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# Structure of Cycloguanil Hydrochloride by Neutron Diffraction*

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**Abstract.** 4,6-Diamino-1-(*p*-chlorophenyl)-1,2-dihydro-2,2-dimethyl-*s*-triazine hydrochloride, $C_{11}H_{15}ClN_5^+.Cl^-$, $M_r = 288{\cdot}20$, monoclinic, $P2_1/c$, $a = 8{\cdot}783$ (2), $b = 10{\cdot}267$ (2), $c = 17{\cdot}234$ (3) Å, $\beta = 115{\cdot}72$ (1)°, $U = 1400{\cdot}1$ (5) Å$^3$, $Z = 4$, $D_x = 1{\cdot}337$ Mg m$^{-3}$, $\lambda = 1{\cdot}15882$ (7) Å for unit-cell determination and 1·04702 (7) Å for collection of intensity data, $\mu = 0{\cdot}191$ mm$^{-1}$, $T = 15{\cdot}0$ (5) K, final $R(F^2) = 0{\cdot}050$ and $wR(F^2) = 0{\cdot}063$ for 3099 independent reflections. Five atoms of the triazine ring are nearly coplanar. The sixth, the quaternary C(2), is displaced from this plane ($P1$) so that the bond to one of its methyl substituents is nearly perpendicular to $P1$ while the other methyl substituent lies almost in the plane. The chlorophenyl-ring plane is nearly perpendicular to $P1$. The heterocycles form cyclic dimers *via* hydrogen bonds from the 6-amino group to ring atom N(5) of an adjacent molecule. All other N—H units are hydrogen bonded to the $Cl^-$ counter ion. The ring is protonated at position N(3).

**Introduction.** A variety of 2,4-diamino-1,3-diazine heterocyclic systems inhibit the important enzyme dihydrofolate reductase (DHFR). Of the various classes of heterocycles, the pyrimidine antifolates have been most extensively investigated by diffraction methods (Schwalbe & Cody, 1983) including one neutron diffraction study, of 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine [trimethoprim (Koetzle & Williams, 1976)]. Fewer *s*-triazine antifolate structures have been analyzed; these include the anti-cancer drugs 4,6-diamino-1-[3-chloro-4-(*m*-dimethylcarbamoylbenzyloxy)phenyl]-1,2-dihydro-2,2-dimethyl-*s*-triazine ethanesulfonate (I) and 4,6-diamino-1-[4-(4′-fluorosulfonyl-3′-methylanilinocarbonylethyl)phenyl]-1,2-dihydro-2,2-dimethyl-*s*-triazine ethanesulfonate dihydrate (II) (Camerman, Smith & Camerman, 1979) as well as the antimalarial drugs 4,6-diamino-1-[(3,4-dichlorophenyl)methoxy]-1,2-dihydro-2,2-dimethyl-*s*-triazine hydrochloride 0·29-hydrate (III) (Ammon & Plastas, 1979) and 4,6-diamino-1-(*p*-chlorophenyl)-1,2-dihydro-2,2-dimethyl-*s*-triazine hydrochloride (IV, cycloguanil hydrochloride) (Bailey, 1954; Schwalbe & Hunt, 1978; Hunt, Schwalbe, Bird & Mallinson, 1980). Cody & Sutton (1987) have comprehensively reviewed the structural information available about triazine antifolates and reported the structures of homologs of active triazines, including the hydrochlorides of 4,6-diamino-1-(3-cyano-4-methoxyphenyl)-1,2-dihydro-2,2-dimethyl-*s*-triazine (V) and 4,6-diamino-1-(1-naphthyl)-1,2-dihydro-2,2-dimethyl-*s*-triazine (VI). In view of the importance of developing the best possible therapeutic activity we have extended the existing X-ray diffraction data on a representative triazine antifolate to higher precision by carrying out a low-temperature neutron diffraction study of cycloguanil hydrochloride.

