4-ACYL-5-METHYL-2-PHENYLPYRAZOLONES: NMR AND X-RAY STRUCTURE INVESTIGATIONS

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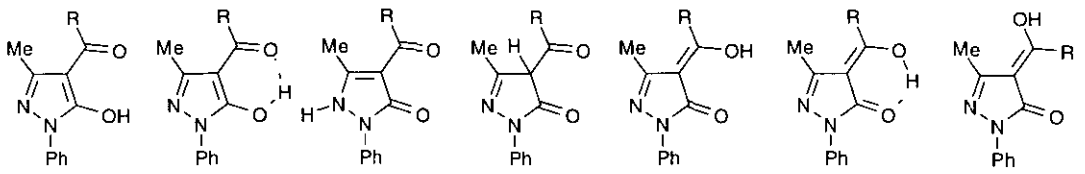
Abstract - ^{1}H- and ^{13}C-NMR investigations with 4-acyl-5-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-ones (**1-6**) are presented, indicating these compounds to exist predominantely as hydroxypyrazoles in $CDCl_3$ or benzene-d_6 solution, whereas in DMSO-d_6 also a considerable amount of NH tautomer is present. X-Ray crystal analyses revealed that in the solid state the 4-propionyl compound (**2**) is present as hydroxypyrazole, the 4-(2-thienyl) derivative (**6**) as NH isomer and the 4-cinnamoyl product (**4**) to have an exocyclic double bond structure stabilized by an intramolecular hydrogen bond. Cyclisation of the latter compound (**4**) in acidic medium leads to the formation of 3-methyl-1,6-diphenyl-5,6-dihydro-1*H*-pyrano[2,3-*c*]pyrazol-4-one (**7**) in very low yields.

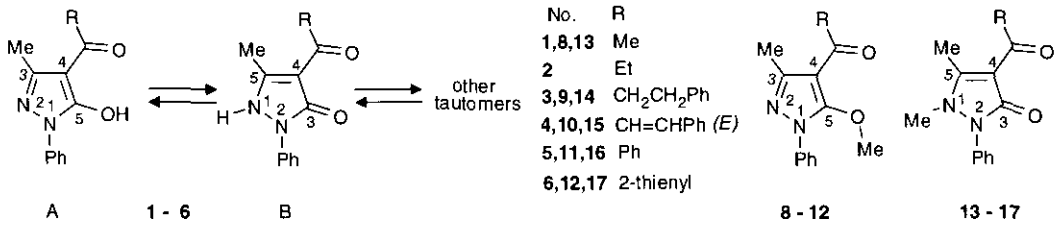
Pyrazolones with an acyl group attached in 4-position to the heterocyclic system are interesting compounds due to various reasons. They can act as effective chelating and extracting reagents for many metal ions[1] and they are used as starting materials for the construction of condensed systems[2] and biologically active compounds.[3] 4-Acylpyrazolones can exist in several tautomeric forms (depicted for 4-acyl-3-methyl-1-phenylpyrazolones in Scheme 1), with the OH (form **A**), the NH (form **B**), the CH (form **C**), and the hydroxymethylene forms (**D**, **E**) as the main representatives, forms **A** and **D** having the possibility to be stabilized *via* an intramolecular hydrogen bond (**A'**), (**D'**).[4] The tautomerism of such pyrazolones has been the subject of various studies.[4,5] In the solid state some unambiguous results were obtained by single-crystal X-Ray analyses,[5-8] showing the compounds being present either in the chelated hydroxypyrazole form (**A'**) or as NH-isomers (**B**) stabilized by intermolecular hydrogen bonds; forms **C**, **D**, and **E** were not detected. Occasionally, different isomeric forms of one pyrazolone species could be

Scheme 1. Tautomeric forms of 4-acylpyrazolones



isolated,[7,8] mainly depending on the solvent of recrystallisation. The situation in solution is more complicated, which led to some contradictory and also incorrect proposals in the older literature.[9] Based on extensive ^{1}H- and ^{13}C-NMR studies it was finally concluded by Russian authors, that in $CDCl_3$ solution and at low temperature the 4-acetyl (R = Me) (**1**) and the 4-benzoyl derivative (R = Ph) (**5**) are mainly present in the chelated OH-form (**A'**) with a minor portion of NH-isomer (**B**), the presence of forms **C** and **D** could be definitely excluded.[10] However, the composition of isomeric forms was shown to be strongly dependent on concentration, temperature and substituents attached to the heterocyclic system. In the light of these findings and in continuation to our previous investigations on pyrazolones (hydroxyprazoles)[11-14] we here present detailed NMR spectroscopic data of 4-acylpyrazolones (**1-6**) in different solvents as well as those of corresponding 'fixed' tautomers, i.e. *O*-methyl (**8-12**) or *N*-methyl derivatives (**13-17**). Additionally, the results of single-crystal X-Ray analyses with compounds (**2**), (**4**), and (**6**) are given.

Scheme 2. Investigated compounds with numbering of atoms: 4-acylpyrazolones (**1-6**) in the hydroxy-pyrazole (A) and pyrazolone form (B), 'fixed' OCH_3 (**8-12**) and NCH_3 (**13-17**) congeners.



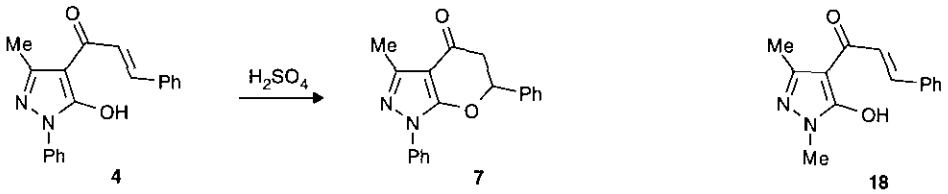
No.	R
1,8,13	Me
2	Et
3,9,14	CH_2CH_2Ph
4,10,15	CH=CHPh *(E)*
5,11,16	Ph
6,12,17	2-thienyl

Chemistry

Compounds (**3**), (**4**), *and* (**6**) *were prepared in good yields from 3-methyl-1-phenyl-2-pyrazolin-5-one and* the appropriate carboxylic acid chlorides using the method described by Jensen[15] (dioxane, $Ca(OH)_2$). The synthesis of *O*-methyl and *N*-methyl compounds (**8-17**) from educts (**1-6**) is described in refs.[13,14] The 4-cinnamoyl derivative (**4**) could be cyclized to compound (**7**) - which formally represents a pyrazole

analogue of flavanone - by the action of concentrated sulfuric acid in very low yields. Other standard methods used for the ring closure of 2'-hydroxychalcones to flavanones (action of diluted acids in ethanol, action of diluted aqueous NaOH, and other)[16] failed, only unchanged educt (**4**) could be isolated from the reaction mixture. Similar observations were reported in the course of the cyclisation of **18**,[11] which is an *N*-methyl congener of **4**.

Scheme 3



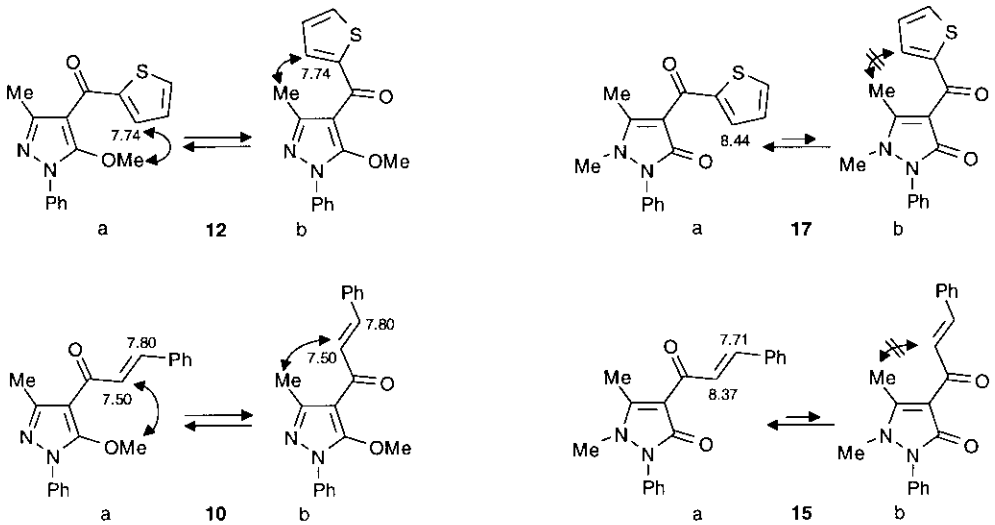
NMR Spectroscopic Investigations

The NMR data of compounds (**1-6**, **8-17**) are given in Tables 1-7. Complete and unambiguous assignment of signals in the ^{1}H- and ^{13}C-NMR spectra was achieved by a combination of different NMR techniques such as fully ^{1}H-coupled ^{13}C-NMR, APT,[17] NOE-difference spectroscopy,[18] 1D-TOCSY,[19] $^{13}C,^{1}H$ shift correlations *via* one bond couplings (HMQC),[20] 1D-HETCOR[21] and long-range INEPT[22] experiments with selective excitation.

