Nucleic Acid Binding Drugs. Part 12.† *X*-Ray Crystallographic and Conformational Studies on the Anti-cancer Drug *m*-AMSA and its Mesyl Derivative

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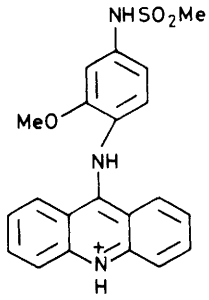
The crystal structures of the anti-tumour agent *m*-AMSA [4'-(acridin-9-ylamino)-3'-methoxymethanesulphonanilide] and its mesyl derivative, as free bases, have been determined. They show a very distinct orientation of the substituted phenyl ring with respect to the acridine group, compared with *m*-AMSA hydrochloride (J. M. Karle, R. L. Cysyk, and I. L. Karle, *Acta Crystallogr.*, 1980, **B36**, 3012). This has been rationalised in terms of intra- and inter-molecular interactions, the latter with ionic species in the salt crystal. Conformational calculations are also reported on these compounds, which indicate that they have interconvertible conformational flexibility.

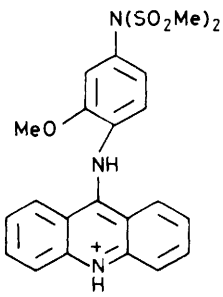
The anti-cancer drug *m*-AMSA [(**I**); 4'-(acridin-9-ylamino)-3'-methoxymethanesulphonanilide] has been intensively studied in terms of structure–activity relationships.[1–5] Small structural differences among the many hundred derivatives examined can lead to very wide variations in biological activity and potency, with the lipophilic–hydrophobic balance, and electronic and steric factors being known to play important roles.[6] It has been shown that, for optimal activity, lipophilicity should be close to that of the parent *m*-AMSA. A strong electron-donating substituent at the 1-position of the anilino ring is required.

In general the structure–activity data support the hypothesis that DNA is the biological target for *m*-AMSA, with DNA-binding ability correlating with anti-cancer activity for many observations.[7–9] There is considerable evidence that the acridine ring of the drug is intercalated between adjacent base pairs.[10–12] It has been suggested[5] that the anilino ring lies in the DNA minor groove, and thus steric inhibition would prevent derivatives with substituents at other than the 1'- and 4'-position from interacting. It remains true, however, that DNA-binding does not by itself explain the exceptional antineoplastic efficiency of *m*-AMSA compared with many other acridines; recent suggestions of specific ternary complexes between drug, DNA, and the enzyme DNA topoisomerase may be relevant to this.[13]

The continuing search for active analogues of *m*-AMSA has led us to the synthesis of its mesyl derivative (**II**), in order to ascertain the effects of increasing the electron-donating properties at the 1'-position. Synthetic and biological studies on this compound will be reported elsewhere. The present study was designed to examine the detailed structural aspects of this compound, which we compare with those of the parent drug, as free base and as its hydrochloride salt. We also report on conformational studies on all three compounds.



(I)



(II)

Experimental

Crystals of both *m*-AMSA and mesyl-*m*-AMSA were obtained by recrystallisation from ethanol. Preliminary unit-cell and space-group data were obtained on Weissenberg cameras. Accurate cell dimensions were obtained by least-squares refinement of 25 θ values measured on an Enraf-Nonius CAD4 diffractometer. Intensity data were collected on the diffractometer using an $\omega - 2\theta$ scan technique, with Ni-filtered Cu-K_α radiation (λ = 1.541 78 Å).

Crystal Data.—m-*AMSA*. $C_{21}H_{19}N_3O_3S$, M = 393.47. Monoclinic a = 11.179(2), b = 21.117(3), c = 8.795(1) Å, β = 112.27(1)°, U = 1 921 Å^3, space group $P2_1/c$, Z = 4, D_c = 1.36 g m^{-3}, $F(000)$ = 824, μ(Cu-K_α) = 16.88 cm^{-1}.

