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Structures of the Diels–Alder Reaction Products of Thymoquinone and 1-Vinylcyclohexene. III. 5-Isopropyl-2-methyltricyclo[8.4.0.0^{2,7}]tetradeca-4,9-diene-3,6-dione, C₁₈H₂₄O₂

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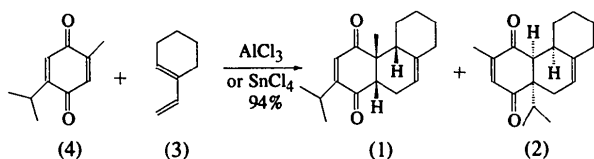
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Abstract

There are two slightly different molecules in the asymmetric unit of the title compound, each having all-*cis* ring fusion and an overall distorted hemispherical conformation. The cyclohexenedione rings are in a distorted half-boat conformation and the cyclohexene rings are in a distorted half-chair conformation, whereas the cyclohexane rings adopt an almost ideal chair conformation.

Comment

The Diels–Alder reactions of thymoquinone (4) and 1-vinylcyclohexene (3) lead to several different products depending mainly upon the reaction conditions used; the thermal reaction products have been analysed in part I (Iulek, Zukerman-Schpector, Brocksom & Silva, 1993). Lewis-acid-catalysed reaction conditions (AlCl₃ or SnCl₄) produce a 1:1 ratio of two principal products (1) and (2). The crystal structure of (2) has already been reported (Iulek, Zukerman-Schpector, Brocksom & Silva, 1994). As (1) is the key precursor in the reaction pathway aiming at the synthesis of naturally occurring cembrane diterpenes which possess interesting biological activities (Tius, 1988), the knowledge of the relative stereochemistry of the three contiguous stereogenic centres helps in the prediction of the steric course of subsequent reactions.



The two independent molecules which have overall distorted hemispherical conformations are rotamers, differing mainly in the isopropyl group orientation. The

methine H atom of the isopropyl group of the unprimed molecule points outwards whereas that of the primed one points inwards in the distorted hemisphere. Cremer and Pople's (1975) puckering parameters of the unprimed molecule show that the cyclohexenedione ring is in a conformation which lies between a half-boat and a half-chair [$Q = 0.411$ (6) Å, $\theta = 56.1$ (9), $\varphi = 313$ (1) $^\circ$], the cyclohexene ring is in a slightly distorted half-chair conformation [$Q = 0.459$ (6) Å, $\theta = 48.3$ (8), $\varphi = 89$ (1) $^\circ$] and the cyclohexane ring is in a chair conformation [$Q = 0.568$ (7) Å, $\theta = 177.0$ (7), $\varphi = 166$ (13) $^\circ$]. While the puckering parameters of the primed molecule show that the cyclohexenedione ring is in a half-boat, distorted towards a boat, conformation [$Q = 0.432$ (6) Å, $\theta = 122.7$ (8), $\varphi = 120$ (1) $^\circ$], the cyclohexene ring is in a distorted half-chair conformation [$Q = 0.452$ (6) Å, $\theta = 131.5$ (8), $\varphi = 266$ (1) $^\circ$] and the cyclohexane ring is in a distorted chair, towards a half-boat, conformation [$Q = 0.567$ (6) Å, $\theta = 6.1$ (6), $\varphi = 4$ (6) $^\circ$].

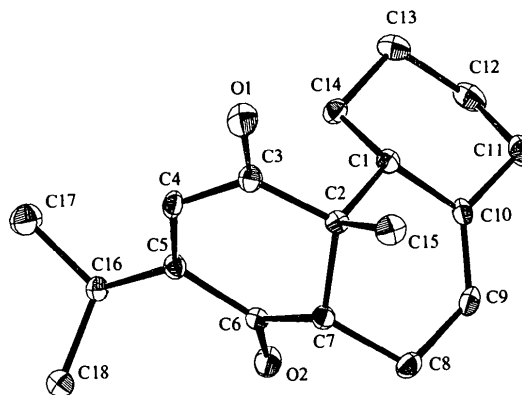


Fig. 1. Projection of the unprimed molecule showing the atom labelling. 50% probability displacement ellipsoids are shown.

