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Conformation of a Double Dibenzotropone Precursor of a Bifunctional Amitriptyline-Type Drug: 7,8,15,16-Tetrahydrodibenzo[*d,d'*]benzo[1,2-*a*; 4,5-*a'*]dicycloheptene-5,13-dione

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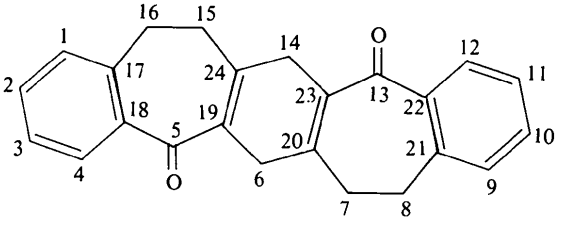
Abstract. $C_{24}H_{18}O_2$, $M_r = 338{\cdot}4$, monoclinic, $P2_1/n$, $a = 8{\cdot}099$ (1), $b = 9{\cdot}909$ (1), $c = 10{\cdot}539$ (1) Å, $\beta = 98{\cdot}30$ (1)°, $V = 836{\cdot}9$ (2) Å^3, $Z = 2$, D_m (NaI flotation) = 1·33 (1), $D_x = 1{\cdot}34$ Mg m^{-3}, λ(Mo $K\alpha$) = 0·7107 Å, $\mu = 0{\cdot}05$ mm^{-1}, $F(000) = 356$, $T = 298$ K, final $R = 0{\cdot}028$ for 690 observed reflections. The overall shape of the molecule is that of an elongated 'S' rather than a shallow 'U'; closely planar benzene rings are linked by seven-membered rings in twisted-boat conformations. The mean plane of the seven-membered rings makes angles of 11·0 (4) and 24·9 (4)°, respectively, with the planes of the outer and central benzene rings; the dihedral angle θ between alternate aromatic rings is 142° [centre-to-centre distance, $\delta = 5{\cdot}2$ (1) Å]. Separate halves (across the carbonyl group) of seven-membered rings have closely similar bond lengths but significantly different bond angles [126·7 (2), 125·9 (2)° for C(5)–C(18)–C(17) and C(16)–C(17)–C(18); 121·9 (1), 120·2 (1)° for C(5)–C(19)–C(24) and C(19)–C(24)–C(15)].

Introduction. Tricyclic systems with a non-planar six- or seven-membered central ring, as in amitriptyline, can show a marked psychotropic activity which may be related to molecular conformation (Rodgers, Horn & Kennard, 1975, 1976). The pentacyclic diketone 7,8,15,16-tetrahydrodibenzo[*d,d'*]benzo[1,2-*a*:4,5-*a'*]-dicycloheptene-5,13-dione (TBCD) may be regarded as a double dibenzotropone derivative (Agranat & Avnir, 1974) and is a precursor of bifunctional pentacyclic antidepressants analogous to amitriptyline [a prototype first-generation tricyclic antidepressant drug (Asscher, Lindley, Rotman & Agranat, 1985)]. Since non-planarity of the polycyclic skeleton is frequently associated with high psychotropic activity (Asscher, Avnir, Rotman & Agranat, 1982), an X-ray crystal-structure determination of TBCD should assist assessment of any distortions of the overall molecular shape that occur when alkylamino side chains are introduced (Horsburgh, Lindley, Stride, Asscher & Agranat, 1984).



TBCD

Experimental. Synthetic sample (Agranat & Avnir, 1974; Asscher *et al.*, 1985) crystallized from chloroform to yield golden lozenge-shaped crystals. Single crystal of dimensions 0·5 × 0·3 × 0·2 mm used to confirm photographically determined cell dimensions (15 reflections, $12 > \theta > 20°$) and for intensity data collection with graphite-monochromatized Mo $K\alpha$ radiation on a Syntex $P2_1$ four-circle diffractometer at Leeds University; intensity data measured using $\omega/2\theta$ step scans over 2θ range 4–40°, scan rates 1·0–29·3° min^{-1}, each reflection scanned 1° either side of α_1 and α_2, index ranges h 0/7, k 0/9, l −10/10, no significant drift in standard reflection 12$\bar{1}$ checked every 49 reflections, 938 measured reflections (including standards) yielded 690 unique data with $I \geq 3\sigma(I)$.

