Molecular Structure Corporation (1992). *TEXSAN. Single Crystal Analysis Software*. MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.
Molecular Structure Corporation (1993). *Rigaku AFC-7R Software*. MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.
Norrestam, R., Mertz, S. & Crossland, I. (1983). *Acta Cryst.* C**39**, 1554–1556.
North, A. C. T., Phillips, D. C. & Mathews, F. S. (1968). *Acta Cryst.* A**24**, 351–359.
Pearce, L. J. & Watkin, D. J. (1993). *CAMERON*. Chemical Crystallography Laboratory, University of Oxford, England.
Perona, J. J., Tsu, C. A., McGrath, M. E., Craik, C. S. & Fletterick, R. J. (1993). *J. Mol. Biol.* **230**, 934–949.
Robert, M. & Gagnon, C. (1994). *Int. J. Androl.* **17**, 232–240.
Sprang, S., Standing, T., Fletterick, R. J., Stroud, R. M., Finer-Moore, J., Xuong, N.-H., Hamlin, R., Rutter, W. J. & Craik, C. S. (1987). *Science*, **237**, 905–909.
Watkin, D. J., Carruthers, J. R. & Betteridge, P. W. (1985). *CRYSTALS User Guide*. Chemical Crystallography Laboratory, University of Oxford, England.

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Diclofenac Salts. IV. Tris(2-hydroxyethyl)-ammonium 2-(2,6-Dichlorophenylamino)-phenylacetate

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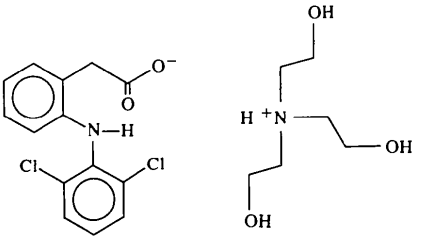
Abstract

The structure of the salt of 2-(2,6-dichlorophenylamino)-phenylacetic acid (HD) with tris(2-hydroxyethyl)amine (TEA), $C_6H_{16}NO_3^+.C_{14}H_{10}Cl_2NO_2^-$, consists of hydrogen-bonded $HTEA^+$ cations and D^- anions, as found in similar acid–base adducts of HTEA. There are no intermolecular hydrogen bonds between the ammonium H atom and the phenylacetate group; this may be attributed to the presence of a weak trifurcated intramolecular N—H···$(O)_3$ hydrogen bond within the cation. Inter-ion hydrogen bonds are established through the OH groups of the cations leading to a two-dimensional network.

Comment

The crystal structure determination of the title compound was carried out as part of a study on acid–base adducts derived from diclofenac (HD), a potent non-steroidal drug widely used in rheumatology as its sodium salt. The aim of this structural study was to look for a relationship between the conformational features of these salts and their solubility. The solid-state structure of HTEA.D contains a sequence of $HTEA^+$ cations and D^- anions linked by hydrogen bonds (Fig. 1). The presence of ionic moieties agrees with the model of Huyskens & Zeegers-Huyskens (1964) which predicts that a difference of about four orders of magnitude between the acid dissociation constants of the base (TEA, pK_a = 7.8; van Mier, Kanters & Poonia, 1988) and the acid (HD, pK_a = 3.80; Fini, Zecchi & Tartarini, 1985) leads to an almost complete shift of the proton-transfer equilibrium of the O—H···N ↔ O^-···H—N^+ system.



HTEA.D

The interionic linkage can be described as follows: the carboxyl O2 and O1 atoms of D accept two hydrogen bonds from the hydroxyl O3 and O4 atoms of HTEA [O3···O2 2.633 (3) and O4···O1($\frac{3}{2}-x$, $\frac{1}{2}+y$, $-z$) 2.613 (3) Å], while the O5 atom of one HTEA molecule is bonded to the O4 atom of another [O5···O4($\frac{1}{2}+x$, $\frac{3}{2}-y$, z) 2.744 (3) Å]. The former two cation–anion hydrogen bonds generate an infinite two-dimensional network along the [010] and [100] base vectors, respectively. We note that this network of hydrogen bonds can persist in solvents of low dielectric

