STUDY ON ENOL – ENOL TAUTOMERISM OF 5-(4-CHLOROPHENYL)-1-PHENYL-4-ACETYL-3-HYDROXY -3-PYRROLIN-2-ONE BASED ON NMR SPECTROSCOPY RECORDED IN DMSO-D6

NGHIÊN CỨU QUÁ TRÌNH TAUTOMER HOÁ ENOL – ENOL CỦA 5-(4-CHLOROPHENYL)-1-PHENYL-4-ACETYL-3-HYDROXY -3-PYRROLIN-2-ONE DỰA VÀO PHỔ CỘNG HƯỞNG TỪ HẠT NHÂN ĐƯỢC ĐO TRONG DUNG MÔI DMSO-D6

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Abstract - Tautomerism is a special chemical phenomenon that involves the migration of a proton between two tautomeric structures. Moreover, this dynamic equilibrium also plays a crucial role in modern medicinal chemistry due to its existence in the mechanism of many drugs' actions. This study has explored the enol – enol tautomerization of 5-(4-chlorophenyl)-1-phenyl-4-acetyl-3-hydroxy-3-pyrrolin-2-one in deuterated dimethyl sulfoxide *via* NMR measurement. The recorded spectra have shown that there was a fast chemical equilibrium process in NMR time-scale between two enolic structures which resulted in the broadening of ^{13}C resonance signals. More importantly, the spin – spin coupling between hydrogens and carbons has been recorded *via* 2D HSQC and HMBC spectra in which the resonance signals of all individual atoms have been recognized.

Key words - Tautomerism; tautomerization; enol – enol tautomerism; 1,5-disubstituted-4-acetyl-3-hydroxy-3-pyrrolin-2-one; enol – enol tautomerization

Tóm tắt - Tautomer hoá là một hiện tượng hoá học đặc biệt liên quan đến sự chuyển dịch của một nguyên tử hydrogen giữa các dạng tautomer khác nhau. Ngoài ra, quá trình cân bằng động học này cũng đóng vai trò rất quan trọng trong nghiên cứu hoá dược hiện đại do sự có mặt của nó trong cơ chế hoạt động của nhiều loại thuốc. Trong nghiên cứu này, quá trình tautomer hoá enol – enol của hợp chất 5-(4-chlorophenyl)-1-phenyl-4-acetyl-3-hydroxy-3-pyrrolin-2-one trong dung môi dimethyl sulfoxide đã được nghiên cứu dựa vào phổ cộng hưởng từ hạt nhân. Kết quả ghi phổ đã cho thấy cân bằng hoá học giữa hai cấu trúc tautomer dạng enol đã xảy ra nhanh hơn so với khả năng ghi nhận các tần số cộng hưởng riêng lẻ ở mỗi tautomer của thiết bị đo và dẫn đến xuất hiện một số peak chân rộng trong phổ ^{13}C NMR. Đặc biệt, tương tác spin – spin giữa các nguyên tử hydrogen và carbon trong hợp chất đã được ghi nhận và phân tích thông qua các phổ hai chiều HSQC và HMBC.

Từ khóa - Tautomerism; tautomerization; enol – enol tautomerism; 1,5-disubstituted-4-acetyl-3-hydroxy-3-pyrrolin-2-one; enol – enol tautomerization

1. Introduction

3-Pyrrolin-2-one core has been found in numerous bioactive natural products and synthetic compounds with potential pharmacokinetic activities against cancer [1], [2], bacteria [3], [4], inflammation [5], and radical [6]. For instance, natural product ZG-149 alpha (Figure 1) has been isolated from the culture broth of *Penicillium rubrum* which exhibited promising anti-inflammatory activity (IC_{50} = 3 μM) [7]. There are libraries of 1,5-disubstituted-4-acyl-3-hydroxy-3-pyrrolin-2-ones synthesized *via* multi-component reaction of aromatic aldehyde, amine, and ester of acylpyruvic acid in glacial acetic acid [8]. More importantly, these non-natural 1,5-dihydro-2*H*-pyrrol-2-one derivatives have been proven to possess antimicrobial and anti-inflammatory activity [9], [10].

