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7-hydroxy-3-(1-hydroxyethyl)-5-methoxy-3-4-dimethylisobenzofuran-a(3H)-one and 4, 8-dihydroxy-6-methoxy-3,4,5-trimethyIisochroman-1-one using MOPAC Software

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Abstract

A benzofuranone type of compound known as 7-hydroxy-3-(1-hydroxyethyl)-5methoxy-3,4-dimethylisobenzofuran-1 (3H)-one (1) and 4,8-dihydroxy-6-methoxy-3,4,5trimethylisochroman-l-one (2) were studied for the molecular modeling using MOPAC. Compound 1 was originally isolated from the fungus Leptosphaeria sp. KTC 727. Initial Nuclear Magnetic Resonance (NMR) analyses using I H, 13C, Correlation Spectroscopy (COSY), Heteronuclear Multiple Quantum Coherence (HMQC), Heteronuclear Multiple Bond Coherence (HMBC) and Mass Spectrometry (MS) suggested 1 and 2 as the candidate planar structures. Succeeding chemical experiments confirmed it to be 1 and not 2. This study provided new confirmatory evidence about the exclusion of 2 as possible candidate compound via theoretical computation approach using MOPAC software.

Keywords: benzofuranone, molecular modeling, Molecular Orbital Package (MOPAC), Nuclear Magnetic Resonance (NMR), theoretical calculation, z-matrix

Introduction

Molecular modeling has increasingly become a powerful tool to chemists in recent years. It involves theoretical approach in computing, predicting and simulating the three-dimensional structures and chemical properties of molecules. Chemists usually used ball and stick models to understand, study and appreciate the structural aspects of molecules. However, as the interest has shifted to bigger molecules, the limitations of mechanical models became challenging and Severe. Computers to the rescue! One can now calculate, visualize, rotate, manipulate and optimize the geometry of molecules on a computer display. Molecular Orbital Package (MOPAC) software is one of the free computational chemistries programs available to handle different aspects of these problems (Tayone 1995, p 5; Fattorusso and others 2006, p 7094; (3) Ohkatsu and others 2000, p 541; Shinohara and Others 1999, p 231; Singh and others 2004, p 171; Song and others 1999, p 175). In the course of the author's investigations of biologically active metabolites from ecologically unique fungi (Tayone and others 2009, p 7464; Tayone and others 2011 , p 2390; Tayone and Takada 2012, p 9), the author together with other Japanese researchers recently isolated and published (Tayone and others 2011, p 425) a novel isobenzofuranone compound 7-hydroxy-3-(1-hydroxyethyl)-5-methoxy-3, 4-dimethylisobenzofuran-l (3H)-one (1) (Figure 1) from Leptosphaeria sp. KTC 727 fungus. Initial attempt to elucidate its structure using NMR and MS analyses suggested 2 as well, as the possible planar structure. Furthermore, the HMBC and IR spectra did not rule out any of these two. However, irradiation of the arylmethyl (C-11) in 1 (Figure 2) induced a considerable Nuclear Overhauser Effect (NOE) at the doublet methyl (C-9) and singlet methyl at C-IO, which unambiguously excludes the possibility of 2. These correlations established the fact that the said methyl groups are spatially near from each other. Moreover, there was no NOE correlation detected between C-9 and 0-10 methyl groups implying thatthey must be anti and far from each other. These were corroborated by several experimental results that then ensued. The relative configuration of 1 was established by NOE correlations while the absolute configuration of this molecule was determined to be (3R,8S) by combination of modified Mosher's method and CD spectra analyses after derivatizations (Tayone and others 2011, p 425). This study was focus on the molecular modeling of 7-hydr0xy-3-(1-hydroxyethyl)5-meth oxy-3, 4-dimethylisobenzofuran1 (3H)-one (1) and 4,8-dihydroxy-6methoxy-3,4,5-trimethylisochroman-1-one (2) using MOPAC software. It is one of the chemical softwares used for the theoretical and in-silico studies especially for molecular modeling of molecules that are too

