Structures of 1-(3,3-Dimethylamino)propyl Naphtho[2,1-b]thiophene-4-carboxylate and N-(3,3-Dimethylamino)propyl-8-methoxynaphtho[2,1-b]thiophene-4-carboxamide, Intercalators into Double-Helical DNA

By R. McKenna* and S. Neidle†

Cancer Research Campaign Biomolecular Structure Unit, The Institute of Cancer Research, Sutton, Surrey SM2 5NG, England

and W. D. Wilson

Department of Chemistry, Georgia State University, Atlanta, Georgia 30303, USA

Abstract. (1) $C_{18}H_{19}NO_2S$, $M_r = 313.42$, monoclinic, $P2_1/c$, $a = 11.503$ (3), $b = 15.932$ (2), $c = 9.133$ (2) Å, $\beta = 102.17$ (2)°, $V = 1636.1$ Å^3, $\lambda(Cu\ K\alpha) = 1.54178$ Å, $\mu = 1.762$ mm^{-1}, $F(000) = 664$, $T = 293$ (1) K, $R = 0.047$ for 2044 significant reflections. (2) $C_{19}H_{21}NO_3S$, $M_r = 343.45$, triclinic, $P\bar{1}$, $a = 9.873$ (2), $b = 13.163$ (3), $c = 14.065$ (3) Å, $\alpha = 101.33$, $\beta = 94.30$ (3), $\gamma = 91.35$ (3)°, $V = 1785.8$ Å^3, $Z = 4$, $D_x = 1.28$ Mg m^{-3}, $\lambda(Cu\ K\alpha) = 1.54178$ Å, $\mu = 1.699$ mm^{-1}, $F(000) = 728$, $T = 293$ (1) K, $R = 0.052$ for 1787 significant reflections. The torsion angle between the naphthothiophene ring and the carbonyl O atom of the side chain is 5.5 (4)° in structure (1) and 25 (2) and -32 (2)° in the two independent molecules of (2). This difference is due to out-of-plane distortions in (2) that arise from steric hindrance between H atoms on the amide and the ring system, at position 2.

Experimental. Both compounds were crystallized from a petroleum ether (35–60)–methylene chloride mixture to produce colourless prismatic crystals.

(1)

(2)
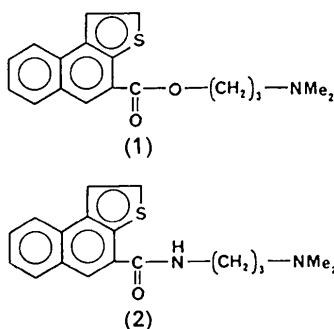
* Now at: Department of Biology, Purdue University, Lafayette, Indiana 47097, USA.
† Address correspondence to this author.

Crystals used for the analysis had dimensions $0.2 \times 0.2 \times 0.1$ mm (1) and $0.15 \times 0.20 \times 0.10$ mm (2). Accurate cell dimensions were obtained by least-squares refinement of, in each case, 25 reflections, in the ranges $10 < \theta < 29°$ (1) and $9 < \theta < 26°$ (2). Intensity data were collected on an Enraf–Nonius CAD-4 diffractometer using graphite-mono-chromated Cu $K\alpha$ radiation and an ω–2θ scan technique with max. scan times of 120 s (1) and 150 s (1). In both cases, unique data sets were collected. Data collection ranges were for (1): $1.5 < \theta < 60°$ with $0 \le h \le 10$, $0 \le k \le 18$, $-13 \le l \le 13$; for (2): $1.5 < \theta < 60°$ with $0 \le h \le 11$, $-14 \le k \le 14$, $-15 \le l \le 15$. For (1), 2827 unique reflections were measured, of which 2044 had $I > 3\sigma(I)$; systematic absences, $0k0$, $k = 2n + 1$ and $h0l$, $h = 2n + 1$ were found, denoting the space group as $P2_1/c$. For (2), 5376 unique reflections were obtained, with 1787 having $I > 1.5\sigma(I)$. Monitoring of standard reflections during the data collections showed no significant crystal decay. Intensity data were corrected for Lorentz, polarization and (post structure refinement) absorption effects using an empirical absorption correction (Walker & Stuart, 1983). Max. and min. transmission values were 1.12 and 0.87 for (1) and 1.15, 0.83 for (2). The structures were solved by direct methods: (1) using *MULTAN*82 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1982) and (2) using *SHELXS*86 (Sheldrick, 1986) with two independent molecules in the asymmetric unit. Refinements were by full-matrix least squares on F. Non-H atoms were refined anisotropically. In the case of (1), H-atom positions were located in difference Fourier maps and were included in the later rounds of refinement with their thermal parameters fixed at 5.0 Å^2. H-atom positions for (2) were generated from standard geometric considerations with C—H bond lengths of 0.95 Å and temperature factors of 5.0 Å^2.

