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On the Application of Homonuclear NOE Difference Spectroscopy as a Convenient Tool for Configurational Assignment of Compounds with a C=N Bond **

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Summary. The applicability of homonuclear NOE difference spectroscopy for configurational assignment of compounds characterized by a $-CH=N-R$ substructure is evaluated employing phenylhydrazones, benzenesulfonylhydrazones, (thio)semicarbazones, and oxime ethers derived from heteroaromatic carbaldehydes.

Keywords. 1-Benzylpyrazol-4-carbaldehyde derivatives; Configurational assignment of hydrazones, (thio)semicarbazones, oxime derivatives; Homonuclear NOE difference spectroscopy; Pyridazinecarbaldoxime methyl ethers.

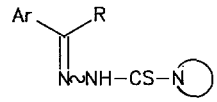
Über die Anwendung homonuklearer NOE-Differenz-Spektroskopie zur Konfigurationszuordnung von Verbindungen mit einer C=N-Bindung

Zusammenfassung. Am Beispiel von Phenylhydrazonen, Benzolsulfonylhydrazonen, (Thio)Semicarbazonen und Oximethern, abgeleitet von heteroaromatischen Carbaldehyden, wird die Eignung homonuklearer NOE-Differenz-Spektroskopie-Experimente zur Ermittlung der Konfiguration von Verbindungen mit $-CH=N-R$-Teilstruktur diskutiert.

Introduction

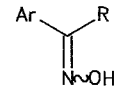
Due to the importance of aldehyde-derived condensation products (hydrazones [1], (thio)semicarbazones [2, 3], azomethines, oximes, and O-substituted oximes [4, 5]) as bio-active substances or as valuable synthetic intermediates, there is continuing interest in convenient methods permitting the rapid determination of the stereochemistry of compounds containing the C=N substructure. NMR spectroscopy has been widely employed for this purpose, mainly utilizing differences in chemical shifts (^1H [6, 7], ^{13}C [8]) and coupling constants [9] observed between *E*- and *Z*-isomers. Recently, we proposed homonuclear NOE difference spectroscopy as a versatile tool for configurational assignment of compounds of type A and B [10, 11]. In extension of these studies, the present report deals with attempts to apply this technique to additional compounds containing a C=N bond as represented by general formula C.

** Dedicated to Prof. Dr. F. Sauter with cordial wishes on the occasion of his 60th anniversary



R = H, CH_3

A



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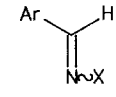
B



X = NHPh
$NHSO_2Ph$
$NHCONH_2$
$NHCSNH_2$
OCH_3
Ph

C

Results and Discussion

As model substances of known stereochemistry [12] we prepared 2-pyridinecarbaldehyde phenylhydrazones *E*-**1** and *Z*-**1**. Expectedly, irradiation of the NH-resonance resulted in a positive NOE on the phenyl protons H-2 and H-6 with both isomers. In the spectrum of *E*-**1**, additionally the signal of the iminyl proton was significantly enhanced as shown in spectrum **b** recorded in *DMSO-d_6* solution (Fig. 1). The use of this solvent, on the other hand, did not permit to demonstrate the absence of an NOE on the iminyl-H signal in *Z*-**1**, since in this case there is an overlap with the signals of phenyl protons (spectrometer frequency: 80 MHz). However, as shown in Fig. 2, this problem could be simply overcome by performing the NOE experiment in $CDCl_3$ solution.

In order to evaluate the general applicability of NOE difference spectroscopy for configurational assignment of compounds characterized by a $-CH=N-R$ substructure, the condensation products **3**–**9** were employed. These compounds were prepared by conventional methods from 1-benzyl-1*H*-pyrazole-4-carbaldehyde (**2**) [13] and the appropriate N-nucleophiles.

