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CONFORMATIONS IN THE TETRAHYDROPYRAN-2-ONE RING

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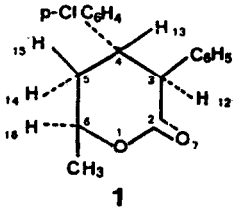
Abstract - Force-field calculations in combination with ^{1}H NMR spectroscopy, IR data and X-rays diffraction unambiguously delineate the conformational properties of tetrahydropyran-2-one derivatives which exhibit psychostimulant and antidepressive activity.

For some years ago we have studied pyran-2 one and tetrahydropyran-2 one compounds [1] and we had the opportunity to bring into evidence their marked biological activity [2]. Thus the (3R) (4R) (6R)-6 methyl-3 phenyl-4 (p-chlorophenyl) tetrahydropyran-2-one **1** has a strong psychostimulant activity as well as an antidepressive effect. The (3R) (4R) (6S)-6 methyl-3 phenyl-4 (p-chlorophenyl) tetrahydropyran-2 one **2** in which the methyl group is in the equatorial position shows a lowered antidepressant activity and has no psychostimulant effect.



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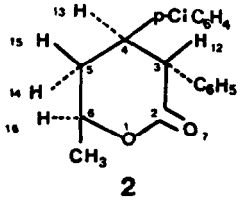

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Among the many factors considered as related to the pharmacological activity of a drug a prominent role is attributed to its conformation. Knowledge of the preferred conformations of molecules which interact with biological receptors is a useful adjunct in discussions concerned with the relationship between chemical structure and biological activity [3]. Our aim in this study is to examine the conformation of the tetrahydropyran-2 one ring in the molecules **1** and **2**. Pertinent information on drug molecules is usually derived for the solid state from X-ray cristallography and for solutions from NMR spectra. X-ray cristallography is capable of giving very precise conformational information, though the possibility that the conformation observed in the crystal is influenced by crystal packing forces must be borne in mind. One difficulty of this method is that the compound must be obtained in suitable crystalline form and all our attempts to obtain a suitable crystal of **2** have failed.

A very interesting alternative method for determining structure is the calculational method (quantum or force-field calculations) which gives the most stable form of the isolated molecule.

The δ-valerolactone molecule has two possible conformations. These conformations **A** and **B** are called "flattened chair" and "boat" respectively [4].

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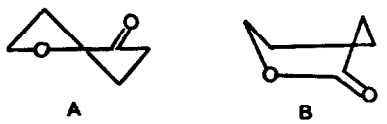

Our study shows that the molecule **2** exists in the conformation **A** and that the molecule **1** exists in the form of a slightly twisted boat form.

NMR AND IR DATA

Proton chemical shifts (δ = 250 MHz), ^1H coupling constants (Hz) and IR stretching (cm^{-1}) are given in Table 1.

Table 1 - Proton chemical shifts, ^1H coupling constants (Hz) and IR stretching (cm^{-1})

	δ	J	$\nu C=O$
1	H_{16} : 5,4 (m) , H_{12} : 4,22 (d) , H_{13} : 3,62 (m) , H_{14}, H_{15} : 2,24 (m) CH_3 : 1,44 (d)	$J_{H_{16},H_{14}}$ = 6,5 , $J_{H_{16},H_{15}}$ = 6,5 $J_{H_{12},H_{13}}$ = 11,5 , $J_{H_{13},H_{12}}$ = 11,5	1750
2	H_{16} : 4,78 (m), H_{12} : 3,68 (d) H_{13} : 3,30 (m), H_{14-15} : 2,15 (m) CH_3 : 1,50 (d)	$J_{H_{16},H_{15}}$ = 3,0 , $J_{H_{16},H_{14}}$ = 10,5 $J_{H_{12},H_{13}}$ = 11,5 , $J_{H_{13},H_{12}}$ = 11,5 $J_{H_{13},H_{15}}$ = 3,0 , $J_{H_{13},H_{14}}$ = 11,5 J_{H_{16},CH_3} = 6,5	1745

After irradiation of the methyl group
After irradiation of the proton H_{14}

For **1** the $J_{H16\ H14}$ and $J_{H16\ H15}$ NMR couplings have the same value (6,5 Hz) and this is taken as a diagnostic of a tetrahydropyran-2 one derivative in the boat conformation.

For **2** large vicinal coupling constants ($J_{H12,H13}$= 11,5 Hz, $J_{H13,H14}$ = 11,5 Hz) between protons may be identified with an approximate diaxial orientation of the atoms while the smaller splitting ($J_{H13,H15}$=3,0 Hz) is associated with an axial equatorial interaction in a flattened chair form.

