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Structure of 8-Chloro-2-[2-(diethylammonio)ethyl]-2*H*-[1]benzothiopyrano-[4,3,2-*cd*]indazole-5-methanol Monomethanesulfonate. An Antischistosomal Analog of Hycanthone*†

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Abstract

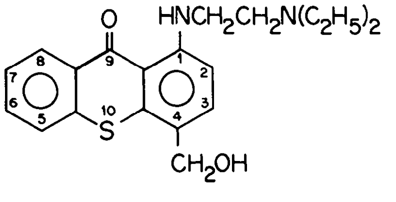
The crystal and molecular structure of the title compound, $C_{20}H_{23}ClN_3OS^+ \cdot CH_3SO_3^-$, has been determined by X-ray analysis of three-dimensional counter data up to a 2θ value of 125° with Cu $K\alpha$ radiation. The crystals are triclinic, space group $P\bar{1}$, with $Z = 2$ and cell parameters $a = 8{\cdot}7282$ (8), $b = 11{\cdot}444$ (2), $c = 12{\cdot}338$ (2) Å, $\alpha = 111{\cdot}71$ (1), $\beta = 94{\cdot}28$ (1) and $\gamma = 99{\cdot}68$ (1)°. The structure, solved by the standard heavy-atom technique, was refined by the full-matrix least-squares method to $R(F) = 0{\cdot}049$ based on 2813 reflections (corrected for absorption) with $F_o^2 \geq 3\sigma(F_o^2)$. All H atoms were located, but some were not refined. E.s.d.'s of bond lengths and bond angles involving only C, N and O atoms are of the order of 0·005 Å and 0·3°. The molecular parameters are all within the range of expected values. The whole fused four-ring system can be regarded as nearly planar. The diethylaminoethyl side chain, protonated at N, has a conformation distinctly different from that in the crystal of hycanthone methanesulfonate, thus demonstrating the conformational lability of this portion of the molecule. The proton attached to the terminal N and the hydroxyl H atoms are hydrogen bonded to two different O atoms of two neighboring methanesulfonate anions. The methanesulfonate anion, which has an expected C_{3v} symmetry, in turn furnishes two of its three O atoms as acceptors in the network of interionic hydrogen bonds with two neighboring cations of the title compound, thus forming an infinite hydrogen-bonded chain in the *b* direction.

Introduction

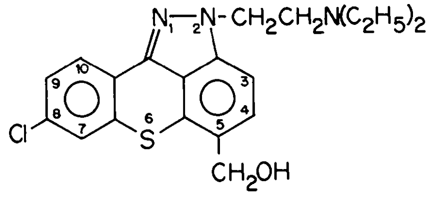
Hycanthone (I) is a drug widely used in Brazil, Africa and the Middle East for the treatment of schistosomiasis, a parasitic disease (Hulbert, Bueding & Hartman, 1974), and its structure has recently been determined by X-ray diffraction in our laboratory (Wei & Einstein, 1978). The structure of a closely related drug, lucanthone (or Miracil D), of which hycanthone is the active metabolite, had previously been determined (Neidle, 1976).

It has been postulated that the biological activities of these drugs are due to intercalation of the drug molecule with DNA. The coplanarity of the thioxanthene ring system is perhaps essential for providing strong hydrophobic interaction with adjacent base pairs, and the terminal N has been thought to play an important stabilizing role in that it could extend to the periphery of the DNA helix to interact with phosphate residues (for reviews, see Weinstein & Hirschberg, 1971; Hirschberg, 1975).

Although hycanthone is a clinically useful drug, it has not been regarded as fully safe because of its possible genetic hazard (Hartman, Levine, Hartman & Berger, 1971). In a search for safer drugs of this family, Bueding (1975) reported that alterations of the thioxanthene fragment of hycanthone to benzothiopyranoindazole-type derivatives yielded marked reduction in mutagenic activity without decreasing antischistosomal potency. Among them, a chlorobenzo-



(I)



(II)

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thiopyranoindazole derivative (II), the title compound [designated IA-4 (Bueding, Fisher & Bruce, 1973)], has been shown to be much less toxic than hycanthone, while maintaining the same antischistosomal activity in mice (Bueding, Fisher & Bruce, 1973; Bueding, 1975). The present investigation of the methanesulfonate of this compound was undertaken to provide additional information for structure-activity studies.