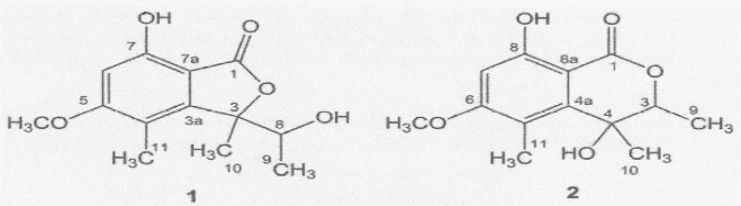


Figure 1. Planar structures of **1** and **2.**

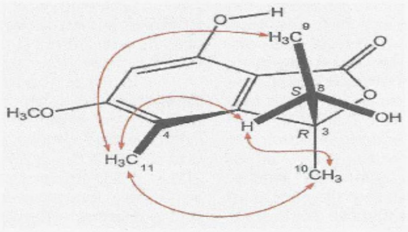


Figure 2. Selected NOEs observed in **1.**

Materials and Method

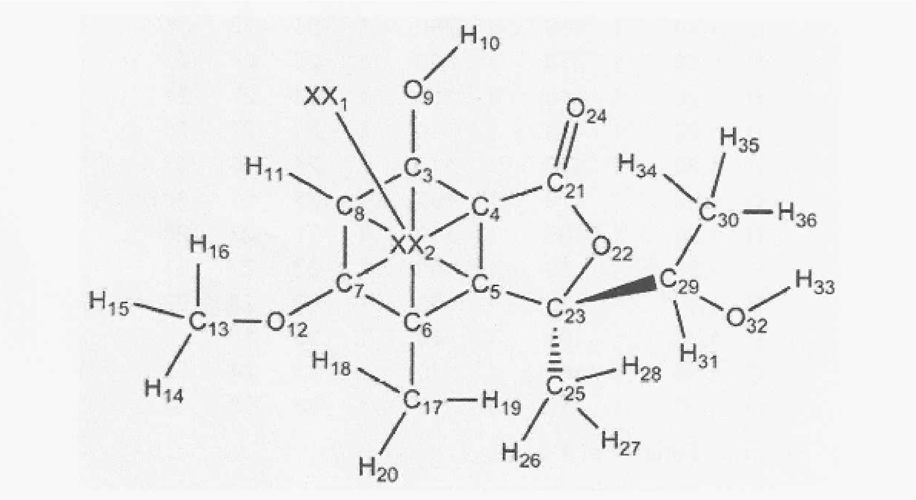
The MOPAC version used in this study was WinMopac7.21 which was written by Dr. Roman Shchepin and Dmitriy Litvinov. It is a powerful tool for semi-empirical calculations of chemical molecules. This program has combined an old DOS version of MOPAC7 with some improvements such as a Convenient windows interface and an integrated external molecular viewer called RasWin for easy viewing and manipulation of the three-dimensional structures. This program is compatible with Windows XP, Vista and Windows 7 (both 32 and 64 bit). It also conveniently runs under WINE in both Ubuntu and Macintosh versions (http://winmopac.narod.ru/english.html). MOPAC is written and armed with several concepts in quantum theory and thermodynamics and employs advanced mathematics that users need not be familiar with. The input data were kept as simple as possible so users can give their attention to the chemistry involved and not to concern themselves with quantum and thermodynamic exotica (MOPAC7 Manual).

