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The Structure of a Biological Alkylating Agent with Antitumor Properties: *N*-{2-[(2-Chloroethyl)thio]ethyl}-10-methyl-9-anthracenemethylamine Hydrochloride and of its Self-Alkylation Product 10-Methyl-9-[(4-thiomorpholino)methyl]anthracene

BY WILLIAM C. STALLINGS, CLAIRE T. MONTI AND JENNY P. GLUSKER

The Institute for Cancer Research, The Fox Chase Cancer Center, Philadelphia, PA 19111, *USA*

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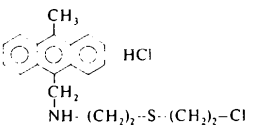
Abstract

The structures of a biological alkylating agent, *N*-{2-[(2-chloroethyl)thio]ethyl}-10-methyl-9-anthracenemethylamine hydrochloride (I), with antitumor properties, and of its self-alkylation product, 10-methyl-9-[(4-thiomorpholino)methyl]anthracene (II), have been determined. Crystal data for (I) are $C_{20}H_{23}ClNS^+.Cl^-$, $M_r = 380{\cdot}38$, $a = 22{\cdot}748$ (2), $b = 13{\cdot}007$ (1), $c = 6{\cdot}3443$ (8) Å, $V = 1877{\cdot}2$ (4) Å^3, $D_c = 1{\cdot}35$ Mg m^{-3}, space group $P2_12_12_1$, $Z = 4$. Crystal data for (II) are $C_{20}H_{21}NS$, $M_r = 307{\cdot}46$, $a = 35{\cdot}816$ (6), $b = 6{\cdot}8965$ (9), $c = 13{\cdot}895$ (2) Å, $\beta = 105{\cdot}89$ (1)°, $V = 3300{\cdot}9$ (8) Å^3, $D_c = 1{\cdot}24$ Mg m^{-3}, space group $P2_1/a$, $Z = 8$ (2 molecules per asymmetric unit). The final R values were 0·050 for 1220 observed data for (I) and 0·047 for 4513 observed data for (II). In the alkylating agent (I) there is *no* internal NH···S hydrogen bond in the side chain, unlike the case of other ICR compounds which are acridine alkylating agents with intramolecular NH···N hydrogen bonds in their side chains. This lack of hydrogen bonding in (I) may facilitate the self-alkylation process. The flexibility of the anthracene ring system is shown by the variability in the angle between the planes of the two outer rings as observed in these and other structures. In both structures the anthracene ring systems of the molecules do not overlap in planes 3·4 Å apart, but they do lie in parallel planes, approximately 3·5 Å apart, with a remarkably similar motif for each.

Introduction

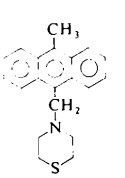
The alkylating agent *N*-{2-[(2-chloroethyl)thio]ethyl}-10-methyl-9-anthracenemethylamine hydrochloride (I) is one of a series of polycyclic and heterocyclic aromatic nitrogen and sulfur mustards (Peck, O'Connell & Creech, 1967, 1970; Creech, Preston, Peck, O'Connell & Ames, 1972) having a wide range of antitumor activity against Ehrlich ascites tumors in albino mice (the ICR series of compounds); its molecular formula is:



(I)

It is believed to exert its activity in a bifunctional manner (Peck & O'Connell, 1972); that is, if DNA is a critical macromolecular target, the alkylation of DNA by the side chain of molecule (I) is accompanied by intercalation of the aromatic portion between the base pairs of double-helical DNA. The active forms of some nitrogen and sulfur mustards have been shown by Price, Gaucher, Koneru, Shibakawa, Sowa & Yamaguchi (1969) in NMR studies to be a cyclic immonium or sulfonium ion. This compound (I) represents the first in this series of compounds studied crystallographically, whose side chain contains both an amino N and an S atom.

The compound 10-methyl-9-[(4-thiomorpholino)-methyl]anthracene (II), which is the self-alkylation product of (I), was isolated from an attempted preparation of the N(3) alkylation product of adenine by (I) following a procedure for N(3) alkylation of adenine by benzyl chloride (Montgomery & Thomas, 1964). Although an elemental analysis indicated that the desired reaction product had not been formed, we decided to initiate a three-dimensional X-ray crystallographic analysis of the product obtained (II) to determine its chemical structure. Once it was elucidated, we examined details of its molecular geometry in order to understand the conformation of the ring–ring interaction as well as the effects of self-alkylation on the geometry of the methylanthracene moiety.



(II)

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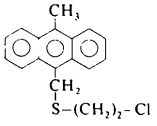
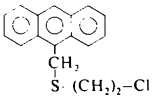
Earlier structural studies of polycyclic and heterocyclic aromatic alkylating agents have included the nitrogen mustard analogues ICR-191-OH (Carrell, 1972), ICR-171-OH (Glusker, Minkin & Orehowsky, 1972), ICR-170-OH (Berman & Glusker, 1972), ICR-449-OH (Glusker, Gallen & Carrell, 1973), ICR-372-OH (Glusker, Carrell, Berman & Gallen, 1975) and ICR-292-OH (Stallings & Glusker, 1977) which are derivatives of acridine, azaacridine and benz[*c*]acridine and whose alkylating side chains, similar to that of quinacrine, contain two amino N atoms separated by two or more methylene C atoms; also studied crystallographically were the monofunctional sulfur mustards 9-{[(2-chloroethyl)thio]methyl}-10-methylanthracene (III) (Glusker & Zacharias, 1972) and 9-{[(2-chloroethyl)thio]methyl}anthracene (IV) (Lewis, Carrell, Glusker & Sparks, 1976).



(III)



(IV)

Experimental

Compound (I)

Crystals of compound (I) were provided by Drs R. M. Peck, R. K. Preston and H. J. Creech of this Institute; they exist in the form of pale-yellow rectangular parallelepipeds. Three-dimensional X-ray data were collected on a Syntex automated diffractometer with graphite-monochromatized Cu $K\alpha$ radiation and the θ–2θ scan technique over a dispersion-corrected base width of 2·0°; the scan speed was variable over the range 1–24° min^{-1}. There was no decrease in intensity as a function of time in periodically measured standard reflections.