The NMR data of *O*-methyl (**8-12**) and *N*-methyl derivatives (**13-17**) are given in Tables 2-7. These compounds represent 'fixed' OH and NH tautomers of pyrazolones (**1**, **3-6**) and thus are very valuable for comparison purposes in order to determine tautomeric composition of the corresponding pyrazolones. NOE-difference experiments with *O*-methyl derivatives (**8-12**) revealed that these compounds are obviously present in conformation **a** as well as in conformation **b** (shown for **10** and **12** in Scheme 4), as NOEs between OMe and suitable protons of the 4-substituent R as well as between C3-Me and R can be detected. In contrast, with *N*-methyl derivatives (**13-17**) only conformation **a** plays a role, as form **b** is energetically less favoured due to the spatial closeness of the two carbonyl oxygen atoms which provide electrostatic obstacles (AM1-calculations[23,24] with **13** gave a ~ 7 kcal/mol lower energy for form **a** compared to form **b**). This is confirmed by NOE difference experiments, as with **13-17** irradiation of the C-Me resonance never led to an NOE on proton signals of R. Moreover, dominance of form **a** is supported by the observation that protons of R, which come close to the pyrazolone C=O suffer a marked downfield shift due to the anisotropy of bond magnetic susceptibility of the latter, which is only possible in form **a** and not in **b**. Thus, for instance, in $CDCl_3$ solution the thiophene H-3 signal in **17** has a 0.7 ppm larger chemical shift than that of the corresponding *O*-methyl derivative (**12**) (Scheme 4). A similar trend is found

for the COC**H**= signal in the pair **10** (δ 7.50 ppm in $CDCl_3$, δ 7.48 ppm in DMSO-d_6) and **15** (δ 8.37 ppm in $CDCl_3$, δ 8.24 ppm in DMSO-d_6) (Scheme 4). For cinnamoyl compounds (**10**) and (**15**), respectively, *s-cis* conformation for the enone moiety is assumed according to findings in the literature.[25]

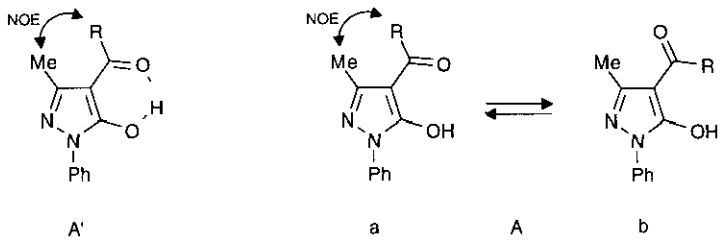
Scheme 4. Conformational analysis of *O*-methyl (**10**,**12**) and *N*-methyl (**15**,**17**) compounds *via* characteristic NOEs (arrows) and ^{1}H chemical shifts (δ ppm, in $CDCl_3$).



The NMR data of pyrazolones (**1-6**) indicate these compounds to exist mainly as 5-hydroxypyrazoles in $CDCl_3$ solution at 28°C, which is in accordance with findings in the literature.[10,26,27] Thus, the ^{1}H and ^{13}C chemical shifts of these compounds resemble much more those of the corresponding 'fixed' *O*-methyl derivatives (**8-12**)[13] than that of the *N*-methyl congeners (**13-17**)[13] (Figure 1, **5** as a representative example). The absence of NOEs between acidic proton and the C-methyl group gives a further hint for the insignificant contribution of the NH-form (**B**). However, it was shown that the amount of **B** increases with decrease of temperature[10,27] (**5**: 15% NH isomer in $CDCl_3$-solution at -62°C).[27] The ^{13}C chemical shifts of the ketone carbonyl C-atom in **1**, **3**, **5**, and **6** show a downfield shift compared to that of the corresponding *O*-methyl congeners (**8**, **9**, **11**, and **12**); a possible explanation of this phenomenon consists in the assumption that the C=O moiety is involved into hydrogen bonding leading to a downfield shift for the carbonyl-C resonances.[28] Using the strong acceptor DMSO-d_6 as the solvent and thus breaking C=O···H bonds results in an upfield shift for the C=O resonances (Δδ 2.1 - 2.5 ppm, compared to $CDCl_3$), however, also a change in isomeric composition may play a role here. From several investigations[10,26,27] it was concluded that in $CDCl_3$ solution at room temperature compound (**5**) mainly (or exclusively)[26] exists in chelated form **A'**. Using NOE difference experiments with **1-6** we found relative strong NOEs between

pyrazole-3-Me and suitable protons of R in $CDCl_3$ as well as in benzene-d_6 solution, whereas in DMSO-d_6 the corresponding through-space connectivities were comparably weaker. This supports a high amount of form **A'** in non-polar solvents (Scheme 5), in which the spatial closeness of 3-Me and R is 'fixed' *via* the chelation, whereas in form **A** contribution of two conformations (**a**, **b**) has to be considered with **b** lacking an NOE between 3-Me and R[29] (Scheme 5). However, the strong concentration dependence of δ(OH) (sharp signals with δ > 13 ppm in concentrated, very broad signals with δ < 9 ppm in diluted $CDCl_3$ solutions, compare Table 1), which is not typical for intramolecular hydrogen bonding, hints to a more complex situation which calls for further investigations. Thus, it was proposed that the marked concentration dependence of δ(OH) (in $CDCl_3$) found for the cinnamoyl derivative (**18**)[11] (Scheme 3) might be caused by involvement of the OH proton in a three-centre bond as found in the solid state, where the chelated enol form (**A'**) shows an additional weak intermolecular interaction with O of an adjacent molecule of **18**.[8] However, the interaction in solid state[8] is disputable and in solution this would imply the (weak) intermolecular hydrogen bond to cause a much larger deshielding of OH than the strong intramolecular hydrogen bond does.

Scheme 5

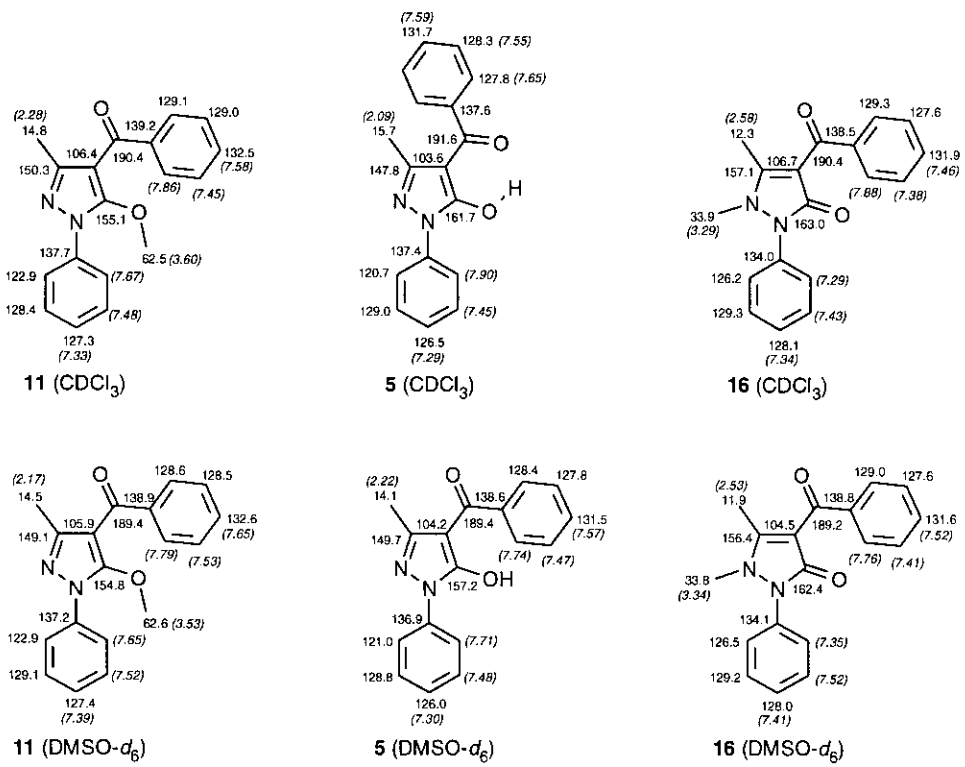


Comparing the NMR data of **5** in DMSO-d_6 solution with those of the corresponding *O*-Me (**11**) and *N*-Me (**16**) congeners, respectively, again shows more similarity with the former. The intramolecular hydrogen bond is considered to be broken (form **A**), however, also substantial contribution of the NH-tautomer (**B**) can be assumed due to the following reasons. In an NOE-experiment with **5**, upon irradiation of the methyl resonance an NOE on the signal of the acidic proton is detected (Figure 2e) (and also reversely an NOE on methyl upon perturbation of the acidic proton line, Figure 2f), which is only possible in NH-tautomer (**B**), where the involved protons are spatially close. In contrast, in similar experiments in $CDCl_3$ or benzene-d_6 no such through-space connectivity was observed (Figures 2b,c). Additionally, line broadening (e.g. pyrazole **C**5-OH of **5,** thiophene H-3 in **6**) indicates a dynamic behaviour and hints to an equilibrium of tautomers.[30] Of high diagnostic value are the ^{1}H-signals of thiophene H-3 in **6** and of COC**H**= in **4**, as these resonances suffer a drastic downfield shift when switching from unploar solvents ($CDCl_3$, benzene-d_6) to DMSO-d_6 solution, what can be explained by a considerable contribution of form

B in a conformation with the mentioned protons coming close to the pyrazolone C=O moiety (similar to the conformation **a** for *N*-methylpyrazolones (**15**) and (**17**) depicted in Scheme 4). Thus, for compound (**6**) δ(Th H-5) in $CDCl_3$ is 7.75 ppm (the OMe congener (**12**) has δ(Th H-5) 7.74 ppm in $CDCl_3$), whereas in DMSO-d_6 8.22 ppm were detected, coming close to δ(Th H-5) of the corresponding *N*-methyl derivative (**17**) (δ 8.44 ppm, see Scheme 4).

With 4-benzoyl derivative (**5**), the situation in acetone-d_6 resembles that in $CDCl_3$ (NOE between 3-Me and COPh H-2,6; no NOE between 3-Me and acidic proton; δ (C=O) = 191.8 ppm) hinting to form **A'** as the major isomer. In methanol-d_4 an NOE on COPh H-2,6 was detected upon irradiation of 3-Me, however, an unambiguous statement concerning isomeric composition cannot be made on basis of the present data.

