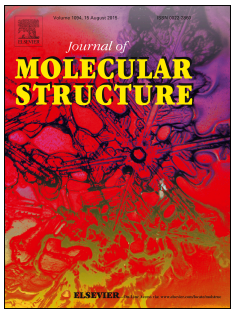

Crystal structure determination of *N*- and *O*-alkylated tautomers of 1-(2-pyridinyl)-5-hydroxypyrazole

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Crystal structure determination of *N*- and *O*-alkylated tautomers of 1-(2-pyridinyl)-5-hydroxypyrazole

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Abstract

The crystal structure determination of tautomeric products produced by the alkylation of 1-(2-pyridinyl)-3-phenyl-4-propyl-1*H*-5-hydroxypyrazole **2** was investigated. Treatment of ***2*** with isopropyloxycarbonyloxymethyl iodide and potassium carbonate under phase-transfer conditions affords two major products out of three possible *O*-, *N*-, and *C*-alkylated tautomers. The tautomeric structures of *O*-alkylated **3a** and *N*-alkylated **3c** were elucidated by means of NMR spectroscopic investigations and confirmed by single crystal X-ray analysis. The single crystal structures of alkylated compounds provide clear difference between the tautomeric pyrazole and pyrazolone ring systems in terms of bond lengths and torsional angles, moreover, conformational changes between two tautomers.

Keywords: 1-(2-Pyridinyl)-5-hydroxypyrazole, *N*-Alkylation, *O*-Alkylation, Tautomerism, ^{13}C NMR, Crystal structure.

1. Introduction

Pyrazoles are interesting structural units which are frequently found in natural products to pharmaceuticals. Such heterocyclic frameworks serve as important core structures possessing a broad spectrum of biological activities. The representative examples of drugs containing the moieties include celecoxib, rimonabant, metamizole, antipyrene, and sildenafil [1-3]. Moreover, there has been considerable interest in their capability to prototropic tautomerism between 5-pyrazolones and 5-hydroxypyrazoles [4-6]. We thus focused on peripheral modifications of pyrazole scaffold through exploiting the pyrazolone-pyrazole tautomerization [7-9].

From our recent efforts to identify lead compounds targeting NADPH oxidase (Nox) enzymes for the modulation of the excessive oxidase damage induced by reactive oxygen species (ROS) production, we found that 1-(2-pyridnyl)pyrazole **1** block the RANKL-dependent cell signaling cascade leading to reduced differentiation of osteoclast cells [10]. Further structure-activity relationships revealed enhanced physicochemical properties by the introduction of an alkyl group onto the parent molecule (e.g., **2**, Figure 1). We next investigated a prodrug **3a** likely to optimize the physicochemical properties and to improve pharmacological and toxicological profile.

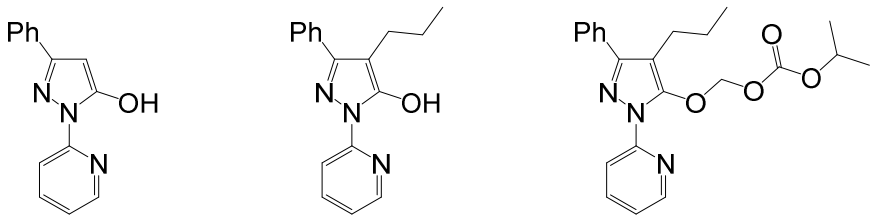


Figure 1. Peripheral modification of 1-(2-pyridinyl)pyrazole scaffold.

2. Experimental

2-1. General

All solvents and reagents were purchased from commercial sources and used as received without further purification, unless otherwise stated. Reactions were monitored by thin layer chromatography carried out on S-2 0.25 mm E. Merck silica gel plates (60F-254) using UV light as the visualizing agent and an acidic mixture of anisaldehyde or a ninhydrin solution in ethanol and heat as developing agents. E. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash column chromatography. All yields were calculated from isolated products. Melting points were recorded on Electrothermal IA9200 apparatus and are uncorrected. All NMR spectra were recorded on either Bruker AV-500 or AV-300 instruments. ^{1}H and ^{13}C NMR spectra were referenced internally to the residual undeuterated chloroform (δ_H = 7.26 ppm and δ_C = 77.0 ppm). The NMR data were analyzed using MNova 10.0 processing software (Mestrelab Research). The following abbreviations are used to designate multiplicities: s = singlet, d = doublet, t = triplet, td = triplet of doublets, sept = septet, m = multiplet, br s = broad singlet, ddd = doublet of doublets of doublets. Chemical shifts are reported in ppm and coupling constants are in Hertz (Hz). High resolution mass spectra using Electronic Ionization (HRMS-EI) were recorded on Joel JMS-700 mass spectrometer.

