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# Structure and Conformation of Substituted Cycloheptatrienes. I. 2,5-Dimethyl-3,4-diphenyl-1,3,5-cycloheptatriene

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# Abstract

 $C_{21}H_{20}$  is monoclinic, space group  $P2_1/c$ , with  $a = 11\cdot312$  (5),  $b = 8\cdot503$  (5),  $c = 16\cdot91$  (1) Å,  $\beta = 98\cdot04$  (1)°, Z = 4. The structure was refined to  $R = 0\cdot044$  for 1119 counter reflections. The sevenmembered ring is boat-shaped with structure angles  $\alpha = 52\cdot6^{\circ}$  and  $\beta = 34\cdot3^{\circ}$ . Empirical force-field calculations of the isolated molecule predict  $\alpha = 51\cdot0^{\circ}$  and  $\beta = 27\cdot5^{\circ}$ , while  $\alpha = 51\cdot9^{\circ}$  and  $\beta = 31\cdot9^{\circ}$  were calculated considering packing effects. The enthalpy of the inversion barrier between the two boat forms has been calculated to be 59 kJ mol<sup>-1</sup>.

## Introduction

Structures and conformations of seven-membered ring systems have been of interest for many years (for a review see Tochtermann, 1970). Cycloheptatriene displays a flexible boat-shaped structure, which can be influenced by substituents over a wide range, up to the valence isomer norcaradiene [(I); Berson, Hartter, Klinger & Grubb, 1968].



Conformations of substituted cycloheptatrienes have been investigated mainly by NMR spectroscopy (Lambert, Durham, Lepoutere & Roberts, 1965; Günther, Görlitz & Meisenheimer, 1974; Kessler, 1979) and force-field calculations (Kao & Allinger, 1977; Lindner, 1979). One microwave (Butcher, 1965) and one electron diffraction analysis of cycloheptatriene (Trætteberg, 1964) have been reported and one X-ray analysis of a substituted cycloheptatriene [(II); Davis & Tulinsky, 1966].



In our attempt to clarify the influence of substituents on the conformation of the cycloheptatriene moiety, we determined the crystal structures of a series of its methyl and phenyl derivatives. In this work, we report the structure of 2,5-dimethyl-3,4-diphenyl-1,3,5-cycloheptatriene (III).



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## Experimental

Crystals were prepared by Kessler & Bicker (1976) (see also Bicker, 1977) as long transparent blocks (axis [010]) from CDCl<sub>3</sub>. Systematic absences hol and 0k0 for odd indices determined the space group as  $P2_1/c$ . Crystal data are summarized in Table 1. Intensities were collected on a Stoe two-circle diffractometer (Cu  $K\alpha$  radiation) equipped with a graphite monochromator; the crystal was oriented along **b**. 2525 symmetry-independent reflections hol to h6l with  $2.5 \le \theta \le 60^\circ$  were measured in the  $\omega - 2\theta$  scan mode. The data were corrected for background, Lorentz and polarization factors. 1119 reflections had  $|E| > 3\sigma_E$ .

## Structure analysis and refinement

The structure was determined by direct methods with SHELX 77 (Sheldrick, 1977). Full-matrix least-squares refinement of the atomic coordinates and anisotropic thermal parameters reduced R to 0.112; H atoms were located by a difference synthesis. With weights  $w = 1/\sigma(|F|)^2$  and isotropic H-atom thermal parameters, the final R was 0.044. None of the heavy-atom parameters shifted more than  $0.07\sigma$  in the last cycle. Positional parameters are listed in Table 2.\*

### Results

2,5-Dimethyl-3,4-diphenyl-1,3,5-cycloheptatriene exhibits a boat structure with alternating bond lengths (Fig. 1). The bond angles at the folding lines are about 120°, while they are enlarged at the stern (125°) and reduced to a normal  $sp^3$  angle (109°) at the bow. Torsion angles are 65 and 40° at bow and stern respectively. The double bonds are not twisted (Fig. 2). No effects of conjugation between the phenyl rings and the rear double bond are observed. The connecting bonds show single-bond nature (1.50 Å). The planes of the two phenyl rings form an angle of 58° (Table 3).

