The Structure of 4-Benzoyl-5-methyl-2-phenylpyrazol-3-one Oxime and Its Methyl Derivatives

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^{1}H and ^{13}C NMR spectroscopic investigations of 4-benzoyl-5-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one oxime (**4**) and different methylation products thereof (**5**–**11**) indicate that **4** exists predominantly as 4-enaminopyrazolone in [D_6]DMSO solution. Single-crystal X-ray analysis revealed that in the solid state the same tautomeric structure of **4** was present, and closely resembles that of the corresponding *N*-methylamino product (**6**). Both compounds are stabilised by an intramolecular hydrogen bond between the pyrazolone C=O group and the N-OH proton. A 1,2-dihydro-3*H*-pyrazol-3-one structure was found in a clathrate of *O*-methyloxime **5** and dichloromethane.

Introduction

The tautomerism of 4-acylpyrazolones has been the subject of various studies.[1–5] In the solid state, some unambiguous results have been obtained by single-crystal X-ray analyses,[3,5–8] which show the compounds to be present in the chelated hydroxypyrazole form (**A′**), the NH form (**B**), or as isomers with an exocyclic double bond being stabilised by an intramolecular hydrogen bond (**D′**) (Figure 1). The medium used for recrystallisation obviously plays a crucial role in this context: the use of different solvents can lead to the formation of different tautomeric forms of the same compound.[7–9] The situation in solution is much more complicated, as a fast (relative to the NMR timescale) interconversion of OH and NH forms gives rise to averaged sets of signals that call for a careful analysis. In the older literature, contradictory – and also obviously incorrect – proposals can be found.[9] More relevant investigations[4,5] indicate such compounds to have a complex behaviour in solution, with the chelated hydroxy form being predominant in $CDCl_3$ or C_6D_6, and mixtures of OH and NH tautomers seem to be present in the more-polar [D_6]DMSO.

A related and even more sophisticated problem is the structural assignment of oximes derived from 4-acylpyrazolones. Here, as shown in Figure 2, in addition to tautomerism, also the *E*/*Z* diastereoisomerism at the C=N double bond must be considered (for isomers **A**, **B**, and **C**). Moreover, in a manner similar to 4-acylpyrazolones, forms stabilised by intramolecular hydrogen bonds are also possible, for instance **D′** and **D′′**. Because a number of 4-acylpyrazolone oximes recently synthesised in our group exhibited an interesting reaction behaviour – namely, intramolecular cyclisations to 6*H*-pyrazolo[4,3-*d*]isoxazoles **F** failed and, instead, the formation of 7-methyl-1,5,6-triazaspiro-[2.4]hepta-1,6-dien-4-ones of type **G** took place[10] (Figure 2) – we were interested in gaining a more detailed insight into the structure and tautomerism of the title compounds. Here we present NMR spectroscopic investigations, as well as the results of single-crystal X-ray analyses, of 4-benzoyl-5-methyl-2-phenyl-3*H*-pyrazol-3-one

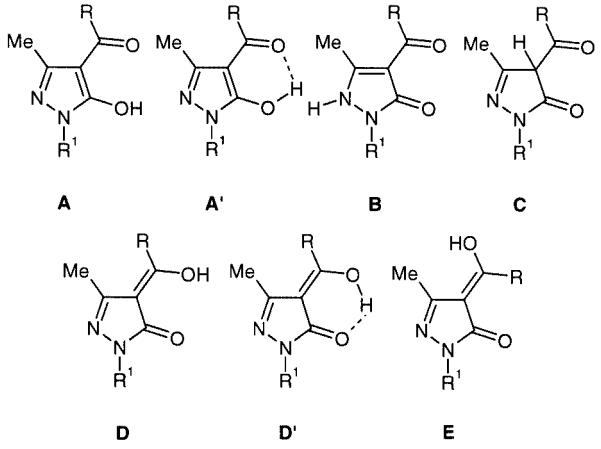

Figure 1. Tautomeric forms of 4-acylpyrazolones

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oxime (**4**) and its methyl derivatives (**5**−**11**) (Scheme 1). Most of the latter derivatives may be considered as "fixed" tautomeric forms that should deliver valuable data for the purpose of determining tautomeric composition of their corresponding des-methyl congeners.

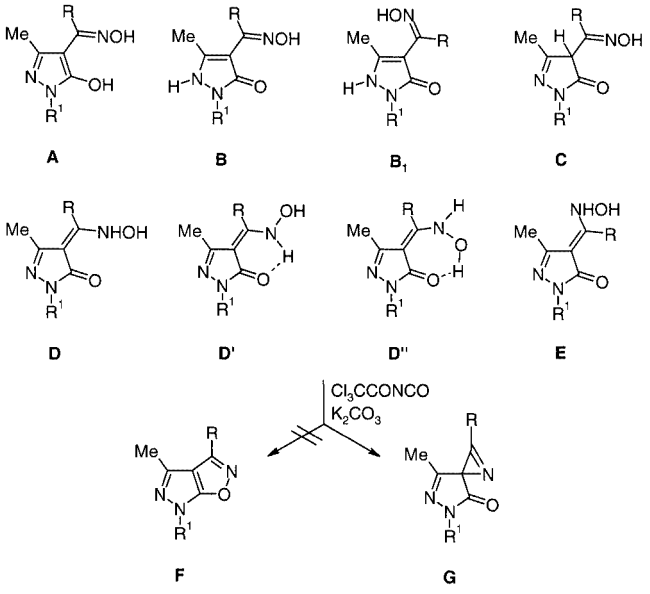
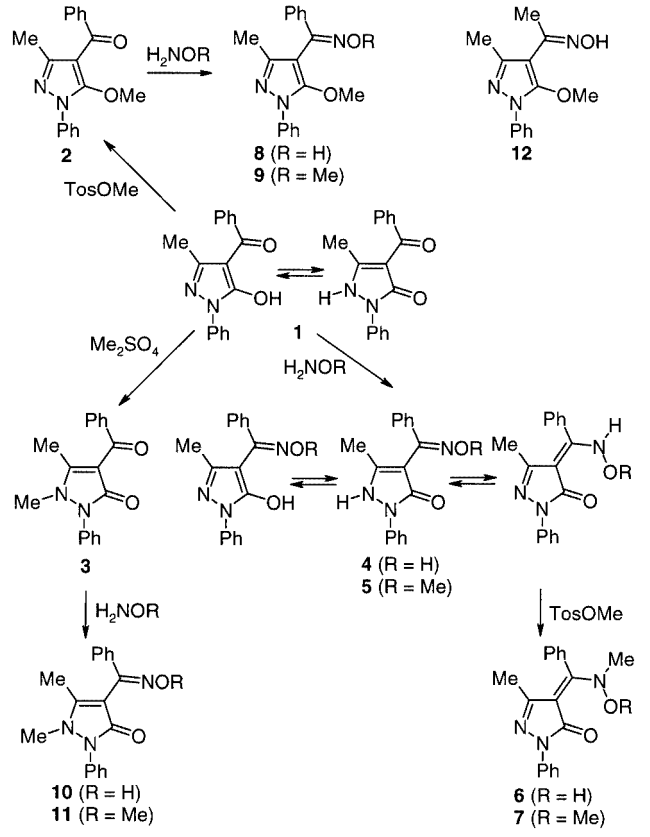


Figure 2. Tautomeric forms of 4-acylpyrazolone oximes and their reaction with trichloroacetyl isocyanate



Scheme 1. Synthesis of compounds **2**−**12**

Results and Discussion

Chemistry

Compounds **2**[11,12] and **3**[12,13] are known, but a more convenient synthesis of **2** was possible by reacting **1** with methyl 4-toluenesulfonate (TosOMe). The synthesis of oximes **4**,[14−16] **8**, **10**, and **12** and those of oxime ethers **5**, **9**, and **11** was accomplished by treatment of the corresponding ketones with hydroxylamine hydrochloride or *O*-methylhydroxylamine hydrochloride, respectively, in ethanol/pyridine (Scheme 1). The *N*-hydroxy-*N*-methylenaminone **6** resulted from reaction of **4** with one equivalent of TosOMe, and methylation of **6** with a further equivalent of TosOMe led to the formation of **7**. All novel compounds were fully characterised by spectroscopic methods (IR, MS, ^{1}H NMR, ^{13}C NMR) as well as by elemental analysis.