**Experimental.** Sample crystal grown from aqueous ethanol by slow evaporation. Colorless prismatic specimen bounded by ten faces, with overall dimensions 2·3 × 2·2 × 1·3 mm. Unit-cell parameters based on averaged $\sin^2\theta$ values measured at 15·0 (5) K with neutrons of wavelength $\lambda = 1{\cdot}15882$ (7) Å for 16 Friedel pairs with $53° < 2\theta < 74°$, and with $\lambda$ calibrated with reference to KBr, $a_0 = 6{\cdot}6000$ Å at $T = 298$ K. Neutron diffraction intensity data collected at 15 (2) K in a Displex® model CS-202 closed-cycle He refrigerator on an automated four-circle diffractometer (Dimmler, Greenlaw, Kelley, Potter, Rankowitz & Stubblefield, 1976; McMullan, Andrews, Koetzle, Reidinger, Thomas & Williams, 1976) at the Brookhaven High Flux Beam Reactor. Data collection by a $\theta/2\theta$ scan technique with $\lambda = 1{\cdot}04702$ (7) Å. Absorption correction by integration over a Gaussian grid (Busing & Levy, 1957) with mass absorption coefficients for C, N and Cl atoms taken from

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*International Tables for X-ray Crystallography* (1968) and 2·48 $m^2 kg^{-1}$ used for H (Koetzle & McMullan, 1980). Maximum $(\sin\theta)/\lambda = 0{\cdot}731$ Å$^{-1}$, $-7 \le h \le 12$, $0 \le k \le 15$, $-26 \le l \le 23$, two intensity monitor reflections remeasured every 100 reflections showed no significant trend, 3099 independent reflections collected. Integrated intensities obtained from scan profiles and assigned errors $\sigma_c$ based on counting statistics. Coordinates obtained by Hunt, Schwalbe, Bird & Mallinson (1980) were refined along with anisotropic thermal parameters for all atoms and a type I isotropic extinction parameter (Becker & Coppens, 1975) [final value $g = 3{\cdot}5\,(1) \times 10^{-5}$] against all data to minimize $\sum w(F_o^2 - k^2F_c^2)^2$. Scattering factors from Koester (1977), 299 parameters refined, weights $w = 1/[\sigma_c^2(F_o^2) + 0{\cdot}025F_o^2)^2]$, $R(F^2) = 0{\cdot}050$, $wR(F^2) = 0{\cdot}063$, $S(F^2) = 1{\cdot}068$, $(\Delta/\sigma)_{max} = 0{\cdot}05$ for positional parameters and 0·25 for thermal parameters, maximum positive and negative residuals on a difference Fourier synthesis = 1·3% of the height of an N-atom peak. Computer programs described in the *CRYSNET* manual (Berman, Bernstein, Bernstein, Koetzle & Williams, 1976). Computer graphics performed with the *CHEM-X* system (Davies, 1986).

**Discussion.** The molecular structure of (IV) and its numbering scheme are shown in Fig. 1. Atomic coordinates and equivalent isotropic temperature factors are given in Table 1, bond distances and angles in Table 2, H-bond geometry in Table 3, and least-squares-plane data in Table 4.* As in the other triazine antifolates, the proton which is supplied by acid and removed by base attaches to N(3), where it creates a stable biguanidinium system. This N(3)—H(7) distance of 1·035 (3) Å is slightly longer than the other N—H distances in cycloguanil hydrochloride and those in

* Lists of squared structure factors and anisotropic thermal parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 51480 (20 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

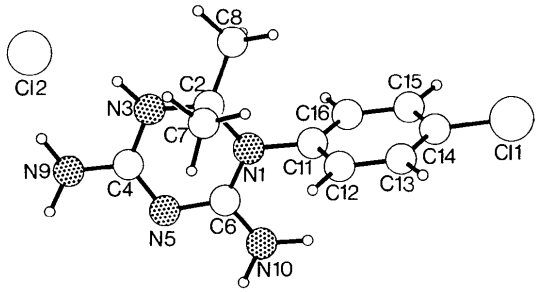


Fig. 1. *PLUTO* (Motherwell & Clegg, 1978) drawing of the structure of cycloguanil hydrochloride showing the numbering scheme.

