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Structure of a Trypsin Inhibitor, *N,N*-Dimethylcarbamoylmethyl *p*-(*p*-Guanidinobenzoyloxy)phenylacetate Methanesulfonate

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Abstract. 4-[[4-[(Aminoiminomethyl)amino]benzoyloxy]benzeneacetic acid, 2-(dimethylamino)-2-oxoethyl ester, monomethanesulfonate (*Chemical Abstracts* name), $C_{20}H_{22}N_4O_5 \cdot CH_3SO_3H$, $M_r = 494.5$, monoclinic, $P2_1/c$, $a = 10.866$ (2), $b = 18.381$ (3), $c = 12.618$ (2) Å, $\beta = 111.14$ (1)°, $V = 2350.6$ (1) Å³, $Z = 4$, $D_x = 1.39$ Mg m⁻³, $\lambda(Mo K\alpha) = 0.71069$ Å, $\mu = 1.654$ mm⁻¹, $F(000) = 1040$, $T = 293$ K, $R = 0.057$ for 4572 unique observed reflections. The molecule is bent at the methylene part of phenylacetate. The dihedral angle between the benzoyloxy and phenyl planes is 63.6 (3)°, whereas that between the guanidyl and benzoyloxy planes is 49.0 (2)°. The guanidyl group forms five intermolecular hydrogen bonds.

Introduction. The title compound (FOY-305) is a potent competitive inhibitor of trypsin. The inhibition mechanism is unique, and the *p*-guanidinobenzoyloxy group was suggested as playing an important role in the binding and releasing process (Tamura, Hirado, Okamura, Minato & Fujii, 1977). The crystal structures of several inhibitor–trypsin complexes have been reported so far; e.g. a natural inhibitor complex (Huber, Kukla, Bode, Schwager, Bartels, Deisenhofer & Steigemann, 1974). In these complexes, the geometric factor of the inhibitor was particularly important for fitting to the binding site of the protein. In this paper, the structure of the title inhibitor itself is described. The X-ray study of the trypsin complex of this inhibitor is in progress.

Experimental. The compound provided by Ono Pharmaceutical Company was recrystallized from aqueous solution; colorless; crystal dimensions 0.5 ×

0.4 × 0.3 mm; 22 reflections ($24 < 2\theta < 34^\circ$) for lattice parameters; intensity data collected on a Rigaku AFC5-RU diffractometer with graphite-monochromated Mo $K\alpha$ radiation; 7119 reflections within range $2\theta < 60^\circ$ ($0 \rightarrow h \rightarrow 15$, $0 \rightarrow k \rightarrow 25$, $-17 \rightarrow l \rightarrow 17$); three standard reflections; intensities corrected for Lorentz and polarization factors, but not for absorption; 4572 observed reflections with $F_o > 3\sigma(F_o)$ used for structure determination. Structure solved by direct methods using *MULTAN78* (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978); full-matrix least-squares refinement minimizing $\sum w(|F_o| - |F_c|)^2$ where $w = [\sigma^2(F) + (0.023F)^2]^{-1}$; anisotropic C, N and O; isotropic H; H atoms located in a difference Fourier map; scattering factors from *International Tables for X-ray Crystallography* (1974); $R = 0.057$; $wR = 0.079$; $S = 1.33$, $(\Delta/\sigma)_{\max} = 0.38$, $\Delta\rho = 0.52$ e Å⁻³. All computations performed on a FACOM M382 or M780 in the Data Processing Center of Kyoto University, using *KPPXRAY* programs (Taga, Higashi & Iizuka, 1985).

Discussion. The final atomic parameters are listed in Table 1. Bond lengths and angles which agree with the usual values are listed in Table 2.* A view of the molecule with numbering scheme is shown in Fig. 1. The guanidyl group links to the benzoyloxy group, and the planar carbamoyl group links to the phenylacetate group.

