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Structural Comparison of *m*-AMSA ($C_{21}H_{19}N_3O_3S$), a New Clinically Active Antitumor Agent, with the Less-Active Related Compounds 2-MeO-AMSA ($C_{21}H_{19}N_3O_3S$) and AMSA ($C_{20}H_{17}N_3O_2S$)

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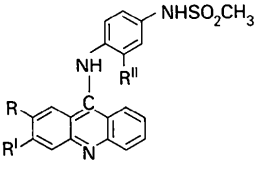
Abstract

The crystal and molecular structures of 4′-(9-acridinylamino)-3′-methoxymethanesulfonanilide hydrochloride (*m*-AMSA.HCl, $C_{21}H_{20}N_3O_3S^+.Cl^-$) and 4′-(2-methoxy-9-acridinylamino)methanesulfonanilide methanesulfonate (2-MeO-AMSA.$MeSO_3H$, $C_{21}H_{20}N_3O_3S^+.CH_3SO_3^-$) were determined by X-ray diffraction and compared to the reported crystal structure for 4′-(9-acridinylamino)methanesulfonanilide hydrochloride (AMSA.HCl, $C_{20}H_{18}N_3O_2S^+.Cl^-$). These three compounds possess strong, negligible, and moderate antitumor activity, respectively. Despite these large differences in antitumor activity, the conformations of these three molecules are quite similar, except for rotations about the S—N and N—C phenyl bonds in the CH_3SO_2NH moieties. The most striking feature of *m*-AMSA is the close proximity of the oxygen of the methoxy group to the acridine ring. The space group and cell parameters of *m*-AMSA are $P2_1/c$ with $a = 10{\cdot}294\,(2)$, $b = 16{\cdot}083\,(5)$, $c = 13{\cdot}525\,(5)$ Å, $\beta = 100{\cdot}1\,(1)°$, and $Z = 4$ and those of 2-MeO-AMSA are $P\bar{1}$ with $a = 10{\cdot}582\,(8)$, $b = 11{\cdot}740\,(2)$, $c = 9{\cdot}785\,(7)$ Å, $\alpha = 81{\cdot}9\,(1)$, $\beta = 110{\cdot}4\,(1)$, $\gamma = 101{\cdot}1\,(1)°$, and $Z = 2$. Final R factors are, respectively, 5·7% for 2623 data with $|F_o| > 0$ and 8·1% for 1495 data with $|F_o| > 5{\cdot}0$.

Introduction

m-AMSA (I), a new antitumor agent presently under phase II clinical evaluation, has demonstrated activity against a variety of human malignancies (Legha *et al.*, 1978; Von Hoff *et al.*, 1978). Although *m*-AMSA has been shown to interact with DNA *in vitro* (Gormley, Sethi & Cysyk, 1978; Waring, 1976) and to produce DNA aberrations *in vivo* (Furlong, Sato, Brown, Chavez & Hurlbert, 1978; Deaven, Oka & Tobey, 1978), the mode of action of *m*-AMSA is as yet undefined. The aminoacridine group allows the molecule to intercalate DNA; however, since inactive substituted aminoacridines intercalate as well as *m*-AMSA (Gormley, Sethi & Cysyk, 1978; Waring, 1976), intercalation alone cannot explain the high activity of *m*-AMSA.



I: R = RI = H, RII = OCH_3
II: R = OCH_3, R = RII = H
III: R = RII = H, RI = NHAc
IV: R = NH_2, RI = RII = H
V: R = RI = RII = H

2-MeO-AMSA (II), which is inactive against L1210 leukemia (Cain, Wilson & Baguley, 1976), differs from *m*-AMSA mainly in the position of substitution of the methoxy group. Since 3-NHAc-AMSA (III) retains most of the activity of *m*-AMSA and 2-NH_2-AMSA (IV) retains much activity (Cain, Wilson & Baguley, 1976), substitution on the acridine ring does not by itself explain the inactivity of 2-MeO-AMSA. In a search for possible conformational reasons for the high activity of *m*-AMSA in comparison to closely related compounds, the structures of *m*-AMSA.HCl and 2-MeO-AMSA.$MeSO_3H$ were determined by X-ray diffraction and compared to AMSA.HCl (Hall, Swann & Waters, 1974) [(V), moderately active (Cain, Wilson & Baguley, 1976)].