Experimental

Orange crystals of IA-4 monomethanesulfonate were grown at room temperature from an ethanol–water (1:1) solution of the specimen, kindly furnished by Professor Ernest Bueding of The Johns Hopkins University. The crystal system and approximate unit-cell parameters were established from Weissenberg and precession photographs. Twelve strong reflections in the 2θ range of 98 to 115° were centered with an Oak Ridge computer-controlled diffractometer (Busing, Ellison, Levy, King & Roseberry, 1968) with Ni-filtered Cu $K\alpha_1$ (λ = 1·54051 Å) radiation, and the cell parameters were refined by the least-squares method. Crystal data are summarized in Table 1.

A crystal with the shape of a trapezoidal prism of dimensions 0·05 × 0·11 × 0·50 mm was glued on the tip of a thin glass fiber and was exposed to air during X-ray intensity data collection. The longest dimension (prism axis), corresponding to the a axis, was nearly parallel to the φ axis of the diffractometer. The maximum mosaic spread of the crystal was estimated to be 0·5°. The intensities were measured up to a 2θ value of 125° (equivalent to a minimum spacing of 0·868 Å) with Ni-filtered Cu $K\alpha$ radiation at 40 kV and 14 mA, with the total estimated exposure time of 105 h. Intensities of standard reflections fluctuated within ±1% during the course of data collection. Details of intensity collection are also given in Table 1. Absorption corrections were applied by the method of Busing & Levy (1957), but no correction for secondary extinction was needed. Weights (w) used in the least-squares refinement of the structure [in which some reflections were not included (see Table 1)] are reciprocals of variances $\sigma^2(F_o^2)$, which were estimated according to the empirical expression used for the structural analysis of hycanthone methanesulfonate (Wei & Einstein, 1978).

Table 1. *Crystal data and intensity collection*

$[C_{20}H_{22}ClN_3OS][CH_4SO_3]$
$M_r = 484{\cdot}05$
Space group $P\bar{1}$
$a = 8{\cdot}7282\ (8)$ Å
$b = 11{\cdot}444\ (2)$
$c = 12{\cdot}338\ (2)$
$\alpha = 111{\cdot}71\ (1)^\circ$
$\beta = 94{\cdot}28\ (1)$
$\gamma = 99{\cdot}68\ (1)$

$V = 1328{\cdot}2$ Å^3
$Z = 2$
$D_{calc} = 1{\cdot}210$ Mg m^{-3}
$D_{obs} = 1{\cdot}23\ (2)$*
$F(000) = 508$
μ(Cu $K\alpha$) = 2·922 mm^{-1}
Transmission = 0·551–0·869
$T = 297$ K

Radiation	Cu $K\alpha$	Total background counting time	20–80 s§
Take-off angle	3°	Number of unique nonzero reflections	3312
Scan type	θ–2θ step scan	Number of reflections used in refinement	2813‖
2θ limit†	125°	Number of variables	346
2θ step size	0·05°	Data-to-variables ratio	8·1
Time per step	2–4 s		
Scan width‡	1·7–1·8°		

* Determined by flotation in mixtures of 1,2,3-trichloropropane and 1-chloropropane.

† In the 125–120° range, only selected strong reflections were measured.

‡ The width of the α_1–α_2 separation was added to these values.

§ Backgrounds were measured at the beginning and end of each scan. The longer times were used for higher 2θ ranges.

‖ The criterion used was $F_o^2 \geq 3\sigma(F_o^2)$.

