

Dynamic ^{13}C NMR Investigation and Crystal Structure of
3-Hydroxy-1,5-benzoxathiepine

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1,5-benzoxathiepine compounds are a novel class of heterocyclic rings that present interesting properties as central nervous system depressants. With the aim to contribute to the elucidation of the structure-activity relationship of this class of compounds we report a structural study of the 3-hydroxy-1,5-benzoxathiepine both in solution and in the solid state. Studies by dynamic ^{13}C -nmr in solution show that three conformations are possible for the oxathiepin ring. A unique chair conformation characterizes the atoms in the oxathiepine ring of the crystallized molecule. The crystal structure was solved by direct methods. Values of bond distances and angles are within the expected range.

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It is known that seven-membered carbo or heterocyclic rings have a more complex conformational behavior than six-membered cycles [1-5]. Moreover, the seven-membered class is less studied by dynamic ^{13}C -nmr spectroscopy [6], and, at the best of our knowledge, there are no reports on the conformational influence of the hydroxyl group for this class of compounds, with the exception of an ir work [7]. It is also noticeable that even relatively small changes in the constitution of seven-membered rings have a much larger influence on determining the preferred conformation than they have on six-membered rings [1-5].

Synthesis and reactivity of benzo-condensed five-, six- and seven-membered heterocyclic compounds containing more than one hetero atom are currently being investigated in our laboratories also in view of their biological activity [8-10]. The synthesis of 1,5-benzoxathiepine derivatives obtained from the reaction among epichloridrine and 1,2-benzenediol has been reported elsewhere [10].

Studies on the biological activity of 1,5-benzoxadiepines showed that, depending on their structure, these molecules can have bronchial dilator [11], analgesic, antiarrhythmic and sedative activity [12]. Preliminary researches on 3-hydroxy-1,5-benzoxathiepine (**1**) showed its activity as depressive of the central nervous system [13].

Since a detailed knowledge of its structure and conformational properties can greatly help to correlate them to the biological activity, we performed a structural study of compound **1** both in the solid state as well as in solution. For the latter we resorted to dynamic ^{13}C -nmr spectroscopy while, for the solid state, an X-ray study has been carried out.

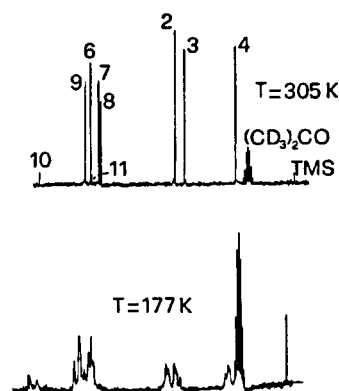


Figure 1

The ^{13}C -nmr spectrum of **1**, run at room temperature (305 K) in perdeuterioacetone, consists of a set of nine sharp lines (Figure 1 and Table 1), suggesting that **1** is inverting rapidly among possible conformations. Figure 1 shows also the dramatic changes that take place when the temperature is lowered to 177 K. It is now easy to note the existence of three different conformers with different intensities. When the temperature is gradually decreased from room temperature, we can observe at first that only the rate of exchange between a major (~80%) and a minor (~20%) conformer becomes slow on the nmr time scale. Down to 187 K, this is the only visible phenomenon, apart from a larger width for the lines of the prevailing conformer compared to those of the less abundant one. A possible explanation of this behavior is that a new exchange is becoming slow. This hypothesis is confirmed since at lower temperatures the lines of the major con-

Table 1
Free Enthalpies of Activation (kJ mol^{-1}) for the Exchange Between Various Conformations of **1**

Exchange [a]	ΔG^\ddagger [b]	Solvent	Population <i>ec</i> (temperature)	Population <i>ac + eb</i> (temperature)	Population <i>ac</i> (temperature)	Population <i>eb</i> (temperature)
$ec \rightleftharpoons ac + eb$	41.2	$(\text{CD}_3)_2\text{CO}$	0.20 (187 K)	0.80 (187 K)	---	---
$ec \rightleftharpoons ac + eb$	41.2	CD_2Cl_2	0.67 (186 K)	0.33 (186 K)	---	---
$ac \rightleftharpoons eb$	37.0	$(\text{CD}_3)_2\text{CO}$	---	---	0.48 (0.52) (177 K)	0.52 (0.48) (177 K)