Experimental

Orange hollow tubular crystals of *m*-AMSA.HCl (NSC-141549) were grown from MeOH/EtOAc

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Table 1. *Fractional coordinates* ($\times 10^4$) *for m*-AMSA

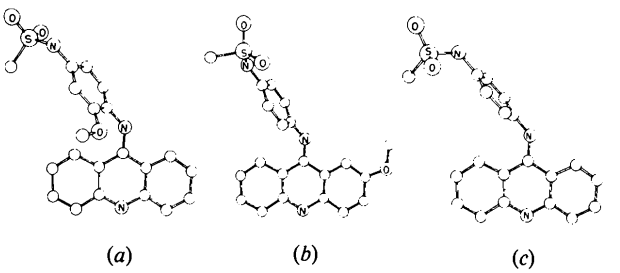
$B_{eq.} = \frac{4}{3}\sum_i \sum_j \beta_{ij} \mathbf{a}_i . \mathbf{a}_j$.

	x	y	z	$B_{eq.}$ (Å^2)
C(1)	688 (5)	797 (3)	7292 (3)	3·4
C(2)	−322 (5)	451 (3)	7690 (4)	4·1
C(3)	−1544 (5)	283 (3)	7068 (4)	3·9
C(4)	−1734 (5)	468 (3)	6073 (3)	3·4
C(4a)	−715 (4)	834 (3)	5654 (3)	2·8
C(5a)	−22 (4)	1397 (3)	4207 (3)	2·8
C(5)	−356 (5)	1603 (3)	3177 (3)	3·6
C(6)	585 (5)	1912 (3)	2683 (3)	3·9
C(7)	1889 (5)	2011 (3)	3180 (3)	3·9
C(8)	2224 (5)	1832 (3)	4175 (3)	3·4
C(8a)	1269 (4)	1543 (3)	4743 (3)	2·7
C(9)	1551 (4)	1358 (2)	5795 (3)	2·6
C(9a)	530 (4)	989 (5)	6252 (3)	2·6
N(10)	−944 (3)	1040 (2)	4662 (3)	2·8
N(11)	2741 (3)	1492 (2)	6385 (3)	2·7
C(12)	3788 (4)	2039 (2)	6239 (3)	2·5
C(13)	3543 (4)	2870 (3)	5970 (3)	2·4
C(14)	4574 (4)	3388 (2)	5851 (3)	2·4
C(15)	5866 (4)	3087 (2)	6043 (3)	2·5
C(16)	6126 (4)	2274 (3)	6351 (3)	3·0
C(17)	5078 (4)	1752 (3)	6441 (3)	2·9
N(18)	6895 (3)	3659 (2)	5951 (3)	3·0
S(19)	7939 (1)	3489 (1)	5195 (1)	2·5
O(20)	8628 (3)	2733 (2)	5479 (3)	3·9
O(21)	8674 (3)	4241 (2)	5201 (3)	4·2
C(22)	7010 (5)	3337 (4)	3991 (4)	5·3
O(23)	2257 (3)	3113 (2)	5812 (2)	2·9
C(24)	1967 (5)	3945 (3)	5445 (4)	4·5
Cl−*	5924 (1)	5420 (1)	6677 (1)	3·4
O(25)†	6548 (4)	4309 (3)	8551 (3)	6·0
C(26)†	5334 (7)	3959 (5)	8669 (6)	7·6

* Counterion.
† Solvent molecule.

solution. X-ray intensity data were collected on a four-circle automatic diffractometer with the θ–2θ scan mode using a scan width of $2{\cdot}0° + 2\theta(\alpha_2) - 2\theta(\alpha_1)$ and a scan speed of 2° min^{-1}. Data were collected with Cu $K\alpha$ radiation to a scattering angle of $2\theta = 126°$ for a total of 2761 reflections. Lorentz and polarization corrections were applied, and normalized structure factors were derived with the aid of a K curve. The space group is $P2_1/c$ with a = 10·294 (2), b = 16·083 (5), c = 13·525 (5) Å, β = 100·1 (1)°, Z = 4, V = 2205·6 Å^3, and a calculated density of 1·39 Mg m^{-3} for four *m*-AMSA.HCl molecules plus four MeOH molecules per unit cell.