Solution and refinement of the structure

All least-squares refinements in this analysis were performed with the program *ORXFLS*4 (Busing, Martin & Levy, 1962), the function minimized being $\sum w|F_o^2 - sF_c^2|^2$, where s is a scale factor. Scattering factors used were those of: Dawson (1960) for S and Cl; Berghuis, Haanappel, Potters, Loopstra, MacGillavry & Veenendaal (1955) for C, N and O; Stewart, Davidson & Simpson (1965) for H. The real and imaginary dispersion corrections f' = 0·319 and 0·348 and f'' = 0·557 and 0·702 were employed for S and Cl, respectively (Cromer, 1974).

The structure was solved by the standard heavy-atom technique. The interpretation of a three-dimensional Patterson function, calculated with the aid of a fast-Fourier routine (Levy, 1977), resulted in positions for three heavy atoms in the asymmetric unit. Successive Fourier syntheses phased on these three heavy atoms (to a first approximation, all were initially assigned as S atoms) yielded positions for the remaining 28 nonhydrogen atoms. Distinction was made between the Cl and S atoms based on stereochemical considerations, and all 31 nonhydrogen atoms were refined isotropically, giving the conventional discrepancy index, $R(F)$, of 0·155. The following anisotropic refinements markedly lowered the $R(F)$ value to 0·074. By alternate difference-Fourier syntheses and least-squares refinements, all 26 H atoms were finally located. Attempts to carry out the refinement in which all H atoms were included and treated isotropically were not successful, however, as they led to either large shifts in atomic positions or unusually large thermal parameters for some H atoms of the terminal ethyl groups. Therefore, positional parameters for ten H atoms of the side chain [associated with the four ethyl carbons, C(17), C(18), C(19), and C(20)] were fixed at their reasonable positions, as obtained from a difference-Fourier synthesis, and their individual isotropic thermal parameters were kept as 8 Å^2 for each of the methylene hydrogens and 10 Å^2 for each of the methyl hydrogens. With these constraints, the final refinement resulted in $R(F^2)$ and $R_w(F^2)$ [the latter defined as $(\sum w|F_o^2 - sF_c^2|^2/\sum wF_o^4)^{1/2}$] values of 0·075 and 0·129, respectively, for 2813 reflections with $F_o^2 \geq 3\sigma(F_o^2)$. The value of $R(F)$ stood at 0·049 based on these reflections. When all 3312 nonzero reflections were included, the $R(F)$ value was 0·057. Parameter shifts for nonhydrogen atoms in the last cycle of the refinement were all less than 2% of the corresponding estimated standard deviations (e.s.d.'s), except for 4% shifts for one of the two methyl carbons, C(20), whereas the maximum shift in the H parameters [for H(*b*)] was 6% of the corresponding e.s.d. A final difference-Fourier synthesis showed no residual peaks greater than 0·3 e Å^{-3}.

Table 2. *Positional* ($\times 10^4$) *and equivalent isotropic thermal parameters* (Å^2) *for nonhydrogen atoms*

The e.s.d.'s of the least significant figures are given in parentheses in all tables and in the text. Equivalent isotropic thermal parameters were calculated from the corresponding anisotropic thermal parameters and unit-cell parameters by the relation $B = \frac{4}{3}(\beta_{11}a^2 + \beta_{22}b^2 + \beta_{33}c^2 + 2\beta_{12}ab\cos\gamma + 2\beta_{13}\,ac\cos\beta + 2\beta_{23}\,bc\cos\alpha)$ (Hamilton, 1959).