[a] *ec* = pseudoequatorial OH "chair"; *ac* = pseudoaxial OH "chair"; *eb* = pseudoequatorial OH "boat" (see text). [b] The ΔG^\ddagger values are medium values obtained at different temperatures from different carbon atoms; estimated error $\pm 0.5 \text{ kJ mol}^{-1}$.

former are split again into two lines with slightly different intensity ($\sim 52:48$).

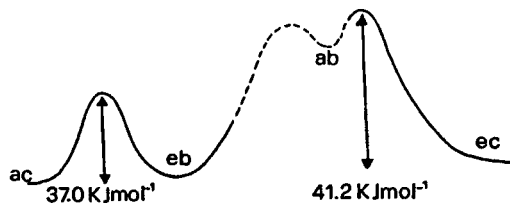


Figure 2

An energy diagram (Figure 2), showing a possible pathway followed for the interchanges between the various conformations, allows an easier understanding of the phenomena. Indeed, an examination of molecular models

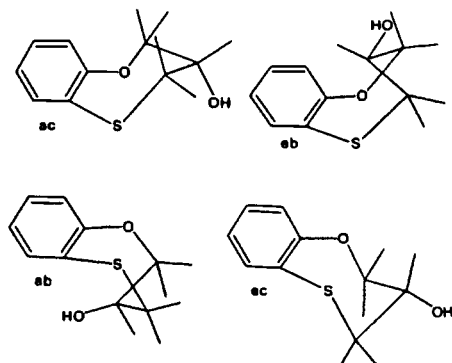


Figure 3

shows that three conformers are possible (Figure 3). Namely a "chair" with the hydroxy group pseudo-equatorial (*ec*), a "boat" with this group pseudo-equatorial (*eb*) and a "chair" with a pseudo-axial hydroxy group (*ac*) which could have roughly comparable energies. It is possi-

ble to rule out the "boat" with a pseudo-axial hydroxy group (*ab*) as this group should be too close to aromatic ring. Also molecular mechanics (MM2) calculations [14,15] give (*ec*) as the preferred conformer. We also think that the two "twisted boat" conformations, with the aromatic ring and O-1, C-2 (or C-4) and S-5 atoms in the same plane are not stable enough because the C-3 hydrogen atom is eclipsed both by the C-2 and C-4 hydrogens in one case and the hydroxy group and the C-3 hydrogen are both eclipsed by the two C-2 hydrogens in the other one.

Our tentative interpretation of this observed trend can be summed up in this way:

i) the first splitting ($\Delta G^\ddagger = 41.2 \text{ kJ mol}^{-1}$) is that between (*ec*) form and a combination of fast exchanging (*ac*) and (*eb*). The "boat" with the pseudo-axial hydroxy group, if at all, can only be present in a negligible quantity without any effect on the nmr spectrum; ii) the second separation ($\Delta G^\ddagger = 37.0 \text{ kJ mol}^{-1}$) is that between (*ac*) and (*eb*).

We must say that it seems surprising that the pseudo-equatorial hydroxy "chair" should be the less abundant conformer, so we studied the dynamic behavior of **1** in a non-oxygenated solvent (CD_2Cl_2) to eliminate the possibility of strong solute-solvent interactions *via* a hydrogen bond. Also in this case by lowering the temperature the lines divide into two new lines of unequal intensities ($\sim 67:33$) but, on further cooling, it is the minor conformer that undergoes a second splitting. The energy barrier for the first exchange is the same (41.2 kJ mol^{-1} in CD_2Cl_2) while it was impossible for us to study quantitatively the second exchange due to the scarce solubility, at low temperatures, of **1** in CD_2Cl_2 and to the small absolute concentration of the less abundant conformers. We can, on the other side, observe that in CD_2Cl_2 the major conformer seems to be the hypothesized one (*ec*).