Table 1. *Fractional atomic coordinates* ($\times 10^5$) *and equivalent isotropic temperature factors* (Å$^2 \times 10^4$) *for all atoms of cycloguanil hydrochloride*

| | $x$ | $y$ | $z$ | $U_{eq}$ |
|---|---|---|---|---|
| Cl(1) | −30502 (11) | 92819 (9) | 4993 (5) | 88 (4) |
| Cl(2) | 60651 (10) | 94523 (8) | 71781 (5) | 67 (4) |
| N(1) | 6201 (10) | 80244 (8) | 42204 (5) | 51 (3) |
| C(2) | 21709 (14) | 88001 (11) | 47179 (7) | 49 (5) |
| N(3) | 25695 (10) | 86001 (8) | 56280 (5) | 59 (4) |
| C(4) | 24137 (14) | 73865 (11) | 58966 (7) | 51 (5) |
| N(5) | 13203 (10) | 65149 (8) | 53723 (5) | 59 (3) |
| C(6) | 3790 (14) | 68830 (12) | 45468 (7) | 49 (5) |
| C(7) | 36526 (15) | 83308 (12) | 45438 (8) | 69 (5) |
| C(8) | 18049 (15) | 102450 (12) | 45140 (8) | 70 (5) |
| N(9) | 33392 (11) | 71005 (9) | 67234 (5) | 78 (4) |
| N(10) | −8373 (11) | 60836 (9) | 40476 (5) | 72 (4) |
| C(11) | −3011 (14) | 82894 (11) | 33151 (7) | 51 (5) |
| C(12) | 2798 (14) | 78010 (12) | 27335 (7) | 65 (5) |
| C(13) | −5733 (14) | 81078 (12) | 18630 (7) | 67 (5) |
| C(14) | −20126 (15) | 88839 (12) | 15848 (7) | 62 (5) |
| C(15) | −26390 (14) | 93485 (12) | 21512 (7) | 71 (5) |
| C(16) | −17661 (14) | 90434 (12) | 30227 (7) | 67 (5) |
| H(1) | 34970 (37) | 86121 (31) | 39006 (17) | 236 (14) |
| H(2) | 38056 (39) | 72794 (28) | 46255 (21) | 223 (15) |
| H(3) | 48083 (33) | 87806 (31) | 50176 (20) | 242 (14) |
| H(4) | 17054 (41) | 104720 (29) | 38744 (19) | 239 (14) |
| H(5) | 28486 (37) | 108176 (29) | 49833 (19) | 230 (14) |
| H(6) | 6384 (35) | 105253 (28) | 45538 (20) | 212 (14) |
| H(7) | 36324 (33) | 90950 (26) | 60524 (16) | 172 (12) |
| H(8) | 43201 (35) | 77040 (27) | 70726 (17) | 196 (13) |
| H(9) | 32905 (36) | 62023 (27) | 69656 (17) | 192 (12) |
| H(10) | −10126 (35) | 52177 (27) | 42986 (17) | 180 (12) |
| H(11) | −15922 (35) | 62633 (28) | 34114 (16) | 198 (13) |
| H(12) | 13971 (34) | 71850 (30) | 29633 (17) | 209 (13) |
| H(13) | −1236 (38) | 77691 (32) | 14024 (17) | 238 (14) |
| H(14) | −37908 (34) | 99272 (29) | 19210 (18) | 217 (13) |
| H(15) | −22207 (35) | 93966 (30) | 34804 (17) | 214 (13) |

Equivalent isotropic temperature factors have been calculated by the equation:

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

Table 2. *Selected bond distances* (Å), *bond angles* (°), *and torsion angles* (°) *with e.s.d.'s in parentheses*