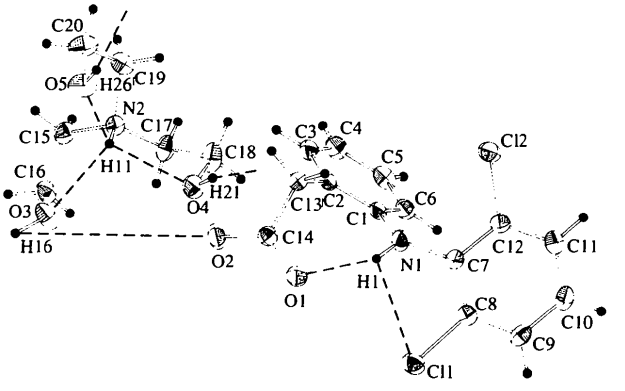


Fig. 1. The molecular conformation of the 1:1 adduct HTEA.D showing the atomic labelling and hydrogen bonds (50% probability displacement ellipsoids and H atoms as spheres of arbitrary size). For clarity, only the main conformer of HTEA is given.

constant reducing the number of active sites available for solvent attack and lowering the solubility of the salt in a hydrophobic environment.

Although HTEA.D is a salt-like adduct, apparently no direct electrostatic interaction between the positively charged ammonium ions and negatively charged acetate groups is observed. An intermolecular hydrogen bond of the N^+—H···O^- type has invariably been observed in the recently reported structures of diclofenac salts (Castellari & Sabatino, 1994, 1996; Castellari & Ottani, 1995). HTEA moieties, however, adopt an *endo* conformation, as in the structures of other acid–base complexes containing the tris(2-hydroxyethyl)ammonium cation (Starova, Frank-Kamenetskaya, Fundamenskii, Semenova & Voronkov, 1981; Brodalla & Lipka, 1984; van Mier, Kanters & Poonia, 1988; Mootz, Brodalla & Wiebcke, 1990; Brancuti, 1993). The three 2-hydroxyethyl arms surround the ammonium group, shielding it from any intermolecular interaction (Fig. 2). A trifurcated intramolecular hydrogen bond is thus formed between atom N2 and the O3, O4 and O5 atoms of the hydroxy groups, with a *gauche* conformation around the C—C bonds. This conformational arrangement follows the '*gauche* rule' (Wolfe, 1972; Exner & Engberts, 1979) which states that in crystal engineering of molecules with adjacent polar bonds and lone pairs, the less symmetrical conformation is preferred. The encapsulation of the proton on the central N2 atom by the polar hydroxyl groups can affect the interionic associations influencing to some degree the solution properties of HTEA.D. As pointed out by Fini, Fazio & Rapaport (1993), the solubility of HTEA.D in water is greater than in octanol, but the hydrophilic contribution of the three hydroxyethyl groups present in the cation is less pronounced than expected. A possible explanation is the screening of the positive charge of the cation by the negative charges localized on the OH groups of HTEA which are responsible for the hydrophilicity of the salt as a whole (D is slightly hydrophobic).

The geometry of the $HTEA^+$ cation is as expected. The C atoms connected to the central N atom, however, are disordered between two positions C15, C17, C19 and C15*a*, C17*a*, C19*a* (Fig. 2). The occupation factors of the two sites were refined so that their sum was constrained to be 1.0.

Atom N2 lies 0.43 (4) Å out of each of the least-squares planes C15, C17, C19 and C15*a*, C17*a*, C19*a*. The mean torsion angles of the 2-hydroxyethyl moieties are 47.6 (4) and −45.1 (6)°, respectively, for the two conformations. These values are lower than those found in other HTEA complexes (Starova *et al.*, 1981; Brodalla & Lipka, 1984; van Mier, Kanters & Poonia, 1988; Mootz, Brodalla & Wiebcke, 1990; Brancuti, 1993), which have a mean value of −55.4°, and also that found in neutral TEA of −63° (Mootz, Brodalla & Wiebcke, 1989).