An orange-coloured hollow prismatic crystal of dimensions 0.07 × 0.17 × 0.34 mm was used for the structure analysis. Intensity data were collected in the range $1.5 < \theta < 60°$ ($0 < h < 9$; $0 < k < 20$; $-12 < l < 12$). The intensities of

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† Part 11, R. Kuroda and M. Sainsbury *J. Chem. Soc., Perkin Trans. 2*, 1984, 1751,

Table 1. Fractional co-ordinates and average thermal parameters for *m*-AMSA. Estimated standard deviations are in parentheses

Atom	*x*	*y*	*z*	*B*/Å²
C(1)	0.103 1(3)	0.186 3(2)	0.709 1(4)	3.99(7)
C(2)	0.039 8(3)	0.223 8(2)	0.776 1(4)	5.28(9)
C(3)	−0.097 2(3)	0.224 2(2)	0.712 5(4)	5.73(9)
C(4)	−0.164 6(3)	0.186 1(2)	0.586 3(4)	4.37(7)
C(4A)	−0.102 4(2)	0.144 3(1)	0.515 5(3)	2.88(6)
N(10)	−0.176 5(2)	0.106 9(1)	0.390 3(2)	2.95(5)
C(5A)	−0.115 9(2)	0.066 3(1)	0.324 7(3)	2.76(5)
C(5)	−0.193 2(2)	0.024 4(2)	0.200 3(3)	3.61(7)
C(6)	−0.138 6(3)	−0.018 9(2)	0.133 1(4)	4.22(7)
C(7)	−0.003 1(3)	−0.024 8(1)	0.189 3(3)	3.87(7)
C(8)	0.073 9(2)	0.013 9(1)	0.307 7(3)	3.35(6)
C(8A)	0.021 4(2)	0.061 9(1)	0.378 7(3)	2.68(5)
C(9)	0.097 7(2)	0.103 0(3)	0.504 5(3)	2.72(5)
C(9A)	0.035 4(2)	0.144 1(1)	0.577 2(3)	2.79(6)
N(11)	0.231 5(2)	0.100 9(1)	0.561 3(3)	3.63(5)
C(12)	0.305 5(2)	0.106 1(1)	0.462 9(3)	2.77(6)
C(17)	0.257 5(2)	0.131 3(1)	0.306 0(3)	3.13(6)
C(16)	0.334 7(2)	0.137 9(1)	0.215 2(3)	2.97(6)
C(15)	0.463 2(2)	0.120 4(1)	0.283 5(3)	2.53(5)
C(14)	0.513 3(2)	0.094 5(1)	0.441 1(3)	2.63(5)
C(13)	0.434 6(2)	0.086 8(1)	0.528 9(3)	2.55(5)
O(23)	0.473 5(2)	0.061 8(1)	0.682 1(2)	3.78(4)
N(18)	0.549 7(2)	0.127 1(1)	0.200 1(2)	2.97(5)
S(19)	0.529 92(6)	0.177 21(4)	0.053 63(7)	3.02(1)
O(21)	0.410 4(2)	0.164 3(1)	−0.078 2(2)	4.73(5)
O(20)	0.646 0(2)	0.175 0(1)	0.022 0(2)	4.13(5)
C(22)	0.516 8(3)	0.252 0(2)	0.131 6(4)	5.02(8)
C(24)	0.607 9(3)	0.049 2(2)	0.769 1(4)	4.28(7)

three reflections were monitored during the data collection; no crystal decay was apparent. A total of 2 923 unique reflections were measured, of which 2 243 had $I > 2\sigma(I)$.

The structure was solved by direct methods, and refined by full-matrix least-squares techniques. The positions of the majority of hydrogen atoms were found in difference Fourier syntheses; others were generated using standard geometric considerations. All hydrogen positional and thermal parameters were kept fixed during the refinement. The final R value was 0.041 and weighted R_w was 0.051, with a maximum shift/error of 0.12. The weighting scheme used was $w = 1/[\sigma^2(I) + (0.03I)^2]^{1/2}$.

Mesyl-m-AMSA. [4′-(Acridin-9-ylamino)-*N*,*N*-bis-methanesulphonyl-3′-methoxyaniline], $C_{22}H_{21}N_3O_5S_2$, $M = 471$. Triclinic, $a = 7.862(1)$, $b = 9.875(1)$, $c = 15.382(2)$ Å, $\alpha = 70.22(1)$, $\beta = 78.94(1)$, $\gamma = 77.79(1)°$, $U = 1\,087.7$ Å³, space group $P\bar{1}$ confirmed by structure analysis, $Z = 2$, $D_c = 1.39$ g cm⁻³, $F(000) = 460$, $\mu(\text{Cu-}K_\alpha) = 24.62$ cm⁻¹.

