Configurational Assignments of Oximes Derived from 5-Formyl and 5-Acyl-1,2,4-triazines

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The configuration of (3-substituted)-1,2,4-triazin-5-ylcarbaldoximes and (3-substituted)alkyl-1,2,4-triazin-5-ylketoximes was determined by means of ^{1}H-nmr, ^{13}C-nmr, ^{15}N-nmr and homonuclear NOE-difference spectroscopy. Oximes resulting from reaction of 1,2,4-triazines with nitroalkanes were found to be either pure *E*-isomers or *E*/*Z*-mixtures with the amount of *E*-isomer greatly predominating. Detailed ^{13}C-nmr data of the oximes investigated are presented.

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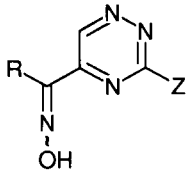
Introduction.

The 1,2,4-triazine system is characterized by its marked π-deficiency [1,2], reflected by the inability of the triazine ring to undergo electrophilic substitution and its significant vulnerability towards nucleophilic attack. Thus, many important methods useful for the preparation of functionalized 1,2,4-triazine derivatives involve nucleophilic substitution of hydrogen [3-6] or of a nucleofugal group [1] in 3-, 5- or 6-position of the heteroaromatic ring. A few years ago, we developed a versatile and also simple route to previously unknown oximes of 5-formyl and 5-acyl-1,2,4-triazines consisting of the reaction of 1,2,4-triazines with nitronate anions [7]. The reaction proceeds in a regiospecific manner *via* formation of the anionic σ-adducts which then undergo conversion into the corresponding oximes in good yields [8]. Compounds of the latter type have been shown to be of considerable synthetic utility [9]. As oximes are of particular interest as enzyme substrates - stereoselective reduction gives either *R* or *S* secondary amines depending on *E*- or *Z*-configuration of the educt - we became interested in the stereoselective synthesis of chiral alcohols and amines by enzymatic reduction (baker's yeast) of oximes containing the 1,2,4-triazine moiety [10]. In order to use substrates of defined stereochemistry in these studies, the configuration of our oximes had to be unequivocally determined. Here we report on configurational assignments with aldoximes **1-7** and ketoximes **9-17** (given in Table 1) by means of ^{1}H- and ^{13}C-nmr spectroscopy including ^{1}H{^{1}H}-NOE-difference experiments.

Table 1. Compounds Investigated

No.	R	Z
1	H	H
2	H	CH_3
3	H	OH
4	H	OCH_3
5	H	SCH_3
6	H	$SCH(CH_3)_2$
7	H	C_6H_5
9	CH_3	H
10	CH_3	OCH_3
11	CH_3	SCH_3
12	CH_3	$SCH(CH_3)_2$
13	CH_3	C_6H_5
14	CH_3CH_2	SCH_3
15	$CH_2CH_2CH_2$	$SCH(CH_3)_2$
16	$CH_3CH_2CH_2CH_2$	SCH_3
17	$CH_3CH_2CH_2CH_2$	C_6H_5



Results and Discussion.

Aldoximes **1-7**.

For configurational assignments with aldoximes and ketoximes numerous nmr-spectroscopic techniques have been used, a survey is given in ref [11]. Moreover, a new method for the determination of the stereochemistry of aldoximes has been recently reported [12]. Assignments with aldoximes are known to be simple in cases when both isomers are at hand, as the resonance of the N=CH proton in the *Z*-isomer is markedly shifted upfield compared to that of the corresponding *E*-isomer [13]. The ^{1}H-nmr spectrum of oxime **1** (^{1}H-nmr data of all compounds investigated are given in Table 2) showed two sets of signals in a ratio 100:7, the main component having the N=CH signal at higher frequencies (δ 8.13 ppm) compared to the minor isomer ($\delta_{N=CH}$ 7.65 ppm), indicating the predominating species to be the *E*-configured oxime [14]. This assignment could be shown by NOE-difference experiments according to lit [11]: irradiation of the NOH transition in **E-1** gave the corresponding N=CH singlet a

Table 2
^{1}H-NMR Data (δ, ppm, in Deuteriodimethyl Sulfoxide) of Compounds Investigated