| | | | |
|---|---|---|---|
| N(1)–C(2) | 1·487 (1) | C(12)–C(13) | 1·391 (2) |
| C(2)–N(3) | 1·466 (1) | C(13)–C(14) | 1·392 (2) |
| N(3)–C(4) | 1·357 (2) | C(14)–C(15) | 1·396 (2) |
| C(4)–N(5) | 1·337 (1) | C(15)–C(16) | 1·394 (2) |
| N(5)–C(6) | 1·353 (1) | C(16)–C(11) | 1·395 (2) |
| C(6)–N(1) | 1·356 (1) | C(14)–Cl(1) | 1·737 (2) |
| C(2)–C(7) | 1·534 (2) | N(3)–H(7) | 1·035 (3) |
| C(2)–C(8) | 1·526 (2) | N(9)–H(8) | 1·019 (3) |
| C(4)–N(9) | 1·331 (2) | N(9)–H(9) | 1·021 (3) |
| C(6)–N(10) | 1·326 (1) | N(10)–H(10) | 1·029 (3) |
| N(1)–C(11) | 1·438 (2) | N(10)–H(11) | 1·023 (3) |
| C(11)–C(12) | 1·400 (2) | | |

| | | | |
|---|---|---|---|
| C(2)–N(1)–C(6) | 119·5 (1) | N(5)–C(6)–N(10) | 117·5 (1) |
| C(2)–N(1)–C(11) | 117·9 (1) | N(1)–C(6)–N(10) | 119·5 (1) |
| C(6)–N(1)–C(11) | 119·9 (1) | N(1)–C(11)–C(12) | 120·1 (1) |
| N(1)–C(2)–N(3) | 106·0 (1) | N(1)–C(11)–C(16) | 119·6 (1) |
| N(1)–C(2)–C(7) | 111·2 (1) | C(11)–C(12)–C(13) | 119·9 (1) |
| N(1)–C(2)–C(8) | 109·8 (1) | C(12)–C(13)–C(14) | 119·0 (1) |
| N(3)–C(2)–C(7) | 109·6 (1) | C(13)–C(14)–C(15) | 122·0 (1) |
| N(3)–C(2)–C(8) | 108·1 (1) | C(13)–C(14)–Cl(1) | 118·6 (1) |
| C(7)–C(2)–C(8) | 111·8 (1) | C(15)–C(14)–Cl(1) | 119·4 (1) |
| C(2)–N(3)–C(4) | 118·8 (1) | C(14)–C(15)–C(16) | 118·5 (1) |
| C(2)–N(3)–H(7) | 114·2 (2) | C(15)–C(16)–C(11) | 120·3 (1) |
| C(4)–N(3)–H(7) | 113·8 (2) | C(4)–N(9)–H(8) | 117·7 (2) |
| N(3)–C(4)–N(5) | 122·2 (1) | C(4)–N(9)–H(9) | 121·5 (2) |
| N(3)–C(4)–N(9) | 117·6 (1) | H(8)–N(9)–H(9) | 118·8 (2) |
| N(5)–C(4)–N(9) | 120·1 (1) | C(6)–N(10)–H(10) | 119·2 (2) |
| C(4)–N(5)–C(6) | 117·1 (1) | C(6)–N(10)–H(11) | 123·3 (2) |
| N(5)–C(6)–N(1) | 122·9 (1) | H(10)–N(10)–H(11) | 117·5 (2) |

| | | | |
|---|---|---|---|
| C(6)–N(1)–C(2)–N(3) | −34·0 (1) | C(6)–N(1)–C(11)–C(12) | −83·0 (1) |
| C(6)–N(1)–C(2)–C(7) | 85·1 (1) | C(6)–N(1)–C(11)–C(16) | 97·5 (1) |
| C(6)–N(1)–C(2)–C(8) | −150·6 (1) | N(5)–C(4)–N(3)–H(7) | −167·0 (2) |
| N(1)–C(2)–N(3)–C(4) | 41·6 (1) | N(5)–C(4)–N(9)–H(8) | 167·8 (2) |
| C(2)–N(3)–C(4)–N(5) | −28·1 (1) | N(5)–C(4)–N(9)–H(9) | 3·8 (2) |
| N(5)–C(6)–N(1)–C(2) | 12·3 (1) | N(5)–C(6)–N(10)–H(10) | −0·7 (2) |
| N(5)–C(6)–N(1)–C(11) | 173·2 (1) | N(5)–C(6)–N(10)–H(11) | −178·1 (2) |