The structure of compound **1** in the crystalline state was obtained by single-crystal X-ray diffraction analysis. A view of the molecule with atomic labelling is shown in Figure 4. Refined atomic coordinates, bond distances and angles are reported in Tables 2 and 3, respectively.

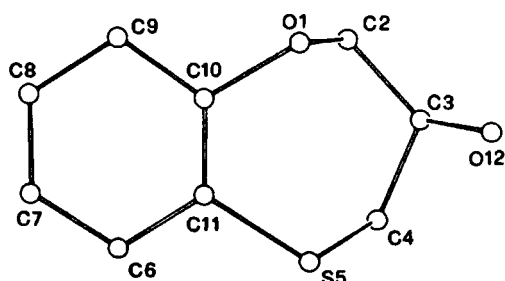


Figure 4

Structural parameters fall in the expected range, although some significant differences among chemically equivalent positions are observed. The quality of refinement, due to disorder, does not however allow any comment on these differences. Two independent molecules, **A** and **B**, are present in the asymmetric unit. Due to structural disorder the

Table 3
Bond Lengths (Å) and Angles (°) with
e.s.d.'s in Parentheses

	Mol A	Mol B	Mol B'
O(1)-C(2)	1.39 (2)	1.51 (3)	
O(1)-C(10)	1.53 (1)	1.45 (1)	
O(1')-C(2')			1.41 (3)
O(1')-C(11)			1.51 (2)
C(2)-C(3)	1.49 (3)	1.51 (3)	
C(2)-C(3')			1.53 (3)
C(3)-C(4)	1.49 (2)	1.52 (2)	
C(3')-C(4')			1.50 (3)
C(3)-O(12)	1.46 (2)	1.45 (3)	
C(3')-O(12')			1.49 (2)
C(4)-S(5)	1.77 (2)	1.79 (2)	
C(4')-S(5')			1.78 (2)
S(5)-C(11)	1.72 (1)	1.76 (2)	
S(5')-C(10)			1.75 (1)
C(6)-C(7)	1.36 (3)	1.42 (2)	
C(6)-C(11)	1.44 (2)	1.43 (1)	
C(7)-C(8)	1.37 (3)	1.34 (2)	
C(8)-C(9)	1.47 (2)	1.42 (2)	
C(9)-C(10)	1.43 (2)	1.44 (2)	
C(10)-C(11)	1.33 (2)	1.32 (2)	
C(2)-O(1)-C(10)	111 (1)	113 (1)	
C(2')-O(1')-C(11)			111 (2)
O(1)-C(2)-C(3)	114 (1)	105 (1)	
O(1')-C(2')-C(3')			99 (2)
C(2)-C(3)-C(4)	115 (1)	116 (2)	
C(2')-C(3')-C(4')			122 (2)
C(2)-C(3)-O(12)	113 (2)	106 (2)	
C(2')-C(3')-O(12')			112 (2)
C(4)-C(3)-O(12)	106 (1)	119 (2)	
C(4')-C(3')-O(12')			104 (2)
C(3)-C(4)-S(5)	115 (1)	117 (2)	
C(3')-C(4')-S(5')			119 (2)
C(4)-S(5)-C(11)	103 (1)	102 (1)	
C(4')-S(5')-C(10)			106 (1)
C(7)-C(6)-C(11)	117 (2)	117 (1)	
C(6)-C(7)-C(8)	123 (2)	123 (1)	
C(7)-C(8)-C(9)	122 (2)	121 (1)	
C(8)-C(9)-C(10)	113 (1)	116 (1)	
O(1)-C(10)-C(9)	115 (1)	118 (1)	
S(5)-C(10)-C(9)			113 (1)
O(1)-C(10)-C(11)	122 (1)	118 (1)	
C(9)-C(10)-C(11)	124 (1)	123 (1)	
S(5)-C(10)-C(11)			123 (1)
C(6)-C(11)-C(10)	122 (1)	120 (1)	
S(5)-C(11)-C(6)	115 (1)	114 (1)	
O(1')-C(11)-C(6)			122 (1)
S(5)-C(11)-C(10)	123 (1)	125 (1)	