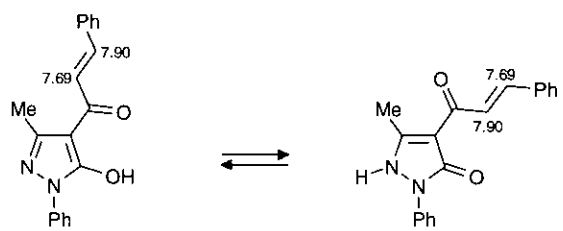
Figure 1. ^{13}C-NMR chemical shifts and ^{1}H-NMR chemical shifts (in italics) of pyrazolone (**5**) and its *O*-methyl (**11**) and *N*-methyl (**16**) congener in $CDCl_3$ and DMSO-d_6 solution.



The NMR spectra of the 4-cinnamoyl derivative (**4**) shows some peculiarities compared with the other pyrazolones investigated. In $CDCl_3$ or benzene-d_6 solution, the signal of COC**H**= is shifted upfield ($CDCl_3$: δ 7.10 ppm, benzene-d_6: δ 6.96 ppm) compared to that of *O*-methyl congener (**10**) (δ 7.50 ppm), a similar

trend is observed for the carbon signal of COCH= ($CDCl_3$: δ 119.1 ppm, benzene-d_6: δ 119.6 ppm; **10** in $CDCl_3$: δ 124.6 ppm, **15** in $CDCl_3$: δ 125.4 ppm). Furthermore, the shift of the carbonyl resonance does not obey the trends observed with the other pyrazolones investigated as in $CDCl_3$ solution one should expect a downfield shift of C=O compared to that of the corresponding 'fixed' *O*-methyl compound (**10**) due to hydrogen bonding. Instead, a reverse trend was observed (**4**: δ(C=O) 177.7 ppm, **10**: δ (C=O) 184.2 ppm, compare with **15**: δ(C=O): 184.9 ppm). A satisfying explanation for this phenomenon cannot be given in the moment. The presence of tautomeric form **D'** (Scheme 1) in considerable amount seems to be improbable as the observed ^{1}H as well as the ^{13}C-chemical shifts of the enone moiety do not resemble those found with compounds having a Ph-CH=CH-C(OMe)= substructure,[31,32] however, a minor contribution cannot be excluded definitely. In DMSO-d_6 solution a pronounced dynamic behaviour was observed resulting in a marked line broadening in the ^{1}H (signal of COC**H**= , Figure 3b) as well as in the ^{13}C NMR spectrum (signals of pyrazole C-3 and of **C**OCH=CH). The most remarkable phenomenon found with **4** in DMSO-d_6 is the observation that the two enone-H signals (δ 7.90 and 7.69 ppm) are involved in a chemical exchange process. Thus, in an NOE-difference experiment selective irradiation of the broadened doublet resonance at 7.90 ppm saturates the 7.69 ppm doublet to the same extent (saturation transfer, Figure 3a), whereas irradiation of the methyl singlet results in an enhancement of both enone-H signals (transferred NOE, Figure 3c) (in contrast, with **4** in other solvents irradiation of 3-Me always led to a marked NOE on COC**H**=, but not on COCH=C**H**). A possible explanation for these observations is an equilibrium process A ⇔ B with $\delta(COC\mathbf{H}{=}CH)_A = \delta(COCH{=}C\mathbf{H})_B$ and $\delta(COCH{=}C\mathbf{H})_A = \delta(COC\mathbf{H}{=}CH)_B$, caused by interconversion of OH and NH-form (Scheme 6), an (also possible) equilibrium between rotameric forms of isomeric form **B** seems to be less probable. Temperature spectra of **4** in DMSO-d_6 (30°, 40°, 50°, 60°, 70°C) showed the signal of the low-field enone-H to move somewhat to higher field (28°C: δ 7.90 ppm, 70°C: δ 7.82 ppm), whereas the other signals are barely affected, also the ^{13}C-NMR spectra at 28° and at 60°C are nearly identical (line broadening with the signals of pyrazole C-3, COCH=**C**H, C=O).

Scheme 6



A 4 B

In conclusion, our NMR experiments with pyrazolones (**1-6**) indicate these compounds to have a complex behaviour in solution with the chelated hydroxy-form (**A'**) being the main isomer in $CDCl_3$ or benzene-d_6. In DMSO-d_6 solution, we believe mainly an equilibrium of OH (**A**) and NH form (**B**) to be present due to the observed line broadenings and the results of the NOE-difference experiments.

Figure 2. NOE-Difference experiments with **5** in benzene-d_6 (a-c, left) and DMSO-d_6 solution (d-f, right).
a, d: ^{1}H-NMR spectrum of **5** in benzene-d_6 (a) and DMSO-d_6 (d).
b, e: NOE-difference spectrum obtained upon irradiation of 3-Me.
c, f: NOE-difference spectrum obtained upon irradiation of the acidic proton.

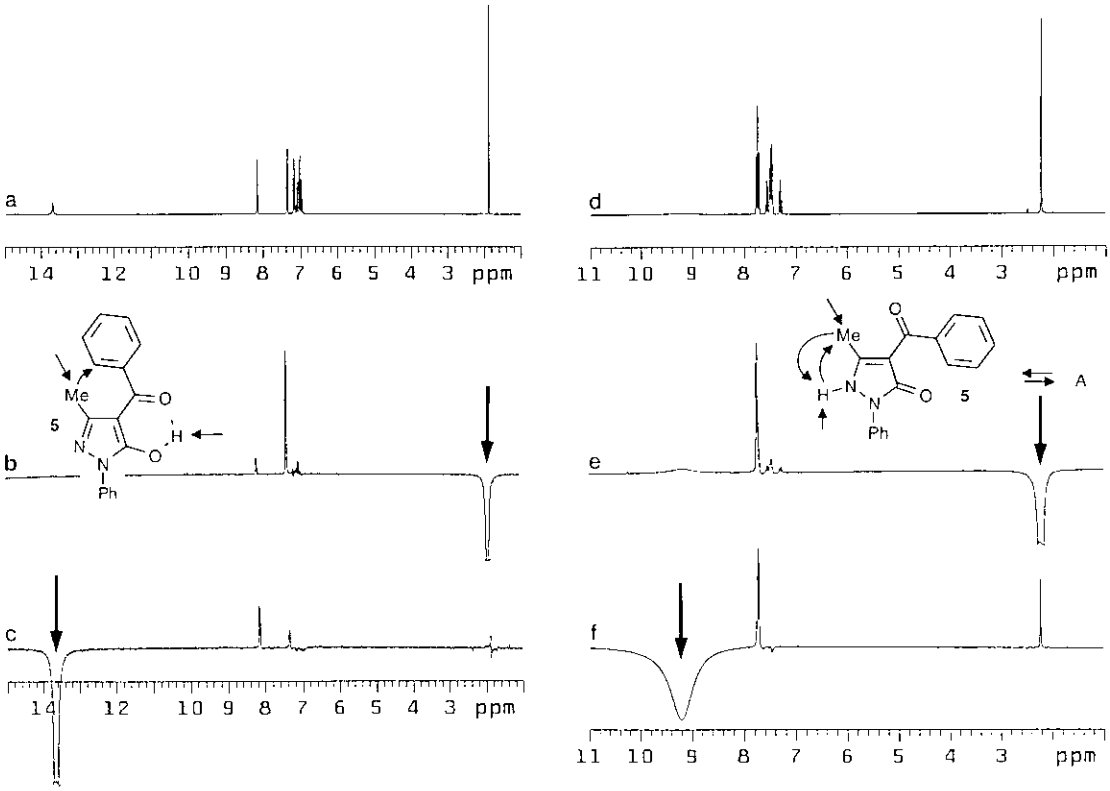


Figure 3. NOE-Difference experiments with **4** in DMSO-d_6 solution.
a: NOE-difference spectrum obtained upon irradiation of d (1H) 7.90 ppm. b: ^{1}H-NMR spectrum of **4**.
c: NOE-difference spectrum obtained upon irradiation of 3-Me.

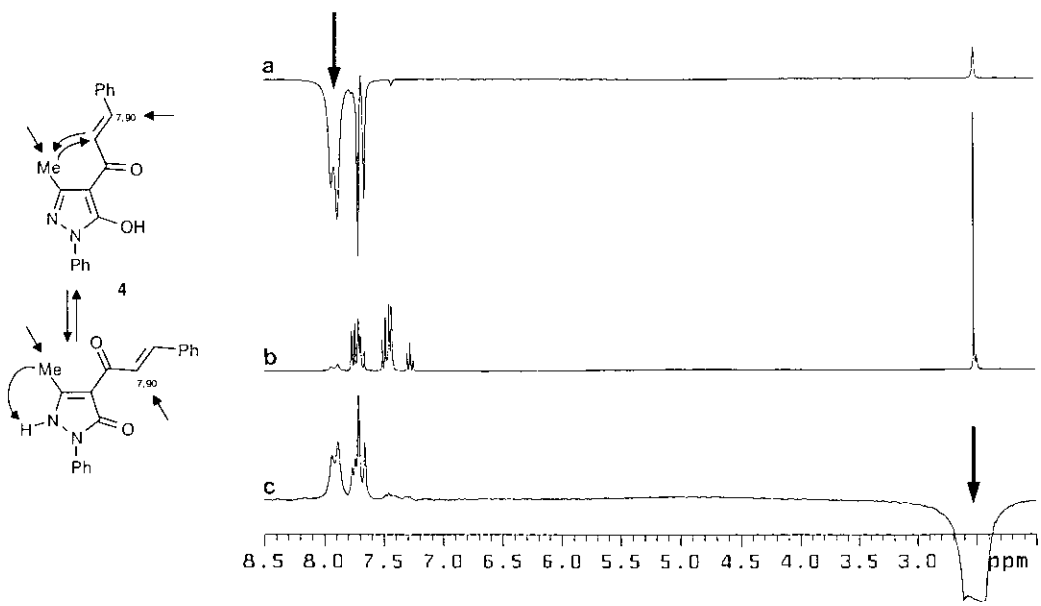


Table 1. ^{1}H-NMR chemical shifts of **1-6** (numbering of atoms for the hydroxypyrazole form = form A in Scheme 2)