The structure of the crystal was solved by the direct method (Karle & Karle, 1966) of phase determination using symbolic addition. Full-matrix least-squares refinement on the 30 non-hydrogen atoms, with weighting based on counting statistics, led to an R factor of 15% for isotropic thermal parameters and 8·5% for anisotropic thermal parameters. Scattering factors used were those listed in *International Tables for X-ray Crystallography* (1962) and the function minimized was $\sum w(|F_o| - |F_c|)^2$. Most of the H atoms were located in a difference map, and coordinates for the remaining H atoms were calculated for ideal positions. The final R factor, where $R = \sum||F_o| - |F_c||/\sum|F_o|$, for all observed data was 6·1%, and 5·7% for 2623 data with $|F_o| > 0$.



(*a*) (*b*) (*c*)

Fig. 1. (*a*) Computer-drawn diagram depicting the conformation of *m*-AMSA. (*b*) Computer-drawn diagram depicting the conformation of 2-MeO-AMSA. (*c*) Computer-drawn diagram depicting the conformation of AMSA (Hall, Swann & Waters, 1974).

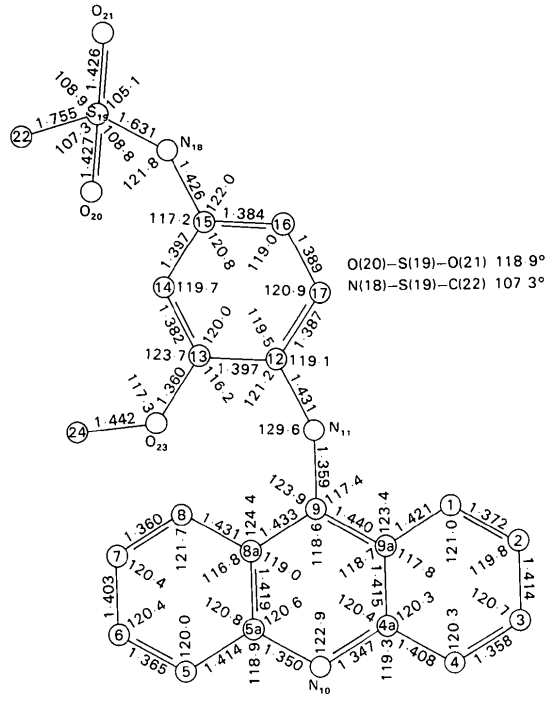
Fractional coordinates are listed in Table 1. The molecule of *m*-AMSA is depicted in Fig. 1(*a*). Bond lengths and bond angles are shown in Fig. 2(*a*).*

Deep red–orange plates of 2-MeO-AMSA.$MeSO_3H$ were obtained from the Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute. X-ray intensity data were collected in the same manner as for *m*-AMSA to a scattering angle of $2\theta = 126°$ for a total of 3290 reflections, many of which were extremely weak. The space group is $P\bar{1}$ with a = 10·582 (8), b = 11·740 (2), c = 9·785 (7) Å, α = 81·9 (1), β = 110·4 (1), γ = 101·1 (1)°, Z = 2, V = 1114·6 Å^3, and a calculated density of 1·46 Mg m^{-3}.