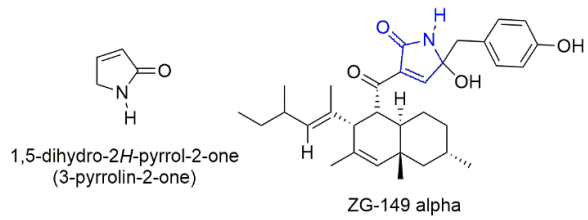

Figure 1. *Structure of 3-pyrrolin-2-one subunit containing ZG-149 alpha*

Prototropic tautomerism is a chemical equilibrium, which occurs due to intramolecular and intermolecular proton transfers, where the tautomers are dynamic interconvertible [11] - [14]. In general, one of the tautomers is more stable than the other, and intramolecular hydrogen bonds stabilize the tautomers [15]. Moreover, tautomerism plays an extremely important role in the study of modern medicinal chemistry due to the presence of heterocyclic substructures in many drugs which could exist in different tautomeric forms [16]. For instance, *R* stereoisomer of thalidomide, a pyrrolidine-2,5-dione core-containing drug, has been used in the treatment of myeloma and leprosy while its *S* stereoisomer is highly toxic (Figure 2) [17]. The study on the keto-enol tautomerism *via* NMR measurement was first reported in 1957 [18] and this spectroscopic method has been proven to be the reliable one in exploring the keto-enol, enol-enol tautomerization equilibrium [19]. In this manuscript, the enol-enol tautomerism of 5-(4-chlorophenyl)-1-phenyl-4-acetyl-3-hydroxy-3-pyrrolin-2-one in deuterated dimethyl sulfoxide (DMSO-d6) will be described for the first time *via* nuclear magnetic resonance spectroscopy measurement. Furthermore, 1D NMR and 2D NMR spectra of this 3-hydroxy-3-pyrrolin-2-one derivative will also be analyzed in detail.

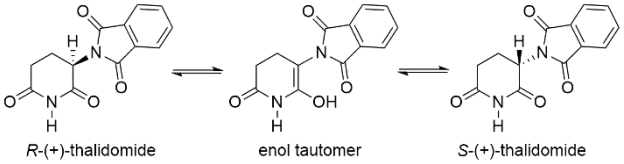

Figure 2. *Keto – enol tautomerism of thalidomide drug*

2. Experimental section

Proton nuclear magnetic resonance spectrum (^{1}H NMR), carbon nuclear magnetic resonance spectrum (^{13}C NMR), homonuclear correlation spectrum (^{1}H – ^{1}H COSY), hetereonuclear single quantum coherence spectrum (^{1}H – ^{13}C HSQC) and heteronuclear multiple bond correlation spectrum (^{1}H – ^{13}C HMBC) were recorded on Bruker Avance II+ 500 MHz spectrometer and DMSO-d6 was used as solvent. Tetramethylsilane [TMS; $(CH_3)_4Si$] has been used as an internal reference to determine chemical shifts that are reported in parts per million (ppm). ^{1}H NMR spectrum was acquired at 300 K, number of scans = 16. ^{13}C NMR spectrum was acquired at 300 K, number of scans = 4000. HMBC spectrum was recorded at 300 K, number of scans = 16, and the low pass J-filter technique was used to remove the single bond correlations.

3. Results and discussion

The synthesis of 5-(4-chlorophenyl)-1-phenyl-4-acetyl-3-hydroxy-3-pyrrolin-2-one, *via* a three-component reaction of 4-chlorobenzaldehyde, aniline, and ethyl 2,4-dioxovalerate in glacial acetic acid, has already been described in the literature [8]. In addition, 1D NMR spectra of this heterocycle have also been outlined without deep analysis of enol - enol tautomerization and characterization of 2D NMR [8].

In the ^{1}H NMR spectrum recorded in deuterated dimethyl sulfoxide (DMSO-d6), there were resonance signals in the chemical shift region of 7.00 – 7.60 ppm corresponding to nine (9) hydrogen atoms of two substituted benzene rings at 1,5-positions of 1,5-dihydro-2*H*-pyrrol-2-one core. In addition, two singlet peaks at 6.06 ppm and 2.33 ppm represent protons which directly attached to carbon atoms at the 5-position and 19-position, respectively (Figure 3).