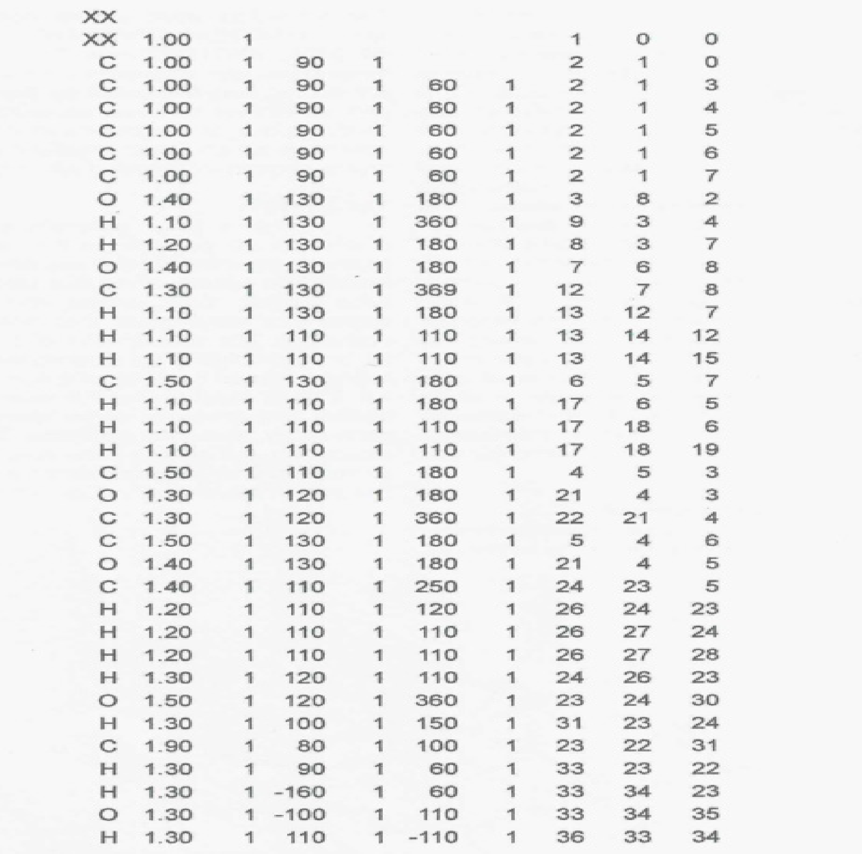
How the program worked

The first task was to specify the type of calculation and was controlled by keywords. The keywords used in the computation were CHARGE=O, GNORM-O. I, BONDS, GEO-OK, VECTORS and DENSITY. The initial molecular geometry (in the form of a z-matrix) was then read by the program and performed iterative computations as starting point of the optimization process until the program found a realistic and most stable geometry (Tayone 1995, p 5).

The Z-matrix

Z-matrix is a geometrical means of defining the positions of the atoms in a molecule as arranged in three-dimensional space. The column of I ‘s that follows after bond lengths, bond angles and dihedral angles are parameters that need to be optimized. The descriptions of the atoms for both candidate compounds were most easily achieved by using of a dummy atom XX. This is simply a point in space that is treated and imagined as an atom for the purpose of geometry definition. After the calculation, the dummy atom was removed so that only the real molecule remained. The Z-matrix of 1 is shown in Figure 3 below;



