expected to pass *via* a ring *B* boat conformation (Lamothe, Ndibwami & Deslongchamps, 1988*b*), an energetically preferred half-chair conformation is adopted by ring *B*. While the C(2) and C(7) methyl groups of ring *C* remain *gauche* to one another regardless of ring *B* conformation, a sterically more favourable interaction between the appropriate ring *A* and ring *C* protons is established when ring *B* adopts a half-chair conformation. As a result, the chair conformation of ring *C* carries the C(2) methyl group in an axial position, while the C(7) methyl group becomes equatorial.

The bond between C(7) and C(8) can be considered as an axial substituent on the chair conformation of ring *C*. Consequently, it would appear from Fig. 2 that the axial ester group on ring *C*, *i.e.* the bond between C(5) and C(19), is extended slightly outwards to minimize as much as possible the pseudo-1,3-diaxial interaction. No abnormally short intermolecular contacts were noted.

References

CIMINO, G., GAVAGNIN, M., SODANO, G., PULITI, R., MATTIA, C. A. & MAZZARELLA, L. (1988). *Tetrahedron*, **44**(8), 2301–2310.

JOHNSON, C. K. (1976). *ORTEP*II. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.

LAMOTHE, S., NDIBWAMI, A. & DESLONGCHAMPS, P. (1988*a*). *Tetrahedron Lett.* **29**, 1641–1644.

LAMOTHE, S., NDIBWAMI, A. & DESLONGCHAMPS, P. (1988*b*). *Tetrahedron Lett.* **29**, 1639–1640.

MARINIER, A. & DESLONGCHAMPS, P. (1988). *Tetrahedron Lett.* **29**, 6215–6219.

MICHEL, A. G., BOULAY, G. & MARINIER, A. (1989). *Acta Cryst.* C**45**, 325–327.

MICHEL, A. G., MICHEL-DEWEZ, N. & ROUGHTON, A. L. (1989). *Acta Cryst.* C**45**, 327–329.

MICHEL, A. G., PROULX, M. & MICHEL-DEWEZ, N. (1988). *Acta Cryst.* C**44**, 1646–1648.

OKAYA, Y. & FRENZ, B. A. (1984). *SDP-Plus Structure Determination Package*. College Station, Texas, USA.

SHELDRICK, G. M. (1986). *SHELXS*86. Program for crystal structure determination. Univ. of Göttingen, Federal Republic of Germany.

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Structure of Metformin Hydrochloride*†

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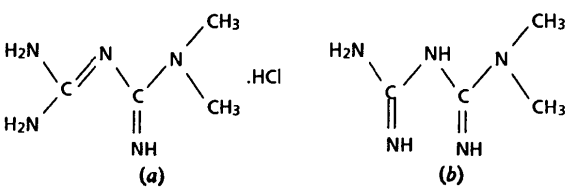
Abstract. *N,N*-Dimethylbiguanide hydrochloride, $C_4H_{12}N_5^+.Cl^-$, $M_r = 165{\cdot}6$, monoclinic, $P2_1/a$, $a = 7{\cdot}991\ (3)$, $b = 13{\cdot}950\ (5)$, $c = 8{\cdot}020\ (2)$ Å, $\beta = 114{\cdot}98\ (3)°$, $V = 810{\cdot}4\ (5)$ Å^3, $Z = 4$, $D_m = 1{\cdot}35\ (1)$, $D_x = 1{\cdot}357$ Mg m^{-3}, Mo $K\alpha$, $\lambda = 0{\cdot}7107$ Å, $\mu = 0{\cdot}41$ mm^{-1}, $T = 295$ K, $F(000) = 352{\cdot}0$, $R = 0{\cdot}038$, $wR = 0{\cdot}032$ for 980 observed reflections with $I > 3\sigma(I)$. The protonation occurs at one of the imino groups and the molecules are stabilized by means of N–H···Cl and N–H···N types of hydrogen bond.

Introduction. The title compound, a dimethylbiguanide, is an oral hypoglycaemic drug and is found to have fewer side effects when compared to the other biguanides, *e.g.* phenformin (Herrnstadt, Mootz, Wunderlich & Mohrle, 1979). The sample compound was obtained from Franco Indian Pharmaceuticals Pvt. Ltd., Bombay, India. The structural analysis was undertaken to establish the structure–activity relationship of the biguanides. Of the two tautomeric forms shown below (Ray, 1961), the compound takes the form (*a*).