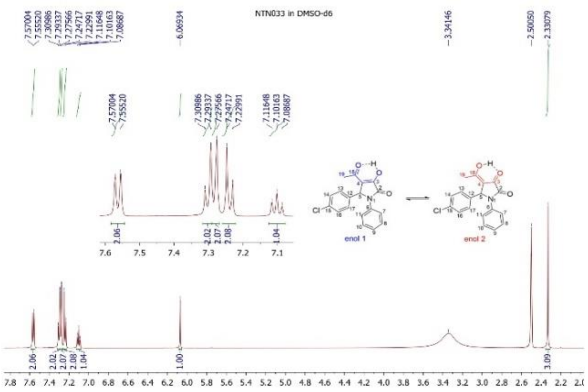

Figure 3. *^{1}H NMR spectrum of studied compound in DMSO-d6 [8]*

It is undeniable that 5-(4-chlorophenyl)-1-phenyl-4-acetyl-3-hydroxy-3-pyrrolin-2-one exists in the enol form which is stabilized by intramolecular hydrogen bond in a six-membered ring. Therefore, there would be an interconversion of two tautomeric structures, enol 1 and enol 2, *via* proton transfer which is called tautomerism (Figure 4) [20]. In addition, 5-(4-chlorophenyl)-1-phenyl-4-acetyl-3-hydroxy-3-pyrrolin-2-one has an asymmetric structure and hence, the two enolic tautomers, enol 1 and enol 2, are not chemically equivalent. However, these two tautomers did not produce unique resonances separately in ^{1}H NMR spectrum. Therefore, it could be concluded that the enol 1 - enol 2 tautomerism in DMSO-d6 was faster than the NMR time-scale and their NMR spectra corresponded to a weighted average of the two tautomers.

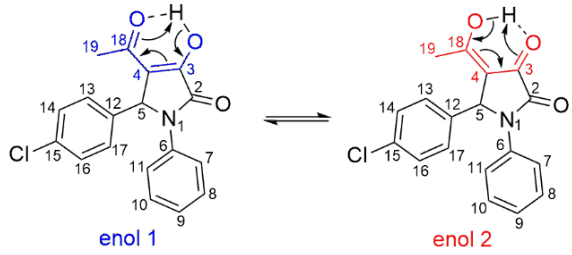

Figure 4. *Enol – enol tautomerism of studied compound in DMSO-d6 [8]*

There was no resonance signal of the hydrogen atom of the enolic hydroxyl group of 5-(4-chlorophenyl)-1-phenyl-4-acetyl-3-hydroxy-3-pyrrolin-2-one displayed in the spectrum (Figure 3). This observation is in line with ^{1}H NMR spectra of other 1,5-disubstituted-4-acetyl-3-hydroxy-3-pyrrolin-2-ones acquired in DMSO-d6 and $CDCl_3$ [8], [21]. It is clear that both acetyl (CH_3CO–) and hydroxyl (–OH) groups lie on the same plane with that of 1,5-dihydro-2*H*-pyrrol-2-one moiety and O–H bond is eclipsed with C=O bond of acetyl group [22]. One lone pair of electrons on hydroxyl oxygen atom will be delocalized into the π system of C=C bond at 3,4-positions and C=O bond at 18-position which results in the charge separation in the structure of this nitrogen-containing heterocycle (Figure 5). Due to the presence of water in deuterated dimethyl sulfoxide, which has been confirmed by the broad resonance signal at 3.34 ppm in ^{1}H NMR spectrum (Figure 3), the positive charge on the oxygen atom will be neutralized *via* the loss of a proton and then leaving the negative charge on the other oxygen atom (Figure 5). The resulting enolate anion has the negative charge delocalized over both oxygen atoms and each of oxygen atoms will carry half of the negative charge in a similar manner as the carboxylate anion [23], [24]. Therefore, the acidity of the enolic hydroxyl hydrogen atom of 5-(4-chlorophenyl)-1-phenyl-4-acetyl-3-hydroxy-3-pyrrolin-2-one is likely similar to that of carboxylic acid. In conclusion, in addition to fast interconversion between two tautomeric structures in NMR time-scale, the acidity of 5-(4-chlorophenyl)-1-phenyl-4-acetyl-3-hydroxy-3-pyrrolin-2-one brought about the exchangeability of hydrogen atom of enolic hydroxyl group with proton of water present in deuterated solvent during ^{1}H NMR measurement and the resonance signal of hydroxyl proton was broadened enough to disappear into the baseline.