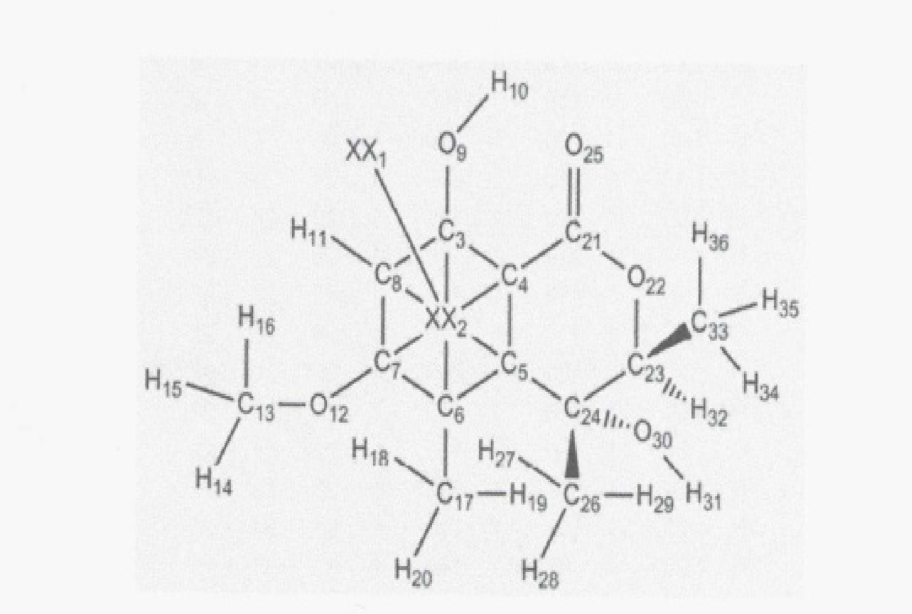


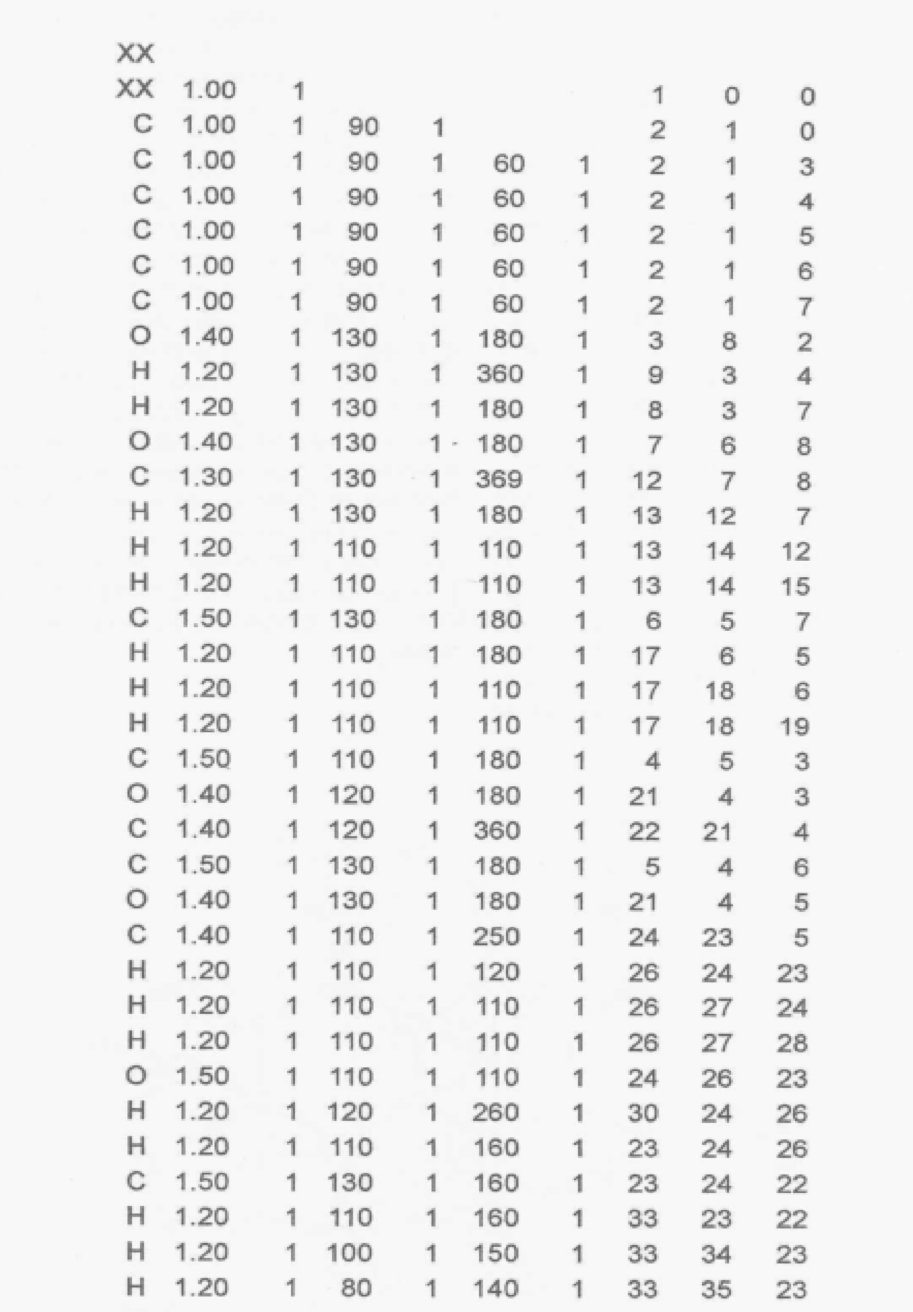
```
XX
XX  1.00  1                          1   0   0
C   1.00  1   90  1                  2   1   0
C   1.00  1   90  1   60  1          2   1   3
C   1.00  1   90  1   60  1          2   1   4
C   1.00  1   90  1   60  1          2   1   5
C   1.00  1   90  1   60  1          2   1   6
C   1.00  1   90  1   60  1          2   1   7
O   1.40  1  130  1  180  1          3   8   2
H   1.10  1  130  1  360  1          9   3   4
H   1.20  1  130  1  180  1          8   3   7
O   1.40  1  130  1  180  1          7   6   8
C   1.30  1  130  1  369  1         12   7   8
H   1.10  1  130  1  180  1         13  12   7
H   1.10  1  110  1  110  1         13  14  12
H   1.10  1  110  1  110  1         13  14  15
C   1.50  1  130  1  180  1          6   5   7
H   1.10  1  110  1  180  1         17   6   5
H   1.10  1  110  1  110  1         17  18   6
H   1.10  1  110  1  110  1         17  18  19
C   1.50  1  110  1  180  1          4   5   3
O   1.30  1  120  1  180  1         21   4   3
C   1.30  1  120  1  360  1         22  21   4
C   1.50  1  130  1  180  1          5   4   6
O   1.40  1  130  1  180  1         21   4   5
C   1.40  1  110  1  250  1         24  23   5
H   1.20  1  110  1  120  1         26  24  23
H   1.20  1  110  1  110  1         26  27  24
H   1.20  1  110  1  110  1         26  27  28
H   1.30  1  120  1  110  1         24  26  23
O   1.50  1  120  1  360  1         23  24  30
H   1.30  1  100  1  150  1         31  23  24
C   1.90  1   80  1  100  1         23  22  31
H   1.30  1   90  1   60  1         33  23  22
H   1.30  1 -160  1   60  1         33  34  23
O   1.30  1 -100  1  110  1         33  34  35
H   1.30  1  110  1 -110  1         36  33  34
```