No.	OH	H-6	Protons of R	Protons of Z
E-**1**	12.86	9.67	8.13	9.73, ^{5}J(H-3, H-6) = 2.2 Hz
Z-**1**	[a]	10.12	7.65	9.93, ^{5}J(H-3, H-6) = 2.0 Hz
E-**2**	12.77	9.49	8.08	2.75
Z-**2**	[a]	9.96	7.59	[a]
E-**3**	13.08	8.24	7.89	13.08
E-**4**	12.83	9.33	8.05	4.07
Z-**4**	[a]	9.81	7.56	[a]
E-**5**	12.86	9.33	8.04	2.61
Z-**5**	[a]	9.80	7.56	[a]
E-**6**	12.83	9.31	8.02	3.98 (SCH), 1.40 (CH_3)
Z-**6**	[a]	9.78	7.55	[a]
E-**7**	12.86	9.58	8.20	8.50-8.37 (Ph H-2,6), 7.73-7.51 (Ph H-3,4,5)
Z-**7**	[a]	10.03	7.72	[a]
E-**8**	[b,c]	9.68	8.77	8.52-8.37 (Ph H-2,6), 7.71-7.54 (Ph H-3,4,5)
E-**9**	12.65	9.71	2.17	9.71
E-**10**	12.65	9.39	2.14	4.05
E-**11**	12.67	9.37	2.12	2.61
E-**12**	12.67	9.35	2.12	3.98 (SCH), 1.41 (CH_3)
E-**13**	12.63	9.61	2.28	8.53-8.41 (Ph H-2,6), 7.68.7.52 (Ph H-3,4,5)
E-**14**	12.64	9.36	2.72 (CH_2), 1.03 (CH_3)	2.61
Z-**14**	[a]	9.46	[a] (CH_2), 1.06 (CH_3)	[a]
E-**15**	12.60	9.35	2.72 (=C-CH_2), 1.50 (CH_2), 0.88 (CH_3)	3.94 (SCH), 1.41 (CH_3)
E-**16**	12.50	9.36	2.74 (=C-CH_2), 1.70-1.16 (CH_2-CH_2), 0.86 (CH_3)	2.61
E-**17**	12.59	9.61	2.91 (=C-CH_2), 1.70-1.22 (CH_2-CH_2), 0.90 (CH_3)	8.51-8.39 (Ph H-2,6), 7.65-7.53 (Ph H-3,4,5)

[a] Overlap with signals of the predominant *E*-isomer. [b] *E*-**8** = (*E*)-*O*-Acetyl-3-phenyl-1,2,4-triazin-5-yl aldoxime. [c] δ $COCH_3$: 2.30 ppm.

marked NOE, whereas the triazine H-6 signal was only slightly affected. In contrast perturbation of the N=CH line led to an enhancement of the OH-signal. These findings are a clear proof for the spatial closeness between OH and N=CH in the main component of **1** and thus for the *E*-configuration of this species.

Aldoximes **2, 4, 5,** and **7** turned out to be nearly pure *E*-isomers, however, a second set of signals in the aromatic region of the ^{1}H-nmr spectrum can be taken as a hint that they are accompanied by small amounts (**7**: 4%, **2, 4, 5**: below 1%) of the corresponding *Z*-isomer. Whereas the resonances of the N=CH protons in the *Z*-configured compounds were shifted 0.47-0.51 ppm upfield compared to those of the corresponding *E*-isomers, for the triazine H-6 protons 0.45-0.48 ppm downfield shifts were observed. The *E*-configuration of the pure isomers **3** and **6** can be deduced on the basis of the following arguments: The chemical shift of the N=CH proton in compound **6** (δ 8.02 ppm) is in the same range with the N=CH resonances of the closely related *E*-isomers **2, 4, 5,** and **7** (δ 8.02-8.20 ppm); the small upfield shift of the N=CH proton in oxime **3** (compared to *E*-configured oximes **E-1, E-2, E-4 - E-7**) can be attributed to the electron-donating effect of the hydroxy function in 3-position of the triazine ring. Moreover, the *E*-configuration of compounds **3** and **6** as well as that of the main components of oximes **2, 4, 5,** and **7** was independently determined by NOE-difference experiments as described above for compound *E*-**1**.

Another hint for the *E*-configuration of these compounds is the similar magnitude of the ^{1}J(^{13}C, ^{1}H) coupling constants of the iminyl (N=CH) fragments (^{1}J = 172.8-174.1 Hz, for all ^{13}C-nmr data see Table 3). Such type of coupling constants are known to be strongly dependent on the position of the non-bonding electron pair of the N-atom relative to the iminyl-H (*cis*-position of lone-pair and iminyl-H leads to a 10-15 Hz larger coupling constant than the *trans*-position) [15,16]. Thus, for instance, the minor component of **7** (*Z*-**7**) exhibits a ^{1}J(N=CH) coupling constant of 184.6 Hz conclusively indicating *Z*-configuration, whereas *E*-configuration has to assigned to the main isomer *E*-**7** with a ^{1}J(N=CH) value of 173.1 Hz.

