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The Structures of Antischistosomal Compounds. I. Structure of Crystals of *trans*-5-Amino-3-[2-(5-nitro-2-furyl)vinyl]-1,2,4-oxadiazole and *N*,*N*-Dimethylformamide

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Crystals of co-crystallized *trans*-5-amino-3-[2-(5-nitro-2-furyl)vinyl]-1,2,4-oxadiazole (ANFVO) and *N*,*N*-dimethylformamide, $C_8H_6O_4N_4.C_3H_7NO$, are monoclinic, space group $C2/c$, with eight molecules in a unit cell of dimensions $a = 22{\cdot}340$ (7), $b = 11{\cdot}834$ (4), $c = 10{\cdot}645$ (3) Å, $\beta = 97{\cdot}9$ (4)°. Intensity data for 1465 reflections were collected on an automatic diffractometer. The structure was determined by direct methods and the final parameters of the non-hydrogen atoms were refined by full-matrix least squares. The final R and weighted R values are 0·062 and 0·056 respectively for the 1106 reflections with $I > 2\sigma I$. The ANFVO molecules are planar and the system of three conjugated double bonds in the molecule has both single bonds in the *s–trans* configuration. There is a pair of N···H–N intermolecular hydrogen bonds (2·95 Å) across a center of inversion between two 5-amino-1,2,4-oxadiazole rings. The geometry of this pair of hydrogen bonds resembles that of 'base-paired' nucleotides in DNA molecules. The *N*,*N*-dimethylformamide molecule is disordered.

Schistomiasis is an endemic parasitic disease which is thought to afflict some 200 million individuals in underdeveloped areas of the world. Many compounds have been investigated in attempts to develop safe and effective drugs for the treatment of affected humans. Several nitro-heterocyclic compounds, including compounds of the 5-nitro-2-thiazolyl and 5-nitro-2-furyl series (Lin, Hulbert, Bueding & Robinson, 1974), were found to be active against some species of schistosoma. The mode of action of the two series of compounds is probably the same and therefore it is likely that both series of compounds have common structural characteristics that can be correlated with their pharmacological properties. Based on simple chemical arguments the conformations of the compounds in these series were predicted and a model for the correlation of structure and activity was proposed by Robinson, Bueding & Fisher (1970). This model can explain the observed pharmacological properties of some of the compounds. However, it is evident that knowledge of the precise three-dimensional structure of these compounds is essential to establish structure–activity relationships.

In this paper we describe the structure of *trans*-5-amino-3-[2-(5-nitro-2-furyl)vinyl]-1,2,4-oxadiazole (ANFVO), which is a highly active antischistosomal agent in animals. This compound is also a very active antimicrobial, antifungal and antitrichonomal agent (Gadebusch, Breuer, Miraglia, Baschi & Semar, 1969).

Experimental

The compound was synthesized as described previously (Breuer, 1969). Well formed crystals of ANFVO were obtained from *N*,*N*-dimethylformamide (DMF) solutions. When the crystals were removed from the solution for mounting, they dried with complete loss of crystallinity. Attempts to crystallize ANFVO from other solvents were unsuccessful because of the very low solubility of the compound in most polar and nonpolar solvents. For these reasons the crystals of ANFVO obtained from DMF solutions were mounted inside quartz capillaries in the presence of the saturated solutions. Excess liquid was removed from the crystals by touching them with filter paper. Enough liquid was left to keep them fixed to the capillary wall and to keep the volume saturated with DMF vapor. The capillary was sealed with one drop of mercury at each end and further protected with wax seals. With this mounting

Table 1. *Complete crystal data*

Molecular formula: $C_8H_6O_4N_4 . C_3H_7NO$
$a = 22{\cdot}340\ (7)$ Å
$b = 11{\cdot}834\ (4)$
$c = 10{\cdot}645\ (3)$
$\beta = 97{\cdot}9\ (4)^\circ$
$Z = 8$
$V = 2787{\cdot}53$ Å^3
Space group $C2/c$
Maximum $(\sin\theta)/\lambda = 0{\cdot}50$
$\rho_m = 1{\cdot}39$ g cm^{-3}
$\rho_c = 1{\cdot}407$
$\mu(\text{Mo } K\alpha) = 0{\cdot}869$ cm^{-1}

