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

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(*Received* 10 *April* 1979; *accepted* 21 *May* 1979)

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 α-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 availability of norepinephrine (NE) at post-synaptic receptor sites. It has been recently found that antidepressant treatments decrease the sensitivity of the NE α-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-2,4-dione (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

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graphite-monochromated Mo $K\alpha$ radiation at room temperature.

The $\theta/2\theta$ scanning method, with a minimum rate of $1°$ min^{-1} and an invariant scan width of $1{\cdot}2°$, was used. Of the 2583 independent reflections, 2023 had $F > 6\sigma(F)$. The intensities were corrected for Lorentz and polarization effects but not for absorption or extinction. Crystal data are given in Table 1.

Structure determination

The three reflections fixing the origin were not determined by the normal procedure of *MULTAN* (Germain, Main & Woolfson, 1971). An insufficiency of reflections in the different parity groups did not permit a start from convergence. The selected reflections and the values of the normalized structure factors (E) are given in Table 2. One of 32 computed sets of phases revealed the positions of all the non-hydrogen atoms ($R = 0{\cdot}16$). Full-matrix least-squares refinement of scale, positional and isotropic thermal parameters converged at $R = 0{\cdot}10$. Introduction of anisotropic temperature factors for all atoms and further refinement lowered R to 0·07. A difference map located the H atoms which were given isotropic thermal factors equal to those of the carrier atoms. A last refinement of all parameters except isotropic temperature factors of the H atoms gave a final R of 0·052.* The final atomic parameters are listed in Tables 3 and 4. The absolute values of peaks and troughs in the final difference synthesis did not exceed 0·25 e Å^{-3}. Fig. 1 gives a perspective view of the molecule.

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34504 (20 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Crystal data*

Molecular formula $C_{15}H_{18}N_4O_2$, M_r = 286, space group $P2/c$

a (Å)	7·109 (3)	V (Å^3)	1395·2
b (Å)	12·766 (3)	Z	4
c (Å)	16·110 (4)	D_c (Mg m^{-3})	1·33
β (°)	97·52 (5)		

Table 2. *Starting reflections*

	h	k	l	$\|E\|$	φ
Origin	2	1	0	3·84	360°
	1	10	3	3·59	360
	3	2	12	3·24	360
Σ_1 relation	4	0	0	3·26	360
	8	0	0	2·63	360
Symbols	0	3	13	3·71	
	1	7	$\overline{10}$	3·52	
	4	1	0	3·42	
	6	1	$\bar{2}$	3·15	
	6	1	0	2·77	

Thermal-vibration analysis

Fig. 2 shows that the C—C distances of the phenyl ring are shorter than the standard values. It was expected that these discrepancies were caused by the thermal agitation, and a least-squares analysis of rigid-body motion of the molecule was carried out (Schomaker & Trueblood, 1968).

Table 3. *Final positional parameters* ($\times 10^4$) *of the non-hydrogen atoms and their e.s.d.'s in parentheses*

	x	y	z
C(1)	4257 (6)	2151 (2)	4313 (2)
C(2)	5654 (6)	1347 (3)	4105 (2)
C(3)	7545 (7)	1557 (3)	4264 (3)
C(4)	8879 (8)	813 (4)	4070 (4)
C(5)	8275 (9)	−130 (4)	3760 (4)
C(6)	6432 (9)	−341 (4)	3615 (4)
C(7)	5135 (8)	382 (4)	3781 (4)
C(8)	2764 (6)	2704 (3)	2932 (2)
C(9)	2605 (5)	4533 (3)	2590 (2)
C(10)	2688 (5)	4759 (3)	3421 (2)
C(11)	3104 (5)	3909 (3)	4067 (2)
C(12)	2576 (5)	5809 (3)	3693 (2)
C(13)	2415 (6)	6369 (3)	2221 (2)
C(14)	2218 (6)	5099 (3)	1096 (2)
C(15)	2388 (8)	7672 (3)	3327 (3)
N(1)	4002 (4)	3015 (2)	3693 (2)
N(2)	2667 (4)	3527 (2)	2296 (2)
N(3)	2425 (4)	6576 (2)	3063 (2)
N(4)	2425 (4)	5324 (2)	1998 (2)
O(1)	2359 (5)	7061 (2)	1700 (2)
O(2)	2676 (4)	6079 (2)	4430 (1)