Additionally, the *E*-configuration of *E*-**7** independently follows from the coupled ^{15}N-nmr spectrum (INEPT): among the four ^{15}N-signals detected only one (δ 36.8 ppm), which can be unambiguously attributed to the triazine N-1 atom on basis of chemical shift considerations [1,17], is split by a larger coupling (^{2}J(N-1,H-6) = (−)11.9 Hz, sign not determined), all other resonances (δ 24.2 ppm, J = 3.7 Hz, oxime-N; −18.9 ppm, J = 3.3 Hz, triazine N-2; −98.6 ppm, J = 1.8 Hz, triazine N-4) show couplings smaller

Table 3
^{13}C-NMR Data of Compounds Investigated (in Deuteriodimethyl Sulfoxide)

	^{13}C-Chemical Shifts (δ, ppm)					^{13}C,^{1}H-Coupling Constants (Hz)	
	Triazine-C						
	C-3	C-5	C-6	C=N	R	Z	
***E*-1**	157.4	151.4	146.4	146.1	--	--	173.2 ($^{1}J_{N=C-H}$), [a]
***E*-2**	166.4	151.4	143.6	146.2	--	23.2	172.8 ($^{1}J_{N=C-H}$), [a]
***E*-3**	161.5	153.8	129.8	146.8	--	--	174.1 ($^{1}J_{N=C-H}$), [a]
***E*-4**	165.2	154.1	141.1	146.0	--	55.5	173.2 ($^{1}J_{N=C-H}$), [b]
***E*-5**	172.5	151.1	141.8	145.9	--	13.2	173.6 ($^{1}J_{N=C-H}$), [c]
***E*-6**	172.3	151.3	141.8	145.9	--	35.4 (SCH), 22.5 (CH_3)	173.6 ($^{1}J_{N=C-H}$), [d]
***E*-7**	162.5	151.8	144.2	146.4	--	134.4 (C-1), 131.9 (C-4), 129.1 (C-3,5), 127.8 (C-2,6)	173.1 ($^{1}J_{N=C-H}$), [e]
Z-7	[a]	[a]	147.9	142.9	--	[a]	184.6 ($^{1}J_{N=C-H}$)
***E*-9**	157.0	153.3	146.1	152.3	8.9	--	[f]
***E*-10**	165.0	155.9	140.8	152.5	8.9	55.3	[a]
***E*-11**	172.2	152.7	141.5	152.1	8.8	13.2	[g]
***E*-12**	172.1	152.9	141.4	152.1	8.8	35.4 (SCH), 22.4 (CH_3)	[h]
***E*-13**	162.1	153.4	143.9	152.6	9.0	134.5 (C-1), 131.8 (C-4), 129.0 (C-3,5), 127.7 (C-2,6)	[i]
***E*-14**	172.3	152.2	141.7	156.4	16.2 (CH_2), 10.1 (CH_3)	13.2	[j]
Z-14	173.1	150.2	146.0	151.7	25.0 (CH_2), 11.1 (CH_3)	13.2	[k]
***E*-15**	172.1	152.6	141.5	155.2	24.6 (C_α), 18.7 (C_β), 14.0 (CH_3)	35.4 (SCH), 22.4 (CH_3)	[a]
***E*-16**	172.2	152.5	141.6	155.4	27.4 (C_β), 22.2 ($C_\alpha C_\gamma$), 13.5 (CH_3)	13.1	[l]
***E*-17**	162.0	153.1	144.0	155.8	27.5 (C_β), 22.4 (C_α), 22.3 (C_γ), 13.6 (CH_3)	134.6 (C-1), 131.7 (C-4), 129.0 (C-3,5), 127.6 (C-2,6)	[a]