Compound (II)

A solution of 0·0886 g (0·655 mmol) of adenine and 0·7433 g (1·95 mmol) of (I) in 50 ml of *N*,*N*-dimethylacetamide was heated at 394 K for 18 h. After heating, the clear brown solution was allowed to evaporate; the residue was dissolved in 50 ml of warm absolute ethanol and crystals formed as the solution cooled. The melting point, as determined on a Hershberg apparatus, is 412–413 K. Elemental analysis showed C 77·95, H 6·90, N 4·55, and S 10·38% (calculated for $C_{20}H_{21}NS$: C 78·13, H 6·88, N 4·56, and S 10·43%).

Crystals of the title compound are well formed golden-brown parallelepipeds. They contain two molecules in the asymmetric unit. Three-dimensional X-ray data were collected on a Syntex automated diffractometer with graphite-monochromatized Cu $K\alpha$ radiation and the θ–2θ scan technique over a dispersion-corrected base width of 1·4°; the scan speed was variable over the range 2·02–29·30° min^{-1}. There was no decrease in intensity as a function of time in periodically measured standard reflections.

Table 1. *Additional crystal data and some details of the collection*

	Compound (I)	Compound (II)
Crystal size	0·3 × 0·07 × 0·03 mm	0·1 × 0·1 × 0·4 mm
Crystal shape	Rectangular parallelepipeds	Parallelepipeds
Crystal color	Light yellow	Golden brown
Number of unique reflections measured (excluding those systematically absent)	2005	6159
Maximum sin θ/λ	0·61 Å^{-1}	0·61 Å^{-1}
Criterion for threshold value	$I_o = 2{\cdot}33\,\sigma(I)$	$I_o = 2{\cdot}33\,\sigma(I)$
Number of reflections below the threshold value	785	1646
Criterion for $\sigma(I)$	Counting statistics	Counting statistics
$\sigma(F) = (F/2)\{[\sigma^2(I)/I^2] + \delta^2\}^{1/2}$ where δ = instrumental uncertainty		
	$\delta = 0{\cdot}0425$	$\delta = 0{\cdot}0132$
Refinement $R_{observed}$	0·050	0·047
$R_{weighted}$	0·055	0·058
$R_{all\ data}$	0·102	0·066

Both compounds

The intensity data were converted to structure amplitudes by the application of Lorentz and polarization factors. No absorption correction was applied. Additional crystal data and details of the data collection are summarized in Table 1.

Structure solution and refinement

Compound (I)

The structure of compound (I) was solved easily by direct methods using the program *MULTAN* (Main, Woolfson & Germain, 1971). The first *E* map calculated revealed the positions of 19 of the 24 non-hydrogen atoms in the molecule; the remaining five atoms were readily located in subsequent Fourier maps. The structure was refined by the method of full-matrix least squares; the non-hydrogen atoms after initial isotropic refinement were refined anisotropically and H atoms, located from difference syntheses, were refined isotropically.

The methylene H atoms of C(14) and C(15), although resolved in difference Fourier syntheses, could not be refined, probably as a result of some disorder at the end of the alkylating side chain. This is evidenced by high thermal parameters for C(14), C(15) and Cl(1) (r.m.s. amplitudes of vibration 0·34–0·46 Å) and the finding that the C(14)–C(15) bond length is shorter than that expected for a C–C single bond. A similar problem is observed for an ethyl group at the end of the

side chain in the crystal structure of 7-{3-[ethyl(2-hydroxyethyl)amino]propylamino}benz[*c*]acridine, ICR-292-OH (Stallings & Glusker, 1977). Therefore, because of this disorder, during the final cycles of refinement, the H atoms on C(14) and C(15) were placed at calculated positions and assigned fixed isotropic temperature factors: 8·0 Å^2 for H1(C14) and H2(C14) and 9·3 Å^2 for H1(C15) and H2(C15). The coordinates of these H atoms were not refined.

Table 2. *Final refined positional and thermal parameters* (B_{eq} *for non-hydrogen atoms*) *for compound* (I)

Values in parentheses are estimated standard deviations given with respect to the last digit reported. The anisotropic temperature-factor expression is $T = \exp[\frac{1}{4}(-h^2a^{*2}B_{11} - k^2b^{*2}B_{22} - l^2c^{*2}B_{33} - 2hka^*b^*B_{12} - 2hla^*c^*B_{13} - 2klb^*c^*B_{23})]$ and $B_{eq} = (B_{11} + B_{22} + B_{33})/3$. The isotropic temperature-factor expression is $T = \exp(-B\sin^2\theta/\lambda^2)$. Values of B_{ij} have been deposited.