The interatomic distances and bond angles within the D^- anion are all similar to those found in diclofenac derivatives (Castellari & Sabatino, 1994, 1996; Castellari & Ottani, 1995). The C—O distances in the carboxylate group are 1.248 (3) and 1.238 (3) Å, suggesting a complete charge delocalization. The variations in the geometry of the different diclofenac salts arise almost exclusively from a different orientation of the two aromatic moieties. The dihedral angle between the two phenyl rings of HTEA.D is 64.08 (9)° and differs from the mean value of 68.65 (5)° found in other diclofenac derivatives. Also, the internal N1—H1···O1 hydrogen bond displays contacts which are slightly shorter than the corresponding mean values [H1···O1 2.08 (2), mean 2.16 (1), and N1···O1 2.853 (3), mean 2.941 (1) Å].

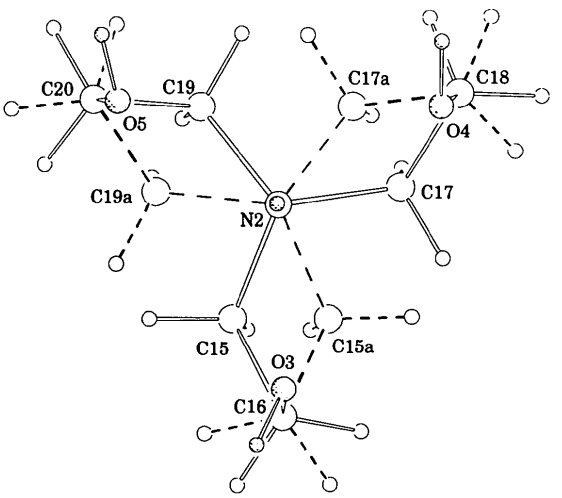


Fig. 2. A perspective view of HTEA showing the two conformations.

Experimental

Diclofenac (IBSA, Lugano, Switzerland) was dissolved in acetone. To the solution was added an equivalent amount of triethanolamine (Fluka, Buchs, Switzerland). Crystals of HTEA.D were obtained from an acetone solution at room temperature. The density D_m was measured by flotation in a 1-bromo-2-chloroethane/*p*-xylene mixture.

Crystal data

$C_6H_{16}NO_3^+.C_{14}H_{10}Cl_2NO_2^-$
M_r = 445.33
Monoclinic
$P2_1/a$
a = 10.589 (3) Å
b = 9.396 (2) Å
c = 21.132 (5) Å
β = 93.24 (2)°
V = 2099.3 (9) Å^3
Z = 4
D_x = 1.40 Mg m^{-3}
D_m = 1.41 Mg m^{-3}
Mo $K\alpha$ radiation
λ = 0.71069 Å
Cell parameters from 25 reflections
θ = 6–10°
μ = 0.344 mm^{-1}
T = 293 (2) K
Prism
0.25 × 0.18 × 0.075 mm
Colourless

Data collection

Enraf–Nonius CAD-4 diffractometer	R_{int} = 0.1050
Profile data from ω scans	θ_{max} = 27.97°
Absorption correction: none	$h = -13 \rightarrow 13$
10 213 measured reflections	$k = 0 \rightarrow 12$
5053 independent reflections	$l = 0 \rightarrow 27$
1936 observed reflections $[I > 2\sigma(I)]$	3 standard reflections
	frequency: 160 min
	intensity variation: none

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0344P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$R(F)$ = 0.0464	$(\Delta/\sigma)_{max}$ = 0.005
$wR(F^2)$ = 0.1006	$\Delta\rho_{max}$ = 0.201 e Å^{-3}
S = 0.955	$\Delta\rho_{min}$ = −0.209 e Å^{-3}
5051 reflections	Extinction correction: none
307 parameters	Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)
H atoms riding except for H1, H11, H16, H21 and H26 for which all parameters were refined	