2-2. Crystallographic data

Single-crystal X-ray diffractions were measured on a Bruker APEX-II CCD diffractometer equipped with a monochromatic Mo-Kα radiation (λ = 0.71073 Å). The data were collected at low temperature of 100K by the φ–ω scan method. The collected data were integrated by using Bruker-SAINT software and an absorption correction wasn't applied. The structure were solved and refined through the least-squares method with SHELXT and SHELXL

program, respectively. All the non-hydrogen atoms were refined anisotropically and hydrogen atoms were placed in calculated positions. Table 1 presented the crystallographic data and structural refinements. Structural information was deposited at the Cambridge Crystallographic Data Center (CCDC reference numbers are 1902060 and 1902059 for **3a** and **3c**, respectively). Crystallographic data of 1-(2-pyridinyl)-3-phenyl-5-hydroxypyrazole (**1**, CCDC 805262) [9] have been obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

2-3. Synthesis of 1-(2-pyridinyl)-3-phenyl-4-propyl-1*H*-5-hydroxypyrazole (**2**) [10]

In a flame-dried flask, 2-hydrazinopyridine (3.67g, 33.6 mmol) and ethyl 2-benzoylpentanoate (8.04 g, 34.3 mmol) were mixed under neat conditions and then heated to 160 ^{o}C for 12h under argon atmosphere. Upon completion, the reaction mixture was cooled to room temperature. The crude product was purified by silica gel column chromatography (hexane/EtOAc = 8/2) to afford the title compound as a white solid, which then recrystallized with hexane/Et_2O to give colorless needles (8.16 g, 87%); mp: 68.6- 69.4 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 12.53 (brs, 1H), 8.26-8.23 (ddd, *J* = 0.7, 1.6, 5.0 Hz, 1H), 7.99 (d, *J* = 8.8 Hz, 1H), 7.86-7.70 (td, *J* = 1.8, 7.4 Hz, 1H), 7.71 (dd, *J* = 1.3, 7.9 Hz, 2H), 7.46-7.34 (m, 3H), 7.13-7.08 (ddd, *J* = 1.0, 5.2, 7.3 Hz, 1H), 2.54 (t, *J* = 7.8 Hz, 2H), 1.60 (septet, *J* = 7.3 Hz, 2H), 0.94 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 154.5, 154.0, 152.4, 145.2, 139.8, 134.1, 128.5, 128.1, 127.8, 119.7, 112.2. 100.2, 24.3, 23.0, 14.0; HRMS (EI) *m/z* $[M+H]^+$ calc for $C_{17}H_{17}N_3O$, 279.1372; observed: 279.1371.

2-4. Synthesis of *N*- and *O*-alkylated tautomers (**3a** and **3c**)

The title compounds were synthesized from the reaction of 1-(2-pyridinyl)-3-phenyl-4-propyl-5-hydroxypyrazole (**2**, 438 mg, 1.56 mmol) and isopropyloxycarbonyloxymethyl

iodide (497 mg, 2.03 mmol) with potassium carbonate (650 mg, 4.70 mmol) in the presence of tetrabutylammonium hydrogen sulfate (532 mg, 1.56 mmol) in dichloromethane (7.5 mL) and water (7.5 mL) for 12 hr at ambient temperature. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 x 5 mL). The combined organic layers were dried over anhydrous magnesium sulfate and filtered, and then the solvents were removed. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 10/1) to give 1-(2-pyridinyl)-3-phenyl-4-propyl-5-isopropyloxycarbonyloxymethyloxypyrazole (**3a**, 360 mg, 58%) and 1-isopropyloxycarbonyloxymethyl-2-(2-pyridiyl)-4-propyl-5-phenyl-1,2-dihydro-3*H*-pyrazol-3-one (**3c**, 210 mg, 34% yield), respectively. Single crystals from these two regioisomers suitable for X-ray diffraction were prepared by slow evaporation of a solution in ethyl acetate at room temperature.