Table 1. *Fractional coordinates and equivalent isotropic thermal parameters* ($Å^2$) *with e.s.d.'s in parentheses*

$$U_{eq} = (1/3)\sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i . \mathbf{a}_j.$$

	x	y	z	U_{eq} ($Å^2$)
S1	0·45422 (5)	0·21350 (4)	0·76746 (8)	3·85 (1)
C2	0·4070 (3)	0·3115 (2)	0·8061 (3)	4·48 (6)
C3	0·4683 (2)	0·3741 (2)	0·7594 (3)	4·24 (6)
C4	0·5589 (2)	0·3435 (2)	0·6864 (3)	3·40 (5)
C5	0·6399 (2)	3·3914 (2)	0·6205 (3)	3·60 (5)
C6	0·6394 (3)	0·4801 (2)	0·6163 (4)	4·74 (7)
C7	0·7174 (3)	0·5222 (2)	0·5507 (4)	5·64 (8)
C8	0·7992 (3)	0·4797 (2)	0·4873 (4)	5·67 (7)
C9	0·8032 (3)	0·3936 (2)	0·4883 (4)	4·81 (7)
C10	0·7228 (2)	0·3469 (2)	0·5540 (3)	3·74 (5)
C11	0·7227 (2)	0·2581 (2)	0·5555 (3)	3·76 (5)
C12	0·6449 (2)	0·2125 (2)	0·6177 (3)	3·27 (5)
C13	0·5617 (2)	0·2563 (2)	0·6833 (3)	3·14 (5)
C14	0·6420 (2)	0·1191 (2)	0·6142 (3)	3·57 (5)
O15	0·5695 (2)	0·0776 (1)	0·6585 (2)	4·35 (4)
O16	0·7296 (2)	0·0870 (1)	0·5564 (2)	4·41 (4)
C17	0·7323 (2)	−0·0042 (2)	0·5543 (3)	4·12 (6)
C18	0·8399 (2)	−0·0230 (2)	0·4803 (3)	4·12 (6)
C19	0·8638 (2)	−0·1160 (2)	0·4513 (3)	4·06 (6)
N20	0·8680 (2)	−0·1681 (1)	0·5838 (3)	4·10 (5)
C21	0·8579 (3)	−0·2568 (2)	0·5421 (4)	6·65 (9)
C22	0·9811 (3)	−0·1532 (3)	0·6849 (4)	7·0 (1)

Compound (2)