[a] Not determined. [b] ^{3}J(C-3, OCH_3): 3.7 Hz; ^{4}J(C-3,H-6): 1.1 Hz; ^{2}J(C-5, H-6): 8.8 Hz; ^{2}J(C-5, N=CH): 6.1 Hz; ^{1}J(C-6, H-6): 192.3 Hz; ^{3}J(C-6, N=CH): 3.8 Hz; $^{1}J(OCH_3)$: 147.8 Hz. [c] ^{3}J(C-3,SCH_3): 4.2 Hz; ^{4}J(C-3, H-6): 1.2 Hz; ^{2}J(C-5, H-6): 8.1 Hz; ^{2}J(C-5, N=CH): 6.2 Hz; ^{1}J(C-6, H-6): 192.4 Hz; ^{3}J(C-6, N=CH): 3.8 Hz; $^{1}J(SCH_3)$: 142.2 Hz. [d] ^{2}J(C-5, H-6): 8.2 Hz; ^{2}J(C-5, N=CH): 6.2 Hz; ^{1}J(C-6, H-6): 192.2 Hz; ^{3}J(C-6, N=CH): 3.8 Hz; ^{1}J(SCH): 145.8 Hz; ^{2}J(SCH, CH_3): 4.3 Hz; $^{1}J(CH_3)$: 127.5 Hz. [e] ^{3}J(C-3, Ph-H-2,6): 3.7 Hz; ^{2}J(C-5, H-6): 7.8 Hz; ^{2}J(C-5, N=CH): 6.2 Hz; ^{1}J(C-6, H-6): 191.8 Hz; ^{3}J(C-6, N=CH): 3.8 Hz. [f] ^{1}J(C-3, H-3): 207.8 Hz; ^{2}J(C-5, H-6): 7.2 Hz; ^{3}J(C-5, CH_3): 3.0 Hz; ^{1}J(C-6, H-6): 191.1 Hz; ^{4}J(C-6, H-3): 2.0 Hz; $^{1}J(CH_3)$: 130.1 Hz. [g] ^{2}J(C-5, H-6): 7.8 Hz; ^{3}J(C-5, CH_3): 3.0 Hz; ^{1}J(C-6, H-6): 192.7 Hz; ^{2}J(C=N, CH_3): 6.6 Hz; $^{1}J(SCH_3)$: 142.2 Hz; $^{1}J(CCH_3)$: 130.1 Hz. [h] ^{2}J(C-5, H-6): 7.6 Hz; ^{3}J(C-5, CH_3): 2.9 Hz; ^{1}J(C-6, H-6): 192.7 Hz; ^{2}J(C=N, CH_3): 6.9 Hz; ^{1}J(SCH): 145.5 Hz; $^{1}J(SC-CH_3)$: 127.6 Hz; $^{1}J(N=C-CH_3)$: 130.1 Hz. [i] ^{3}J(C-3, Ph-H-2,6): 3.6 Hz; ^{2}J(C-5, H-6): 7.5 Hz; ^{3}J(C-5, CH_3): 3.0 Hz; ^{1}J(C-6, H-6): 192.0 Hz; ^{2}J(C=N, CH_3): 6.8 Hz; $^{1}J(CH_3)$: 130.0 Hz. [j] ^{3}J(C-3, CH_3): 4.4 Hz; ^{5}J(C-3, H-6): 1.3 Hz; ^{2}J(C-5, H-6): 7.7 Hz; ^{3}J(C-5, CH_2): 3.6 Hz; ^{1}J(C-6, H-6): 192.6 Hz; ^{2}J(C=N, CH_2): 4.8 Hz; $^{1}J(SCH_3)$: 142.1 Hz; $^{1}J(CH_2)$: 130.8 Hz; $^{2}J(CH_2,CH_3)$: 4.2 Hz; $^{1}J(CH_3)$: 128.0 Hz; $^{2}J(CH_3, CH_2)$: 5.4 Hz. [k] ^{3}J(C-3, CH_3): 4.3 Hz; ^{5}J(C-3, H-6): 1.3 Hz; ^{1}J(C-6, H-6): 195.4 Hz; $^{1}J(CH_2)$: 127.1 Hz. [l] ^{3}J(C-3, SCH_3): 4.4 Hz; ^{5}J(C-3, H-6): 1.3 Hz; ^{2}J(C-5, H-6): 7.8 Hz; ^{3}J(C-5, CH_2): 3.6 Hz; ^{1}J(C-6, H-6): 192.6 Hz; $^{1}J(SCH_3)$: 142.1 Hz.