2-4-1. 1-(2-Pyridinyl)-3-phenyl-4-propyl-5-isopropyloxycarbonyloxymethyloxypyrazole (**3a**). mp 97-98 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 8.49 (d, 1H, *J* = 4.7 Hz), 7.91 (d, 1H, *J* = 8.0 Hz), 7.83-7.80 (m, 1H), 7.75-7.73 (m, 2H), 7.46 (t, 2H, *J* = 7.25 Hz), 7.41-7.38 (m, 1H), 7.22-7.20 (m, 1H), 5.87 (s, 2H), 4.95-4.90 (m, 1H), 2.61 (t, 2H, *J* = 7.8 Hz), 1.60-1.55 (m, 2H), 1.32 (d, 6H, *J* = 6.2 Hz), 0.94 (t, 3H, *J* = 7.3 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 153.6, 152.1, 150.9, 149.3, 148.0, 138.3, 134.0, 128.4, 128.0, 127.7, 121.3, 116.0, 110.0, 92.7, 72.8, 24.7, 23.0, 21.7, 14.1 ppm; HRMS (EI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{25}N_3O_4$, 395.1845, found 395.1844; and the crystallographic data of **3a** are summarized in Table 1.

2-4-2. 1-Isopropyloxycarbonyloxymethyl-2-(2-pyridiyl)-4-propyl-5-phenyl-1,2-dihydro-3*H*-pyrazol-3-one (**3c**).

mp 83-84 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 8.51-8.49 (m, 1H), 8.19 (d, 1H, *J* = 8.5 Hz), 7.86-7.82 (m, 1H), 7.61-7.59 (m, 2H), 7.54-7.51 (m, 3H), 7.18-7.16 (m,1H), 5.70 (s, 2H), 4.67-4.62 (m, 1H), 2.38 (t, 2H, *J* = 7.5 Hz), 1.63-1.55 (m, 2H), 1.17 (d, 6H, *J* = 6.2 Hz), 0.88 (t, 3H, *J* = 7.0 Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 166.4, 154.9, 153.3, 149.0, 147.9, 138.2, 130.3, 129.4, 128.9, 128.5, 120.5, 116.6, 116.1, 73.6, 72.5, 24.7, 21.9, 21.5, 13.9 ppm; HRMS (EI) *m/z* $[M+H]^+$ calcd for $C_{22}H_{25}N_3O_4$, 395.1845, found 395.1845; and the crystallographic data of **3c** are summarized in Table 1.

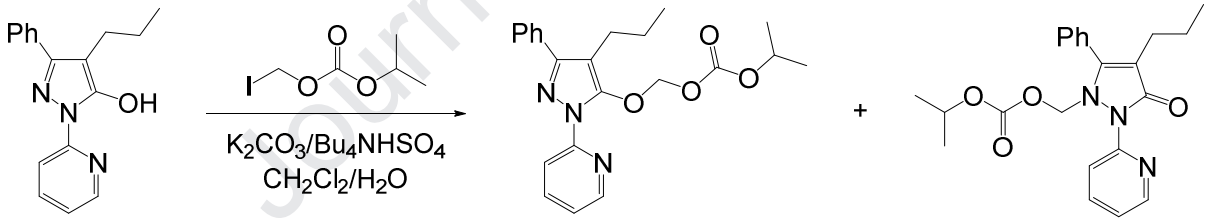
Table 1. Crystallographic data of **3a** and **3c.**