Upon irradiation of the hydrazone N–H in the phenylhydrazone **3**, the benzenesulfonylhydrazone **4**, the semicarbazone **5**, and the thiosemicarbazone **6** a

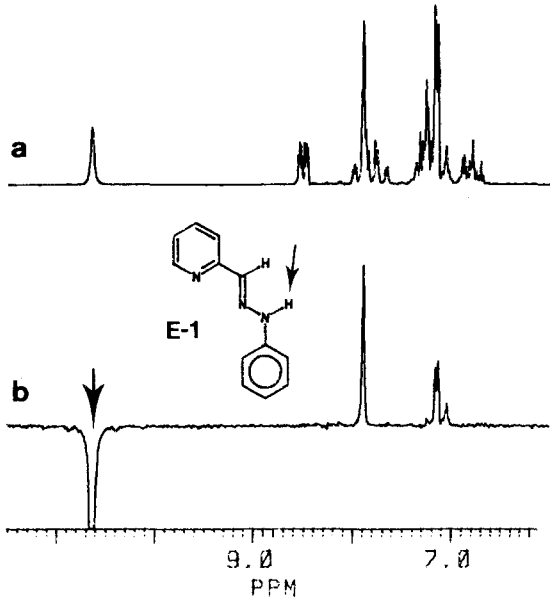


Fig. 1. a ^{1}H-NMR spectrum of *E*-**1** (*DMSO-d_6*), **b** NOE difference spectrum of *E*-**1** resulting from irradiation of NH

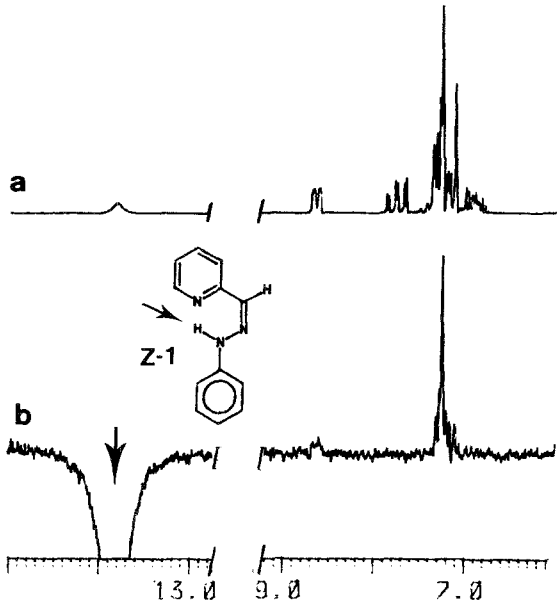
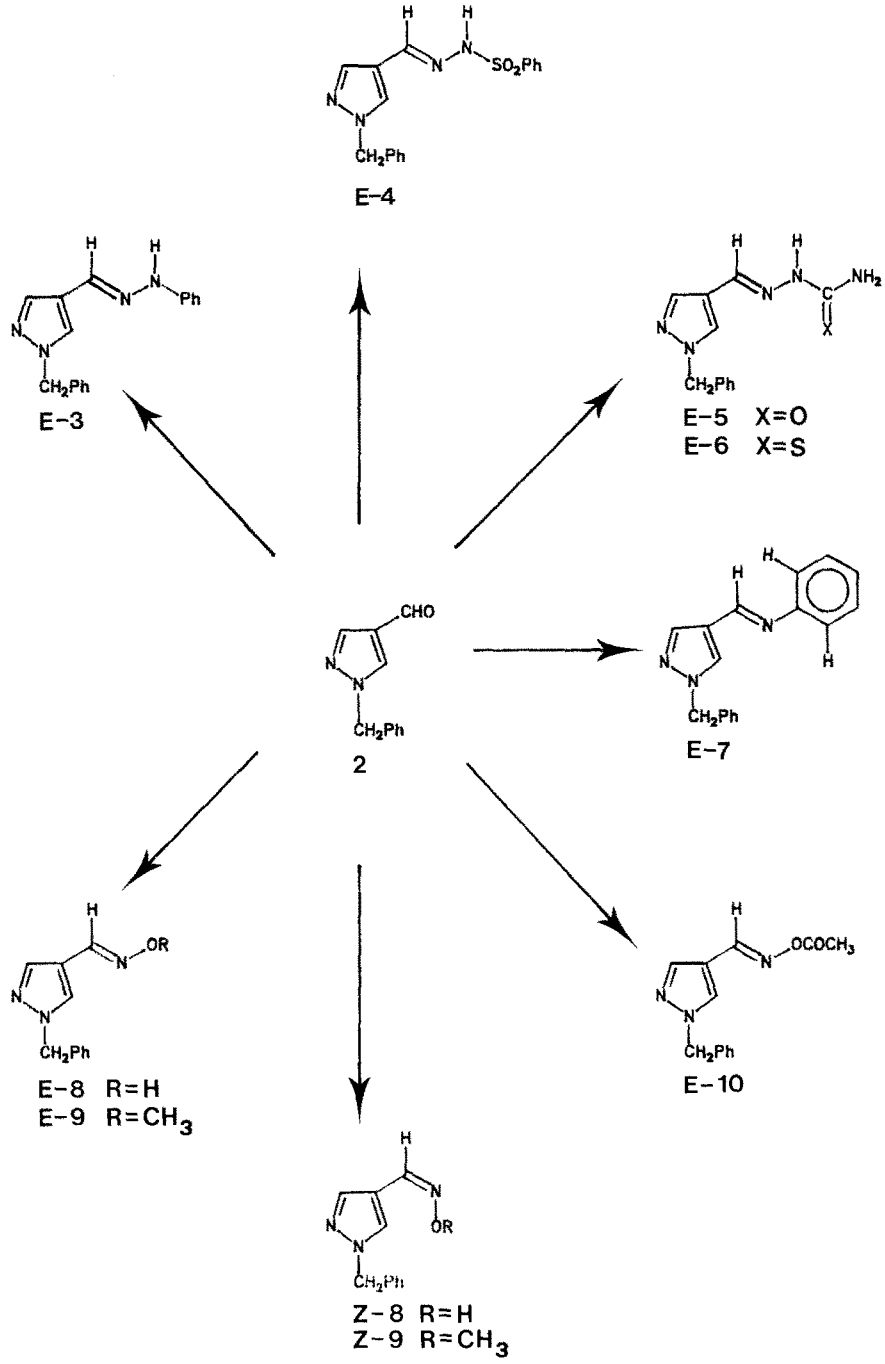