than 3.7 Hz. For aldoximes it is well known, that *cis*-position of the oxime-nitrogen's lone-pair and the iminyl-proton (*Z*-configuration) gives rise to a large, negative $^{2}J(^{15}N, ^{1}H)$ coupling constant (~ -15 Hz), whereas the *trans*-position (*E*-configuration) leads to a small, positive value ($\sim$ 3 Hz) [16,18,19]. Thus, the small geminal ^{15}N, ^{1}H-coupling constant in the iminyl-substructure of structure **7** (δ 24.2 ppm, J = 3.7 Hz) unequivocally calls for *E*-configuration. Analogously, *E*-configuration of *O*-acetyloxime **8**, which was obtained from reaction of **7** with acetic anhydride, could be deduced on the basis of its coupled ^{15}N-nmr spectrum (see Experimental). Chemical shift considerations ($\delta_{N=CH}$ 8.77 ppm) and NOE-difference experiments (NOE on N=CH upon irradiation of the methyl-H resonance) confirm the above assignment for compound **8**.

Ketoximes **9-17**.

A well established and widely used method for the discrimination between isomeric ketoximes is based on the γ-effect: carbon atoms being in the γ-position (α to C=N)

to a *syn* located oxime-oxygen suffer an upfield shift compared to the γ-atoms in *anti*-position due to steric compression [20,21]. However, assignments according to this method can be problematic in cases when only one isomeric form is at hand, as it is based on comparison of ^{13}C-chemical shifts between *E*- and *Z*-isomers. Although some ketoximes investigated were found to be obviously mixtures of stereoisomers, except for structure **14** the amount of the second isomer was too small (below 1%) to apply this method. However, oximation of ethyl 3-methylthio-1,2,4-triazin-5-yl ketone with hydroxylamine hydrochloride in acidic medium led to a 4:1 mixture of isomeric oximes, which now could be differentiated on the basis of their ^{13}C-chemical shifts. It turned out that the main component had the *E*-configuration (*E*-**14**, δ(CH_2) 16.2 ppm, δ (triazine C-5) 152.2 ppm, see Table 3), whereas *Z*-**14** (δ (CH_2) 25.1 ppm, δ (triazine C-5) 150.2 ppm) was the minor component. Peforming the above mentioned oximation reaction in alkaline medium gave only a single isomer identical with *E*-**14**, which was also obtained as a single isomer upon reaction of 3-methylthio-1,2,4-triazine with the ethyl nitronate anion according to ref [7].

Oximes derived from methyl 1,2,4-triazin-5-yl ketones (compounds **9-13**) turned out to consist practically of one isomeric form [22]. In such cases, NOE-difference spectroscopy was proven to be a valuable method for configurational assignments on the condition that the molecule bears protons suitable as probes for the detection of distinct through-space connectivities [11,23]. Thus, for instance, irradiation of the methyl transition in oxime **9** gave large NOEs to the OH proton as well as the triazole H-6 (Figure 2), the former interaction being evidence for spatial closeness of the OH and the methyl groups and thus for the *E*-configuration. In contrast, irradiation of the OH-line enhanced the methyl signal.

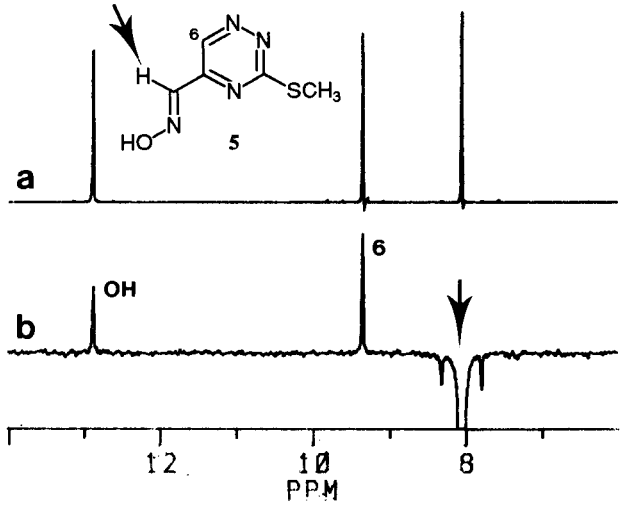


Figure 1. a) ^{1}H-nmr spectrum of **5** (deuteriodimethyl sulfoxide, 6.0-14.0 ppm), b) NOE-difference spectrum of **5** resulting from irradiation of the iminyl-H resonance.