Compound	**3a**	**3c**
Empirical formula	$C_{22}H_{25}N_3O_4$	$C_{22}H_{25}N_3O_4$
Formula weight	395.45	395.45
Crystal system	Monoclinic	Monoclinic
Space group	P2(1)/c	P2(1)/c
Unit cell dimensions	a = 12.8907(3) Å	a = 10.2804(4) Å
	b = 10.7224(2) Å	b = 13.4480(6) Å
	c = 15.8982(3) Å	c = 14.9828(6) Å
	β = 112.5900(10)°	β = 99.181(2)°
Volume	2028.84(7) Å^3	2044.85(15) Å^3
Density (calculated)	1.295 Mg/m^3	1.285 Mg/m^3
Reflections collected	5067	18751
Final R indices [I>2sigma(I)]	R_1[a] = 0.0399, wR_2[b] = 0.0940	R_1[a] = 0.0391, wR_2[b] = 0.1019
R indices (all data)	R_1 = 0.0539, wR_2 = 0.1048	R_1 = 0.0454, wR_2 = 0.1073

[a] $R_1 = ||F_o| - |F_c||/\Sigma|F_o|$. [b] $wR_2 = [\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]]^{1/2}$.

3. Results and Discussion

Prodrugs are chemically modified derivatives of drug-like molecules that are used to improve the charge and lipophilicity in favor of pharmacokinetic and toxicological properties of the parent drug [11]. Apparently, alkoxycarbonyloxymethyl prodrugs are soft alkyl derivatives of active phenolic drugs that are used to overcome the bioavailability problems related to stability and solubility. Indeed, the alkyloxycarbonyloxymethyl prodrugs have been exploited as novel permeation-enhancing derivatives of phenolic, antiviral, and nucleoside phosphate prodrugs [12-14]. During the reaction of 2 and isopropyloxycarbonyloxymethyl iodide with potassium carbonate under phase-transfer conditions, we identified two products having exactly the same molecular weight (Scheme 1).

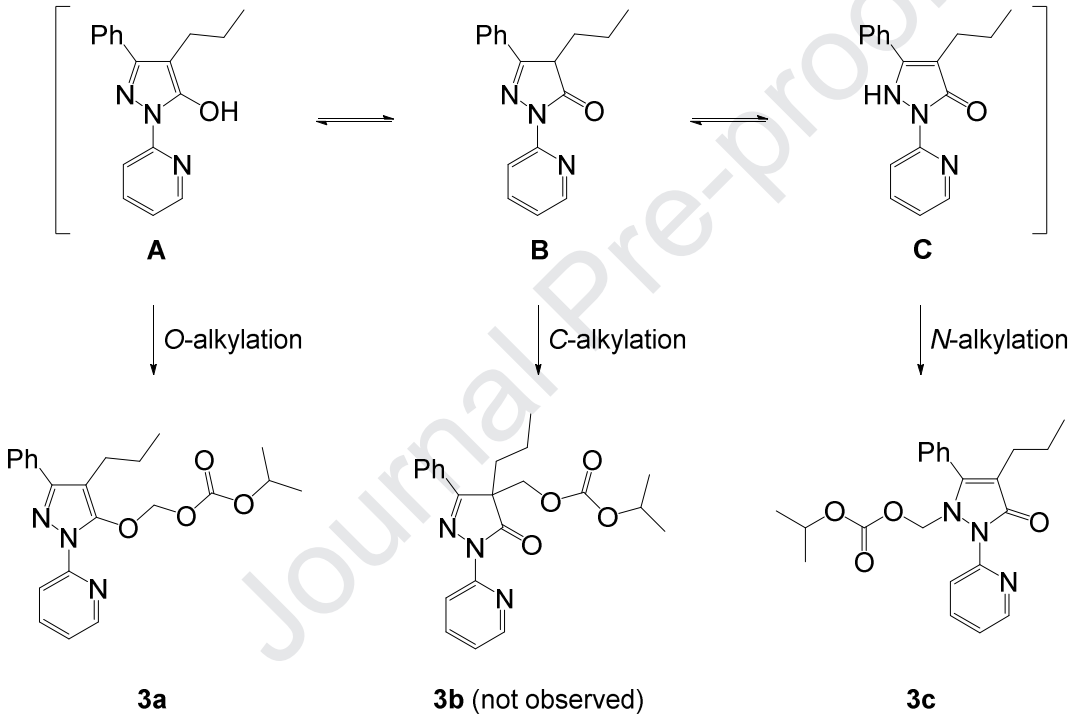


2 **3a** (58%) **3c** (34%)