Table 2. *Final positional parameters* ($\times 10^4$)

Standard deviations are in parentheses.

	x	y	z
O(1)	1719 (1)	3059 (3)	5046 (3)
C(2)	1518 (2)	4021 (5)	4414 (5)
C(3)	1734 (3)	4925 (5)	5105 (6)
C(4)	2083 (3)	4551 (6)	6200 (6)
C(5)	2059 (2)	3419 (5)	6115 (6)
C(6)	1129 (2)	3888 (5)	3243 (5)
C(7)	940 (2)	2934 (5)	2705 (5)
C(8)	545 (2)	2843 (5)	1529 (5)
N(9)	324 (2)	3760 (3)	828 (4)
C(10)	−15 (3)	3285 (5)	−114 (6)
O(11)	−30 (2)	2148 (3)	−71 (3)
N(12)	359 (2)	1869 (4)	1070 (4)
N(5)	2325 (2)	2570 (5)	6950 (5)
O(51)	2218 (2)	1594 (4)	6664 (4)
O(52)	2641 (2)	2890 (4)	7923 (4)
N(10)	−349 (2)	3758 (4)	−1110 (4)
O(13)	3851 (2)	2213 (4)	1839 (5)
C(14)	3639 (4)	2956 (10)	1004 (8)
N(15)	3781 (2)	4015 (4)	1138 (4)
C(16)	3563 (6)	4881 (9)	117 (10)
C(17)	4205 (6)	4418 (12)	2176 (12)
C(14′)	4036 (8)	3240 (20)	2070 (20)
C(16′)	4028 (14)	5163 (25)	1006 (60)
C(17′)	3277 (8)	3553 (17)	144 (16)

Table 3. *Final positional parameters* ($\times 10^3$) *and temperature factors* ($\times 10^2$) *for the* H *atoms*

Standard deviations are in parentheses.
Isotropic temperature factor: $\exp(-8\pi^2 U \sin^2\theta/\lambda^2)$.

	x	y	z	U (Å^2)
H(3)	171 (4)	543 (7)	478 (7)	9 (3)
H(4)	226 (3)	483 (7)	669 (7)	8 (3)
H(6)	109 (4)	440 (7)	291 (7)	9 (3)
H(7)	112 (3)	239 (7)	285 (7)	9 (3)
H(10*A*)	−60 (6)	349 (12)	−154 (13)	6 (5)
H(10*B*)	−33 (5)	427 (9)	−113 (10)	3 (3)
H(10*A*′)	−87 (9)	394 (19)	−51 (19)	16 (8)
H(10*B*′)	9 (7)	385 (14)	−173 (14)	10 (6)
H(14)	340 (5)	294 (10)	36 (10)	9 (4)
H(16*A*)	336 (4)	439 (8)	−19 (9)	4 (3)
H(16*B*)	354 (6)	519 (12)	64 (12)	7 (5)
H(16*C*)	387 (4)	515 (9)	101 (9)	4 (3)
H(17*A*)	455 (5)	378 (11)	216 (12)	10 (5)
H(17*B*)	455 (6)	507 (14)	153 (13)	14 (6)
H(17*C*)	396 (6)	465 (12)	266 (13)	14 (5)

the crystals were remarkably stable and did not show appreciable deterioration during the data collection. A crystal of dimensions $0{\cdot}6 \times 0{\cdot}2 \times 0{\cdot}2$ mm was used for all the experiments.