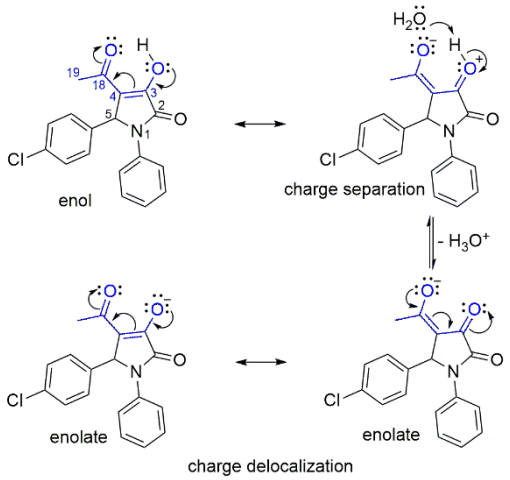

Figure 5. *Resonance stabilization of studied compound in DMSO-d6*

There were fourteen (14) resonance signals in the ^{13}C NMR spectrum of 5-(4-chlorophenyl)-1-phenyl-4-acetyl-3-hydroxy-3-pyrrolin-2-one in which those at 30.19, 120.28, 153.07 and 191.96 ppm are weak and broad ones (Figure 6). In both enolic structures, carbon atoms at 3-, 4-, 18- and 19-positions have been affected directly by the tautomerization. The hydroxyl oxygen atom of enol 2 can donate electron density into its adjacent C=C double bond *via* conjugation (Figure 4) and thus, the electron density on the carbon atom at 18-position will be higher than that on carbonyl carbon at the similar position of enol 1. Consequently, carbon atoms at 3-, 4-, 18- and 19-positions of enol 1 will resonate at different frequencies as compared to those of enol 2. However, the ^{13}C NMR spectrum appeared only a resonance signal corresponding to sp^3-hybridized saturated carbon atoms of both tautomers at 30.19 ppm which was broad and low intensity. More importantly, carbonyl carbon at 18-position has been shown by a weak and broadened signal at 191.96 ppm. In addition to the fast chemical equilibrium process, the temperature at which the ^{13}C NMR spectrum was acquired was close to the coalescence point, and thus, the resonance signals of carbons at 3-, 4-, 18- and 19-positions were broadened out in ^{13}C NMR spectrum [25], [26].

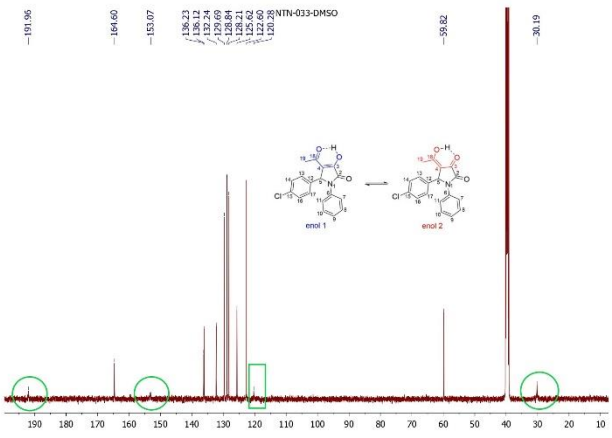

Figure 6. *^{13}C NMR spectrum of studied compound in DMSO-d6. Broad signals were highlighted by light green rectangles and circles [8]*

Along with one-dimensional nuclear magnetic resonance spectroscopy, two-dimensional nuclear magnetic resonance spectroscopy was also recorded to analyze and elucidate the structure of 5-(4-chlorophenyl)-1-phenyl-4-acetyl-3-hydroxy-3-pyrrolin-2-one. In the ^1H – ^{13}C HSQC spectrum, there was a cross peak arising from the correlation between methyl group protons resonance at 2.33 ppm and carbon atom representing by a broad signal at 30.19 ppm. This is to confirm that the fast tautomerization process and coalescence temperature resulted in the broadening of the carbon signal at the 19-position. At the coalescence point, the small difference in chemical shifts (expressed in Hz) of two methyl carbons at 19-positions of two enolic tautomers is comparable to the reciprocal of the lifetime of individual structures, enol 1 and enol 2 [27]. In addition, hydrogen atom at 5-position, H5, resonating at 6.06 ppm as a singlet, has shown spin-spin correlation with carbon atom resonance at 59.82 ppm as a sharp signal (Figure 6, Figure 7). Consequently, the sharp peak at 59.82 ppm in ^{13}C NMR belongs to carbon C5 at 5-position.