* Lists of structure factors, atomic coordinates of H atoms, and anisotropic thermal parameters of C, N and O atoms have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 51637 (24 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. Atomic parameters for non-hydrogen atoms

$$B_{\text{eq}} = \frac{1}{3} \sum_i \sum_j \beta_{ij} \mathbf{a}_i \cdot \mathbf{a}_j$$

| | x | y | z | B _{eq} (Å ²) |
|-------|-------------|------------|------------|-----------------------------------|
| N(1) | 1.2264 (2) | 0.7294 (1) | 0.6106 (2) | 4.12 (9) |
| N(2) | 1.0604 (2) | 0.7273 (1) | 0.4370 (2) | 3.92 (11) |
| C(3) | 1.1112 (2) | 0.7539 (1) | 0.5399 (2) | 3.22 (11) |
| N(4) | 1.0534 (2) | 0.8075 (1) | 0.5772 (2) | 3.71 (8) |
| C(5) | 0.9256 (2) | 0.8371 (1) | 0.5209 (2) | 3.15 (8) |
| C(6) | 0.9117 (2) | 0.9122 (1) | 0.5236 (2) | 3.88 (9) |
| C(7) | 0.7897 (2) | 0.9439 (1) | 0.4764 (2) | 3.84 (9) |
| C(8) | 0.6783 (2) | 0.9008 (1) | 0.4254 (2) | 3.01 (11) |
| C(9) | 0.6927 (2) | 0.8255 (1) | 0.4229 (2) | 3.08 (11) |
| C(10) | 0.8157 (2) | 0.7938 (1) | 0.4710 (2) | 3.20 (9) |
| C(11) | 0.5480 (2) | 0.9371 (1) | 0.3783 (2) | 3.21 (11) |
| O(12) | 0.5289 (2) | 1.0009 (1) | 0.3815 (2) | 4.39 (11) |
| O(13) | 0.4500 (2) | 0.8882 (1) | 0.3312 (2) | 4.67 (11) |
| C(14) | 0.3186 (2) | 0.9127 (1) | 0.2911 (2) | 3.70 (9) |
| C(15) | 0.2385 (3) | 0.8876 (2) | 0.3454 (2) | 4.61 (11) |
| C(16) | 0.1068 (3) | 0.9077 (2) | 0.3049 (3) | 4.63 (11) |
| C(17) | 0.0574 (2) | 0.9532 (1) | 0.2117 (2) | 3.89 (9) |
| C(18) | 0.1395 (2) | 0.9765 (2) | 0.1583 (3) | 4.50 (9) |
| C(19) | 0.2712 (2) | 0.9562 (2) | 0.1971 (2) | 4.40 (9) |
| C(20) | -0.0863 (2) | 0.9770 (2) | 0.1708 (3) | 5.01 (11) |
| C(21) | -0.1779 (2) | 0.9159 (1) | 0.1120 (2) | 3.77 (9) |
| O(22) | -0.1835 (2) | 0.8874 (1) | 0.0259 (2) | 5.50 (11) |
| O(23) | -0.2563 (2) | 0.8981 (1) | 0.1691 (2) | 4.36 (8) |
| C(24) | -0.3363 (2) | 0.8347 (2) | 0.1322 (3) | 4.16 (9) |
| C(25) | -0.2580 (2) | 0.7680 (1) | 0.1877 (2) | 3.45 (8) |
| O(26) | -0.1377 (2) | 0.7724 (1) | 0.2352 (1) | 4.34 (8) |
| N(27) | -0.3258 (2) | 0.7065 (1) | 0.1811 (2) | 3.85 (8) |
| C(28) | -0.4680 (3) | 0.7007 (2) | 0.1255 (4) | 5.16 (12) |
| C(29) | -0.2564 (4) | 0.6408 (2) | 0.2333 (3) | 5.23 (13) |
| S(30) | 1.3330 (1) | 0.8558 (1) | 0.8688 (1) | 3.56 (2) |
| C(31) | 1.4207 (4) | 0.9293 (2) | 0.8447 (4) | 5.65 (15) |
| O(32) | 1.1966 (2) | 0.8627 (1) | 0.7937 (2) | 5.99 (9) |
| O(33) | 1.3429 (2) | 0.8627 (1) | 0.9853 (2) | 5.74 (11) |
| O(34) | 1.3936 (2) | 0.7910 (1) | 0.8463 (2) | 5.35 (9) |

