$C_{16}H_{18}N_2O$

$^{-3}$, ratio of
SHELX76.
e shown in

Fig. 1, molecular packing in Fig. 2, positional parameters and equivalent values of the anisotropic temperature factors for the non-H atoms are given in Table 1,* interatomic distances, angles and torsion angles in Table 2.

*Lists of structure factors, anisotropic thermal parameters, H-atom parameters and bond distances and angles involving H atoms, have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 51775 (18 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Structure of the Antimalarial Halofantrine Hydrochloride

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Abstract. 1,3-Dichloro-α-[2-(dibutylamino)ethyl]-6-(trifluoromethyl)-9-phenanthrenemethanol hydrochloride, $C_{26}H_{31}Cl_2F_3NO^+.Cl^-$, $M_r = 536{\cdot}9$, monoclinic, $P2_1/n$, $a = 8{\cdot}169$ (3), $b = 32{\cdot}924$ (13), $c = 22{\cdot}775$ (6) Å, $\beta = 98{\cdot}99$ (3)°, $V = 6050{\cdot}2$ Å^3, $Z = 8$, $D_x = 1{\cdot}18$ g cm^{-3}, Cu $K\alpha$, $\lambda = 1{\cdot}54178$ Å, $\mu = 15{\cdot}51$ cm^{-1}, $F(000) = 2240$, room temperature, final $R = 18{\cdot}3\%$ for 2899 reflections with $|F_o| > 3\sigma$. The crystal structure of halofantrine hydrochloride was determined to 1·0 to 1·1 Å resolution. The high R factor is due to poor crystal quality. In order to have a crystal with sufficient thickness for data collection, it was necessary to use a crystal that had grown in layers. The high R factor is also due to a disordered CF_3 group, a disordered solvent channel, and high thermal factors on the long hydrocarbon chains. The two halofantrine conformers stack such that the phenanthrene rings are nearly on top of each other with the chlorine and CF_3 groups on opposite sides and with the hydrocarbon side chains projected away from each other, but on the same side of the phenanthrene rings. Atoms in the phenanthrene rings of the two stacked conformers are separated by 3·4 to 3·7 Å. On each of the halofantrine conformers, one of the *n*-butyl groups extends in a linear fashion whereas the other *n*-butyl group is bent back towards the phenanthrene ring. The crystal structure contains a pseudo twofold axis, parallel to the *b* axis, which intersects Cl(3) and passes through the center ring of the phenanthrene ring system of both conformers. Cl(3) is hydrogen bonded with O(1) (3·14 Å) and O(51) (3·09 Å) and perhaps makes a hydrogen-bond distance of 3·16 Å with a peak of electron density not found at full weight (symbolized Os, part of disordered solvent). Six disordered solvent peaks lie in a channel parallel to

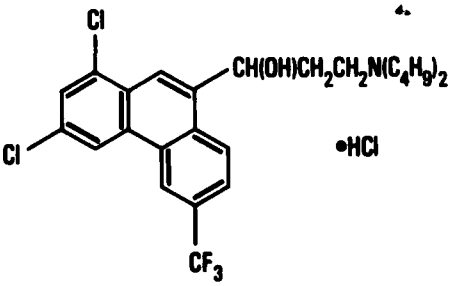

Fig. 1. Chemical structure of halofantrine hydrochloride.

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atoms, the heterocyclic ring is in a twist-like conformation. The benzene rings fused to the heterocycle ring form a dihedral angle of 95·4 (1)°. The neighbouring molecules are linked together by an intermolecular hydrogen bond of type N–H···N, with distances N···N 3·171 (4) and N···H 3·32 (2) Å and angle N–H···N 171 (1)°. The molecules linked by hydrogen bonds are arranged parallel to the twofold axes.

Experimental. This paper is a continuation of the study of the structure–biological activity relationship of dibenzoxazacycloalkenes. The title compound was obtained by hydrogenolysis of 6,9-ditosyldibenzo-[*b,j*]perhydro-1-oxa-5,8-diazacycloundecane with metallic sodium in boiling *n*-pentanol. The formula was confirmed by MS, IR and NMR spectra. The compound shows neuroleptic activity (Glinka, 1986).