Experimental. White needle of dimensions 0·55 × 0·50 × 0·18 mm from methanol. D_m by flotation. Three-dimensional intensity data on an Enraf–Nonius CAD-4 diffractometer at the Indian Institute of Technology, Madras. $\omega/2\theta$ scan technique. 25 accurately centred reflections with $16 \le 2\theta \le 38°$ for cell refinement. 2101 unique reflections in the range $4 < 2\theta < 50°$ with $0 < h \le 10$, $0 \le k \le 18$, $-10 \le l < 10$; 980 reflections with $I \ge 3\sigma(I)$. Two standard reflections ($3\bar{4}0$, 091) monitored for every 100 reflections. Maximum variation in intensity 6·4%. Intensity data corrected for Lorentz and polarization effects but not for absorption. Structure solution by Patterson and

* DCB contribution No. 726.

† Alternative name: *N,N*-dimethylimidodicarbonimidic diamide hydrochloride.

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heavy-atom techniques. All non-H atoms from heavy-atom-phased Fourier map. H atoms from difference map. Full-matrix refinement, with anisotropic temperature factors for non-H atoms and isotropic for H atoms, using *SHELX*76 (Sheldrick, 1976). Final $R = 0{\cdot}038$ and $wR = 0{\cdot}032$, weighting based on counting statistics $w = k/(\sigma^2 F_o + gF_o^2)$ with $k = 1{\cdot}0$ and $g = 0{\cdot}01603$. $\Delta\rho$ excursions $< \pm 0{\cdot}28$ e Å^{-3} in the final difference map. $(\Delta/\sigma)_{max} = 0{\cdot}108$, $(\Delta/\sigma)_{av} = 0{\cdot}096$. All atomic scattering factors for non-H atoms from *International Tables for X-ray Crystallography* (1974), and for H atoms from Stewart, Davidson & Simpson (1965).

Discussion. Atomic positions and equivalent isotropic temperature factors of all the non-H atoms are listed in Table 1.* The bond distances and angles are given in Table 2. A thermal ellipsoid plot (Johnson, 1976) at 50% probability level is shown in Fig. 1.

As in other biguanide structures, the C—N bonds [average C—N = 1·336 (4) Å] in this structure are intermediate between single and double bonds and the distances range from 1·330 (4) to 1·348 (3) Å. The N—C—N angles vary from 116·7 (3) to 124·0 (3)°, similar to those observed in other related structures. The protonation occurs at the imino group attached to C5 and this is substantiated by the H atom which forms intermolecular hydrogen bonds, located from the ΔF map, whereas in phenformin hydrochloride (Herrnstadt *et al.*, 1979) and other biguanide salts the protonation occurs at the terminal imino group.

The two guanide groups are not planar with $\chi^2 = 32{\cdot}4$ and 178·8, and the angle between the two guanide planes is 67·9 (1)° which is comparable with other dihedral-angle values reported in related structures.

There is no intramolecular N—H···N type of hydrogen bond which has been reported to be responsible for the hypoglycaemic activity of the biguanide compounds (Shapiro, Parrino, Rogow & Freedman, 1959). The molecules in the unit cell are stabilized by N—H···N and N—H···Cl types of hydrogen bond. Chlorine is involved in five hydrogen bonds.

The packing of the molecules in the unit cell down the *c* axis is shown in Fig. 2. The Cl atoms are sandwiched between layers of molecules along the *b* axis. There is a network of hydrogen bonds of N—H···Cl type around the centres of inversion as seen in the packing diagram (Fig. 2).

* Lists of structure factors, anisotropic thermal parameters of non-H atoms, H-atom parameters, bond lengths and angles involving H atoms, some relevant torsion angles, least-squares-planes calculations and hydrogen-bond geometry have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 51659 (13 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Positional parameters and equivalent isotropic thermal parameters of non-*H *atoms, with e.s.d.'s in parentheses*

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

	x	y	z	U_{eq}(Å^2)
Cl	0·2801 (1)	0·5158 (1)	1·1556 (1)	0·0322 (2)
N1	0·0309 (4)	0·3532 (2)	0·7649 (4)	0·0308 (9)
C2	0·1830 (4)	0·3386 (2)	0·7394 (4)	0·0228 (8)
N3	0·3323 (4)	0·3907 (2)	0·8387 (4)	0·0352 (10)
N4	0·1976 (3)	0·2725 (2)	0·6265 (3)	0·0263 (8)
C5	0·0498 (4)	0·2373 (2)	0·4825 (3)	0·0238 (8)
N6	0·0374 (4)	0·1424 (2)	0·4659 (4)	0·0344 (10)
N7	−0·0690 (3)	0·2930 (2)	0·3503 (3)	0·0276 (9)
C8	−0·2257 (5)	0·2542 (3)	0·1915 (4)	0·0388 (13)
C9	−0·0404 (5)	0·3962 (2)	0·3450 (5)	0·0413 (15)

Table 2. *Bond lengths* (Å) *and bond angles* (°) *involving non-*H *atoms, with e.s.d.'s in parentheses*