	x	*y*	*z*	B_{eq} or *B* (Å^2)
C(1)	0·1510 (3)	1·0558 (5)	0·0585 (13)	3·5 (3)
C(2)	0·1840 (3)	1·0872 (5)	0·2190 (15)	4·5 (4)
C(3)	0·2063 (3)	1·0164 (6)	0·3649 (13)	4·2 (3)
C(4)	0·1968 (3)	0·9138 (5)	0·3386 (11)	3·4 (3)
C(5)	0·1083 (3)	0·6311 (5)	−0·0888 (13)	3·8 (4)
C(6)	0·0749 (3)	0·6019 (5)	−0·2556 (12)	3·9 (3)
C(7)	0·0532 (3)	0·6748 (6)	−0·4011 (13)	4·3 (4)
C(8)	0·0631 (3)	0·7772 (5)	−0·3665 (12)	3·5 (3)
C(9)	0·1540 (3)	0·7692 (5)	0·1281 (11)	3·2 (3)
C(10)	0·1057 (3)	0·9182 (5)	−0·1565 (12)	3·1 (3)
C(1a)	0·1391 (3)	0·9493 (5)	0·0210 (12)	3·1 (3)
C(4a)	0·1638 (3)	0·8749 (4)	0·1622 (10)	2·8 (3)
C(5a)	0·1206 (3)	0·7390 (5)	−0·0464 (11)	3·1 (3)
C(8a)	0·0965 (3)	0·8118 (5)	−0·1893 (12)	3·0 (3)
C(11)	0·1789 (2)	0·6899 (5)	0·2747 (11)	3·1 (3)
N	0·2345 (2)	0·6408 (3)	0·1941 (9)	3·1 (2)
C(12)	0·2892 (3)	0·7022 (5)	0·2184 (11)	2·8 (2)
C(13)	0·3417 (3)	0·6303 (5)	0·2006 (12)	3·4 (3)
S	0·41198 (8)	0·6929 (1)	0·2259 (3)	3·7 (7)
C(14)	0·4256 (4)	0·7440 (7)	−0·0318 (5)	5·9 (5)
C(15)	0·4282 (5)	0·6779 (9)	−0·2079 (17)	8·4 (6)
Cl(1)	0·4759 (1)	0·5709 (2)	−0·1951 (5)	9·0 (2)
C(16)	0·0776 (3)	0·9950 (5)	−0·2995 (14)	4·8 (4)
Cl(2)	0·23615 (8)	0·3974 (1)	0·2144 (3)	3·7 (7)
H(C1)	0·136 (2)	1·096 (3)	−0·037 (7)	1 (1)
H(C2)	0·196 (3)	1·163 (5)	0·239 (11)	5 (2)
H(C3)	0·236 (3)	1·037 (4)	0·497 (10)	5 (2)
H(C4)	0·213 (2)	0·864 (4)	0·447 (8)	2 (1)
H(C5)	0·120 (2)	0·582 (4)	0·013 (9)	3 (1)
H(C6)	0·067 (2)	0·532 (4)	−0·307 (10)	4 (1)
H(C7)	0·027 (2)	0·662 (4)	−0·527 (9)	3 (1)
H(C8)	0·052 (3)	0·827 (4)	−0·471 (9)	4 (1)
H1(C11)	0·154 (2)	0·642 (4)	0·292 (9)	3 (1)
H2(C11)	0·187 (3)	0·725 (5)	0·394 (12)	6 (2)
H1(N)	0·235 (3)	0·582 (4)	0·208 (11)	4 (1)
H2(N)	0·234 (3)	0·624 (6)	0·018 (13)	7 (2)
H1(C12)	0·289 (2)	0·760 (4)	0·106 (9)	3 (1)
H2(C12)	0·285 (4)	0·724 (7)	0·334 (18)	10 (3)
H1(C13)	0·341 (2)	0·588 (4)	0·071 (9)	3 (1)
H2(C13)	0·340 (2)	0·582 (4)	0·342 (8)	2 (1)
H1(C14)†	0·411	0·809	−0·074	8
H2(C14)†	0·474	0·771	−0·009	8
H1(C15)†	0·388	0·652	−0·216	9
H2(C15)†	0·461	0·696	−0·346	9
H1(C16)	0·090 (4)	0·991 (8)	−0·437 (15)	8 (3)
H2(C16)	0·032 (3)	0·996 (6)	−0·300 (14)	8 (2)
H3(C16)	0·081 (4)	1·063 (6)	−0·327 (16)	8 (2)

† Parameters for these atoms were not refined.

Final refined positional and thermal parameters for (I) are listed in Table 2 with estimated standard deviations. The final *R* value for observed data is 0·050 with a weighted *R* of 0·055; the final *R* value on all data is 0·102. A final difference Fourier map using all of the parameters of Table 2 revealed the presence of no peaks greater than 0·3 e Å^{-3}.*

Compound (II)

The structure of compound (II) was solved using Patterson-superposition and Fourier techniques. The positions of the S atoms were located from a sharpened Patterson function and superposition of the origin of the Patterson function on all eight of these positions revealed recognizable fragments of the anthracene ring systems. A subsequent Fourier map phased from the positions of atoms located in this manner revealed the positions of the missing atoms.

The structure was refined by the method of full-matrix least squares; nonhydrogen atoms, after initial isotropic refinement, were refined anisotropically and H atoms, located from difference Fourier syntheses, were refined isotropically. The final *R* value for observed data is 0·047 with a weighted *R* of 0·058; the final *R* value on all data is 0·066.

Final refined positional and thermal parameters for (II) are listed in Table 3 with estimated standard deviations. A final difference Fourier map revealed the presence of no peaks greater than 0·22 e Å^{-3}.*

Both compounds

The weights, *w*, for reflections used in the least-squares refinement were $\sigma^{-2}(F)$ with weights of zero for reflections below the threshold value. The function minimized in the least-squares process was $\sum w(|F_o| - |F_c|)^2$. The atomic scattering factors used for S, N and C atoms were from *International Tables for X-ray Crystallography* (1962), and those for H atoms were from Stewart, Davidson & Simpson (1965). The value for *f'* (the real component of anomalous scattering) used for S atoms was that given by Cromer & Liberman (1970). Computer programs used include *ICRFMLS* (Gantzel, Sparks, Long & Trueblood,

* Lists of structure factors and anisotropic thermal parameters for both compounds have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36101 (43 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 3. *Final refined positional and thermal parameters (B_{eq} for non-hydrogen atoms) for the self-alkylation product, compound* (II)

Values in parentheses are estimated standard deviations given with respect to the last digit reported. The anisotropic temperature-factor expression is $T = \exp[\frac{1}{4}(-h^2 a^{*2} B_{11} - k^2 b^{*2} B_{22} - l^2 c^{*2} B_{33} - 2hka^* b^* B_{12} - 2hla^* c^* B_{13} - 2klb^* c^* B_{23})]$ and $B_{eq} = (B_{11} + B_{22} + B_{33})/3$. The isotropic temperature-factor expression is $T = \exp(-B \sin^2 \theta/\lambda^2)$. Values of B_{ij} have been deposited.

	x	y	z	B_{eq} or B (Å^2)
*A*S	0·22106 (3)	0·2176 (1)	0·6061 (1)	7·04 (4)
*A*C(1)	0·10670 (7)	−0·3623 (4)	0·0862 (2)	5·03 (10)
*A*C(2)	0·14354 (8)	−0·4107 (4)	0·0903 (2)	5·96 (11)
*A*C(3)	0·17408 (7)	−0·2920 (5)	0·1413 (2)	6·55 (12)
*A*C(4)	0·16715 (7)	−0·1272 (4)	0·1854 (2)	5·87 (12)
*A*C(5)	0·07294 (6)	0·3237 (3)	0·2722 (2)	4·39 (9)
*A*C(6)	0·03625 (7)	0·3629 (4)	0·2748 (2)	4·91 (10)
*A*C(7)	0·00597 (7)	0·2336 (4)	0·2314 (2)	5·01 (10)
*A*C(8)	0·01306 (6)	0·0722 (4)	0·1844 (2)	4·57 (10)
*A*C(9)	0·12110 (6)	0·1068 (3)	0·2287 (1)	4·16 (9)
*A*C(10)	0·05883 (6)	−0·1430 (3)	0·1284 (1)	4·05 (9)
*A*C(1a)	0·09742 (6)	−0·1890 (3)	0·1321 (1)	4·18 (9)
*A*C(4a)	0·12877 (6)	−0·0658 (4)	0·1834 (2)	4·42 (9)
*A*C(5a)	0·08246 (6)	0·1517 (3)	0·2267 (1)	3·88 (9)
*A*C(8a)	0·05142 (6)	0·0242 (3)	0·1779 (1)	3·91 (9)
*A*C(11)	0·15321 (6)	0·2476 (4)	0·2776 (2)	4·83 (10)
*A*N	0·16328 (5)	0·2530 (3)	0·3876 (1)	4·32 (7)
*A*C(12)	0·19451 (7)	0·3952 (4)	0·4219 (2)	5·49 (11)
*A*C(13)	0·20475 (8)	0·4319 (4)	0·5338 (2)	5·89 (12)
*A*C(14)	0·18027 (10)	0·0662 (5)	0·5442 (2)	7·06 (16)
*A*C(15)	0·17420 (8)	0·0639 (4)	0·4321 (2)	5·40 (11)
*A*C(16)	0·02597 (8)	−0·2711 (4)	0·0714 (2)	5·51 (11)
*B*S	0·23631 (2)	0·2294 (1)	0·0932 (1)	6·00 (4)
*B*C(1)	0·44515 (6)	0·8089 (4)	0·2433 (2)	4·75 (10)
*B*C(2)	0·43642 (7)	0·8338 (4)	0·1427 (2)	5·42 (11)
*B*C(3)	0·41453 (7)	0·6940 (4)	0·0784 (2)	5·36 (10)
*B*C(4)	0·40093 (7)	0·5355 (4)	0·1154 (2)	4·84 (10)
*B*C(5)	0·38718 (6)	0·1630 (4)	0·4101 (2)	4·55 (10)
*B*C(6)	0·39497 (7)	0·1429 (4)	0·5110 (2)	5·24 (10)
*B*C(7)	0·41781 (7)	0·2805 (4)	0·5747 (2)	5·23 (10)
*B*C(8)	0·43276 (8)	0·4328 (4)	0·5374 (2)	4·72 (10)
*B*C(9)	0·39369 (5)	0·3424 (3)	0·2612 (2)	3·87 (9)
*B*C(10)	0·44132 (6)	0·6204 (3)	0·3922 (2)	4·16 (9)
*B*C(1a)	0·43198 (6)	0·6443 (3)	0·2872 (2)	4·02 (8)
*B*C(4a)	0·40855 (6)	0·5036 (3)	0·2215 (2)	4·02 (9)
*B*C(5a)	0·40228 (6)	0·3215 (3)	0·3661 (2)	3·94 (9)
*B*C(8a)	0·42602 (6)	0·4611 (3)	0·4313 (2)	4·03 (9)
*B*C(11)	0·36848 (6)	0·1915 (3)	0·1956 (2)	4·18 (9)
*B*N	0·32732 (5)	0·2054 (3)	0·1951 (1)	3·94 (7)
*B*C(12)	0·30639 (7)	0·0354 (4)	0·1456 (2)	5·00 (11)
*B*C(13)	0·26507 (7)	0·0288 (4)	0·1530 (2)	5·88 (12)
*B*C(14)	0·26939 (8)	0·4159 (4)	0·1539 (2)	6·27 (18)
*B*C(15)	0·31028 (7)	0·3848 (4)	0·1460 (2)	5·15 (11)
*B*C(16)	0·46749 (8)	0·7656 (4)	0·4603 (2)	5·64 (11)
*A*H(C1)	0·0857 (7)	−0·450 (4)	0·051 (2)	6·1 (6)
*A*H(C2)	0·1484 (6)	−0·521 (4)	0·059 (2)	6·0 (6)
*A*H(C3)	0·2000 (8)	−0·331 (4)	0·147 (2)	7·7 (7)
*A*H(C4)	0·1869 (6)	−0·052 (3)	0·218 (2)	5·0 (5)
*A*H(C5)	0·0928 (6)	0·407 (3)	0·300 (2)	5·2 (5)
*A*H(C6)	0·0313 (6)	0·478 (3)	0·310 (2)	5·4 (5)
*A*H(C7)	−0·0201 (7)	0·257 (4)	0·235 (2)	6·0 (6)
*A*H(C8)	−0·0057 (6)	−0·016 (3)	0·156 (2)	5·5 (5)
*A*H1(C11)	0·1769 (6)	0·218 (3)	0·257 (2)	5·3 (5)
*A*H2(C11)	0·1442 (6)	0·382 (3)	0·255 (2)	4·8 (5)
*A*H1(C12)	0·2190 (7)	0·349 (4)	0·401 (2)	6·0 (6)
*A*H2(C12)	0·1841 (7)	0·520 (4)	0·387 (2)	6·1 (6)
*A*H1(C13)	0·2265 (8)	0·531 (5)	0·553 (2)	9·1 (8)
*A*H2(C13)	0·1829 (7)	0·489 (4)	0·557 (2)	7·5 (7)
*A*H1(C14)	0·1860 (8)	−0·063 (5)	0·574 (2)	9·0 (8)
*A*H2(C14)	0·1565 (9)	0·130 (5)	0·564 (2)	10·8 (10)

Table 3 (*cont.*)

	x	y	z	B_{eq} or B (Å^2)
*A*H1(C15)	0·1978 (7)	0·011 (4)	0·414 (2)	6·3 (6)
*A*H2(C15)	0·1524 (7)	−0·034 (4)	0·403 (2)	6·4 (6)
*A*H1(C16)	0·0263 (9)	−0·388 (5)	0·102 (2)	10·3 (9)
*A*H2(C16)	0·0021 (9)	−0·221 (5)	0·057 (2)	9·6 (9)
*A*H3(C16)	0·0297 (10)	−0·300 (5)	0·006 (3)	10·6 (10)
*B*H(C1)	0·4593 (6)	0·905 (3)	0·288 (2)	4·8 (5)
*B*H(C2)	0·4458 (6)	0·952 (3)	0·118 (2)	5·6 (6)
*B*H(C3)	0·4093 (7)	0·702 (4)	0·008 (2)	5·7 (6)
*B*H(C4)	0·3846 (6)	0·442 (3)	0·071 (2)	5·2 (5)
*B*H(C5)	0·3731 (6)	0·061 (3)	0·370 (2)	4·8 (5)
*B*H(C6)	0·3840 (6)	0·034 (3)	0·537 (2)	5·3 (6)
*B*H(C7)	0·4232 (6)	0·270 (3)	0·643 (2)	5·4 (6)
*B*H(C8)	0·4492 (6)	0·524 (3)	0·578 (2)	4·9 (5)
*B*H1(C11)	0·3709 (6)	0·194 (3)	0·125 (2)	4·7 (5)
*B*H2(C11)	0·3775 (6)	0·059 (3)	0·225 (2)	5·1 (5)
*B*H1(C12)	0·3202 (7)	−0·082 (4)	0·182 (2)	6·7 (7)
*B*H2(C12)	0·3076 (7)	0·030 (4)	0·072 (2)	7·2 (7)
*B*H1(C13)	0·2510 (8)	−0·094 (4)	0·123 (2)	8·1 (8)
*B*H2(C13)	0·2655 (7)	0·032 (4)	0·222 (2)	6·4 (6)
*B*H1(C14)	0·2700 (7)	0·409 (4)	0·226 (2)	5·8 (6)
*B*H2(C14)	0·2595 (8)	0·543 (5)	0·121 (2)	8·8 (8)
*B*H1(C15)	0·3111 (8)	0·367 (4)	0·072 (2)	8·7 (8)
*B*H2(C15)	0·3263 (7)	0·488 (4)	0·181 (2)	6·9 (7)
*B*H1(C16)	0·4807 (9)	0·715 (5)	0·520 (2)	9·5 (9)
*B*H2(C16)	0·4549 (10)	0·869 (5)	0·468 (3)	11·3 (10)
*B*H3(C16)	0·4891 (10)	0·792 (5)	0·439 (3)	9·9 (9)

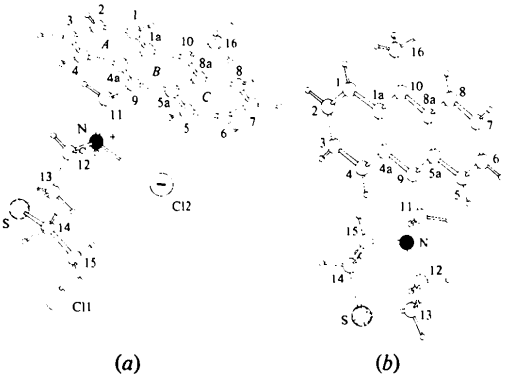


Fig. 1. Labelling of the atoms for (*a*) the drug (I) and (*b*) for its self-alkylation product (II). In (I), the Cl^- ion is Cl(2).

1969; Carrell, 1975), those of the *CRYSNET* package (Bernstein *et al.*, 1974) as well as the computer graphics programs *VIEW* (Carrell, 1976) and *DOCK* (Badler, Stodola & Wood, 1979).

Descriptions of structures

Compound (I)

The labelling of the atoms is illustrated in Fig. 1. Bond lengths and interbond angles are listed in Table 4. As noted earlier, values involving C(14), C(15) and Cl(1) are greatly modified by thermal disorder, and therefore no inferences can be made from them. The bond lengths in the methylanthracene moiety approximate those predicted by simple resonance theory.

Table 4. *Bond lengths* (Å) *and interbond angles* (°)

	Compound (I)	Compound (II) Molecule *A*	Compound (II) Molecule *B*
C(1)–C(2)	1·329	1·347	1·357
C(1)–C(1a)	1·431	1·436	1·429
C(2)–C(3)	1·401	1·394	1·400
C(3)–C(4)	1·362	1·346	1·354
C(4)–C(4a)	1·439	1·431	1·441
C(1a)–C(4a)	1·433	1·433	1·435
C(5)–C(6)	1·357	1·352	1·360
C(5)–C(5a)	1·456	1·429	1·429
C(6)–C(7)	1·412	1·406	1·399
C(7)–C(8)	1·369	1·349	1·346
C(8)–C(8a)	1·430	1·440	1·441
C(5a)–C(8a)	1·421	1·434	1·431
C(1a)–C(10)	1·417	1·405	1·414
C(8a)–C(10)	1·415	1·405	1·402
C(4a)–C(9)	1·410	1·408	1·409
C(5a)–C(9)	1·399	1·411	1·412
C(10)–C(16)	1·493	1·511	1·514
C(9)–C(11)	1·500	1·516	1·509
C(11)–N	1·506	1·472	1·475
N–C(12)	1·487	1·466	1·459
C(12)–C(13)	1·521	1·518	1·512
C(13)–S	1·801	1·793	1·788
S–C(14)	1·792	1·810	1·795
C(14)–C(15)	1·411	1·513	1·514
C(15)–C(1)	1·767	–	–
N–C(15)	–	1·450	1·463
C(1a)–C(1)–C(2)	122·1	122·1	122·0
C(1)–C(2)–C(3)	120·6	119·9	120·1
C(2)–C(3)–C(4)	120·4	120·7	120·7
C(3)–C(4)–C(4a)	121·5	122·5	121·6
C(1)–C(1a)–C(4a)	118·4	118·0	118·0
C(1)–C(1a)–C(10)	120·6	121·1	121·4
C(4a)–C(1a)–C(10)	120·9	120·9	120·6
C(4)–C(4a)–C(9)	123·0	123·0	122·4
C(4)–C(4a)–C(1a)	116·9	116·9	117·5
C(9)–C(4a)–C(1a)	120·0	120·1	120·2
C(5a)–C(5)–C(6)	121·4	122·0	121·6
C(5)–C(6)–C(7)	121·2	120·2	120·2
C(6)–C(7)–C(8)	119·4	120·4	120·7
C(7)–C(8)–C(8a)	121·3	122·0	121·8
C(5)–C(5a)–C(8a)	116·8	118·1	118·2
C(9)–C(5a)–C(8a)	121·8	120·3	120·6
C(5)–C(5a)–C(9)	121·4	121·7	121·2
C(8)–C(8a)–C(10)	120·1	122·1	121·9
C(8)–C(8a)–C(5a)	119·8	117·3	117·4
C(5a)–C(8a)–C(10)	120·1	120·6	120·6
C(4a)–C(9)–C(5a)	118·8	119·1	119·1
C(4a)–C(9)–C(11)	121·1	121·7	122·4
C(5a)–C(9)–C(11)	120·2	119·2	118·6
C(1a)–C(10)–C(16)	121·4	120·3	119·9
C(1a)–C(10)–C(8a)	118·4	118·9	118·9
C(8a)–C(10)–C(16)	120·1	120·8	121·1
C(9)–C(11)–N	113·5	114·9	112·9
C(11)–N–C(12)	116·1	107·6	109·5
N–C(12)–C(13)	108·6	113·2	112·2
C(12)–C(13)–S	114·4	112·8	113·3
C(13)–S–C(14)	103·9	96·5	96·5
S–C(14)–C(15)	120·2	111·4	113·1
C(14)–C(15)–Cl(1)	118·0	–	–
C(14)–C(15)–N	–	112·1	112·0
C(11)–N–C(15)	–	112·4	110·2
C(12)–N–C(15)	–	111·7	111·4

In compound (I), the average estimated standard deviation in a reported bond length is 0·01 Å, and 0·7° in a reported interbond angle. For compound (II), these values are, respectively, 0·003 Å and 0·2°.

The bonds C(1)–C(2), C(3)–C(4), C(5)–C(6) and C(7)–C(8) have almost pure double-bond character. The 14 atoms of the anthracene ring are coplanar to within experimental error; the r.m.s. deviation from the least-squares plane calculated using the coordinates of these atoms is 0·017 Å, the maximum deviation being 0·033 Å for C(2). The deviations from this plane for C(11) and C(16) are, respectively, 0·03 and 0·11 Å, the deviations being in opposite senses. Angles between the planes of the outer six-membered rings are listed in Table 5.

Torsion angles which describe the conformation of the side chain are listed in Table 6. As illustrated in Fig. 2, the side chain extends initially up and away from the aromatic ring system, somewhat biased toward ring *C* (see Fig. 1). At the amino N, the side chain turns toward ring *A* and then extends in a *trans* zigzag conformation. At the S atom, the side chain turns back in towards (but above) the aromatic rings and develops a helical conformation which extends to the Cl atom at the end of the chain. Also illustrated in Fig. 2 are the side-chain conformations observed for (III) and (IV). The S–C–C–Cl conformation is fully extended in these compounds, while in compound (I) it is helical. In (III) and (IV), the Cl atoms are 0·81 and 1·24 Å, respectively, out of the planes of the anthracene rings; in (I), this value is 7·39 Å.

The packing is illustrated in Fig. 3. Each (protonated) N atom is hydrogen bonded to two Cl^- ions [3·169 (4) and 3·155 (6) Å] and, in addition, is involved in a close contact [3·404 (6) Å] to a third

Table 5. *Angles between the planes of the outer rings*

Compound	Angle*
(I)	0·4 (6)°
(II*A*)	5·22 (9)
(II*B*)	2·96 (8)
(III)	8·7 (Glusker & Zacharias, 1972)
(IV)	4·8 (Lewis *et al.*, 1976)

* The estimated standard deviation of the interplanar angle (S. Litwin and J. P. Glusker, unpublished) was determined analytically as $\sigma(\theta) = [\sum(\partial\theta/\partial x_i)^2\sigma^2(x_i)]^{1/2}$.

Table 6. *Some torsion angles* (°) *observed in the two structures*

	Compound (I)	Compound (II) Molecule *A*	Compound (II) Molecule *B*
C(4a)–C(9)–C(11)–N	−99·3 (9)	−108·3 (3)	−106·6 (3)
C(5a)–C(9)–C(11)–N	80·4 (9)	73·0 (3)	72·8 (3)
C(9)–C(11)–N–C(12)	78·5 (8)	180·0 (2)	−169·7 (2)
C(11)–N–C(12)–C(13)	161·0 (6)	173·6 (2)	173·4 (2)
N–C(12)–C(13)–S	179·8 (5)	60·4 (3)	62·2 (3)
C(12)–C(13)–S–C(14)	−82·0 (7)	−52·0 (3)	−51·6 (2)
C(13)–S–C(14)–C(15)	−59·2 (11)	54·1 (3)	51·7 (2)
S–C(14)–C(15)–Cl(1)	−52·5 (13)	–	–
C(9)–C(11)–N–C(15)	–	56·5 (3)	67·4 (3)
S–C(14)–C(15)–N	–	−65·0 (3)	−62·3 (3)
C(14)–C(15)–N–C(12)	–	65·1 (3)	64·6 (3)
C(15)–N–C(12)–C(13)	–	−62·5 (3)	−64·4 (3)

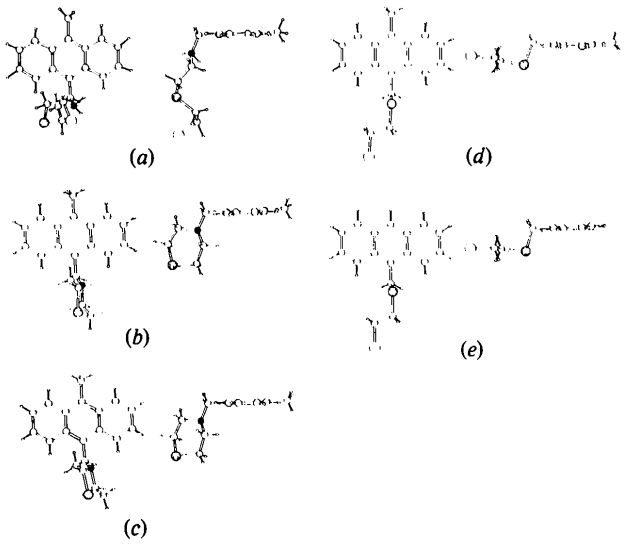


Fig. 2. The conformations of (I) and (II) are compared with related compounds, (III) and (IV). Large, medium and small unfilled circles correspond, respectively, to Cl, C and H atoms. N atoms are filled circles and S atoms are stippled. (*a*) (I), (*b*) (II*A*), (*c*) (II*B*), (*d*) (III), (*e*) (IV).

Cl^- ion; this latter is probably a charge–charge stabilizing interaction. Likewise each Cl^- ion is surrounded by three N atoms, only two of which are actually involved in hydrogen bonds with that Cl^- ion. The result is a series of tetragons of two N atoms and two Cl^- ions which ribbon throughout the crystal structure. Although there is no overlap of the aromatic ring system in planes 3·4 Å apart, the molecules do lie in parallel planes which are separated by 3·5 Å.

The packing around the S atom is dominated by two close contacts between S and C(8) (3·573 Å) and C(15) (3·616 Å) of neighboring molecules. Because they lie close to the C–S–C plane of the reference molecule, it is possible that C(8) and C(15) have a residual negative charge, since it has been pointed out (Rosenfield, Parthasarathy & Dunitz, 1977) that groups which lie in this plane tend to donate electrons to S. The Cl atom at the end of the alkylating side chain lies almost directly over C(10) of a related molecule, the C(10)···Cl(1) vector (at 3·71 Å) being approximately normal to the methylanthracene ring system.

Compound (II)

The reaction product, compound (II), that was isolated, was identified as 10-methyl-9-[(4-thiomorpholino)methyl]anthracene, the self-alkylation product of (I). The labelling of the atoms is illustrated in Fig. 1. Bond distances and interbond angles are listed in Table 4. As observed in the structure of the parent compound, the geometry of the methylanthracene moieties closely resembles those observed in related

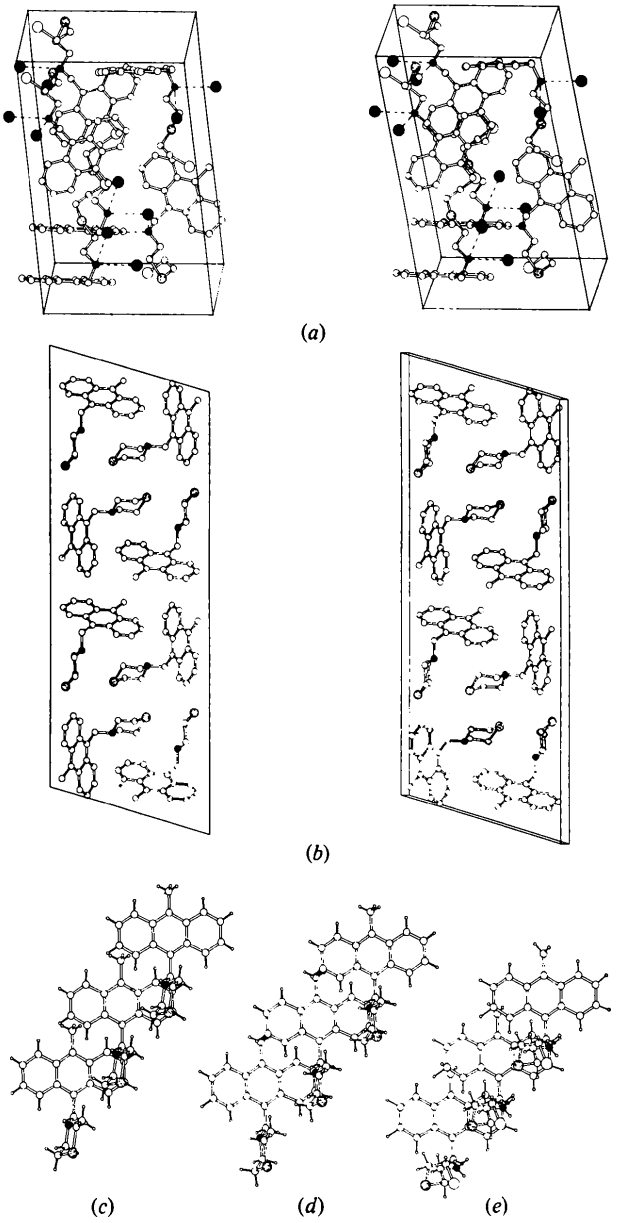


Fig. 3. The packing of (I) and (II). Large, medium and small unfilled circles correspond, respectively, to Cl, C and H atoms. Large filled circles correspond to Cl^- ions; medium filled circles correspond to N atoms, and S atoms are stippled. (*a*) A stereoview of the unit cell of (I). The hydrogen-bond relationships between the protonated amino N atom and the Cl^- ion, Cl(2), are as follows: N–H1(N)···Cl(2)(x,y,z; relative to Table 2): N–H1(N) 0·77 (5), H1(N)···Cl(2) 2·40 (5), N···Cl(2) 3·169 (4) Å, ∠N–H1(N)···Cl(2) 174 (7)°; N–H2(N)···Cl(2)($\frac{1}{2}-x$, $1-y$, $z-\frac{1}{2}$): N–H2(N) 1·14 (8), H2(N)···Cl(2) 2·06, N···Cl(2) 3·155 Å, ∠N–H2(N)···Cl(2) 160 (5)°. The H1(N)···Cl(2)···H2(N) and N···Cl(2)···N angles involving the hydrogen-bonded amino protons and amino protons are 99·9 and 101·5°, respectively. (*b*) A stereoview of the unit cell of (II). (*c*) The packing of molecules (I) along *c* (6·3443 Å). The molecules lie in planes 3·5 Å apart. (*d*) The packing of molecules (II*A*) along *b* (6·8965 Å). The molecules lie in planes 3·5 Å apart. (*e*) The packing of molecules (II*B*) along *b* (6·8965 Å). The molecules lie in planes 3·6 Å apart.

structures. With regard to bond lengths and bond angles, there is good agreement in these values between molecules *A* and *B* and, except where noted, their overall conformations are identical.

The anthracene rings are not planar, as shown in Table 5. The angle between the outer rings is 5·2° for molecule *A* and 3·0° for molecule *B*. These values contrast sharply with those for the almost planar anthracene portion of the parent alkylating agent. The r.m.s. deviations from the least-squares planes calculated using the coordinates of the 14 atoms of the anthracene ring are 0·049 and 0·300 Å for the two molecules in the asymmetric unit.

The thiomorpholine rings are in the chair conformation for both molecules and torsion angles about these rings are listed in Table 6. The six-membered thiomorpholine rings possess a plane which passes through the S and N atoms and which bisects the C(12)–N–C(15) and C(13)–S–C(14) angles. The cross-ring S···N separation is 3·18 Å in (II); in the parent alkylating agent (I), these atoms are separated by 4·10 Å.

The relationship between the anthracene ring system and the thiomorpholine ring is illustrated in Fig. 2; this relationship is governed by the conformation about the C(9)–C(11) and C(11)–N bonds. The rings are almost perpendicular to each other; the angle between the least-squares planes calculated using the coordinates of the 14 atoms of the anthracene moiety and those of the six atoms of the thiomorpholine ring is 80·6° for molecule *A* and 75·4° for molecule *B*. The N atom extends out of the plane of the anthracene rings. There is a slight bias in the tilt of the thiomorpholine ring towards one side of the aromatic ring system which bears a relationship to the lone pair of electrons on the N atom and the conformation of the thiomorpholine ring; it is the lone pair of electrons on the N atom which is positioned nearer the aromatic ring system than the bulkier C(12) methylene group which is consequently pushed away. This relationship is evidenced by the C(4a)–C(9)–C(11)–N and C(5a)–C(9)–C(11)–N torsion angles and, therefore, is governed by the conformation about the C(9)–C(11) bond. The most significant difference between molecules *A* and *B* is a 10° difference in the torsion angle about the C(11)–N bond.

The packing in the crystal structure is illustrated in Fig. 3. In this structure there are no intermolecular contacts less than 3·8 Å between S atoms and non-hydrogen atoms. As for (I), the methylanthracene ring systems do not overlap in planes 3·4 Å apart but, rather, they lie in planes separated by approximately 3·5 Å.

Conclusions

This analysis has shown the nature of self-alkylation of the side chain. A thiomorpholino ring is formed (compound II). The side chain in compound (I) is flexible. The flexibility of the anthracene ring structure is shown by the fact that it is planar in compound (I) but folded by 3–5° in compound (II). Although there is no overlap of ring systems in adjacent molecules in the crystal structures of either anthracene derivative, in both crystal structures, the molecules lie in parallel planes, approximately 3·5 Å apart, in a remarkably similar manner. In the parent alkylating agent (compound I) there is no internal N–H···S hydrogen bond, unlike the case for the ICR compounds that are acridine alkylating agents and have an intramolecular N–H···N hydrogen bond. In compound (I) the S and Cl atoms lie with a Cl–CH_2–CH_2–S torsion angle of −52·5°, unlike some similar alkylating agents (III and IV) in which this group is fully extended.

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Structural Features at the Anomeric Center in Aryl Pyranosides: Structure of *p*-Nitrophenyl α-D-Glucopyranoside

BY P. SWAMINATHAN

Department of Biochemistry, College of Agricultural & Life Sciences, University of Wisconsin–Madison, Madison, Wisconsin 53706, *USA*

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Abstract

$C_{12}H_{15}NO_8$, $M_r = 301{\cdot}26$, is monoclinic, $P2_1$, with $a = 28{\cdot}810\ (10)$, $b = 6{\cdot}747\ (3)$, $c = 6{\cdot}729\ (5)$ Å, $\beta = 103{\cdot}68\ (5)°$, $Z = 4$, $V = 1271$ Å^3, $D_c = 1{\cdot}574$ Mg m^{-3}, μ(Cu $K\alpha$) $= 1{\cdot}173$ mm^{-1}. The structure was refined to an R of 0·039 for 1900 reflections. The valence angles at the bridge oxygen atom O(1′) are significantly different between the two molecules. In both molecules the endocyclic C—O bond lengths are unequal (Δl = 0·044, 0·035 Å) and the glycosidic bond lengths are close to the mean C—O bond length. A comparison of the present axial glucoside structure with the known equatorial aryl pyranosides indicates that the molecular geometry around the anomeric center is not significantly different between the α and β anomers.

Introduction

A detailed analysis of the structural and conformational properties of alkyl glucosides has improved the understanding of the difference in the electronic properties of α- and β-pyranosides and the preferred *gauche* conformation about the glycosidic bonds (Lemieux & Chu, 1958; Berman, Chu & Jeffrey, 1967; Sundaralingam, 1968; Lemieux, Koto & Voisin, 1979; Jeffrey, 1979). In contrast to the large amount of crystal structure data available on the alkyl glucosides, only two crystal structures of aryl glucosides, *viz.* *p*-nitrophenyl *N*-acetyl-β-D-glucosaminide monohydrate (Brehm & Moult, 1975) and 1-naphthyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (Makinen & Isaacs, 1978), have been reported so far. As a general program of research on sugars in these laboratories, the crystal structure of *p*-nitrophenyl α-D-glucopyranoside has been determined. The present structure indicates that the geometrical features around the α anomeric center are similar to those observed in aryl β-D-glucosides.

Needle-shaped crystals of *p*-nitrophenyl α-D-glucopyranoside growing along the *c* axis were obtained by slow evaporation of an aqueous solution of the substance. Zero- and first-layer Weissenberg photographs collected about the *c* axis showed that the reflections with odd *h* indices were systematically weaker than the rest of the reflections. This suggested the presence of a pseudotranslational symmetry in the structure. A crystal of dimensions 0·1 × 0·1 × 0·4 mm mounted along the *c* axis was used for data collection on a four-circle Picker FACS-I automatic diffractometer. Intensities of 2255 reflections were measured

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