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tert-Butyl 5-methoxy-3-pentylindole-1-carboxylate

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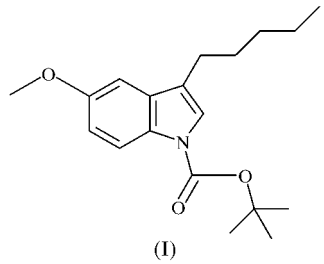
The molecule of the title compound, $C_{19}H_{27}NO_3$, is essentially planar, with all non-H atoms within 0.2 Å of the nine-membered indole plane, except for the three *tert*-butyl C atoms. The C_5 pentyl chain is in an extended conformation, with three torsion angles of 179.95 (13), 179.65 (13) and −178.95 (15)° (the latter two angles include the C atoms of the C_5 chain only). Three intramolecular C—H···O=C contacts are present (C···O < 3.05 Å and C—H···O > 115°), and an intermolecular C—H···O=C contact and π–π stacking complete the intermolecular interactions.

Comment

The key biochemical roles played by the indole ring in nature ensure that this heterocyclic system continues to attract scrutiny from medicinal and synthetic chemists. It is a common motif for drug targets and, as such, the development of new diversity-tolerant routes to this privileged biological scaffold continues to be of significant benefit (Gribble, 1996) and forms the basis of a wide variety of drugs, including the anti-inflammatory agent Indomethacin, Reserpine (exploited as a hypotensive agent) and Sumatriptan (used for the treatment of migraine). Historically, interest in indoles arose from the isolation and characterization of indole alkaloids, which, along with their semi-synthetic derivatives, have potent central nervous system activity. Many recent advances in indole synthesis have focused on metal-mediated procedures, with copper, palladium, tin, titanium and zirconium being the most prevalent (Sundberg, 1996; Gribble, 2000).

Recently, we reported a new approach to the synthesis of the indole scaffold, exploiting a controlled organolithium addition to functionalized styrenes, with the C—C bond formation reaction as the key synthetic step. A significant benefit of this strategy is that it can provide a direct route for the introduction of further structural diversity onto the ring system (Coleman & O'Shea, 2003), which may be of benefit for combinatorial library generations. Despite the prevalence of indole structures in the Cambridge Structural Database (CSD; Allen, 2002), there are no structures that contain the indole skeleton and atoms substituted at the 1- (C), 3- (C) and 5-positions (O) for direct comparison with the title compound, (I). However, many derivatives that contain the tryptophan residue are present in the CSD.



(I)

Pertinent bond lengths and angles for (I) are listed in Table 1 and the molecular structure is depicted in Fig. 1. The bond lengths and angles are as expected for indole systems (Fig. 1). Localization in the aromatic rings is discernible in (I), with a C1*A*—C2*A* bond length of 1.3481 (19) Å [the other NC_4-ring C—C lengths are 1.4496 (19) and 1.4090 (18) Å], and C—N distances of 1.4022 (16) and 1.4076 (18) Å; in the C_6 ring, the C13—C14 and C15—C16 bond lengths are 1.379 (2) and 1.386 (2) Å, respectively. In the C_5 pentyl chain, the C—C bond lengths for atoms C1–C5 are in the narrow range 1.509 (2)–1.5195 (19) Å; the C2*A*—C1—C2 angle opens to 114.98 (12)°, and the remaining C—C—C angles along the chain are in the range 113.71 (12)–113.86 (12)°, indicating a slight opening up by 4° from the ideal (109.5°) tetrahedral angle. The pentyl chain is in an extended conformation, with

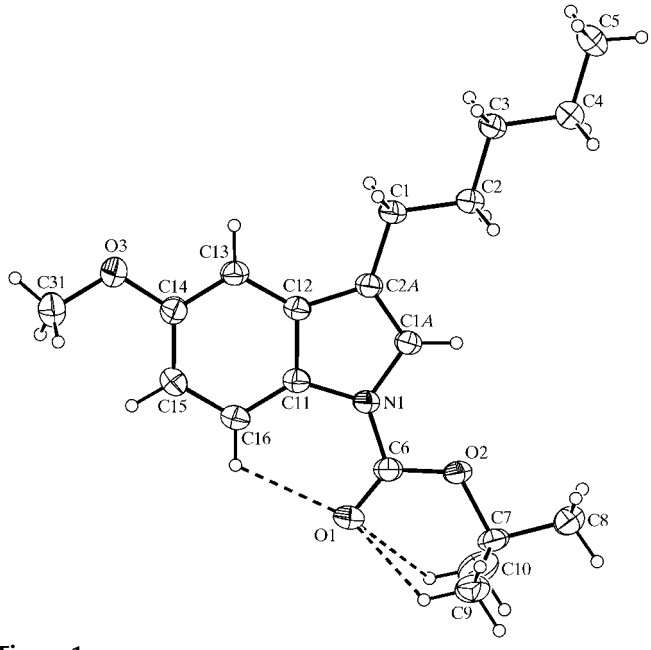


Figure 1
A view of (I), with the atomic numbering scheme. Displacement ellipsoids are drawn at the 30% probability level.

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three torsion angles of 179.95 (13) (C2*A*—C1—C2—C3), 179.65 (13) (C1—C2—C3—C4) and −178.95 (15)° (C2—C3—C4—C5). Indeed, the C_5 pentyl chain makes an angle of 4.41 (13)° with the NC_4 ring, and the largest deviation of an atom from the C_5 plane is 0.011 (1) Å for atom C3. In the *tert*-butoxycarbonyl group, the three C—C bond lengths lie between 1.511 (2) and 1.515 (2) Å, while the three O—C—C angles are 102.60 (12), 109.89 (12) and 108.92 (13)°, the lowest being that involving atom C8, which is not involved in an intramolecular contact; the three *tert*-butyl C—C—C angles are in the range 109.58 (14)–113.28 (15)°.

The five- and six-membered rings are coplanar, with an interplanar angle of 1.74 (8)°. The molecule of (I) is essentially planar, the largest deviations of non-H atoms from the indole plane being for the two atoms of the *tert*-butyl group [1.110 (3) Å for atom C10 and 1.402 (3) Å for atom C9]; all other atoms are within 0.2 Å of the nine-membered indole plane (apart from the three *tert*-butyl C atoms). The MeO group at atom C14 displays an O—C—C distortion, with O3—C14—C13/C15 angles of 115.60 (13) and 123.34 (13)° (*transoid* to atom C13 and the C_5 chain). These distortions, especially that of the C_{Me}—O—C—C torsion-angle orientation with respect to the O—C—C angle, have been commented on previously (Bruno *et al.*, 2001; Gallagher *et al.*, 2001; Wiedenfeld *et al.*, 2003).

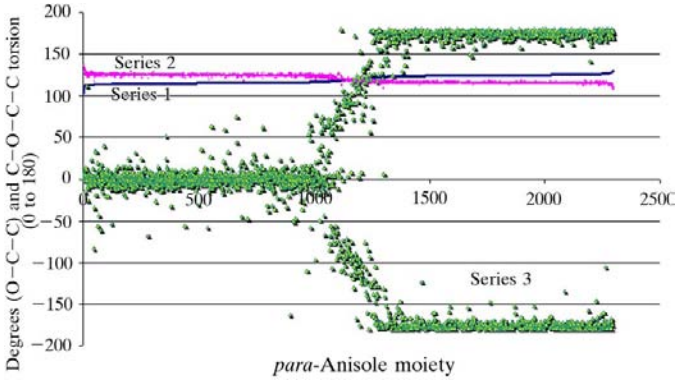

Figure 2
A graph of O_{Me}—C—C-angle differences plotted against their corresponding C—O—C—C torsion angle for 2299 [$-C_6H_4$–O–CH_3] structures (*x* axis) (CSD; Version 5.24 of July 2003; Allen, 2002). The intersect of the O—C—C lines (∼120°) correlates well with the C—O—C—C angles (triangles) between 60 and 120° (*y* axis).

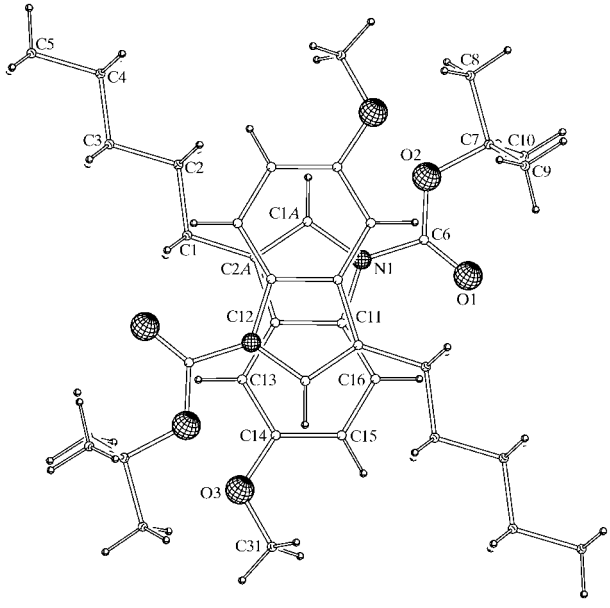

Figure 3
A view of the overlay of the alternating indole rings in the π–π stacking arrangement.