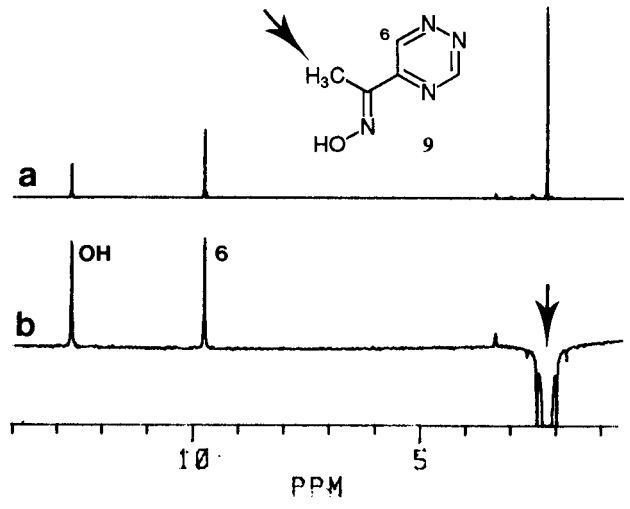


Figure 2. a) ^{1}H-nmr spectrum of **9** (deuteriodimethyl sulfoxide), b) NOE-difference spectrum of **9** resulting from irradiation of the methyl transition.

Analogously, NOE-difference experiments enabled us to assign the *E*-configuration also to structures **10-13**. This could be further confirmed considering the chemical shifts of the methyl-C atoms in compounds **9-13** (δ 8.8-9.0 ppm, Table 3), which closely resemble those obtained for other oximes of similar type having the methyl group and the OH-group in the *syn*-position [24].

Compounds **15-17**, characterized by longer acyl moieties, also were present in one isomeric form [22]. Comparison of the ^{13}C-chemical shifts of the alkyl chain with literature data of related oximes (CSEARCH, [24]) rather point to *E*-configuration of these compounds. This suspicion is confirmed by the fact that oxime **15** and its despropylene congener **12**, which is unambiguously *E*-configured as outlined above, exhibit nearly identical chemical shifts for the carbon atoms of the triazine part (Table 3). A completely parallel trend was also observed for the homologues **16** and **11** as well as for **15** and **13**. Additionally, NOE-difference experiments (irradiation of OH, NOE on N=C-CH_2) also give a hint that oximes **15-17** have the acyl-chain and the hydroxyl group in the *cis*-position.

In summary, from our nmr-spectroscopic investigations it emerged, that oximes **1-7** and **9-17**, obtained mainly from reaction of (3-substituted)-1,2,4-triazines with nitronate anions according to ref [7], were either pure *E*-isomers or *E*/*Z*-mixtures with very low amounts of *Z*-isomers.

In Table 3 detailed ^{13}C-nmr data of the investigated oximes are presented, including also a number of ^{13}C, ^{1}H coupling constants. Assignments of chemical shifts are based on multiplicity selection by the J-modulated spin-

echo technique [25], on coupling information obtained from fully ^{1}H-coupled ^{13}C-nmr spectra, on selective heteronuclear decoupling experiments irradiating unambiguously assigned ^{1}H-nmr lines as well as on comparison with literature data [1].

EXPERIMENTAL

Melting points were determined on a Büchi melting point apparatus and are uncorrected. The ir spectra were recorded on a Unicam SP-200 instrument. The nmr spectra were recorded from deuteriodimethyl sulfoxide solutions on a Bruker AC-80 spectrometer (spectrometer frequency for ^{1}H: 80.13 MHz, for ^{13}C: 20.15 MHz) or on a Bruker AM 400 WB instrument (spectrometer frequency for ^{1}H: 400.14 MHz, for ^{13}C: 100.61 MHz). The INEPT ^{15}N-nmr spectra of compounds **7** and **8** (in deuteriodimethyl sulfoxide) were obtained on a Bruker AM 500 instrument, chemical shifts were related to nitromethane as the reference. NOE-difference experiments were performed at 30° from non-degassed solutions using the frequency cycling method of Kinns and Sanders (Bruker NOEMULT) [25]; acquisition parameters: 8 K data points; spectral width: 1441 Hz; acquisition time: 2.84 s; digital resolution: 0.35 Hz/data point; pulse width: 3 μs (90°); relaxation delay 0.5 s; pre-irradiation time: 5 s; irradiation power: 55-59 dB below 0.2 W; number of scans: 64-400. The ^{1}H-coupled ^{13}C-nmr spectra were obtained with the gated decoupling mode (digital resolution 0.5 Hz/data point). The $^1J(^{13}C, ^1H)$ spin coupling constant of the iminyl N=CH fragment in aldoximes 1-7 was also determined considering the ^{13}C-satellites of the N=CH singlet in the ^{1}H-nmr spectra of these compounds.

The synthesis of oximes **1, 2, 7, 11,** and **13** is described in ref [7], all other oximes (except *Z*-**14** and *E*-**14** see below) were prepared similarly, details will be published in our forthcoming paper [9].

(*E*)-1-(3-Methylthio-1,2,4-triazin-5-yl)propanonoxime (*E*-**14**).

Compound *E*-**14** was prepared from 3-methylthio-1,2,4-triazine and nitropropane according to the procedure given in ref [7], yield 65%, mp 153-154° (ethanol-water).

Anal. Calcd. for $C_7H_{10}N_4OS$: C, 42.41; H, 5.08; N, 28.26. Found: C, 42.51; H, 5.05; N, 28.34.

Reaction of Ethyl 3-Methylthio-1,2,4-triazin-5-yl Ketone with Hydroxylamine Hydrochloride in Acidic Medium.

Ethyl 3-methylthio-1,2,4-triazin-5-yl ketone [9] (183 mg, 1 mmole) was added to a solution of hydroxylamine hydrochloride (75 mg, 1.1 mmoles) and sodium acetate trihydrate (150 mg, 1.1 mmoles) in 10 ml of dry ethanol. After stirring at room temperature for 24 hours, the precipitate was filtered off and recrystallized from ethanol-water to afford 110 mg (60%) of a mixture consisting of oximes *E*-**14** and *Z*-**14** (ratio 4:1 according to ^{1}H-nmr analysis), mp 147-153°.

Anal. Calcd. for $C_7H_{10}N_4OS$: C, 42.41; H, 5.08; N, 28.26. Found: C, 42.68; H, 5.13; N, 27.94.

Reaction of Ethyl 3-Methylthio-1,2,4-triazin-5-yl Ketone with Hydroxylamine Hydrochloride in Alkaline Medium.

Ethyl 3-methylthio-1,2,4-triazin-5-yl ketone [9] (183 mg, 1 mmole) was added to a solution of hydroxylamine hydrochloride (68 mg, 1 mmole) and sodium hydroxide (80 mg, 2 mmoles) in 8 ml of water. After stirring for one hour at room temperature, the mixture was neutralized with acetic acid. The precipitate was filtered off and recrystallized from ethanol-water to give prisms of the pure oxime *E*-**14** (150 mg, 75%), mp 153-154°.

Anal. Calcd. for $C_7H_{10}N_4OS$: C, 42.41; H, 5.08; N, 28.26. Found: C, 42.49; H, 5.01; N, 28.16.

(*E*)-*O*-Acetyl-(3-phenyl-1,2,4-triazin-5-yl)methylidenehydroxylamine (*E*-**8**).

To a solution of **7** (200 mg, 1 mmole) and pyridine (112 mg, 1.1 mmoles) in 5 ml of benzene, acetic anhydride (87 mg, 1.1 mmoles) was added at room temperature and the resulting reaction mixture was stirred for one hour. Then the solvent was evaporated *in vacuo* and the crude product was purified by column chromatography (silica gel, eluent: chloroform) to give 206 mg (85%) of **8**, mp 130-131°; ^{1}H-nmr (deuteriochloroform): δ 9.78 (s, 1H, triazine H-6), 8.59-8.54 (m, 2H, Ph H-2,6), 8.47 (s, 1H, N=CH), 7.60-7.58 (m, 3H, Ph H-3,4,5), 2.32 (s, 3H, CH_3); ^{15}N-nmr (deuteriodimethyl sulfoxide): δ 42.1 (triazine N-1, ^2J = 11.8 Hz), 6.7 (oxime-N, ^2J = 1.9 Hz), −9.7 (triazine N-2), −95.1 (triazine N-4, ^3J = 3.7 Hz); ir (potassium bromide): cm^{-1} 1795 ($CH_3C=O$); ms: m/z 242 (M^+).

Anal. Calcd. for $C_{12}H_{10}N_4O_2$: C, 59.50; H, 4.16; N, 23.13. Found: C, 59.40; H, 4.13; N, 22.95.