Experimental

Crystals of the title compound were obtained by slow evaporation from hexane.

Crystal data

C₁₈H₂₄O₂

$M_r = 272.386$

Triclinic

$P\bar{1}$

$a = 8.707$ (1) Å

$b = 12.106$ (2) Å

$c = 14.704$ (4) Å

$\alpha = 92.03$ (1) $^\circ$

$\beta = 91.55$ (1) $^\circ$

$\gamma = 96.86$ (1) $^\circ$

$V = 1537.08$ (52) Å³

$Z = 4$

$D_x = 1.1771$ Mg m⁻³

D_m not measured

Mo $K\alpha$ radiation

$\lambda = 0.71073$ Å

Cell parameters from 25 reflections

$\theta = 8.28$ – 17.05 $^\circ$

$\mu = 0.075$ mm⁻¹

$T = 293$ K

Irregular

$0.20 \times 0.15 \times 0.13$ mm

Yellow

Data collection

Enraf-Nonius CAD-4 diffractometer	$R_{\text{int}} = 0.0464$
$\omega/2\theta$ scans	$\theta_{\text{max}} = 23.02^\circ$
Absorption correction: none	$h = -9 \rightarrow 9$
4616 measured reflections	$k = -13 \rightarrow 13$
4284 independent reflections	$l = 0 \rightarrow 16$
1684 observed reflections [$I > 2\sigma(I)$]	2 standard reflections
	frequency: 1800 min
	intensity decay: -0.9%

Refinement

Refinement on F^2	$\Delta\rho_{\text{max}} = 0.280 \text{ e } \text{\AA}^{-3}$
$R(F) = 0.0609$	$\Delta\rho_{\text{min}} = -0.202 \text{ e } \text{\AA}^{-3}$
$wR(F^2) = 0.1273$	Extinction correction: <i>SHELXL93</i> (Sheldrick, 1993)
$S = 1.158$	Extinction coefficient: 0.0090 (14)
4284 reflections	Atomic scattering factors from <i>International Tables for Crystallography</i> (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)
364 parameters	
H atoms: one common U for each molecule	
$w = 1/[\sigma^2(F_o^2) + (0.0505P)^2 + 1.2072P]$	
where $P = (F_o^2 + 2F_c^2)/3$	
$(\Delta/\sigma)_{\text{max}} = -0.001$	

Table 1. Fractional atomic coordinates and equivalent isotropic displacement parameters (\AA^2)
$$U_{\text{eq}} = (1/3)\sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i \cdot \mathbf{a}_j.$$