Structure solved by direct methods with *MULTAN*78 (Main, Lessinger, Woolfson, Germain & Declercq, 1977) from highest 152 of E values. After isotropic refinement [$\sum w(|F_o| - |F_c|)^2$ minimized] of all 13 non-H atoms in the asymmetric unit enabled R to reach 0·13, a difference Fourier synthesis revealed positions of all nine H atoms. With full-matrix anisotropic refinement on F (unit weights, *CRYSTALS*; Carruthers, 1978) for C and O, and with U_{iso} fixed for all H, R fell to 0·051. For the final stages,

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weighting was $w = [\sigma(F_o)^2 + 1{\cdot}8 \times 10^{-3} | F_o |^2]^{-1}$, with separate common U_{iso} for alkyl and ring H atoms, and final residuals $R = 0{\cdot}0282$, $wR = 0{\cdot}0391$ for 147 parameters and 690 contributing reflections, $(\Delta/\sigma)_{max} = 0{\cdot}3$. The final ΔF synthesis showed only random features $\leq 0{\cdot}2$ e Å^{-3}. Scattering factors from Cromer & Mann (1968) and (for H) from Stewart, Davidson & Simpson (1965). No correction for absorption.

Discussion. Final fractional coordinates of C and O atoms are in Table 1,* bond lengths, C—C—C and C—C—O bond angles in Table 2. The asymmetric unit in the centrosymmetric crystal structure of TBCD consists of one half-molecule; overall, the molecule (Figs. 1, 2) has an elongated 'S' shape (rather than a planar or shallow 'U' shape). The two independent six-membered rings (*A* and *C*) are closely planar with a mutual inclination of 37·9 (5)° [distance between ring centres, $\delta = 5{\cdot}2$ (1) Å]. Of the atoms adjoining the outer ring *A*, C(5) lies almost in and C(16) significantly [−0·09 (2) Å] out of plane *A*; C(5) is displaced significantly [−0·09 (2) Å] out of, and C(15) lies almost in [−0·01 (2) Å], the central benzene-ring plane, *C*. The mean plane of the seven-membered ring *B* makes angles of 11·0 (4) and 24·9 (5)° with the planes of the outer (*A*) and central (*C*) benzene rings, respectively.

The non-planar seven-membered cycloheptatriene ring (*B*) has a twisted-boat conformation and a mean endocyclic ring torsion angle of 36°. It has about the same degree of puckering as the corresponding ring in the crystal structures of two derivatives of TBCD more closely related to amitriptyline (Horsburgh *et al.*, 1984), 5,7-bis(3-dimethylaminopropyl)-5,7,12,13,15,16-hexahydrodibenzo[*d,d'*]benzo[1,2-*a*:5,4-*a'*]dicycloheptene-5,7-diol (I) and 5,13-bis(3-dimethylaminopropyl)-5,7,8,13,15,16-hexahydrodibenzo[*d,d'*]benzo[1,2-*a*:4,5-*a'*]dicycloheptene-5,13-diol (II), for which average torsion angles are 37·1 and 34·4°, respectively. In TBCD, (I) and (II), separate halves of the seven-membered rings (*B*) have closely similar bond lengths but appreciably different bond angles, in contrast to structures of dibenzotricyclic compounds with an unsaturated central (seven-membered) ring, *e.g.* dibenzo[*b,f*]azepine (Reboul, Cristau, Estienne & Astier, 1980) and dibenz[*b,f*]oxepine (Drake & Jones, 1982). In pentacyclic TBCD, (I) and (II), the outermost angles adjacent to ring *A* are significantly greater than the inner ones adjacent to ring *C*.