The unit-cell and intensity data were measured on a Syntex $P\bar{1}$ computer-controlled diffractometer. The Mo radiation in the incident beam was monochromatized by a graphite crystal. Comparison of the observed and calculated crystal densities clearly indicated that the crystals of ANFVO contained co-crystallized DMF molecules in a 1:1 molar ratio (Table 1). The reflections were measured by a $2^\circ(\theta\text{–}2\theta)$ scan with scanning rates between 2 and 24° min^{-1}. Background was measured for each reflection, counting at both sides of the peak. 1465 unique reflexions were measured for $\sin\theta/\lambda \le 0{\cdot}50$. The 1106 reflections that satisfied the condition $I > 2\sigma(I)$ were used in the structure determination [$\sigma^2(I) = S + B + 0{\cdot}03I$, where S = scan and B = background].

The intensities were corrected for Lorentz and polarization effects. No absorption correction was applied to these intensities ($\mu_{\text{Mo}} = 0{\cdot}869$ cm^{-1}).

Solution and refinement of the structure

The structure was solved by direct methods with the programs written by Ahmed & Hall (1967). The E values for the 60$\bar{2}$, 12,0,$\bar{4}$ and 18,0,$\bar{6}$ reflections were 6·55, 5·60 and 3·94 respectively, indicating that most of the atoms in the crystals were in planes parallel to the (60$\bar{2}$) crystallographic plane. This condition and the fact that reflections of the type $3l,k,\bar{l}$ with l odd were weak introduced serious difficulties in the phase-determination process. Fortunately, the sign of the 60$\bar{2}$ reflection could be estimated from independent considerations. The two possible signs for the 60$\bar{2}$ reflection correspond to most of the atoms in the cell lying in planes parallel to the (60$\bar{2}$) plane either passing through $x = 0$ or through $x = 1/12$ respectively. For atoms in these planes the fractional coordinates follow the relation $z = 3x + m/4$, with m even and odd respectively. It can be seen that in space group $C2/c$ for atoms contained in planes parallel to the (60$\bar{2}$) plane which pass through $x = 0$ (that is m even, reflection 60$\bar{2}$ positive) the expression for the structure factor becomes zero for reflections of the kind $3lkl$ with l odd. No similar condition exists for atoms contained in the planes parallel to (60$\bar{2}$) which pass through $x = 1/12$ (that is m odd, reflection 60$\bar{2}$ negative). All reflections of the type $3lk\bar{l}$ with l odd had very weak intensities making the negative sign very unlikely for the 60$\bar{2}$ reflection; thus a positive sign was used as input in all starting sets.

One of 16 possible E maps gave enough information to completely solve the structure. After several full-matrix least-squares refinement cycles minimizing $\Sigma\,(|F_o| - |F_c|)^2$ the temperature factors for the C atoms in DMF were found to be abnormally large. A difference map indicated that the DMF molecules were disordered about an axis passing through the O and N atoms. Three atoms were introduced [C(14′), C(15′), C(16′)], and after refinement the population parameters of the two disordered molecules were adjusted to 0·65 and 0·35 in order to have comparable temperature factors in both sets of positions. After several cycles of refinement with anisotropic temperature factors for all atoms, the H atoms were located in a difference Fourier map. For the DMF molecule, positive density for the H atoms was found only in the molecule with the higher population parameters. Two hydrogens [H(10*A*′) and H(10*B*′)] were introduced as alternative positions of H(10*A*) and H(10*B*) and given a population parameter of 0·5. Additional cycles of full-matrix least-squares refinement, varying scale factor, the coefficient for secondary extinction, positional parameters and anisotropic temperature factors for all non-hydrogen atoms with $w = 1/\sigma^2(F)$, resulted in a final R $[=\Sigma\ (|F_o| - |F_c|)/\Sigma\ |F_o|]$ of 0·062 and an R' $\{=[\Sigma\ w(|F_o| - |F_c|)^2/\Sigma\ w|F_o|^2]^{1/2}\}$ of 0·056.* The final positional parameters and isotropic temperature factors are presented in Tables 2 and 3. The calculations were done with the XRAY 70 system (Stewart, Kundell & Baldwin, 1970) as implemented at Brookhaven National Laboratory for a CDC-7600 computer.

