Structures of 1-Phenyl-3-methyl-pyrazolone-5 and its Benzoyl Derivatives+

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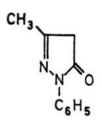
Benzoylated 1-Phenyl-3-methyl-pyrazolones-5, NMR Spectra, Mass Spectra, IR Spectra

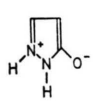
The structures of 1-phenyl-3-methyl-pyrazolone-5 and its benzoyl derivatives have been investigated by means of IR, UV, NMR, and mass spectral spectroscopy. 1-Phenyl-3-methyl-pyrazolone-5 is found to exist as a zwitter ion in the solid state. in the 5-keto form in chloroform and dioxane, and in the 5-hydroxy form in pyridine. The 4-benzoyl derivative of 1-phenyl-3-methyl-pyrazolone-5 is shown to exist in two different tautomeric enol forms and not an enol form and a keto form as was formerly reported. The structures of two other benzoyl derivatives were investigated and assigned as the C-5-O-benzoyl derivative and C-4-benzoyl-C-5-O-benzoyl derivative, respectively.

1-Phenyl-3-methyl-pyrazolone-5

The structure of 1-phenyl-3-methyl-pyrazolone-5 is usually written as

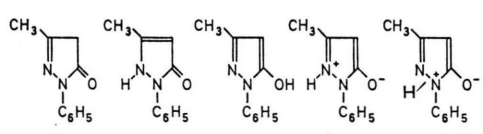


From spectral data it has been concluded that 2-pyrazolin-5-ones having aryl substitution at N-1 generally exist in the oxo (keto) forms [1]. However, fairly recently, De Stevens and co-workers [2] on the basis of infrared studies suggested that 2-pyrazolin-5-ones having H, alkyl and aryl at N-1 and alkyl groups at C-3 possess the betaine (zwitterionic) form



as the principal tautomeric form of these compounds.

The following tautomeric isomers are possible for 1-phenyl-3-methyl-pyrazolone-5.



a b c d e

Scheme 1.

It is claimed [3] that UV and IR spectroscopy have established unequivocally that the 5-keto and 5-hydroxy forms are the chief tautomeric contributors of pyrazolin-5-ones. Gomez [4] has concluded that no deductions can be drawn from the UV spectra of 1-methyl-3-phenyl-2-pyrazolin-5-one and 1-phenyl-2,3-dimethyl-3-pyrazolin-5-one because of the tautomeric equilibria present.

On the other hand, Jensen and Friedinger [5] and Brown *et al.* [6] have obtained abnormally high dipole moments for 1-phenyl-2,3-dimethyl-3-pyrazolin-5-one and this was considered to be due to resonance contributions of the zwitterionic form to the extent of 35 per cent. The question of resonance contributions have been extensively reviewed by R. H. Wiley and P. Wiley [7].

Because of these conflicting views involving tautomerism and the theory of resonance, it was decided to investigate the actual structure of 1-phenyl-3-methyl-pyrazolone-5 both in the solid state and in various solutions using a combination of infrared and proton magnetic resonance spectroscopy. Out of the theoretically possible tautomeric forms (Scheme 1) three have been identified under completely different conditions as follows:

Form I: Solid phase IR of 1-phenyl-3-methyl-pyrazolone-5 (KBr pellets) reveals a satellite of two broad absorption bands between 1700 cm^{-1} and 3000 cm^{-1} centered at 1850 cm^{-1} and 2650 cm^{-1} respectively without any absorption band in the carbonyl region. The solid phase IR spectrum of 1-phenyl-2,3-dimethyl-pyrazolone-5 (antipyrine), on the other hand reveals no absorption band between 2000–2700 cm^{-1} but exhibits a carbonyl absorption band at 1670 cm^{-1}. The satellite of absorption bands

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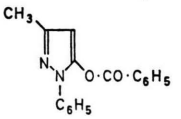
between 2000–2700 cm^{-1} is usually observed in the spectra of amino acids and similar compounds that exist in the zwitterionic form [8]. It is interesting to note that the only difference between 1-phenyl-3-methyl-pyrazolone-5 and antipyrine is that the N-2 in antipyrine carries a methyl group. On the basis of the above IR evidence it is concluded that 1-phenyl-3-methyl-pyrazolone-5 exists as the zwitterion (d) in Scheme 1 in the solid state.

Form II: Solution phase IR of 1-phenyl-3-methyl-pyrazolone-5 in chloroform reveals the absence of the satellite absorption peaks between 2000 to 2700 cm^{-1} that exist in the solid KBr IR but exhibits the presence of carbonyl absorption frequency at 1700 cm^{-1}. This evidence coupled with evidence from proton NMR spectrum in $CDCl_3$ in which there is a peak at δ 2.15 ppm integrated for three protons and ascribed to the methyl group. a signal at δ 3.47 ppm integrated for two protons and attributed to methylene protons and a multiplet between δ 7.00–8.00 ppm integrated for five protons and attributed to the phenyl group confirms that this compound exists as the keto form (a)) in Scheme 1) in chloroform.