For ring *B* of TBCD, C—C bonds shared with aromatic rings are much shorter (about 1·40 Å) than other C—C bonds (1·49–1·51 Å) in the ring. In solution

Table 1. *Fractional atomic coordinates and equivalent isotropic temperature factors* (Å^2 × 10^2) *for the* O *and* C *atoms, with e.s.d.'s in parentheses*

$U_{eq} = \frac{1}{3}(U_{11} + U_{22} + U_{33})$.

	x	y	z	U_{eq}
O(1)	−0·3323 (2)	0·3327 (1)	−0·0116 (1)	56 (1)
C(1)	0·1661 (2)	0·1247 (2)	0·1810 (2)	51 (1)
C(2)	0·2565 (3)	0·2249 (2)	0·1341 (2)	56 (1)
C(3)	0·1762 (3)	0·3212 (2)	0·0550 (2)	56 (1)
C(4)	0·0069 (3)	0·3157 (2)	0·0226 (2)	48 (1)
C(5)	−0·2719 (2)	0·2240 (2)	0·0245 (1)	41 (1)
C(6)	−0·4958 (2)	0·0898 (2)	−0·0981 (1)	39 (1)
C(15)	−0·2691 (2)	0·0297 (2)	0·2355 (2)	48 (1)
C(16)	−0·0900 (3)	0·0050 (2)	0·2162 (2)	52 (1)
C(17)	−0·0070 (2)	0·1158 (2)	0·1512 (1)	42 (1)
C(18)	−0·0882 (2)	0·2141 (1)	0·0697 (1)	39 (1)
C(19)	−0·3849 (2)	0·1043 (2)	0·0134 (1)	38 (1)
C(24)	−0·3882 (2)	0·0137 (1)	0·1144 (1)	38 (1)

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

C(1)–C(2)	1·368 (3)	C(17)–C(18)	1·399 (2)
C(2)–C(3)	1·368 (3)	C(5)–O(1)	1·221 (2)
C(3)–C(4)	1·365 (3)	C(19)–C(24)	1·396 (2)
C(4)–C(18)	1·401 (2)	C(1)–H(1)	0·96 (2)
C(18)–C(5)	1·498 (3)	C(2)–H(2)	0·96 (2)
C(5)–C(19)	1·492 (2)	C(3)–H(3)	0·91 (2)
C(19)–C(6)	1·380 (2)	C(4)–H(4)	0·99 (2)
C(6)–C(20)	1·384 (3)	C(6)–H(6)	0·96 (2)
C(15)–C(24)	1·493 (2)	C(15)–H(151)	0·97 (2)
C(15)–C(16)	1·513 (3)	C(15)–H(152)	1·02 (2)
C(16)–C(17)	1·503 (2)	C(16)–H(161)	0·99 (2)
C(1)–C(17)	1·395 (3)	C(16)–H(162)	1·01 (2)

C(1)–C(2)–C(3)	119·6 (2)	C(19)–C(6)–C(20)	122·0 (2)
C(2)–C(3)–C(4)	119·8 (2)	C(6)–C(19)–C(24)	120·1 (2)
C(3)–C(4)–C(18)	121·6 (2)	C(19)–C(24)–C(14)	118·0 (1)
C(4)–C(18)–C(5)	114·3 (1)	C(19)–C(24)–C(15)	121·9 (1)
C(4)–C(18)–C(17)	119·0 (2)	C(15)–C(24)–C(19)	120·2 (1)
C(18)–C(5)–O(1)	119·4 (1)	C(16)–C(15)–C(24)	112·4 (2)
C(5)–C(18)–C(17)	126·7 (2)	C(15)–C(16)–C(17)	116·3 (2)
C(18)–C(5)–C(19)	122·8 (1)	C(16)–C(17)–C(18)	125·9 (2)
O(1)–C(5)–C(19)	117·6 (1)	C(16)–C(17)–C(1)	116·4 (2)
C(5)–C(19)–C(6)	117·8 (1)	C(1)–C(17)–C(18)	117·6 (2)
C(5)–C(19)–C(24)	121·9 (1)	C(17)–C(1)–C(2)	122·5 (2)

C(20) is the centrosymmetric equivalent of C(24).