<sup>\*</sup> Lists of structure factors and thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34499 (10 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Molecular formula  $C_{21}H_{20}$ ,  $M_r = 272$ , space group  $P2_1/c$ 

a = 11.312(5)  Å	Z = 4
b = 8.503(5)	$\rho_o = 1 \cdot 11 \text{ Mg m}^{-3}$ (flotation)
c = 16.91(1)	$\rho_c = 1 \cdot 12$
$\beta = 98.04(1)^{\circ}$	$\mu = 0.41 \text{ mm}^{-1}$
$V = 1610.5 \text{ Å}^3$	

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	x	У	Z
C(1)	0.6329 (4)	-0.1452 (5)	0.0868 (3)
C(2)	0.7326(3)	-0.1766 (4)	0.1365 (2)
C(3)	0.7477(3)	<i>−</i> 0·1220 (4)	0.2201 (2)
C(4)	0.7102(3)	0.0183 (4)	0.2456 (2)
C(5)	0.6523(3)	0.1412 (5)	0.1930 (2)
C(6)	0.5696 (3)	0.1068 (6)	0.1309 (3)
C(7)	0.5307 (4)	<i>−</i> 0·0552 (5)	0.1119 (3)
C(21)	0.8298 (4)	<i>−</i> 0·2744 (6)	0.1079 (3)
C(31)	0.8116 (3)	−0·2352 (5)	0.2800 (2)
C(32)	0.9359 (4)	<i>−</i> 0·2494 (6)	0.2916 (3)
C(33)	0.9928 (5)	<i>−</i> 0·3513 (6)	0.3470 (3)
C(34)	0.9269 (5)	-0.4430 (7)	0.3916 (3)
C(35)	0.8047 (5)	-0.4302 (6)	0.3812 (3)
C(36)	0.7476 (4)	<i>−</i> 0·3277 (5)	0.3253 (2)
C(41)	0.7322 (3)	0.0603 (4)	0.3325 (2)
C(42)	0.8428 (4)	0.0911 (4)	0.3726 (3)
C(43)	0.8597 (4)	0.1321 (5)	0.4530 (3)
C(44)	0.7630 (5)	0.1403 (6)	0.4929 (3)
C(45)	0.6516 (5)	0.1102 (5)	0.4543 (3)
C(46)	0.6352 (4)	0.0700 (5)	0.3746 (3)
C(51)	0.6863 (5)	0.3093 (6)	0.2125 (3)
H(C1)	0.633 (4)	<i>−</i> 0·201 (4)	0.034 (2)
H(C6)	0.539 (3)	0.206 (4)	0.104 (2)
H(C7)	0.506 (3)	<i>−</i> 0·127 (4)	0.156 (2)
H′(C7)	0.461 (3)	-0.067 (4)	0.071 (2)
H(C21)	0.847 (4)	<i>−</i> 0·398 (6)	0.142 (3)
H′(C21)	0.907 (3)	-0.214(4)	0.119(2)
H"(C21)	0.806 (3)	-0.298 (5)	0.049(3)
H(C32)	0.978(3)	-0.177(4)	0.264(2)
H(C33)	1.079(3)	-0.34/(4)	0.355(2)
H(C34)	0.960(3)	-0.522(5)	0.435 (2)
H(C35)	0.758(3)	-0.507(5)	0.414(2)
H(C36)	0.660(3)	-0.316(3)	0.318(2)
H(C42)	0.907 (3)	0.077 (4)	0.348 (2)
H(C43)	0.946 (3)	0.145 (4)	0.480(2)
H(C44)	0.778 (3)	0.142(5)	0.546(3)
H(C45)	0.580 (4)	0.101(5)	0.484(3)
H(C46)	0.553(3)	0.046(4)	0.345(2)
H(C51)	0.765 (3)	0.328(4)	0.221(2)
H'(C51)	0.663 (4)	0.333(6)	0.264(3)
H"(C51)	0.652 (3)	0.387 (4)	0.169 (2)



Fig. 1. Bond lengths (Å) and angles (°) of 2,5-dimethyl-3,4diphenyl-1,3,5-cycloheptatriene ( $\sigma_{cc} = 0.005 \text{ Å}, \sigma_{ccc} = 0.2^{\circ}$ ).

The local  $C_s$  symmetry of the cycloheptatriene ring is disturbed; this can be explained by packing effects (see *Discussion*).

The shortest non-bonded intramolecular distance is between C(1) and C(6) (2.41 Å), which might partly be due to homoconjugation between these two centres (Lindner, 1979; Warner, 1976).

# Packing

The boat axis, formed by C(7) and the centre to the bond between C(3) and C(4), is almost aligned with respect to **a** and tilted in **b**. The molecule forms translational chains along **b** with shortest intermolecular distances between methyl and phenyl groups  $[C(51)\cdots C(36) 3.64 \text{ Å}, \text{Table 4}]$  and between two methyl groups  $[C(51)\cdots C(21) 4.37 \text{ Å}, \text{ Fig. 3}]$ . A second row is formed by the screw axis, the cycloheptatriene rings lying in the holes between the parallel phenyl rings of adjacent molecules in the first row with shortest distances between C(45) and C(7) (3.60 Å).

# Table 3. Least-squares planes with maximumdeviations out of the planes, rotation angles and<br/>structure angles

				Maxi	mum on (Å)
Plane				$(\sigma = 0 \cdot$	005 Å)
(I) (II) (III) (IV) (V)	C(6)-C(7)-C(1) C(1)-C(2)-C(5)- C(2)-C(3)-C(4)- C(31)-C(32)-C(4)- C(41)-C(42)-C(4)- C(41)-C(42)-C(4)-	-C(6) -C(5) 33)—C(34 43)—C(44	)–C(35)–C(36) )–C(45)–C(46)	0.003 0.010 0.004 0.003	C(6) C(3) C(34) C(43)
Rotati	on angles (°) ( $\sigma = 0$	)•4°)			
Pheny Pheny Pheny	l (IV)/(III) l (V)/(III) l (IV)/phenyl (V)	79·9 70·6 58·4	Phenyl (IV Phenyl (V)	/)/(II) )/(II)	97·2 56·8
Structure angles (°) ( $\sigma = 0.4$ °)					
	$\alpha = (I)/(II) = 5$	2.6	$\beta = (III)/(II) = 1$	34.3	
	<sup>€</sup> 6 <sup>H</sup> 5 ⟨	/	Celle		



Fig. 2. Dihedral angles (°) ( $\sigma_{\text{CCCC}} = 0.4^{\circ}$ ).

A third row is generated by the inversion centre with the bows of the molecules placed against each other at a distance of 3.87 Å [C(7)...C(7), Fig. 4], and contacts between two phenyl groups [C(34)...C(34), 3.93 Å]. The last row of molecules, interrelated to the first by the inverted screw axis, forms shortest distances to the first row between methyl and phenyl groups [C(21)...C(44) 3.69 Å] and heptatriene and phenyl rings [C(34)...C(6) 4.04 Å].

Table 4.	Shortest	intra-	and	intermolecular	distances
		(Å) (σ	= 0	-01 Å)	

		Symmetry operation on second atom
$C(6)\cdots C(1)$	2.41	
$C(51)\cdots C(36)$	3.64	(+x, 1 + y, +z)
$C(51) \cdots C(21)$	4.37	· · ·
$C(7)\cdots C(7)$	3.87	(1 - x, -y, -z)
$C(45) \cdots C(45)$	4.38	(1 - x, -y, 1 - z)
$C(44) \cdots C(33)$	4.01	(2-x, -y, 1-z)
$C(34) \cdots C(34)$	3.93	(2-x, -1-y, 1-z)
$C(6) \cdots C(36)$	3.80	(1-x, 0.5+y, 0.5-z)
$C(45) \cdots C(7)$	3.60	
$C(3)\cdots C(33)$	4.02	(2 - x, 0.5 + y, 0.5 - z)
$C(21) \cdots C(34)$	3.94	
$C(42) \cdots C(21)$	3.85	
$C(21) \cdots C(35)$	4.18	(+x, -0.5 - y, -0.5 + z)
$C(21) \cdots C(44)$	3.69	
$C(34)\cdots C(6)$	4.04	(+x, -1.5 - y, -1.5 + z)
$C(44)\cdots C(51)$	3.95	
$C(45)\cdots C(6)$	4.04	



Fig. 3. A view down **a** with **b** horizontal and **c** vertical. Ball and stick model; the unit cell is outlined.



Fig. 4. Van der Waals representation of Fig. 3; the unit cell is outlined.

### Discussion

The structure angles  $\alpha = 52.6^{\circ}$  and  $\beta = 34.3^{\circ}$  of (III) may be compared with  $\alpha = 47.9^{\circ}$  and  $\beta = 24.4^{\circ}$  of (II) (Davis & Tulinsky, 1966). Both angles are smaller in the latter structure, but the influence of the bulky substituent in the 3-position is larger than the effect of the 7,7-dimethyl substitution.