Table 2

Positional Parameters ($\times 10^4$) and Thermal Parameters ($\text{\AA}^2 \times 10^2$), with e.s.d.'s in Parentheses. Disordered Atoms (* labelled) were Assigned Occupance Factor of 0.5

$$U_{eq} = (U_{11} + U_{22} + U_{33} + 2U_{13}\cos\beta)/3.$$

$$U_{iso} = *$$

	x	y	z	U_{eq} or U_{iso}
Molecule A				
O(1)	4674 (7)	2775 (5)	6359 (6)	5.6 (4)
C(2)	5727(13)	2945(11)	6274(17)	11.5 (9)
C(3)	5701(12)	2569 (9)	5149(20)	10.0(10)
C(4)	4918(13)	3201(11)	4091(14)	8.8 (9)
S(5)	3369 (3)	3135 (3)	3694 (3)	8.8 (2)
C(6)	2370(11)	4775 (9)	4282(15)	8.7 (8)
C(7)	2193(14)	5387(12)	5077(21)	10.6(11)
C(8)	2803(17)	5228(13)	6259(21)	11.1(12)
C(9)	3703(14)	4371(10)	6759(15)	9.6(10)
C(10)	3837(10)	3740 (8)	5884(12)	5.8(32)
C(11)	3229 (8)	3916 (8)	4739(11)	5.3 (5)
O(12)	5334 (8)	1449 (6)	4886(11)	12.3 (8)
Molecule B				
O(1)	-2439(11)	1120(10)	-5907(11)	4.3 (4)*
C(2)	-2367(20)	-71(18)	-6106(20)	6.8 (7)*
C(3)	-2494(16)	-619(15)	-5111(16)	4.3 (5)*
C(4)	-1457(20)	-469(18)	-3900(20)	7.0 (7)*
S(5)	-1253 (6)	844 (5)	-3260 (6)	6.7 (2)*
C(6)	292(10)	2213(10)	-3476(12)	7.6 (7)
C(7)	715(11)	2861 (9)	-4130(15)	7.2 (9)
C(8)	186(12)	2886 (9)	-5302(14)	6.7 (7)
C(9)	-840(11)	2256 (9)	-5954(12)	6.7 (7)
C(10)	-1282 (8)	1623 (7)	-5288 (9)	4.3 (5)
C(11)	-759 (9)	1594 (7)	-4129(10)	4.6 (5)
O(12)	-3689(12)	-371(11)	-5277(12)	5.7 (4)*
O(1')	-1427(12)	1036(12)	-3545(12)	5.7 (4)*
C(2')	-1047(23)	-39(21)	-3257(24)	9.1 (9)*
C(3')	-2054(15)	-611(14)	-4290(16)	3.8 (5)*
C(4')	-2228(20)	-469(18)	-5523(20)	6.8 (7)*
S(5')	-2525 (6)	840 (6)	-6160 (6)	8.1 (2)*
O(12')	-3251(11)	-369(11)	-4363(12)	5.6 (4)*

molecule **B** can be described in terms of two equi-probable atomic distributions, **B** and **B'**. The phenyl rings are planar (maximum deviation is 0.01 Å). The extra-ring atoms O(1) and S(5) deviate from ring plane max 0.24 and 0.06 Å, respectively. The seven-membered ring in the three independent molecules shows a chair conformation with the hydroxy group in the pseudo-equatorial configuration. The maximum values for the asymmetry coefficients are $\Delta C_2 = 0.17$ (the twofold axis passes through the C(11) atom and the middle of the C(2)-C(3) distance) and

$\Delta C_m = 0.08$ (the mirror plane passes through the C(3) and the middle of the C(10)-C(11) distance). The least-squares plane fitted through the atoms O(1), C(10), C(11), S(5) and that fitted through C(2), O(1), S(5), C(4) form an angle of $\sim 60^\circ$. The second plane forms an angle of $\sim 60^\circ$ with the plane containing C(2), C(3), C(4) atoms. The molecular configuration found in the crystal structure is in accordance with the conclusion based on the nmr and MM2 studies.