Colourless, thin tabular crystals from ethanol at room temperature; crystal size 0·1 × 0·2 × 0·4 mm, Stoe diffractometer using θ–2θ scan technique; unit-cell parameters from 38 reflections, $\theta_{max} = 22{\cdot}3°$, Cu $K\alpha$ radiation, range of h, k and l $0 \leftrightarrow 5$, $0 \leftrightarrow 11$, $-30 \leftrightarrow 30$, respectively. Total of 1998 unique reflections measured to $\sin\theta/\lambda = 0{\cdot}56$ Å^{-1}, data not corrected for absorption. Standard reflections 0,0,12 and 042, maximum change of 4·0% and 1·5% respectively, 1711 reflections with $I > 2{\cdot}5\sigma(I)$ used in calculations; solution by direct methods using *SHELX*86 (Sheldrick, 1986), refinement using *SHELX*76 (Sheldrick, 1976), H atoms located from difference Fourier map, refinement by full-matrix least-squares procedure on F magnitudes, 244 parameters. Refinement to final $R = 0{\cdot}033$, $S = 0{\cdot}4643$, unit weights. Largest peaks on a final

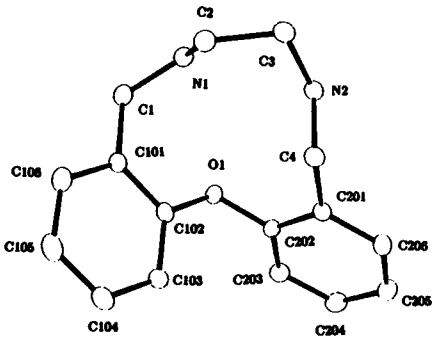

Fig. 1. The structure of the molecule with the atom-numbering scheme.

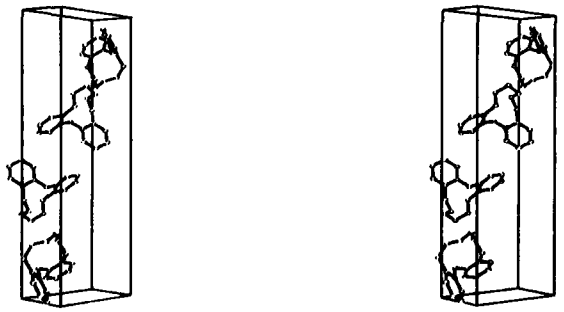

Fig. 2. A stereoview of the molecular packing, viewed down the *a* axis.

Table 1. *Final positional and thermal parameters* (× 10⁴) *with e.s.d.'s in parentheses*

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

	x	y	z	U_{eq}(Å²)
O1	6269 (2)	−994 (1)	1191 (0)	402 (6)
C1	7535 (4)	−3498 (2)	1640 (1)	472 (11)
N1	7857 (3)	−2628 (2)	2077 (1)	439 (9)
C2	10602 (4)	−2262 (2)	2205 (1)	486 (11)
C3	10687 (4)	−911 (2)	2475 (1)	490 (11)
N2	9061 (3)	76 (2)	2198 (1)	421 (8)
C4	10247 (4)	545 (2)	1742 (1)	405 (10)
C101	8720 (3)	−3025 (2)	1160 (1)	399 (9)
C102	8063 (3)	−1785 (2)	942 (1)	364 (9)
C103	9084 (4)	−1397 (2)	492 (1)	440 (10)
C104	10833 (4)	−2224 (2)	256 (1)	554 (12)
C105	11552 (4)	−3444 (2)	465 (1)	599 (13)
C106	10505 (4)	−3827 (2)	910 (1)	511 (12)
C201	8206 (3)	1173 (2)	1392 (1)	364 (9)
C202	6351 (3)	405 (2)	1119 (1)	358 (8)
C203	4466 (4)	986 (2)	801 (1)	441 (10)
C204	4366 (4)	2375 (2)	752 (1)	489 (11)
C205	6160 (4)	3159 (2)	1017 (1)	504 (11)
C206	8060 (4)	2563 (2)	1332 (1)	462 (11)