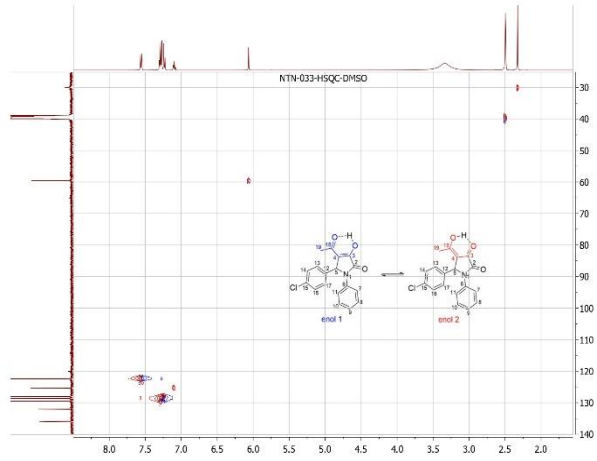

Figure 7. *^1H – ^{13}C HSQC spectrum of studied compound*

In the ^1H - ^{13}C HMBC spectrum of 5-(4-chlorophenyl)-1-phenyl-4-acetyl-3-hydroxy-3-pyrrolin-2-one (Figure 8), hydrogen atoms H19 and H5 resonance at 2.33 ppm and 6.06 ppm, respectively, in ^1H NMR all showed cross signals with the same carbonyl carbon C18 at 191.96 ppm as a broad and low-intensity peak in ^{13}C NMR spectrum. In addition, H19 and H5 also displayed correlation signals with the same carbon atom representing a very low intensity and broad peak at 120.28 ppm (Figure 6, Figure 8). Consequently, a broad resonance signal at 120.28 ppm in ^{13}C NMR (Figure 6) must be associated with carbon C4 at 4-position. Furthermore, hydrogen atom H5 also exhibited coupling signals with carbon resonance at 164.60 ppm as a sharp signal and at 153.07 ppm as a broad and low-intensity peak, respectively. Therefore, ^{13}C resonance signals at 164.60 ppm and 153.07 ppm in ^{13}C NMR must be those of carbon atoms C2 and C3, respectively. It is undoubtedly that the fast tautomerization process between two enolic structures and ^{13}C NMR spectrum measuring at coalescence temperature resulted in the broadening of resonance signals of four carbon atoms C3, C4, C18, and C19.

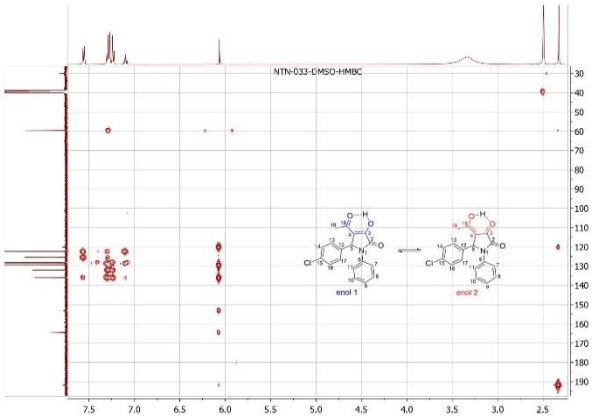

Figure 8. *$^{1}H - ^{13}C$ HMBC spectrum of studied compound*

There were four sharp, high-intensity peaks exhibited in the aromatic ring region of ^{13}C NMR spectrum (Figure 6). The $^{1}H - ^{13}C$ HMBC spectrum appeared a cross signal resulting from the correlation between proton H5 and carbons resonance as a high-intensity signal at 129.57 ppm in ^{13}C NMR. It could be concluded that the resonance peak at 129.57 ppm must be that of two chemically equivalent carbon atoms C13 + C17. In addition, there was a cross signal shown in the 2D HSQC spectrum corresponding to the interaction between carbons C13 + C17 and hydrogens H13 + H17 resonance at around 7.28 ppm in ^{1}H NMR as an overlapped signal (Figure 7). Furthermore, HMBC spectrum showed that hydrogen H5, two chemically equivalent hydrogen atoms H13 + H17, and two hydrogens displaying by a doublet at 7.23 ppm (^{3}J(H,H) = 8.63 Hz) all correlated with the same carbon atom resonating as a low-intensity peak at 136.12 ppm (Figure 8). Consequently, resonance signals at 7.23 ppm in ^{1}H NMR and 136.12 ppm in ^{13}C NMR must belong to chemically equivalent protons H14 + H16, and carbon C12, respectively. In combination with HSQC spectrum (Figure 7), two hydrogen atoms H14 + H16 exhibited a correlation signal with carbons C14 + C16, resonating at 128.21 ppm, which are directly attached. Hydrogens H14 + H16, and H13 + H17, but not hydrogen H5, all displayed long-range spin – spin coupling with low-intensity carbon peak at 132.24 ppm in ^{13}C NMR and thus, this signal must be that of C15.

