# Identification of some Isomeric 3,5-Unsymmetrically Substituted 1-Aroyl-pyrazole Derivatives by NMR Spectroscopy



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The $^1H$ and $^{13}C$ nmr chemical shifts are used for the structural assignment of isomeric 1-aroyl-4,5-dihydro-5-hydroxy-4,4-dimethyl-1*H*-pyrazoles **1** unsymmetrically substituted with phenyl or methyl in the 3,5-positions of the pyrazole ring. The $^1H$ nmr spectra of 1-aroyl- or 1-acetyl-4-methyl-1*H*-pyrazoles **2** are useful in structure elucidation of unsymmetrically 3- or 5-methyl substituted derivatives.

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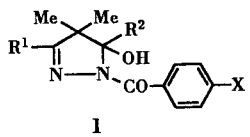
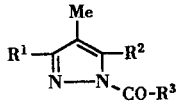
The main purpose of this work is the identification of isomeric 1-aroyl-4,5-dihydro-5-hydroxy-4,4-dimethyl-1*H*-pyrazoles **1** and 1-aroyl-4-methyl-1*H*-pyrazoles **2** unsymmetrically substituted with phenyl or methyl in the 3,5-positions of the pyrazole ring by means of $^1H$ and $^{13}C$ nmr spectroscopy.



**1**

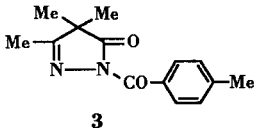
**a**, $R^1 = R^2 = Me$, X = H
**b**, $R^1 = R^2 = X = Me$
**c**, $R^1 = R^2 = Me$, X = Cl
**d**, $R^1 = H$, $R^2 = X = Me$
**e**, $R^1 = X = Me$, $R^2 = H$
**f**, $R^1 = X = H$, $R^2 = Ph$
**g**, $R^1 = Ph$, $R^2 = X = H$
**h**, $R^1 = X = Me$, $R^2 = Ph$
**i**, $R^1 = Ph$, $R^2 = X = Me$



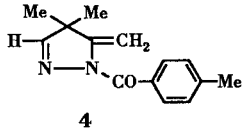
**2**

**a**, $R^1 = R^3 = Me$, $R^2 = Ph$
**b**, $R^1 = Ph$, $R^2 = R^3 = Me$,
**c**, $R^1 = Me$, $R^2 = R^3 = Ph$,
**d**, $R^1 = R^3 = Ph$, $R^2 = Me$
**e**, $R^1 = Me$, $R^2 = Ph$, $R^3 = p\text{-}MeC_6H_4$
**f**, $R^1 = Ph$, $R^2 = Me$, $R^3 = p\text{-}MeC_6H_4$

It has been reported [1,2] that by refluxing a chloroform solution of an unsymmetrical 1,3-diketone with aroylhydrazines two isomeric 1-aroyl-4,5-dihydro-5-hydroxy-4,4-dimethyl-1*H*-pyrazoles **1d** and **1e**, **1h** and **1i** were formed. The 3-methyl-5-hydroxy substituted derivative **1e** was identical with the product isolated from the sodium borohydride reduction of the pyrazolone **3**, whereas the isomeric 5-methyl-5-hydroxy derivative **1d** was identified from thermolysis product **4** [3].



**3**



**4**

However, the general problem of identification of isomeric 3- and 5-unsymmetrically substituted 4,5-dihydro-1*H*-pyrazoles **1** arising from previous publications [1-4] needed further investigation. For the present study the unknown pair **1f** and **1g** was prepared (see Experimental).