	x	y	z	U_{eq}
O1	0.6167 (6)	1.3256 (4)	0.8761 (3)	0.081 (2)
O2	0.7326 (5)	0.9619 (4)	0.6968 (3)	0.0667 (13)
C1	0.4725 (7)	1.2009 (4)	0.6960 (4)	0.045 (2)
C2	0.6422 (6)	1.2407 (4)	0.7302 (4)	0.0426 (15)
C3	0.6478 (7)	1.2442 (5)	0.8324 (4)	0.053 (2)
C4	0.6873 (7)	1.1458 (5)	0.8805 (4)	0.054 (2)
C5	0.7223 (6)	1.0517 (5)	0.8383 (4)	0.045 (2)
C6	0.7346 (6)	1.0496 (5)	0.7385 (4)	0.043 (2)
C7	0.7527 (6)	1.1605 (5)	0.6939 (4)	0.0435 (15)
C8	0.7475 (7)	1.1489 (5)	0.5909 (4)	0.057 (2)
C9	0.5864 (8)	1.1380 (5)	0.5533 (4)	0.056 (2)
C10	0.4639 (7)	1.1616 (5)	0.5977 (4)	0.050 (2)
C11	0.3014 (8)	1.1408 (6)	0.5598 (4)	0.071 (2)
C12	0.2011 (7)	1.0568 (6)	0.6142 (6)	0.077 (2)
C13	0.2113 (7)	1.0928 (6)	0.7131 (5)	0.074 (2)
C14	0.3777 (7)	1.1139 (5)	0.7507 (4)	0.053 (2)
C15	0.6895 (7)	1.3571 (5)	0.6956 (5)	0.068 (2)
C16	0.7515 (7)	0.9479 (5)	0.8866 (4)	0.056 (2)
C17	0.6916 (9)	0.9376 (6)	0.9796 (5)	0.096 (3)
C18	0.9236 (8)	0.9349 (6)	0.8844 (5)	0.070 (2)
O1'	0.6949 (6)	0.2184 (4)	0.1138 (3)	0.080 (2)
O2'	0.8196 (5)	0.6125 (3)	0.2744 (3)	0.0677 (13)
C1'	0.8770 (6)	0.3034 (4)	0.2906 (4)	0.0412 (15)
C2'	0.7115 (6)	0.3200 (4)	0.2553 (4)	0.0422 (15)
C3'	0.7064 (7)	0.3094 (5)	0.1524 (4)	0.049 (2)
C4'	0.7222 (6)	0.4110 (5)	0.0989 (4)	0.048 (2)
C5'	0.7505 (6)	0.5145 (5)	0.1359 (4)	0.0423 (15)
C6'	0.7566 (7)	0.5277 (5)	0.2364 (4)	0.047 (2)
C7'	0.6700 (6)	0.4350 (5)	0.2873 (4)	0.046 (2)
C8'	0.6838 (7)	0.4524 (5)	0.3907 (4)	0.059 (2)
C9'	0.8219 (7)	0.4088 (5)	0.4306 (4)	0.054 (2)
C10'	0.9070 (6)	0.3422 (5)	0.3878 (4)	0.0415 (15)
C11'	1.0514 (7)	0.3075 (5)	0.4301 (4)	0.054 (2)
C12'	1.1909 (7)	0.3504 (5)	0.3755 (4)	0.056 (2)
C13'	1.1659 (7)	0.3210 (5)	0.2752 (4)	0.059 (2)
C14'	1.0152 (6)	0.3546 (5)	0.2363 (4)	0.047 (2)
C15'	0.5969 (7)	0.2282 (5)	0.2921 (4)	0.064 (2)
C16'	0.7816 (7)	0.6163 (5)	0.0804 (4)	0.054 (2)
C17'	0.7137 (8)	0.6044 (6)	-0.0147 (5)	0.077 (2)
C18'	0.9541 (8)	0.6540 (6)	0.0807 (5)	0.092 (3)

Table 2. Geometric parameters (\AA , $^\circ$)