A review of the CSD (Version 5.24 of July 2003; Allen, 2002) was undertaken for structures containing an aromatic MeO group (analysed for *para*-C_6H_4–O–CH_3 with three-dimensional coordinates, $R < 0.10$ and no disorder). In Fig. 2, 2299 structures are plotted along the *x* axis (1 → 2299), with both O_{Me}—C—C angles plotted (between 100 and 140°, *y* axis) and correlated with their corresponding C—O—C—C angles. The overall trend is that when the C—O—C—C torsion angles (series 3 in Fig. 2) are ∼0 or 180°, corresponding to a nearly planar C—O—C—C fragment, the methoxy group usually exhibits a 5–10° difference between the two O—C—C angles (series 1 and 2 in Fig. 2); when the disposition of the C—O—C—C torsion angle tends towards 90° [mid-table on the *x* axis (abscissa)] for structures 1100–1300 and 60–120° on the *y* axis (ordinate), both O—C—C angles are usually ∼120°. For structures 1–1100/1300–2299, the O—C—C angles differ from 120° as the C—O—C—C angle tends towards 0/180°. The majority of *para*-anisole derivatives have a C—O—C—C angle close to planarity (< 15° or > 165°), with a significant difference in their O—C—C angles that can be attributed to steric and electronic effects. Two related examples have been reported by Wiedenfeld *et al.* (2003).

There are three C—H···O=C_{ester} intramolecular contacts present, involving atoms C9, C10 and C16 [with C···O distances shorter than 3.050 (2) Å and C—H···O angles larger than 115°; Table 2]. A direction-specific C15—H15···O1^{i} contact about inversion centres generates a weakly bonded dimer [C15···O15^{i} = 3.4812 (19) Å; symmetry code: (i) $-x, 1-y, 1-z$]. These dimeric units stack through aryl π–π stacking interactions. The mean planes of the indole units in these π–π stacks lie within 3.54 Å of one another, and the separations of the aromatic ring centroids are 3.6843 (9) and 3.6846 (9) Å for *Cg*1···*Cg*1^{ii} and *Cg*1···*Cg*2^{ii}, respectively [symmetry code: (ii) $1-x, 1-y, 1-z$; *Cg*1 and *Cg*2 are the centroids of the five- and six-membered rings; Fig. 3]. These interactions are 0.2 Å longer than, although similar in nature to, the π–π stacking in graphite, where the interplanar spacing is 3.35 Å (Wells, 1984). Examination of the structure with *PLATON* (Spek, 2003) showed that there were no solvent-accessible voids in the crystal lattice.

Experimental

tert-Butyl (4-methoxy-2-vinylphenyl)carbamate (0.4 g, 1.6 mmol) and tetramethylethylenediamine (0.48 ml, 3.2 mmol) were dissolved in dry diethyl ether (25 ml) and cooled to 195 K under N_2. *n*-BuLi (3.3 ml, 1.87 *M* in pentane, 6.4 mmol) was added dropwise, *via* a

syringe, over a period of 30 min. The temperature was raised to 248 K and the mixture was stirred for 2 h, during which time an orange–red colour developed. The solution was cooled to 195 K, anhydrous dimethylformamide (1.5 ml, 20 mmol) was added and the solution was warmed to room temperature. The diethyl ether was evaporated and replaced by tetrahydrofuran (THF, 25 ml), and the mixture was stirred at room temperature under N_2 for 5 h. The THF was then evaporated, and the residue was extracted with diethyl ether (2 × 30 ml) and dried over sodium sulfate. The solvent was evaporated to give a dark-yellow oil. Flash chromatography, eluting with hexane/diethyl ether (9:1), gave the product as a white solid (yield 0.40 g, 80%; m.p. 327–328 K). Colourless crystals were obtained by slow evaporation of an ethanol solution. IR (cm^{-1}): $\nu_{C=O}$ 1721 (KBr); ^{1}H NMR (300 MHz, d_6-DMSO): δ 0.88 (*t*, *J* = 7 Hz, 3H), 1.24–1.37 (*m*, 4H), 1.61 (*s*, 9H), 1.62–1.68 (*m*, 2H), 2.62 (*t*, *J* = 7.3 Hz, 2H), 3.80 (*s*, 3H), 6.93 (*dd*, *J* = 2.5, 8.9 Hz, 1H), 7.06 (*d*, *J* = 2.5 Hz, 1H), 7.38 (*s*, 1H), 7.90 (*d*, *J* = 8.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 22.7, 25.1, 28.5, 29.0, 32.0 56.0, 83.2, 102.3, 112.6, 116.1, 125.3, 130.1, 133.2, 150.1, 155.9; EI–MS: *m*/*z* 317.3. HRMS: $(M+H)^+$ 318.2080 found; $C_{19}H_{27}NO_3$ requires 318.2069. Analysis calculated for $C_{19}H_{27}NO_3$: C 71.89, H 8.57, N 4.41%; found: C 71.94, H 8.60, N 4.33%.