Fig. 2. **a** ^{1}H-NMR spectrum of *Z*-**1** ($CDCl_3$), **b** NOE difference spectrum of *Z*-**1** resulting from irradiation of NH

marked increase of the signal of the iminyl-H is observed. This through-space connection permits unequivocal assignment of *E*-configuration to these compounds. Fig. 3 may serve as a typical example.

The lack of a positive NOE on the iminyl-H upon irradiation of the hydroxyl proton in the oxime **8** (prepared as described previously [14]) was considered as a hint for *Z*-configuration. Acid-induced partial isomerization of this compound led to a 85:15 mixture of *Z*-**8** and *E*-**8** (also obtained from **2**/hydroxylamine hydrochloride/NaO*Et*/*Et*OH), the ^{1}H-NMR spectrum of which enabled us to acquire the spectral data also for the second isomer. Comparison of the δ-values of the iminyl-H (see Table 1) reveals a marked difference between *E*-**8** and *Z*-**8** due to the influence of the oxygen's lone-pair [15], thus clearly indicating *Z*-configuration of the oxime described in Ref. [14]. The resonance frequency of the iminyl-H (7.92 ppm, in *DMSO-*d_6) in the *O*-acetyl oxime **10** (obtained upon treatment of *Z*-**8** with acetic anhydride [14]) resembles closely that of the oxime *E*-**8** and of the corresponding methyl ether *E*-**9**. Together with the ease of HO*Ac*-elimination observed with **10** [14], this prompts us to assign *E*-configuration to this compound.

Marked differences in the chemical shifts of the iminyl-H together with ^{13}C-NMR data (see Tables 1 and 2) enabled us to assign *Z*-configuration to the main component of the 80:20 mixture of oxime ethers **9** obtained upon reaction of **2** with *O*-methyl hydroxylamine hydrochloride. In this case, NOE experiments did not permit the unequivocal determination of stereochemistry. However, investigations employing the recently prepared [16] methyl ethers of 3-pyridazinecarbaldoxime (**11**) and 4-pyridazinecarbaldoxime (**12**) revealed the utility of NOE difference spectroscopy for configurational assignment also in the oxime ether series. Irradiation of the methyl resonance in both compounds resulted in a marked increase of the iminyl-H signal, clearly indicating *E*-configuration (in addition, NOE's were observed also for H-4 in compound **11** and for H-3 and H-5 in oxime ether **12**).



Upon irradiation of the iminyl-H in the azomethine **7** (obtained as the sole product from the reaction of carbaldehyde **2** and aniline), a positive NOE on the protons H-2 and H-6 of the aldimine-phenyl group was observed. This finding is consistent with the fact that N-aryl aldimines generally exist in the far more stable *E*-form at ambient temperature [17–19]. It should be noted that in the azomethine series X-ray analysis or the $^2J(^{15}N,H_{iminyl})$ coupling constant [18] permits an unequivocal assignment of configuration, whereas the ^1H chemical shift of the iminyl

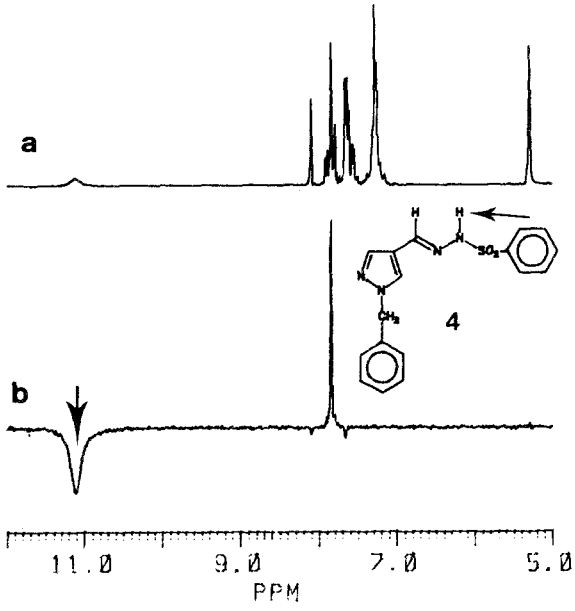


Fig. 3. **a** ^{1}H-NMR spectrum of **4** (*DMSO-d_6*), **b** NOE difference spectrum of **4** resulting from irradiation of NH

Table 1. ^{1}H-NMR data of compounds **2–9** (*DMSO-d_6*)

Comp. no.	Pyrazole-H		Iminyl-H	Benzene-H (benzyl)	$-CH_2-$	Other H
	H-3	H-5				
2[a]	8.00	8.56	–	7.32	5.40	9.80 (CHO)
E-3	7.72	8.05	7.78	7.30	5.32	9.90 (NH)[b], 7.30–6.58 (N-Phenyl)
E-4	7.66	8.09	7.83	7.27	5.29	11.12 (NH)[b], 7.92–7.72 (S-Ph H−2,6), 7.65–7.49 (S-Ph H-3,4,5)
E-5	7.81	8.09	7.73	7.29	5.31	9.93 (NH)[b], 6.27 (NH_2)[b]
E-6	7.90	8.19	7.95	7.29	5.31	11.19 (NH)[b], 7.99, 7.70 (NH_2)[b]
E-7	7.94	8.36	8.44	7.32	5.39	7.50–7.00 (N-Phenyl)
E-8	7.65	8.02	7.98	–[c]	5.31	10.66 (OH)[b]
Z-8[a]	7.82	8.34	7.34	7.32	5.36	11.19 (OH)[b]
E-9	7.68	8.08	8.08	–[c]	5.32	3.78 (OCH_3)
Z-9	7.82	8.31	7.39	7.29	5.36	3.89 (OCH_3)

[a] Ref. [14]
[b] Exchangeable with D_2O
[c] Not observed due to overlap with signals of the *Z*-isomer

proton does not provide sufficient information even when both isomeric species are at hand [19].

In conclusion, NOE experiments may be considered as a convenient tool for the discrimination between *E*- and *Z*-isomers not only for oximes [11] and thiosemicarbazones [10] but also for phenylhydrazones, benzenesulfonylhydrazones, semicarbazones[1], and oxime ethers of general type C.

[1] For a recent application of this technique with semicarbazones derived from cyclic ketones see Ref. [20]

Table 2. ^{13}C-NMR data of compounds **2–9** (*DMSO-d_6*)

Comp. no.	^{13}C Chemical shifts (δ, ppm)									
	Pyrazole-C			Iminyl-C (Formyl-C)	Phenyl-C of benzyl				$-CH_2-$	Other C
	C-3	C-4	C-5		C-1′	C-2′,6′	C-3′,5′	C-4′		
2[b]	140.04	124.02	134.62	184.45	136.26	127.73	128.50	127.73	55.19	
E-3	136.98	119.34	–[c]	130.26	137.17	127.53	128.42	128.18	54.95	N-Phenyl: 145.68 (1), 128.91 (3, 5), 118.05 (4), 111.70 (2, 6)
E-4	137.76	117.23	130.05	141.22	136.82	127.55	128.41	127.63	54.93	S-Phenyl: 139.21 (1), 132.70 (4), 128.97 (3, 5), 127.06 (2, 6)
E-5	137.65	118.54	129.43	132.92	137.16	127.54	128.52	127.69	55.03	C=O: 157.05
E-6	138.16	117.88	130.33	135.78	136.92	127.54	128.50	127.69	55.06	C=S: 177.37
E-7	139.22	121.36	132.04	152.75	136.82	127.66	128.47	127.70	55.07	N-Phenyl: 152.07 (1), 129.01 (3, 5), 125.16 (4), 120.61 (2, 6)
Z-8[b]	140.70	113.23	132.67	137.95	137.07	127.67	128.51	127.67	54.80	
E-9	137.56	114.40	129.79	141.64	–[d]	–[d]	–[d]	–[d]	54.89	OCH_3: 60.99
Z-9	141.03	112.69	133.01	138.30	136.88	127.50	128.42	127.58	54.76	OCH_3: 61.50

[a] The long-range couplings ^3J (C-5, H-3) and ^3J (C-5, H-Im) could not be determined unambiguously due to overlap with ^3J (C-5, CH_2)

[b] Ref. [14]

[c] Not unambiguously determined due to overlap with other signals

[d] Overlap with signals of the predominant *Z*-isomer

Acknowledgement

The authors would like to express their gratitude to Mr. E. Möllner for recording the IR spectra.

Experimental

Melting points (uncorrected) were determined on a Kofler hot-stage microscope. Elemental analyses were carried out by Mikroanalytisches Laboratorium, Institute of Physical Chemistry, University of Vienna. The IR spectra were recorded on a Jasco IRA-1 spectrometer. The mass spectra were obtained on a Varian MAT 311 A spectrometer (70 eV). The NMR spectra were recorded on a Bruker AC 80 instrument (80.13 MHz for ^{1}H, 20.15 MHz for ^{13}C) equipped with an Aspect 3000 computer. Chemical shifts are reported in δ-units downfield from tetramethylsilane. Homonuclear NOE difference spectra were recorded from nondegassed solutions (approx. 0.1 *M*) at 30 °C, acquisition parameters: 8 K data points; spectral width: 1 362 Hz; acquisition time: 3 s; digital resolution: 0.33 Hz/point; pulse width: 2 μs (56°); relaxation delay: 3 s; irradiation time: 3 s; irradiation power: 45–49 L; number of scans:

$^{13}C,^{1}H$. Coupling constants (Hz)

Pyrazole C, H[a]							Iminyl $^{1}J(C,H)$	Other couplings
C-3, H-3	C-3, H-5	C-3, H-Im	C-4, H-3	C-4, H-5	C-4, H-Im	C-5, H-5		
188.7	7.1	3.1	–[c]	–[c]	–[c]	191.3		$^{1}J(CH=O)$: 174.7 $^{1}J(CH_2)$: 141.8
186.5	7.4	3.7	9.0	7.6	9.0	–[c]	160.0	$^{1}J(CH_2)$: 141.5
187.4	7.4	3.7	9.2	7.8	8.6	190.4	163.2	$^{1}J(CH_2)$: 141.2
187.2	7.2	3.6	9.1	7.7	9.1	189.8	161.9	$^{2}J(C=O,NH)$: 5.3 $^{1}J(CH_2)$: 141.0
188.4	7.1	3.8	8.9	7.8	8.9	190.5	164.1	$^{1}J(CH_2)$: 140.0 $^{2}J(C=S,NH)$: 6.4
187.4	7.4	3.8	9.2	7.7	11.5	190.0	159.7	$^{1}J(CH_2)$: 141.0
188.0	7.4	4.1	9.4	7.4	7.4	193.3	174.1	$^{1}J(CH_2)$: 140.9
187.3	7.4	4.1	9.3	7.8	6.5	190.2	164.7	$^{1}J(OCH_3)$: 143.1
188.7	7.4	4.3	9.4	7.8	6.0	193.3	174.8	$^{1}J(OCH_3)$: 143.2 $^{1}J(CH_2)$: 140.4

160–320. Acquisition parameters for the ^{1}H-coupled ^{13}C-NMR spectra ("Gated Decoupling"): 32 K data points; spectral width: 4 629 Hz; acquisition time: 3.54 s; digital resolution: 0.28 Hz/point.