Form III: Proton NMR spectrum of 1-phenyl-3-methyl-pyrazolone-5 in deuterio-pyridine (pyridine-d_5) reveals a signal at δ (2.27 ppm) integrated for three protons and attributable to methyl protons, a peak at δ (5.55 ppm) ascribed to a vinyl proton (C=CH), a multiplet between δ 7.00–8.40 ppm integrated for five protons attributable to phenyl protons and a resonance at δ (12.33 ppm) ascribed to a hydroxy proton involved in some hydrogen-bonding. The integrations for the vinyl and the hydrogen-bonded hydroxy protons do not correspond exactly to one proton each. But there is a peak at δ 8.62 ppm which corresponds exactly to the position of C-α protons in pyridine, which was not there in the PMR spectrum of the deuterated solvent used. So certainly, some proton-deuterium exchange must have occured between the active protons in the 1-phenyl-3-methyl-pyrazolone-5 and the solvent pyridine-d_5. There is a noteworthy absence of any signal due to methylene protons between δ 3.00 and 4.00 ppm as was observed in $CDCl_3$. Structure (c) of Scheme 1 is therefore indicated.

Infrared evidence reveals that this compound exists as the keto form (structure (a) in Scheme 1) in dioxane (C=O: 1710 cm^{-1}). This compound also exists in the keto form in carbon tetrachloride. The PMR spectrum in this solvents reveals a signal at δ (2.13 ppm) integrated for three protons and attributable to methyl protons, a resonance at δ (3.26 ppm) integrated for two protons and ascribable to methylene protons, and a multiplet at δ (7.00–8.00 ppm) integrated for five protons and attributable to phenyl protons. Proton NMR studies in these solvents reveal no cases of tautomeric equilibria, only single species being identified in each solvent.

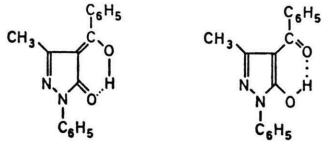
C-5-O-benzoyl derivative: Direct benzoylation of 1-phenyl-3-methyl-pyrazolone-5 with benzoyl chloride in dioxane and in pyridine yields the same product with m.p. 73–75 °C after recrystallisation from ethanol. The IR of this solid product shows carbonyl absorption at 1750 cm^{-1} revealing the presence of a –O.CO-group in the molecule. The proton NMR of the compound in $CDCl_3$ indicates clearly the structure of the compound. There is a signal at δ 2.32 ppm integrated for three protons and attributable to a methyl group, followed by another signal at δ 6.27 ppm integrated for one proton and ascribable to a vinyl proton and finally a multiplet at δ 7.20 to 8.20 ppm integrated for ten protons and assigned to two phenyl groups. Mass spectral data gives a molecular weight of 278 (M^+). These assignments require that the compound in question be formulated as



But the reactions in dioxane and in pyridine proceed *via* different mechanisms. In the case of dioxane as solvent the substrate, 1-phenyl-3-methyl-pyrazolone-5 exists in the keto form (IR (dioxane), C=O: 1710 cm^{-1}) so the attack by the benzoyl chloride molecule is at the C-4 position where there are two labile protons. Migration of the –CO.ph group to the C-5 position occurs later. In the case of pyridine as solvent the substrate, 1-phenyl-3-methyl-pyrazolone-5 exists in the C-5-hydroxy form and consequently the point of attack is on the –OH located at the C-5 position.

The C-4-benzoyl derivatives: Benzoylation of 1-phenyl-3-methyl-pyrazolone-5 with benzoyl chloride

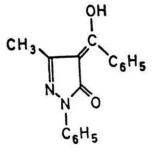
in dioxane in the presence of calcium hydroxide yields the 4-benzoyl derivative [9]. Recrystallisation of the product from *n*-hexane yields a canary yellow crystalline compound with m.p. 89–90 °C. The proton NMR of this compound in $CDCl_3$ recorded immediately after dissolution reveals a signal at δ 2.07 ppm integrated for three protons and ascribable to methyl protons, a multiplet at δ 7.20 to 8.00 ppm integrated for ten protons and attributable to two phenyl groups, and a peak downfield at δ 13.33 ppm attributable to a highly deshielded proton of a hydroxy group involved in intramolecular hydrogen bonding. The PMR data is in agreement with Jensen's conclusion [9] that this tautomer is an enol with structure (1) in Scheme 2.



I II

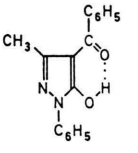
Scheme 2.

But two enol tautomers are possible as depicted in Scheme 2 (structures **1** and **2**) even though the possibility of a tautomer with structure **2** has been ruled out by Jensen [9]. The IR spectrum (KBr) of the bright yellow compound indicates clearly the absence of any hydroxy absorption. The absence of –OH and –C=O absorption bands could be due to very strong hydrogen bonding within the chelate ring. This type of effect has been previously noted in some chelate rings with strong hydrogen bonding [10]. On the basis of the IR evidence the other



possible structural (geometrical) isomer would be ruled out since if this were the case, an OH absorption frequency would have been observed around ~3500 cm^{-1} [11], and also the carbonyl absorption frequency at around 1700 cm^{-1} (for these pyrazolones-5) would have been present.

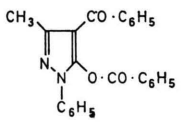
It is interesting to observe that rapid crystallisation of the compound from ethanol in an ice-salt mixture yields the same yellow tautomer contrary to the accepted knowledge that β-diketo forms are always isolated from alcoholic solvents. However, when slow crystallisation is carried out from 95% ethanol and the crystals allowed to deposit on their own slowly, a white crystalline compound, m.p. 115–117 °C is obtained. This compound has been described by Jensen [9] as a β-diketo form. However, on the basis of solid phase IR (KBr) spectrum an incontrovertible evidence is produced to show that this is another enol form and not a β-diketo form. The big dip (absorption band) centered at 2550 cm^{-1} in the IR spectrum is typical of –OH absorption band arising from the vibration of –OH involved in intramolecular hydrogen-bonding. Similar observations have been previously noted by Hallam [12]. Also the IR spectrum reveals a carbonyl absorption at 1640 cm^{-1} typical of enol forms of β-diketones [13]. Confirmatory evidence that this white form is also an enol is obtained from the proton NMR of the white tautomer recorded immediately after dissolution in $CDCl_3$. The PMR spectrum shows a peak at δ 2.07 ppm integrated for three protons and ascribable to the methyl protons, a multiplet at δ 7.20 to 8.00 ppm integrated for ten protons and attributed to the protons of the two phenyl groups, and a signal downfield at δ 12.67 ppm attributable to a deshielded proton of a hydroxy group involved in intramolecular hydrogen bonding. On the basis of the above evidence the following structure is put forward for this white tautomer



A close look at structures **1** and **2** in Scheme 2 would reveal that **1** has a greater number of C=C double bonds in conjugation than **2** and assigning structure **1** to the yellow tautomer and structure **2** with less number of double bonds in conjugation to the white tautomer agrees with conclusions arrived at by IR and NMR evidence.

The C-4-benzoyl-C-5-O-benzoyl derivative: In the process of preparing the C-4-benzoyl derivative using benzoyl chloride in dioxane in the presence of calcium hydroxide, a by-product is sometimes isolated. The amount of the by-product formed appears to depend on the relative quantities of the reactants

used in the reaction and to possibly some other as yet unidentified factors. An appreciable amount of this by-product is formed when the 1-phenyl-3-methyl-pyrazolone-5, benzoyl chloride and calcium hydroxide are not in stoichiometric amounts but when stoichiometric quantitites were used this by-product was not obtained. This by-product is sparingly soluble in boiling *n*-hexane while the pure C-4-benzoyl derivative dissolves in boiling *n*-hexane and crystallises out as the yellow tautomer. Traces of white flakes of this by-product are recovered from *n*-hexane as a second fraction with m.p. 151–152 °C. The IR (KBr) of this compound shows two carbonyl absorption bands, one at 1638 cm^{-1} and the other at 1759 cm^{-1}, suggesting a structure with a –Co.ph and a –O.CO– groups. The NMR spectrum ($CDCl_3$) reveals a signal at δ 2.47 ppm integrated for three protons and therefore attributable to methyl protons, and a multiplet at δ 7.20 to 7.90 ppm integrated for fifteen protons and therefore attributed to three phenyl groups. Mass spectrum gives a molecular weight of MS (*m/e*) 382 (M^+). On the basis of the above data the following structure has been assigned to this by-product



Experimental

Infrared spectra were recorded with either a Perkin-Elmer model 257 or a Unicam SP 1000 infrared spectrophotometer, while ultraviolet spectra were obtained with a Unicam SP 8000 spectrophotometer. Proton NMR were recorded on a Varian Associates T-60 spectrometer. Melting points were recorded on a Fisher-Johns melting point apparatus and were uncorrected.

Reagents

1-Phenyl-3-methyl-pyrazolone-5, antipyrine, benzoyl chloride, calcium hydroxide, pyridine, chloroform and dioxane were of analar quality and were supplied by Merck.

Reaction I

Benzoylation of 1-phenyl-3-methyl-pyrazolone-5 with benzoyl chloride in dioxane: 1-Phenyl-3-methyl-pyrazolone-5 (17.5 g) was dissolved in dioxane (100 ml) with gentle warming and was treated drop by drop with benzoyl chloride (12 ml). The solid product was removed by filtration and recrystallised from 95% ethanol to give cream crystals, m.p. 73–75 °C.

Elemental analysis for $C_{17}H_{14}N_2O_2$

Calcd	C 73.36	H 5.07	N 10.07,
Found	C 73.47	H 5.18	N 10.20.

NMR [$CDCl_3$]: δ 2.32 (3H, S, CH_3), 6.27 (1H, S, C=CH), 7.20–8.20 (10H, m, $2C_6H_5$).

IR (KBr disc) cm^{-1} 1750 (O. C=O), 1250 (br, C–O–C), UV (MeOH) nm 235 (30,592), MS (*m/e*) 278 (M^+).

Reaction II

Benzoylation of 1-phenyl-3-methyl-pyrazolone-5 with benzoyl chloride in pyridine: 1-Phenyl-3-methyl-pyrazolone-5 (17.5 g) was dissolved in pyridine (100 ml) with gentle warming. Benzoyl chloride (12 ml) was added drop by drop with stirring. The reaction mixture was poured into excess distilled water, the solid product was filtered, washed with water and recrystallised from 95% ethanol to give cream crystals m.p. 73–75 °C.

Elemental analysis for $C_{17}H_{14}N_2O_2$

Calcd	C 73.36	H 5.07	N 10.0,
Found	C 73.28	H 5.17	N 10.24.

NMR [$CDCl_3$]: δ 2.32 (3H, S, CH_3), 6.27 (1H, S, C=CH), 7.20–8.20 (10H, m, $2C_6H_5$).

IR (KBr disc) cm^{-1} 1750 (O. C=O), 1250 (br, C–O–C), UV (MeOH) nm 235 (30,592), MS (*m/e*) 278 (M^+).

Reaction III

Benzoylation of 1-phenyl-3-methyl-pyrazolone-5 with benzoyl chloride in dioxane in the presence of stoichiometric amount of calcium hydroxide: 1-Phenyl-3-methyl-pyrazolone-5 (17.5 g) was dissolved in dioxane (100 ml) with gentle warming. Calcium hydroxide (7.4 g) was added and a paste was formed. Benzoyl chloride (12 ml) was added drop by drop within 2–3 min with stirring. The exothermic reaction was allowed to cool off after beeing refluxed gently for one hour. The yellowish brown reaction mixture was cooled and poured into 3 N hydrochloric acid (400 ml) with stirring to decompose the calcium complex formed. A brown solid was obtained and filtered. Crystallisation from *n*-hexane gave bright yellow crystals m.p. 89–90 °C.

Elemental analysis for $C_{17}H_{14}O_2N_2$

Calcd	C 73.36	H 5.07	N 10.07,
Found	C 73.40	H 5.02	N 10.00.

NMR [$CDCl_3$]: δ 2.07 (3H, S, CH_3), 7.20–8.00) (10H, m, $2C_6H_5$), 13.33 (1H, S, OH···O).

IR (KBr disc) cm^{-1} 1190 (C–O), UV (MeOH) nm 270 (66,049).

Double slow crystallisation from 95% ethanol yielded pure white crystals m.p. 115–117 °C.

Elemental analysis for $C_{17}H_{14}O_2N_2$

Calcd	C 73.36	H 5.07	N 10.07,
Found	C 73.51	H 5.18	N 9.98.

NMR [$CDCl_3$]: δ 2.07 (3H, S, CH_3), 7.20–8.00 (10H, m, $2C_6H_5$), 12.67 (1H, S, OH···O).

IR (KBr disc) cm^{-1} 2550 (br, OH···O), 1640 (C=O), 1195 (C–O), UV (MeOH) nm 275 (18,773).

Reaction IV

Benzoylation of 1-phenyl-3-methyl-pyrazolone-5 with benzoyl chloride in the presence of calcium hydroxide (benzoyl chloride less than stoichiometric amount): Same as reaction III except that 10 ml of benzoyl chloride was used instead of 12 ml. The final reaction contained a solid by-product which was found to be sparingly soluble in *n*-hexane but very soluble in ethanol. White flakes of this by-product were recovered from *n*-hexane as a second fraction and has m.p. 151–152 °C.

Elemental analysis for $C_{24}H_{18}O_3N_2$

Calcd	C 74.50	H 4.75	N 7.33,
Found	C 74.62	H 4.89	N 7.40.

NMR [$CDCl_3$]: δ 2.47 (3H, S, CH_3), 7.20–7.90 (15H, m, $3C_6H_5$).

IR (KBr disc) cm^{-1} 1759 (O. C=O), 1638 (C=O), 1240 (C–O–C), UV (MeOH) nm 235 (34,069), 275 (21,554), MS (*m/e*) 382 (M^+).

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