It is interesting to compare the results of the structure analysis with those obtained by empirical force-field calculations, to predict the influence of packing on the molecular conformation. Calculations have been carried out with the program MCA (molecular conformation analysis; Huler & Warshel, 1974) with modified and extended parameters for force-field and  $\pi$ -SCF calculation (Stegemann, 1979) and by the program PIMM ( $\pi$ -SCF-MO molecular mechanics program; Lindner, 1974).

Most empirical force-field calculations consider either isolated molecules or packing patterns of rigid bodies. The influence of crystal forces on the intramolecular structure has been treated so far only by the program MCA. The structure alteration due to the crystal packing should be considered by force-field calculations especially for flexible molecules to give a better agreement with X-ray results. In a flexible ringshaped molecule like cycloheptatriene mainly the dihedral angles will be influenced by the crystal packing.

The results of an *MCA* calculation of the isolated molecule are shown in Fig. 5. The seven-membered ring is slightly distorted from  $C_s$  symmetry and significantly flatter in the stern region than in the crystal structure. An *MCA* calculation including crystal packing leads to bond lengths and bond angles identical with those in Fig. 5, but different torsion angles (Fig. 6). The torsion angles at the stern of the boat are enlarged by 2 and 6°, the phenyl ring at C(4) is rotated by 8° and the seven-membered ring shows greater deviations from  $C_s$  symmetry. These packing effects are mainly due to close contacts between the phenyl ring at C(4) and the surrounding groups. The calculated heat of sublimation ( $\Delta H_s = -126$  kJ mol<sup>-1</sup>) lies in the



Fig. 5. Dihedral angles (°) and bond lengths (Å) from a singlemolecule calculation.



Fig. 6. Dihedral angles (°) and bond angles (°) from a packedmolecule calculation.

expected range. A comparison of Figs. 2, 5 and 6 demonstrates the good agreement between MCA packing calculations and experiment and allows an estimate of the influence of crystal packing on the conformation of the substituted cycloheptatriene.

The inversion barrier between the two boat forms of (III) has been calculated to be 59 kJ mol<sup>-1</sup> (*PIMM*) in agreement with the observed value  $\Delta G^* = 55.0$  kJ mol<sup>-1</sup> (Kessler, 1979). The enthalpy difference between (III) and the isomeric norcaradiene structure is estimated to be about 46 kJ mol<sup>-1</sup>.

The calculations were carried out at the Rechenzentrum der Technischen Hochschule Darmstadt.

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# The Crystal and Molecular Structure of a New Antidepressant, 6-Benzyl-1,2,3,4,5,6,7,8octahydro-1,3-dimethylpyrimido[4,5-d]pyrimidine-2,4-dione

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### Abstract

In order to correlate the conformation with the biological activity of a new pyrimido [4,5-d]pyrimidine, its crystal structure was determined. The crystal data are  $a = 7 \cdot 109$  (3),  $b = 12 \cdot 766$  (3),  $c = 16 \cdot 110$  (4) Å,  $\beta = 97 \cdot 52$  (5)°, Z = 4, space group P2/c. The stereochemistry and the interatomic distances are in accordance with the proposed information relevant to the geometry and properties of the binding sites of the adrenergic  $\alpha$ -receptors.

# Introduction

Because of the widespread use of antidepressants, extensive studies have been carried out to investigate the precise mechanism of their action. It is generally accepted that at least part of the therapeutic action of antidepressants may be a consequence of an increased 0567-7408/79/092165-04\$01.00 availability of norepinephrine (NE) at post-synaptic receptor sites. It has been recently found that antidepressant treatments decrease the sensitivity of the NE  $\alpha$ -receptors (Crews & Smith, 1978). This activity on the receptor mediation explains the feedback inhibition of brain NE neurons (Svensson & Usdin, 1978). We have synthesized (Bernier, Lefebvre, Lespagnol, Navarro & Perio, 1977) a series of pyrimidopyrimidines in which only one compound exhibited antidepressant activity: 6-benzyl-1,2,3,4,5,6,7,8-octahydro-1,3-dimethylpyrimido[4,5-d]pyrimidine-2,4dione (BDPD). It was interesting to study the crystal structure of BDPD in order to correlate its conformation with its biological activity.

### Experimental

Single crystals were transparent parallelepipeds. The data were collected on a Philips diffractometer with © 1979 International Union of Crystallography