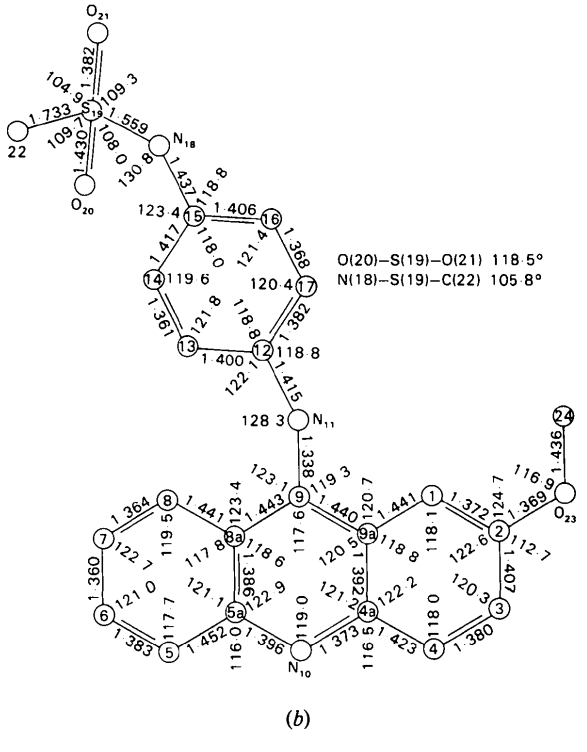
The structure of the crystal was solved by the direct method (Karle & Karle, 1966) of phase determination using symbolic addition. Full-matrix least-squares refinement on the 32 non-hydrogen atoms, with weighting based on counting statistics, led to an R factor of 21% for isotropic thermal parameters and 14% for anisotropic thermal parameters. Coordinates for H atoms for the acridine and phenyl moieties were found in a difference map whereas idealized positions for some of the H atoms in the various methyl groups were used. Inclusion of the H atom positions as constant parameters reduced the final R factor to 8·1% for 1495 reflections with $|F_o| > 5{\cdot}0$.

Fractional coordinates are listed in Table 2. The molecule of 2-MeO-AMSA is depicted in Fig. 1(*b*). Bond lengths and bond angles are shown in Fig. 2(*b*).*

* Lists of structure factors, anisotropic temperature factors, and approximate coordinates for hydrogen atoms have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 35408 (34 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.



(*a*)



(*b*)

Fig. 2. (*a*) Bond lengths (Å) and bond angles (°) for *m*-AMSA. Standard deviations, based on the least-squares fit, are 0·006 Å for bond lengths and 0·5° for bond angles. (*b*) Bond lengths (Å) and bond angles (°) for 2-MeO-AMSA. Standard deviations, based on the least-squares fit, are 0·018 Å for bond lengths and 1·5° for bond angles.

Table 2. *Fractional coordinates* ($\times 10^4$) *for* 2-MeO-AMSA

$B_{eq.} = \frac{4}{3}\sum_i \sum_j \beta_{ij}\, \mathbf{a}_i . \mathbf{a}_j$.

	x	*y*	*z*	$B_{eq.}$ (Å^2)
C(1)	9095 (11)	3539 (10)	3368 (11)	4·6
C(2)	9311 (12)	4031 (12)	2096 (12)	5·2
C(3)	8920 (13)	5108 (13)	1426 (13)	6·2
C(4)	8231 (13)	5690 (11)	2004 (13)	5·9
C(4a)	7993 (11)	5194 (11)	3321 (13)	5·2
C(5)	6305 (12)	6027 (12)	5664 (18)	7·7
C(5a)	7033 (12)	5345 (15)	5151 (16)	5·4
C(6)	6105 (14)	5655 (15)	6989 (18)	7·2
C(7)	6551 (15)	4670 (15)	7766 (15)	7·3
C(8)	7207 (13)	3994 (12)	7295 (12)	6·5
C(8a)	7428 (11)	4312 (12)	5910 (12)	5·1
C(9)	8137 (11)	3665 (11)	5340 (11)	4·3
C(9a)	8403 (11)	4142 (11)	4011 (11)	4·6
N(10)	7271 (9)	5777 (9)	3845 (11)	5·7
N(11)	8560 (9)	2660 (9)	5991 (9)	4·7
C(12)	7960 (12)	1792 (11)	6833 (11)	4·9
C(13)	6558 (12)	1376 (13)	6371 (11)	5·8
C(14)	5996 (12)	503 (13)	7152 (12)	6·6
C(15)	6853 (13)	−49 (13)	8428 (11)	6·2
C(16)	8261 (12)	367 (13)	8869 (11)	6·0
C(17)	8799 (11)	1262 (12)	8082 (12)	5·6
N(18)	6349 (10)	−994 (12)	9299 (10)	7·5
S(19)	5153 (4)	−2023 (3)	8847 (3)	5·5
O(20)	4606 (9)	−1956 (8)	7285 (8)	7·0
O(21)	5584 (13)	−3048 (9)	9580 (10)	10·8
C(22)	3940 (14)	−1791 (16)	9552 (16)	9·9
O(23)	9933 (9)	3551 (8)	1351 (8)	6·3
C(24)	10381 (13)	2453 (13)	1956 (13)	6·2
S*	1936 (3)	1137 (3)	6613 (3)	4·3
O(*A*)*	843 (7)	1817 (7)	5786 (7)	5·5
O(*B*)*	1683 (9)	389 (9)	7755 (9)	7·8
O(*C*)*	3233 (8)	1941 (7)	7102 (9)	6·5
C*	2097 (12)	280 (13)	5379 (12)	6·7

* Counterion.

Results

m-AMSA, AMSA, and 2-MeO-AMSA possess nearly identical conformations as shown by the computer drawings in Fig. 1, except for the CH_3SO_2 moieties. The striking similarity in the conformations of these three molecules demonstrates the subtlety of the difference between activity and inactivity. The most striking feature of *m*-AMSA is the close proximity of the oxygen of the methoxy group to the acridine ring: C(9)···O(23) 2·913, C(8a)···O(23) 3·002, and C(8)···O(23) 3·030 Å. A normal van der Waals value for a C···O separation is ~3·2 Å. There is an apparent attraction of the O atom to the acridine ring. This attraction holds the phenyl ring more firmly in position than in 2-MeO-AMSA where the phenyl ring was found to have some rotational freedom as indicated by high thermal parameters observed for C(13–16), N(18), O(21), and C(22).

Although 9-aminoacridine is a planar molecule (Talacki, Carrell & Glusker, 1974), the least-squares

Table 3. *Deviations of atoms* (Å) *from the least-squares plane through the atoms listed for each plane*

For *m*-AMSA the e.s.d.'s are near 0·008 Å and for 2-MeO-AMSA they are near 0·014 Å.

	Plane *A*			Plane *B*	
	m-AMSA	2-MeO-AMSA		*m*-AMSA	2-MeO-AMSA
C(1)	+0·053	+0·022	C(1)	+0·014	+0·011
C(2)	+0·027	+0·004	C(2)	+0·017	+0·024
C(3)	−0·039	−0·058	C(3)	−0·006	−0·017
C(4)	−0·069	−0·038	C(4)	−0·021	−0·008
C(4a)	−0·026	−0·017	C(4a)	−0·005	−0·019
C(5)	+0·077	+0·050	C(9)	−0·011	−0·013
C(5a)	+0·041	+0·034	C(9a)	−0·017	−0·008
C(6)	+0·036	−0·017	N(10)	+0·028	+0·030
C(7)	−0·073	−0·070		Plane *C*	
C(8)	−0·084	−0·053			
C(8a)	+0·020	+0·046	C(5)	+0·043	+0·032
C(9)	+0·040	+0·041	C(5a)	+0·010	−0·002
C(9a)	+0·006	+0·014	C(6)	+0·033	+0·006
N(10)	−0·009	+0·041	C(7)	−0·040	−0·023
			C(8)	−0·047	−0·021
			C(8a)	+0·025	+0·034
			C(9)	+0·047	+0·011
			N(10)	−0·071	−0·037

planes of the acridine moiety in *m*-AMSA and 2-MeO-AMSA given in Table 3 (plane *A*) reveal a marked degree of non-planarity, with *m*-AMSA possessing the larger deviations. In both of these molecules and in AMSA, the two outer rings of the acridine moiety are twisted such that C(7), C(8), C(3), and C(4) are on one side of the average plane and C(1), C(2), C(5), and C(5a) are on the other side. In *m*-AMSA the ring closest to the methoxy group (plane *C*) is severely distorted from planarity. The close proximity of O(23) to the acridine ring in *m*-AMSA may be producing a favorable charge distribution for exerting the desired biological effects. It would be worth making theoretical calculations, possibly even *ab initio* calculations, to examine the charge distribution.