No.	solvent	3-Me	N-Phenyl H-2,6	N-Phenyl H-3,5	N-Phenyl H-4	OH[a]	H of 4-substituent R
1	$CDCl_3$	2.42	7.82	7.42	7.26	12.67	2.43 (Me)
1	DMSO-d_6	2.40	7.70	7.47	7.27	11.83	2.41 (Me)
2	$CDCl_3$	2.46	7.82	7.43	7.27	12.10	2.76(CH_2), 1.24 (CH_3)
2	DMSO-d_6	2.41	7.68	7.47	7.28	11.46	2.83 CH_2), 1.03 (CH_3)
3	$CDCl_3$	2.43	7.86	7.45	7.29	11-12	3.08 ($COCH_2CH_2$), 7.29 (Ph-2,6), 7.33 (Ph-3,5), 7.24 (Ph-4)
3	DMSO-d_6	2.43	7.68	7.47	7.28	11.82	3.15 ($COCH_2$), 2.87 (CH_2Ph), 7.25 (Ph-2,3,5,6), 7.17 (Ph-4)
4	$CDCl_3$	2.54	7.93	7.42	7.22	13.72	7.10[b] (COCH), 7.89[b] (CHPh), 7.59 (Ph-2,6), 7.41 (Ph-3,4,5)
4	DMSO-d_6	2.51	7.76	7.48	7.28	9-12	7.90[b] (COCH), 7.69[b] (CHPh), 7.70 (Ph-2,6), 7.44 (Ph-3,4,5)
4	C_6D_6	2.09	8.34	7.21	6.96	10-12	6.75[b] (COCH), 7.85[b] (CHPh), 7.20 (Ph-2,6), 7.05 (Ph-3,4,5)
4	acetone-d_6	2.61	7.99	7.48	7.25	[c]	7.38[b] (COCH), 7.95[b] (CHPh), 7.82 (Ph-2,6), 7.47 (Ph-3,4,5)
4	CD_3OD	2.59	7.79	7.46	7.29	[c]	7.71[b] (COCH), 7.82[b] (CHPh), 7.69 (Ph-2,6), 7.43 (Ph-3,4,5)
5	$CDCl_3$	2.09	7.90	7.45	7.29	[d]	7.65 (Ph-2,6), 7.55 (Ph-3,5), 7.59 (Ph-4)
5	DMSO-d_6	2.22	7.71	7.48	7.30	[e]	7.74 (Ph-2,6), 7.47 (Ph-3,5), 7.57 (Ph-4)
5	C_6D_6	1.88	8.16	7.18	6.97	13.69	7.37 (Ph-2,6), 7.03 (Ph-3,5), 7.10 (Ph-4)
5	acetone-d_6	2.06	7.92	7.51	7.33	8.76	7.74 (Ph-2,6), 7.58 (Ph-3,5), 7.65 (Ph-4)
5	CD_3OD	2.20	7.70	7.48	7.34	[c]	7.73 (Ph-2,6), 7.48 (Ph-3,5), 7.57 (Ph-4)
6	$CDCl_3$	2.44	7.88	7.46	7.30	11.40	7.75 (Th-3), 7.18 (Th-4), 7.69 (Th-5)
6	DMSO-d_6	2.36	7.70	7.49	7.31	11.09	8.22 (Th-3), 7.19 (Th-4), 7.91 (Th-5)

[a] The chemical shift of the acidic proton is strongly dependent on the concentration of the sample. [b] ^3J = 15.6-15.9 Hz. [c] Not determined unambiguously. [d] 13.12 (c = 1 M), 12.90 (c = 0.5 M), 12.65 (c = 0.33 M), 12.42 (br, c = 0.25 M), 11.51 (very br, c = 0.125 M), ~10.50 (very br, c = 0.0625 M), ~9.20 (very br, c = 0.031 M). [e] 9.26 (c = 0.5 M), 8.53 (c = 0.25 M).

Table 2. ^{1}H-NMR chemical shifts of **8-12**[10] (numbering of atoms see Scheme 2)

No.	solvent	3-Me	N-Phenyl H-2,6	N-Phenyl H-3,5	N-Phenyl H-4	OMe	H of 4-substituent R
8	$CDCl_3$	2.46	7.63	7.44	7.33	3.76	2.45 (Me)
9	$CDCl_3$	2.51	7.66	7.47	7.36	3.71	3.15 ($COCH_2$), 3.07 (CH_2Ph), 7.29 (Ph-2,6), 7.28 (Ph-3,5), 7.19 (Ph-4)
10	$CDCl_3$	2.55	7.70	7.48	7.36	3.83	7.50[a] (COCH), 7.80[a] (CHPh), 7.63 (Ph-2,6), 7.39 (Ph-3,4,5)
10	DMSO-d_6	2.41	7.75	7.55	7.44	3.85	7.48[b] (COCH), 7.68[b] (CHPh), 7.68 (Ph-2,6), 7.46 (Ph-3,4,5),
11	$CDCl_3$	2.28	7.67	7.48	7.33	3.60	7.86 (Ph-2,6), 7.45 (Ph-3,5), 7.58 (Ph-4)
11	DMSO-d_6	2.17	7.65	7.52	7.39	3.53	7.79 (Ph-2,6), 7.53 (Ph-3,5), 7.65 (Ph-4)
12	$CDCl_3$	2.34	7.66	7.43	7.30	3.68	7.74 (Th-3), 7.13 (Th-4), 7.67 (Th-5)

[a] ^3J = 15.8 Hz [b] ^3J = 15.9 Hz

Table 3. ^{1}H-NMR chemical shifts of **13-17**[10] (numbering of atoms see Scheme 2)

No.	solvent	5-Me	N-Phenyl H-2,6	N-Phenyl H-3,5	N-Phenyl H-4	NMe	H of 4-substituent R
13	$CDCl_3$	2.59	7.24	7.44	7.34	3.26	2.50 (Me)
14	$CDCl_3$	2.63	7.28	7.48	7.38	3.26	3.34 ($COCH_2$), 2.98 (CH_2Ph), 7.27 (Ph-2,6), 7.21 (Ph-3,5), 7.11 (Ph-4)
15	$CDCl_3$	2.70	7.29	7.48	7.38	3.28	8.37 (COCH)[a], 7.71 (CHPh), 7.62 (Ph-2,6), 7.29 (Ph-3,4,5)
15	DMSO-d_6	2.67	7.38	7.55	7.46	3.34	8.24 (COCH)[a], 7.58 (CHPh), 7.40 (Ph-2,4, 6), 7.60 (Ph-3,4,5),
16	$CDCl_3$	2.58	7.29	7.43	7.34	3.29	7.88 (Ph-2,6), 7.38 (Ph-3,5), 7.46 (Ph-4)
16	DMSO-d_6	2.53	7.35	7.52	7.41	3.34	7.76 (Ph-2,6), 7.41 (Ph-3,5), 7.52 (Ph-4)
17	$CDCl_3$	2.57	7.30	7.47	7.37	3.29	8.44 (Th-3), 7.05 (Th-4), 7.54 (Th-5)

[a] ^3J = 15.9 Hz

Table 4. ^{13}C-NMR chemical shifts of **1-6, 8-12** (numbering of atoms in pyrazolones (**1-6**) for the hydroxypyrazole form = form A in Scheme 2)