Figure 3. Z-matrix of **1**.

The first atom (XX_1) was placed at the origin of coordinate system and on top of the z-matrix. Its position and connectivity could not be defined yet since there is no atom that precedes it. The second atom. the second dummy atom (XX_2) in Figure 3, must now be defined. Only the distance from atom 1 need be defined because the second atom is always placed on a predetermined axis. The second line means that XX_2 is bound to atom 1 (XX_1) at a distance of 1.00 angstrom. The third atom, C, in Figure 3, is defined using the distance from the XX_2 dummy atom and the XX_1 -XX_2-C_3 angle. The third line in Figure 3 implies that the carbon atom is bound to the second dummy atom (XX_2), at a distance of 1 00 angstrom and makes an angle with the first dummy atom (XX_1) of 900. The fourth atom (C_4) was defined exactly as the third except that an extra parameter was needed to specify its position uniquely. The exact position was defined using a dihedral angle to C_3 Thus, the fourth line in Figure 3 defines a carbon atom that is bonded to atom number 2 (XX_2) at a distance of 1.00 angstrom, making an angle with the first atom (XX_1) of 900 and a dihedral angle with atom number 3 (C_3) of 600. The exact positions of the remaining atoms were distinctly defined by the bond lengths, bond angles and dihedral angles in similar fashion described above. On the Other hand, the z-matrix of the most stable conformer of 2 is depicted in Figure 4.

The molecules are now completely defined. The z-matrices were then converted to its corresponding MOPAC input independently for iterative calculations. The semi-empirical method used in these theoretical calculations was Modified Neglect of Diatomic Overlap (MNDO). The calculations were run using Acer Aspire computer in VMnd0', vE 7 Ultimate with Intel @ Processor core™ 32367M CPU @ 1.40 GHz and 4.00 GB Random Access Memory (RAM).





```
XX
XX  1.00  1                                1   0   0
 C  1.00  1   90   1                       2   1   0
 C  1.00  1   90   1    60   1             2   1   3
 C  1.00  1   90   1    60   1             2   1   4
 C  1.00  1   90   1    60   1             2   1   5
 C  1.00  1   90   1    60   1             2   1   6
 C  1.00  1   90   1    60   1             2   1   7
 O  1.40  1  130   1   180   1             3   8   2
 H  1.20  1  130   1   360   1             9   3   4
 H  1.20  1  130   1   180   1             8   3   7
 O  1.40  1  130   1   180   1             7   6   8
 C  1.30  1  130   1   369   1            12   7   8
 H  1.20  1  130   1   180   1            13  12   7
 H  1.20  1  110   1   110   1            13  14  12
 H  1.20  1  110   1   110   1            13  14  15
 C  1.50  1  130   1   180   1             6   5   7
 H  1.20  1  110   1   180   1            17   6   5
 H  1.20  1  110   1   110   1            17  18   6
 H  1.20  1  110   1   110   1            17  18  19
 C  1.50  1  110   1   180   1             4   5   3
 O  1.40  1  120   1   180   1            21   4   3
 C  1.40  1  120   1   360   1            22  21   4
 C  1.50  1  130   1   180   1             5   4   6
 O  1.40  1  130   1   180   1            21   4   5
 C  1.40  1  110   1   250   1            24  23   5
 H  1.20  1  110   1   120   1            26  24  23
 H  1.20  1  110   1   110   1            26  27  24
 H  1.20  1  110   1   110   1            26  27  28
 O  1.50  1  110   1   110   1            24  26  23
 H  1.20  1  120   1   260   1            30  24  26
 H  1.20  1  110   1   160   1            23  24  26
 C  1.50  1  130   1   160   1            23  24  22
 H  1.20  1  110   1   160   1            33  23  22
 H  1.20  1  100   1   150   1            33  34  23
 H  1.20  1   80   1   140   1            33  35  23
```

Figure 4. Z-matrix of **2**.

