amide planes nearly orthogonal. The N—C(4)—C(3)—S(1) torsion angle in this structure is −18·9 (3)°; previously observed values for the equivalent torsion angle are in the range +9·5 (3) to −23·0 (3)° for the six '*B*' conformers, and −171·1 (2) and 141 (1)° for the other two compounds. The C(3)—S(1)—C(2)—C(1) torsion angle in this structure is 179·2 (2)°. Similar *trans* conformers have been observed in three other dithioesters and distorted *gauche* conformations in the rest.

The conformational feature which most obviously distinguishes this structure from the previous dithio- and thiolesters is the dihedral angle between the phenyl and amide groups, which is 58·9° here and 5·8 to 18·5° in the other structures. Because the amide and ester groups are nearly perpendicular in all these thioesters (dihedral angles in the range 81·9 to 89·0°), the difference in the amide–phenyl conformation is reflected in the phenyl–ester dihedral angles, 26·6° here but 72·5 to 82·4° in the other molecules.

The resonance Raman spectra of dithioesters are primarily sensitive to the geometry and environment of the dithioester groups. As the thiol analogue of the present dithio compound lacks the chromophore necessary to produce a resonance Raman spectrum, it is not known whether the extra ethyl bridge common to both compounds and missing from the *N*-benzoyl analogues is an important factor with respect to the
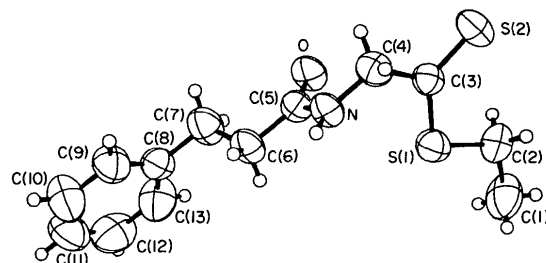
Fig. 1. *ORTEP* plot (Johnson, 1976) of the title compound with the numbering scheme. H atoms are shown as spheres of 0·1 Å radius, and the anisotropic ellipsoids enclose 50% probability.

spectral properties. It seems rather unlikely that the change in phenyl–ester dihedral angle could be responsible for the different spectral features observed for (I); the closest intramolecular approach of a phenyl ring atom to the ester group is 6·77 Å [C(8)···S(1)]. It is of interest, however, (see below) that the phenyl–amide dihedral angle may be even larger (and thus the phenyl–ester angle smaller) in the solution conformation than in the solid-state structure.

Comparison of the bond lengths and bond angles in the present structure with corresponding values in the other thioesters shows good agreement in general. The short phenyl ring bond lengths are a result of considerable thermal motion (*cf.* Fig. 1). There is an r.m.s. libration component of 11·6° nearly parallel to the C(8)—C(11) direction, and the second librational axis (6·4°) for the C(7)···C(13) fragment is nearly normal to the ring.

A molecular-mechanics calculation starting from the observed coordinates led to a similar structure in most respects, but in the minimum-energy conformation the O—C(5)—C(6)—C(7) torsion angle is −2·4°, in contrast to −25·7° in the crystal structure. As the ethyl bridge remains essentially perpendicular to the phenyl ring, the phenyl–amide dihedral angle becomes 81·9°. The apparent energy difference between the two conformations is 4·2 kJ; intermolecular hydrogen bonding stabilizes the solid-state structure, but its effect is not included in the calculations. Selected observed and calculated torsion angles are compared in Table 3.

Fig. 2 shows the packing arrangement. Molecules are linked into chains along the *b* axis by intermolecular hydrogen bonds involving the amide proton and carbonyl oxygen. The N—H bond length is 0·80 (2) Å, the N···O and H···O distances are 2·857 (3) and 2·07 (2) Å, respectively, and the N—H···O and H···O=C angles are 169 (2) and 165·5 (6)°, respectively.

Table 3. *Selected torsion angles* (°)

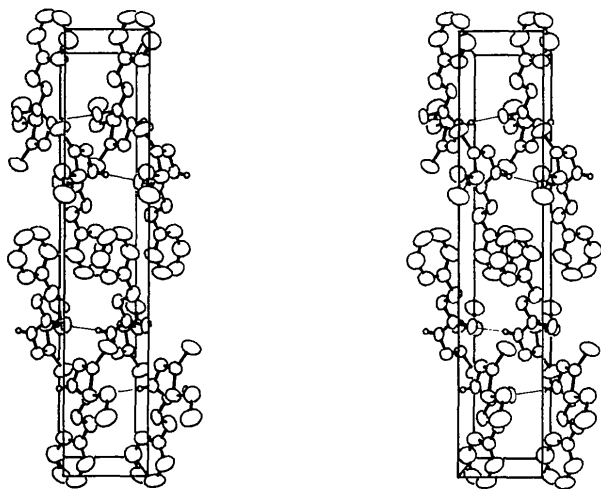|	Observed	*MM*
C(1)—C(2)—S(1)—C(3)	179·2 (2)	178·7
C(2)—S(1)—C(3)—C(4)	−179·1 (2)	−179·8
C(2)—S(1)—C(3)—S(2)	−0·5 (2)	−1·4
S(1)—C(3)—C(4)—N	−18·9 (3)	−19·0
S(2)—C(3)—C(4)—N	162·5 (2)	162·5
C(3)—C(4)—N—C(5)	−75·4 (3)	−77·2
C(4)—N—C(5)—C(6)	−175·1 (2)	179·8
C(4)—N—C(5)—O	5·6 (4)	−0·8
O—C(5)—C(6)—C(7)	−25·7 (4)	−2·4
N—C(5)—C(6)—C(7)	154·9 (2)	177·1
C(5)—C(6)—C(7)—C(8)	−178·4 (2)	−176·1
C(6)—C(7)—C(8)—C(9)	83·0 (4)	83·0
C(6)—C(7)—C(8)—C(13)	−96·2 (4)	−96·9
C(7)—C(8)—C(9)—C(10)	178·8 (3)	−180·0

Fig. 2. Stereoview (Johnson, 1976) of the packing arrangement, *b* horizontal, *c* vertical. Hydrogen atoms, except for the amide proton, have been omitted. Hydrogen bonds are indicated by single lines.

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