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REFERENCES AND NOTES

[1a] V. N. Charushin, S. G. Alexeev, O. N. Chupahkin and H. C. van der Plas, *Adv. Heterocyclic Chem.*, **46**, 73 (1989); [b] H. Neunhoeffer, Comprehensive Heterocyclic Chemistry, Vol **3**, A. R. Katritzky and C. W. Rees, eds, Pergamon Press, Oxford, 1984, p 385.

[2] W. W. Paudler and M. V. Jovanovic, *Org. Magn. Reson.*, **19**, 192 (1982).

[3] S. Konno, M. Sagi, N. Yoshida and H. Yamanaka, *Heterocycles*, **26**, 3111 (1987).

[4] S. Konno, S. Ohba, M. Sagi and H. Yamanaka, *Heterocycles*, **24**, 1243 (1986).

[5] A. Rykowski and H. C. van der Plas, *Synthesis*, 884 (1985).

[6] A. Rykowski and M. Makosza, *Liebigs Ann. Chem.*, 627 (1988).

[7] A. Rykowski and M. Makosza, *Tetrahedron Letters*, **25**, 4795 (1984).

[8] M. Makosza, *Polish J. Chem.*, **66**, 3 (1992).

[9] A. Rykowski, E. Guzik, P. van Ly and M. Makosza, results will be submitted for publication to *J. Heterocyclic Chem.*, **30**, (1993).

[10] A. Rykowski, E. Guzik, P. Guzik and E. Olender, poster presentation at the XVth European Colloquium on Heterocyclic Chemistry, Noordwijkerhout, the Netherlands, July 1992, book of abstracts, p 82.

[11] G. Heinisch and W. Holzer, *Tetrahedron Letters*, **31**, 3109 (1990).

[12] J.-M. Coustard, J.-C. Jacquesy and B. Violeau, *Tetrahedron Letters*, **33**, 939 (1992).

[13] W. D. Phillips, *Ann. N. Y. Acad. Sci.*, **70**, 817 (1958); E. Lustig, *J. Phys. Chem.*, **65**, 491 (1961); G. J. Karabatsos, R. A. Taller and F. M. Vaine, *J. Am. Chem. Soc.*, **85**, 2326 (1963); G. J. Karabatsos and R. A.

Taller, *Tetrahedron*, **24**, 3347 (1968).

[14] The *E*/*Z*-mixture of compound **1** as well as those of all other oxime mixtures investigated in this study showed only one signal for the OH-protons of *E*- and *Z*-isomer.

[15] H.-O. Kalinowski, S. Berger and S. Braun, ^{13}C-NMR-Spektroskopie, Georg Thieme Verlag, Stuttgart - New York, 1984, p 457.

[16] V. M. S. Gil and W. von Philipsborn, *Magn. Reson. Chem.*, **27**, 409 (1989).

[17] S. Berger, S. Braun and H.-O. Kalinowski, NMR-Spektroskopie von Nichtmetallen, Band 2: ^{15}N-NMR-Spektroskopie, Georg Thieme Verlag, Stuttgart - New York, p 55.

[18] Ref 17, p 86.

[19] D. Crepaux and J. M. Lehn, *Org. Magn. Reson.*, **7**, 524 (1975).

[20] Ref 15, p 220.

[21] G. E. Hawkes, K. Herwig and J. D. Roberts, *J. Org. Chem.*, **39**, 1017 (1974); G. C. Levy and G. L. Nelson, *J. Am. Chem. Soc.*, **94**, 4897 (1972).

[22] With oximes **10**, **12-15**, and **17** the appearance of an additional singlet-signal in the range of the triazole H-6 shifts (δ 9.46-9.71 ppm) was observed. However, due to the very low intensity of this signal (below 1%) and obvious overlap of other resonances belonging to this additional species with signals of aliphatic and OH protons of the main component, the suspicion that small amounts of corresponding *Z*-isomer are also present, could not unequivocally be proved on the basis of ^{1}H-nmr or ^{13}C-nmr spectra.

[23] G. Heinisch and W. Holzer, *Collect. Czech. Chem. Commun.*, **56**, 2251 (1991).

[24a] Sadtler Collection, Sadtler Research Laboratories, Philadelphia, PA, USA; [b] H. Kalchhauser and W. Robien, *J. Chem. Inform. Comput. Sci.*, **25**, 103 (1985).

[25] C. LeCocq and J.-Y. Lallemand, *J. Chem. Soc., Chem. Commun.*, 150 (1981).

[26] M. Kinns and J. K. M. Sanders, *J. Magn. Reson.*, **56**, 518 (1984).