Careful examination of the $^1H$ nmr data (Table 1) of the isomeric pairs **1f** and **1g**, and **1h** and **1i** and using as reference compounds **1d** and **1e** led us to the following conclusions. A hydrogen in the 3-position of the pyrazole ring resonates at about $\delta$ 6.75, whereas a hydrogen in the 5-position at about $\delta$ 5.68. A methyl in the 3-position resonates at about $\delta$ 1.90 compared to a methyl in the 5-position which resonates at $\delta$ 1.75. A phenyl substituent in the 5-position of the pyrazole ring, as in compounds **1f** and **1h**, causes a diamagnetic shift to the protons of one of the 4-methyl groups which resonate at about $\delta$ 0.60. This diamagnetic shift of the 4-methyl protons was also previously observed [5] in some 5-hydroxy-4,4-dimethyl-5-phenylsubstituted isoxazoline derivatives. In addition the 5-phenyl aromatic protons appear as a multiplet centered at about $\delta$ 7.30. In contrast, in the 3-phenyl substituted isomers **1g** and **1i** the 3-phenyl aromatic protons resonate as an *o*-proton multiplet at about $\delta$ 7.70 and a *m*- and *p*-proton multiplet at about $\delta$ 7.40. The reduced coplanarity between the pyrazole ring and the 5-phenyl substituent in **1f** and **1h** most probably accounts for the above observation.

The $^{13}C$ nmr data (Table 2) for pairs of isomeric pyrazolines demonstrate its use as an alternative confirmatory technique in isomer determination especially in the case of the 3- and 5-methyl regioisomers, but also in the case of the 3*H*- and 5*H*-regioisomers. Thus, in the case of **1i** the C-5 methyl carbon, attached to an $sp^3$ carbon, appeared as a quartet at $\delta$ 21.35 compared with the isomeric 5-hydroxy-3-methyl derivative **1h**, where the C-3 methyl carbon attached to an $sp^2$ carbon, appeared as a quartet at $\delta$ 12.33 in agreement with previous results [6]. In addition the C-5 methyl carbon in the reference compound **1d** appeared at $\delta$ 21.19 whereas the C-3 methyl carbon in **1e** at $\delta$ 11.63. Unequivocal identification of **1f** and **1g** was based on their proton coupled $^{13}C$ spectra, where in the case of **1f** the singlet at $\delta$ 155.66 was resolved into a doublet proving thus the existence of a hydrogen in the 3-position of the pyrazole ring, whereas in the case of **1g** the singlet at $\delta$

Table 1

$^1$H NMR Spectral data (in δ) and Coupling Constants (in Hz) of Isomeric Pairs of 1-Aroyl-4,5-dihydro-5-hydroxy-1*H*-pyrazoles 1 in Deuteriochloroform solution

| Compound | $R^1$ | 4,4-Me | $R^2$ | COAR | OH | p-Me |
|---|---|---|---|---|---|---|
| **1d** | 6.73 (s, 1H) | 1.15 and 1.22 (two s, 2 x 3H) | 1.75 (s, 3H) | 7.19 (d, 2H), 7.69 (d, 2H), J 9.0 | 3.73 (br s, 1H) | 2.36 (s, 3H) |
| **1e** | 1.86 (s, 3H) | 1.11 and 1.19 (two s, 2 x 3H) | 5.61 (s, 1H) | 7.16 (d, 2H), 7.81 (d, 2H), J 9.0 | 4.86 (br s, 1H) | 2.33 (s, 3H) |
| **1f** | 6.77 (s, 1H) | 0.66 and 1.34 (two s, 2 x 3H) | 7.21-7.42 (m, 5H) | 7.43-7.58 (m, 3H), 7.78-8.08 (m, 2H) | 4.56 (br s, 1H) | — |
| **1g** | 7.30-7.54 (m, 3H) [a] 7.65-7.83 (m, 2H) | 1.47 (s, 6H) | 5.74 (s, 1H) | 7.30-7.54 (m, 3H) [a] 7.92-8.13 (m, 2H) | 4.68 (br s, 1H) | — |
| **1h** | 1.94 (s, 3H) | 0.61 and 1.30 (two s, 2 x 3H) | 7.18-7.42 (m, 5H) | [b] 7.86 (d, 2H), J 9.5 | 5.25 (br s, 1H) | 2.38 (s, 3H) |
| **1i** | 7.30-7.41 (m, 3H) 7.56-7.75 (m, 2H) | 1.31 and 1.43 (two s, 2 x 3H) | 1.76 (s, 3H) | 7.21 (d, 2H), 7.85 (d, 2H), J 9.0 | 5.11 (br s, 1H) | 2.36 (s, 3H) |

[a] The $R^1$ and COAr protons coincide. [b] Obscured by the $R^2$ protons.