	x	y	z	B
S(1)	1570 (1)	−978 (1)	−66 (1)	4·4
S(2)	2779 (1)	5172 (1)	2732 (1)	4·2
Cl	1730 (2)	155 (1)	−3875 (1)	6·6
C(1)	4564 (4)	1314 (3)	2878 (3)	3·7
C(2)	4240 (5)	784 (4)	3722 (3)	4·5
C(3)	3039 (5)	−294 (4)	3349 (4)	4·7
C(4)	2164 (4)	−876 (3)	2215 (3)	4·1
C(5)	1860 (4)	−191 (3)	−1836 (3)	4·1
C(6)	2524 (5)	535 (4)	−2418 (3)	4·4
C(7)	3814 (5)	1539 (4)	−1890 (3)	4·1
C(8)	4392 (4)	1842 (3)	−744 (3)	3·8
C(9)	4346 (4)	1469 (3)	1128 (3)	3·3
C(10)	3713 (4)	748 (3)	1754 (3)	3·3
C(11)	2502 (4)	−348 (3)	1395 (3)	3·6
C(12)	2482 (4)	105 (3)	−666 (3)	3·4
C(13)	3759 (4)	1154 (3)	−98 (3)	3·3
C(14)	898 (6)	−2075 (4)	1896 (4)	5·3
C(15)	6789 (6)	3237 (4)	3858 (4)	5·2
C(16)	7888 (5)	4161 (4)	3512 (4)	4·9
C(17)	7124 (5)	6265 (4)	4579 (5)	6·1
C(18)	8691 (6)	7047 (5)	5227 (6)	8·6
C(19)	7903 (6)	5829 (6)	2628 (5)	7·2
C(20)	7324 (7)	5115 (6)	1377 (5)	8·6
C(21)	1815 (7)	3870 (5)	1457 (5)	6·2
N(1)	5646 (3)	2325 (3)	2876 (2)	3·8
N(2)	7177 (4)	5199 (3)	3378 (3)	4·6
N(3)	5513 (3)	2425 (3)	1802 (2)	3·6
O(1)	1247 (5)	−3179 (3)	1037 (3)	6·2
O(2)	3490 (4)	6143 (3)	2326 (4)	7·7
O(3)	1598 (3)	5552 (4)	3464 (3)	7·1
O(4)	3951 (3)	4705 (3)	3262 (2)	5·4

Table 3. *Positional* ($\times 10^3$) *and isotropic thermal parameters* (Å^2) *for hydrogen atoms*

Hydrogen atoms are numbered according to the C atoms to which they are attached, except for H(*a*) and H(*b*) which are bonded to O(1) and N(2), respectively.

	x	y	z	B
H(2)	493 (4)	117 (3)	442 (3)	3·9 (8)
H(3)	289 (5)	−70 (4)	389 (3)	5·0 (9)
H(5)	100 (4)	−83 (3)	−223 (3)	3·3 (7)
H(7)	427 (5)	196 (4)	−231 (4)	6·0 (11)
H(8)	530 (4)	245 (4)	−38 (3)	4·0 (8)
H(14*a*)	83 (4)	−226 (3)	268 (3)	3·3 (7)
H(14*b*)	−11 (6)	−199 (5)	154 (4)	7·0 (13)
H(15*a*)	743 (5)	273 (4)	415 (4)	5·8 (10)
H(15*b*)	630 (5)	378 (5)	446 (4)	6·3 (12)
H(16*a*)	821 (5)	371 (4)	279 (4)	6·1 (11)
H(16*b*)	881 (5)	456 (4)	413 (4)	5·4 (10)
H(17*a*)	644	685	433	8·0
H(17*b*)	666	587	504	8·0
H(18*a*)	847	778	593	10·0
H(18*b*)	900	760	473	10·0
H(18*c*)	970	676	516	10·0
H(19*a*)	734	681	290	8·0
H(19*b*)	909	580	276	8·0
H(20*a*)	774	417	108	10·0
H(20*b*)	771	551	87	10·0
H(20*c*)	619	492	111	10·0
H(*a*)	199 (6)	−326 (5)	141 (5)	7·7 (17)
H(*b*)	628 (5)	490 (4)	310 (4)	5·2 (10)
H(21*a*)	101 (6)	408 (5)	110 (4)	7·0 (13)
H(21*b*)	148 (6)	316 (5)	175 (4)	7·5 (14)
H(21*c*)	258 (8)	348 (6)	99 (6)	10·6 (19)

The final atomic positional parameters and equivalent isotropic thermal parameters are given in Table 2 for nonhydrogen atoms and in Table 3 for H atoms (positional and isotropic thermal parameters).*