O1—C3	1.219 (6)	O1'—C3'	1.213 (6)
O2—C6	1.205 (6)	O2'—C6'	1.215 (6)
C1—C10	1.504 (8)	C1'—C10'	1.495 (7)
C1—C14	1.525 (7)	C1'—C14'	1.541 (7)
C1—C2	1.562 (7)	C1'—C2'	1.557 (7)
C2—C3	1.501 (8)	C2'—C3'	1.513 (8)
C2—C15	1.529 (7)	C2'—C15'	1.526 (7)
C2—C7	1.538 (7)	C2'—C7'	1.541 (7)
C3—C4	1.477 (8)	C3'—C4'	1.479 (8)
C4—C5	1.349 (8)	C4'—C5'	1.341 (7)
C5—C6	1.474 (8)	C5'—C6'	1.479 (8)
C5—C16	1.509 (7)	C5'—C16'	1.504 (7)
C6—C7	1.508 (7)	C6'—C7'	1.509 (8)
C7—C8	1.515 (8)	C7'—C8'	1.527 (8)
C8—C9	1.483 (8)	C8'—C9'	1.485 (8)
C9—C10	1.320 (8)	C9'—C10'	1.315 (7)
C10—C11	1.496 (8)	C10'—C11'	1.499 (7)
C11—C12	1.523 (9)	C11'—C12'	1.524 (8)
C12—C13	1.500 (9)	C12'—C13'	1.509 (8)
C13—C14	1.526 (8)	C13'—C14'	1.523 (7)
C16—C17	1.481 (9)	C16'—C17'	1.498 (8)
C16—C18	1.527 (8)	C16'—C18'	1.516 (8)
C10—C1—C14	108.5 (5)	C10'—C1'—C14'	107.2 (5)
C10—C1—C2	112.2 (5)	C10'—C1'—C2'	112.5 (5)
C14—C1—C2	117.7 (5)	C14'—C1'—C2'	117.7 (4)
C3—C2—C15	110.1 (5)	C3'—C2'—C15'	108.9 (5)
C3—C2—C7	109.8 (5)	C3'—C2'—C7'	110.3 (5)
C15—C2—C7	109.5 (5)	C15'—C2'—C7'	110.0 (5)
C3—C2—C1	108.6 (5)	C3'—C2'—C1'	108.6 (5)
C15—C2—C1	108.5 (5)	C15'—C2'—C1'	108.4 (4)
C7—C2—C1	110.4 (4)	C7'—C2'—C1'	110.5 (4)
O1—C3—C4	119.7 (6)	O1'—C3'—C4'	119.9 (6)
O1—C3—C2	121.1 (6)	O1'—C3'—C2'	120.6 (6)
C4—C3—C2	119.2 (6)	C4'—C3'—C2'	119.5 (5)
C5—C4—C3	124.0 (6)	C5'—C4'—C3'	123.8 (5)
C4—C5—C6	118.3 (5)	C4'—C5'—C6'	117.8 (5)
C4—C5—C16	124.3 (6)	C4'—C5'—C16'	123.2 (5)
C6—C5—C16	117.4 (5)	C6'—C5'—C16'	118.9 (5)
O2—C6—C5	119.8 (6)	O2'—C6'—C5'	120.9 (6)
O2—C6—C7	123.3 (6)	O2'—C6'—C7'	122.5 (6)
C5—C6—C7	116.9 (5)	C5'—C6'—C7'	116.4 (5)
C6—C7—C8	112.6 (5)	C6'—C7'—C8'	113.8 (5)
C6—C7—C2	113.3 (5)	C6'—C7'—C2'	111.8 (5)
C8—C7—C2	112.6 (5)	C8'—C7'—C2'	112.2 (5)
C9—C8—C7	111.6 (5)	C9'—C8'—C7'	112.7 (5)
C10—C9—C8	125.8 (6)	C10'—C9'—C8'	125.2 (6)
C9—C10—C11	124.2 (6)	C9'—C10'—C11'	123.1 (5)
C9—C10—C1	122.7 (6)	C9'—C10'—C1'	122.4 (6)
C11—C10—C1	112.8 (6)	C11'—C10'—C1'	114.3 (5)
C10—C11—C12	112.0 (5)	C10'—C11'—C12'	109.9 (5)
C13—C12—C11	109.8 (6)	C13'—C12'—C11'	112.0 (5)
C12—C13—C14	112.8 (6)	C12'—C13'—C14'	113.0 (5)
C1—C14—C13	110.6 (5)	C1'—C14'—C13'	110.4 (5)
C17—C16—C5	116.2 (5)	C17'—C16'—C5'	114.9 (5)
C17—C16—C18	111.8 (5)	C17'—C16'—C18'	111.3 (6)
C5—C16—C18	109.2 (5)	C5'—C16'—C18'	109.9 (5)

H atoms were placed on stereochemical grounds and included as fixed contributors with an overall isotropical thermal parameter for each independent molecule that converged to $U = 0.076$ (4) and 0.075 (4) \AA^2 for the unprimed and primed molecules, respectively.