Scheme 1. Preparation of *O*- and *N*-alkylated tautomers

The pyrazolone tautomerism is an everlasting issue in pyrazole chemistry and thus it has been the subject of a considerable number of investigations. For example, 5-pyrazolones are of particular interest due to their ability to exist in the tautomeric equilibria between the OH (**A**), CH (**B**), and NH form (**C**) as illustrated in Scheme 2. Therefore the ratio of products is highly depending on not only the tautomeric contributions but also the nature of reagents and solvents used both in acylation [15,16] and alkylation of tautomeric pyrazolones [17-19].

Since the products share essentially the same pattern, the structures should be assigned based on careful analysis of chemical shifts of ^{1}H and ^{13}C NMR favorably with NOEs and long-range INEPT experiments [18,19], but the most convincingly with X-ray crystallography [4-6]. Here we report the structural assignments based on X-ray crystal structure determination since three possible *O*-, *N*-, and *C*-alkylated tautomers have quite similar spectroscopic properties.



Scheme 2. Tautomeric contributions of 5-pyrazolone and possible products distribution

The ^{1}H and ^{13}C NMR of the crude revealed the presence of two isomeric forms in the ratio of 1.7:1. Most signals of the two products are duplicated and they have exactly the same molecular weight. The significant difference between **3a** and **3c**, however, was that the singlets of a methylene group of the carbonate resonated at 5.87 and 5.70 in ^{1}H, and 92.7 and 73.6 ppm in ^{13}C NMR, respectively. The downfield shifting of the methylene group clearly shows that it is bonded to a heteroatom, and implying the presence of OH and NH forms

rather than CH form. In ^{13}C NMR study, it has been reported that pyrazolone carbonyl of the CH form resonates at 170 ppm in contrast to the upfield resonances of 155 ppm and 160 ppm corresponding to OH and NH forms, respectively [20,21]. Moreover, the differentiation between the pyrazolone carbonyl and the carbonate carbon is not justified as the latter nearly centers at 155 ppm in all the three forms [22].

Even though the presence of pyrazolone carbonyl group of **3c** resonating at 166.4 ppm somewhat assures the presence of *N*-alkylated product, the ^{13}C NMR study does not provide crucial features to distinguish between the three tautomers since they are sets of isomeric protonation states with the same carbon atoms. To clarify this structural ambiguity, then the structure determination by X-ray crystallography should be investigated and the ORTEP drawings are shown in Figure 2 and 3. It is noteworthy, since the 5-pyrazolone tautomerism involves the relocation of proton in which single and double bonds are interconvertible, that the single crystal structures of alkylated compounds are of great help in structural information between the tautomeric ring systems.