Discussion and description of the structure

The molecules of ANFVO are planar with all 16 non-hydrogen atoms in the molecule belonging to the same plane (Table 4). The system of three conjugated double bonds that includes the C(2)–C(3), C(6)–C(7) and C(8)–N(12) bonds has all its single bonds [C(2)–C(6), C(7)–C(8)] in the *s–trans* configuration (Fig. 1) as proposed by Robinson, Bueding & Fisher (1970). The exocyclic angles of the furan ring are similar to those found in other substituted furans (Amzel, Baggio & Isern, 1973; Baggio & Amzel, 1973); that is the angles C(6)–C(2)–O(1) and N(5)–C(5)–O(1) (117·2 and 116·4° respectively) are significantly smaller than C(3)–C(2)–C(6) and C(4)–C(5)–N(5) (133·8 and 131·0° respectively). It is interesting to compare these values with those of the antischistosomal compound 1-(5-nitro-2-thiazolyl)-2-imidazolidinone (niridazole) which is thought to have a mode of action similar to that of ANFVO (Robinson, Bueding & Fisher, 1970). Comparison of space-filling models of both compounds showed that if the nitro-heterocyclic moieties were superimposed, the two N atoms of the imidazolidinone ring of niridazole were aligned with the C=C and an oxadiazole N of ANFVO respectively (Robinson, Bueding & Fisher, 1970). These similarities were considered important in correlating the activities of the two compounds. However, when the X-ray-determined structures are compared the alignment is less precise than that found by model comparison. The most important structural differences in this respect can be attributed to the difference between the exocyclic angles of the two nitro-heterocyclic moieties. The angles S(1)–C(2)–N(6) and S(1)–C(5)–N(12) in niridazole are 122·4 and 122·1° respectively (Puckett & Biffar, 1972) while the equivalent angles in ANFVO are 117·2 and 116·4°.

In spite of the recent interest in 3 and 5 derivatives of 1,2,4-oxadiazole (Repke, Albrecht & Moffatt, 1975; Hynes & Gratz, 1972; Imai & Shimamoto, 1973) no structure has been reported for compounds of this kind. The bond orders within the 1,2,4-oxadiazole ring can be estimated from the values of the interatomic distances. The N(12)–O(11) bond has a length of 1·432 ± 0·006 Å, indicating a very low double-bond character. For example, the length of the N–O bond in the microwave-determined structure of formaldoxime is 1·408 Å, and the estimated value for a N–O single bond is 1·44 Å (Levine, 1963). The double-bond character of the C–N and C–O bonds can be estimated from the observed interatomic distances (Pauling, 1960). The estimated bond orders for the C–N and C–O bonds in the oxadiazole ring based on the structure of ANFVO are: C(8)–N(9), 1·38; C(10)–N(9), 1·83; C(10)–O(11), 1·28; and C(8)–N(12), 1·84. These values seem to in-

Table 4. *Least-squares planes and deviations* (Å) *from the planes*

The equation of the plane is given in direct space. Atoms with an asterisk were used to calculate the planes.

Plane 1: $19{\cdot}4493x - 0{\cdot}2522y - 6{\cdot}4563z = -0{\cdot}0270$

O(1)	0·035*	N(5)	−0·030*
C(2)	0·028*	O(51)	−0·018*
C(3)	−0·021*	O(52)	−0·025*
C(4)	−0·039*	N(10)	−0·030*
C(5)	−0·003*	O(13)	0·203
C(6)	0·031*	C(14)	0·095
C(7)	0·035*	N(15)	−0·068
C(8)	0·028*	C(16)	−0·282
N(9)	0·028*	C(17)	−0·212
C(10)	−0·011*	C(14′)	0·018
O(11)	−0·040*	C(16′)	−0·605
N(12)	−0·013*	C(17′)	0·259

Plane 2: $19{\cdot}0131x - 2{\cdot}0914y - 6{\cdot}4581z = 5{\cdot}6564$

O(13)	0·015*	C(16)	0·022*
C(14)	−0·004*	C(17)	0·009*
N(15)	−0·042*		

Plane 3: $16{\cdot}6710x - 3{\cdot}1877y - 7{\cdot}5103z = 4{\cdot}2358$

O(13)	0·098*	C(16′)	0·078*
C(14′)	−0·095*	C(17′)	−0·014*
N(15)	−0·067*		

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* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32463 (16 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

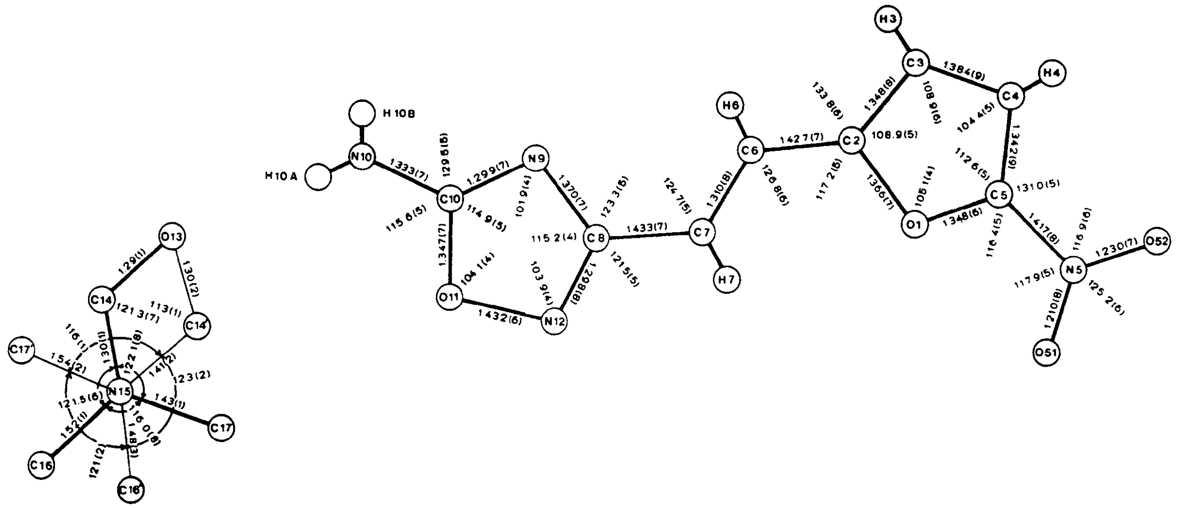


Fig. 1. Bond lengths (Å) and bond angles (°) of nonhydrogen atoms, with their estimated standard deviations in parentheses.