Table 2. Bond lengths (Å) and valence angles (°)

| | | | |
|-------------|-----------|-------------|-----------|
| N(1)–C(3) | 1.327 (3) | N(2)–C(3) | 1.309 (3) |
| C(3)–N(4) | 1.342 (3) | N(4)–C(5) | 1.420 (3) |
| C(5)–C(6) | 1.390 (3) | C(5)–C(10) | 1.383 (3) |
| C(6)–C(7) | 1.372 (3) | C(7)–C(8) | 1.395 (3) |
| C(8)–C(9) | 1.395 (3) | C(8)–C(11) | 1.482 (3) |
| C(9)–C(10) | 1.382 (3) | C(11)–O(12) | 1.194 (3) |
| C(11)–O(13) | 1.356 (3) | O(13)–C(14) | 1.406 (3) |
| C(14)–C(15) | 1.367 (4) | C(14)–C(19) | 1.368 (4) |
| C(15)–C(16) | 1.385 (4) | C(16)–C(17) | 1.384 (4) |
| C(17)–C(18) | 1.366 (4) | C(17)–C(20) | 1.521 (3) |
| C(18)–C(19) | 1.386 (3) | C(20)–C(21) | 1.507 (4) |
| C(21)–O(22) | 1.188 (4) | C(21)–O(23) | 1.340 (4) |
| O(23)–C(24) | 1.428 (4) | C(24)–C(25) | 1.512 (4) |
| C(25)–O(26) | 1.229 (3) | C(25)–N(27) | 1.335 (3) |
| N(27)–C(28) | 1.452 (4) | N(27)–C(29) | 1.450 (4) |
| S(30)–C(31) | 1.742 (4) | S(30)–O(32) | 1.448 (2) |
| S(30)–O(33) | 1.440 (3) | S(30)–O(34) | 1.438 (2) |

| | | | |
|-------------------|-----------|-------------------|-----------|
| N(1)–C(3)–N(2) | 119.9 (2) | N(1)–C(3)–N(4) | 117.4 (2) |
| N(2)–C(3)–N(4) | 122.6 (2) | C(3)–N(4)–C(5) | 127.1 (2) |
| N(4)–C(5)–C(6) | 117.6 (2) | N(4)–C(5)–C(10) | 122.3 (2) |
| C(6)–C(5)–C(10) | 119.9 (2) | C(5)–C(6)–C(7) | 120.5 (2) |
| C(6)–C(7)–C(8) | 120.1 (2) | C(7)–C(8)–C(9) | 119.2 (2) |
| C(7)–C(8)–C(11) | 118.3 (2) | C(9)–C(8)–C(11) | 122.5 (2) |
| C(8)–C(9)–C(10) | 120.5 (2) | C(5)–C(10)–C(9) | 119.8 (2) |
| C(8)–C(11)–O(12) | 125.5 (2) | C(8)–C(11)–O(13) | 111.3 (2) |
| O(12)–C(11)–O(13) | 123.2 (2) | C(11)–O(13)–C(14) | 118.7 (2) |
| O(13)–C(14)–C(15) | 117.3 (2) | O(13)–C(14)–C(19) | 121.0 (2) |
| C(15)–C(14)–C(19) | 121.5 (2) | C(14)–C(15)–C(16) | 119.0 (3) |
| C(15)–C(16)–C(17) | 120.5 (3) | C(16)–C(17)–C(18) | 119.1 (2) |
| C(16)–C(17)–C(20) | 119.9 (3) | C(18)–C(17)–C(20) | 121.0 (2) |
| C(17)–C(18)–C(19) | 121.1 (3) | C(14)–C(19)–C(18) | 118.8 (3) |
| C(17)–C(20)–C(21) | 111.6 (2) | C(20)–C(21)–O(22) | 125.9 (3) |
| C(20)–C(21)–O(23) | 110.6 (2) | O(22)–C(21)–O(23) | 123.5 (2) |
| C(21)–O(23)–C(24) | 117.0 (2) | O(23)–C(24)–C(25) | 109.6 (2) |
| C(24)–C(25)–O(26) | 119.6 (2) | C(24)–C(25)–N(27) | 116.9 (2) |
| O(26)–C(25)–N(27) | 123.5 (2) | C(25)–N(27)–C(28) | 124.0 (2) |
| C(25)–N(27)–C(29) | 119.5 (2) | C(28)–N(27)–C(29) | 116.5 (3) |
| C(31)–S(30)–O(32) | 108.2 (1) | C(31)–S(30)–O(33) | 105.4 (2) |
| C(31)–S(30)–O(34) | 106.8 (2) | O(32)–S(30)–O(33) | 110.0 (2) |
| O(32)–S(30)–O(34) | 112.1 (1) | O(33)–S(30)–O(34) | 113.8 (1) |