Table 2. *Interatomic distances* (Å), *bond angles* (°) *and selected torsion angles* (°) *with e.s.d.'s in parentheses*

O1–C102	1·387 (2)	C102–C103	1·383 (2)
O1–C202	1·403 (2)	C103–C104	1·375 (3)
C1–C101	1·514 (2)	C105–C106	1·377 (3)
C1–N1	1·461 (2)	C106–C101	1·390 (2)
N1–C2	1·461 (2)	C201–C202	1·392 (2)
C2–C3	1·524 (3)	C202–C203	1·379 (2)
C3–N2	1·463 (2)	C203–C204	1·387 (3)
N2–C4	1·458 (2)	C204–C205	1·370 (3)
C4–C201	1·502 (2)	C205–C206	1·387 (3)
C101–C102	1·397 (2)		

C102–O1–C202	118·1 (1)	C103–C104–C105	120·1 (2)
C101–C1–N1	117·6 (1)	C104–C105–C106	119·5 (2)
C1–N1–C2	114·4 (2)	C105–C106–C101	122·3 (2)
N1–C2–C3	109·9 (2)	C4–C201–C202	122·1 (1)
C2–C3–N2	110·0 (1)	C4–C201–C206	121·1 (1)
C3–N2–C4	113·7 (1)	C202–C201–C206	116·8 (2)
N2–C4–C201	111·4 (1)	O1–C202–C201	119·4 (1)
C1–C101–C102	122·3 (2)	O1–C202–C203	118·4 (2)
C1–C101–C106	120·9 (2)	C201–C202–C203	122·0 (2)
C106–C101–C102	116·8 (2)	C202–C203–C204	119·7 (2)
O1–C102–C101	116·4 (1)	C203–C204–C205	119·7 (2)
O1–C102–C103	122·2 (1)	C204–C205–C206	120·0 (2)
C101–C102–C103	121·4 (2)	C205–C206–C201	121·8 (2)
C102–C103–C104	120·0 (2)		

O1–C102–C101–C1	0·5 (3)	C3–N2–C4–C201	161·1 (2)
C102–C101–C1–N1	−56·3 (3)	N2–C4–C201–C202	−74·2 (3)
C101–C1–N1–C2	−54·5 (3)	C4–C201–C202–O1	3·7 (3)
C1–N1–C2–C3	152·8 (2)	C201–C202–O1–C102	−82·2 (2)
N1–C2–C3–N2	−49·1 (3)	C202–O1–C102–C101	154·4 (2)
C2–C3–N2–C4	−73·1 (2)		

the *a* axis. Cl(4) links the two halofantrine conformers *via* hydrogen bonding to N(1) (2·99 Å) and N(51) (3·04 Å).

Experimental. Title compound (WR 171,669) (Fig. 1) was obtained from Smith Kline & French Canada (Mississauga, Ont., Canada) and was crystallized from ethanol. Diffraction data were collected in the form of broad spots from a very thin plate containing inclusions and probably consisting of a stack of slightly misaligned crystals, 0·20 × 0·30 × 0·04 mm, in the θ–2θ mode to a maximum 2θ value of 100° on an *R*3*m* Nicolet four-circle diffractometer using Cu $K\alpha$ radiation with a graphite monochromator. Range of indices: h 0→8, k 0→21, and l −22→21. The total number of independent reflections was 6228. The standard reflections 2,0,12, 0,14,0, and 400 were monitored after every 60 intensity measurements. The standards remained constant within 7%. The lattice parameters were based on 23 centered reflections with 2θ values between 15 and 52°. No correction for absorption or extinction was used. The structure was solved routinely by direct phase determination (Karle & Karle, 1966) using the programs in *SHELXTL* (Sheldrick, 1980). All but nine of the non-H atoms in the two independent molecules were found in the first *E* map. The remaining terminal atoms of the *n*-butyl chains were found in the first difference map. In subsequent difference maps, atoms were found which correspond to alternate positions for one CF_3 group. The H atoms attached to the C atoms were placed in idealized positions. Least-squares refinement was performed using 2899 reflections with $|F_o| > 3\sigma(F_o)$. Coordinates for all non-H atoms except C(11) were refined (on *F*) by a blocked cascade program in *SHELXTL*. Anisotropic thermal parameters for the ring C atoms, the Cl atoms, and for one CF_3 group and isotropic thermal parameters for the remaining C, F, N and O atoms were refined for a total of 491 parameters. Six weaker peaks representing disordered solvent molecules appeared in a large channel (4·5 × 7·5 Å cross section) bounded by eight *n*-butyl groups from four halofantrine molecules and were included at half weight in the least-squares refinement. Their refined *U* values ranged from 0·18 to 0·40 Å^2. Neither the type of disorder nor the identification of the solvent molecules was established. Final $R = 18{\cdot}3\%$ and $wR = 17{\cdot}6\%$, $w = 1/[\sigma^2(|F|) + 0{\cdot}001(F_o)^2]$. $(\Delta/\sigma)_{max} = 0{\cdot}21$. Final difference electron density $|\rho| < 0{\cdot}82$ e Å^{-3}. Atomic scattering factors were those incorporated in *SHELXTL*.