N1—C2	1·331 (5)	C5—N6	1·330 (4)
C2—N3	1·335 (4)	C5—N7	1·334 (3)
C2—N4	1·332 (4)	N7—C8	1·461 (4)
N4—C5	1·348 (3)	N7—C9	1·461 (4)
N1—C2—N3	118·0 (3)	N4—C5—N7	122·7 (3)
N1—C2—N4	124·0 (3)	N6—C5—N7	120·2 (3)
N3—C2—N4	118·0 (3)	C5—N7—C8	122·5 (3)
C2—N4—C5	122·5 (3)	C5—N7—C9	122·0 (3)
N4—C5—N6	116·7 (3)	C8—N7—C9	115·3 (3)

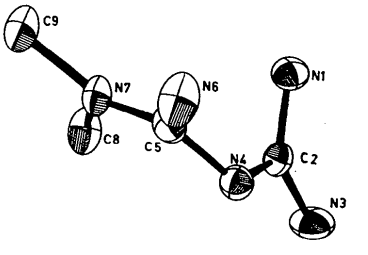

Fig. 1. *ORTEP* plot of the molecule at 50% probability level.

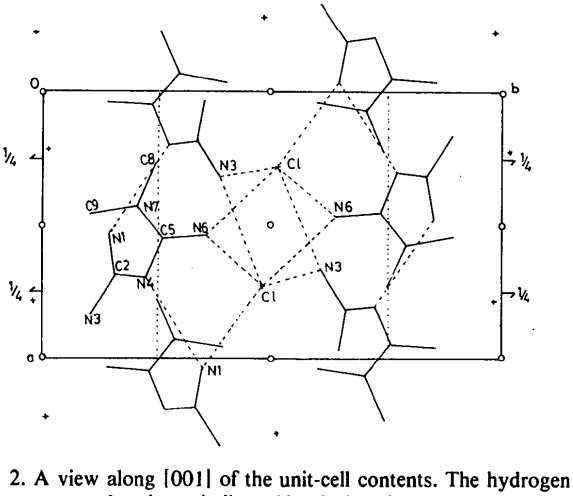

Fig. 2. A view along [001] of the unit-cell contents. The hydrogen bonds are indicated by dashed lines.

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References

HERRNSTADT, C., MOOTZ, D., WUNDERLICH, H. & MOHRLE, H. (1979). *J. Chem. Soc. Perkin Trans.* 2, pp. 735–740.

International Tables for X-ray Crystallography (1974). Vol. IV. Birmingham: Kynoch Press. (Present distributor Kluwer Academic Publishers, Dordrecht.)

JOHNSON, C. K. (1976). *ORTEP*II. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.

RAY, P. (1961). *Chem. Rev.* **61**, 313–359.

SHAPIRO, S. L., PARRINO, V. A., ROGOW, E. & FREEDMAN, L. (1959). *J. Am. Chem. Soc.* **81**, 3728–3736.

SHELDRICK, G. M. (1976). *SHELX*76. Program for crystal structure determination. Univ. of Cambridge, England.

STEWART, R. F., DAVIDSON, E. R. & SIMPSON, W. T. (1965). *J. Chem. Phys.* **42**, 3175–3187.

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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]benzoyl]-oxy]benzeneacetic acid, 2-(dimethylamino)-2-oxoethyl ester, monomethanesulfonate (*Chemical Abstracts* name), $C_{20}H_{22}N_4O_5.CH_3SO_3H$, $M_r = 494{\cdot}5$, monoclinic, $P2_1/c$, $a = 10{\cdot}866\ (2)$, $b = 18{\cdot}381\ (3)$, $c = 12{\cdot}618\ (2)$ Å, $\beta = 111{\cdot}14\ (1)°$, $V = 2350{\cdot}6\ (1)$ Å^3, $Z = 4$, $D_x = 1{\cdot}39$ Mg m^{-3}, λ(Mo $K\alpha$) = 0·71069 Å, $\mu = 1{\cdot}654$ mm^{-1}, $F(000) = 1040$, $T = 293$ K, $R = 0{\cdot}057$ for 4572 unique observed reflections. The molecule is bent at the methlyene 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 ($24 < 2\theta < 34°$) for lattice parameters; intensity data collected on a Rigaku AFC5-RU diffractometer with graphite-monochromated Mo $K\alpha$ radiation; 7119 reflections within range $2\theta < 60°$ ($0 \rightarrow h \rightarrow 15$, $0 \rightarrow k \rightarrow 25$, $-17 \rightarrow l \rightarrow 17$); 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 *MULTAN*78 (Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978); full-matrix least-squares refinement minimizing $\sum w(|F_o| - |F_c|)^2$ where $w = [\sigma^2(F) + (0{\cdot}023F)^2]^{-1}$; 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); $R = 0{\cdot}057$; $wR = 0{\cdot}079$; $S = 1{\cdot}33$, $(\Delta/\sigma)_{max} = 0{\cdot}38$, $\Delta\rho = 0{\cdot}52$ 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.

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