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On the Structure of Guanylhydrazones Derived from Aromatic Aldehydes

Wolfgang Holzer[1,*] and **Zoltán Györgydeák**[2]

[1] Institut für Pharmazeutische Chemie, Universität Wien, A-1090 Wien, Austria
[2] Department of Organic Chemistry, University of Debrecen, H-4010 Debrecen, Hungary

Summary. The synthesis of some novel guanylhydrazones derived from aromatic aldehydes (benzylideneaminoguanidines) is described. Structural assignments of these compounds as well as of some already known congeners, particularly with respect to the configuration of the HC=N double bond, were achieved using ^{1}H- and ^{13}C-NMR data as well as homonuclear NOE difference spectroscopy.

Keywords. Benzaldehyde guanylhydrazones, substituted Benzylideneaminoguanidines; ^{1}H-NMR spectroscopy; ^{13}C-NMR spectroscopy; NOE Difference spectroscopy.

Zur Struktur von Guanylhydrazonen aromatischer Aldehyde

Zusammenfassung. Die Synthese einiger neuer Guanylhydrazone abgeleitet von aromatischen Aldehyden (Benzylidenaminoguanidine) wird beschrieben. Die Strukturzuordnung bei diesen Verbindungen sowie bei einigen literaturbeschriebenen Analoga – besonders im Hinblick auf die Konfiguration an der HC=N Doppelbindung – erfolgte mittels ^{1}H- und ^{13}C-NMR Spektroskopie sowie mit Hilfe homonuklearer NOE-Differenzspektroskopie.

Introduction

The strongly basic guanidine function is part of many biologically active compounds. Interesting species containing this substructure are condensation products of aminoguanidine with aldehydes or ketones ("guanylhydrazones", "alkylideneaminoguanidines", "diaminomethylenehydrazones", Chem. Abstr.: "2-alkylenecarboximidamides") due to antihypertensive [1 – 5], cardiac [6], antiviral [7], antibacterial [3, 8], antimalarial [9], trypanocidal [10], antileukemic [11], antimitotic [12], CNS depressant [13, 14], antisecretory antidiarrheal [15], and some other activities observed. An important representative of this class of compounds is the centrally acting antihypertensive agent Guanabenz (2,6-dichlorobenzaldehyde guanylhydrazone, **4**), which is used in form of its monoacetate (Guanabenz acetate, **4** · *Ac*OH) in the treatment of high blood pressure [16]. In view of this fact also a number of closely related congeners have been synthesized for biological testing (structural modifications on the benzene part, introduction of substituents onto the guanidine moiety).

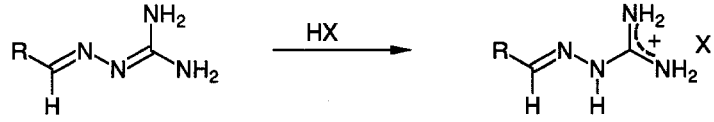
Compared to the well known biological aspects, so far relatively little attention has focussed on the stereochemistry of guanylhydrazones - usually these compounds can exist as *E*- or *Z*-isomers; only a few investigations in this regard can be found in the literature (e. g. for guanylhydrazones of isatine [17], of 2,6-dichlorobenzaldehyde [18, 19], of testosterone [20], of indanone [15] and tetralone [15]).

The present study is mainly devoted to NMR spectroscopic studies with compounds related to Guanabenz (see formulas), resulting from reaction of aromatic aldehydes with (substituted) aminoguanidines or from N-alkylation (or N-acylation) of N-unsubstituted guanylhydrazones, carried out particularly in order to elucidate the configuration of the *Ar*-C=N- double bond.

Results and Discussion

Syntheses

The synthesis of guanylhydrazones carrying no substituent at the guanidine moiety (compounds **1** – **6**, **15**) was achieved following conventional methods: from reaction of the appropriate aldehydes with aminoguanidine salts (bicarbonate, hydrochlo-



ride, acetate) guanylhydrazone salts were obtained, which were transformed into the corresponding bases by treatment with diluted KOH, NaOH or ammonia. N-Methyl compounds **7** and **8** were prepared by reaction of benzaldehyde or 2,6-dichlorobenzaldehyde, respectively, with 1-amino-3-methylguanidine hydroiodide followed by treatment with 2 *N* KOH. Structures **9** and **10** resulted from acetylation of **1** or **6** with acetic anhydride, whereas compounds **11, 12**, and **13** were obtained upon treatment of **1, 2**, or **11** with iodomethane. Compound **14** was obtained from reaction of **11** with benzoyl chloride. The preparation of compounds **16** and **17** was carried out by reaction of 2,6-dichlorobenzaldehyde with the appropriate heterocyclic substituted hydrazines. In all these cases, from reaction of (subst.) benzaldehyde (or 4-pyridinecarbaldehyde) with (subst.) aminoguanidine the resulting guanylhydrazones were obtained as single isomers. Finally, compound (*Z*)-**4** · *Ac*OH was prepared by UV-irradiation of **4** · *Ac*OH.

Spectroscopic Investigations

The utility of NOE difference spectroscopy for the determination of the stereochemistry with compounds containing a C=N bond has been recently demonstrated [21 – 23]. This approach turned out to be advantageous particularly in cases when only one isomeric form is at hand, as it does not require comparison of chemical shifts or coupling constants between *E*- and *Z*-isomer. As – except the pair **4** · *Ac*OH/(*Z*)-**4** · *Ac*OH – all compounds investigated throughout this study are present as single isomers, the NOE method was applied to guanylhydrazones **1** – **17**. Irradiation of the N-CH_3 resonance in compound **12** led to a strong enhancement of the corresponding N=CH singlet, indicating spatial closeness of these two spins and thus (*E*)-configuration (Fig. 1 a, b). In an analogous manner, (*E*)-configuration was

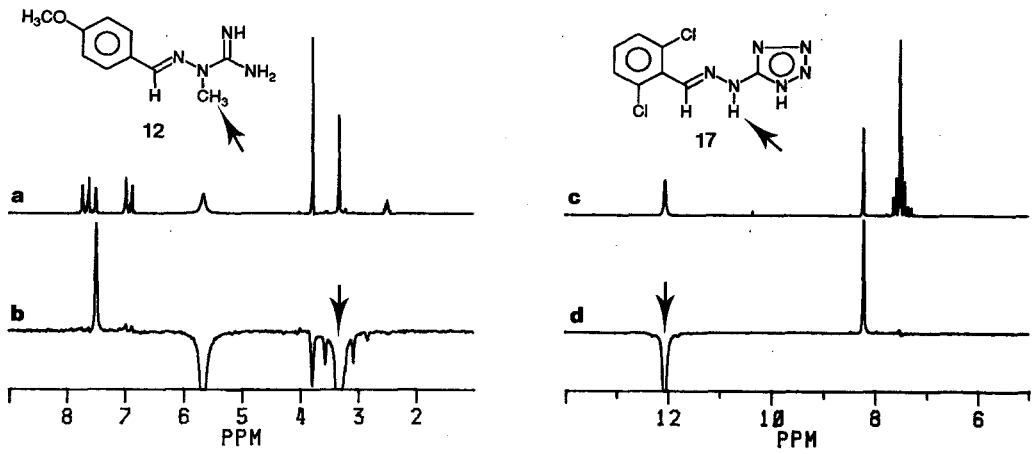


Fig. 1. *a* ^{1}H-NMR spectrum of **12** (*DMSO-d_6*), *b* NOE-difference spectrum of **12** resulting from irradiation of NCH_3, *c* ^{1}H-NMR spectrum of **17** (*DMSO-d_6*), *d* NOE-difference spectrum of **17** resulting from irradiation of "guanidine"-NH

Table 1. ^{1}H-NMR data (δ, ppm, in *DMSO-d_6*) and NOE data of compounds investigated

No.	N=CH	aromatic H	other H	irrad.[a]	NOE on[b]
1	7.98	7.72-7.60 (2,6), 7.44-7.21 (3,4,5)	5.89 (NH_2), 5.53 (NH_2)	NH_2(both)	N=CH (w)
1·HNO$_3$	8.15	7.92-7.80 (2,6), 7.52-7.40 (3,4,5)	11.49 (NH), 7.66 (NH_2, NH_2)	NH[c]	N=CH[c](m)
2	7.95	7.64-7.50 (2,6), 6.94-6.83 (3,5)	5.79 (NH_2), 5.40 (NH_2), 3.75 (OCH_3)	NH_2(both)	N=CH (m)
3	8.21	8.30-7.30 (3,4,5,6)	6.01 (NH_2), 5.82 (NH_2)	NH_2(both)	N=CH (m)
3·HNO$_3$	8.58	8.45-7.65 (3,4,5,6)	11.93 (NH), 7.78 (NH_2, NH_2)	NH	N=CH (s)
4	8.18	7.53-7.13 (3,4,5)	5.83 (NH_2), 5.75 (NH_2)	NH_2	N=CH (w)
4·AcOH	8.20	7.55-7.17 (3,4,5)	11.00-9.50 (NH), 6.32 (NH_2, NH_2), 1.86 (Ac)	NH_2 (NH)	N=CH (s)
Z-4·AcOH	7.20	7.52-7.24 (3,4,5)	10.00-8.00 (NH), 6.15 (NH_2, NH_2), 1.83 (Ac)	NH_2 (NH)	-[d]
5	7.92	6.98 (2,6)	5.94 (NH_2), 5.50 (NH_2), 3.80 (3,5-OCH_3), 3.65 (4-OCH_3)	NH_2(both)	N=CH (w)
6·AcOH	8.24	8.19 (6), 7.56 (3), 7.36 (5)	7.20-6.10 (NH_2, NH_2, NH), 1.85 (Ac)	N=CH	NH_2 (s)
7	8.04	7.73-7.57 (2,6), 7.40-7.20 (3,4,5)	5.78 (NH_2, NH), 2.70 (CH_3)	NH_2 (NH)	N=CH (w)
8	8.23	7.53-7.13 (3,4,5)	6.01 (NH), 5.76 (NH_2), 2.72 (CH_3)	NH_2 (NH)	N=CH (w)
9	8.16	7.84-7.72 (2,6), 7.40-7.27 3,4,5)	10.48 (NH), 8.00-6.70 NH_2), 2.04 (CH_3)	NH	N=CH (w)
9·0.5H$_2$SO$_4$	8.29	7.92-7.80 (2,6), 7.46-7.38 (3,4,5)	9.00-7.00 (NH_2, NH), 2.14 (CH_3)	---[e]	---
10	8.57	8.30 (6), 7.70 (3), 7.52 (5)	10.50 (NH), 10.15 (NH)	NH (both)	N=CH (w)
11·HI	8.16	8.02-7.90 (2,6), 7.49-7.40 (3,4,5)	7.85 (NH_2, NH_2), 3.42 (CH_3)	CH_3	N=CH (s)
12	7.49	7.72-7.64 (2,6), 6.98-6.89 (3,5)	5.64 (NH_2, NH), 3.77 (OCH_3), 3.31 (NCH_3)	NCH_3	N=CH (s)
13	7.54	7.81-7.69 (2,6), 7.44-7.29 (3,4,5)	6.50-4.00 (NH, NH), 3.33 (CH_3), 2.75 (CH_3=R^9)	NCH_3(3.3)	N=CH (s)
14	8.06	8.02-7.90 (2,6), 7.50-7.35 (3,4,5)	9.80 (NH), 8.25 (NH), 8.23-8.11 (benzoyl-2,6), 7.50-7.35 (benzoyl-3,4,5), 3.68 (CH_3)	NCH_3	N=CH (s)
15	7.92	8.49-8.41 (p-2,6), 7.62-7.54 (p-3,5)	6.10 (NH_2), 5.76 (NH_2)	NH_2(both)	N=CH (w)
16	8.31	7.63-7.27 (3,4,5)	11.00 - 9.70 (NH, OH), 5.51 (C=CH), 2.09 (CH_3)	NH[c]	N=CH[c] (s)
17	8.21	7.63-7.25 (3,4,5)	16.00-14.00 (NH tetrazole), 12.05 (NH)	NH[c](12.05)	N=CH[c] (s)

[a] Due to chemical exchange between different types of NH_2 or NH protons it is not possible to irradiate one type of NH_2 or NH selectively (saturation transfer). This is made clear by entries such as "NH_2 (both)" or "NH_2 (NH)" in column "irrad."

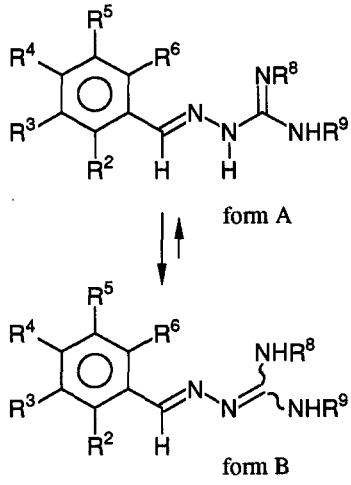
[b] w = weak, m = medium, s = strong enhancement

[c] Entries in column "irrad." and "NOE on" can be interchanged (reverse NOE experiment performed)

[d] Very weak enhancement of the N=CH signal

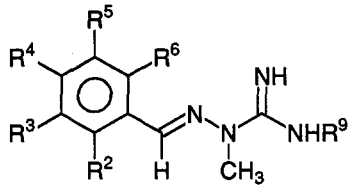
[e] No selective irradiation possible (overlap of NH, NH_2-signals with aromatic H and N=CH)

also assigned to compounds **11** · HI, **13**, and **14** due to intensive through-space connections between the guanidine N^1-methyl group and the N = CH proton. With compounds **16** and **17**, in which the guanidine system is incorporated into a heterocyclic system, the N = CH proton received a strong NOE upon irradiation of the NH transition, again unambiguously indicating these species to be (*E*)-isomers (Fig. 1 c, d).



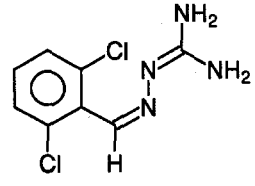
1 - 10

No.	R^2	R^3	R^4	R^5	R^6	R^8	R^9
1	H	H	H	H	H	H	H
2	H	H	OCH_3	H	H	H	H
3	NO_2	H	H	H	H	H	H
4	Cl	H	H	H	Cl	H	H
5	H	OCH_3	OCH_3	OCH_3	H	H	H
6	Cl	H	Cl	H	H	H	H
7	H	H	H	H	H	H	CH_3
8	Cl	H	H	H	Cl	H	CH_3
9	H	H	H	H	H	H	$COCH_3$
10	Cl	H	Cl	H	H	$COCH_3$	$COCH_3$

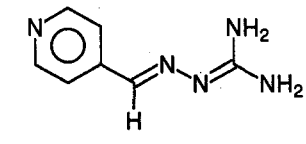


11 - 14

No.	R^2	R^3	R^4	R^5	R^6	R^9
11	H	H	H	H	H	H
12	H	H	OCH_3	H	H	H
13	H	H	H	H	H	CH_3
14	H	H	H	H	H	COPh



Z-4



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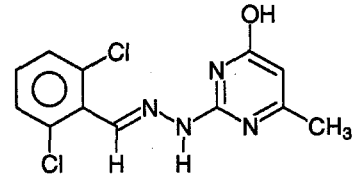

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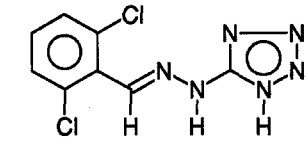

17

Table 2. ^{13}C-NMR data of compounds investigated (solvent: *DMSO-d_6*)

^{13}C chemical shifts (δ, ppm)										^{13}C,^{1}H coupling constants (Hz)	
No.	C-1	C-2	C-3	C-4	C-5	C-6	N=CH	N-C-N	other C	^{1}J(N=CH)[a]	other couplings
1	136.9	126.2	128.4	127.8	128.4	126.2	143.4	160.7	---	159.6	---
1·HNO$_3$	135.5	127.7	128.8	130.7	128.8	127.7	147.3	155.4	---	165.1	---
2	129.6	127.6	113.9	159.3	113.9	127.6	143.5	160.2	55.1 (OCH_3)	159.3	$^{1}J(OCH_3)$: 144.4
3	130.7	147.3	124.0	127.8	132.4	127.8	137.0	161.8	---	169.5	---
4	131.8	133.3	129.2	128.7	129.2	133.3	137.5	161.5	---	166.4	---
4·AcOH	130.5	133.8	129.1	130.5	129.1	133.8	139.8	158.2	173.7 (C=O), 22.1 (CH_3)	170.4	$^{1}J(CH_3)$: 127.5
Z-4·AcOH	134.1	133.2	127.9	130.4	127.9	133.2	136.5	160.0	173.2 (C=O), 22.0 (CH_3)	188.8	---
5	132.5	103.6	153.0	137.7	153.0	103.6	143.5	160.4	60.0 (4-OCH_3), 55.8 (3,5-OCH_3)	160.6	^{1}J(4-OCH_3): 144.1 ^{1}J(3,5-OCH_3):144.4
6·AcOH	132.8[c]	131.5[c]	129.0	133.9	127.4	128.3	138.7	158.8	175.1 (C=O), 23.2 (CH_3)	167.1	$^{1}J(CH_3)$: 126.8
7	137.0	126.2	128.3	127.7	128.3	126.2	144.1	160.4	27.4 (NCH_3)	160.0	$^{1}J(NCH_3)$: 136.6
8	131.8	133.3	129.0	128.6	129.0	133.3	138.4	161.2	27.3 (NCH_3)	166.3	$^{1}J(NCH_3)$: 136.7
9	135.7	127.1	128.4	129.1	128.4	127.1	149.4	155.9	172.6 (C=O), 23.9 (NCH_3)	160.8	
9·0.5H$_2$SO$_4$	133.7	127.8	128.6	130.6	128.6	127.8	150.7	152.9	172.7 (C=O), 24.1 (NCH_3)	162.0	$^{1}J(NCH_3)$: 129.4
10	134.4[c]	130.5[c]	129.2	135.7	127.6	129.7	150.8	147.2	170.0 C=O), 169.5 (C=O), 24.7 (NCH_3), 24.1 (NCH_3)	168.0	---
11·HI	133.3	128.0	128.4	130.3	128.4	128.0	144.6	155.8	32.0 (NCH_3)	165.8	$^{1}J(NCH_3)$: 141.1
12	128.5	127.6	114.0	159.4	114.0	127.6	133.4	156.8	55.1 (OCH_3), 28.7 (NCH_3)	162.2	$^{1}J(OCH_3)$: 144.3 $^{1}J(NCH_3)$: 138.5
13	135.9	126.2	128.4	127.9	128.4	126.2	132.7	154.3	30.9 (NCH_3=R^9), 29.1 (NCH_3)	162.8	$^{1}J(NCH_3)$: 138.5 $^{1}J(NCH_3$=$R^9)$:134.0
14	134.4		131.0 - 127.4[b]				141.3	159.3	176.0 (C=O), 138.4 (Ph' C-1)· 131.0-127.4 (Ph'-C)[b], 29.4 (NCH_3)	[c]	---
15	---	149.6	120.4	144.3	120.4	149.6	140.3	161.9	---	163.0	---
16	129.8	133.8	129.2	130.6	129.2	133.8	140.2	152.3	161.9 (C-O), 161.4 (-C-CH_3), 101.1 (OC-CH), 21.9 (CH_3)	169.8	---
17	130.5	134.0	128.9	130.9	128.9	134.0	138.6	156.1		172.0	---

[a] In many cases this coupling constant can be easily extracted from the ^{1}H-NMR spectra considering the ^{13}C-satellites of the N=CH singlet

[b] An unambiguous assignment of the signals due to C-2, C-3, C-4, C-5, and C-6 of both phenyl groups of **14** was not possible

[c] Not unambiguously assigned

In the ^{1}H-NMR spectra of compounds **1**−**5** and **15** (carrying no substituents on the guanidine moiety) two different singlet signals due to NH protons were observed (relative intensity 2:2). Irradiation of these NH_2-resonances gave the corresponding N=CH signals only weak to medium NOEs [24]. In the ^{1}H-NMR spectra of the corresponding salts (**1** · HNO_3, **4** · *Ac*OH, (*Z*)-**4** · *Ac*OH), an additional NH-signal (δ 8 − 12 ppm, relative intensity 1) occurs, whereas the two original NH_2 signals collapse to one singlet of relative intensity 4. Irradiation of this additional NH resonance (or the NH_2-signal [24]) now leads to a remarkably stronger NOE on the N=CH signal than irradiation of the NH_2-resonances of the corresponding free bases does (see NOE data in Table 1). All these observations are a strong hint that the free bases **1**−**5** and **15** preferably exist as structures B (see formulas) in *DMSO-d_6* solution. According to Scheme 1, protonation of the guanidine C=N nitrogen in the corresponding salts then gives rise to two equivalent NH_2-groups. The spatial closeness between the NH and the N=CH proton in salts **1** · HNO_3, **3** · HNO_3, and **4** · *Ac*OH provides a plausible explanation for the larger NOEs observed with these species compared to that of the corresponding bases **1**, **3**, and **4**.