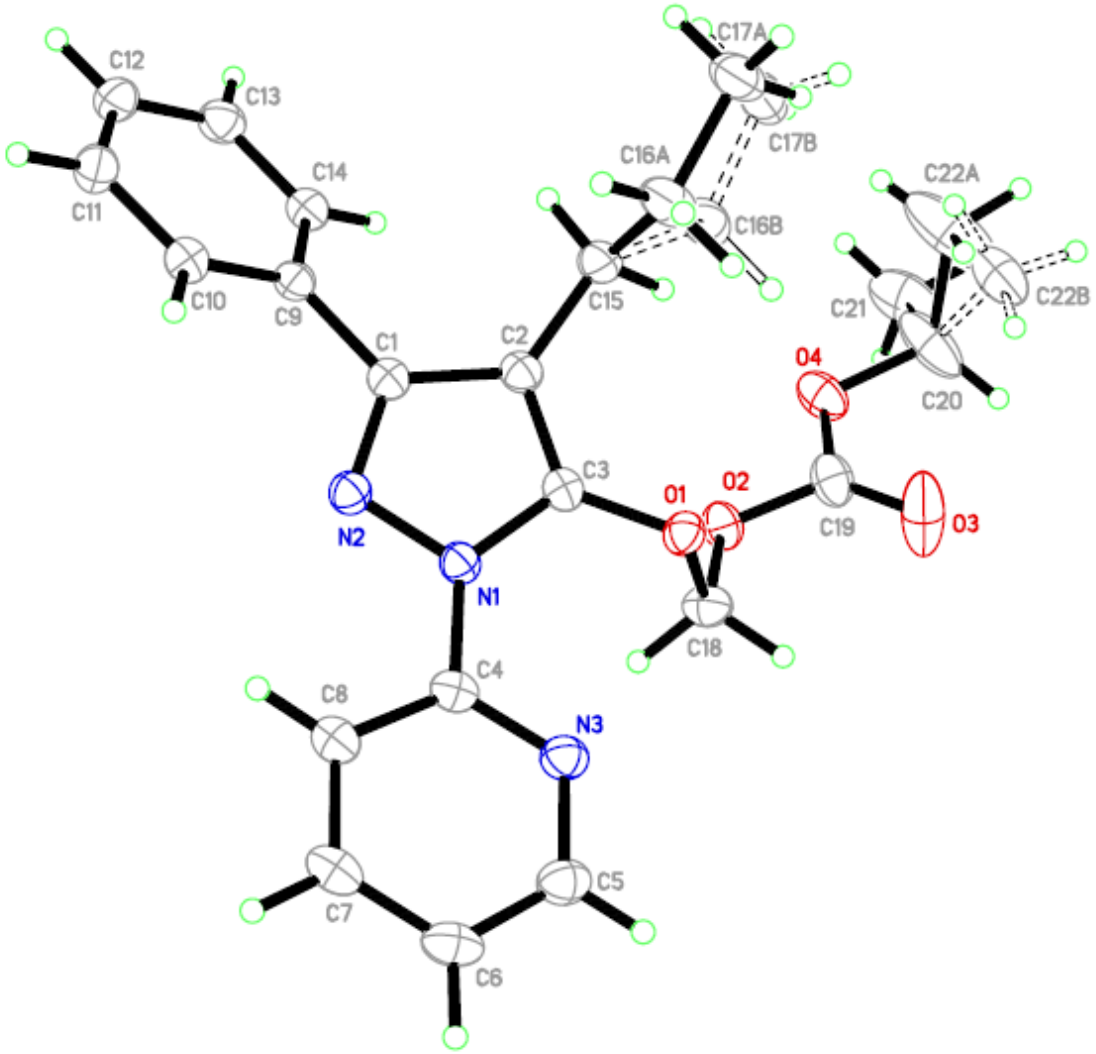


Figure 2. Crystal structure of **3a**. Thermal ellipsoids are shown at the 50% probability level.