Coordinates and U_{eq} values for the non-H atoms for the two conformers are listed in Table 1.* The bond

Table 1. *Fractional coordinates* (× 10^4) *and thermal parameters* U_{eq} (Å^2 × 10^3) *with e.s.d.'s in parentheses*

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

	x	*y*	*z*	U_{eq}
Molecule (I)				
Cl(1)	3524 (8)	1699 (3)	10962 (3)	105 (3)
Cl(2)	2550 (12)	115 (3)	10492 (4)	157 (5)
F(1)*	−1161 (43)	653 (11)	7190 (15)	148 (12)†
F(2)*	−2298 (49)	312 (9)	7834 (12)	135 (11)†
F(3)*	−3609 (36)	792 (9)	7319 (13)	125 (10)†
F(1)'*	−1231 (58)	349 (15)	7592 (22)	138 (17)†
F(2)'*	−3563 (66)	498 (16)	7673 (22)	147 (17)†
F(3)'*	−2184 (85)	782 (16)	7083 (22)	147 (21)†
N(1)	1540 (21)	3080 (5)	7851 (7)	61 (5)†
O(1)	640 (17)	2623 (4)	9582 (6)	70 (5)†
C(1)	2713 (34)	1302 (10)	10482 (13)	81 (14)
C(2)	2921 (30)	916 (10)	10624 (10)	117 (16)
C(3)	2199 (31)	594 (9)	10284 (10)	85 (13)
C(4)	1334 (37)	700 (11)	9732 (14)	103 (16)
C(4a)	1023 (32)	1105 (10)	9569 (11)	80 (13)
C(4b)	54 (26)	1222 (7)	8981 (11)	55 (10)
C(5)	−580 (29)	917 (9)	8593 (11)	81 (13)
C(6)	−1576 (29)	1039 (7)	8043 (9)	83 (11)
C(7)	−1800 (35)	1422 (9)	7909 (11)	90 (13)
C(8)	−1231 (27)	1720 (8)	8271 (9)	78 (11)
C(8a)	−164 (23)	1626 (6)	8852 (9)	49 (9)
C(9)	424 (26)	1953 (7)	9209 (10)	52 (10)
C(10)	1382 (28)	1834 (8)	9746 (9)	65 (11)
C(10a)	1757 (30)	1436 (8)	9899 (10)	76 (11)
C(11)*	−2150	700	7700	149 (13)†
C(12)	256 (26)	2362 (6)	9082 (8)	59 (7)†
C(13)	1208 (24)	2524 (6)	8590 (8)	50 (6)†
C(14)	809 (25)	2948 (6)	8412 (8)	55 (6)†
C(15)	730 (29)	3449 (7)	7593 (10)	79 (8)†
C(16)	756 (35)	3830 (9)	7914 (12)	125 (11)†
C(17)	−320 (46)	4174 (12)	7573 (16)	171 (15)†
C(18)	314 (67)	4530 (16)	7922 (23)	288 (27)†
C(19)	3435 (27)	3150 (7)	8062 (10)	86 (8)†
C(20)	4265 (41)	3275 (10)	7496 (13)	143 (12)†
C(21)	6042 (40)	3122 (10)	7546 (13)	130 (12)†
C(22)	6413 (39)	2652 (10)	7609 (14)	150 (13)†
Molecule (II)				
Cl(51)	3308 (8)	1748 (3)	7783 (3)	115 (4)