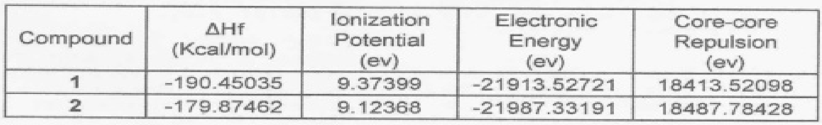
Results and Discussion

The Summary of results in MOPAC calculation were obtained from the archive file outputs (Table 1). The theoretically computed AH, of 1 was lower than those of 2 which makes it more energetically stable. Furthermore, the ionization potential of 1 was greater than that of 2 which can be attributed to its electrons that are more firmly held to the nucleus and thus more stable.

The final heat of formation (ΔH,) is the most stable molecular orbital after optimization. This is the heat of reaction resulting from the compound's formation by direct union of its elements. The ionization potential is the energy required to remove an electron from the molecular orbitals that does not change upon ionization. The computed ionization potential was based on Koopman's theorem.

The MOPAC computed geometry of 1 (Figure 5) corroborates the previous findings shown in Figure 2. The aryl methyl of 1 at C-11 was spatially near to two methyl groups at C-9 and C-10_ The quartet methine (H-B in 1) was also near to $^{10}CH_3$ and $^{11}CH_3$ On the other hand, the doublet methyl at C-9 of 2 was too far from the aryl methyl at C-11 and was block as well by the hydroxyl (CA) and methyl (C-10) substituents in between. The quartet methine (H-3 in 2) was also far from both $^{10}CH_3$ and $^{11}CH_3$ which contradicted the NMR spectroscopic data observed. The calculated MOPAC interatomic distances (Table 2) Of 1 and 2 supported the above discussion.

Table 1. Summary of results in MOPAC computation.



Compound	ΔHf (Kcal/mol)	Ionization Potential (ev)	Electronic Energy (ev)	Core-core Repulsion (ev)
1	-190.45035	9.37399	-21913.52721	18413.52098
2	-179.87462	9.12368	-21987.33191	18487.78428

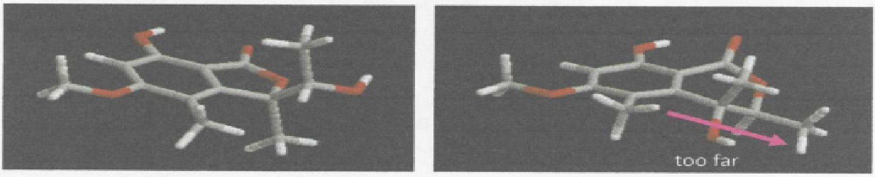
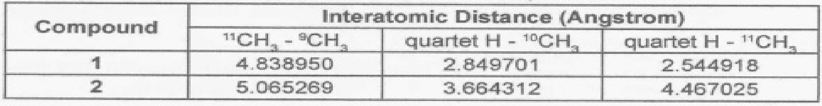


Figure 5. Final geometries obtained after optimization of **1** (left) and **2** (right).

Table 2. Selected interatomic distances of the compounds **1** and **2**.



Compound	Interatomic Distance (Angstrom)		
	$^{11}CH_3$ - $^{9}CH_3$	quartet H - $^{10}CH_3$	quartet H - $^{11}CH_3$
1	4.838950	2.849701	2.544918
2	5.065269	3.664312	4.467025

The puckering of the pyran ring in 2 has forced the methyl group (C-9) to occupy the equatorial position, The most stable conformer of 2 should therefore be in this confirmation because substituents that are in the axial (up and down) position are more crowded. The groups would be closer together which results in more steric interference, thus making the compound less stable. However. if it is in equatorial position, it's always going to be further away from the ring and other groups thus creating less steric strain (Morrison and Boyd, 1987 p 453). Therefore, the substituent extends into space, away from the rest of the molecule. The methyl substituent at C-9 in 2 is in equatorial position and thus, the most stable conformer. Though this is the most favored conformer of 2, it contradicted the observed NOE correlations detected in the NMR analyses. This therefore confirmed the published findings (Tayone and others 2011, p 425) that the compound being isolated is indeed 1 and not 2.

Acknowledgment

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