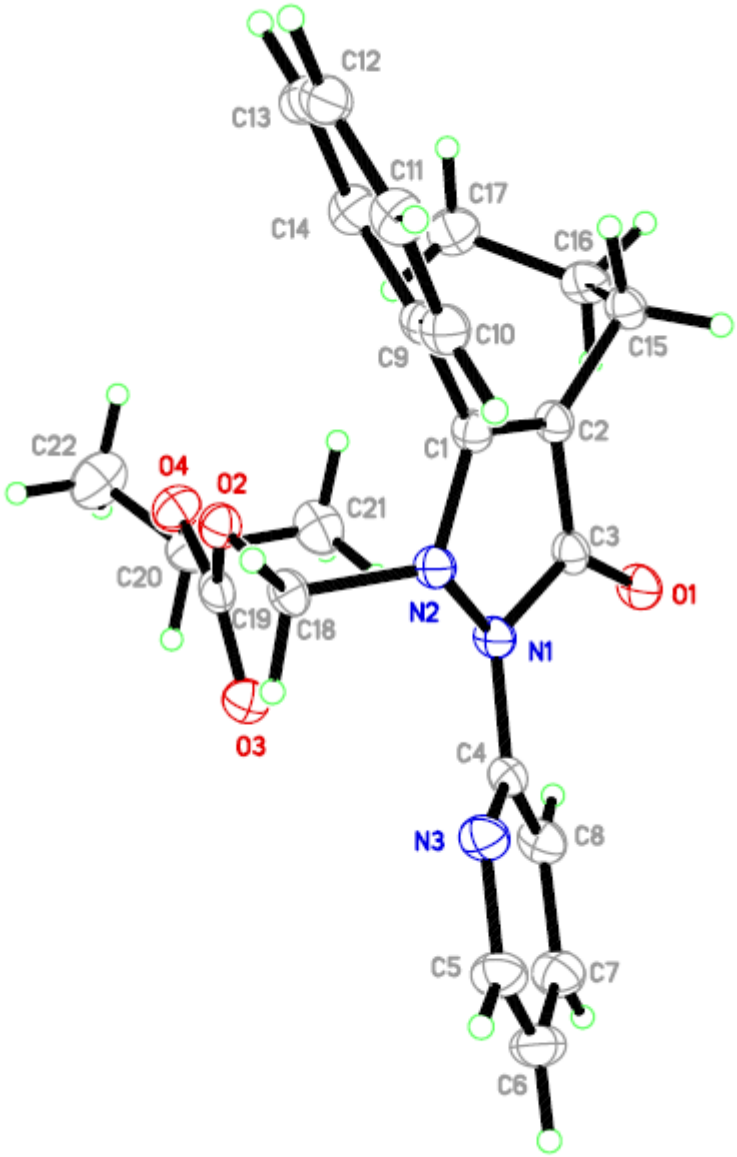


Figure 3. Crystal structure of **3c**. Thermal ellipsoids are shown at the 50% probability level.

X-Ray diffraction analysis revealed that **3a** belongs to the monoclinic space group P2(1)/c with a = 12.8907(3) Å, b = 10.7224(2) Å, c = 15.8982(3) Å, α = 90°, β = 112.5900(10)°, γ = 90° and V = 2028.84(7) $Å^3$. The molecular structure of **3a** comprises a near coplanar tetra-substituted pyrazole ring with an r.m.s deviation of the fitted atoms being 0.002 Å. All bond distances in the pyrazole ring show partial double bond character, which suggests a

delocalized π-electronic system throughout the ring. The bond lengths and bond angles in the pyrazole ring are within the normal ranges reported in the literatures [4-6]. The bond length of C(3)-O(1), 1.3585(14) Å is little longer than that of the parent compound. This is expected that the C-O bond of **1** attains a partial double bond character because of the keto-enol tautomerization. The bond distances of N(2)-C(1) and C(2)-C(3) are consistent with the average of the length of C=N and C=C double bonds, respectively. However, the C(1)-C(2) bond length of 1.4193(16) Å is apparently longer than a double bond. The X-ray crystal analysis of **3a** is consistent with the OH tautomer (Table 2).

The molecular structure of **3c** indicated that the crystal belongs to the monoclinic space group P2(1)/c with a = 10.2804(4) Å, b = 13.4480(6) Å, c = 14.9828(6) Å, α = 90°, β = 99.181(2)°, γ = 90° and V = 2044.85(15) $Å^3$, and comprises near planar tri-substituted pyrazolone ring with an r.m.s deviation of the fitted atoms being 0.005 Å. The C(1)-C(2) bond length is 1.3513(14) Å is consistent with that of C=C double bond and the C(2)-C(3) is 1.4561(14) Å is corresponding to C-C single bond length. The length of N(2)-C(1) is 1.4118(13) Å, and in similar line with C-N single bond of amines. The 1.2273(12) Å of C(3)-O(1) clearly show a C=O double character. All these three bond lengths clearly confirms the presence of the NH tautomer (Table 2).

Table 2. Comparison of bond length (Å)

Description[a]	**1**[b]	**3a**	**3c**
N(1)-N(2)	1.3782(15)	1.3687(14)	1.4159(12)
N(2)-C(1)	1.3261(18)	1.3348(15)	1.4118(13)
C(1)-C(2)	1.4130(2)	1.4193(16)	1.3513(14)
C(2)-C(3)	1.3560(2)	1.3673(17)	1.4561(14)

C(3)-O(1)	1.3384(16)	1.3585(14)	1.2273(12)
C(3)-N(1)	1.3750(18)	1.3791(15)	1.3992(12)

[a] For a comparative discussion of X-ray crystal structures, the numbering of atoms is given based on the pyrazole skeleton (see: Fig. 2). [b] Data taken from CCDC 805262.