Table 2

Carbon Atom Chemical Shifts (δ, ppm) of 1-Aroyl-4,5-dihydro-5-hydroxy-1*H*-pyrazoles 1 [a]

| Compound | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1a** | 163.54 | 52.86 | 94.87 | 11.96 | 18.21, 21.37 | 19.99 | 169.18 | 134.19 | 127.28 | 129.48 | 130.81 | — |
| **1b** | 163.50 | 53.01 | 95.03 | 12.17 | 18.35, 21.54 [b] | 20.23 | 169.55 | 131.46 | 128.20 | 129.77 | 141.45 | 21.36 [b] |
| **1c** | 164.10 | 53.08 | 95.03 | 12.15 | 18.26, 21.49 | 20.28 | 168.12 | 132.71 | 127.69 | 131.20 | 137.07 | — |
| **1d** | 155.88 | 52.41 | 94.23 | — | 18.55, 21.44 [b] | 21.19 [b] | 170.57 | 131.44 | 128.37 | 129.66 | 141.78 | 21.39 [b] |
| **1e** | 164.38 | 49.72 | 87.68 | 11.63 | 16.63, 23.80 | — | 168.07 | 130.67 | 128.18 | 129.90 | 141.42 | 21.32 |
| **1f** [c] | 155.66 | 53.92 | 96.57 | — | 18.64, 24.16 | — | 170.02 | 133.70 | 127.57 | 129.72 | 131.39 | — |
| **1g** [d] | 162.84 | 49.81 | 89.87 | — | 17.83, 25.63 | — | 168.72 | 133.31 | 127.56 | 130.25 | 131.43 | — |
| **1h** [e] | 163.06 | 54.66 | 97.53 | 12.33 | 18.63, 23.16 | — | 169.52 | 131.06 | 128.38 | 130.10 | 141.95 | 21.47 |
| **1i** [f] | 162.07 | 53.16 | 96.61 | — | 19.71, 21.35 [b] | 21.35 [b] | 170.03 | 131.30 | 128.45 | 130.25 | 141.90 | 21.53 [b] |

[a] Although the assignments of some carbons in the -COAr group may be interchanged and are not given with certainty it does not have any influence on the isomeric pairs. [b] Assignments may be interchanged. [c] For $R^2$ = Ph C-1" 139.62, C-2" 125.25, C-3" 128.04, C-4" 127.86. [d] for $R^2$ = Ph C-1" 130.82, C-2" 127.66, C-3" 128.45, C-4" 129.82. [e] For $R^2$ = Ph C-1" 140.41, C-2" 125.42, C-3" 128.14, C-4" 127.88 [f] For $R^2$ = Ph C-1" 131.41, C-2" 127.59, C-3" 128.37, C-4" 129.72.

89.87 was resolved into a doublet due to the presence of a hydrogen atom in the 5-position of the pyrazole ring. Furthermore, in the case of the C-3 unsubstituted derivatives **1d** and **1f** the C-3 pyrazole ring carbon appears on the average approximately 8 ppm further upfield relative to the 3-methyl or 3-phenyl derivatives, whereas a C-5 unsubstituted ring carbon, **1e** and **1g**, appears also upfield by 6.5 ppm relative to the 5-methyl or 5-phenyl derivatives.

Although there are some reports [7,8] concerning the utility of $^1$H nmr spectroscopy in structural assignment of isomeric pairs of pyrazoles, formed either by acylation of unsymmetrically substituted 1*H*-pyrazoles or from the reaction of aroylhydrazines with the appropriate 1,3-diketone, we wish to report some additional nmr data for the isomeric pairs of 1-aroyl and 1-acetylpyrazoles **2a** and **2b**, **2c** and **2d**, and **2e** and **2f**. Although in the $^{13}$C nmr the chemical shift of 3- or 5-methyl substituted 1-aroyl and 1-acetylpyrazoles is similar and therefore is not of diagnostic value, the $^1$H nmr chemical shift of 3- or 5-methyl protons can be used for differentiation of isomeric 3- or 5-methyl substituted pairs. More specifically in 1-aroyl or 1-acetyl substituted pyrazoles the 5-methyl protons resonate at about 2.50 δ, whereas the 3-methyl protons at about 2.20 δ in agreement with previous results [7].