The phenyl ring [C(5), C(6), C(7), C(8), C(9) and C(10)] and the ester group [C(11), O(12), O(13) and C(14)] are coplanar within 0.09 Å. The torsion angles C(7)–C(8)–C(11)–O(13) and C(8)–C(11)–O(13)–C(14) are 179.6 (2) and 174.6 (2)°, respectively. The benzoyloxy group and the phenyl ring [C(14), C(15), C(16), C(17), C(18) and C(19)] are not coplanar. The dihedral angle between these planes is 63.0 (3)°. The torsion angle C(11)–O(13)–C(14)–C(19) is 69.4 (3)°. The conformation of this phenylbenzoyloxy group seems to be energetically flexible (Birner, Kugler, Simon & Naray-Szabo, 1982), but similar conformations have been found in many other compounds, e.g. phenyl benzoate (Adams & Morsi, 1976), 4'-nitrophenyl 4-octyloxybenzoate (Kaiser, Richter, Lemke & Golič, 1980), 2,9-dimethyl-3'-hydroxy-5-phenyl-6,7-benzomorphan (Clarke, Jaggi & Lovell, 1978). In these compounds, the torsion angles corresponding to C(11)–O(13)–C(14)–C(19) are in the range from 60 to 68°. Thus the observed twist of the phenylbenzoyloxy group may be one of fairly stable forms. The planar guanidyl group tilts to the connected benzoyloxy group with a dihedral angle of 49.0 (2)°. The torsion angle

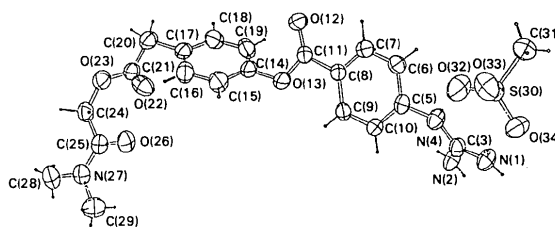


Fig. 1. A perspective view of the molecule with the numbering scheme.

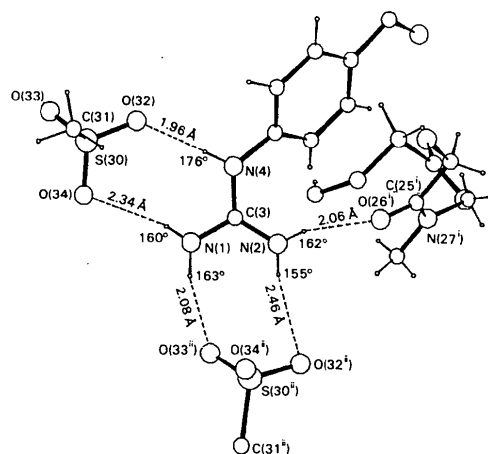


Fig. 2. The hydrogen bonds around the guanidyl group. The dotted lines show hydrogen bonds. Symmetry operations are: (i) $1+x, y, z$; (ii) $x, \frac{1}{2}-y, -\frac{1}{2}+z$. The estimated standard deviations of the H...O distances are less than 0.04 Å, and those of the N–H...O angles are less than 3°.