Data collection: *CAD-4 Software* (Enraf-Nonius, 1989). Cell refinement: *CAD-4 Software*. Data reduction: *CAD-4 Software*. Program(s) used to solve structure: *SHELXS86* (Sheldrick, 1985). Program(s) used to refine structure: *SHELXL93* (Sheldrick, 1993). Molecular graphics: *ZORTEP* (Zsolnai, 1995).

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: LI1143). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Methyl 2,7,7-Trimethyl-4-(3-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate and 3-Acetyl-2,7,7-trimethyl-4-phenyl-1,4,5,6,7,8-hexahydro-5-quinolone

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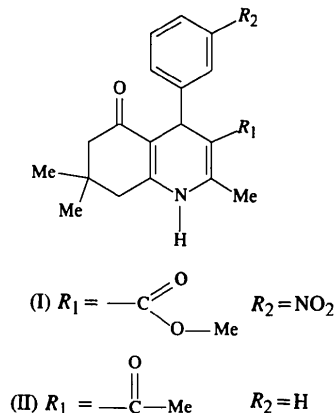
Abstract

The 1,4-dihydropyridine (1,4-DHP) ring and the cyclohexanone ring adopt similar conformations in both the title compounds, methyl 2,7,7-trimethyl-4-(3-nitrophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate, C₂₀H₂₂N₂O₅, (I) and 3-acetyl-2,7,7-trimethyl-4-phenyl-1,4,5,6,7,8-hexahydro-5-quinolone, C₂₀H₂₃NO₂, (II). The 1,4-DHP rings have boat conformations with the aryl group occupying the pseudo-axial position and orthogonal to the plane through the 1,4-DHP ring. The cyclohexanone ring has an intermediate half-chair/sofa form. In both compounds, the carboxyl group is coplanar

to the endocyclic double bond as a consequence of π conjugation. The molecules are linked by N—H···O hydrogen bonds but the packing is different in each case. In compound (I) a hydrogen bond is formed between the N—H and the carboxyl group while in compound (II), a hydrogen bond is formed between the N—H and the O atom of the cyclohexanone ring.

Comment

1,4-Dihydropyridines (1,4-DHP) such as nifedipine and other related structures are the most important calcium antagonists and are well established drugs for the treatment of cardiovascular diseases (Bosert & Vater, 1989; Martín-León & Seoane, 1990). In contrast to this, derivatives of 1,4-DHP which are closely related in structure can act as calcium agonists (Goldmann & Stoltefuss, 1991) whereby the 1,4-DHP agonist enhances Ca²⁺ influx across the cell membrane and thus produces quite the opposite pharmacological effect. It has been reported that the presence of fused five-membered lactones or cyclohexanone rings in the 1,4-DHP system leads to compounds which exhibit calcium agonist (Martín-León *et al.*, 1995; Goldmann & Stoltefuss, 1991), or similar effects (Rose & Dräger, 1992). The crystal structure analyses of the title compounds (I) and (II) were carried out in order to investigate the conformational features of 1,4-DHP when fused with a cyclohexanone ring.



The 1,4-DHP ring and the cyclohexanone ring adopt similar conformations in both compounds. The 1,4-DHP ring has a boat conformation [$Q_T = 0.257$ (3) and 0.266 (5) Å for compounds (I) and (II), respectively] with two local pseudo-mirror planes, one running along N1···C4 and the other through the midpoints of the C2—C2 and C4a—C8a bonds. The aryl group occupies the pseudo-axial position in both compounds and is orthogonal to the mean plane through the 1,4-DHP ring. In compound (I), the nitro substituent on the phenyl ring is synperiplanar to the H atom H(4) of the 1,4-DHP ring. This is in agreement with the previously reported