(E)-1-Benzyl-1 H-pyrazole-4-carbaldehyde Phenylhydrazone (*E*-**3**)

To a solution of 186 mg (1 mmol) of **2** in 1 ml of ethanol 108 mg (1 mmol) of phenylhydrazine in 2 ml of ethanol – water (1 : 1) were added and the resulting mixture was stirred for 5 min. Upon addition of water (15 ml) a solid precipitated, which was collected by filtration, washed several times with water and dried to yield 229 mg (83%) of analytically pure colorless crystals, m.p. 113–116 °C. IR (KBr): 3 300 cm^{-1} (NH); MS (m/z): 276 (M^+, 73%), 91 (100%), 77 (14%), 65 (32%). Anal. calcd. for $C_{17}H_{16}N_4$ (276.34): C 73.89, H 5.84, N 20.27. Found: C 73.97, H 6.00, N 20.32.

(E)-1-Benzyl-1 H-pyrazole-4-carbaldehyde Benzenesulfonylhydrazone (*E*-**4**)

To a solution of 186 mg (1 mmol) of **2** in 1 ml of ethanol a solution of 172 mg (1 mmol) of benzenesulfonyl hydrazide in 1 ml of ethanol was added and the mixture was stirred at room temperature for 1.5 hours. The precipitated solid was collected, washed with cold ethanol and recrystallized from this solvent to afford 255 mg (75%) of colorless crystals, m.p. 177–180 °C. IR (KBr): 3 000 cm^{-1} (NH); MS (m/z): 340 (M^+, 6%), 171 (10%), 91 (100%), 77 (28%). Anal. calcd. for $C_{17}H_{16}N_4O_2S$ (340.40): C 59.98, H 4.74, N 16.46. Found: C 60.00, H 4.80, N 16.61.

(E)-1-Benzyl-1 H-pyrazole-4-carbaldehyde Semicarbazone (*E*-**5**)

To a solution of 186 mg (1 mmol) of **2** in 2 ml of ethanol – water (2 : 1) 90 mg (1.1 mmol) of sodium acetate in 0.5 ml of water and 111.5 mg (1 mmol) of semicarbazide hydrochloride in 0.5 ml of water were added successively. After 15 min stirring at room temperature 5 ml of water were added and the mixture was cooled. The precipitated solid was removed by filtration, washed with cold water and dried to yield 200 mg (82%) of analytically pure colorless crystals, m.p. 176–178 °C. IR (KBr): 3 450, 3 200 cm^{-1} (NH), 1 700, 1 660 cm^{-1} (C=O); MS (m/*z*): 243 (M^+, 12%), 184 (10%), 182 (14%), 91 (100%), 65 (15%). Anal. calcd. for $C_{12}H_{13}N_5O$ (243.27): C 59.25, H 5.39, N 28.79. Found: C 59.49, H 5.33, N 28.75.

(E)-1-Benzyl-1 H-pyrazole-4-carbaldehyde Thiosemicarbazone (*E*-**6**)

To a solution of 186 mg (1 mmol) of **2** in 3 ml of ethanol 100 mg (1.1 mmol) of thiosemicarbazide in 1 ml of ethanol – water (1 : 1) were added. After stirring for 15 min at room temperature the precipitated solid was filtered off, washed with cold water and recrystallized from ethanol to afford 207 mg (80%) of colorless crystals, m.p. 184–187 °C. IR (KBr): 3 380, 3 240, 3 180 cm^{-1} (NH); MS (m/*z*): 259 (M^+, 19%), 184 (14%), 91 (100%), 76 (14%), 65 (18%). Anal. calcd. for $C_{12}H_{13}N_5S$ (259.33): C 55.58, H 5.05, N 27.01. Found: C 55.67, H 4.82, N 26.90.

(E)-N-[(1-Benzyl-4-pyrazolyl)methylene] Phenylamine (*E*-**7**)

A solution of 186 mg (1 mmol) of **2** and 93 mg (1 mmol) of aniline in 3 ml of dry ethanol was heated to reflux for 30 min. After cooling, 10 ml of water were added and the resulting mixture was extracted several times with dichloromethane. The combined organic layers were washed with water, dried over anhydrous sodium sulfate and evaporated under reduced pressure to give 199 mg (76%) of a nearly colorless oil, which solidified with time. Recrystallization from diisopropyl ether afforded colorless crystals, m.p. 54–56 °C. MS (m/*z*): 261 (M^+, 44%), 260 (22%), 91 (100%), 77 (34%), 65 (32%). Anal. calcd. for $C_{17}H_{15}N_3 \cdot 3/10\ H_2O$ (266.73): C 76.55, H 5.90, N 15.75. Found: C 76.56, H 5.60, N 15.72.

1-Benzyl-1 H-pyrazole-4-carbaldoxime (**8**)

(a) To a solution of 204 mg (3 mmol) sodium ethoxide in 4 ml of dry ethanol 208 mg (3 mmol) of hydroxylamine hydrochloride in 1 ml of water and 186 mg (1 mmol) of **2** in 4 ml of ethanol were added successively. The solution was kept at room temperature for 3 days and was then poured into an excess of water. The mixture was extracted several times with dichloromethane, the combined organic layers were washed with water, dried and evaporated to dryness. The resulting solid (200 mg, 99%) consisted in a mixture of *Z*-**8** and *E*-**8** in a ~85 : 15 ratio (according to the ^{1}H-NMR spectrum). Recrystallization from diisopropyl ether – ethanol afforded 150 mg (75%) of pure *Z*-**8**.

(b) An equilibrium mixture of *Z*-**8** and *E*-**8** containing ~15% of the *E*-isomer was also obtained by the following procedure: a solution of pure *Z*-**8** in acetone-d_6 or dimethyl sulfoxide-d_6 was treated with traces of 30% DCl and the reaction was monitored by ^{1}H-NMR. After 2 h at room temperature, an equilibrium state with *Z*-**8**/*E*-**8** in a ~85 : 15 ratio was reached.

(c) For preparation of *Z*-**8** see also Ref. [14].

1-Benzyl-1 H-pyrazole-4-carbaldoxime O-Methyl Ether (**9**)

To a solution of 186 mg (1 mmol) of **2** in 2 ml of ethanol 90 mg (1.1 mmol) of sodium acetate in 0.5 ml of water and 84 mg (1 mmol) of *O*-methylhydroxylamine hydrochloride in 1 ml of ethanol – water (1 : 1) were added successively. The solution was stirred at room temperature for 20 h, then 20 ml of

water were added. The resulting mixture was extracted exhaustively with dichloromethane, the combined organic layers were washed with water, dried over anhydrous sodium sulfate and evaporated in vacuo. The residue was subjected to column chromatography (silica gel, eluent: dichloromethane – ethyl acetate, 5 : 1) to afford 100 mg (46%) of a colorless oil containing *Z*-**9** and *E*-**9** in a 5 : 1 ratio (according to ^{1}H-NMR). Due to the similar chromatographic behaviour of *Z*-**9** and *E*-**9** no further attempt was made to separate these isomers chromatographically. MS (m/*z*): 215 (M^+, 89%), 91 (100%), 65 (21%). Anal. calcd. for $C_{12}H_{13}N_3O$ (215.26): C 66.96, H 6.09, N 19.52. Found: C 66.95, H 6.11, N 19.78.

(E)-3-Pyridazinecarbaldoxime O-Methyl Ether (**11**) [16]

^{1}H-NMR (*DMSO-d*$_6$): δ (ppm) 9.22 (m, 1 H, H-6), 8.41 (s, 1 H, iminyl-H), 8.01 (m, 1 H, H-4), 7.73 (m, 1 H, H-5), 3.99 (s, 3 H, OCH_3).

(E)-4-Pyridazinecarbaldoxime O-Methyl Ether (**12**) [16]

^{1}H-NMR (*DMSO-d*$_6$): δ (ppm) 9.38 (m, 1 H, H-3), 9.26 (m, 1 H, H-6), 8.30 (s, 1 H, iminyl-H), 7.78 (m, 1 H, H-5), 3.98 (s, 1 H, OCH_3).

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