Discussion

The crystal structure of IA-4 monomethanesulfonate consists of IA-4 cations and methanesulfonate $[CH_3SO_3]^-$ anions linked together by hydrogen bonds. The numbering scheme (including H atoms) and thermal ellipsoids for nonhydrogen atoms of the IA-4 cation are depicted in Fig. 1.* This and all subsequent figures were prepared with *ORTEP*-II (Johnson, 1976). The numbering scheme of the cation is given in Fig. 2 with bond lengths, bond angles and their corresponding e.s.d.'s, calculated by the program *ORFFE*4 (Busing, Martin & Levy, 1964). For the sake of clarity,

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* Lists of structure factors and anisotropic thermal parameters and a stereoview of Fig. 1 have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 35591 (5 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

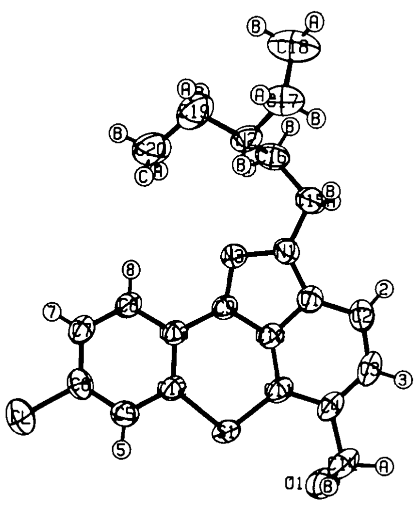

Fig. 1. Numbering scheme and thermal ellipsoids (enclosing 50% probability) for nonhydrogen atoms of the IA-4 cation. The hydroxyl H(*a*) atom attached to O(1) and the H(18*c*) attached to C(18) are hidden. (The stereoscopic view has been deposited.)

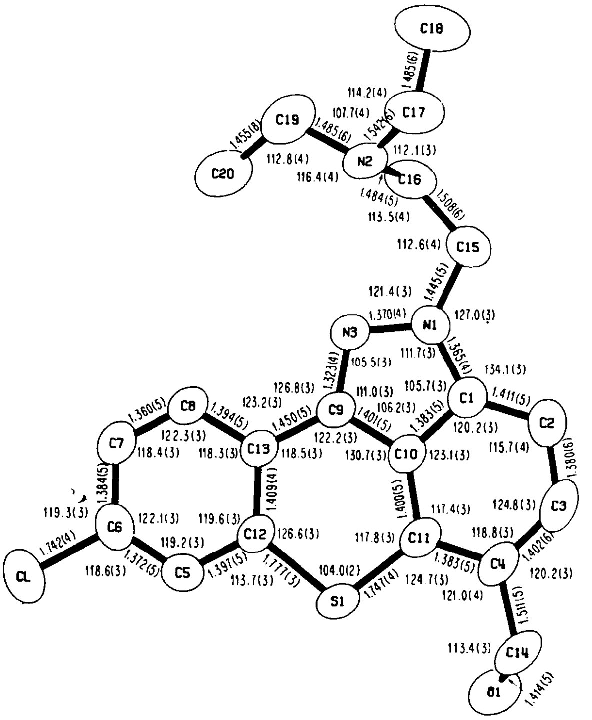

Fig. 2. Bond lengths (Å) and bond angles (°) for nonhydrogen atoms with their e.s.d.'s.

however, H atoms are not shown in Fig. 2. The calculations show that two C—H distances for C(19)—H(19*a*) and C(20)—H(20*a*) are exceptionally larger than the normal value, being 1·25 and 1·14 Å, respectively. The remaining C—H, N—H and O—H distances are all reasonable, ranging from 1·07 (3) Å [for C(14)—H(14*a*)] to 0·79 (4) Å [for N(2)—H(*b*)], with an average value of 0·96 Å.

The framework of the fused four-ring heterocyclic system in this structure can be considered to be formed by the fusion of [1]benzothiopyran and indazole along common C(9)—C(10)—C(11) sides, resulting in the 2*H*-[1]benzothiopyrano[4,3,2-*cd*]indazole framework (Patterson, Capell & Walker, 1960). Consequently, the proximal N atom of the hycanthone cation becomes a member of the five-member ring, leading to marked decreases in bond angles for N(1)—C(1)—C(10) [from 120·6 (1) to 105·7 (3)°] and C(10)—C(11)—C(4) [from 122·5 (1) to 117·4 (3)°], but an increase for C(1)—C(10)—C(11) [from 117·8 (1) to 123·1 (3)°]. Similar phenomena have been observed in the structure of another hycanthone analog, dechloro IA-4 monohydrate (Wei, 1980). All C atoms of the two outer six-member rings are nearly coplanar as shown in Table 4 (*a*) and (*b*), whereas the middle six-member ring atoms, C(9) and S(1), are further from these planes. The dihedral angle between the least-squares planes (*a*) and (*b*) is 177·0 (1)° as compared to that of 167·7° for the hycanthone cation, indicating that the IA-4 cation has a thioxanthene ring system much closer to coplanarity. The five-member ring in this structure is essentially planar (Table 4*c*). When all 14 atoms of the thioxanthene ring system are included in the plane calculation (Table 4*d*), the mean deviation from the least-squares plane is 0·025 (1) Å, which can be compared with 0·116 Å for the hycanthone cation and 0·05 Å for lucanthone (Neidle, 1976). The dihedral angle between the best least-squares planes for the five- and six-member rings of the indazole fragment is

Table 4. *Equations of best molecular planes, and distances* (Å) *of atoms from these planes*

The coordinates *X*, *Y* and *Z* (in Å) refer to a Cartesian system with unit vectors **i** along **b** × **c***, **j** along **b** and **k** along **c***. Calculations were performed with the program *ORFFE*4 (Busing, Martin & Levy, 1964) and the program written by Smith (1962) with all atoms equally weighted.

(*a*) $0{\cdot}7104X - 0{\cdot}6321Y - 0{\cdot}3012Z - 1{\cdot}7759 = 0$
(*b*) $0{\cdot}6778X - 0{\cdot}6688Y - 0{\cdot}3055Z - 1{\cdot}7028 = 0$
(*c*) $0{\cdot}7003X - 0{\cdot}6531Y - 0{\cdot}2923Z - 1{\cdot}7647 = 0$
(*d*)† $0{\cdot}7025X - 0{\cdot}6470Y - 0{\cdot}2964Z - 1{\cdot}7863 = 0$

	(*a*)		(*b*)		(*c*)
C(1)	−0·003 (3)	C(5)	−0·001 (3)	N(1)	0·001 (2)
C(2)	0·003 (3)	C(6)	−0·012 (3)	N(3)	−0·001 (2)
C(3)	−0·002 (3)	C(7)	0·015 (3)	C(9)	0·001 (2)
C(4)	−0·000 (3)	C(8)	−0·004 (3)	C(10)	0·000 (2)
C(11)	0·001 (2)	C(13)	−0·010 (2)	C(1)	−0·001 (2)
C(10)	0·001 (2)	C(12)	0·012 (2)	C(15)	−0·032 (7)‡
C(9)	0·037 (5)‡	C(9)	−0·043 (5)‡		
S(1)	0·053 (5)‡	S(1)	0·126 (5)‡		
		Cl	−0·034 (5)‡		

† Deviations of atoms are not given for this plane, which was calculated for all 14 atoms of the thioxanthene ring system.

‡ Atoms not included in the calculation of the least-squares plane.

178·6 (2)°, while the angle between the planes for the five-member and the thioxanthene rings is 179·6 (1)°. Thus, the whole fused four-ring system can be regarded as nearly planar, as proposed previously by Weinstein & Hirschberg (1971) and Hirschberg (1975) for this family of drugs.

The major difference between this structure and that of hycanthone is that the carbonyl O atom in hycanthone is substituted by N(3), which is bonded to the otherwise proximal N atom in this structure, giving rise to the loss of the intramolecular hydrogen bond. Nevertheless, the coplanarity of the chromophore is maintained, and the torsion angle for atoms C(15)–N(1)–C(1)–C(2) is −4·0 (7)°, a value compatible with the corresponding values of −2·0° for hycanthone and −9° for lucanthone.* It has been recognized that the terminal N(2) atom and its ethyl substituents are conformationally labile even in the crystalline state. This is reflected not only in the large thermal motions for the terminal ethyl carbons (Table 2), but also in a different configurational arrangement of the diethylaminoethyl side chain with respect to the chromophore framework, as compared with the cases of hycanthone and lucanthone. This can be partly seen by examination of the relative orientation of the two N atoms, N(1) and N(2), about the C(16)–C(15) bond. The torsion angles C(16)–C(15)–N(1)–C(1) and N(2)–C(16)–C(15)–N(1) in this structure are 175·1 (3) and 77·3 (5)° compared to −81·1 and 164·7° for hycanthone, and −156 and −77° for lucanthone.†

In this structure, and in the structure of hycanthone, protonation takes place at the terminal N atom, which then acts as a donor in an intermolecular hydrogen bond to an O atom of the methanesulfonate group. When these drugs bind to DNA by means of intercalation, it would be stereochemically feasible for their terminal N atoms to interact with the phosphate oxygens in a similar way so as to stabilize the drug–DNA complexes.

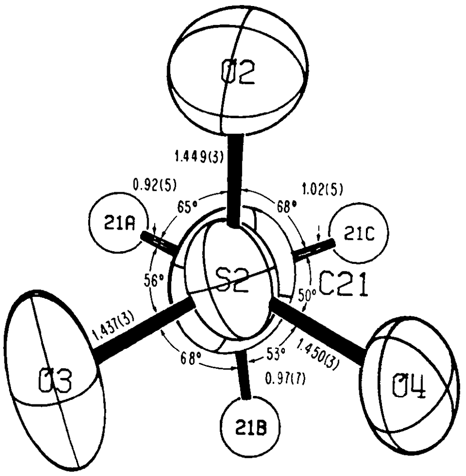

Fig. 3. Configuration of the methanesulfonate anion as viewed down the S(2)–C(21) bond direction. The hidden S(2)–C(21) bond has a length of 1·746 (5) Å. The bond angles (°) involving nonhydrogen atoms are as follows: O(2)–S(2)–C(21) 105·2 (3); O(3)–S(2)–C(21) 106·5 (3); O(4)–S(2)–C(21) 106·1 (2); O(2)–S(2)–O(3) 113·6 (2); O(3)–S(2)–O(4) 112·9 (2); and O(4)–S(2)–O(2) 111·8 (2). The triangular array of the three O atoms can be seen to be nearly equilateral by the angles: O(2)–O(3)–O(4) 59·8 (1); O(3)–O(4)–O(2) 60·3 (1); and O(4)–O(2)–O(3) 59·9 (1)°. (Distances shown are in Å.)

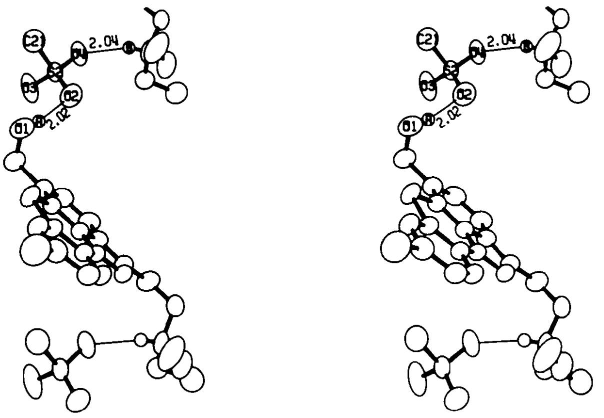

Fig. 4. Stereoscopic view of interionic hydrogen-bonding scheme along the *b* direction. This infinite hydrogen-bonded chain is separated from neighboring ones in the *c* direction by 11·46 (1) Å. (Distances shown are in Å.)