The infrared absorption band arising from the C=O stretching vibration can be used to determine the conformation of lactones [5]. The 1750 cm^{-1} peak should be attributable to a boat conformation while the 1745 cm^{-1} peak should be typical for a flattened chair form.

X-RAY ANALYSIS

Crystals of the studied product (compound **1**) obtained from ethanol solution are monoclinic, space group $P2_1/a$, with a = 13.687 (3) Å , b = 10.707 (1) Å , c = 10.723 (2) Å, β=102,14°(1); F (000) = 632 for 4 molecules in the unit cell ; $d_{calc.}$ = 1,304 gcm^{-3}. Intensity data were measured on a Nonius CAD 4 diffractometer with Cu K_α radiation Ni filtered ; the crystal was sealed in a glass capillary of 0,3 mm diameter ; 3344 reflections with $\Theta < 73°$ were measured, 2504 of them considered to be observed ($I > 3\ \sigma\ (I)$) were used in the structure determination.

The structure was solved by direct methods with the program MULTAN [6]. A Wilson statistical calculation gave an overall temperature factor of 4,84 $Å^2$. An initial E map based on 200 reflections (E >1.92)revealed all non-hydrogen atoms of the molecule. Refinement first with isotropic temperature factors, then with anisotropic,one reduced R and gave the possibility of calculation of a difference map which revealed all hydrogen atoms. The final refinement was carried out by SHELX [7] with anisotropic thermal parameters for Cl, C and O atoms and isotropic temperature factors for H atoms. The final reliability factor R is 0.062 for 3147 reflections. There are no peaks greater than 0.2 e $Å^{-3}$ on the final difference map. The final parameters of all atoms are listed in table 2 with thermal parameters ; only H atoms of tetrahydropyran-2 one are listed. Bond distances and angles are listed in Table 3 and 4 with numbering scheme given on the stereoscopie view (Fig.1).

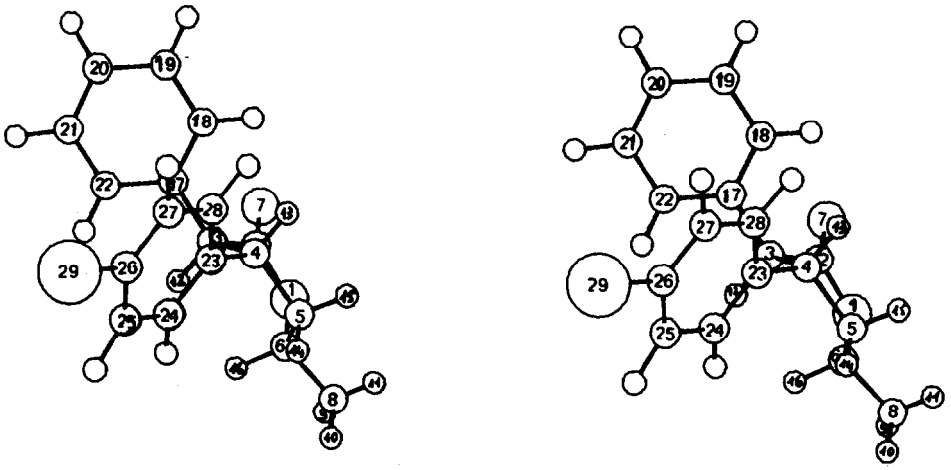

Fig. 1 - Stereoscopic view of the molecule and numbering scheme

Table 2 - Final fractional coordinates ($x10^4$) and anisotropic or isotropic thermal parameters ($x10^4$) with corresponding e.s. d's in parentheses.