The molecules **1** and **2** exclusively exist in the enol form as seeing that the X-ray crystal structure of **1** clearly shows that the carbonyl oxygen and pyridine nitrogen adopt an almost *syn*-periplanar arrangement that is capable of accommodating intramolecular hydrogen bonding [9, 23, 24]. The dihedral angles of **3a** supporting the planarity of pyrazole ring is given in Table 3. The dihedrals of O(1)-C(3)-C(2)-C(15) and C(9)-C(1)-C(2)-C(15) of **3a** are nearly coplanar with the angles of -4.5(2)^{o} and 6.2(2)^{o}, respectively, regarding to the plane defined by the pyrazole ring. However, crystal structure of **3a** does not exhibit a defined structure within two flexible alkyl chains. The dihedral angle of C(3)-N(1)-C(4)-N(3) suggests that **3a** still adopt an almost *syn*-periplanar arrangement. While **3c** also shows the dihedrals of O(1)-C(3)-C(2)-C(15) and C(9)-C(1)-C(2)-C(15) are nearly coplanar to the pyrazole ring, the dihedral of C(9)-C(1)-N(2)-C(18) is displaced out of plane by 53.12(13)^{o} with pyrimidalization of the nitrogen atom. The torsion angle of C(3)-N(1)-C(4)-N(3) of **3c** changes remarkably with 143.49(10)° contrary to that of **3a**. This clearly suggests that the pyridine nitrogen and the pyrazolone ketone adopt an *anti*-periplanar arrangement probably due to the close proximity and the repulsion between them. The results of X-ray single-crystal analysis is consistent with those of NMR study.

Table 3. Comparison of dihedral angle (^{o})

Description[a]	**1**[b]	**3a**	**3c**
C(3)-N(1)-C(4)-N(3)	2.3(2)	-13.08(18)	143.49(10)

O(1)-C(3)-C(2)-(15)	-	-4.5(2)	0.34(17)
C(9)-C(1)-C(2)-(15)	-	6.2(2)	3.94(19)
C(9)-C(1)-N(2)-(18)	-	-	53.12(13)

[a] For a comparative discussion of X-ray crystal structures, the numbering of atoms is given based on the pyrazole skeleton (see: Fig. 2 and 3). [b] Data taken from CCDC 805262.

In conclusion, two prodrug-type tautomers have been isolated from the reaction of 1-(2-pyridinyl)-3-phenyl-4-propyl-1*H*-5-hydroxypyrazole **2** with isopropyloxycarbonyloxymethyl iodide and potassium carbonate under phase-transfer conditions, among three possible *O*-, *N*-, and *C*-alkylated products. The two tautomeric products have been identified as *O*-and *N*-alkylated ones by NMR and mass spectroscopic analysis. However, the differentiation was still demanding as the pyrazolone carbonyl and carbonate peaks are considerably overlap with a number of aromatic carbons, we thus have confirmed the structures by single crystal X-ray crystallography. Finally, the tautomeric structures of *O*-alkylated **3c** and *N*-alkylated **3c** were elucidated by means of NMR spectroscopic investigations and confirmed by single crystal X-ray analysis. The single crystal structures of alkylated compounds provide much structural difference between the tautomeric ring systems can be specified in terms of bond lengths and torsional angles. It is noteworthy that the orientation of the pyridine nitrogen of the OH form is *syn*-periplanar, whereas *anti*-periplanar to the keto functionality in the NH-form.

4. **Supplementary Materials**

Atomic coordinates and crystallographic parameters of **3a** (CCDC 1902060) and **3c** (CCDC 1902059) have been deposited at the Cambridge Crystallographic Data Centre. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via

www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgments

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Highlights

- Alkylation of 5-hydroxypyrazole produces *O*- and *N*-alkylated tautomers.
- Two tautomeric structures were elucidated by single crystal X-ray diffractions.
- The *O*-alkylated tautomer exists in pyrazole, whereas *N*-tautomer in pyrazolone ring.
- Conformational changes have been observed between two tautomers.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: