# CONFORMATIONAL AND MOLECULAR STUDY OF THE 4-(2-CARBOXYETHYL)-1,2,3,4-TETRAHYDROCYCLOPENT[b]INDOLE

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Abstract - A conformational study of the title compound has been carried out in solution and solid states. The molecules are packed in the crystal forming a charge-transfer complex, where two different molecular pairs are found. Visible spectra data show two weak absorption bands.

### INTRODUCTION

The 4-(2-carboxyethyl)-1,2,3,4-tetrahydrocyclopent[b]indole is structurally related to Indomethazin, a well known antiinflammatory drug used in clinic. The tricyclic indole nucleous, present in this molecule with a 4-(3-dimethylamine-propyl) chain, has antidepressant action.<sup>1</sup> This study has been carried out to determine the molecular conformation in both solution and solid states. Moreover, the occurrence of both a red-violet colour of the crystals and two absorption bands in the visible spectrum, suggested to us the possible formation of a charge-transfer complex. Crystals of other similar [b]indoles are colourless and do not show the above mentioned bands.

### DISCUSSION

<sup>1</sup>H-nmr spectrum of the title compound shows two triplet signals of the CH<sub>2</sub>-CH<sub>2</sub> fragment of the chain of the A<sub>2</sub>B<sub>2</sub>-type, a complex multiplet of the cyclopentane ring methylenes of apparent AA'BB'CC'-type and the low-field half broadened signal due to the long range coupling of the aromatic protons.

A first analysis of the  ${}^{1}$ H-nmr spectrum of the AA'BB'CC' system in solution of DCCl<sub>3</sub> with the program LAOCOON III was not successful due to the overlapping of the triplet signals of the CH<sub>2</sub>-CO with the signals of the C-1, C-3 methylenes. To avoid this difficulty, a  ${}^{1}$ H-nmr analysis of the 1,2,3,4-tetrahydrocyclopent-[b]indole nucleus was made. It shows identical cycloalkane proton spectrum that the one from the acid compound. A first aproximation analysis was done but difficulties were observed to estimate accurately the long-range coupling constants between C-1, C-3 methylenes, since agreement between the experimental and computer simulated was not correct in all the spectrum. Proton irradiation techniques to estimate these long-range coupling constants were not successful.

An analysis of the <sup>1</sup>H-nmr spectrum of the partially deuterated 1,2,3,4-tetrahydrocyclopent[b]indole and their 4-(2-carboxyethyl) derivatives were attempted to improve the above results and thus, deuterated derivatives IV, V, VI and VII were obtained, Scheme 1. <sup>1</sup>H-nmr spectra of the deuterated derivatives IV and V, show two multiplet signals for both cyclopentane ring methylenes of AA'BB'-type. Both deuterated derivatives and their acids VI and VII, show identical proton coupling system and J values, within experimental error Fig 1, and thus, the results from the analysis with the iterative program LAOCOON III for the compound IV, together with the probable errors are  $W_1 = W_2 = 577.79$  (0.02),  $W_3 = W_4 = 507.71$  (0.02),  $J_{12} = -15.60$  (0.03),  $J_{13} = J_{24} = 9.24$  (0.03),  $J_{14} = J_{23} = 5.29$  (0.03) and  $J_{34} = -12.95$  (0.03) Hz, with a r.m.s. error (observed vs. calculated) of 0.07 Hz (for V,  $W_1 = W_2 = 579.74$  and  $W_3 = W_4 = 507.71$  Hz). Note that in the iteration  $J_{13}$  and  $J_{24}$  are varied together as are  $J_{14}$  and  $J_{23}$ , but  $J_{12}$  and  $J_{34}$  are iterated separately. The agreement between the observed and computer simulated spectrum confirms the correctness of the analysis, Fig 1.

A conformational analysis of the cyclopentane protons was carried out following the Altona's equation <sup>2</sup>:  $J_{HH} = P_1 \cos^2 \Phi + P_2 \cos \Phi + P_3 + \Sigma \Delta X_i \{P_4 + P_5 \cos^2 (\xi_i \Phi + P_6 | \Delta X_i|)\}.$ 

The best dihedral angles resulting from this equation are shows in Table 1 and their Newmann's projections are in Fig 2.

A new analysis of the <sup>1</sup>H-nmr spectrum of the title compound was now attempted to investigate the conformational behaviour of the  $CH_2-CH_2$  chain of the propionic acid. The results obtained from this analysis are:  $W(CH_2-N) = 869.17$ ,  $W(CH_2-CO) = 567.42$  and  $J_{AB} = 7.12$  Hz. The two gauche forms of the staggered conformers of the compound under investigation are mirror images and hence of equal energy. The observed value of  $J_{AB}$  is then simply obtained as the weighted average of the values in the trans-  $(J_t)$  and gauche-  $(J_g)$  conformations according to the method of Abraham and Gatti, <sup>3</sup> with

$$J_{AB} = n_g J_g + n_t J_t$$

$$n_g + n_t = 1$$

$$\Delta E = E_g - E_t = RT ln | 2 (J_{AB} - J_g) / (J_t - J_{AB}) |$$

Here  $n_t$  and  $n_g$  are the populations of the trans- and gauche-conformers, respectively and  $\Delta E$  being the excess of energy (strictly free energy) of the gauche form.  $J_t$  (8.68 Hz) and  $J_g$  (6.52 Hz) values for the  $CH_2-CH_2$  fragment have been obtained from a previous paper.<sup>3</sup> Thus,  $n_g = 72\%$ ,  $n_t = 28\%$  and  $\Delta E = -0.16$  kcal mol<sup>-1</sup>. No appreciable changes of  $n_g$  and  $n_t$  were observed with dilution.

### X-ray structural determination

Fig 4 shows a perspective view of the two crystallographically independent molecules, which form dimers through centrosymmetric hydrogen bonds. Tables 2 and 3 list the bond distances and angles, respectively. The geometry around C(2)-C(3) and C(21)-C(31) clearly indicate the existence of double bonds between those atom pairs. These bond lengths are shorter than the ones present in other analogous cycloalkan[b]indoles.<sup>4</sup>

The crystal packing shows a molecular ring overlap between centrosymmetric molecules (Fig 5), forming an apparent charge-transfer complex, with interplanar distances of 3.55 and 3.68 Å for both independent molecular pairs. The visible spectrum in HCCl<sub>3</sub>, shows two weak absorption bands at 577 and 557 nm. Moreover, several dilutions of this compound in chloroform were analyzed in the visible spectrum and absorbance values obtained vs. concentration show deviations from the Beer-Lambert law. The  $\varepsilon$  values related to those absorption bands were  $\varepsilon_{577} = 32$  and  $\varepsilon_{557} = 23$  from Benesi-Hildebrand equation.<sup>5</sup> Other structural related cyclohexane, cycloheptane and cyclooctane[b]indoles do not show the above mentioned absorption bands.

#### EXPERIMENTAL

-Synthesis of 1,2,3,4-tetrahydrocyclopent[b]indole (I).

Phenylhydrazine 1.08 g.(10 mmol) and cyclopentanone 0.84 g.(10 mmol) were refluxed in benzene under a nitrogen atmosphere to remove water azeotropically. Benzene was removed and phenylhydrazone was obtained as an orange oil. Then, 50 ml of ethylenglycol were added and the mixture was heated at 180 °C during 24 h. The mixture was poured on ice-water and a brown solid was precipitated, recrystallized from ethanol-water providing a colourless solid (82% yield), mp 105-6 °C.

Synthesis of  $[1,1-^2H_2]$  and  $[3,3-^2H_2]-1,2,3,4-tetrahydrocyclopent[b]indo$ les (IV and V ).

A solution of 2,3-dichloro-5,6-dicyanobenzoquinone, 1.82 g.(8 mmol) in 10 ml of tetrahydrofuran was dropped at 0 °C ( or 50 °C) on a solution of I, 0.62 g. (4 mmol) in 30 ml of tetrahydrofuran-water (9:1). The mixture was stirred first during 2 h at 0 °C ( or 50 °C ) and finally overnight at room-temperature. Then 4.40 g. of powdered potassium carbonate were added on the mixture and stirred during 3 h. Solution to available a provide a provide a provide a stirred for the solution of the s Then. during 3 h. Solvent was evaporated providing a residual brown solid, which was chromatographied on silica gel column eluted with ethyl acetate- chloroform (4:1) to give the two carbonyl derivatives II and III. II was obtained in 25% of yield, mp 257-9 °C (dec.) and III in 9% of yield, mp 228-30 °C (dec.), at 0 °C ( or 38 and 6% respectively at 50 °C ).

and 6% respectively at 50 °C ). Carbonyl derivative II, 0.14 g.( or III, 0.10 g.) in tetrahydrofuran, under nitrogen atmosphere were added into a suspension of lithium aluminum deuteride, 0.10~g.( or 0.07~g.) in tetrahydrofuran. The mixture was warmed first at 50 during 2 h and finally at room-temperature overnight. Then, 3 ml ( or 2 ml ) of potassium hydroxide (10%) were added into the reaction mixture and extracted with dichloromethane. When dichloromethane was evaporated, a residual solid (or oil) were recovered and chromatographied on silica gel column, eluted with ethyl acetate-hexane (1:1) to give a colourless solid, in 89% (or 18%) of yield, which have the same mp that the compound I.

-Synthesis of the 4-(2-carboxyethyl)-1,2,3,4-tetrahydrocyclopent[b]ındole ( or the  $[1,1^{-2}{\rm H}_2]$  and  $[3,3^{-2}{\rm H}_2]$  deuterated derivatives VI and VII).

The propionic chain was introduced by Michael-type reaction between 1,2,3,4-tetrahydrocyclopent[b]indole ( or the deuterated derivatives IV and V ) and the acrylonitrile in tetrahydrofuran in presence of NaH at room-temperature ( 76% yield, mp 113-4 °C ) and finally aqueous-ethanolic (2:1) KOH hydrolysis of the nitrile group to the acid (91% yield). This crude product was recrystallized in methanol-water mixture to give red-violet crystals, mp 113-5 °C (deuterated derivatives show identical mp).

 $^1\mathrm{H-nmr}$  spectra were recorded on a Bruker WM-200-SY spectrometer. The simulation was carried out with a PANIC program on a Aspec -2000 computer. The UV-visible spectra on a Pye Unicam SP8 100 spectrophotometer.

Crystals of the 4-(2-carboxyethyl)-1,2,3,4-tetrahydrocyclopent[b]indole,  $C_{14}H_{17}NO_2$ , M = 231.32, are triclinic, space group PI with a = 11.642(1), b = 9.950(1), c = 11.455(1) Å,  $\alpha$  = 107.11(1),  $\beta$  = 110.13(1),  $\gamma$  = 82.53(1)°, V = 1190.1(2) Å<sup>3</sup>, Z = 4, observed reflections 3529 up to 0 = 60°,  $\lambda$ (Cu K $\alpha$ ) = 1.54178 Å. Intensity data were collected on a four-circle diffractometer (graphite monochromated radiation,  $\omega/20$  scan mode). Of the 3529 independent re-flections, 2324 were considered as observed with I> 3 $\sigma$  (I). The data were corrected for Lorentz and polarization factors but no absorption correction was applied. The structure was solved by direct methods' and Fourier synthesis. Refinement was done by full-matrix 1.s. analysis with anisotropic temperature factors. All H-atoms were found in a difference synthesis and included in subsequent refinements as isotropic contribution. A convenient weighting scheme was used to prevent bias on <w  $\Delta^2F>$  vs  $<\!Fo>$  and vs  $<\!sin$   $0/\lambda>$ . Final R = was used to prevent bias on  $<\!w~\Delta^2F\!>$  vs  $<\!Fo\!>$  and vs  $<\!sin~\Theta/\lambda^>$ . Final R = 0.056 and Rw = 0.059. Most calculations were done with the XRAY 70 System. A list of atomic parameters and Fo-Fc list can be obtained from the authors on request.

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Figure 1. Partial <sup>1</sup>H-n.m.r. spectra of a) VI, irradiated at the CH<sub>2</sub>-N frequency, b) IV, c) IV, calculated.



م



σ



Figure 3. Newmann representation of the chain in the title compound from X-Ray calculations.



Figure 4. Perspective view of the crystal structure. Dashed lines represent hydrogen bonds. Some symmetry related atoms are also shown for clarity. For symmetry codes see Table 2.



Molec. 2

Molec. 1

Figure 5. Perspective view of the molecular overlap occurring through symmetry centres.

Table 1.

<sup>3</sup> J <sub>HH</sub> (Hz)		φ (°)
<sup>J</sup> 13	9.24	28
<sup>J</sup> 14	5.29*	128
J <sub>23</sub>	5.29*	128
J <sub>24</sub>	9.24	28

\*( Here, J<sub>14</sub> and J<sub>23</sub>, and also the calculated Φ dihedral angles, are averaged values between those concerning with the conformational eqilibrium A≒B, Figure 2 )

Table 2. Bo	nd lengths	(Å), E.s.d.'s in parent	heses
N(1) = C(2)	1,378(5)	N(11) - C(21)	1.385(6)
N(1) -C(7A)	1.382(6)	N(11) -C(71A)	1.382(5)
N(1) - C(11)	1.459(5)	N(11) - C(111)	1.459(5)
C(2) -C(3)	1.354(5)	C(21) -C(31)	1.333(5)
C(2) -C(8)	1,477(7)	C(21) -C(81)	1.490(7)
C(3) -C(4A)	1,422(7)	C(31) -C(41A)	1,426(7)
C(3) -C(10)	1.509(6)	C(31) -C(101)	1,507(7)
C(4A)-C(4)	1,389(7)	C(41A)-C(41)	1.398(6)
C(4A)-C(7A)	1.418(5)	C(41A)-C(71A)	1.421(5)
C(4) -C(5)	1.378(8)	C(41) - C(51)	1.377(8)
C(4) -H(4)	1.02(5)	C(41) - H(41)	1.01(5)
C(5) - C(6)	1,400(7)	C(51) - C(61)	1.389(7)
C(5) - H(5)	1.03(5)	C(51) - H(51)	0.98(5)
C(6) - C(7)	1,394(8)	C(61) -C(71)	1.381(7)
C(6) -H(6)	1.00(6)	U(61) -M(61)	1.01(6)
C(7) -C(7A)	1.3/9(/)		1.331(7)
C(7) -H(7)	0.91(3)		V.38(3) ( 537/7)
C(8) - C(9)	1.00(6)	C(81) ~C(31) C(81) _H(811)	1.05(6)
C(8)	0.94(4)	C(81) =H(817)	1.05(4)
	1 539(7)	C(91) -C(101)	1.547(8)
C(3) = C(10)	1.01(6)	C(91) -H(911)	1.00(7)
C(3) -H(31)	0 97(4)	C(91) -H(912)	0.99(5)
C(10)-H(101)	1.05(5)	C(101)-H(1011)	0.99(5)
C(10)-H(107)	0.99(5)	C(101)-H(1012)	0.90(5)
C(11) - C(12)	1.528(6)	C(111)-C(121)	1.517(7)
C(11)-H(111)	1.06(5)	C(111)-H(1111)	1.01(6)
C(11)-H(112)	1,02(6)	C(111)-H(1112)	1.02(5)
C(12)-C(13)	1.502(8)	C(121)-C(131)	1.503(6)
C(12)-H(121)	1.01(4)	C(121)-H(1211)	1.02(4)
C(12)-H(122)	0.99(5)	C(121)-H(1212)	1.10(6)
C(13)-O(14)	1.322(5)	C(131) - O(141)	1.314(6)
C(13)-O(15)	1.213(5)	C(131)~Q(151)	1.200(6)
O(14)-H(14)	0.97(7)	D(141)-H(141)	0.85(5)

## Hydrosen bonds

X-HY	XY	X-H	ΗΥ	<х-нY
$D(14) = H(14) \dots D(15)^{i}$	2.715(5)Å	0.97(7)Å	1.75(7)Å	172(4) <sup>*</sup>
$D(141) = H(141) \dots D(151)^{i}$	2.662(4)	0.85(5)	1.81(5)	176(5)

Symmetry operations

(I) 1-x,1-y,1-z (II) 2-x,2-y,1-z

	Table 3. Bond	anales (•). E	s.d.'s in parentheses	
C(2)	-N(1) -C(7A)	107.5(3)	C(21) = -N(11) = C(71A)	107.1(3)
C(2)	-N(1) - C(11)	127.3(4)	C(21) = N(11) = C(111)	126.9(4)
C(7A)	-N(1) - C(11)	125.1(4)	C(71A) = N(11) = C(111)	126.1(4)
C(3)	-C(2) -C(8)	115.1(4)	C(31) - C(21) - C(81)	115.2(4)
C(3)	-C(2) -N(1)	110.5(4)	C(31) - C(21) - N(11)	110.8(4)
N(1)	-C(2) -C(8)	134.3(3)	N(11) - C(21) - C(B1)	133.8(4)
C(2)	-C(3) -C(4A)	107.7(3)	C(21) - C(31) - C(41A)	108.2(4)
C(2)	-C(3) -C(10)	111.0(4)	C(21), $-C(31)$ $-C(101)$	111.2(4)
C(4A)	-C(3) -C(10)	141.2(4)	C(41A) = C(31) = C(101)	140.5(4)
C(3)	-C(4A)-C(4)	134.8(4)	C(31) -C(41A)-C(41)	136.1(4)
C(3)	-C(4A)-C(7A)	106.0(3)	C(31) -C(41A)-C(71A)	105.5(3)
C(4)	-C(4A)-C(7A)	119.2(4)	C(41) -C(41A)-C(71A)	118.5(4)
C(4A)	-C(4) -C(5)	118.8(4)	C(41A) -C(41) -C(51)	118.8(4)
C(4A)	-C(4) -H(4)	121(3)	C(41A) -C(41) -H(41)	117(3)
C(5)	-C(4) -H(4)	120(3)	C(51) -C(41) -H(41)	125(3)
C(4)	-C(5) -C(6)	121.5(5)	C(41) -C(51) -C(61)	122.3(5)
C(4)	-C(5) -H(5)	123(3)	C(41) -C(51) -H(51)	116(3)
C(6)	-C(5) -H(5)	115(3)	C(61) -C(51) -H(51)	121(3)
C(3)	-C(6) -C(7)	120.7(5)	C(51) -C(61) -C(71)	120.5(5)
C(5)	-C(6) -H(6)	120(3)	C(51) -C(61) -H(61)	124(2)
C(7)	-C(6) -H(6)	119(3)	C(71) -C(61) -H(51)	115(2)
C(5)	-C(7) -C(7A)	117.5(4)	C(61) -C(71) -C(71A)	117.9(4)
C(6)	-C(7) -H(7)	119(4)	C(61) -C(71) -H(71)	123(3)
C(7A)	-C(7) -H(7)	123(4)	C(71A) -C(71) -H(71)	119(3)
C(4A)	-C(7A)-C(7)	122.3(4)	C(41A) -C(71A)-C(71)	122.1(4)
N(1)	-C(7A)-C(7)	129.4(4)	N(11) - C(71A) - C(71)	129.5(3)
N(1)	-C(7A)-C(4A)	108.3(4)	N(11) - C(71A) - C(41A)	108.4(4)
C(2)	-C(8) -C(9)	101.7(4)	C(21) - C(81) - C(91)	100.6(4)
6(2)	-C(8) -H(81)	114(3)	C(21) - C(81) - H(811)	116(3)
C(9)	-C(8) -H(81)	110(3)	C(91) -C(81) -H(811)	113(3)
0(2)	-C(8) -H(82)	115(3)	C(21) -C(81) -H(812)	112(3)
C(9)	-C(8) -H(82)	110(2)	C(91) -C(81) -H(812)	117(2)
H(81)	-C(8) -H(82)	106(4)	H(811) -C(81) -H(812)	99(4)
		109.1(4)	C(91) = C(91) = C(101)	109.3(5)
		110(3)	L(81) -L(91) -H(911)	114(3)
C(10)	-0(9) -4(91)	110(3)	C(81) -C(91) -H(911)	111(3)
	-0(3) -8(32)	116(3)	C(101) -C(91) -H(912)	111(3)
H(91)	-C(9) -H(92)	101(5)	H(911) -C(91) -H(912)	105(5)
C(3)	-0(10)-0(9)	103 1(3)	C(31) -C(101)-C(91)	101 9(4)
C(3)	-C(10) -H(101)	113(3)	C(31) = C(101) = C(31)	114(4)
C(9)	-C(10) - H(101)	113(3)	C(91) = C(101) = H(1011)	117(7)
C(3)	-C(10)-H(102)	110(3)	$\Gamma(31) = \Gamma(101) - H(1017)$	114(3)
C(9) '	-C(10) - H(102)	117(4)	E(91) = -C(101) - H(1012)	110(4)
H(101)	-C(10) - H(102)	105(4)	H(1011) - C(101) - H(1012)	104(4)
N(1)	-C(11)-C(12)	112.8(3)	N(11) = C(111) - C(121)	113.7(4)
N(1)	-C(11)-H(111)	108(2)	N(11) = C(111) = H(1111)	103(3)
C(12)	-C(11)-H(111)	110(3)	C(121) - C(111) - H(1111)	114(3)
N(1)	-C(11)-H(112)	106(3)	N(11) = C(111) - H(1112)	108(7)
C(12)	-C(11)-H(112)	110(2)	C(121) = C(111) = H(1112)	109(3)
H(111)	-C(11)-H(112)	110(4)	H(1111) - C(111) - H(1112)	109(4)
C(11)	-C(12)-C(13)	114.1(4)	C(111) -C(121)-C(131)	112.8(4)
C(11)	-C(12)-H(121)	113(3)	C(111) -C(121)-H(1211)	113(3)
C(13)	-C(12)-H(121)	108(4)	C(131) -C(121)-H(1211)	107(2)
C(11)	-C(12)-H(122)	108(3)	C(111) -C(121)-H(1212)	111(3)
C(13)	-C(12)-H(122)	103(4)	C(131) -C(121)-H(1212)	110(3)
H(121)	-C(12)-H(122)	110(4)	H(1211)-C(121)-H(1212)	103(4)
C(12)	-C(13)-O(14)	113.1(4)	C(121) -C(131)-O(141)	112.8(4)
C(12)	+C(13)-8(15)	124.2(4)	C(121) -C(131)-O(151)	124.1(4)
0(14)	-C(13)-O(15)	122.7(5)	0(141) -C(131)-O(151)	123.2(4)
C(13)	-0(14)-H(14)	105(3)	C(131) -O(141)-H(141)	109(4)