Atom	X	Y	Z	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
Cl (29)	5562 (1)	6794 (1)	9715 (1)	789 (6)	1197 (6)	767 (6)	- 251 (5)	331 (5)	220 (6)
C (26)	6508 (2)	6336 (3)	8954 (3)	580 (17)	756 (20)	436 (15)	- 145 (14)	121 (13)	113 (15)
C (25)	6951 (2)	5189 (3)	9225 (3)	715 (19)	573 (18)	551 (17)	- 57 (14)	279 (15)	- 52 (15)
C (24)	7703 (2)	4832 (3)	8607 (3)	665 (18)	448 (15)	533 (16)	- 16 (12)	245 (14)	44 (13)
C (23)	8004 (2)	5605 (2)	7719 (2)	575 (15)	441 (14)	361 (12)	- 50 (10)	135 (11)	17 (12)
C (28)	7537 (3)	6752 (3)	7471 (3)	927 (24)	588 (18)	521 (17)	141 (14)	298 (17)	228 (17)
C (27)	6794 (3)	7123 (4)	8089 (3)	990 (27)	786 (23)	583 (19)	121 (17)	317 (18)	441 (21)
C (4)	8808 (2)	5221 (2)	7025 (2)	515 (14)	443 (13)	412 (13)	- 52 (11)	149 (11)	- 34 (11)
C (3)	8435 (2)	4136 (2)	6070 (2)	468 (13)	423 (13)	375 (12)	34 (10)	130 (10)	- 19 (11)
C (17)	7536 (2)	4463 (2)	5059 (2)	479 (13)	444 (13)	423 (12)	- 63 (11)	159 (10)	2 (11)
C (18)	7577 (2)	5321 (3)	4110 (3)	525 (16)	531 (16)	529 (16)	27 (13)	111 (13)	- 29 (13)
C (19)	6749 (2)	5606 (3)	3187 (3)	649 (19)	598 (18)	572 (18)	78 (15)	27 (14)	30 (15)
C (20)	5840 (2)	5025 (3)	3201 (3)	508 (17)	754 (22)	710 (21)	- 39 (18)	- 13 (15)	69 (16)
C (21)	5787 (2)	4179 (4)	4139 (4)	498 (17)	757 (23)	783 (22)	- 77 (18)	122 (16)	- 75 (16)
C (22)	6617 (2)	3884 (3)	5058 (3)	497 (15)	574 (17)	584 (17)	- 46 (14)	168 (13)	- 70 (13)
C (5)	9793 (2)	4853 (3)	7922 (3)	518 (16)	640 (19)	476 (16)	- 127 (14)	61 (13)	- 34 (14)
C (6)	10102 (2)	3519 (3)	7735 (3)	494 (15)	595 (17)	444 (14)	75 (13)	73 (13)	- 31 (13)
O (1)	10123 (1)	3337 (2)	6415 (2)	522 (11)	572 (11)	475 (10)	0 (9)	121 (8)	92 (9)
C (2)	9317 (2)	3665 (2)	5529 (2)	522 (14)	404 (13)	393 (13)	- 23 (10)	113 (11)	- 11 (11)
O (7)	9328 (1)	3577 (2)	4429 (2)	651 (12)	702 (13)	445 (10)	- 72 (9)	186 (9)	96 (10)
C (8)	11128 (3)	3188 (4)	8493 (3)	565 (19)	894 (27)	565 (19)	131 (19)	27 (15)	77 (18)
H (13)	8942 (20)	5918 (26)	6432 (26)	506 (77)					
H (12)	8234 (20)	3414 (26)	6626 (25)	507 (76)					
H (9)	11150 (21)	3170 (27)	9396 (29)	550 (83)					
H (10)	11630 (26)	3798 (34)	8182 (32)	826 (113)					
H (11)	11363 (30)	2275 (42)	8348 (38)	1093 (145)					
H (16)	9623 (23)	2840 (29)	8034 (29)	711 (95)					
H (14)	10328 (25)	5497 (32)	7738 (32)	811 (107)					
H (15)	9852 (19)	4890 (26)	8825 (27)	491 (76)					

Table 3 - Bond distances (Å) with e.s. d's in parentheses

C(25)-C(26)	1.373 (5)	C(6) -C(8)	1.510 (4)	C(21)-C(22)	1.374 (4)
C(24)-C(25)	1.389 (5)	O(1) -C(2)	1.342 (3)	C(22)-C(17)	1.403 (4)
C(23)-C(24)	1.388 (4)	C(2) -C(3)	1.531 (4)	C(4) -H(13)	1.02 (3)
C(23)-C(28)	1.383 (4)	C(3) -C(4)	1.562 (4)	C(5) -H(14)	1.06 (4)
C(27)-C(28)	1.384 (6)	C(2) -O(7)	1.186 (3)	C(5) -H(15)	0.96 (3)
C(26)-C(27)	1.369 (5)	C(3) -C(17)	1.501 (3)	C(6) -H(16)	1.07 (3)
C(26)-Cl(29)	1.740 (3)	C(17)-C(18)	1.380 (4)	C(16)-H(9)	0.96 (3)
C(23)-C(4)	1.509 (4)	C(18)-C(19)	1.373 (4)	C(16)-H(10)	1.01 (4)
C(4) -C(5)	1.534 (4)	C(19)-C(20)	1.393 (5)	C(16)-H(11)	1.05 (5)
C(5) -C(6)	1.514 (4)	C(20)-C(21)	1.367 (5)	C(3) -H(12)	1.05 (3)
C(6) -O(1)	1.436 (3)				