Table 4. *Hydrogen-atom coordinates* ($\times 10^3$), *isotropic temperature factors and bond distances* (Å)

	x	y	z	B (Å^2)	C,O,N—H
H(C1)	314 (5)	186 (3)	440 (2)	3·5	0·90 (4)
H(C1)	478 (4)	249 (2)	485 (2)	3·5	1·00 (3)
H(C8)	132 (4)	255 (2)	307 (2)	3·6	1·09 (3)
H(C8)	334 (4)	212 (2)	270 (2)	3·6	0·95 (3)
H(C11)	185 (4)	365 (2)	428 (2)	3·0	1·04 (3)
H(C11)	404 (4)	415 (2)	455 (2)	3·0	1·01 (3)
H(C16)	140 (4)	563 (2)	79 (2)	4·2	0·98 (3)
H(C16)	355 (5)	499 (2)	881 (2)	4·2	1·06 (4)
H(C16)	164 (5)	454 (2)	98 (2)	4·2	0·83 (4)
H(C15)	199 (5)	810 (3)	286 (2)	5·2	0·94 (3)
H(C15)	120 (5)	782 (3)	350 (2)	5·2	0·94 (4)
H(C15)	342 (5)	785 (2)	371 (2)	5·2	0·93 (3)
H(C4)	997 (6)	100 (3)	433 (2)	7·2	0·87 (4)
H(C5)	919 (6)	−57 (3)	369 (2)	7·2	0·88 (4)
H(C6)	600 (6)	−97 (3)	351 (2)	7·2	0·87 (4)
H(C7)	400 (5)	23 (3)	373 (2)	6·0	0·82 (4)
H(C3)	788 (5)	207 (2)	444 (2)	5·0	0·75 (4)
H(N2)	366 (4)	340 (2)	190 (2)	3·3	1·02 (4)

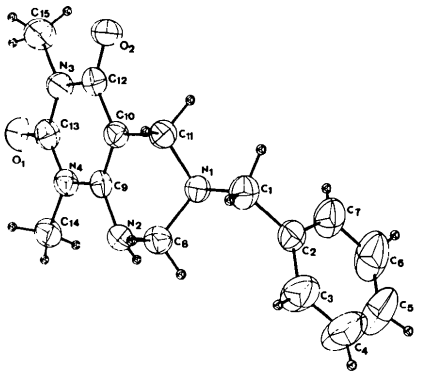

Fig. 1. A perspective view of the molecule (Johnson, 1970).

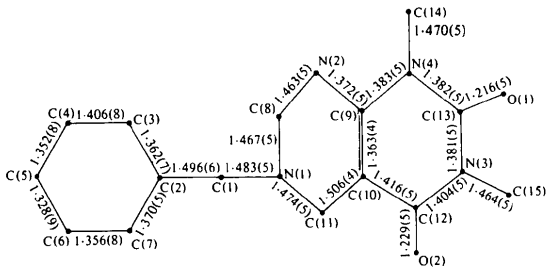

Fig. 2. Interatomic distances (Å) in the molecule. The e.s.d.'s are given in parentheses.

Table 5. *Rigid-body-vibration parameters for the heavy atoms of the phenyl ring with adjacent atom*

	538 (30)	−39 (25)	−68 (30)
T (Å^2) (×10^4)		414 (27)	14 (30)
			686 (53)
	164 (24)	−146 (20)	4 (11)
L (rad^2) (×10^4)		253 (33)	−29 (14)
			51 (10)
	−1 (19)	38 (17)	−119 (12)
S (rad Å)	32 (21)	−38 (21)	−66 (14)
	58 (9)	46 (8)	40 (64)
r.m.s. ($U^{\circ} - U^{c}$)	0·0049 Å^2	e.s.d. U_{ij}^{obs}	0·0064 Å^2

The results show that the whole molecule cannot be considered as rigid. The root-mean-square difference between the observed U_{ij} terms and those calculated from the derived **T**, **L** and **S** for the phenyl ring with the adjacent atom taken as origin is 0·0049 Å^2 (Table 5).

The bond lengths corrected for the effects of molecular vibrations (Busing & Levy, 1964) (Table 6) are in better agreement with the standard values.

Results and discussion

The bond distances and angles are displayed in Figs. 2 and 3, and Table 6.

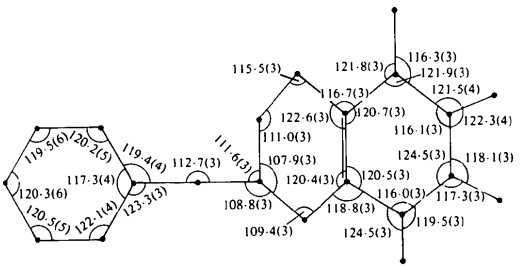

Fig. 3. Interatomic angles (°) in the molecule. The e.s.d.'s are given in parentheses.