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å²)*

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

	x	y	z	U_{eq}
Cl1	1.00944 (8)	0.30235 (8)	−0.27967 (4)	0.0536 (2)
Cl2	0.71952 (7)	0.53735 (8)	−0.47155 (3)	0.0496 (2)
N1	0.8032 (2)	0.4903 (3)	−0.33357 (12)	0.0421 (7)
C1	0.7882 (3)	0.6387 (3)	−0.33201 (12)	0.0341 (7)
C2	0.6931 (3)	0.6966 (3)	−0.29658 (11)	0.0356 (7)
C3	0.6768 (3)	0.8431 (3)	−0.29849 (13)	0.0470 (8)
C4	0.7511 (3)	0.9315 (3)	−0.33287 (14)	0.0534 (9)
C5	0.8459 (3)	0.8731 (3)	−0.36610 (13)	0.0477 (8)
C6	0.8651 (3)	0.7281 (3)	−0.36538 (12)	0.0423 (8)
C7	0.8718 (3)	0.4188 (3)	−0.37814 (12)	0.0344 (7)
C8	0.9683 (3)	0.3243 (3)	−0.36001 (12)	0.0374 (7)
C9	1.0341 (3)	0.2474 (3)	−0.40280 (14)	0.0468 (8)
C10	1.0055 (3)	0.2653 (3)	−0.46677 (14)	0.0495 (8)
C11	0.9096 (3)	0.3562 (3)	−0.48710 (13)	0.0447 (8)
C12	0.8432 (2)	0.4298 (3)	−0.44327 (12)	0.0372 (7)
C13	0.6071 (3)	0.6034 (3)	−0.26038 (12)	0.0403 (7)
C14	0.6678 (3)	0.5393 (3)	−0.19963 (13)	0.0387 (7)
O1	0.7422 (2)	0.4378 (2)	−0.20587 (9)	0.0575 (6)
O2	0.6388 (2)	0.5910 (2)	−0.14856 (9)	0.0656 (7)
N2	0.7760 (2)	0.4674 (3)	0.09141 (11)	0.0360 (6)
C15†	0.7561 (6)	0.3594 (5)	0.0402 (2)	0.045 (2)
C15a‡	0.6648 (9)	0.3884 (8)	0.0604 (4)	0.046 (3)
C16	0.6583 (3)	0.4008 (3)	−0.00933 (14)	0.0493 (8)
O3	0.6786 (2)	0.5428 (2)	−0.02630 (10)	0.0613 (7)
C17†	0.6680 (6)	0.4755 (5)	0.1333 (3)	0.049 (2)
C17a‡	0.7568 (11)	0.4990 (9)	0.1589 (4)	0.057 (3)
C18	0.6661 (3)	0.6098 (3)	0.1708 (2)	0.0625 (10)
O4	0.6830 (2)	0.7283 (2)	0.13161 (9)	0.0534 (6)
C19†	0.9006 (5)	0.4422 (6)	0.1292 (3)	0.050 (2)
C19a‡	0.8978 (7)	0.3962 (8)	0.0805 (5)	0.052 (3)
C20	1.0095 (3)	0.4832 (3)	0.0942 (2)	0.0631 (10)
O5	0.9928 (2)	0.6214 (2)	0.06853 (11)	0.0620 (6)

† Occupancy of 0.613 (6). ‡ Occupancy of 0.387 (6).

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

N1—C7	1.394 (3)	C16—O3	1.401 (3)
N1—C1	1.404 (3)	C18—O4	1.405 (3)
C14—O2	1.238 (3)	C20—O5	1.414 (3)
C14—O1	1.248 (3)		
C7—N1—C1	123.9 (2)	O2—C14—C13	117.7 (3)
C2—C13—C14	114.8 (2)	O1—C14—C13	116.8 (2)

Table 3. *Hydrogen-bonding geometry (Å, °)*

D—H···A	H···A	D···A	D—H···A
N1—H1···O1	2.08 (2)	2.853 (3)	155 (2)
N2—H11···O3	2.32 (2)	2.732 (3)	111 (2)
N2—H11···O4	2.38 (2)	2.792 (3)	111 (2)
N2—H11···O5	2.35 (2)	2.779 (3)	112 (2)
O3—H16···O2	1.81 (2)	2.633 (3)	166 (2)
O4—H21···O1^{i}	1.80 (3)	2.613 (3)	166 (3)
O5—H26···O4^{ii}	1.91 (3)	2.744 (3)	168 (2)

Symmetry codes: (i) $\frac{3}{2} - x, y - \frac{1}{2}, -1 - z$; (ii) $\frac{1}{2} + x, \frac{3}{2} - y, z$.

The H atoms involved in hydrogen bonding were located and their coordinates and displacement coefficients refined isotropically. The initial torsion angles of the OH groups were chosen to maximize the electron density. In subsequent refinement cycles, these groups were re-idealized with retention of the torsion angle and with restraints to make all the O—H distances approximately equal (e.s.d. of 0.03 Å). The remaining H atoms were placed in calculated positions and refined riding on their parent atoms [C(aromatic)—H = 0.93, Csp^3—H = 0.97 Å].

Data collection: *CAD-4 Software* (Enraf–Nonius, 1989). Cell refinement: *CAD-4 Software*. Data reduction: *MolEN* (Fair, 1990). Program(s) used to solve structure: *SHELXS86* (Sheldrick, 1990). Program(s) used to refine structure: *SHELXL93* (Sheldrick, 1993). Molecular graphics: *SCHAKAL-92* (Keller, 1992), *ORTEP*II (Johnson, 1976). Software used to prepare material for publication: *SHELXL93*.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: AB1345). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

References

Brancuti, A. J. (1993). *J. Crystallogr. Spectrosc. Res.* **23**, 669–673.

Brodalla, D. & Lipka, A. (1984). *Z. Naturforsch. Teil B*, **39**, 1167–1171.

Castellari, C. & Ottani, S. (1995). *Acta Cryst.* C**51**, 2612–2615.

Castellari, C. & Sabatino, P. (1994). *Acta Cryst.* C**50**, 1723–1726.

Castellari, C. & Sabatino, P. (1996). *Acta Cryst.* C**52**, 1708–1712.

Enraf–Nonius (1989). *CAD-4 Software*. Version 5. Enraf–Nonius, Delft, The Netherlands.

Exner, O. & Engberts, J. B. F. H. (1979). *Collect. Czech. Chem. Commun.* **44**, 3378–3384.

Fair, C. K. (1990). *MolEN. An Interactive Intelligent System for Crystal Structure Analysis*. Enraf–Nonius, Delft, The Netherlands.

Fini, A., Fazio, G. & Rapaport, I. (1993). *Drugs Exp. Clin. Res.* **19**, 81–88.

Fini, A., Zecchi, V. & Tartarini, A. (1985). *Pharm. Acta Helv.* **60**, 58–62.

Huyskens, P. & Zeegers-Huyskens, T. (1964). *J. Chim. Phys. Phys.-Chim. Biol.* **61**, 81–86.

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

Keller, E. (1992). *SCHAKAL92. Computer Program for the Graphic Representation of Molecular and Crystallographic Models*. University of Freiburg, Germany.

Mier, G. P. M. van, Kanters, J. A. & Poonia, N. S. (1988). *Acta Cryst.* C**44**, 334–337.

Mootz, D., Brodalla, D. & Wiebcke, M. (1989). *Acta Cryst.* C**45**, 754–757.

Mootz, D., Brodalla, D. & Wiebcke, M. (1990). *Acta Cryst.* C**46**, 797–799.
Sheldrick, G. M. (1990). *Acta Cryst.* A**46**, 467–473.
Sheldrick, G. M. (1993). *SHELXL93. Program for the Refinement of Crystal Structures*. University of Göttingen, Germany.
Starova, G. L., Frank-Kamenetskaya, O. V., Fundamenskii, V. S., Semenova, N. V. & Voronkov, M. G. (1981). *Dokl. Akad. Nauk SSSR*, **260**, 888; *Sov. Phys. Dokl.* **26**, 911–913.
Wolfe, S. (1972). *Acc. Chem. Res.* **5**, 102–111.

Acta Cryst. (1996). C**52**, 2622–2627

Four Simple Pyridazin-3(2*H*)-ones

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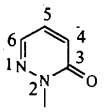
Abstract

The structures of four simple pyridazin-3(2*H*)-ones, the isomeric 4-methylpyridazin-3(2*H*)-one [$C_5H_6N_2O$, (5)], 5-methylpyridazin-3(2*H*)-one monohydrate and 6-methylpyridazin-3(2*H*)-one monohydrate [$C_5H_6N_2O.H_2O$, (6).H_2O and (7).H_2O] and 2-(*p*-tolyl)pyridazin-3(2*H*)-one [$C_{11}H_{10}N_2O$, (8)], have been determined. Compounds (6) and (7), which crystallize as monohydrates, show extensive hydrogen bonding while molecules of (5) form hydrogen-bonded dimers. In (8), there are no strong hydrogen bonds as in compounds (5)–(7), the closest intermolecular contacts being pairwise C—H···O interactions.

Comment

The pyridazin-3(2*H*)-one heterocyclic system (1) has important pharmaceutical (Baraldi *et al.*, 1994; Prout *et al.*, 1994) and agrochemical (Cremlyn, 1991) applications, but relatively little is known about the structural characteristics of simple derivatives of this ring system. Examples in the literature include an extensive range of 6-aryl derivatives [*e.g.* (2)] which was studied to ascertain the relationship between their structures and their cardiovascular properties (Prout *et al.*, 1994), the 6-methoxy compound (3) (Ottersen, 1974) and the 5,6-dialkyl derivative (4) (Moreau, Metin, Coudert & Couquelet, 1995). Some years ago, one of the present authors developed a convenient route to 2-, 5- and 6-substituted pyridazinones (McNab & Stobie, 1982) and published details of their NMR spectra (McNab, 1983). With the availability of samples from this earlier work, we now report the results of our structural studies on 4-, 5- and 6-methylpyridazin-3(2*H*)-one, (5)–(7), and the simple 2-aryl derivative, (8).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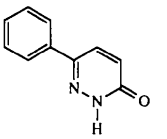
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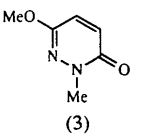
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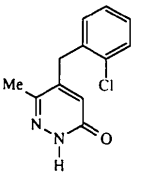
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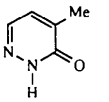
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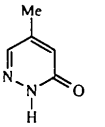
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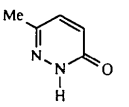
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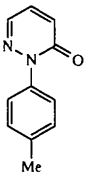
(8)

Compounds (6) and (7) crystallized as monohydrates and while this clearly affects the crystal packing (see below), it appears to have little effect on the intramolecular geometric parameters. The majority of the bond lengths in compounds (5)–(8) lie within the ranges published previously (Prout *et al.*, 1994); for the C-methyl derivatives (5)–(7), corresponding bond lengths generally lie within two e.s.d.'s of each other. The most substantial differences are in the N1/C6/C5 region of the 4-methyl compound (5) where both N1—C6 and C6—C5 are the shortest in the series. In the *N*-aryl example (8), the C6—C5 bond length is again short but the N2—N3 bond is unusually long. This last feature may be due to competitive delocalization of the N2 lone pair into the aryl ring rather than into the adjacent carbonyl group; this effect is also reflected in the short C=O bond length.

The bond angles at the carbonyl group are essentially the same in all four compounds (5)–(8) and are independent of the presence of substituents on either N2 or C4. The endocyclic angle is always about 115.5° with the exocyclic angles having values around either 119 or 125°. In all cases, the presence of a substituent reduces the endocyclic angle at that position; for example, the mean angle at C6 for compounds (5), (6) and (8) is 124.5 (4) but this is reduced to 121.3 (2)° in the 6-substituted compound (7). The exocyclic bond angles at the substituents are unsymmetrical and differ by 3.5–

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