		pyrazole-C					C of N-Phenyl					
No.	solvent	C-3	C-4	C-5	3-Me	OMe	C-1	C-2,6	C-3,5	C-4	C=O	C of 4-substituent R
1	$CDCl_3$	147.5	104.1	160.5	15.4	---	137.2	120.5	129.0	126.4	194.0	26.4 (Me)
1	DMSO-d_6	149.6	104.7	160.6	14.4	---	136.6	120.4	128.9	125.8	191.5	27.3 (Me)
2	$CDCl_3$	147.3	103.4	160.3	15.6	---	137.3	120.6	129.0	126.4	198.1	32.4 (CH_2), 8.1 (CH_3)
2	DMSO-d_6	149.8	104.1	159.6	14.3	---	136.5	120.5	129.0	125.9	195.6	32.8 (CH_2), 8.1 (CH_3)
3	$CDCl_3$	147.2	103.9	160.7	15.7	---	137.4	120.7	129.0	126.5	196.0	40.6 ($CO\underline{C}H_2$), 30.3 ($\underline{C}H_2Ph$), 140.6 (Ph-1), 128.3 (Ph-2,6), 128.6 (Ph-3,5), 126.4 (Ph-4)
3	DMSO-d_6	150.1	104.2	159.8	14.1	---	136.3	120.6	129.0	125.9	193.9	41.5 ($CO\underline{C}H_2$), 29.6 ($\underline{C}H_2Ph$), 141.6 (Ph-1), 128.3 (Ph-2,6), 128.2 (Ph-3,5), 125.7 (Ph-4)
4	$CDCl_3$	146.9	104.7	165.2	16.4	---	137.7	119.6	128.9	125.7	177.7	119.1 ($CO\underline{C}H$), 143.9 ($\underline{C}HPh$), 134.4 (Ph-1), 128.5 (Ph-2,6), 129.0 (Ph-3,5), 130.9 (Ph-4)
4	DMSO-d_6	150.2	104.8	161.8	14.7	---	136.6	120.1	129.0	125.7	180.6	123.3 ($CO\underline{C}H$), 140.9 ($\underline{C}HPh$), 134.8 (Ph-1), 128.3 (Ph-2,6), 129.0 (Ph-3,5), 130.3 (Ph-4)
4	C_6D_6	146.7	105.3	166.4	16.1	---	138.8	119.5	129.2	125.6	177.0	119.6 ($CO\underline{C}H$), 143.4 ($\underline{C}HPh$), 134.9 (Ph-1), 128.6 (Ph-2,6), 129.1 (Ph-3,5), 130.7 (Ph-4)
5	$CDCl_3$	147.8	103.6	161.7	15.7	---	137.4	120.7	129.0	126.5	191.6	137.6 (Ph-1), 127.8 (Ph-2,6), 128.3 (Ph-3,5), 131.7 (Ph-4)
5	DMSO-d_6	149.7	104.2	157.2	14.1	---	136.9	121.0	128.8	126.0	189.4	138.6 (Ph-1), 128.4 (Ph-2,6), 127.8 (Ph-3,5), 131.5 (Ph-4)
5	C_6D_6	147.9	104.5	163.2	16.3	---	138.7	120.8	129.7	126.7	191.2	138.1 (Ph-1), 128.7 (Ph-2,6), 128.7 (Ph-3,5), 132.0 (Ph-4)
5	acetone-d_6	148.8	104.5	162.5	16.0	---	138.6	121.3	130.0	127.4	191.8	138.5 (Ph-1), 129.0 (Ph-2,6), 129.4 (Ph-3,5), 132.9 (Ph-4)
5	CD_3OD	151.3	105.5	160.8	14.7	---	137.8	123.1	130.2	128.2	193.1	140.0 (Ph-1), 129.6 (Ph-2,6), 129.3 (Ph-3,5), 133.1 (Ph-4)
6	$CDCl_3$	146.9	102.9	161.7	16.6	---	137.4	120.9	129.0	126.7	182.9	141.2 (Th-2), 132.0 (Th-3), 127.4 (Th-4), 132.6 (Th-5)
6	DMSO-d_6	150.8	104.3	156.5	13.9	---	136.7	121.3	128.9	126.1	180.4	145.0 (Th-2), 133.5 (Th-3), 128.1 (Th-4), 133.5 (Th-5)
8	$CDCl_3$	150.5	108.9	155.6	15.5	62.3	137.5	122.8	129.2	127.6	192.2	29.1 (Me)
9	$CDCl_3$	150.6	108.5	155.4	15.6	62.3	137.6	122.9	129.2	127.7	194.0	42.7 ($CO\underline{C}H_2$), 30.0 ($\underline{C}H_2Ph$), 141.5 (Ph-1), 128.3 (Ph-2,6), 128.4 (Ph-3,5), 125.9 (Ph-4)
10	$CDCl_3$	151.1	108.9	155.3	15.4	63.0	137.5	122.9	129.2	127.6	184.2	124.6 ($CO\underline{C}H$), 142.5 ($\underline{C}HPh$), 135.1 (Ph-1), 128.2 (Ph-2,6), 128.9 (Ph-3,5), 130.1 (Ph-4)
10	DMSO-d_6	149.7	108.2	155.1	15.2	63.2	137.1	122.9	129.3	127.7	183.4	124.8 ($CO\underline{C}H$), 141.8 ($\underline{C}HPh$), 134.6 (Ph-1), 128.3 (Ph-2,6), 129.0 (Ph-3,5), 130.3 (Ph-4)
11	$CDCl_3$	150.3	106.4	155.1	14.8	62.5	137.7	122.9	128.4	127.3	190.4	139.2 (Ph-1), 129.1 (Ph-2,6), 129.0 (Ph-3,5), 132.5 (Ph-4)
11	DMSO-d_6	149.1	105.9	154.8	14.5	62.6	137.2	122.9	129.1	127.4	189.4	138.9 (Ph-1), 128.6 (Ph-2,6), 128.5 (Ph-3,5), 132.6 (Ph-4)
12	$CDCl_3$	149.6	106.1	154.0	14.3	62.5	137.6	122.8	128.9	127.2	181.5	144.9 (Th-2), 133.5 (Th-3), 127.9 (Th-4), 133.9 (Th-5)

Table 5. ^{13}C-NMR chemical shifts of **13-17**[10] (numbering of atoms see Scheme 2)

		pyrazole-C					C of N-Phenyl					
No.	solvent	C-3	C-4	C-5	5-Me	NMe	C-1	C-2,6	C-3,5	C-4	C=O	C of 4-substituent R
13	$CDCl_3$	164.1	106.1	155.4	12.3	33.3	133.7	126.3	129.3	128.3	194.4	29.5 (Me)
14	$CDCl_3$	163.9	105.8	155.7	12.3	33.3	133.8	126.3	129.4	128.3	196.1	42.8 ($CO\underline{C}H_2$), 29.9 ($\underline{C}H_2Ph$), 141.7 (Ph-1), 128.4 (Ph-2,6), 128.0 (Ph-3,5), 125.5 (Ph-4)
15	$CDCl_3$	164.0	106.2	156.1	12.5	33.3	133.6	126.6	129.4	128.5	184.9	125.4 ($CO\underline{C}H$), 140.9 ($\underline{C}HPh$), 135.5 (Ph-1), 128.3 (Ph-2,6), 128.5 (Ph-3,5), 129.6 (Ph-4)
15	DMSO-d_6	163.2	104.3	155.3	12.2	33.4	133.7	127.1	129.3	128.4	183.2	125.7 ($CO\underline{C}H$), 139.5 ($\underline{C}HPh$), 135.2 (Ph-1), 128.9 (Ph-2,6), 127.9 (Ph-3,5), 129.8 (Ph-4)
16	$CDCl_3$	163.0	106.7	157.1	12.3	33.9	134.0	126.2	129.3	128.1	190.4	138.5 (Ph-1), 129.3 (Ph-2,6), 127.6 (Ph-3,5), 131.9 (Ph-4)
16	DMSO-d_6	162.4	104.5	156.4	11.9	33.8	134.1	126.5	129.2	128.0	189.2	138.8 (Ph-1), 129.0 (Ph-2,6), 127.6 (Ph-3,5), 131.6 (Ph-4)
17	$CDCl_3$	162.5	106.6	156.9	12.4	33.8	133.9	126.4	129.4	128.3	180.9	145.2 (Th-2), 134.4 (Th-3), 127.8 (Th-4), 132.9 (Th-5)

Table 6. Selected $^{13}C,^{1}H$ spin coupling constants (Hz) of **1-6, 8-12**[10] (numbering of atoms of **1-6** for the hydroxypyrazole form = form A in Scheme 2)

No.	solvent	^{1}J(3-Me)	^{2}J(C3,3-Me)	^{3}J(C4,3-Me)	^{1}J(OMe)	other couplings (R)
1	$CDCl_3$	128.4	6.8	[a]	---	$^{1}J(CO\underline{Me}) = 128.1$, $^{2}J(\underline{C}O,CO\underline{Me}) = 5.9$
1	DMSO-d_6	129.5	6.6	[a]	---	$^{1}J(CO\underline{Me}) = 127.6$
2	$CDCl_3$	128.4	6.8	[a]	---	$^{1}J(\underline{CH_2}) = 126.3$, $^{1}J(\underline{CH_3}) = 128.6$
2	DMSO-d_6	129.5	6.6	2.3	---	$^{1}J(\underline{CH_2}) = 126.9$, $^{1}J(\underline{CH_3}) = 127.2$
3	$CDCl_3$	128.4	6.8	2.7	---	$^{1}J(CO\underline{CH_2}) = 128.8$, $^{1}J(\underline{CH_2}Ph) = 130.6$
3	DMSO-d_6	129.8	[a]	[a]	---	
4	$CDCl_3$	128.5	7.0	2.5	---	$^{1}J(CO\underline{CH}) = 158.3$, $^{1}J(\underline{CH}Ph) = 157.2$
4	DMSO-d_6	129.6	[a]	2.4	---	
5	$CDCl_3$	128.8	7.0	2.7	---	
5	DMSO-d_6	129.1	6.9	2.5	---	
5	C_6D_6	128.7	7.0	2.6	---	
5	acetone-d_6	128.8	7.1	2.6	---	
5	CD_3OD	129.6	6.9	2.7	---	
6	$CDCl_3$	128.9	6.8	2.6	---	^{1}J of Th-C: C3:168.7, C4: 167.0, C5:185.8
6	DMSO-d_6	129.5	[a]	2.4	---	^{1}J of Th-C: C3:170.5, C4: 169.7, C5:186.5
8	$CDCl_3$	128.8	7.0	2.3	147.4	$^{1}J(CO\underline{Me}) = 127.5$, $^{2}J(\underline{C}O,CO\underline{Me}) = 6.0$
9	$CDCl_3$	128.8	6.9	2.3	147.3	$^{1}J(CO\underline{CH_2}) = 128.4$
10	$CDCl_3$	128.8	7.0	2.3	147.5	$^{1}J(CO\underline{CH}) = 154.6$, $^{1}J(\underline{CH}Ph) = 151.1$
11	$CDCl_3$	128.6	6.9	2.6	147.4	^{3}J(C5,OMe) = 4.2
11	DMSO-d_6	128.3	6.9	2.6	147.9	^{3}J(C5,OMe) = 4.3
12	$CDCl_3$	128.6	6.8	2.6	147.4	^{1}J of Th-C: C3:169.2, C4: 169.8, C5:185.1

[a] Not determined (unambiguously).

Table 7. Selected $^{13}C,^{1}H$ spin coupling constants (Hz) of **13-17**[10] (numbering of atoms see Scheme 2)

No.	solvent	^{1}J(5-Me)	^{2}J(C5,5-Me)	^{3}J(C4,5-Me)	^{1}J(NMe)	other couplings (R)
13	$CDCl_3$	130.8	6.6	2.5	141.9	$^{1}J(CO\underline{Me}) = 127.9$, $^{2}J(\underline{C}O,CO\underline{Me}) = 6.1$
14	$CDCl_3$	130.8	6.8	2.5	141.9	$^{1}J(CO\underline{CH_2}) = 128.2$, $^{1}J(\underline{CH_2}Ph) = 127.9$, $^{3}J(C5,NMe) = 2.9$
15	$CDCl_3$	130.9	6.8	2.5	142.1	$^{1}J(CO\underline{CH}) = 160.9$, $^{1}J(\underline{CH}Ph) = 154.6$
15	DMSO-d_6	130.8	6.8	2.5	142.9	$^{1}J(CO\underline{CH}) = 159.8$, $^{1}J(\underline{CH}Ph) = 155.1$
16	$CDCl_3$	130.6	6.7	2.7	141.9	^{3}J(C5,NMe) = 2.9
16	DMSO-d_6	130.8	[a]	[a]	142.6	
17	$CDCl_3$	130.9	6.8	2.7	141.9	^{1}J of Th-C: C3:171.5, C4: 169.0, C5:184.1 ^{3}J(C5,NMe) = 2.9

[a] Not determined (unambiguously).

Crystal Structures of Compounds (2), (4), and (6)

Technical details on the crystal structure determinations are described in the experimental section. Views of the molecules encounterd in the crystalline state are shown in Figures 4-6. Selected bond lengths and bond angles of the three compounds are presented in Table 11. The three compounds behave with respect to bonding in the region of the pyrazolone moiety remarkably different. The propionyl compound (**2**), crystallized from diisopropylether, is in the enol form (Figure 4) corresponding to tautomeric form **A'** of Scheme 1. The molecule is essentially flat with respect to non-hydrogen atoms. It forms a short and bent intramolecular hydrogen bond of O(1)...O(2) = 2.533(2) Å from the enolic pyrazole-bonded oxygen O(1) [C(3)-O(1) = 1.314 Å] to the exocyclic keto oxygen O(2) [C(11)-O(2) = 1.256 Å]. This compound fits well into the presently known pattern of other 4-acyl-3-methyl-1-phenyl-5(2*H*)-pyrazololes and related compounds with known crystal structures, closely related examples being a 4-butyryl,[6] a 4-benzoyl,[7] and a 4-cinnamoyl-1-methyl compound.[8] All these compounds form in crystalline state essentially planar molecules with the pyrazolole oxygen in enol form **A'** (Scheme 1) donating intramolecular hydrogen bonds of O...O = 2.583 - 2.663 Å, pyrazolole C-O bond lengths of 1.319 - 1.324 Å, and exocyclic keto C-O bond lengths of 1.243 - 1.273 Å. Compared with the C-O standard bond length of unsaturated ketones, C-O = 1.233 Å, the observed lengthening of the exocyclic C-O-bonds may be attributed not only to hybridization effects of the pyrazolole moiety but also to inductive effects of the short and strong intramolecular enol hydrogen bonds accepted by them.

In comparison to the previous examples the cinnamoyl compound (**4**), crystallized from $CDCl_3$, exhibits an unprecedented feature (Figure 5). In crystalline state the molecule is almost flat and in an enol form alike previous examples. However, in contrast to them the enolic hydrogen in **4** is not primarily bonded to the pyrazolone oxygen O(1) but to the exocyclic oxygen O(2) forming a short 'reverted' intramolecular hydrogen bond of O...O = 2.558 Å. This conclusion is not only based on the X-Ray position of the hydrogen atom but is also clearly supported by the C-O bond lengths C(3)-O(1) = 1.261 Å for the pyrazolone oxygen and C(11)-O(2) = 1.312 Å for the exocyclic oxygen. To our knowledge this is the first proven example for a crystalline pyrazolone corresponding in principle to the tautomeric form **D'** of Scheme 1. Since compound (**4**) in $CDCl_3$ solution at room temperature was found by NMR spectroscopy to adopt mainly structure **A'**, we conclude that intermolecular effects may contribute to the stabilization of structure **D'** in crystalline state. This view is supported by the crystal structure of a related cinnamoyl compound with a methyl group instead of the N(1)-bonded phenyl,[8] which shows the normal 5-hydroxy-pyrazole structure (**A'**) closely corresponding to compound (**2**) in hydrogen bond and C-O bond lengths.These findings point again to delicate and relatively labile hybridization effects in acylpyrazolones.

As a rule of tumb acylpyrazolones crystallized from nonpolar solvents will preferably form enol forms with intramolecular hydrogen bonds while from more polar solvents the NH forms are obtained.[7] The thienoyl compound (**6**), which was recrystallized from ethanol, conforms to this rule as shown in Figure 6. Here the molecule is distinctly non-planar and both the phenyl ring as well as the thiophene ring are inclined by 36.5° and 42.0° to the pyrazole ring. Moreover, the two C=O functionalities are oriented *trans* to each other not permitting an intramolecular hydrogen bond. The active hydrogen atom is attached to the

nitrogen atom N(2) and involved in a N-H...O hydrogen bond of N...O = 2.669 Å to the pyrazolone oxygen of a neighboring molecule. The two C=O bond lengths of (**6**) [C(3)-O(1) = 1.246 Å and C(11)-O(2) = 1.230 Å] are in reasonable agreement with corresponding figures found in crystalline keto forms of 4-benzoyl-1-phenyl-3-methylpyrazolone with *cis*-oriented keto groups, a distinctly non-planar conformation and a intermolecular hydrogen bond N(H)...O = 2.67 Å to the pyrazolone oxygen, and of 4-cinnamoyl-1,3-dimethylpyrazolone monohydrate with *trans*-oriented keto groups, a planar conformation and a intermolecular hydrogen bond N(H)...O = 2.69 Å to the water molecule.

Table 8. Atomic coordinates and equivalent isotropic displacement parameters of non-hydrogen atoms for $C_{13}H_{14}N_2O_2$ (**2**).

	x/a	y/b	z/c	U_{eq} [x 10^3 Å^2]
O(1)	0.25521(13)	0.36887(7)	0.41355(7)	69(1)
O(2)	0.35901(14)	0.44885(8)	0.25495(7)	75(1)
N(1)	0.23670(12)	0.51638(8)	0.52920(7)	52(1)
N(2)	0.27208(14)	0.63466(9)	0.53436(8)	59(1)
C(1)	0.32768(16)	0.66474(10)	0.44935(9)	56(1)
C(2)	0.33287(15)	0.56870(10)	0.38574(9)	52(1)
C(3)	0.27386(14)	0.47678(10)	0.44109(9)	52(1)
C(4)	0.37700(2)	0.78786(12)	0.43144(11)	78(1)
C(5)	0.17552(14)	0.45751(11)	0.61184(9)	54(1)
C(6)	0.13880(17)	0.34012(11)	0.60919(10)	65(1)
C(7)	0.08292(17)	0.28480(13)	0.69081(11)	75(1)
C(8)	0.06190(19)	0.34401(15)	0.77474(12)	78(1)
C(9)	0.09580(2)	0.46003(15)	0.77677(11)	79(1)
C(10)	0.15282(19)	0.51806(13)	0.69581(10)	67(1)
C(11)	0.37383(16)	0.54960(11)	0.28759(9)	57(1)
C(12)	0.43339(18)	0.64455(12)	0.22280(10)	67(1)
C(13)	0.44900(3)	0.61105(16)	0.11942(11)	93(1)

Table 9. Atomic coordinates and equivalent isotropic displacement parameters of non-hydrogen atoms for $C_{19}H_{16}N_2O_2$ (**4**).

	x/a	y/b	z/c	U_{eq} [x 10^3 Å^2]
O(1)	-0.2255(3)	0.10678(5)	0.48230(9)	66(1)
O(2)	0.1333(3)	0.03787(6)	0.44208(9)	69(1)
N(1)	-0.4158(3)	0.15712(6)	0.33472(10)	53(1)
N(2)	-0.3880(3)	0.15793(6)	0.22980(11)	61(1)
C(1)	-0.2014(4)	0.12144(8)	0.21826(13)	55(1)
C(2)	-0.0985(3)	0.09440(7)	0.31399(12)	47(1)
C(3)	-0.2459(3)	0.11867(7)	0.38755(13)	50(1)
C(4)	-0.1202(4)	0.11370(9)	0.11472(13)	77(1)
C(5)	-0.5975(3)	0.19497(7)	0.37073(14)	54(1)
C(6)	-0.6173(4)	0.19811(9)	0.47440(16)	74(1)
C(7)	-0.7999(5)	0.23486(9)	0.50749(19)	85(1)
C(8)	-0.9610(4)	0.26774(9)	0.43899(22)	82(1)
C(9)	-0.9377(4)	0.26502(9)	0.33616(20)	82(1)
C(10)	-0.7569(4)	0.22888(8)	0.30111(16)	69(1)
C(11)	0.0929(3)	0.05338(7)	0.34475(12)	50(1)
C(12)	0.2547(3)	0.02506(7)	0.27894(12)	50(1)
C(13)	0.4216(3)	-0.01679(7)	0.31214(13)	54(1)
C(14)	0.5920(3)	-0.04876(7)	0.25329(12)	50(1)
C(15)	0.5974(4)	-0.03991(9)	0.14916(14)	68(1)
C(16)	0.7651(5)	-0.07070(10)	0.09764(15)	80(1)
C(17)	0.9314(4)	-0.11109(8)	0.14809(16)	69(1)
C(18)	0.9296(4)	-0.12054(8)	0.25072(15)	65(1)
C(19)	0.7601(4)	-0.09021(7)	0.30269(14)	58(1)