NMR Spectroscopic Investigations

The NMR spectroscopic data of compounds **4**−**12** are given in Table 1−3. 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 (gated decoupling), 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.

Whereas the ^{1}H and ^{13}C NMR spectra of the title compound **4** in $CDCl_3$ [23] exhibit sharp signals (except for the resonance of the acidic protons), the corresponding spectra in [D$_6$]DMSO are characterised by marked line broadening, indicating dynamic behaviour, especially for the signals of the pyrazole C-4 (δ = 96.0 ppm), pyrazole C-3(5) (δ = 158.8 ppm), Ph-*C*−N (δ = 152.9 ppm), and *C*-phenyl C-1 (δ = 132.1 ppm) units. A single broad signal (δ = 12.90 ppm) is observed for the two acidic protons (Figure 3). The existence of a CH tautomer of **4** (form **C** in Figure 2) can be ruled out because of the lack of signals representing a C(sp^3)−H fragment in the ^{1}H and ^{13}C NMR spectra. Because NOE difference experiments revealed a strong NOE, and thus spatial closeness, between the methyl protons and 2,6-H of the *C*-phenyl unit (Figure 4), the (*E*)-configured structure (**E** of Figure 2) can also be excluded. Moreover, only weak through-space interactions observed between the acidic protons and 2,6-H of the *N*-phenyl group make the dominance of an NH-tautomeric form **B** less probable. Comparison of the NMR spectroscopic data of **4** with those of methyl congeners **6**, **8**, and **10** provides a strong hint for the existence of **4** predominantly in the enaminopyrazolone form in [D$_6$]DMSO solution. In particular, there is a close resemblance of the chemical shifts in the ^{13}C NMR spectra of **4** and **6**, with no more than 1.4 ppm difference between the shifts of their corresponding carbon atoms (Figure 3). On the other hand, there is markedly more deviation in the comparison with the *O*-methyl (**8**) or the *N*-methyl derivative (**10**), which are "normal" oximes with a characteristic shift of the **C**=NOH atom of ca.

Table 1. ^{1}H NMR chemical shifts (δ/ppm) of **4**−**12**

No.	Solvent	H of *N*-phenyl				H of *C*-phenyl			Other H
		3(5)-Me	2,6-H	3,5-H	4-H	2,6-H	3,5-H	4-H	
4	[D$_6$]DMSO	1.61	7.89	7.44	7.21	7.57	7.52	7.53	12.90[a] (NH, OH)
4	$CDCl_3$	1.61	7.92	7.43	7.24	7.53	7.53	7.62	12.17[a] (OH)
5	[D$_6$]DMSO	1.91	7.74	7.45	7.24	7.56	7.39	7.39	11.38[a] (NH, OH), 3.95 (OMe)
5a	$CDCl_3$	1.69	7.82	7.45	7.30	7.54	7.44	7.43	8.62[a] (NH, OH), 4.14 (OMe)
5b	$CDCl_3$	1.60	7.85	7.47	7.27	7.37	7.45	7.45	8.62[a] (NH, OH), 3.86 (OMe)
6	[D$_6$]DMSO	1.22	7.91	7.43	7.20	7.58	7.57	7.62	16.11 (OH), 3.44 (NMe)
6	$CDCl_3$	1.35	7.94	7.41	7.20	7.39	7.53	7.54	16.03 (OH), 3.47 (NMe)
7	[D$_6$]DMSO	1.27	8.01	7.35	7.06	7.55	7.55	7.62	3.75 (NMe), 3.52 (OMe)
7	$CDCl_3$	1.41	8.03	7.37	7.10	7.53	7.48	7.57	3.83 (NMe), 3.53 (OMe)
(*Z*)-**8**	[D$_6$]DMSO	1.89	7.67	7.47	7.30	7.60	7.40	7.40	11.67 (=NOH), 3.71 (OMe)
(*Z*)-**8**	$CDCl_3$	2.06	7.72	7.43	7.28	7.67	7.40	7.40	8.78[a] (=NOH), 3.78 (OMe)
(*Z*)-**9**	[D$_6$]DMSO	1.85	7.65	7.47	7.32	7.60	7.43	7.43	3.98 (=NOMe), 3.69 (5-OMe)
(*Z*)-**9**	$CDCl_3$	2.02	7.72	7.43	7.28	7.68	7.40	7.39	4.07 (=NOMe), 3.75 (5-OMe)
(*E*)-**9**	[D$_6$]DMSO	1.91	7.62	7.47	7.33	7.49	7.42	7.43	3.88 (=NOMe), 3.65 (5-OMe)
(*E*)-**9**	$CDCl_3$	2.06	7.67	7.42	7.28	7.60	7.40	7.42	4.01 (=NOMe), 3.71 (5-OMe)
(*Z*)-**10**	[D$_6$]DMSO	2.13	7.36	7.50	7.32	7.59	7.35	7.38	11.48 (=NOH), 3.19 (NMe)
(*Z*)-**10**	$CDCl_3$	2.00	7.42	7.49	7.35	7.61	7.35	7.35	9.54 (=NOH), 3.24 (NMe)
(*E*)-**10**	[D$_6$]DMSO	2.25	7.31	[b]	[b]	7.36	[b]	[b]	11.22 (=NOH), 3.15 (NMe)
(*Z*)-**11**	[D$_6$]DMSO	2.11	7.35	7.50	7.34	7.59	7.38	7.39	3.93 (=NOMe), 3.21 (NMe)
(*Z*)-**11**	$CDCl_3$	2.11	7.42	7.42	7.28	7.65	7.33	7.33	4.02 (=NOMe), 3.18 (NMe)
(*E*)-**12**	[D$_6$]DMSO	2.33	7.61	7.48	7.33	2.11 (N=C-Me)			10.99 (=NOH), 3.74 (5-OMe)
(*E*)-**12**	$CDCl_3$	2.36	7.66	7.44	7.30	2.27 (N=C-Me)			8.97 (=NOH), 3.76 (5-OMe)

[a] Broad signal. [b] Not unequivocally assigned because of overlap with signals of the predominant isomer (*Z*)-**10**.

Table 2. ^{13}C NMR chemical shifts (δ/ppm) of **4**−**12**

No.	Solvent	C of pyrazole system				C of *N*-phenyl				C of *C*-phenyl					
		C-Me	C-4	*C*-O	3(5)-Me	C-1	C-2,6	C-3,5	C-4	C-1	C-2,6	C-3,5	C-4	Ph-*C*=N	Other C
4	[D$_6$]DMSO	147.5	96.0[a]	158.8[b]	14.5	138.5	119.5	128.8	124.9	132.1[a]	128.8	128.6	130.7	152.9[b]	
4	$CDCl_3$	148.1	96.3	160.8	15.2	138.4	120.6	128.8	125.7	130.4	129.4	129.4	132.3	155.3	
5	[D$_6$]DMSO	147.3[a]	96.1[a]	152.5[b]	13.5	138.0[a]	120.4[a]	128.8	125.3	135.3	127.0	128.3	129.2	149.0	61.7 (=NOMe)
5a	$CDCl_3$	147.7	97.2	151.8	14.7	138.0	121.8	128.9	126.5	134.9	128.8	128.5	129.8	153.2	62.6 (=NOMe)
5b	$CDCl_3$	147.1	96.5	153.8	14.3	138.0	120.8	128.9	126.1	131.8	127.8	128.4	129.3	156.8	62.5 (=NOMe)
6	[D$_6$]DMSO	147.7	97.4	160.2	14.4	138.4	119.2	128.8	124.9	132.0	129.4	129.1	131.3	154.2	45.4 (NMe)
6	$CDCl_3$	148.4	98.1	160.4	14.7	138.6	120.3	128.7	125.3	132.7	129.3	129.3	131.3	154.6	45.4 (NMe)
7	[D$_6$]DMSO	147.9	98.0	161.0	15.2	139.7	117.6	128.4	123.0	131.9	130.6	128.3	131.6	161.6	62.4 (OMe), 43.5 (NMe)
7	$CDCl_3$	148.6	99.2	161.7	15.4	139.5	119.0	128.5	123.7	131.8	131.1	128.3	131.8	161.6	62.9 (OMe), 44.3 (NMe)
(*Z*)-**8**	[D$_6$]DMSO	146.7	95.6	151.7	13.4	138.1	121.7	128.9	126.2	136.4	126.4	128.6	129.0	148.5	59.0 (5-OMe)
(*Z*)-**8**	$CDCl_3$	148.0	94.8	152.5	13.7	138.3	122.5	128.7	126.5	135.9	127.1	128.8	129.7	151.4	59.4 (5-OMe)
(*Z*)-**9**	[D$_6$]DMSO	146.5	95.6	151.8	13.3	137.9	121.8	128.9	126.4	135.3	126.7	128.7	129.6	149.1	61.9 (=NOMe), 59.4 (5-OMe)
(*Z*)-**9**	$CDCl_3$	147.8	95.8	152.3	13.7	138.4	122.4	128.8	126.3	136.0	127.1	128.6	129.5	149.8	62.3 (=NOMe), 59.4 (5-OMe)
(*E*)-**9**	[D$_6$]DMSO	147.5	102.1	152.4	13.8	137.8	122.0	129.0	126.6	133.0	129.0	128.0	129.1	149.4	61.8 (=NOMe), 61.4 (5-OMe)
(*E*)-**9**	$CDCl_3$	148.7	102.4	152.8	14.0	138.3	122.5	128.9	126.6	133.3	129.5	128.0	129.3	149.9	62.3 (=NOMe), 61.3 (5-OMe)
(*Z*)-**10**	[D$_6$]DMSO	155.7	100.9	162.6	12.6	135.1	123.9	129.0	126.3	135.8	126.4	128.2	128.6	148.0	35.4 (NMe)
(*Z*)-**10**	$CDCl_3$	153.6	102.8	163.1	13.0	135.7	125.2	129.4	127.6	134.2	127.6	128.4	129.3	151.4	35.2 (NMe)
(*E*)-**10**	[D$_6$]DMSO	155.1	105.6	163.5	11.5	[c]	124.0	[c]	[c]	133.4	[c]	[c]	[c]	148.1	35.2 (NMe)
(*Z*)-**11**	[D$_6$]DMSO	155.2	100.3	162.1	12.4	135.0	124.2	129.0	126.5	134.8	126.7	128.3	129.2	148.8	61.8 (=NOMe), 35.2 (NMe)
(*Z*)-**11**	$CDCl_3$	154.9	103.1	162.8	12.8	135.0	124.2	129.0	126.6	135.1	127.1	128.3	129.2	148.8	62.2 (=NOMe), 35.5 (NMe)
(*E*)-**12**	[D$_6$]DMSO	146.5	104.1	151.8	14.7	137.9	122.0	129.2	126.7	13.8 (N=C-*Me*)				147.7	62.1 (5-OMe)
(*E*)-**12**	$CDCl_3$	147.5	103.8	152.5	14.7	138.1	122.5	129.0	126.8	14.1 (N=C-*Me*)				150.7	62.0 (5-OMe)

[a] Broad signal. [b] Very broad signal. [c] Not unequivocally assigned.

Table 3. Selected $^{13}C,^{1}H$ spin coupling constants (Hz) of **4**−**12**

No.	Solvent	^{1}J(3-Me) ^{1}J(5-Me)	^{2}J(C3,3-Me) ^{2}J(C5,5-Me)	^{3}J(C4,3-Me) ^{3}J(C4,5-Me)	Other couplings
4	[D$_6$]DMSO	128.0	7.0	[a]	
5	[D$_6$]DMSO	128.2	[a]	[a]	$^{1}J_{OMe}$ = 143.5, ^{3}J(C=N,*C*-Ph H2,6) = 3.9
5a	$CDCl_3$	128.4	6.8	[a]	$^{1}J_{OMe}$ = 145.2
5b	$CDCl_3$	128.4	6.7	[a]	$^{1}J_{OMe}$ = 143.9
6	[D$_6$]DMSO	128.2	6.8	2.4	$^{1}J_{NMe}$ = 143.2
6	$CDCl_3$	128.4	6.8	2.5	$^{1}J_{NMe}$ = 142.5
7	[D$_6$]DMSO	127.9	7.0	2.3	$^{1}J_{NMe}$ = 142.9, $^{1}J_{NOMe}$ = 146.3
7	$CDCl_3$	128.3	6.9	2.3	$^{1}J_{NMe}$ = 142.6, $^{1}J_{NOMe}$ = 146.2
(*Z*)-**8**	[D$_6$]DMSO	127.5	6.7	3.2	$^{1}J_{OMe}$ = 147.0, ^{3}J(C5,OMe) = 4.3
(*Z*)-**8**	$CDCl_3$	128.1	6.7	3.4	$^{1}J_{OMe}$ = 146.7, ^{3}J(C5,OMe) = 4.3
(*Z*)-**9**	[D$_6$]DMSO	127.6	6.7	3.1	^{1}J(5-OMe) = 147.1, ^{3}J(C5,OMe) = 4.4, $^{1}J_{NOMe}$ = 143.9
(*Z*)-**9**	$CDCl_3$	127.9	6.7	3.2	^{1}J(5-OCH_3) = 146.6, ^{3}J(C5,OMe) = 4.3, $^{1}J_{NOMe}$ = 143.7
(*E*)-**9**	[D$_6$]DMSO	127.8	6.8	2.8	^{1}J(5-OMe) = 147.1, ^{3}J(C5,OMe) = 4.2, $^{1}J_{NOMe}$ = 143.5
(*E*)-**9**	$CDCl_3$	128.1	6.8	[a]	^{1}J(5-OMe) = 146.7, ^{3}J(C5,OMe) = 4.0, $^{1}J_{NOMe}$ = 143.5
(*Z*)-**10**	[D$_6$]DMSO	129.7	6.5	3.7	$^{1}J_{NMe}$ = 141.0, ^{3}J(C5,NMe) = 3.2
(*Z*)-**10**	$CDCl_3$	130.0	6.4	3.6	$^{1}J_{NMe}$ = 141.0, ^{3}J(C5,NMe) = 3.2
(*E*)-**10**	[D$_6$]DMSO	129.7	[b]	[b]	$^{1}J_{NMe}$ = 141.0
(*Z*)-**11**	[D$_6$]DMSO	129.8	6.5	3.8	$^{1}J_{NMe}$ = 141.2, ^{3}J(C5,NMe) = 3.2, $^{1}J_{NOMe}$ = 143.6
(*Z*)-**11**	$CDCl_3$	129.8	6.5	3.8	$^{1}J_{NMe}$ = 140.6, ^{3}J(C5,NMe) = 3.1, $^{1}J_{NOMe}$ = 143.6
(*Z*)-**12**	[D$_6$]DMSO	127.7	6.9	[a]	^{1}J(5-OMe) = 147.1, ^{3}J(C5,OMe) = 4.0, ^{1}J(N=C*Me*) = 128.9, ^{2}J(N=C,N=CMe) = 6.5, ^{3}J(N=C,OH) = 8.2
(*Z*)-**12**	$CDCl_3$	128.1	6.8	2.9	^{1}J(5-OMe) = 146.6, ^{3}J(C5,OMe) = 3.8, ^{1}J(N=C*Me*) = 129.4, ^{2}J(N=C,N=CMe) = 6.5, ^{3}J(C4,N=CMe) = 2.9

[a] Not resolved. [b] Not unequivocally determined (overlap with other signals).

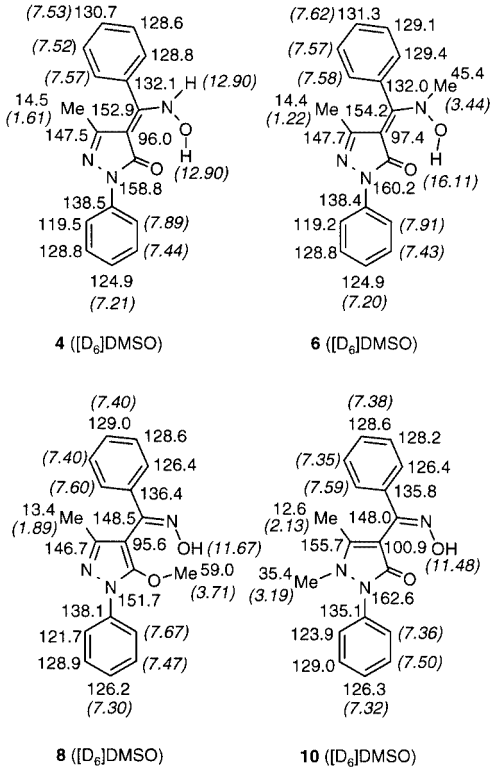


Figure 3. ^{13}C NMR chemical shifts and ^{1}H NMR chemical shifts (in italics) of **4** and its methyl congeners **6**, **8**, and **10** in [D$_6$]DMSO solution

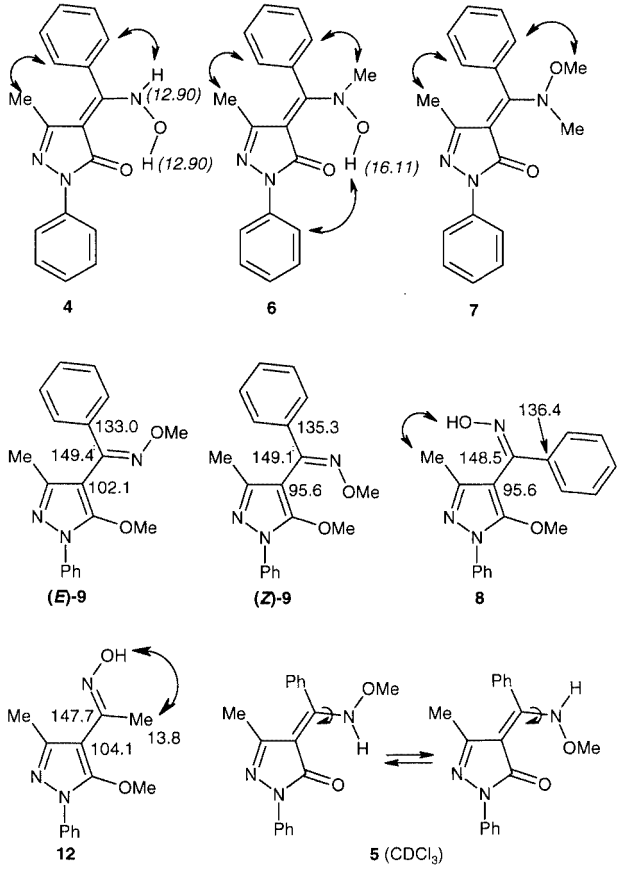


Figure 4. Conformational and configurational analysis of **4**−**9**, and **12** by characteristic NOEs (arrows) and ^{13}C (^{1}H) chemical shifts (δ/ppm, in [D$_6$]DMSO)

δ = 148 ppm (Figure 3). It should be noted that an enaminopyrazolone structure for **4** (form **D′** in Figure 2, stabilised by an intramolecular hydrogen bond between the NH and pyrazolone C=O units) and related compounds was already suggested in 1988 by Hennig and Mann, but no spectral support for these assumptions was provided.[14]

The ^{1}H NMR spectra of **6** exhibit an extremely deshielded OH proton (δ = 16.11 ppm in [D$_6$]DMSO, δ = 16.03 ppm in $CDCl_3$; Figure 3) that can be explained by it being involved in a strong intramolecular hydrogen bond to the pyrazolone C=O unit. This configurational fixation is also confirmed by a strong NOE on the *C*-Ph 2,6-H signal upon irradiation of the *N*-methyl resonance (whereas such an interaction between the NMe group and the *N*-Ph 2,6-H protons was not detected) and an NOE between the OH and *N*-Ph 2,6-H protons (Figure 4). From similar NOE difference experiments with **7**, the *O*-methyl derivative of **6**, a conformation with the OMe group close to the *C*-phenyl ring emerged (Figure 4). Otherwise, the data of **7** closely resemble those of **6** (Table 1−3).

The reaction of **2** with *O*-methylhydroxylamine hydrochloride afforded a pair of isomeric oxime ethers **9** (Scheme 1), which were discriminated and configurationally assigned by considering γ-effects: carbon atoms in the γ-position (α to C=N) to a *syn*-located oxime (ether) oxygen atom experience an upfield shift compared to the γ-atoms in an *anti* position as a result of steric compression.[24] Thus, the C-1 signal of the *C*-phenyl group in (*E*)-**9** shows a smaller ^{13}C NMR chemical shift (δ = 133.0 ppm in [D$_6$]DMSO) than that in the corresponding (*Z*)-**9** (δ = 135.3 ppm in [D$_6$]DMSO), whereas a reverse trend is observed for the pyrazole C-4 signal [(*E*)-**9**: δ = 102.1 ppm, (*Z*)-**9**: δ = 95.6 ppm; Figure 4]. (*E*)-**10** and (*Z*)-**10** can be distinguished in a similar way. In cases when only one isomeric form was present, comparison with the data of **9** and **10** and, particularly, NOE difference experiments allowed an unambiguous determination of the stereochemistry at the C=N double bond.[25−27] Thus, for instance, a strong NOE on the methyl signal upon irradiation of the OH proton unequivocally assigns a (*Z*) configuration to oxime **8** (Figure 4), whereas a clear through-space connection between OH and the protons of the "acetyl" methyl group confirms an (*E*) configuration for oxime **12**. The ^{13}C NMR chemical shifts for the pyrazole C-4 unit in **8** (δ = 95.6 ppm) and **12** (δ = 104.1 ppm) are in full agreement with the assigned configurations (Figure 4).

An interesting phenomenon was observed with product **5**. In [D$_6$]DMSO solution a single compound was detected and although marked line broadening for several signals was observed, the ^{1}H NMR and especially the ^{13}C NMR chemical shift data hint to the presence of a partial structure of an oxime ether (similar to form **A** in Figure 2, Ph-***C***=N: δ = 149.0 ppm) in a (*Z*) configuration (pyrazole C-4: δ = 96.1 ppm, NOE between C-Me and OMe protons). In $CDCl_3$ solution, however, two sets of signals were found (**5a**/**5b** ≈ 1.4:1), with the corresponding Ph-***C***−N signals at δ = 153.2 (**5a**) and δ = 156.8 ppm (**5b**) fitting an enaminopyrazolone structure. On the other hand, the shifts of the pyrazole C−O units (**5a**: δ = 151.8 ppm, **5b**: 153.8 ppm) better match a 5-hydroxypyrazole structure. Additionally, other diagnostic carbon resonances (pyrazole C-4, C-1 of C-phenyl) rule out that **5a** and **5b** are simple *E*/*Z* isomers about an oxime (ether) C=N bond. In NOE difference experiments, saturation transfer between corresponding signals of **5a** and **5b** was observed (CMe, OMe), indicating an equilibrium process and, thus, the interconversion **5a** ↔ **5b**. A possible interpretation of these observations is that there is a significant contribution made by the enamino form (similar to form **D** in Figure 2) in $CDCl_3$ solution, with species **5a** and **5b** resulting from restricted rotation around the =C-N bond (Figure 4), a phenomenon that already has been observed with related enaminopyrazolones.[28−30] An unambiguous confirmation for this suspicion, however, cannot be given since ^{1}H NMR spectra recorded at elevated temperatures (up to 60 °C) did not exhibit any marked changes.

Crystal Structures of Compounds 4, 5, and 6

Technical details on the crystal structure determinations of 4-benzoyl-5-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one oxime (**4**), the *O*-methyloxime **5** and the *N*-methylamino product **6** are described in the Exp. Sect., and views of their molecular geometries encountered in the crystalline state are shown in Figure 6−8, respectively. Selected bond lengths of the three compounds are presented in Table 4.

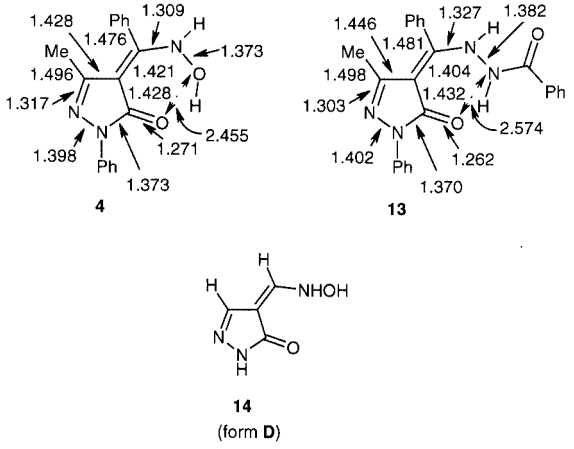


Figure 5. Comparison of selected bond lengths (Å) in **4** and **13**;[32] model compound **14** (form **D** according to Figure 2) was used in the density functional calculations (Table 6).

In all derivatives an extended planar structural motif is formed by the pyrazolone ring (C3−C4−N5−N6−C7), the methyl group C9, the oxygen atom O8 and the C2 atom. The oxime groups (N1−O22−H22) show a deviation from these structural units and they are situated above the ring plane. The phenyl substituents are attached at different sites of the planar subunit and their planes form dihedral angles of around 50°.

In compounds **4** and **6**, an intramolecular ring including O22−H22···O8−C4−C3−C2−N1 (form **D′′** in Figure 2) is closed by the hydrogen bond O22−H22···O8 (Table 5). The NH-pyrazolone motif in compound **5** in the solid state

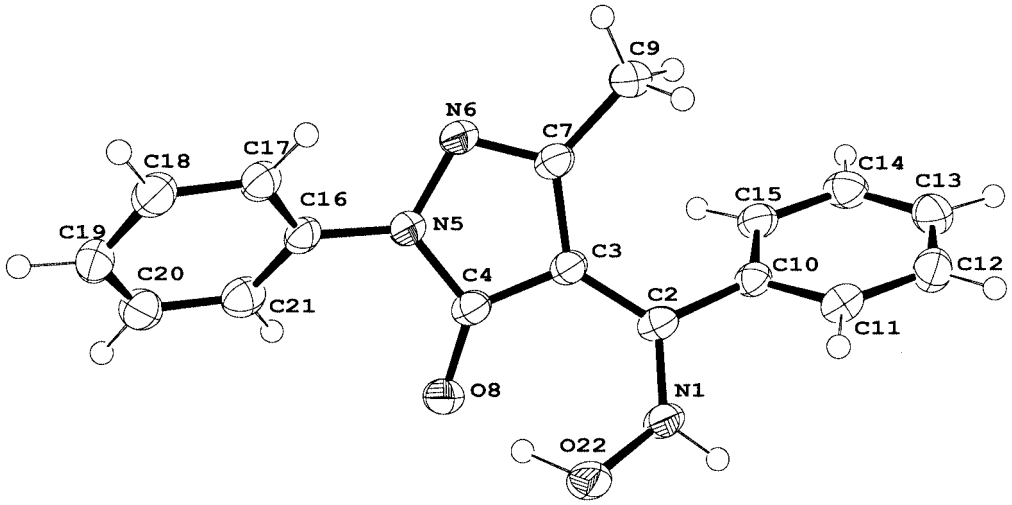


Figure 6. Molecular structure of **4** with atomic numbering

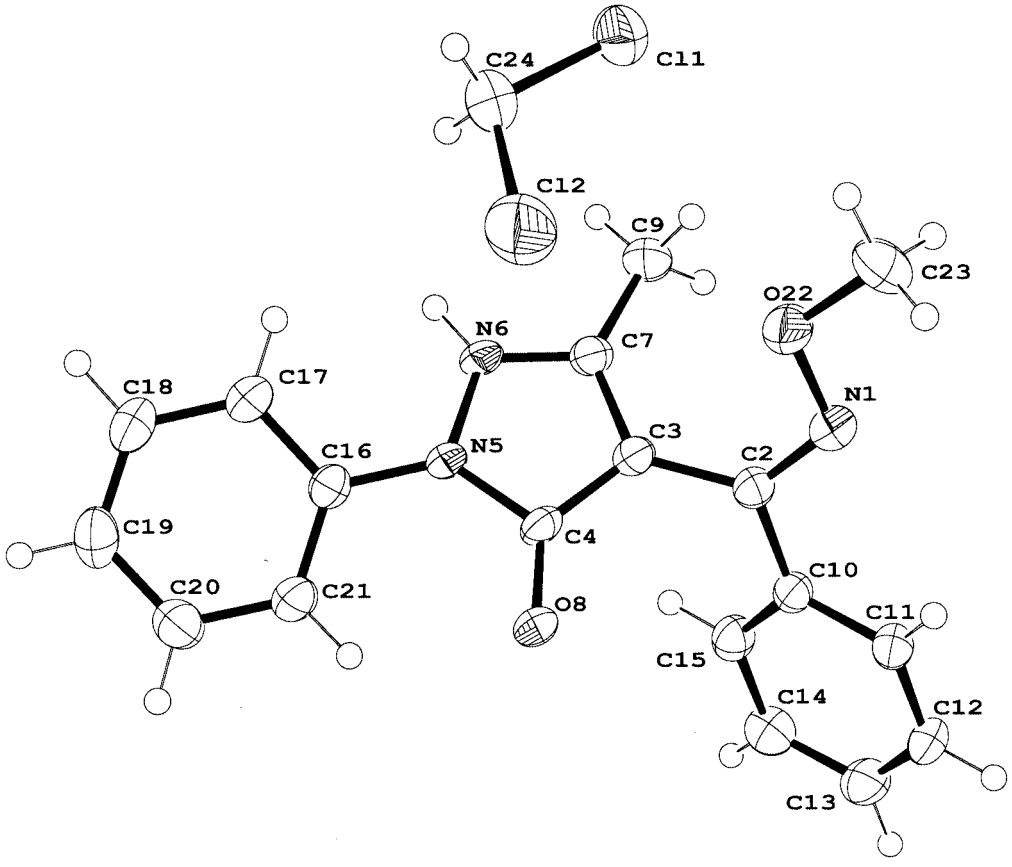


Figure 7. Molecular structure of **5** with atomic numbering

(form $\mathbf{B_1}$) is stabilised by co-crystallisation with dichloromethane. In the oxime structure **4**, there is an intermolecular hydrogen bond (2.872 Å) between the N1 (oxime) and the N6 (imino) atoms. In the crystalline structure of **6** two molecules, denoted *A* and *B*, were found in the asymmetric unit.

Only a few X-ray crystal structures of related compounds are known. For instance, the thiosemicarbazone of **1**, crystallised from methanol, showed an NH-pyrazolone structure (form **B** in Figure 2),[31] whereas **13**,[32] the *N*′-benzoylhydrazone of **1**, exhibited an enaminopyrazolone structure similar to that of **4** (Figure 5).

DFT Calculations

To rationalise the experimental results on the tautomeric forms of 4-acylpyrazolone oximes shown in Figure 2, we performed density functional theory calculations at the B3LYP level using the Gaussian basis set 6−31G** on a

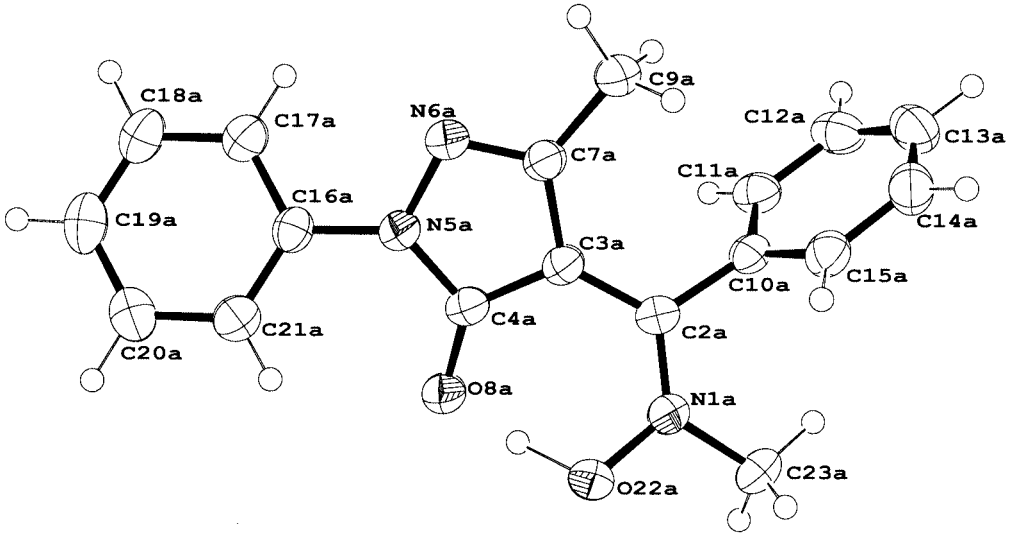


Figure 8. Molecular structure of **6** with atomic numbering

Table 4. Comparison of selected bond lengths in the crystal structures **4**, **5** and **6**

Bond lengths	**4**	**5**	**6** mol A	mol B
C3−C2	1.421(2)	1.474(2)	1.424(2)	1.425(2)
C3−C4	1.428(2)	1.420(2)	1.416(2)	1.412(2)
C3−C7	1.428(2)	1.383(2)	1.439(2)	1.438(2)
C4−N5	1.373(2)	1.393(2)	1.366(2)	1.363(2)
N5−N6	1.398(2)	1.379(2)	1.396(2)	1.398(2)
N6−C7	1.317(2)	1.332(2)	1.312(2)	1.316(2)
C2−C10	1.476/2)	1.480(2)	1.487(2)	1.482(2)
C4−O8	1.271(2)	1.260(2)	1.285(2)	1.288(2)
C7−C9	1.496(2)	1.490(2)	1.491(2)	1.488(2)
N1−C2	1.309(2)	1.290(2)	1.314(2)	1.314(2)
N1−O22	1.373(2)	1.401(2)	1.374(2)	1.373(2)
N1−C23	−	−	1.464(2)	1.468(2)

simplified model **14** (Figure 5), in which the methyl and the phenyl substituents (Figure 2) have been replaced by hydrogen atoms. Tautomers related to **A**, **B**, $\mathbf{B_1}$, **C**, **D′**, **D′′** and **E** have been fully optimised (no imaginary frequencies) and their intrinsic properties are gathered in Table 6.

As encountered for compounds **4** and **6** in the solid state, the tautomeric form **D′′** with an intramolecular O···H−O hydrogen bond in a seven membered ring is the most stable one. The **D′** form with an intramolecular O···H−N hydrogen bond in a six membered ring is higher in energy by about 4 kcal·mol^{-1}. Calculations also predict form **A** to be stable, but condensed phases (solution and solid state) favour tautomers with large values of dipole moment. The existence of compound **5** in the solid state in the form $\mathbf{B_1}$ is probably a consequence of packing forces.

Table 5. Donor (D) and acceptor (A) geometry of hydrogen bonds (N1-H1···N6 and O22-H22···O8) in the crystal structure of **4**, **5** and **6**

Compound		Type	D−H···A	D−H	H···A	D···A	D−H···A
4		Inter	N(1)−H(1)···N(6)[a]	0.92(2)	1.96(2)	2.872(2)	173.9(16)
		Intra	O(22)−H(22)···O(8)[b]	1.075(9)	1.39(2)	2.455(2)	168.8(15)
		Inter	C(14)−H(14)···O(8)[c]	1.01(2)	2.57(2)	3.428(2)	142.0(15)
		Inter	C(19)−H(19)···O(22)[d]	0.99(2)	2.54(2)	3.486(2)	160.3(18)
5		Inter	N(6)−H(1)···O(8)[e]	0.89(2)	1.80(2)	2.656(2)	160.2(19)
		Inter	C(17)−H(17)···O(8)[e]	0.98(2)	2.44(2)	3.315(2)	148.3(15)
		Intra	C(21)−H(21)···O(8)[b]	0.92(2)	2.32(2)	2.924(2)	122.7(14)
		Intra	C(9)−H(9C)···O(22)[b]	0.97(3)	2.48(2)	3.033(2)	115.5(19)
6	A	Intra	O(22A)−H(22A)···O(8A)[b]	1.180(2)	1.261(2)	2.435(4)	172.05(3)
	B	Intra	O(22B)−H(22B)···O(8B)[b]	1.204(3)	1.227(2)	2.423(5)	170.44(3)
	A	Intra	C(21A)−H(21A)···O(8A)[b]	0.93(2)	2.41(2)	2.968(2)	118.2(12)
	B	Intra	C(17B)−H(17B)···O(8B)[b]	0.94(2)	2.39(2)	2.964(2)	119.1(12)

[a] Symmetry transformations used to generate equivalent atoms: $-1/2 + x, -1/2 - y, -1/2 + 2$. [b] x, y, z. [c] $-1/2 + x, -1/2 + y, z$. [d] $1 + x, 1 - y, 1/2 + z$. [e] $-1/2 + x, y, 1/2 - z$.

Table 6. Calculated (B3LYP/6-31G**) absolute energies (in hartrees) and relative stabilities (in kcal·mol^{-1}) of model compound **14** (Figure 5); dipole moments in D

Tautomer simlar to	Absolute value	Relative stability	Relative stability (with ZPE correction)	Dipole moment
A	470.065619	0.09	0	1.89
B	470.047702	11.34	11.50	4.79
B$_1$	470.055310	6.56	6.22	5.19
C	470.048571	10.79	11.52	2.18
D′	470.059325	4.04	4.05	3.43
D′′	470.065769	0	0.28	4.11
E	470.048726	10.70	10.98	4.68

Conclusions

On the basis of data obtained from detailed NMR spectroscopic investigations and X-ray crystal structural analysis, "oxime" **4** derived from 4-benzoyl-5-methyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one (**1**) is present in an enaminopyrazolone form (isomer **D′′** in Figure 2) in solution as well as in the solid state. The latter is characterised by a high degree of delocalisation and is stabilised by a strong intramolecular hydrogen bond. These findings are also supported by ab initio calculations performed on a simplified model compound. The structure of **4** also explains its particular reaction behaviour when treated with trichloroacetyl isocyanate/potassium carbonate (Figure 2): the lack of the hydroxypyrazole form **A** prevents cyclisation to a 6*H*-pyrazolo[4,3-*d*]isoxazole (**F**). Instead, the isocyanate reagent likely attacks the OH group of the hydroxyamino moiety of the more stable form **D**. After proton abstraction, a Lossen-type reaction occurs with formation of a nitrene that cyclises to the spiro-aziridines **G**.[10]

Experimental Section

General: Melting points were detected on a Kofler hot-stage microscope and are uncorrected. Mass spectra were obtained on a Shimadzu QP 1000 spectrometer (EI, 70 eV). IR spectra were 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 solvent signals were used as internal standards which were related to TMS with δ = 7.26 ppm (^{1}H, $CDCl_3$), δ = 2.49 ppm (^{1}H, [D$_6$]DMSO), δ = 77.0 ppm (^{13}C, $CDCl_3$), and δ = 39.5 ppm (^{13}C, [D$_6$]DMSO). 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. The elemental analyses were performed by the Mikroanalytisches Laboratorium, Institute of Physical Chemistry, University of Vienna. Light petroleum refers to the fraction of b.p. 50−70 °C. Pyrazolone **1** is commercially available, the *N*-methylpyrazolone **3** was prepared according to the literature.[13]

(5-Methoxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)(phenyl)methanone (2): Methyl 4-toluenesulfonate (2.944 g, 15.8 mmol) was added to a mixture of **1** (4.190 g, 15.1 mmol) and K_2CO_3 (4.170 g, 30.2 mmol) in dry DMF (40 mL), and then the mixture was stirred at 50 °C for 24 h. The reaction mixture was poured onto water (400 mL) and extracted with diethyl ether (4 × 100 mL). The combined etheral extracts were washed with water, dried (Na_2SO_4) and the solvents evaporated in vacuo. The residue (2.572 g, containing ca. 10% of *N*-methyl product **3** according to TLC) was recrystallised from ethanol to afford yellowish crystals (1.903 g, 43%) of m.p. 80−81 °C (ref.[12] m.p. 79−80 °C); ^{1}H and ^{13}C NMR spectra identical with those of an authentic sample.[12]

General Procedure for the Preparation of Oximes 4, 8, 10, 12 and Oxime Ethers 5, 9, 11: A mixture of 4-acylpyrazole (**1**, **2**, or **3**) (10 mmol), H_2NOR·HCl (R = H, Me) (40 mmol), pyridine (3 mL), and ethanol (20 mL) was heated under reflux for 4 h. After cooling, the mixture was poured onto water (150 mL), resulting in the formation of either a precipitate (a) or an emulsion (b). Workup (a): After standing for 2 h in the refrigerator, the mixture was filtered with suction, the residue was washed with water (several times) and purified as described below, if necessary. Workup (b): The mixture was exhaustively extracted with CH_2Cl_2, the combined organic phases were washed with water (several times), dried (Na_2SO_4), and the solvents evaporated in vacuo. The residue was purified as described below, if necessary.

(*Z*)-2,4-Dihydro-4-[(hydroxyamino)(phenyl)methylene]-5-methyl-2-phenyl-3*H*-pyrazol-3-one (4): Recrystallisation from ethanol (addition of charcoal) yielded cream-coloured crystals (2.229 g, 76%), m.p. 162−170 °C (decomp) (ref.[14] m.p. 168−172 °C; ref.[15] m.p. 166 °C; ref.[16] m.p. 167−169 °C). IR (KBr): ṽ = 2722 (very broad, OH), 1602 (C=O) cm^{-1}. MS: *m*/*z* (%) = 293 (7) [M$^+$], 275 (15), 231 (28), 91 (56), 77 (100), 67 (22), 51 (59).

(*Z*)-4-[(Methoxyamino)(phenyl)methylene]-5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (5): Yield: 2.213 g (72%); colourless crystals, pure according to TLC and NMR spectroscopy. For analytical purposes a sample (100 mg) was recrystallised from ethanol to afford **5** (76 mg), m.p. 168−170 °C (decomp). IR (KBr): ṽ = 1619 (C=O) cm^{-1}. MS: *m*/*z* (%) = 307 (53) [M$^+$], 275 (61), 274 (37), 142 (28), 105 (23), 104 (26), 91 (100), 77 (81), 51 (28). $C_{18}H_{17}N_3O_2$ (307.35): calcd. C 70.34, H 5.58, N 13.67; found C 70.12, H 5.63, N 13.54.

(*Z*)-(5-Methoxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)(phenyl)-methanone Oxime (8): Yield: 2.643 g (86%); colourless crystals, pure according to TLC and NMR spectroscopy. An analytical sample recrystallised from ethanol had m.p. 198−202 °C. IR (KBr): ṽ = 3143, 2844 (OH) cm^{-1}. MS: *m*/*z* (%) = 307 (30) [M$^+$], 275 (13), 248 (37), 188 (20), 105 (91), 91 (37), 77 (100), 51 (46). $C_{18}H_{17}N_3O_2$ (307.35): calcd. C 70.34, H 5.58, N 13.67; found C 70.09, H 5.56, N 13.50.

(*Z*)/(*E*)-(5-Methoxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)(phenyl)-methanone *O*-Methyloxime [(*Z*)-9 and (*E*)-9]: The oily residue (1.864 g, 58%; consisting of **(*Z*)-9** and **(*E*)-9** in a ratio of 3:4] was subjected to medium-pressure liquid chromatography (silica gel;

light petroleum/ethyl acetate, 95:5) to afford **(*Z*)-9** (225 mg, 7%; faster eluting component), a *Z*/*E* mixture (578 mg, 18%) and **(*E*)-9** (418 mg, 13%), all as yellowish oils.

(*Z*)-9: MS: *m*/*z* (%) = 321 (37) [M^+], 290 (78), 275 (33), 105 (62), 91 (37), 77 (100), 67 (23), 51 (37). $C_{19}H_{19}N_3O_2$ (321.38): calcd. C 71.01, H 5.96, N 13.07; found C 71.00, H 5.97, N 12.88.

(*E*)-9: MS: *m*/*z* (%) = 321 (29) [M^+], 290 (62), 275 (31), 105 (56), 91 (36), 77 (100), 67 (27), 57 (23), 51 (34). $C_{19}H_{19}N_3O_2$ (321.38): calcd. C 71.01, H 5.96, N 13.07; found C 71.20, H 5.87, N 12.82.

(*Z*)/(*E*)-1,2-Dihydro-4-[(hydroximino)(phenyl)methyl]-1,5-dimethyl-2-phenyl-3*H*-pyrazol-3-one [(*Z*)-10 and (*E*)-10]: Yield: 2.490 g (81%); colourless crystals, pure according to TLC and NMR (ratio *Z*/*E* of 10:1). An analytical sample recrystallised from ethanol had m.p. 184−187 °C. IR (KBr): $\tilde{\nu}$ = 3425, 3238 (OH), 1646 (C=O) cm^{-1}. MS: *m*/*z* (%) = 308 (17), 307 (100) [M^+], 306 (46), 290 (13), 288 (14), 105 (44), 77 (50), 56 (86), 51 (21). $C_{18}H_{17}N_3O_2$ (307.35): calcd. C 70.34, H 5.58, N 13.67; found C 70.11, H 5.51, N 13.41.

(*Z*)-1,2-Dihydro-4-[(methoxyimino)(phenyl)methyl]-1,5-dimethyl-2-phenyl-3*H*-pyrazol-3-one [(*Z*)-11]: Yield: 2.571 g (80%); colourless crystals, pure according to TLC and NMR spectroscopy. An analytical sample recrystallised from ethanol had m.p. 150 °C. IR (KBr): $\tilde{\nu}$ = 1663 (C=O) cm^{-1}. MS: *m*/*z* (%) = 321 (7) [M^+], 291 (26), 290 (100), 105 (54), 77 (14), 56 (27). $C_{19}H_{19}N_3O_2$ (321.38): calcd. C 71.01, H 5.96, N 13.07; found C 71.05, H 5.85, N 12.93.

(*E*)-1-(5-Methoxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethanone Oxime (12): Compound **12** was prepared from 1-(5-methoxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)ethanone[11,12] by treatment with hydroxylamine hydrochloride according to the general procedure given above. Recrystallisation from diisopropyl ether afforded colourless crystals (1.545 g, 63%), m.p. 142 °C. MS: *m*/*z* (%) = 245 (39) [M^+], 228 (14), 118 (15), 105 (14), 91 (28), 77 (100), 69 (15), 67 (31), 51 (59), 43 (30). $C_{13}H_{15}N_3O_2$ (245.28): calcd. C 63.66, H 6.16, N 17.13; found C 63.48, H 6.27, N 17.00.

(*Z*)-2,4-Dihydro-4-[(*N*-hydroxy-*N*-methylamino)(phenyl)methylene]-5-methyl-2-phenyl-3*H*-pyrazol-3-one (6): Methyl 4-toluenesulfonate (2.00 g, 10.7 mmol) was added to a mixture of **4** (3.00 g, 10.2 mmol) and K_2CO_3 (2.83 g, 20.5 mmol) in dry DMF (15 mL), and then the mixture was stirred at room temperature for 2.5 h. Water (250 mL) was added and then the mixture was continuously extracted with diethyl ether (2 × 350 mL). The combined ethereal extracts were concentrated to a volume of 20 mL and then left in the refrigerator for several hours. The precipitated crystals were filtered off and washed with cold diethyl ether. Yield: 2.263 g (72%); yellow crystals, m.p. 130 °C (recrystallisation from ethanol did not alter the m.p.). MS: *m*/*z* (%) = 307 (100) [M^+], 292 (25), 291 (65), 290 (74), 261 (40), 187 (22), 158 (68), 129 (18), 118 (41), 91 (83), 80 (22), 77 (94), 56 (33), 51 (43). $C_{18}H_{17}N_3O_2$ (307.35): calcd. C 70.34, H 5.58, N 13.67; found C 70.64, H 5.47, N 13.70.

(*Z*)-2,4-Dihydro-4-[(*N*-methoxy-*N*-methylamino)phenylmethylene]-5-methyl-2-phenyl-3*H*-pyrazol-3-one (7): Methyl 4-toluenesulfonate

Table 7. Crystal data and some selected experimental details from the crystal structures of compounds **4**, **5** and **6**

	4	**5**	**6**
Crystallised from	toluene	dichloromethane	ethanol
Empirical formula	$C_{17}H_{15}N_3O_2$	$C_{18}H_{17}N_3O_2{\cdot}CH_2Cl_2$	$C_{18}H_{17}N_3O_2$
Molecular mass (g/mol)	293.32	392.27	307.35
Crystal system	monoclinic	orthorhombic	triclinic
Space group	*Cc*	*Pbca*	$P\bar{1}$
a (Å)	5.889(1)	11.7581(3)	9.123(2)
b (Å)	17.718(4)	16.0078(4)	9.933(2)
c (Å)	13.990(3)	19.9912(5)	17.845(4)
α (°)	90	90	91.40(3)
β (°)	96.66(3)	90	102.79(3)
γ (°)	90	90	97.51(3)
V (Å^3)	1452.6(5)	3762.7(2)	1516.1(6)
Z	4	8	4
D_c (Mg·m^{-3})	1.341	1.385	1.308
Absorb. μ (mm^{-1})	0.091	0.364	0.087
F(000)	616	1632	648
Crystal size (mm)	0.31 × 0.25 × 0.20	0.40 × 0.35 × 0.35	0.25 × 0.15 × 0.15
Crystal habit	cube	cube	cube
Crystal colour	colourless	transparent	transparent yellow
Temperature (K)	200(2)	200(2)	200(2)
Radiation used (λ, Å)	Mo-K_α, 0.71073	Mo-K_α, 0.71073	Mo-K_α, 0.71073
Index ranges	*h* (−8.8)	*h* (−13.13)	*h* (−10.10)
	k (−25.24)	*k* (−18.18)	*k* (−11.11)
	l (−19.19)	*l* (−23.23)	*l* (−21.21)
Unique reflections	4223	3311	5481
Reflections [$I > 2\sigma(I)$]	3563	2736	4305
Refinement method	Full-matrix/F^2	Full-matrix/F^2	Full-matrix/F^2
Data/restraints/parameter	4223/2/260	3311/0/311	5481/0/552
Goodness-of-fit on F^2	1.033	1.036	1.046
*R*1 [$I > 2\sigma(I)$]	0.0405	0.0357	0.0399
*R*1 (all data)	0.0542	0.0459	0.0578
*wR*2 (all data)	0.0839	0.0970	0.0975
$\Delta\rho_{fin}$ (max./min.) (e·Å^{-3})	0.19/−0.16	0.23/−0.38	0.16/−0.17

(132 mg, 0.71 mmol) was added to **6** (200 mg, 0.65 mmol) and K_2CO_3 (187 mg, 1.35 mmol) in dry DMF (1 mL) and the resulting mixture was stirred at room temperature for 2.5 h. The mixture was poured onto water (15 mL) and extracted with CH_2Cl_2 (4 × 6 mL). The combined organic extracts were washed with water, dried (Na_2SO_4) and then the solvents were evaporated in vacuo. The remaining orange oil (131 mg, 63%) slowly solidified on standing. For analytical purposes, a sample was recrystallised from diisopropyl ether to afford orange crystals of m.p. 147−149 °C. IR (KBr): $\tilde{\nu}$ = 1642 (C=O) cm^{-1}. MS: *m/z* (%) = 322 (13), 321 (52) [M^+], 291 (21), 290 (72), 278 (20), 261 (25), 187 (47), 118 (100), 105 (18), 91 (43), 77 (78), 51 (28). $C_{19}H_{19}N_3O_2$ (321.38): calcd. C 71.01, H 5.96, N 13.07; found C 71.09, H 5.82, N 12.95.

X-ray Structure Determination

Preparation of Crystallography Sample: Crystals suitable for X-ray investigation were prepared by slow evaporation of solutions of the respective compounds. Crystals were grown from toluene in the case of **4**, and from ethanol in the case of **6**. Crystallisation of **5** from dichloromethane gave the clathrate [**5**·CH_2Cl_2 (1:1)].

Data Collection, Structural Analysis and Refinement: Crystallographic data of the oxime structures **4**, **5** and **6** are summarised in Table 7. Intensity data for all structures where obtained on a Nonius Kappa instrument with CCD detector at 200 K with a crystal-to-detector distance of 35 mm. All three structures were solved by direct methods, using the program SIR92[34] and refined with SHELXL-97.[35] The geometrical analyses were calculated with programs implemented in PLATON,[36] structure drawings were prepared using Diamond 2.1a.[37] WINGX v.1.63.01[38] was used for the coordination of the programs.

In structure **4** the residual peaks of electron density are situated meanly around the ring atoms. The systematic absences permit the space group to be either *Cc* or *C*2/*c*; *Cc* was chosen and confirmed by analysis (MISSYM-algorithm, Le Page, implemented in PLATON[36]). In addition, the structure could not be solved in space group *C*2/*c*.

To avoid decomposition of the clathrate [**5**·CH_2Cl_2 (1:1)], a single crystal of reasonable quality and appropriate size was cooled down, and the orthorhombic space group was uniquely determined by the systematic absences.

CCDC-186899 (**4**), 186900 (**5**) and CCDC-186901 (**6**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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