Table 6. *Selected bond distances* (Å)

	Uncorrected	Corrected
C(1)—N(1)	1·483 (5)	1·502
C(1)—C(2)	1·496 (5)	1·506
C(2)—C(3)	1·362 (7)	1·386
C(2)—C(7)	1·370 (5)	1·392
C(3)—C(4)	1·406 (8)	1·415
C(7)—C(6)	1·356 (8)	1·367
C(4)—C(5)	1·352 (8)	1·375
C(6)—C(5)	1·328 (9)	1·352

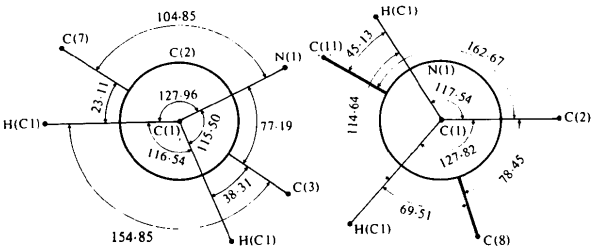

Fig. 4. Newman projections along C(1)—C(2) and C(1)—N(1).

The Newman projections (Fig. 4) and mean planes (Table 7) show the non-planar structure of the molecule. The mean plane of the phenyl ring is perpendicular to the plane of the heterocyclic residue. None of the intermolecular distances between C—C, C—O or C—N atoms is shorter than 3·45 Å except N(2)—H(N2)···N(1)^{1} 3·09 Å (bond angle 169·56°) and C(14)···O(2)^{2} 3·13 Å [symmetry positions: (1) $1-x$, y, $\frac{1}{2}-z$; (2) $1-x$, $y-1$, $\frac{1}{2}-z$]. We may consider that the molecules are bound by van der Waals contacts (Fig. 5).

Comparison with NE and α-adrenergic agonists

The distances N(1)—N(2), N(1)—phenyl ring, N(1)—phenyl-ring center are respectively 2·40, 1·30 and 5·30 Å. The distance between N(2) and the phenyl-ring center is 3·73 Å.

It is obvious that BDPD shows a shape similar to the general bent conformation of NE when it reacts at the

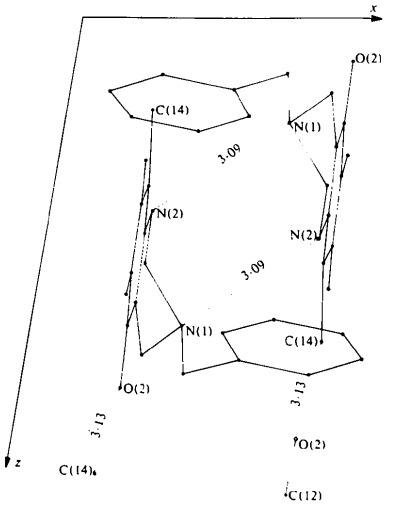

Fig. 5. Projection along **b** with the shorter intermolecular distances (Å).

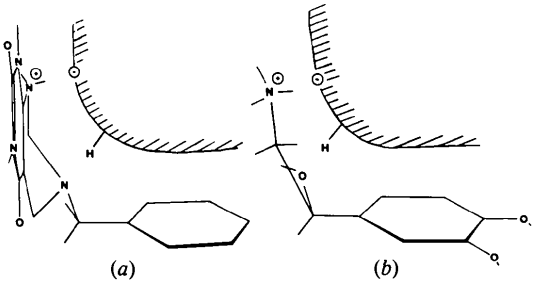

Fig. 6. Mode of binding at the α-receptor site for (*a*) BDPD and (*b*) NE.

α-receptor sites. Moreover, the relative positions of the different functional groups are in accord with the proposals for the mode of binding of agonists at the adrenergic α-receptor (Coubeils, Courriere & Pullman, 1972; Kier, 1968; Pullman, Coubeils, Courriere & Gervois, 1972).

Table 7. *Angles between principal planes of the molecules*

E.s.d.'s are *ca* 1°.

*P*1: C(2), C(3), C(4), C(5), C(6), C(7)
*P*2: N(1), N(2), C(8), C(9), C(10), C(11)
*P*3: C(9), C(10), N(3), N(4), C(13), C(12)

$P1 \wedge P2$	81°	$P1 \wedge P3$	88°	$P2 \wedge P3$	14°

The major binding sites for BDPD may be the phenyl moiety, the N(2)—H group and the N(1) atom compared with the catechol moiety, the basic amine and the β-hydroxyl group respectively (Fig. 6).

This work was supported in part by CNRS (ERA No. 465, Dynamique des Cristaux Moléculaires) and by INSERM (U16). We thank Mme C. Carpentier for the preparation of the crystals.

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