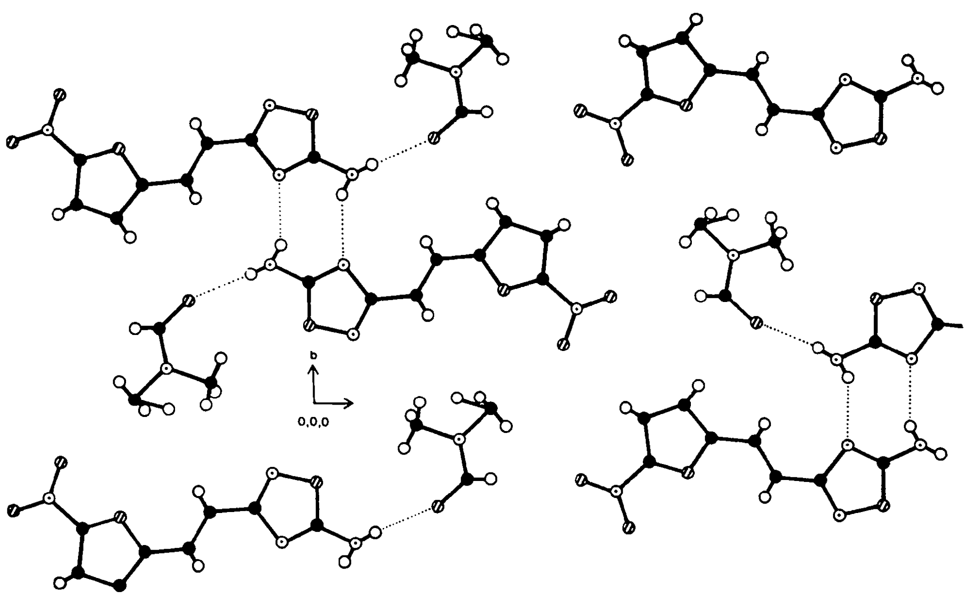
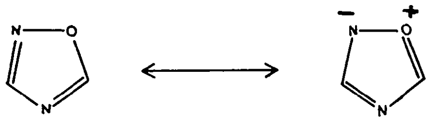


Fig. 2. View of the packing of ANFVO and DMF in a (60$\bar{2}$) plane. The direction of the *b* axis and its perpendicular in the (60$\bar{2}$) plane at the origin (0,0,0) are given. Hydrogen bonding between N(9)$\cdots$H(10*B*)–N(10) and O(13)$\cdots$H(10*A*)–N(10) are designated by the dotted lines. Only the 66% occupancy orientation of the DMF molecule is shown. The atom code is as follows: ● carbon; ▨ oxygen; ⊙ nitrogen; ○ hydrogen.

dicate that two main resonant forms contribute to the structure of 1,2,4-oxadiazole:



The DMF molecules in the ANFVO.DMF crystals are very nearly planar, but their planes are tilted with respect to the plane of the ANFVO molecule by 9 and 17°. The distances and angles observed for the two orientations of DMF agree with previously reported values for co-crystallized DMF (Cobbledick & Small, 1973, 1975; Ito, Kashino & Haisa, 1976). It is interesting to point out that in two of these structures DMF was also found to be disordered, suggesting that DMF could have a general tendency to co-crystallize in more than one orientation.

Packing

All the molecules in the ANFVO.DMF crystals lie approximately in (60$\bar{2}$) planes with an interplanar spacing of 3·24 Å. This plane contains the inversion centers at (0,0,0) and equivalents, and the twofold screw axis ($\frac{1}{4}$,y,$\frac{1}{4}$) and equivalents, but does not contain the inversion centers at ($\frac{1}{4}$,$\frac{1}{4}$,0) or the twofold axes at (0,y,$\frac{1}{4}$). Within a plane, two ANFVO molecules are hydrogen bonded across an inversion center such that N(10) and N(9) of one molecule are bound to N(9) and N(10) of the other. The N(9)–N(10) distance is 2·95 Å and the N(9)$\cdots$H(10*B*)–N(10) angle is 168° (Fig. 2). This pair of hydrogen bonds resembles the geometry of 'base-paired' nucleotides in DNA molecules and may be related to the biological action of ANFVO. It is interesting to point out that the possibility that 1,2,4-oxadiazoles could give this type of hydrogen bonding was predicted and used as the rationale for developing ribofuranosyl derivatives of 1,2,4-oxadiazole (Repke, Albrecht & Moffatt, 1975).

Another hydrogen bond is present between O(13) of DMF and N(10) in ANFVO with a distance of 2·86 Å and an angle of 164°. The rest of the interactions in these planes consist of van der Waals contacts between ANFVO molecules and between ANFVO and DMF molecules (Fig. 2). No close van der Waals contacts between DMF molecules exist within these planes. Interactions between planes are given by the stacking of ANFVO and DMF molecules. An interplanar hydrogen bond probably exists between O(1) and N(10) through H(10*A*).

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