An orange-coloured prismatic needle-shaped crystal of dimensions 0.04 × 0.07 × 0.31 mm was used for data collection. Intensities for $1.5 < \theta < 65°$ were measured in the ranges $0 < h < 9$; $-11 < k < 11$; $-18 < l < 18$. A total of 3 684 unique reflections were obtained, of which 2 838 had $I > 2\sigma(I)$. Structure determination and refinement followed the same procedures as for *m*-AMSA. The final R value was 0.039, and weighted R_w was 0.042, with a maximum shift/error of 0.13.

Final atom co-ordinates are given in Tables 1 and 2. Thermal parameters as Supplementary Publication No. SUP 561525 and structure-factor listings are available from the editorial office.

All calculations were performed on a PDP 11/34A computer using the Enraf-Nonius SDP package.

Conformational Calculations.—Energy differences between conformers related by rotation around single bonds were calculated using approximation (1), where $E_{\text{non-bonded}}$ is given by

Table 2. Fractional co-ordinates and average thermal parameters for mesyl-*m*-AMSA. Estimated standard deviations are in parentheses

Atom	*x*	*y*	*z*	*B*/Å²
S(20)	0.071 75(8)	0.256 45(6)	0.474 44(4)	3.04(1)
S(24)	0.414 43(9)	0.347 92(7)	0.405 65(4)	3.36(1)
O(21)	0.005 2(3)	0.403 3(2)	0.424 9(1)	4.75(5)
O(22)	−0.015 2(2)	0.189 3(2)	0.563 6(1)	4.03(4)
C(25)	0.344 3(4)	0.530 6(3)	0.401 5(2)	4.57(7)
O(26)	0.584 9(2)	0.300 0(2)	0.435 1(1)	4.96(5)
N(10)	0.743 7(3)	−0.352 2(2)	0.995 5(1)	3.47(5)
N(11)	0.452 0(3)	0.053 6(2)	0.855 8(1)	3.53(5)
N(19)	0.279 7(3)	0.250 6(2)	0.491 1(1)	2.77(4)
C(1)	0.282 9(4)	−0.158 6(3)	1.008 6(2)	4.12(7)
C(2)	0.209 7(4)	−0.260 8(4)	1.080 6(2)	4.99(8)
C(3)	0.313 1(4)	−0.394 1(4)	1.124 1(2)	5.18(8)
C(4)	0.486 1(4)	−0.421 8(3)	1.095 8(2)	4.54(7)
C(4A)	0.570 9(3)	−0.317 9(3)	1.020 8(2)	3.29(6)
C(5)	1.005 9(4)	−0.288 2(3)	0.898 4(2)	3.74(6)
C(5A)	0.821 7(3)	−0.253 1(2)	0.923 9(2)	3.12(5)
C(6)	1.091 9(4)	−0.192 3(3)	0.828 6(2)	4.18(7)
C(7)	1.003 4(4)	−0.054 1(3)	0.780 0(2)	4.03(6)
C(8A)	0.729 1(3)	−0.114 3(3)	0.873 8(2)	3.00(5)
C(8)	0.827 5(4)	−0.016 9(3)	0.801 9(2)	3.68(6)
C(9A)	0.465 2(3)	−0.182 1(3)	0.975 6(2)	3.23(5)
C(9)	0.549 0(3)	−0.081 9(2)	0.901 0(1)	2.99(5)
C(12)	0.412 2(3)	0.095 9(2)	0.765 4(1)	2.67(5)
C(13)	0.309 6(3)	0.234 2(2)	0.732 6(1)	2.59(5)
C(14)	0.266 4(3)	0.285 2(2)	0.642 9(2)	2.61(5)
C(15)	0.323 9(3)	0.197 4(2)	0.585 4(1)	2.60(5)
C(16)	0.420 3(3)	0.060 5(2)	0.617 7(2)	3.05(5)
C(17)	0.464 5(3)	0.010 2(2)	0.707 3(2)	2.99(5)
O(18)	0.259 6(3)	0.306 4(2)	0.797 1(1)	3.95(4)
C(23)	0.089 5(4)	0.148 0(3)	0.402 4(2)	5.41(8)
O(27)	0.386 4(3)	0.331 6(2)	0.321 4(1)	4.64(5)
C(18)	0.157 5(4)	0.448 5(3)	0.771 1(2)	4.16(7)