Table 4 - Bond angles (°) with e.s. d's in parentheses

C(27)-C(26)-Cl(29)	119.4 (3)	O(1)-C(6)-C(8)	106.8 (3)
C(25)-C(26)-Cl(29)	119.5 (3)	C(6)-O(1)-C(2)	118.5 (2)
C(27)-C(26)-C (25)	121.1 (3)	O(1)-C(2)-C(3)	114.5 (2)
C(26)-C(25)-C (24)	118.9 (3)	O(1)-C(2)-O(7)	120.1 (3)
C(25)-C(24)-C (23)	121.3 (3)	C(3)-C(2)-O(7)	125.4 (2)
C(24)-C(23)-C (28)	118.0 (3)	C(2)-C(3)-C(4)	108.5 (2)
C(24)-C(23)-C (4)	121.8 (2)	C(2)-C(3)-C(17)	113.3 (2)
C(28)-C(23)-C (4)	120.2 (3)	C(4)-C(3)-C(17)	113.9 (2)
C(23)-C(28)-C (27)	121.2 (3)	C(18)-C(17)-C(3)	122.3 (2)
C(28)-C(27)-C (26)	119.4 (3)	C(18)-C(17)-C(22)	118.0 (2)
C(23)-C(4) -C (5)	113.4 (2)	C(3) -C(17)-C(22)	119.7 (2)
C(23)-C(4) -C (3)	110.8 (2)	C(17)-C(22)-C(21)	120.2 (3)
C(5) -C(4) -C (3)	110.3 (1)	C(22)-C(21)-C(20)	121.1 (3)
C(4) -C(5) -C (6)	113.1 (2)	C(21)-C(20)-C(19)	119.3 (3)
C(5) -C(6) -O (1)	108.8 (2)	C(20)-C(19)-C(18)	119.7 (3)
C(5) -C(6) -C (8)	113.8 (3)	C(19)-C(18)-C(17)	121.6 (3)

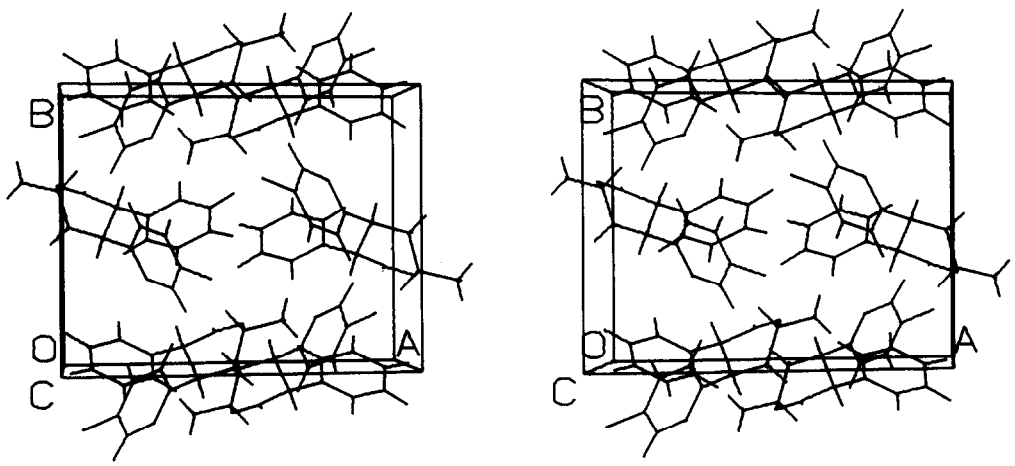

Figure 2 - Stereoscopic view of the crystal arrangement of molecules

Different least-squares planes and atoms deviations from them have been calculated and show that the two benzene ring planes are planar (χ^2 = 4.27 and 3.47). The heterocycle has a boat conformation as seen on the stereoscopic view (Fig.1). Some dihedral angles between planes are calculated : so angle between the two benzene ring planes is 58°.74 ; angle between planes C(3)-C(6)-C(2)-O(1) and C(6)-C(3)-C(5) C(4) is 54°.84 : the two parts of the heterocycle seem like an opened book.

Some torsional angles have been calculated and listed in table 5 with those calculated in the second part of this paper. The torsional angle ϕ (i,j,k,l) denotes the angle between a plane defined by atoms i,j,k and a plane defined by j,k,l. A positive dihedral angle denotes a clockwise rotation of plane j,k,l with respect to the reference plane i,j,k when viewing the assembly from j to k.

Arrangement of molecules in the unit cell is shown in Fig.2. We can see some short bonds between molecules in the crystals by example between chlorine atom and carbons of benzene rings.