Table 3. *Geometry of hydrogen bonds*

| *D*—H···*A* | *D*···*A* (Å) | H···*A* (Å) | *D*—H···*A* (°) |
|---|---|---|---|
| N(3)—H(7)···Cl(2) | 3·195 (2) | 2·206 (3) | 159·2 (2) |
| N(9)—H(8)···Cl(2) | 3·248 (1) | 2·316 (3) | 151·5 (2) |
| N(9)—H(9)···Cl(2$^{i}$) | 3·223 (1) | 2·236 (3) | 162·2 (2) |
| N(10)—H(10)···N(5$^{ii}$) | 2·944 (1) | 1·921 (3) | 171·7 (3) |
| N(10)—H(11)···Cl(2$^{iii}$) | 3·237 (2) | 2·344 (3) | 145·2 (2) |

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

Table 4. *Deviations* (Å) *from least-squares planes*

Atoms defining a plane are starred. E.s.d.'s are < 0·01 Å.

Plane *P*1 (triazine): N(1)* 0·04, C(2) 0·49, N(3)* −0·03, C(4)* 0·03, N(5)* 0·01, C(6)* −0·05, C(11) 0·12, C(7) 2·02, C(8) −0·15, H(7) 0·20, Cl(2) 0·87, N(9) 0·05, H(8) 0·25, H(9) 0·10, Cl(2$^{i}$) 0·42, N(10) −0·22, H(10) −0·28, N(5$^{ii}$) −0·20, H(11) −0·25, Cl(2$^{iii}$) −0·61.

Plane *P*2 (benzene): C(11)* 0·01, C(12)* −0·01, C(13)* 0·00, C(14)* 0·01, C(15)* −0·01, C(16)* −0·01, N(1) 0·07, H(12) −0·03, H(13) 0·02, Cl(1) 0·05, H(14) −0·03, H(15) −0·01.

Symmetry code as in Table 3.

unprotonated trimethoprim (Koetzle & Williams, 1976).

A common structural feature of triazine antifolates (Cody & Sutton, 1987) is the near coplanarity of the atoms of the heterocycle (plane *P*1), with the exception of the quaternary C(2) (Table 4). Of the two methyl groups attached to C(2), C(8) lies close to plane *P*1, while the C—C bond to C(7) is nearly perpendicular to this plane. This arrangement of atoms ensures that many of the important functional groups of cycloguanil and 2,4-diamino-5-(*p*-chlorophenyl)-6-ethylpyrimidine (pyrimethamine) are almost superimposable; these antifolates both have antimalarial activity.

The sterically demanding dimethyl substitution at C(2) and the presence of the 6-amino group force the chlorophenyl group and *P*1 to be nearly perpendicular. The angle between these two planes of 80·4 (1)° is similar to the 78·9 (3)° in (I) and the 85·1 (4)° in (II). In the less crowded chlorophenylpyrimidine derivatives, where the atom analogous to C(2) bears only one alkyl substituent, smaller twist angles are expected, and the minimum energy predicted for pyrimethamine is at a twist of 58° (Sykes & Schwalbe, 1987).

Four of the N atoms in protonated cycloguanil are bonded to three neighbors. The sum of bond angles at N(1), N(9), and N(10) is close to 360° and indicative of $sp^2$ hybridization. The sum at N(3) is only 346·8 (3)°, showing partial $sp^3$ character.

Molecules are linked by hydrogen bonds (Table 3 and Fig. 2) in the same manner as for most protonated diaminopyrimidine antifolates (Schwalbe & Cody, 1983). The $Cl^-$ ion straddles one side of the triazine ring and is H-bonded to the amino N(9) *via* H(8) and to N(3) *via* H(7). It also acts as a proton acceptor for amino groups of molecules in two other equivalent positions, accepting a total of 4 hydrogen bonds. Thus 3 of the 4 amino H atoms are involved with the counter