S1*A*	0·4909 (4)	0·4790 (3)	0·7622 (3)	4·4 (1)
C2*A*	0·498 (1)	0·4043 (9)	0·8510 (9)	5·0 (4)
C3*A*	0·600 (2)	0·4389 (9)	0·9216 (9)	4·4 (4)
C4*A*	0·680 (1)	0·5258 (9)	0·9038 (9)	3·7 (4)
C5*A*	0·796 (1)	0·5764 (9)	0·9684 (9)	3·8 (4)
C6*A*	0·844 (1)	0·5512 (9)	1·0563 (8)	3·5 (4)
C7*A*	0·955 (2)	0·606 (1)	1·1053 (9)	4·9 (4)
C8*A*	1·022 (1)	0·683 (1)	1·070 (1)	4·6 (4)
C9*A*	0·981 (1)	0·7054 (9)	0·9816 (9)	4·5 (4)
C10*A*	0·863 (1)	0·653 (1)	0·9297 (8)	4·3 (4)
C11*A*	0·818 (1)	0·6800 (9)	0·8416 (9)	3·7 (4)
C12*A*	0·704 (1)	0·6328 (8)	0·7825 (8)	3·1 (3)
C13*A*	0·636 (1)	0·5525 99)	0·8152 (8)	2·9 (3)
C14*A*	0·645 (1)	0·6592 (9)	0·6865 (8)	3·5 (3)
O15*A*	0·5222 (8)	0·6459 (7)	0·6625 (6)	5·0 (3)
N16*A*	0·734 (1)	0·7022 (8)	0·6401 (7)	5·1 (3)
C17*A*	0·693 (2)	0·751 (1)	0·556 (1)	7·0 (5)
C18*A*	0·739 (2)	0·696 (1)	0·469 (1)	8·1 (5)
C19*A*	0·710 (2)	0·755 (1)	0·381 (1)	8·4 (6)
N20*A*	0·767 (1)	0·8502 (9)	0·3977 (8)	6·8 (4)
C21*A*	0·908 (2)	0·862 (2)	0·410 (1)	13·5 (7)
C22*A*	0·724 (2)	0·898 (1)	0·318 (1)	13·7 (7)
O23*A*	1·006 (1)	0·5900 (6)	1·1950 (6)	6·3 (3)
C24*A*	0·946 (2)	0·517 (1)	1·2389 (9)	5·5 (4)

S1*B*	0·9922 (4)	0·96169 (3)	0·7457 (3)	5·6 (1)
C2*B*	0·994 (1)	1·027 (1)	0·838 (1)	6·0 (4)
C3*B*	1·092 (1)	1·0250 (9)	0·910 (1)	5·0 (4)
C4*B*	1·171 (1)	0·9341 (9)	0·8956 (8)	3·5 (4)
C5*B*	1·287 (1)	0·9011 (9)	0·9529 (8)	4·1 (4)
C6*B*	1·324 (1)	0·967 (1)	1·0443 (9)	5·7 (4)
C7*B*	1·433 (2)	0·9414 (9)	1·0961 (8)	4·7 (4)
C8*B*	1·508 (1)	0·853 (1)	1·0661 (9)	5·4 (4)
C9*B*	1·468 (1)	0·789 (1)	0·9775 (9)	5·0 (4)
C10*B*	1·350 (1)	0·8086 (9)	0·9189 (9)	4·2 (4)
C11*B*	1·302 (1)	0·7474 (9)	0·8259 (9)	3·9 (4)
C12*B*	1·192 (1)	0·7753 (9)	0·7684 (9)	3·7 (4)
C13*B*	1·128 (1)	0·8693 (9)	0·8080 (8)	4·4 (4)
C14*B*	1·143 (1)	0·707 (1)	0·6728 (9)	4·6 (4)
O15*B*	1·0245 (9)	0·7147 (7)	0·6418 (6)	5·5 (3)
N16*B*	1·233 (1)	0·6540 (8)	0·6242 (7)	4·5 (3)
C17*B*	1·199 (1)	0·600 (1)	0·523 (1)	5·5 (4)
C18*B*	1·272 (2)	0·642 (1)	0·450 (1)	8·3 (6)
N19*B*	1·268 (2)	0·751 (1)	0·457 (1)	8·8 (6)
N20*B*	1·336 (1)	0·8042 (9)	0·3942 (8)	7·2 (4)
C21*B*	1·288 (1)	0·779 (1)	0·296 (1)	8·3 (6)
C22*B*	1·344 (2)	0·910 (1)	0·426 (1)	10·8 (7)
O23*B*	1·494 (1)	0·9915 (6)	1·1848 (6)	5·7 (3)
C24*B*	1·431 (2)	1·082 (1)	1·232 (1)	7·1 (5)