FORCE FIELD CALCULATIONS

Previous work by several groups has shown that it is possible to calculate with a good degree of accuracy the structure of molecules by a semiempirical method referred to as the "molecular mechanics" or "force field" or "Westheimer" method [8]. This method views a molecule as a system of particles held together by forces and the energy of the molecule is described by a set of classical equations of motion which are functions of the atomic positions. The atomic positions are varied until a geometry of minimum energy is found. Figure 3 shows a view of the two molecules drawn with programme PLUTO (Cambridge Crystallographic Data Centre, Cambridge, England). In the present work the MMI program (1973 force field) was used. The calculated conformation of **1** is near-identical with the conclusions of previous X-ray diffrac-

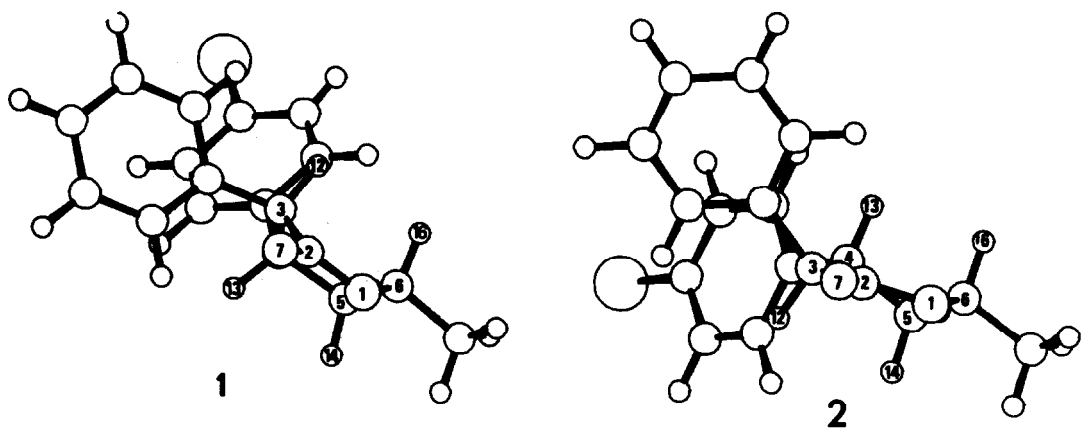

Fig. 3 - Pluto drawing of the molecules **1** and **2**

Table 5 - Torsional angles

Compound	ϕ (i, j, k, l) XR values in parentheses		
	13,4,3,12 : -169.6(-175.8)	14,5,4,13 : 2.5(5.9)	15,5,4,13 : 119.9(123.2)
	16,6,5,15 : 58.0(61.4)	16,6,5,14 : 171.7(172.34)	6,1,2, 3 : 9.8(- 3.3)
	6,5,4, 3 : - 3.0(- 4.9)		
	13,4,3,12 : 168.5	14,5,4,13 : 175.8	15,5,4,13 : - 63.8
	16,6,5,14 : -176.3	16,6,5,15 : 65.1	6,1,2,3 : 14.6

tion. In particular the geometry obtained by the calculations shows that the boat form is slightly twisted, the torsion angles $C_6O_1C_2C_3$ and $C_6C_5C_4C_3$ are 9°8 and -3°0 respectively. It should be noted that calculations determine the most stable form of the isolated molecule, it seems that the conformation of the tetrahydropyran-2 one does not depend on the environment. Some important torsional angles are listed in table 5.

Compound **2** cannot be obtained in suitable crystalline form and force field method is the method of choice for determining the structure of this molecule. In **2** the flattened chair conformation predominates. The calculated dihedral angles (table 5) are in good agreement with the vicinal coupling constants given in table 1.

CONCLUSION

Force field calculations in combination with ^{1}H NMR spectroscopy, IR data and X-ray crystallography unambiguously delineate the conformational properties of 6-methyl-3 phenyl-4 (p-chlorophenyl) tetrahydropyran-2 one compounds. The conformational properties of the isolated molecule is representative of the situation in solution and in the crystal. Of the two classes of biological activity, the psychostimulant property appears to be the more sensitive to structure changes, which suggests that the conformational specifications for psychostimulant activity of tetrahydropyran-2 one are tighter than those for the antidepressant activity. This conclusion is substantiated by our works in progress which indicated that the number of active tetrahydropyran-2 one compounds which present a boat ring is greater than that of tetrahydropyran-2 one existing in the form of a flattened chair. Nevertheless the possibility that these conformations are not representative of the situation of the molecule at the receptor must be borne in mind.

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