## EXPERIMENTAL

The $^1$H nmr spectra were recorded in deuteriochloroform on a Bruker AW 80 (80 MHz) or on a Jeol JNM-GX 270 (270.05 MHz) spectrometer reported as δ value (ppm) relative to tetramethylsilane as an internal standard. The $^{13}$C nmr spectra were obtained in deuteriochloroform on a Jeol JNM-GX 270 (270.05 MHz) spectrometer. Chemical shifts are given in parts per million from tetramethylsilane.

Compounds **1a-e**, **1h**, **1i** and **2a-f** were prepared as reported previously [1-4].

Preparation of 1-Benzoyl-4,5-dihydro-5-hydroxy-4,4-dimethyl-5-phenyl-1*H*-pyrazole (**1f**) and 1-Benzoyl-4,5-dihydro-5-hydroxy-

4,4-dimethyl-3-phenyl-1*H*-pyrazole (**1g**).

To a solution of α-benzoylisobutyraldehyde (1.76 g, 10 mmoles) in toluene (25 ml), benzoic hydrazide (1.5 g, 11 mmoles) was added and the reaction mixture was refluxed for 5 hours. The solvent was then removed under vacuum and the residue was subjected to silica gel column chromatography. Elution with petroleum ether-ethyl acetate (5:1) gave in order of elution:

(a) 1-Benzoyl-4,5-dihydro-5-hydroxy-4,4-dimethyl-5-phenyl-1*H*-pyrazole (**1f**).

This compound was obtained in 43% yield (1.26 g), mp 123-125° (ethanol); ir (Nujol): ν 3490 (OH), 1640 (C=O) $cm^{-1}$; ms: (m/e) 294 ($M^+$, 23), 172 (32), 105 (100).

*Anal.* Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.65; H, 6.06; N, 9.54.

(b) 1-Benzoyl-4,5-dihydro-5-hydroxy-4,4-dimethyl-3-phenyl-1*H*-pyrazole (**1g**).

This compound was obtained in 12% yield (0.35 g), mp 169-171° (ethanol); ir (Nujol): ν 3270 (OH), 1630 (C=O) $cm^{-1}$; ms: (m/e) 294 ($M^+$, 29), 105 (100).

*Anal.* Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.68; H, 6.07; N, 9.39.

## REFERENCES AND NOTES

[1] J. Stephanidou-Stephanatou, *J. Heterocyclic Chem.*, **20**, 845 (1983).

[2] S. Papadopoulos and J. Stephanidou-Stephanatou, *J. Chem. Res. (M)*, 3084 (1986); *(S)*, 368 (1986).

[3] S. Mitkidou and J. Stephanidou-Stephanatou, *J. Heterocyclic Chem.*, **28**, 49 (1991).

[4] S. Mitkidou, S. Papadopoulos and J. Stephanidou-Stephanatou, *J. Org. Chem.*, **55**, 4732 (1990).

[5] F. Petrus, J. Verducci and Y. Vidal, *Bull. Soc. Chim. France*, 3079 (1973); R. Escale, F. Petrus and J. Verducci, *ibid.*, 725 (1974).

[6] R. G. Rees and M. J. Green, *J. Chem. Soc. B*, 387 (1968); J. Elguero, in Comprehensive Heterocyclic Chemistry, Vol **5**, A. R. Katritzky and C. W. Rees, eds, Pergamon Press, Oxford, 1984, p 191.

[7] C. L. Habraken and J. A. Moore, *J. Org. Chem.*, **30**, 1892 (1965); L. G. Tensmeyer and C. Ainsworth, *ibid.*, **31**, 1878 (1966).

[8] P. Cabildo, R. M. Claramunt and J. Elguero, *Org. Magn. Reson.*, **22**, 603 (1984); A. de la Hoz, M. de la Carmen Pardo, J. Elguero and A. Fruchier, *ibid.*, **27**, 603 (1989).