Table 2. *Bond lengths* (Å) *and angles* (°) *with e.s.d.'s in parentheses*

		(1)	(2) Molecule A	Molecule B
S1	C2	1·714 (3)	1·733 (14)	1·739 (13)
S1	C13	1·728 (3)	1·745 (12)	1·740 (14)
C2	C3	1·342 (4)	1·36 (2)	1·34 (2)
C3	C4	1·437 (4)	1·44 (2)	1·44 (2)
C4	C5	1·431 (4)	1·47 (2)	1·47 (2)
C4	C13	1·389 (3)	1·40 (2)	1·386 (15)
C5	C6	1·413 (4)	1·39 (2)	1·42 (2)
C5	C10	1·424 (4)	1·41 (2)	1·40 (2)
C6	C7	1·356 (5)	1·37 (2)	1·34 (2)
C7	C8	1·382 (5)	1·38 (2)	1·41 (2)
C7	O23	–	1·38 (2)	1·379 (14)
C8	C9	1·372 (4)	1·38 (2)	1·38 (2)
C9	C10	1·415 (4)	1·41 (2)	1·43 (2)
C10	C11	1·415 (4)	1·40 (2)	1·44 (2)
C11	C12	1·365 (4)	1·40 (2)	1·41 (2)
C12	C13	1·416 (4)	1·40 (2)	1·43 (2)
C12	C14	1·489 (3)	1·53 (2)	1·50 (2)
C12	O15	1·199 (3)	1·235 (14)	1·228 (15)
C14	N16	–	1·31 (2)	1·30 (2)
C14	O16	1·334 (3)	–	–
N16	C17	–	1·49 (2)	1·475 (15)
O16	C17	1·457 (3)	–	–
C17	C18	1·500 (4)	1·41 (2)	1·48 (2)
C18	C19	1·540 (4)	1·59 (2)	1·43 (2)
C19	N20	1·448 (4)	1·34 (2)	1·42 (2)
N20	C21	1·461 (4)	1·39 (2)	1·40 (2)
N20	C22	1·448 (4)	1·44 (2)	1·38 (2)
O23	C24	–	1·38 (2)	1·43 (2)

C2	S1	C13	91·1 (1)	92·2 (6)	90·4 (6)
S1	C2	C3	113·7 (2)	112 (1)	112 (1)
C2	C3	C4	112·0 (2)	114 (1)	115 (1)
C3	C4	C5	127·8 (2)	124 (1)	133 (1)
C3	C4	C13	111·8 (2)	112 (1)	110 (1)
C5	C4	C13	120·3 (2)	124 (1)	117 (1)
C4	C5	C6	123·1 (3)	126 (1)	115 (1)
C4	C5	C10	117·9 (2)	112 (1)	121 (1)
C6	C5	C10	119·0 (3)	122 (1)	124 (1)
C5	C6	C7	120·5 (2)	117 (1)	117 (1)
C6	C7	C8	121·0 (3)	123 (1)	124 (1)
C6	C7	O23	–	121 (1)	129 (1)
C8	C7	O23	–	116 (1)	107 (1)
C7	C8	C9	120·8 (3)	121 (1)	118 (1)
C8	C9	C10	120·3 (3)	118 (1)	122 (1)
C5	C10	C9	118·4 (2)	119 (1)	115 (1)
C5	C10	C11	119·4 (3)	123 (1)	119 (1)
C9	C10	C11	122·1 (3)	118 (1)	126 (1)
C10	C11	C12	122·6 (3)	124 (1)	123 (1)
C11	C12	C13	118·3 (2)	116 (1)	116 (1)
C11	C12	C14	122·5 (2)	127 (1)	121 (1)
C13	C12	C14	119·2 (2)	117 (1)	123 (1)
S1	C13	C4	111·3 (2)	110·7 (9)	113 (1)
S1	C13	C12	127·2 (2)	128·5 (9)	122·4 (9)
C4	C13	C12	121·5 (2)	121 (1)	124 (1)
C12	C14	O16	112·2 (2)	–	–
C12	C14	N16	–	114 (1)	117 (1)
C12	C14	O15	124·0 (2)	120 (1)	118 (1)
O15	C14	O16	123·9 (2)	–	–
O15	C14	N16	–	126 (1)	125 (1)
C14	O16	C17	116·5 (2)	–	–
C14	N16	C17	–	122 (1)	121 (1)
O16	C17	C18	105·4 (2)	–	–
N16	C17	C18	–	111 (1)	115 (1)
C17	C18	C19	116·7 (2)	111 (1)	115 (1)
C18	C19	N20	112·4 (4)	114 (1)	112 (1)
C19	N20	C21	110·4 (2)	119 (2)	116 (1)
C19	N20	C22	107·7 (3)	108 (1)	113 (1)
C21	N20	C22	109·6 (3)	107 (2)	110 (1)
C7	O23	C24	–	122 (1)	116 (1)