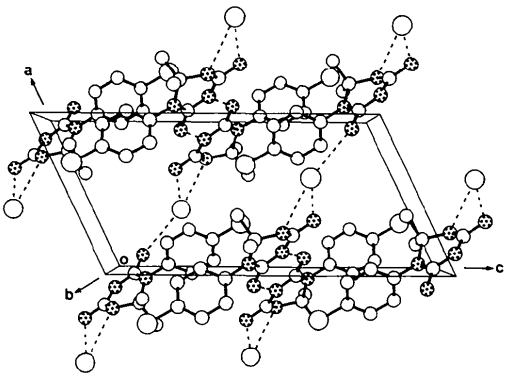


Fig. 2. Packing of molecules in the unit cell drawn by *PLUTO* in perspective projection down the *b* axis. N atoms are stippled and hydrogen bonds shown by dashed lines.

ion. The fourth participates in N—H···N hydrogen bonding to ring N(5), forming a typical cyclic dimer around a center of inversion. Comparison of the data in Tables 3 and 4 shows that every hydrogen-bonded H atom deviates from plane *P*1 on the same side as its proton acceptor atom.

In (III), which also is a hydrochloride salt, the pattern of hydrogen bonds is recognizably similar but modified by a sideways displacement of $Cl^-$. While the hydrogen bond from ring $NH^+$ to $Cl^-$ is retained, a space is created near the adjacent amino group which is partially occupied by water molecules. In the hydrochloride (V) a sideways displacement in the opposite direction affects $Cl^-$ so that it accepts a hydrogen bond from the amino group while space is created for a water molecule to accept a hydrogen bond from the protonated ring N atom. These observations suggest that such facile sideways displacement of hydrogen-bond donors and acceptors in the triazines may possibly help to ensure an energetically favorable interaction with the carboxylate anion present in the active site of DHFR.

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## References

AMMON, H. L. & PLASTAS, L. A. (1979). *Acta Cryst.* B**35**, 3106–3109.

BAILEY, M. (1954). *Acta Cryst.* **7**, 366–369.

BECKER, P. J. & COPPENS, P. (1975). *Acta Cryst.* A**31**, 417–425.

BERMAN, H. M., BERNSTEIN, F. C., BERNSTEIN, H. J., KOETZLE, T. F. & WILLIAMS, G. J. B. (1976). *CRYSNET Manual.* Informal Report BNL 21714. Brookhaven National Laboratory, New York, USA.

BUSING, W. R. & LEVY, H. A. (1957). *Acta Cryst.* **10**, 180–182.

CAMERMAN, A., SMITH, H. W. & CAMERMAN, N. (1979). *Acta Cryst.* B35, 2113–2118.
CODY, V. & SUTTON, P. (1987). *Anti-Cancer Drug Design*, 2, 253–262.
DAVIES, K. (1986). *CHEM-X*, developed and distributed by Chemical Design Ltd, Oxford, England.
DIMMLER, D. G., GREENLAW, N., KELLEY, M. A., POTTER, D. W., RANKOWITZ, S. & STUBBLEFIELD, F. W. (1976). *IEEE Trans. Nucl. Sci.* 23, 398–405.
HUNT, W. E., SCHWALBE, C. H., BIRD, K. & MALLINSON, P. D. (1980). *Biochem. J.* 187, 533–536.
*International Tables for X-ray Crystallography* (1968). Vol. III, 2nd ed., p. 197. Birmingham: Kynoch Press. (Present distributor Kluwer Academic Publishers, Dordrecht.)
KOESTER, L. (1977). *Springer Tracts in Modern Physics*, Vol. 80, *Neutron Physics*, edited by G. HÖHLER, pp. 1–55. Berlin, Heidelberg, New York: Springer-Verlag.
KOETZLE, T. F. & MCMULLAN, R. K. (1980). Unpublished.
KOETZLE, T. F. & WILLIAMS, G. J. B. (1976). *J. Am. Chem. Soc.* 98, 2074–2078.
MCMULLAN, R. K. AND IN PART ANDREWS, L. C., KOETZLE, T. F., REIDINGER, F., THOMAS, R. & WILLIAMS, G. J. B. (1976). *NEXDAS. Neutron and X-ray Data Acquisition System.* Unpublished.
MOTHERWELL, W. D. S. & CLEGG, W. (1978). *PLUTO78*. A program for plotting molecular and crystal structures. Univ. of Cambridge, England.
SCHWALBE, C. H. & CODY, V. (1983). *Chemistry and Biology of Pteridines*, edited by J. A. BLAIR, pp. 511–515. Berlin: de Gruyter.
SCHWALBE, C. H. & HUNT, W. E. (1978). *J. Chem. Soc. Chem. Commun.* pp. 188–190.
SYKES, G. & SCHWALBE, C. H. (1987). *J. Pharm. Pharmac.* 39, 114P.

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# Structures of Bis(3-phenylsydnone) Sulfide (1), Bis[3-(*p*-methoxyphenyl)sydnone] Sulfide (2), and Bis[3-(*p*-ethoxyphenyl)sydnone] Sulfide (3)

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**Abstract.** (1) $C_{16}H_{10}N_4O_4S$, $M_r = 354$, monoclinic, $P2_1/n$, $a = 10{\cdot}347$ (2), $b = 7{\cdot}777$ (1), $c = 19{\cdot}796$ (4) Å, $\beta = 100{\cdot}33$ (2)°, $V = 1567{\cdot}13$ Å$^3$, $Z = 4$, $D_m = 1{\cdot}52$ (3), $D_x = 1{\cdot}50$ g cm$^{-3}$, $\lambda$(Mo $K\alpha$) = 0·7093 Å, $\mu$(Mo $K\alpha$) = 2·26 cm$^{-1}$, $F(000) = 728$, $T = 298$ K, final $R = 0{\cdot}033$ for 2922 observed reflections. (2) $C_{18}H_{14}N_4O_6S$, $M_r = 414$, monoclinic, $P2_1/c$, $a = 14{\cdot}255$ (2), $b = 9{\cdot}344$ (1), $c = 15{\cdot}250$ (2) Å, $\beta = 116{\cdot}61$ (1)°, $V = 1816{\cdot}12$ Å$^3$, $Z = 4$, $D_m = 1{\cdot}50$ (3), $D_x = 1{\cdot}52$ g cm$^{-3}$, $\lambda$(Mo $K\alpha$) = 0·7093 Å, $\mu$(Mo $K\alpha$) = 2·14 cm$^{-1}$, $F(000) = 856$, $T = 298$ K, final $R = 0{\cdot}039$ for 2066 observed reflections. (3) $C_{20}H_{18}N_4O_6S$, $M_r = 442$, monoclinic, $C2/c$, $a = 20{\cdot}724$ (5), $b = 12{\cdot}157$ (3), $c = 8{\cdot}201$ (3) Å, $\beta = 95{\cdot}10$ (2)°, $V = 2057{\cdot}88$ Å$^3$, $Z = 4$, $D_m = 1{\cdot}45$ (3), $D_x = 1{\cdot}43$ g cm$^{-3}$, $\lambda$(Mo $K\alpha$) = 0·7093 Å, $\mu$(Mo $K\alpha$) = 1·94 cm$^{-1}$, $F(000) = 920$, $T = 298$ K, final $R = 0{\cdot}039$ for 1088 observed reflections. The bond lengths of the sydnone ring are similar in all three compounds and comparable to those of other 3,4-disubstituted sydnone derivatives. The N(1)—C(7) bonds of the title compounds are apparently longer than those of 3-substituted sydnone derivatives which may be attributed to steric effects. A survey of S—C bond lengths and angles between planes of different substituted diaryl sulfides does not show any correlation with the type of substituents. The shortening of the S—C bond lengths of the title compounds *versus* the average bond lengths in the cyclic 1,3,5-trithiane may be attributable to orbital electronegativity effects. In contrast to the 'morino' conformation found in most other diaryl sulfides, all three title compounds appear in the butterfly conformation.

**Introduction.** The crystal structures of a few 3,4-disubstituted sydnone derivatives have recently been studied (Ueng, Wang & Yeh, 1987*a*,*b*) and the bond lengths of the sydnone rings were compared with those of 3-substituted sydnone derivatives. As part of a series of studies on 3,4-disubstituted sydnone compounds, the three bis-sydnone sulfide structures were investigated in order to confirm further the steric effect between the phenyl ring and the sydnone ring. In addition, the lone-pair electrons on the S atom may have some effect

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