Cl(52)	3452 (11)	199 (3)	8445 (4)	155 (5)
F(51)	10288 (21)	899 (6)	11536 (6)	160 (10)
F(52)	9061 (24)	425 (5)	10989 (6)	158 (10)
F(53)	7785 (25)	752 (6)	11622 (6)	171 (11)
N(51)	4840 (20)	3128 (5)	10860 (7)	62 (5)†
O(51)	6087 (16)	2702 (4)	9173 (5)	66 (4)†
C(51)	3976 (26)	1344 (7)	8317 (9)	76 (11)
C(52)	3637 (36)	970 (8)	8255 (14)	109 (15)
C(53)	3998 (38)	674 (8)	8633 (17)	97 (16)
C(54)	5005 (33)	767 (10)	9173 (12)	88 (14)
C(54a)	5371 (29)	1165 (9)	9253 (11)	74 (12)
C(54b)	6529 (30)	1293 (10)	9860 (11)	71 (13)
C(55)	7119 (33)	1014 (10)	10229 (12)	91 (15)
C(56)	8052 (35)	1108 (10)	10764 (13)	75 (14)
C(57)	8488 (32)	1497 (10)	10843 (11)	73 (13)
C(58)	7949 (23)	1806 (8)	10510 (8)	69 (11)
C(58a)	6932 (27)	1711 (7)	9953 (9)	73 (10)
C(59)	6198 (22)	2041 (6)	9544 (9)	59 (9)
C(60)	5294 (26)	1903 (8)	8979 (9)	67 (11)
C(60a)	5002 (24)	1485 (7)	8877 (9)	52 (9)
C(61)	8770 (36)	801 (9)	11197 (12)	121 (11)†
C(62)	6477 (23)	2448 (5)	9687 (7)	38 (5)†
C(63)	5283 (24)	2592 (6)	10152 (8)	51 (6)†
C(64)	5775 (26)	3006 (6)	10368 (9)	64 (7)†
C(65)	5608 (38)	3467 (9)	11176 (13)	139 (12)†
C(66)	5914 (44)	3845 (11)	10906 (16)	185 (16)†
C(67)	7229 (63)	4134 (16)	11381 (22)	233 (22)†
C(68)	7541 (83)	4433 (19)	11069 (31)	343 (37)†
C(69)	3143 (33)	3208 (9)	10649 (12)	128 (11)†
C(70)	1968 (56)	3298 (13)	11227 (19)	204 (19)†
C(71)	558 (66)	3089 (15)	11229 (21)	240 (22)†
C(72)	441 (47)	2664 (12)	11136 (16)	173 (15)†
Cl(3)‡	3523 (9)	1579 (2)	4426 (3)	102 (3)
Cl(4)‡	782 (10)	2488 (3)	6847 (3)	124 (4)
Solvent peak				
Oz	−4855 (69)	3895 (18)	9075 (25)	227 (25)†

* Disordered CF_3 group. The primed F atoms were weighted 40%. Atom C(11) was kept fixed throughout the refinement procedure.

† These atoms were refined isotropically. The values represent U_{iso}.

‡ Cl atom of chloride salt.

* 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 51781 (40 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