Table 3. Selected torsion angles (°), with estimated standard deviations in parentheses

	m-AMSA base	*m*-AMSA·HCl[15]	Mesyl-*m*-AMSA
C(8A)–C(9)–N(11)–C(12)	54.2(3)	21(1)	70.5(3)
C(9)–N(11)–C(12)–C(13)	−163.5(3)	48(1)	178.3(3)
N(11)–C(12)–C(13)–O(23)[a]	3.0(3)	−3(1)	−1.6(2)
C(8A)–C(9)–N(11)–H(11)	−145(3)	−149(1)	−126 (2)
H(11)–N(11)–C(12)–C(13)	34(3)	−147(1)	14 (2)

[a] O(23) is labelled as O(18) in mesyl-*m*-AMSA.

equation (2) with parameters A and B taken from reference 14, and were chosen so as to compensate for bond length and angle deformations without having explicitly to vary these parameters, and E_{torsion} is given by equation (3).

$$E_{\text{total}} = E_{\text{non-bonded}} + E_{\text{torsion}} \quad (1)$$

$$E_{\text{non-bonded}} = \frac{A}{r^6} - \frac{B}{r^{12}} \quad (2)$$

$$E_{\text{torsion}} = E_o(1 + \cos n\psi) \quad (3)$$

Torsion barriers E_o about C(9)–N(11) and N(11)–C(12) were taken as 0.5 kcal mol⁻¹.

Results and Discussion

Molecular Structures.—Figures 1 and 2 show the molecular structures of *m*-AMSA and mesyl-*m*-AMSA, as determined in

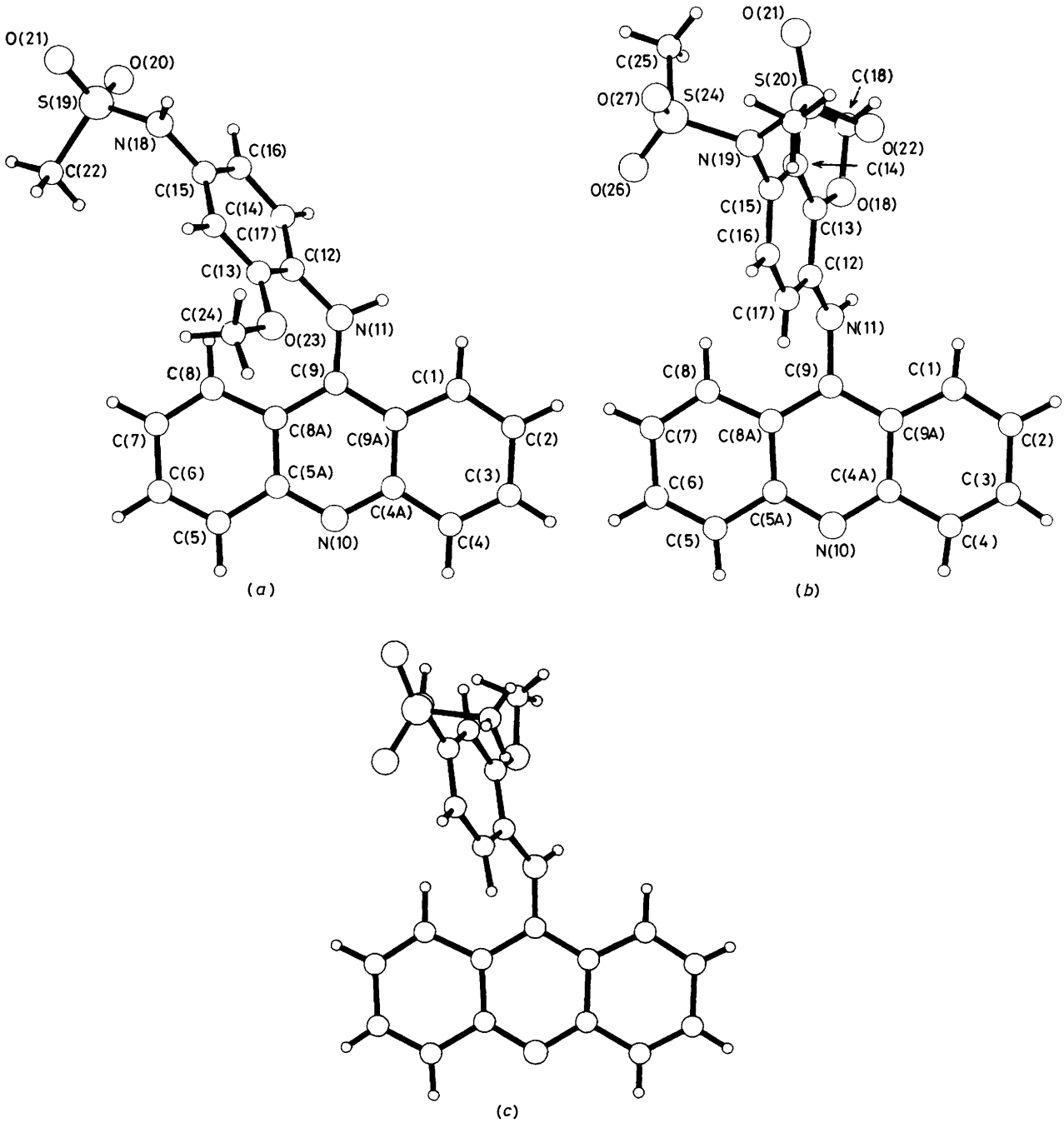

Figure 1. Computer-drawn representations of the molecular structure of (*a*) *m*-AMSA free base; (*b*) mesyl-*m*-AMSA free base; and (*c*) *m*-AMSA·HCl projected onto the mean plane of the acridine group

this study. Figure 3 shows the structure of *m*-AMSA in its hydrochloride salt, as found in an earlier analysis.[15] Comparison of these three structures reveals several major differences between the free bases *m*-AMSA and its mesyl derivative on the one hand, and the protonated salt on the other. It is readily apparent that in the salt, the methoxy group substituent on the phenyl ring is in close proximity to the acridine rings [Figures 1(*c*) and 2(*c*)], and is *trans* to the hydrogen atom on N(11). An attractive interaction between C(8) and O(23) has been suggested to account for their close distance of 3.03 Å.[15] This conformational difference between salt and free-base structure is detailed in Table 3, which shows that there are large differences in the torsion angles around the bonds C(9)–N(11) and N(11)–C(12) that connect the phenyl and acridine rings. In order to understand the nature and relative importance of these conformational differences, two-dimensional energy plots were computed, at 10° intervals of rotation about the two bonds forming the linkage between the ring systems. The plots for all three structures are very similar; Figure 3 shows that for mesyl-*m*-AMSA six low-energy regions are apparent; the crystallographically observed torsion angles are unsurprisingly in one of these, as is the conformation found for *m*-AMSA hydrochloride. Neither are at the global minimum, which for all three structures is at −50°, −50° for the torsion angles around the C(9)–N(11) and N(11)–C(12) bonds. The differences in energy between the global minimum and