The bond lengths of *m*-AMSA in the acridine ring are close to those reported for AMSA and are symmetrical about the axis which runs through C(9) and N(10). Ranging from 1·350 to 1·442 Å, the bond lengths show a greater or lesser degree of double-bond character which is predicted from merging the four Kekulé structures of the acridine ring. In 2-MeO-AMSA, the quality of the crystal was poor and consequently the e.s.d.'s for the bond lengths are high; nevertheless there is agreement in bond lengths in the acridine ring with *m*-AMSA to within 1·5 standard deviations [except for C(5a)–N].

The N(11)–C(9) bond in both molecules is about 0·075 Å smaller than the N(11)–C(12) bond. The bond lengths in the methanesulfonamide of *m*-AMSA compare closely to those for AMSA and to other sulfonamides summarized by Karle (1973); however, in 2-MeO-AMSA, where high thermal parameters are associated with atoms N(18), O(21), and C(22), the bond lengths do not compare as well.

In 9-aminoacridine (Talacki, Carrell & Glusker, 1974) all of the bond angles in the acridine ring are close to 120° except for those around atoms C(8a) and C(9a) where angles C(8)C(8a)C(9) and C(9)C(9a)C(1) are expanded to 123°. The C(5a)N(10)C(4a) angle is also expanded to 122·7°. *m*-AMSA follows a very similar pattern with slightly larger bond-angle variations and asymmetric angles about C(9) in order to accommodate the side group. AMSA displays an angle distribution similar to *m*-AMSA. In 2-MeO-AMSA the bond-angle distribution is different from that for *m*-AMSA; however, the angles show a symmetry about the C(9)–N(10) axis despite the asymmetrical pattern of the bond lengths.

The angles about N(11) in *m*-AMSA, AMSA, and 2-MeO-AMSA are very similar ranging from 127·2–129·6°; however, the angles about N(18) vary widely from 121·8 to 125·0 to 130·8°, respectively. The O(20)S(19)O(21) angle in both *m*-AMSA and 2-MeO-AMSA compares well with the other sulfonamides summarized by Karle (1973).

Torsional angles are listed in Table 4 for *m*-AMSA, AMSA, and 2-MeO-AMSA. The twist of the phenyl ring compared to the acridine ring is approximately the same in all three molecules. The orientation of the methanesulfonamide groups, however, is quite different in all three molecules. The values of the torsional angles as well as Fig. 1(*a–c*), show that rotations have occurred about both the N(18)–S(19) bonds and the N(18)–C(15) bonds. In *m*-AMSA and AMSA, O(21) is *trans* with respect to C(15), while in 2-MeO-AMSA O(20) is *cis* with respect to C(15). The CH_3SO_2N– group has considerable conformational flexibility and is readily influenced by packing forces.

The packing diagram of *m*-AMSA is shown in Fig. 3(*a*). All three N atoms are hydrogen bonded to either the O atom of the methanol molecule or to the Cl^- ion. The Cl^- ion is the acceptor for hydrogen bonds both from N(11) [N(11)···Cl 3·248 Å] and from N(18) [N(18)···Cl 3·215 Å]. The O atom of the methanol molecule accepts a hydrogen bond from N(10) [N(10)···O(25) 2·811 Å] and donates a hydrogen bond to the Cl^- ion [O(25)···Cl 3·088 Å]. In the salt formation, the additional proton was bound to N(10), clearly visible in a difference map.

2-MeO-AMSA packs in a much different manner from *m*-AMSA as shown in Fig. 3(*b*). Each O atom of the methanesulfonate ion accepts a hydrogen bond from a different N atom in three different molecules of

Table 4. *Torsional angles*

The e.s.d.'s for the torsional angles are of the order of 1° for *m*-AMSA and up to 3° for 2-MeO-AMSA.

	m-AMSA	AMSA	2-MeO-AMSA
C(8a)C(9)N(11)C(12)	21°	31°	28°
C(9)N(11)C(12)C(13)	48	47	55
C(14)C(15)N(18)S(19)	−123	36	−50
C(15)N(18)S(19)C(22)	56	−113	−63
C(15)N(18)S(19)O(20)	−60	4	51
C(15)N(18)S(19)O(21)	172	134	−178