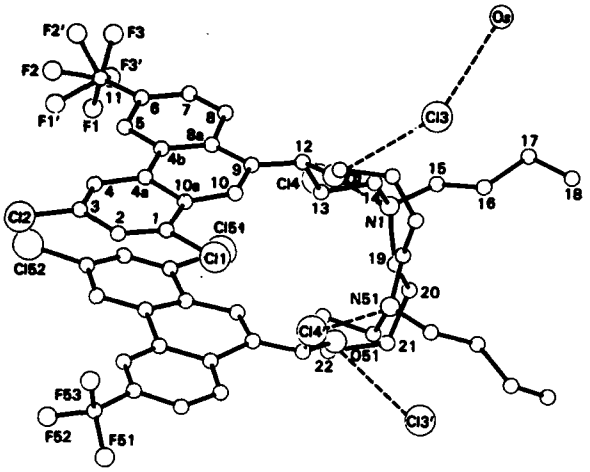

Fig. 2. Diagram of the two halofantrine conformers. The numbering scheme is indicated for the C atoms of one halofantrine conformer, for the heteroatoms of both halofantrine conformers, for the Cl atoms of the hydrochloride salt, and for a solvent atom (symbolized Os) not present at full weight. The numbering of the atoms in molecule (II) differs from the numbering of the atoms in molecule (I) by the addition of 50. Hydrogen bonds are depicted by dashed lines. The size of the circles was arbitrarily chosen to correspond approximately to the atomic weight of the atom.

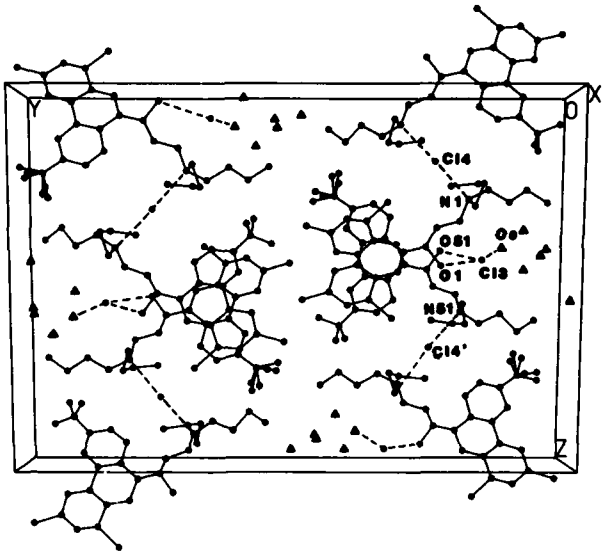

Fig. 3. View of halofantrine hydrochloride down the *a* axis. The packing diagram illustrates the stacking of the two halofantrine conformers such that a pseudo twofold axis, parallel to the *y* direction, passes between the stacked ring systems of molecules (I) and (II) (see near center of diagram). The isolated circles represent Cl atoms from the hydrochloride salt. The triangles represent disordered solvent molecules. Hydrogen bonds are depicted by dashed lines.

length of the H atoms attached to the C atoms was kept fixed at 0·96 Å throughout the refinement procedure. The atomic numbering scheme is shown in Fig. 2, molecular packing in Fig. 3.

Related literature. Halofantrine has demonstrated significant antimalarial activity against multi-drug-resistant malaria especially West African isolates of *Plasmodium falciparum* (Oduola, Milhous, Salako, Walker & Desjardins, 1987) and in humans against endemic *P. falciparum* malaria at the Thai–Kampuchean border (Boudreau *et al.*, 1988).

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Structure of Dimethyl 7,8-Benzobicyclo[2.2.2]octa-2,5,7-triene-2,3-dicarboxy

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Abstract. $C_{18}H_{14}O_4$, $M_r = 270{\cdot}29$, tetragonal, $I\bar{4}$, $a = 13{\cdot}772$ (4), $c = 7{\cdot}957$ (7) Å, $V = 2744$ (2) Å^3, $Z = 8$, $D_x = 1{\cdot}31$ g cm^{-3}, Mo $K\alpha$, $\lambda = 0{\cdot}71069$ Å, $\mu = 0{\cdot}9$ cm^{-1}, $F(000) = 1136$, $T = 295$ K, $R = 0{\cdot}034$ for 608 reflections. The molecule contains a benzobicyclo-octatriene ring system with an average C=C–C angle of 113·3 (5)° and other dimensions close to normal values. One methoxycarbonyl group makes an angle of 8·3° with the plane of the C(2)=C(3) double bond, and is thus conjugated, with C–C = 1·473 (8) Å; the other methoxycarbonyl group is not conjugated, angle 87·1° and C–C = 1·498 (9) Å.

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