As in the cases of hycanthone methanesulfonate, cesium methanesulfonate (Brandon & Brown, 1967) and sodium methanesulfonate (Hingerty & Wei, 1980), the methanesulfonate anion in this structure exhibits a configuration with approximately C_{3v} symmetry. A view down the S(2)–C(21) bond is shown in Fig. 3. The S(2)–C(21) bond length [1·746 (5) Å] as well as the average S–O distance [1·445 (2) Å] are closely parallel to those values [1·749 (3) and 1·446 (1) Å, respectively] observed previously for hycanthone methanesulfonate. Only two of the three O atoms in the methanesulfonate anion [O(2) and O(4)] participate in interionic hydrogen bonding, as observed in the structure of hycanthonesulfonate. It is of interest to note that in each of the two structures, the S–O bond length involving the O atom not participating in the hydrogen bonding is the shortest of the three S–O bond lengths (0·01 Å shorter than the corresponding

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* Torsion angles for lucanthone were calculated from the positional parameters given by Neidle (1976). The numbering scheme (not given in his paper) is such that atoms C(6) and C(7) of the lucanthone molecule correspond to atoms C(1) and C(2) in this structure.

† Inasmuch as the absolute configuration was not reported for this acentric crystal (space group *A*2) of lucanthone, it is not known whether the signs of the three lucanthone torsion angles considered here are all positive or all negative. At the same time, it should be noted that in the centric crystals of hycanthone and IA-4 there are pairs of molecules having torsion angles of opposite sign.

Table 5. *Interionic hydrogen bonds* (A—H$\cdots B$)

Symmetry code: (i) $x, y-1, z$.

A	H	B	$A\cdots B$ (Å)	A—H (Å)	H$\cdots B$ (Å)	$\angle A$—H$\cdots B$ (°)
N(2)	H(b)	O(4)	2·759 (4)	0·79 (4)	2·04 (4)	151 (4)
O(1)	H(a)	O(2^{i})	2·815 (6)	0·81 (5)	2·02 (5)	166 (6)

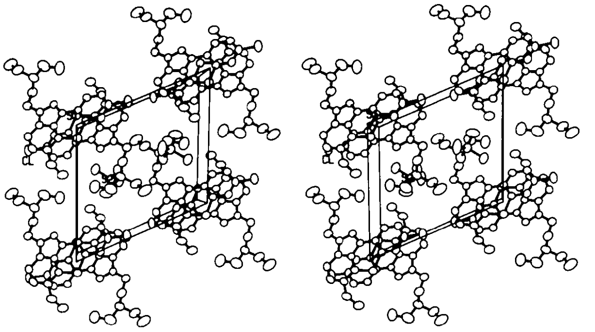

Fig. 5. A stereoscopic pair showing the unit-cell packing down **a**. The axial system is right handed. For the sake of clarity, H atoms are omitted, and only S and Cl atoms of the reference molecule are labeled. The origin of the unit cell is in the upper left, rear corner.

average value), as is consistent with chemical consideration.

As shown in Fig. 4, the hydroxyl H(a) atom is hydrogen bonded to the O(2) atom of the neighboring methanesulfonate anion, and the O(4) atom of the same anion is in turn bonded to H(b) of another IA-4 cation (related to the reference cation by a b-axis translation), resulting in an infinite interionic hydrogen-bonded chain along the b direction. The parameters of these two hydrogen bonds are given in Table 5. A somewhat similar hydrogen-bonded chain, coiled around the twofold screw axis, was observed in the structure of hycanthone methanesulfonate. The chains in the present structure, however, are discrete in the c direction with a separation of 11·46 (1) Å, and stacking of the planar ring system at roughly 3·6 Å spacing occurs in the a direction across the center of symmetry at the origin.

Fig. 5 shows the [100] projection of the unit cell. The closest intermolecular contacts between nonhydrogen atoms and between nonhydrogen and H atoms involve O(3), the only O atom not participating in the interionic hydrogen bondings, with O(3)$\cdots$C(16) and O(3)$\cdots$H(19b) distances being 3·375 (5) and 2·392 (3) Å, respectively. The fact that these closest intermolecular contacts involve the corresponding unique O atoms in the structures of both hycanthone methanesulfonate and IA-4 monomethanesulfonate is of some interest, since the two structures differ in their side-chain conformations.

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