In the HSQC spectrum, there has been a cross peak originating from the interaction between one proton resonance as a triplet at 7.10 ppm (^{3}J(H,H) = 7.42 Hz) in ^{1}H NMR and carbon resonating at 125.62 ppm in ^{13}C NMR (Figure 7). Furthermore, in HMBC spectrum (Figure 8), this above-mentioned proton also shows two cross peaks with carbon atoms exhibiting two high-intensity resonance signals at 122.60 ppm and 128.84 ppm. It means that the peak at 7.10 ppm in ^{1}H NMR and that at 125.62 ppm in ^{13}C NMR must belong to hydrogen H9 and carbon C9, respectively, of the mono-substituted benzene ring of 5-(4-chlorophenyl)-1-phenyl-4-acetyl-3-hydroxy-3-pyrrolin-2-one. More importantly, HSQC spectrum represented the spin – spin coupling between two protons resonance as a doublet at 7.56 ppm (^{3}J(H,H) = 7.42 Hz) and carbons resonance at 122.60 ppm, and these resonance signals were obviously arised from chemically equivalent atoms H7 + H11, and C7 + C11. Moreover, HSQC also indicated that two protons showing by an overlapped signal at approximately 7.29 ppm in ^{1}H NMR exhibited a correlation peak with carbons at 128.84 ppm and thus, these resonance signals are the representative of chemically equivalent atoms H8 + H10, and C8 + C10, respectively. Lastly, *via* HMBC measurement, hydrogens H5, H7 + H11, and H8 + H10 all showed long-range spin – spin interaction with low-intensity carbon atoms at 136.23 ppm, respectively. In conclusion, carbon atom C6 has resonated at the chemical shift of 136.23 ppm in ^{13}C NMR spectrum. The spectroscopic data of 5-(4-chlorophenyl)-1-phenyl-4-acetyl-3-hydroxy-3-pyrrolin-2-one have been summarized in Table 1.

Table 1. *^{1}H NMR, ^{13}C NMR spectroscopic data of 5-(4-chlorophenyl)-1-phenyl-4-acetyl-3-hydroxy-3-pyrrolin-2-one (500/125 MHz, DMSO-d6)*

Position	δ_C (ppm)	δ_H (ppm)	Position	δ_C (ppm)	δ_H (ppm)
2	164.60	--	**9**	125.62	7.10 (t, ^{3}J(H,H) = 7.42 Hz, 1H, Ar-H)
3	153.07 (broad, low intensity)	--	**12**	136.12	--
4	120.28 (broad, low intensity)	--	**13 and 17**	129.57	7.28 (overlapped signal, 2H; Ar-H)
5	59.82	6.06 (s, 1H)	**14 and 16**	128.21	7.23 (d, ^{3}J(H,H) = 8.63 Hz, 2H, Ar-H)
6	136.23	--	**15**	132.24	--
7 and 11	122.60	7.56 (d, ^{3}J(H,H) = 7.42 Hz, 2H, Ar-H)	**18**	191.96 (broad, low intensity)	--
8 and 10	128.84	7.29 (overlapped signal, 2H; Ar-H)	**19**	30.19 (broad, low intensity)	2.33 (S_{br}, 3H; CH_3)

4. Conclusion

There was intramolecular hydrogen bonding in a six-membered ring that occurred in the enolic structure of compound 5-(4-chlorophenyl)-1-phenyl-4-acetyl-3-hydroxy-3-pyrrolin-2-one. Due to the fast enol – enol tautomerization process in deuterated dimethyl sulfoxide as compared to NMR time-scale, ^{1}H NMR and ^{13}C NMR spectra were obtained as a weighted average of two tautomeric structures. In addition, the broadening of resonance peaks in ^{13}C NMR has originated from the coalescence temperature at which the spectrum was recorded. Especially, the acidity of the hydrogen atom of the enolic hydroxyl group led it to be exchangeable with the proton of water present in deuterated dimethyl sulfoxide (DMSO-d6) and consequently, its resonance signal has been broadened and disappeared into the baseline of ^{1}H NMR spectrum.