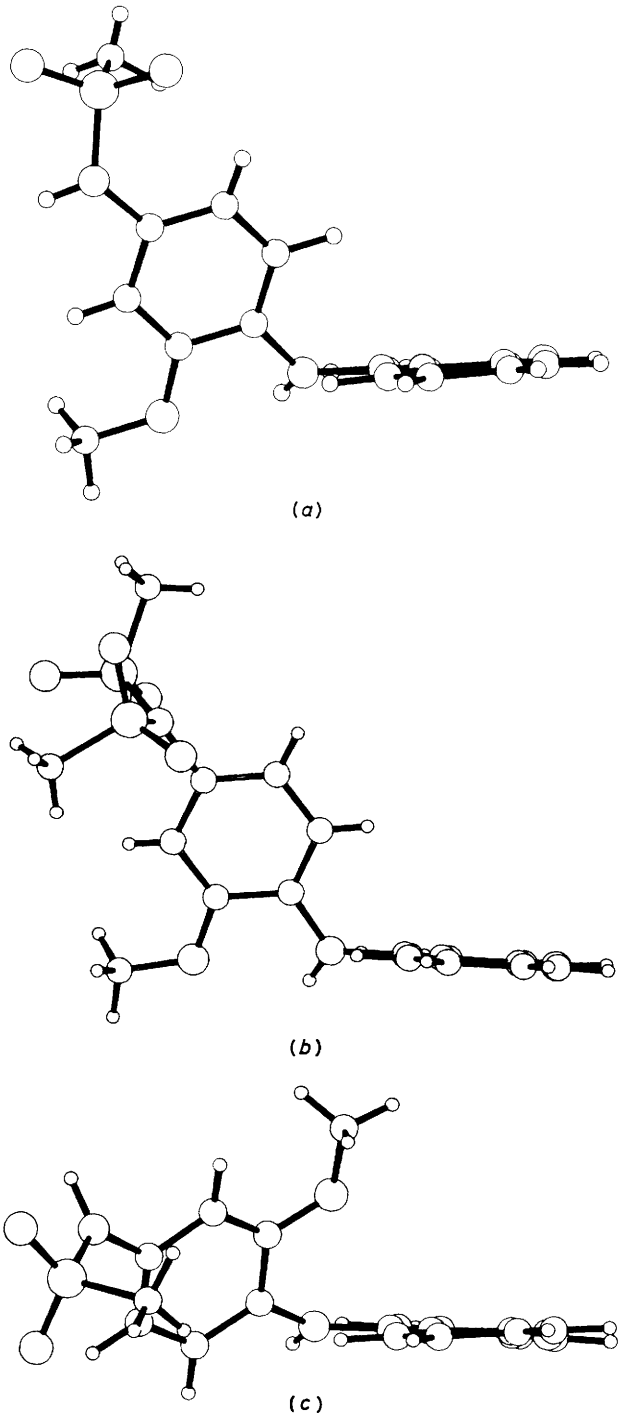

Figure 2. Computer-drawn representations of (*a*) *m*-AMSA free base; (*b*) mesyl-*m*-AMSA free base; and (*c*) *m*-AMSA·HCl projected along the long axis of the acridine group

these other minima is small, between 2 and 4 kcal mol^{-1}, in favour of the free base, and the heights of the barriers between them are no more than 10—12 kcal mol^{-1}. This implies that the various low-energy conformations are all relatively readily interconvertible, and that the observed structures represent particular frozen-out states probably on account of environmental reasons dictated by the pattern of intermolecular interactions in the crystal.

The conformation found in the hydrochloride salt of *m*-

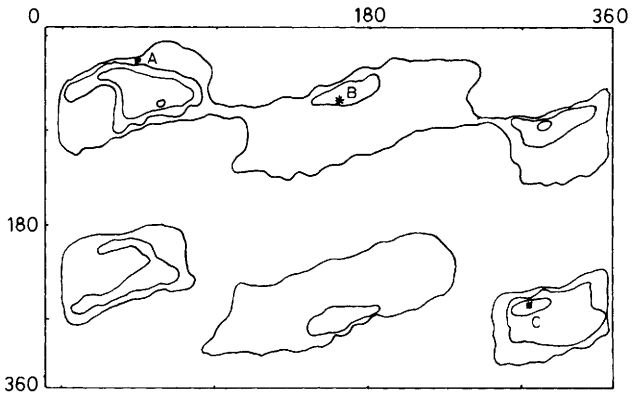

Figure 3. Energy-contour plot for mesyl-*m*-AMSA. Torsion angle C(8A)–C(9)–(11)–C(12) is varied along the vertical axis, and C(9)–N(11)–C(12)–C(13) along the horizontal. Contours have been drawn at intervals of 2 kcal mol^{-1}. Points A and B mark crystallographically observed conformations, and point C indicates the global minimum

Table 4. Selected bond lengths (Å), with estimated standard deviations in parentheses

	m-AMSA base	*m*-AMSA·HCl[15]	Mesyl-*m*-AMSA
C(1)–C(2)	1.338(3)	1.372(6)	1.353(4)
C(1)–C(9A)	1.431(3)	1.421(6)	1.421(4)
C(2)–C(3)	1.418(3)	1.414(6)	1.410(4)
C(3)–C(4)	1.347(3)	1.358(6)	1.343(4)
C(4)–C(4A)	1.407(3)	1.408(6)	1.426(4)
C(4A)–N(10)	1.353(2)	1.347(6)	1.341(3)
C(4A)–C(9A)	1.426(3)	1.415(6)	1.441(4)
C(5)–C(5A)	1.419(3)	1.414(6)	1.423(4)
C(5)–C(6)	1.353(3)	1.365(6)	1.349(4)
C(5A)–C(8A)	1.428(2)	1.419(6)	1.439(3)
C(6)–C(7)	1.410(3)	1.403(6)	1.414(4)
C(7)–C(8)	1.346(3)	1.360(6)	1.358(4)
C(8)–C(8A)	1.427(3)	1.431(6)	1.422(4)
C(8A)–C(9)	1.411(3)	1.433(6)	1.396(4)
C(9)–N(11)	1.387(2)	1.359(6)	1.408(3)
N(11)–C(12)	1.409(2)	1.431(6)	1.387(3)
C(12)–C(13)	1.397(2)	1.397(6)	1.406(3)
C(13)–O(23)[a]	1.356(2)	1.360(6)	1.362(3)
C(14)–N(18)[b]	1.426(2)	1.426(6)	1.448(3)

[a] O(23) is labelled as O(18) in mesyl-*m*-AMSA. [b] N(18) is labelled as N(19) in mesyl-*m*-AMSA.

AMSA has also been observed in its 2-methoxy[15] and demethoxy[16] analogues, as methanesulphonate and hydrochloride salts, respectively. In both *m*-AMSA and 2-methoxy-*m*-AMSA salts, atom N(11) hydrogen-bonds to a chloride ion, and thus acts as a proton donor. By contrast, the two free-base structures reported here have the hydrogen atom attached to N(11) in a *cis* arrangement with respect to the methoxy group on the phenyl ring. The distance between H(11) and the methoxy oxygen atom is 2.344 Å in the *m*-AMSA base and 2.212 Å in the mesyl derivative, whereas it is 3.55 Å in *m*-AMSA hydrochloride.[15] These short distances, together with the implied directionality of the oxygen atom lone pairs pointing towards H(11) [Figure 1(*a*) and (*b*)], suggest that there is an intramolecular hydrogen bond between N(11) and the methoxy oxygen atom, in both free-base structures. Further evidence for this interaction is provided by the near coplanarity of N(11), H(11), the phenyl group, and methoxy oxygen atoms, and thus

Table 5. Selected bond angles (°) with estimated standard deviations in parentheses

	m-AMSA base	*m*-AMSA·HCl[15]	Mesyl-*m*-AMSA
C(8A)–C(9)–C(9A)	118.7(2)	118.6(5)	120.0(2)
C(8A)–C(9)–N(11)	120.7(2)	123.9(5)	120.3(2)
C(9A)–C(9)–N(11)	120.5(2)	117.4(5)	119.7(2)
C(5A)–N(10)–C(4A)	117.8(2)	122.9(5)	117.7(2)
C(9)–N(11)–C(12)	125.4(2)	129.6(5)	125.0(2)
N(11)–C(12)–C(13)	118.4(2)	121.2(5)	117.1(2)

the torsion angle about the N(11)–C(12) bond has a roughly 180° value. The existence of this hydrogen bond necessarily forces the torsion angle about the C(9)–N(11) bond to values some 30—50° higher than in the ionic structures, since otherwise there would be unacceptably close contacts between the hydrogen atoms on C(8) and C(17). The region in the energy plot (Figure 3) with torsion angles around the C(9)–N(11) and N(11)–C(12) bonds having values of 20 and 180°, respectively, (*i.e.*, with values corresponding to salt and free base, respectively), has an energy at least 50 kcal mol^{-1} above the observed conformations. It is notable that because of this interplay of hydrogen bonding and steric hindrance, hydrogen atom H(11) deviates markedly from the least-squares plane of the acridine ring. The hydrochloric and methanesulphonate salts of AMSA do not have the intramolecular hydrogen bond because H(11) is either not available because of involvement in intermolecular hydrogen-bonding as in *m*-AMSA, or because the methoxy group is absent.

These conformational differences have also resulted in differences in bonding geometry between the structures (Tables 4 and 5). The bond length of C(9)–N(11) is significantly shorter (by up to 0.05 Å) and more double-bond in character in the salts of *m*-AMSA[15] and AMSA[16] (1.353 Å). There is a clear correlation between the degree of non-coplanarity of H(11) with the acridine ring, and the C(9)–N(11) bond length. Conversely, bond N(11)–C(12) is significantly shorter in the free-base structures, because of enhanced conjugation between the N(11)–H(11) and N(11)–C(12) bonds, and the phenyl ring. There are numerous other smaller (though sometimes apparently significant) differences between the various structures, especially within the acridine chromophore. Subtle differences in coplanarity of one six-membered ring with respect to another are discernible, but are not thought to reflect meaningful or intrinsic differences. Rather, they are probably the result of the relatively facile deformability of the acridine system, which has been documented in earlier studies from this laboratory.[17]

Acknowledgements

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