Table 10. Atomic coordinates and equivalent isotropic displacement parameters of non-hydrogen atoms for $C_{15}H_{12}N_2O_2S$ (**6**).

	x/a	y/b	z/c	U_{eq} [x 10^3 Å^2]
S	0.11973(5)	0.11300(4)	0.02299(2)	66(1)
O(1)	0.09569(8)	0.36446(10)	0.19149(4)	48(1)
O(2)	0.32701(13)	0.10548(11)	0.10489(6)	74(1)
N(1)	0.28650(10)	0.39760(10)	0.23763(5)	39(1)
N(2)	0.40704(10)	0.35564(11)	0.23157(5)	40(1)
C(1)	0.41276(12)	0.28344(12)	0.18635(6)	39(1)
C(2)	0.29465(12)	0.27623(12)	0.16025(6)	37(1)
C(3)	0.21151(12)	0.34806(12)	0.19436(6)	36(1)
C(4)	0.53503(14)	0.22720(16)	0.17038(8)	55(1)
C(5)	0.25045(12)	0.46483(11)	0.28745(6)	37(1)
C(6)	0.15669(14)	0.54909(13)	0.28103(8)	50(1)
C(7)	0.11780(17)	0.61178(15)	0.32972(10)	64(1)
C(8)	0.17362(19)	0.59382(17)	0.38287(9)	68(1)
C(9)	0.26834(16)	0.51159(16)	0.38856(7)	58(1)
C(10)	0.30657(13)	0.44557(13)	0.34102(6)	44(1)
C(11)	0.26454(13)	0.19586(13)	0.11203(6)	45(1)
C(12)	0.16301(14)	0.22352(13)	0.07077(6)	45(1)
C(13)	0.09961(16)	0.32613(15)	0.05936(7)	54(1)
C(14)	0.01457(18)	0.31391(18)	0.01191(8)	66(1)
C(15)	0.01620(18)	0.20371(18)	-0.01095(8)	68(1)

Table 11. Selected bond lengths [Å] and angles [°] for $C_{13}H_{14}N_2O_2$ (**2**), $C_{19}H_{16}N_2O_2$ (**4**), and $C_{15}H_{12}N_2O_2S$ (**6**).

	(2)	(4)	(6)
C(3)-O(1)	1.313(2)	1.261(2)	1.246(2)
C(11)-O(2)	1.256(2)	1.312(2)	1.230(2)
N(1)-N(2)	1.395(2)	1.404(2)	1.373(2)
N(1)-C(3)	1.346(2)	1.363(2)	1.388(2)
N(1)-C(5)	1.421(2)	1.415(2)	1.422(2)
N(2)-C(1)	1.311(2)	1.306(2)	1.319(2)
C(1)-C(2)	1.424(2)	1.431(2)	1.392(2)
C(1)-C(4)	1.493(2)	1.490(2)	1.492(2)
C(2)-C(3)	1.390(2)	1.430(2)	1.431(2)
C(2)-C(11)	1.426(2)	1.386(2)	1.464(2)
C(11)-C(12)	1.495(2)	1.445(2)	1.467(2)
C(12)-C(13)	1.502(2)	1.325(2)	1.367(2)
<C-C phenyl>	1.377(2)	1.377(2)	1.379(2)
C(3)-N(1)-N(2)	109.9(1)	110.7(1)	108.9(1)
N(1)-N(2)-C(1)	106.0(1)	106.9(2)	109.6(1)
N(2)-C(1)-C(2)	111.7(1)	111.4(2)	109.3(1)
C(1)-C(2)-C(3)	103.8(1)	104.8(2)	106.8(1)
C(2)-C(3)-N(1)	108.6(1)	106.3(2)	105.3(1)
C(2)-C(3)-O(1)	126.7(1)	127.2(2)	131.7(1)
N(1)-C(3)-O(1)	124.7(1)	126.5(2)	123.0(1)
C(3)-C(2)-C(11)	119.4(1)	120.1(2)	128.9(1)
C(2)-C(11)-O(2)	118.3(1)	118.2(2)	119.9(1)
C(2)-C(11)-C(12)	122.5(1)	126.0(2)	120.8(1)

Hydrogen bonds (D = donor, A = acceptor)

	D - H ... A	d(D-H)	d(H...A)	<DHA	d(D...A)
(2)	O(1)-H(1O)...O(2)	1.03(2)	1.58(2)	151(2)	2.533(2)
(4)	O(2)-H(2O)...O(1)	1.06(3)	1.55(3)	156(2)	2.558(2)
(6)	N(2)-H(2N)...O(1')	0.87(2)	1.82(2)	165(2)	2.669(2)

Figure 4. Thermal ellipsoid plot (20% ellipsoids) of $C_{13}H_{14}N_2O_2$ (**2**) in crystalline state with crystallographic atom numbering.

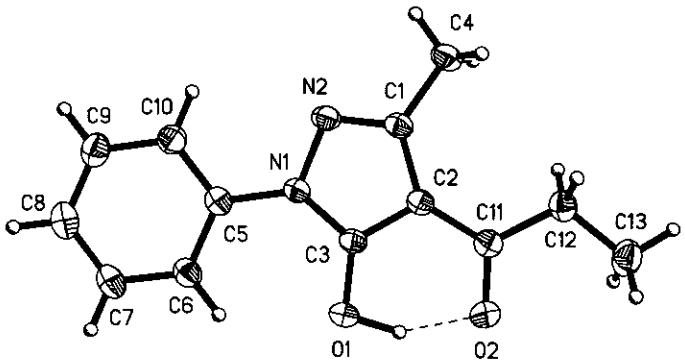


Figure 5. Thermal ellipsoid plot (20% ellipsoids) of $C_{19}H_{16}N_2O_2$ (**4**) in crystalline state with crystallographic atom numbering.

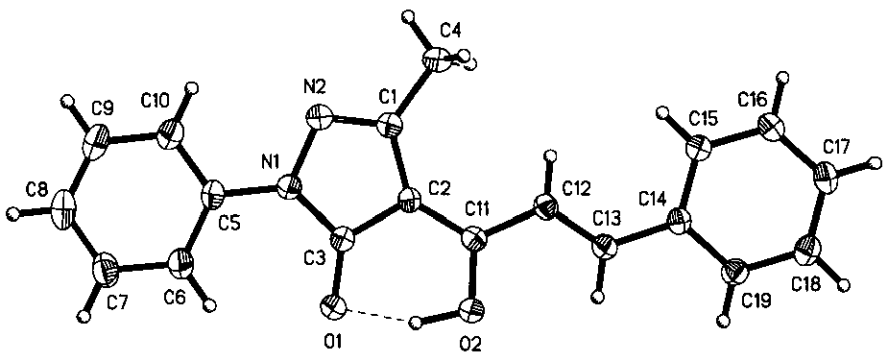
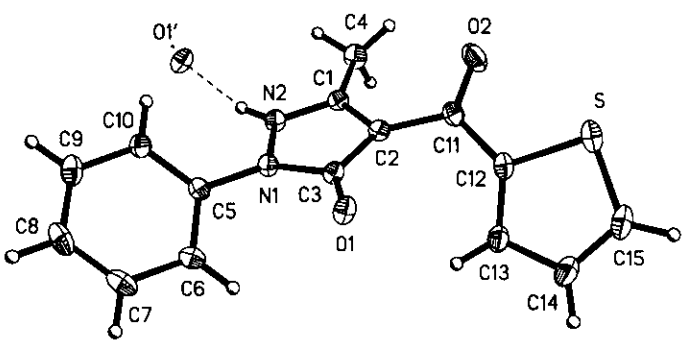


Figure 6. Thermal ellipsoid plot (20% ellipsoids) of $C_{15}H_{12}N_2O_2S$ (**6**) in crystalline state with crystallographic atom numbering. O(1') is the hydrogen bond acceptor of a neighboring molecule.



EXPERIMENTAL

Melting points were detected on a Kofler hot-stage microscope and are uncorrected. The MS spectrum was obtained on a Shimadzu QP 1000 spectrometer (EI, 70 eV), the IR spectrum was obtained on a Perkin Elmer FTIR 1605 spectrophotometer. All NMR spectra were recorded on a Varian Unity*plus* 300 spectrometer (299.95 MHz for ^{1}H, 75.43 MHz for ^{13}C) at 28°C. The center of the solvent signal was used as an internal standard which was related to TMS with δ 7.26 ppm (^{1}H, $CDCl_3$), δ 2.49 ppm (^{1}H, DMSO-d_6), δ 2.05 ppm (^{1}H, acetone-d_6), δ 7.16 ppm (^{1}H, benzene-d_6), δ 3.31 ppm (^{1}H, methanol-d_4), δ 77.0 ppm (^{13}C, $CDCl_3$), δ 39.5 ppm (^{13}C, DMSO-d_6), δ 29.9 ppm (^{13}C, acetone-d_6), δ 128.4 ppm (^{13}C, benzene-d_6), and δ 49.0 ppm (^{13}C, methanol-d_4). The digital resolutions were 0.25 Hz/data point for the ^{1}H-NMR spectra, 0.56 Hz/data point for the broad-band decoupled ^{13}C-NMR spectra and 0.33 Hz/data point for the gated decoupled ^{13}C-NMR spectra. Pyrazolones (**1**), (**2**) and (**5**) are commercially available.

5-Methyl-2-phenyl-4-(3-phenylpropionyl)-1,2-dihydro-3*H*-pyrazol-3-one (**3**)[33]

Compound (**3**) was prepared from 3-methyl-1-phenyl-2-pyrazolin-5-one and 3-phenylpropionyl chloride according to the procedure described by Jensen.[15] Recrystallisation from diisopropyl ether - light petroleum yielded 53% of yellowish crystals of mp 78°C.

5-Methyl-2-phenyl-4-[(E)-3-phenyl-2-propenoyl]-1,2-dihydro-3*H*-pyrazol-3-one (**4**)

Compound (**4**) was prepared from 3-methyl-1-phenyl-2-pyrazolin-5-one and *trans*-cinnamoyl chloride according to the procedure described in ref.[11] Recrystallisation from ethyl acetate yielded 69% of orange crystals of mp 167-168°C (lit.,[34] mp 168°C).

5-Methyl-2-phenyl-4-(2-thienoyl)-1,2-dihydro-3*H*-pyrazol-3-one (**6**)

Compound (**6**) was prepared from 3-methyl-1-phenyl-2-pyrazolin-5-one and 2-thienoyl chloride according to the procedure described by Jensen.[15] Recrystallisation from diisopropyl ether - ethyl acetate yielded 51% of yellowish crystals of mp 145-147°C (lit.,[35] mp 133-136°C).

3-Methyl-1,6-diphenyl-5,6-dihydro-1*H*-pyrano[2,3-c]pyrazol-4-one (**7**)

Pyrazolone (**4**) (1.000 g, 3.29 mmol) was dissolved in 35 mL of conc. sulfuric acid and the solution was kept at rt for 18 h. Then the reaction mixture was poured onto ice/water (80 mL) and extracted with dichloromethane (3 x 50 mL). The combined organic phases were treated with 35 mL of 2N NaOH, the yellow precipitate was filtered off and the CH_2Cl_2 solution was washed with 2N NaOH and water. After

drying over anhydrous Na_2SO_4, the solution was filtered and evaporated *in vacuo*. The residue (45 mg) was subjected to medium pressure liquid chromatography (silica gel, eluent: ethyl acetete) and was then recrystallized from ethanol to afford 11 mg (1%) of cyclisation product (7) as colorless crystals of mp 133-134°C. Acidification of the combined NaOH phases with 2N hydrochloric acid, subsequent extraction with dichloromethane, drying (anhydrous Na_2SO_4) and evporation *in vacuo* recovered 951 mg (95%) of unchanged educt (**4**). Compound (**7**): IR (KBr): 1682 cm^{-1} (C=O); MS: m/z (%) 304 (M^+, 2), 200 (100); ^{1}H-NMR ($CDCl_3$): δ (ppm) 2.52 (s, 3H, 3-Me), 2.74 (dd, J = 17.1 Hz and 3.2 Hz, 1H, H-5'), 3.01 (dd, J = 17.1 Hz and 12.7 Hz, 1H, H-5), 5.74 (dd, J = 12.7 Hz and 3.2 Hz, 1H, H-6), 7.27 (m, 1H, H-4 of N-Ph), 7.41 (m, 2H, H-3,5 of N-Ph), 7.40-7.48 (m, 5H, 6-Ph), 7.76 (m, 2H, H-2,6 of N-Ph); ^{13}C-NMR ($CDCl_3$): δ (ppm) 14.0 (3-Me, ^1J = 128.9 Hz), 43.8 (C-5), 85.0 (C-6), 103.2 (C-3a), 120.7 (C-2,6 of N-Ph), 126.1 (C-2,6 of 6-Ph), 126.7 (C-4 of N-Ph), 128.9 (C-3,5 of 6-Ph), 129.1 (C-3,5 of N-Ph), 129.1 (C-4 of 6-Ph), 137.2 (C-1 of 6-Ph), 137.3 (C-1 of N-Ph), 148.4 (C-3, ^{2}J(C3,3-Me) = 7.1 Hz), 158.3 (C-7a), 185.5 (C-4). *Anal.* Calcd for $C_{18}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20. Found: C, 75.01; H, 5.22; N, 9.28.

X-Ray structure determination of 5-Methyl-2-phenyl-4-propionyl-1,2-dihydro-3*H*-pyrazol-3-one (**2**)

Crystal data: $C_{13}H_{14}N_2O_2$, M_r = 230.26, monoclinic, space group $P2_1/n$ (No. 14), a = 7.465(2) Å, b = 11.569(2) Å, c = 13.972(3) Å, β = 90.79(1)°, V = 1206.5(5) Å^3, Z = 4, Dx = 1.268 g cm^{-3}, λ = 0.71073 Å, μ = 0.087 mm^{-1}, T = 301K. A yellowish prism crystallized from diisopropylether was used for data collection with a Siemens Smart CCD diffractometer (area detector, platform type 3-circle goniometer) and Mo Kα radiation (sealed X-ray tube, graphite monochromator). Intensity data with θ ≤ 25° were harvested over the full sphere of the reciprocal space using 0.3° ω-scan frames. Data were corrected for Lp, decay, absorption and related effects with the empirical method using program SADABS[36]; 12038 reflections collected, 2108 independent, R_{int} = 0.026. The structure was solved with direct methods and was refined with program SHELXL97.[36] Hydrogen atoms were located from a difference Fourier map and were refined riding with the atoms to which they were bonded, except for the O-bonded hydrogen atom H(1O) which was not restrained. An orientation ambiguity of the pyrazole-bonded methyl group was taken into account. The final refinement varied 162 parameters and used all 2108 independent reflections weighted by $w=1/[\sigma^2(F_o^2)+(0.061P)^2+0.07P]$, where $P=(F_o^2+2F_c^2)/3$. Final $R1$ = $\Sigma||F_o|-|F_c||/\Sigma|F_o|$ = 0.043, wR2 = $[\Sigma(w(F_o^2-F_c^2)^2)/\Sigma(w(F_o^2)^2)]^{1/2}$ = 0.099 and S = 1.02 for all data; $R1$ = 0.034 for the 1679 reflections with $F_o^2 > 2\sigma(F_o^2)$. Atomic coordinates are presented in Table 8, selected bond lengths and angles in Table 11.[37]

X-Ray structure determination 5-Methyl-2-phenyl-4-[(E)-3-phenyl-2-propenoyl]-1,2-dihydro-3*H*-pyrazol-3-one (**4**)

Crystal data: $C_{19}H_{16}N_2O_2$, M_r = 304.34, monoclinic, space group $P2_1/n$ (No. 14), a = 5.163(1) Å, b = 23.128(5) Å, c = 13.109(3) Å, β = 98.62(1)°, V = 1547.7(6) Å^3, Z = 4, Dx = 1.306 g cm^{-3}, λ = 0.71073 Å, μ = 0.086 mm^{-1}, T = 297K. A thin orange prism crystallized from $CDCl_3$ was used for data collection with a Siemens Smart CCD diffractometer. Intensity data with θ ≤ 25° were harvested over about one hemisphere of the reciprocal space. They were corrected for Lp, decay, absorption and related effects; 8255 reflections collected, 2692 independent, R_{int} = 0.037. Structure solution with direct methods, structure refinement with SHELXL97.[36] Hydrogen atoms were located from a difference Fourier map and were refined riding with the atoms to which they were bonded, except for the O-bonded hydrogen atom H(2O) which was not restrained. The final refinement varied 214 parameters and used all 2692 independent reflections weighted by w=1/[σ^2(F_o^2)+(0.051P)^2+0.112P]. Final R1 = 0.069, wR2 = 0.109 and S = 1.06 for all data; R1 = 0.043 for the 1939 reflections with $F_o^2 > 2\sigma(F_o^2)$. Atomic coordinates are presented in Table 9.[37]

X-Ray structure determination 5-Methyl-2-phenyl-4-[2-thienoyl]-1,2-dihydro-3*H*-pyrazol-3-one (**6**)

Crystal data: $C_{15}H_{12}N_2O_2S$, M_r = 284.33, orthorhombic, space group $Pbca$ (No. 61), a = 10.626(3) Å, b = 11.311(3) Å, c = 22.866(5) Å, V = 2748.3(12) Å^3, Z = 8, Dx = 1.374 g cm^{-3}, λ = 0.71073 Å, μ = 0.238 mm^{-1}, T = 299K. A yellow block crystallized from ethanol was used for data collection with a Siemens Smart CCD diffractometer and Mo Kα radiation. Intensity data with θ ≤ 27° were harvested over the full sphere of the reciprocal space. They were corrected for Lp, decay, absorption and related; 24381 reflections collected, 2978 independent, R_{int} = 0.039. The structure was solved with direct methods and was refined with SHELXL97.[36] Hydrogen atoms were located from a difference Fourier map and were refined riding with the atoms to which they were bonded, except for the N-bonded hydrogen atom H(2N) which was not restrained. An orientation ambiguity of the methyl group was taken into account. The final refinement varied 188 parameters and used 2978 independent reflections weighted by w=1/[σ^2(F_o^2)+(0.050P)^2+0.44P]. Final R1 = 0.047, wR2 = 0.096 and S = 1.04 for all data; R1 = 0.035 for the 2342 reflections with $F_o^2 > 2\sigma(F_o^2)$. Atomic coordinates are presented in Table 10.[37]

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29. With pyrazolone (**18**), from a 3% NOE on 3-Me upon irradiation of COC**H** and a 7% NOE on COC**H** upon irradiation of 3-Me it was concluded that **18** exclusively exists in form **A'** in $CDCl_3$ solution and form **A** can be definitely excluded.[8] In our opinion this can only be a hint for a high amount of **A'**, as rotameric form **a** of **A** (Scheme 5) is also considered to exhibit NOEs between 3-Me and COC**H**, however, also other rotamers contribute to the 'overall NOE' 3-Me ↔ COC**H** in **A** making it smaller compared to that expected with **A'**. Based alone on the absence of an NOE 3-Me ↔ COC**H** in DMSO-d_6 it was further proposed, that **18** is present as NH-tautomer (**B**) in this and other polar solvents.[8]

30. It should be mentioned that in DMSO-d_6 solution, the ^{1}H and ^{13}C NMR spectra of **5** recorded at 60°C are very similar to those at 28°C indicating no drastic changes in tautomeric composition.

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