REFERENCES

[1] G. Lauro *et al.*, "Discovery of 3-hydroxy-3-pyrrolin-2-one-based mPGES-1 inhibitors using a multi-step virtual screening protocol", *MedChemComm*, vol. 9, no. 12, pp. 2028-2036, 2018. https://doi.org/10.1039/C8MD00497H

[2] X. Del Corte *et al.*, "A multicomponent protocol for the synthesis of highly functionalized γ-lactam derivatives and their applications as antiproliferative agents", *Pharmaceuticals*, vol. 14, no. 8, pp. 782, 2021.

[3] A. Q. Cusumano and J. G. Pierce, "3-Hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones as novel antibacterial scaffolds against methicillin-resistant *Staphylococcus aureus*", *Bioorganic & medicinal chemistry letters*, vol.28, no. 16, pp. 2732-2735, 2018. https://doi.org/10.1016/j.bmcl.2018.02.047

[4] A. López-Pérez *et al.*, "Discovery of pyrrolidine-2,3-diones as novel inhibitors of *P. aeruginosa* PBP3", *Antibiotics*, vol. 10, no. 5, pp. 529, 2021. https://doi.org/10.3390/antibiotics10050529

[5] N. V. O. Zacarías *et al.*, "Pyrrolone derivatives as intracellular allosteric modulators for chemokine receptors: selective and dual-targeting inhibitors of CC chemokine receptors 1 and 2", *Journal of Medicinal Chemistry*, vol. 61, no. 20, pp. 9146-9161, 2018. https://doi.org/10.1021/acs.jmedchem.8b00605

[6] N. T. Nguyen, V. V. Dai, A. Mechler, N. T. Hoa, and Q. V. Vo, "Synthesis and evaluation of the antioxidant activity of 3-pyrroline-2-ones: experimental and theoretical insights", *RSC advances*, vol. 12, no. 38, pp. 24579-24588, 2022. DOI: 10.1039/D2RA04640G

[7] R. R. West *et al.*, "ZG-1494α, a novel platelet-activating factor acetyltransferase inhibitor from *Penicilium rubrum*, isolation, structure elucidation, and biological activity", *The Journal of Antibiotics*, vol. 49, no. 10, pp. 967-973, 1996. https://doi.org/10.7164/antibiotics.49.967

[8] N. T. Nguyen, V. V. Dai, N. N. Tri, L. Van Meervelt, N. T. Trung, and W. Dehaen, "Experimental and theoretical studies on the synthesis of 1,4,5-trisubstituted pyrrolidine-2,3-diones", *Beilstein journal of organic chemistry*, vol. 18, no. 1, pp. 1140-1153, 2022. https://doi.org/10.3762/bjoc.18.118

[9] V. Gein, M. Armisheva, N. Rassudikhina, M. Vakhrin, and E. Voronina, "Synthesis and antimicrobial activity of 1-(4-hydroxyphenyl)-4-acyl-5-aryl-3-hydroxy-3-pyrrolin-2-ones", *Pharmaceutical Chemistry Journal*, vol. 45, no. 3, pp. 162-164, 2011. https://doi.org/10.1007/s11094-011-0584-0

[10] V. Gein, O. Bobrovskaya, R. Valiev, and V. Novikova, "Synthesis and antimicrobial activity of 5-[2-(4-aminosulfonylphenyl)ethyl]-3,4-diaryl-4,6-dihydropyrrolo [3,4-c]pyrazol-6-ones", *Russian Journal of General Chemistry*, vol. 86, pp. 1964-1966, 2016. https://doi.org/10.1134/S1070363216080326

[11] P. Muller, "Glossary of terms used in physical organic chemistry (IUPAC Recommendations 1994)", *Pure and Applied Chemistry*, vol. 66, no. 5, pp. 1077-1184, 1994. https://doi.org/10.1351/pac199466051077

[12] P. Zhang, A. T. Gardini, X. Xu, and M. Parrinello, "Intramolecular and water mediated tautomerism of solvated glycine", *Journal of Chemical Information and Modeling*, vol. 64, no. 9, pp. 3599-3604, 2024. https://doi.org/10.1021/acs.jcim.4c00273