EXPERIMENTAL

The synthesis of 3-hydroxy-1,5-benzoxathiepine (**1**) has been reported in a previous study [10], mp 78° . Its ^{13}C -nmr spectrum in perdeuterioacetone showed this set of signals (ppm from internal TMS at 305 K): δ 38.4 (C-4), 70.7 (C-3), 76.9 (C-2), 122.6, 124.1, 129.0, 132.4 (C-6, C-7, C-8, C-9 interchangeables), 128.5 (C-11) and 160.8 (C-10).

Dynamic ^{13}C -NMR Experiments.

The ^{13}C -nmr spectra were recorded in various solvents, using TMS as the internal standard, in the Fourier transform mode on a Varian FT-80-A nmr spectrometer operating at 20 MHz and equipped with a V 5000 accessory for variable temperatures experiments. The temperature was monitored by a thermocouple inserted in a dummy tube before or after the spectral acquisition. The acquisition time for a spectral width of 4.0 KHz was 0.8 s, 30° pulses normally being employed without delay time. In most cases a few hundred transients were collected for noise-decoupled spectra. The ΔG^\ddagger values were obtained from a total line shape (TLS) analysis of different signals at various temperatures.

The results are summarized in the Table 1.

Crystallographic Analysis.

$\text{C}_9\text{H}_{10}\text{O}_2\text{S}$, $M_w = 182.24$, monoclinic, $P2_1/c$, $a = 12.52(2)$, $b = 12.45(2)$, $c = 12.75(1)$ Å, $\beta = 116.4(3)^\circ$, $V = 1780(6)$ Å³, $Z = 8$, $D_{\text{calc.}} = 1.36$ gcm⁻³, $\lambda(\text{MoK}\alpha) = 0.71069$ Å, $\mu = 3.04$ cm⁻¹, $F(000) = 768$, $T = 293$ K, $R = 0.107$ for 1379 observed reflections. Colorless prismatic crystals of **1** were obtained by slow evaporation of a diethyl ether/chloroform solution at room temperature. A crystal of dimensions 0.25 x 0.30 x 0.30 mm was selected and mounted along the c axis. Data collections have been performed on a Philips 1100 X-ray diffractometer using graphite-monochromated $\text{MoK}\alpha$ radiation. Lattice parameters have been refined with a least-squares fit of 25 high θ reflections. Three standard reflections ($3\bar{1}1$, $3\bar{1}\bar{1}$, 311) monitored every 3 hours showed no significant intensity variation. The intensity measurements were carried out in θ - 2θ scan mode up to $\theta_{\text{max}} = 25^\circ$ (index ranges: $-13 \leq h \leq 13$, $-14 \leq k \leq 14$, $0 \leq l \leq 15$) with a scan speed of 0.05 s⁻¹. 3881 reflections with $I \geq 2\sigma(I)$ were measured and averaged to 2000 unique reflections ($R_{\text{int}} = 0.037$). For the crystal structure refinement 1379 reflections with $I \geq 5\sigma(I)$ were employed. The intensities have been corrected for Lorentz and polarization factors but not for absorption. The structure was solved by direct methods [16] using a preliminary set of data collected on a automatic Siemens AED diffractometer on a crystal coming from a different crystallization

batch. Two molecules, **A** and **B**, are present in the asymmetric unit; E-map gave the position of all atoms in **A** and those of benzene ring and of the heteroatoms in **B**. Successive Fourier syntheses did not have success either in revealing remaining atoms or in distinguishing the two heteroatoms: their rather broad peaks were of comparable height, suggesting a disordered situation. Further Fourier syntheses calculated with the data set collected with the Philips diffractometer revealed that **B** unit is formed by two molecules rotated one with respect to the other, so that there is a full coincidence of the two benzene rings and a partial superposition of the coplanar sulphur and oxygen atoms in the condensed oxathia ring; the peaks of the remaining atoms are all clearly resolved and have very close peak heights.

Four cycles of unit weights full-matrix least squares refinement [17] with isotropic thermal parameters and with fixed occupancy factor of 0.50 for disordered atoms reduced the R factor to 0.212 but led to some values of bond lengths and angles in the disordered oxathia rings that deviate substantially from standard ones. Refinement was determined after four more cycles where all atoms in molecule **A** were assigned anisotropic thermal parameters; in molecules **B** disordered atoms were still assigned an occupancy factor of 0.5, a variable isotropic thermal parameter and the values of C-S, C-O and C-C bond lengths were constrained to lie within 1.75 ± 0.5 , 1.45 ± 0.5 , 1.50 ± 0.5 Å, respectively.

A final difference map was not able to reveal the positions of H atoms that were not included in the refinement. It showed some peaks of residual electron density scattered in the cell; the largest being $0.57 \text{ e}\text{\AA}^{-3}$ in height. Refinement on $\sum(|F_o| - |F_c|)^2$ to $R = 0.107$, $S = 1.0$; $(D/s)_{\text{max}} = 0.52$, $(D/s)_{\text{av}} = 0.10$. The program PARST [18] was used for geometrical calculations. Scattering factors were taken from the International Tables for X-ray Crystallography [19].

Refined atomic coordinates are given in Table 2, while bond lengths and bond angles are shown in Table 3. No relevant intermolecular interactions are evident from analysis of the packing, which is regulated by normal van der Waals forces only.

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REFERENCES AND NOTES

- [1] H. Hart and J. L. Corbin, *J. Am. Chem. Soc.*, **87**, 3135 (1965).
- [2] E. Grunwald and E. Price, *J. Am. Chem. Soc.*, **87**, 3139 (1965).
- [3] K. von Bredow, H. Friebolin and S. Kabuss, *Org. Magn. Reson.*, **2**, 43 (1970), and references therein.
- [4] P. W. W. Hunter and G. A. Webb, *Tetrahedron*, **29**, 147 (1973).
- [5] A. Blanchette, F. Sauriol-Lord and M. St. Jacques, *J. Am. Chem. Soc.*, **100**, 4055 (1978) and references therein.
- [6] F. A. L. Anet and R. Anet, in *Dynamic Nuclear Magnetic Resonance Spectroscopy*, L. M. Jackman and F. A. Cotton, eds, Academic Press, New York, 1975.
- [7] N. Mori, S. Kasuya, H. Miyazaki and T. Takezawa, *Bull. Chem. Soc. Japan*, **52**, 1423 (1979).

- [8] L. Bonsignore, S. Cabiddu, G. Loy and D. Secci, *Heterocycles*, **26**, 1619 (1987) and references therein.
- [9] S. Cabiddu, C. Floris, S. Melis and F. Sotgiu, *J. Heterocyclic Chem.*, **23**, 1815 (1986).
- [10] S. Cabiddu, S. Melis, F. Sotgiu and G. Cerioni, *Phosphorus Sulfur*, **14**, 151 (1983).
- [11] C. S. Rooney, R. S. Stuart, B. K. Wasson and H. W. R. Williams, *Can. J. Chem.*, **53**, 2279 (1975).
- [12] T. Tahara, M. Masago, T. Fujii and N. Anami, *Japan Kokai Tokkyo Koho*, 78 73,581; *Chem. Abstr.*, **90**, 23131r (1979).
- [13] Personal communication about 1,5-benzoxathiepine activity.
- [14] N. L. Allinger, *J. Am. Chem. Soc.*, **99**, 8127 (1977).
- [15] N. L. Allinger and Y. H. Yu, *QCPE* 395.
- [16] G. Cascarano, C. Giacobazzo, C. Burla, M. C. Nunzi, A. Polidori, G. Camalli, M. Spagna, R. Viterbo and D. Viterbo, SIR PROGRAM. *Proc. Ninth Eur. Crystallogr. Meeting*, Torino, Abstr. 1-046, 1983.
- [17] G. M. Sheldrick. SHELX 76. Program for Crystal Structure Determination, University of Cambridge, England, 1976.
- [18] M. Nardelli, *Comput. Chem.*, **7**, 95 (1983).
- [19] International Tables for X-ray Crystallography, Vol IV, Birmingham, Kynoch Press, 1974.