Their contributions were included in structure-factor calculations but not refined. The final R factor for (1) was 0·047 with $wR = 0·060$ using a weighting scheme of the form $1/[\sigma^2(F) + (0·04F)^2]^{1/2}$. For (2), $R = 0·052$, $wR = 0·054$. In both cases the max. shift/e.s.d was $< 0·01$ for the final least-squares cycles. Max. and min. residual electron densities in the final difference Fourier maps were 0·38 and $-0·31\,e\,Å^{-3}$ for (1) and 0·29 and $-0·40\,e\,Å^{-3}$ for (2). Atomic scattering factors were taken from *International Tables for X-ray Crystallography* (1974, Vol. IV). Calculations were performed with *SDP* (Frenz, 1980). Final atomic coordinates are given in Table 1, bond lengths and angles in Table 2.* Figs. 1 and 2 show the molecular structures.

Related literature. The crystal structures of (1) and (2) (without the methoxy substituent) as hydrochloride salts have been reported (Wilson, Chandrasekaran, Kusuma, Boykin & Neidle, 1987). NMR studies and earlier binding analyses of their interactions with DNA (Wilson, Wang, Kusuma, Chandrasekaran, & Boykin, 1986) have shown that the latter compound binds an order of magnitude less strongly to DNA and is significantly less intercalated in between base pairs. This difference has been ascribed to non-coplanarity of the amide substituent with the napthothiophene ring compared to the ester.

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* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 54274 (42 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.
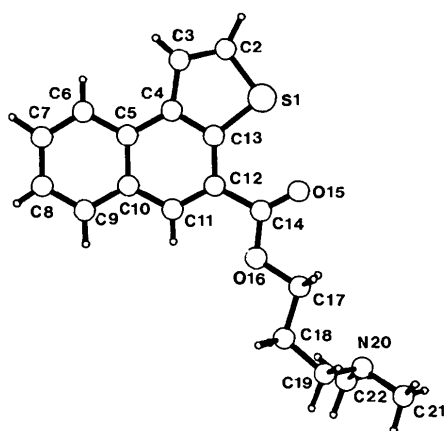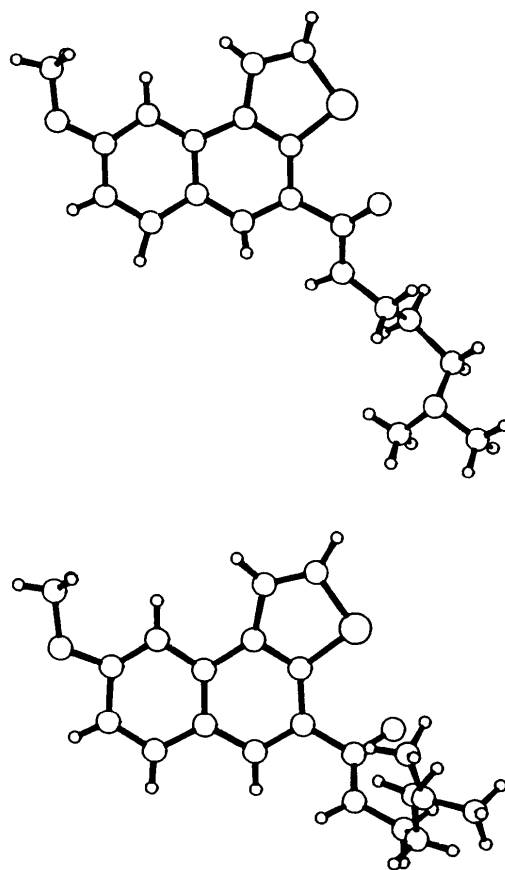

Fig. 2. View showing the two independent molecules for compound (2).

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Fig. 1. View of compound (1) with atom-labelling scheme.