[13] F. Su, Z. Sun, W. Su, and X. Liang, "NMR investigation and theoretical calculations on the tautomerism of benzimidazole compounds", *Journal of Molecular Structure*, vol. 1173, no. 5, pp. 690-696, 2018. https://doi.org/10.1016/j.molstruc.2018.07.038

[14] M. A. Freitag, T. L. Pruden, D. R. Moody, J. T. Parker, and M. Fallet, "On the Keto-Enol Tautomerization of Malonaldehyde: An Effective Fragment Potential Study", *The Journal of Physical Chemistry A*, vol. 111, no. 9, pp. 1659-1666, 2007. https://doi.org/10.1021/jp065979a

[15] K. Lammertsma and P. V. Bharatam, "Keto ⇌ Enol, Imine ⇌ Enamine, and Nitro ⇌ *aci*-Nitro tautomerism and their interrelationship in substituted nitroethylenes. Keto, imine, nitro, and vinyl substituent effects and the importance of H-bonding", *The Journal of organic chemistry*, vol. 65, no. 15, pp. 4662-4670. https://doi.org/10.1021/jo000283d

[16] P. V. Bharatam, O. R. Valanju, A. A. Wani, and D. K. Dhaked, "Importance of tautomerism in drugs", *Drug Discovery Today*, vol. 28, no. 4, pp. 103494, 2023. https://doi.org/10.1016/j.drudis.2023.103494

[17] C. Tian, P. Xiu, Y. Meng, W. Zhao, Z. Wang, and R. Zhou, "Enantiomerization mechanism of thalidomide and the role of water and hydroxide ions", *Chemistry–A European Journal*, vol. 18, no. 45, pp. 14305-14313, 2012. https://doi.org/10.1002/chem.201202651

[18] L. Reeves, "Nuclear magnetic resonance measurements in solutions of acetylacetone: the effect of solvent interactions on the tautomeric equilibrium", *Canadian Journal of Chemistry*, vol. 35, no. 11, pp. 1351-1365, 1957. https://doi.org/10.1139/v57-179

[19] A. Koltsov, "Enol-enol tautomerism in *cis*-keto-enols", *Journal of molecular structure*, vol. 444, no. 1-3, pp. 1-11, 1998. https://doi.org/10.1016/S0022-2860(97)00261-5

[20] K. A. Ebraheem, "^{1}H, ^{13}C and ^{19}F NMR studies on the structure of the intramolecularly hydrogen bonded *cis*-enols of 2-trifluoroacetylcycloalkanones", *Monatshefte für Chemie/Chemical Monthly*, vol. 122, no. 3, pp. 157-163, 1991.

[21] N. T. Nguyen and V. V. Dai, "Synthesis and structural determination of pyrrolidine-2,3-dione derivatives from 4-acetyl-3-hydroxy-5-phenyl-1-(3-nitrophenyl)-3-pyrroline-2-one", *The University of Danang - Journal of Science and Technology*, vol. 21, no. 6.1, pp. 61-66, 2023. https://doi.org/10.31130/ud-jst.2023.519E

[22] Z. Hosseinzadeh, A. Ramazani, H. Ahankar, K. Ślepokura, and T. Lis, "Sulfonic acid-functionalized silica-coated magnetic nanoparticles as a reusable catalyst for the preparation of pyrrolidinone derivatives under eco-friendly conditions", *Silicon*, vol. 11, pp. 2933-2943, 2019. https://doi.org/10.1007/s12633-019-0087-2

[23] L. G. Wade, *Organic chemistry*, 8th edition, USA: Pearson Education, 2008.

[24] J. Clayden, N. Greeves, and S. Warren, *Organic chemistry*, USA: Oxford University Press, 2012.

[25] M. T. Huggins, T. Kesharwani, J. Buttrick, and C. Nicholson, "Variable temperature NMR experiment studying restricted bond rotation", *Journal of Chemical Education*, vol. 97, no. 5, pp. 1425-1429, 2020. https://doi.org/10.1021/acs.jchemed.0c00057

[26] T. Atta-Ur-Rahman, *Nuclear magnetic resonance: basic principles*, USA: Springer Science & Business Media, 2012.

[27] V. Talsi and S. Evdokimov, "New cases of prototropic tautomerism in substituted pyridines", *Journal of Chemical Engineering And Bioanalytical Chemistry*, vol. 1, pp. 38-48, 2017.