C(3)—N(4)—C(5)—C(10) is $46.0(4)^\circ$. The corresponding torsion angle in 5-(1,2-diphenylguanidino)-3*H*-1,2,4-dithiazole-3-thione (Butler, Glidewell & Liles, 1978) is 46.7° , but those in diphenylguanidine (Zakharov, Andrianov & Struchkov, 1980) vary from 22 to 179° . The ester group [C(20), C(21), O(22), O(23) and C(24)] is planar within 0.07 \AA , and the carbamoyl group [C(24), C(25), O(26), N(27), C(28) and C(29)] is also planar within 0.005 \AA . The torsion angles about the covalent bonds linking these planar groups are $-73.4(4)^\circ$ for C(16)—C(17)—C(20)—C(21), $-64.5(3)^\circ$ for C(17)—C(20)—C(21)—O(22), $85.3(3)^\circ$ for C(21)—O(23)—C(24)—C(25) and $166.4(4)^\circ$ for O(23)—C(24)—C(25)—N(27).

The intermolecular interactions around the guanidyl group are illustrated in Fig. 2. The guanidyl group forms five intermolecular hydrogen bonds; the N...O distances are $2.900(4) \text{ \AA}$ for N(1)...O(33) ($x, \frac{3}{2}-y, -\frac{1}{2}+z$), $3.807(3) \text{ \AA}$ for N(1)...O(34), $2.802(2) \text{ \AA}$ for N(2)...O(26) ($1+x, y, z$), $3.182(4) \text{ \AA}$ for N(2)...O(32) ($x, \frac{3}{2}-y, -\frac{1}{2}+z$), and $2.801(3) \text{ \AA}$ for N(4)...O(32). The average H...O distance and N—H...O angle are $2.18(4) \text{ \AA}$ and $163(2)^\circ$, respectively. The topological pattern of these hydrogen bonds is the same as those found in guanidyl carboxylate and guanidyl phosphate derivatives (Salunke & Vijayan, 1981). The hydrogen-bond system is stabilized by coupling of the planar guanidyl group with the two methanesulfonate anions.

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Structure of a Cyclopropyldiaminosulfonium Salt

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Abstract. [N-(*p*-Chlorophenyl)-N-methyl](morpholino)[2-(*p*-nitrophenyl)cyclopropylaminooxosulfonium tetrafluoroborate, $[\text{C}_{20}\text{H}_{23}\text{ClN}_3\text{O}_4\text{S}][\text{BF}_4]$, $M_r = 523.5$, orthorhombic, $P2_12_12_1$, $a = 17.693(3)$, $b = 9.141(1)$, $c = 14.768(3) \text{ \AA}$, $V = 2388(1) \text{ \AA}^3$, $Z = 4$, $D_x = 1.456$, D_m (floatation in aqueous AgNO_3) = $1.446(3) \text{ Mg m}^{-3}$, $\lambda(\text{Mo K}\alpha) = 0.7107 \text{ \AA}$, $\mu = 0.303 \text{ mm}^{-1}$, $F(000) = 1080$, $T = 296 \text{ K}$, $R = 0.061$, $wR = 0.072$, 2393 observations. This compound is a racemate in solution but the single crystal is optically active.

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Introduction. It is well known that oxosulfonium ylides react with carbonyl compounds to give corresponding epoxides (Corey & Chaykovsky, 1965; Trost & Melvin, 1975). However, the reactivity of heteroatom-substituted oxosulfonium ylides is quite different from those of normal oxosulfonium ylides (Chalkley, Snodin, Stevens & Whiting, 1978; Shimagaki, Tsuchiya, Ban & Oishi, 1978). In previous papers, we reported that aminoaryloxosulfonium ylides react with carbonyl compounds to give β -aryloxyalkylsulfonamides and vinylsulfonamides *via* four-membered