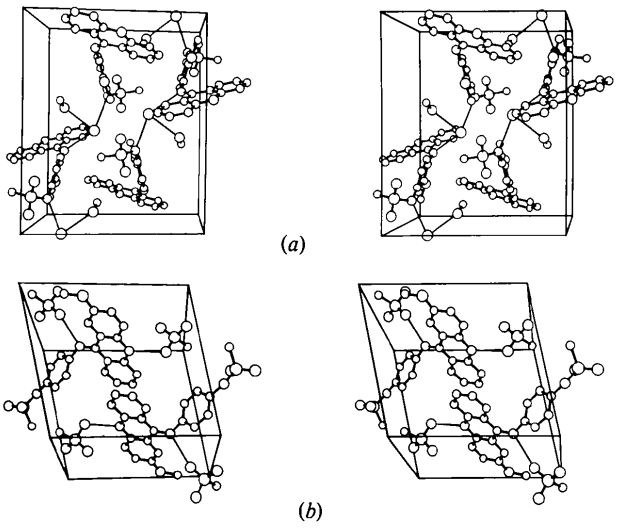


Fig. 3. (*a*) Stereodiagram of the packing of *m*-AMSA.HCl.MeOH. Hydrogen bonds are indicated by thin lines, and the directions of the axes are *b*↑, *c*→, and *a* into the page. (*b*) Stereodiagram of the packing of 2-MeO-AMSA.$MeSO_3H$. Hydrogen bonds are indicated by thin lines, and the directions of the axes are *a*↑, *b*→, and *c* into the page.

2-MeO-AMSA [N(10)···O(*C*) 2·798, N(11)···O(*A*) 2·858, N(18)···O(*B*) 2·995 Å]. Again, the proton of the salt was found to be on N(10), clearly visible in difference maps. In addition to hydrogen bonds, the molecules are also attracted by stacking forces between neighboring molecules as shown by the overlapping of the two end rings in the acridine moiety. This stacking occurs in pairs of acridine rings about one center of symmetry. In alternating molecules *A* (*x*,*y*,*z*) and *B* (1 − *x*, 1 − *y*, 1 − *z*) close proximity is exhibited by: $C(5)^A\cdots C(5)^B$ 3·310, $C(6)^A\cdots C(5a)^B$ 3·336, and $C(5)^A\cdots C(6)^B$ 3·468 Å. These values are characteristic of those found between stacked rings in 9-aminoacridine (Talacki, Carrell & Glusker, 1974) and in charge-transfer compounds (Karle, Bultman & Jurd, 1976). They are also similar to the stacking of bases in DNA which are separated by 3·4 Å (Lehninger, 1970).

Structure–activity relationships

The results of the structure analysis of the molecules studied thus far do not provide an obvious one-to-one correspondence of the molecular structures in the crystals and the clinical activities of these compounds. Among the factors that contribute to chemotherapeutic action could be (1) intercalation, (2) lack of conjugation and planarity in the acridine ring, and (3) the charge distribution in the molecules. In the crystalline state, 2-MeO-AMSA, the compound with no antitumor activity, exhibits stacking of the acridine moieties even though the methoxy group on the acridine moiety would be expected to hinder stacking, while the very active *m*-AMSA does not have such strong attractions between acridine moieties in the crystalline state. These observations are in agreement with the earlier statement that intercalation with DNA occurs with both active and inactive substituted acridines and by itself does not explain cytotoxic activity. Hempel, Hall, Dauter, Bogucka-Ledochowska & Konitz (1979) state that lack of conjugation, and thus lack of planarity, in the acridine moiety is a requirement for biological activity. This may be a necessary condition but it obviously is not a sufficient one since 2-MeO-AMSA possesses it in the crystal and is ineffective. A subtle difference in charge distribution caused, for example, by the proximity of the methoxy group and the increased distortion of the ring from planarity may be an element in contributing to the activity of *m*-AMSA. These similarities in structure, yet vast differences in selective toxicity, may also be indicative of either the subtlety of the receptor for chemotherapeutic action or the need for metabolic activation.

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