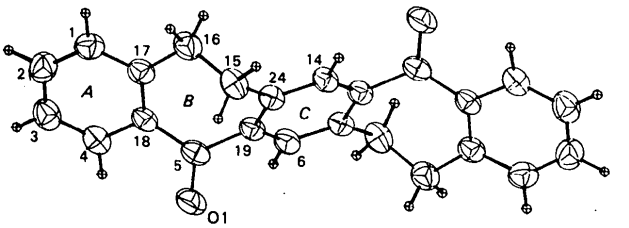

Fig. 1. Thermal vibration ellipsoids drawn at the 50% probability level showing the molecular plane and atom numbering of the asymmetric unit.

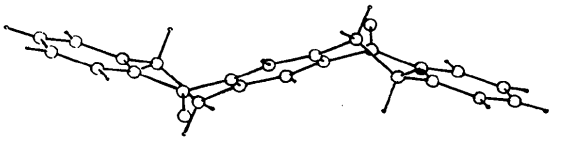

Fig. 2. Projected view of the molecule through the molecular plane.

*Lists of structure factors, anisotropic thermal parameters, parameters of H atoms and bond angles involving H atoms have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 44452 (7 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

there is evidently rapid inversion of the *B* rings at room temperature since the 300 MHz ^{1}H NMR spectrum indicates magnetic equivalence of the H atoms on the aliphatic bridge C(15) and C(16) atoms.

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Structure of 13-Ethyl-17β-hydroxy-11-methylene-18,19-dinor-17α-pregna-4,15-dien-20-yn-3-one (11-Methylenegestodene)

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Abstract. $C_{22}H_{26}O_2$, $M_r = 322{\cdot}45$ (×2), monoclinic, $P2_1$, $a = 11{\cdot}611$ (4), $b = 13{\cdot}316$ (3), $c = 12{\cdot}578$ (1) Å, $\beta = 112{\cdot}78$ (2)°, $V = 1793{\cdot}1$ (8) Å^3, $Z = 4$, $D_x = 1{\cdot}194$ g cm^{-3}, λ(Cu $K\alpha$) = 1·54184 Å, $\mu = 5$ cm^{-1}, $F(000) = 696$, room temperature, $R = 0{\cdot}045$ for 3260 unique reflections with $I \geq 2{\cdot}5\sigma(I)$. The two independent molecules have different conformations with respect to the orientation of the ethyl group and the steroid skeleton in the *A*-ring region. The conformation of the ethyl group, with respect to the *C/D* ring junction, is *trans* and *gauche* above the *D* ring respectively. This observation corresponds to the conformations found for gestodene. The observed conformational variation in the *A*-ring region illustrates the flexibility of this part of the steroid molecule. Molecular mechanics gives a steric energy difference between the relaxed structures of 3 kJ mol^{-1} in favour of the structure with the ethyl group in the *gauche* conformation. Two independent chains of hydrogen-bonded translational-equivalent molecules are formed parallel to **b**.

Introduction. 11-Methylenegestodene is a hybrid molecule of 3-ketodesogestrel (13-ethyl-17β-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one) and gestodene (13-ethyl-17β-hydroxy-18,19-dinor-17α-pregna-4,15-dien-20-yn-3-one). Gestodene is a new orally active progestogen (*e.g.* Losert, Casals-Stenzel & Buse, 1985), while 3-ketodesogestrel is the active metabolite of desogestrel, which has been marketed for oral contraception for some time. For gestodene two different crystal modifications have been observed (van Geerestein, Duisenberg, Duitz, Kanters & Kroon, 1987), wherein the steroid molecules differ in conformation with respect to the orientation of the ethyl group. The conformation with the ethyl group oriented above the *D* ring is energetically favourable in a Δ^{15} steroid, in contrast to steroids with a saturated *D* ring, where the *trans* conformation with respect to the *C/D* ring junction is more favourable. In the crystal structure, the *A* ring of 3-ketodesogestrel was found to be disordered with respect to the positions of C(1) and C(2) (van Geerestein, Kanters & Kroon, 1987). It has been postulated that the conformation of the *A* ring is closely related to the receptor binding. An inverted 1β,2α-half-chair conformation for the *A* ring should be related to a high affinity for the progestogen receptor (*e.g.* Duax, 1986, and references therein).

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