Crystal data

$C_{19}H_{27}NO_3$
M_r = 317.42
Triclinic, $P\overline{1}$
a = 8.9414 (6) Å
b = 8.9955 (6) Å
c = 11.7433 (6) Å
α = 105.001 (4)°
β = 93.265 (6)°
γ = 98.902 (6)°
V = 896.69 (10) Å^3
Z = 2
D_x = 1.176 Mg m^{-3}
Mo *K*α radiation
Cell parameters from 63 reflections
θ = 5.5–21.5°
μ = 0.08 mm^{-1}
T = 294 (1) K
Block, colourless
0.52 × 0.20 × 0.15 mm

Data collection

Bruker *P*4 diffractometer
ω scans
4895 measured reflections
4071 independent reflections
3004 reflections with $I > 2\sigma(I)$
R_{int} = 0.044
θ_{max} = 27.5°
$h = -11 \rightarrow 1$
$k = -11 \rightarrow 11$
$l = -15 \rightarrow 15$
4 standard reflections
every 296 reflections
intensity decay: 1%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.048
$wR(F^2)$ = 0.133
S = 1.03
4071 reflections
213 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0687P)^2 + 0.12P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.38 e Å^{-3}
$\Delta\rho_{min}$ = −0.19 e Å^{-3}

Compound (I) crystallized in the triclinic system; space group $P\overline{1}$ was assumed and confirmed by the analysis. All H atoms were treated as riding atoms using *SHELXL*97 defaults (for 294 K), the C—H distances ranging from 0.93 to 0.98 Å. The three largest peaks in the final difference map are in the vicinity of atom C11.

Data collection: *XSCANS* (Bruker, 1994); cell refinement: *XSCANS*; data reduction: *XSCANS*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 2003); software used to prepare material for publication: *SHELXL*97 and *PREP*8 (Ferguson, 1998).

Table 1
Selected geometric parameters (Å, °).

O1—C6	1.2029 (17)	N1—C11	1.4076 (18)
O2—C6	1.3365 (18)	N1—C1*A*	1.4022 (16)
O2—C7	1.4838 (16)	C1—C2*A*	1.5001 (18)
O3—C14	1.3846 (18)	C1*A*—C2*A*	1.3481 (19)
O3—C31	1.410 (2)	C11—C12	1.4090 (18)
N1—C6	1.3829 (17)	C12—C2*A*	1.4496 (19)
C6—O2—C7	120.16 (11)	N1—C11—C16	131.59 (12)
C14—O3—C31	116.97 (13)	C11—C12—C2*A*	107.87 (12)
C6—N1—C1*A*	127.03 (12)	C13—C12—C2*A*	132.65 (12)
C6—N1—C11	125.12 (11)	O3—C14—C13	115.60 (13)
C1*A*—N1—C11	107.83 (11)	O3—C14—C15	123.34 (13)
O1—C6—O2	126.73 (13)	C2*A*—C1*A*—N1	110.69 (12)
O1—C6—N1	123.03 (14)	C1*A*—C2*A*—C12	106.73 (11)
O2—C6—N1	110.24 (12)	C1*A*—C2*A*—C1	128.14 (13)
N1—C11—C12	106.87 (11)	C12—C2*A*—C1	125.11 (12)
C7—O2—C6—O1	−0.3 (2)	C11—N1—C6—O1	2.7 (2)
C31—O3—C14—C15	10.4 (2)	C2—C1—C2*A*—C1*A*	5.0 (2)

Table 2
Hydrogen-bonding geometry (Å, °).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C9—H9*C*···O1	0.96	2.36	2.944 (2)	119
C10—H10*A*···O1	0.96	2.46	3.033 (2)	118
C16—H16···O1	0.93	2.42	2.9356 (19)	115

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GD1287). Services for accessing these data are described at the back of the journal.

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