The above mentioned through-space connections between NH (NH_2) and N=CH protons also call for (*E*)-configuration of compounds **1**–**5** and **15** as well as of their salts. This is confirmed by the observation that in contrast to **4** · *Ac*OH, with (*Z*)-**4** · *Ac*OH – obtained from **4** · *Ac*OH by UV-induced isomerisation [18] – only a very weak NOE on the N=CH singlet could be observed upon irradiation of the NH_2 (NH) protons (compare also Ref. [18]). (*E*)-Configuration of compounds **1**, **1** · HNO_3, and **2** can be further concluded by the observation that the values of the ^1J(N=**C-H**) spin coupling constant in these compounds are in the same range than those of their N-methyl congeners **11** · HI, **12**, and **13** (which are unambiguously (*E*)-configurated due to very strong NOEs between NCH_3 and N=CH as discussed above). The dependence of this coupling constant on the position of the nitrogen's lone pair relative to the N=CH proton is well documented in the literature [25]: *cis*-position of lone-pair and N=C-H proton, (*Z*)-configuration, gives a 10–20 Hz larger coupling constant than *trans*-position does (compare also Table 2: ^1J(N=**C-H**) of **4** · *Ac*OH: 170.4 Hz, ^1J(N=**C-H**) of (*Z*)-**4** · *Ac*OH: 188.8 Hz).

Configurational assignments for compounds **7**–**10**, characterized by methyl or acetyl substituents attached to the terminal amino function(s), were achieved following the considerations discussed above. Although the only weak NOEs on the N=CH proton upon perturbation of the NH_2 (NH) transitions do not permit an unambiguous determination of stereochemistry, the magnitude of the ^1J(N=**C-H**) coupling constant as well as the chemical shift of the N=CH proton does. Thus, for instance, ^1J(N=**C-H**) values of compound **7** (160.0 Hz) and **8** (166.3 Hz) are nearly identical with those of their (*E*)-configurated des-methyl congeners **1** (159.6 Hz) and **4** (166.4 Hz), assigning also (*E*)-configuration to **7** and **8**. This is confirmed by very similar chemical shifts of the N=**C-H** proton of **7** (δ 8.04 ppm) and **8** (δ 8.23 ppm) compared to those of **1** (δ 7.98 ppm) and **4** (δ 8.18 ppm). It is known from the literature [26] that in compounds of type *R*CH=N-N′*R*′*R*″ the chemical shift of the N=CH proton is strongly dependent on the configuration at the N=C bond: in (*E*)-configurated species the signal of this proton is remarkably shifted downfield compared to the corresponding (*Z*)-isomer due to the anisotropy effect of the lone-pair of N′ being in *cis*-position (compare Table 1, **4** · *Ac*OH: $\delta_{N=CH}$ 8.20 ppm, (*Z*)-**4** · *Ac*OH: $\delta_{N=CH}$ 7.20 ppm). However, as the chemical shift of the N=CH proton is also markedly influenced by the nature of substituents *R*, *R*′, and *R*″ (compare also Table 1), this approach can only be used for configurational assignments when comparing very closely related species. On the basis of similar arguments, ^1J(N=**C-H**) and $\delta_{N=CH}$, also the stereochemistry, (*E*)-configuration, of structures **9** and **10** was determined.

The observation that (*E*)-configurated compounds **8**, **9**, and **10** exhibit two different signals for the amino protons (relative intensity for **8** and **9**: 1 : 2, for **10**: 1 : 1) together with the results of the NOE difference experiments (weak through-space connections between NH (or NH_2) and N=**C-H**) again is indicative for the presence of these compounds in tautomeric form **B** in *DMSO-d*$_6$ solution.

The ^{13}C chemical shifts of compounds **1**–**17** are given in Table 2. Assignments are resting on multiplicity selection by the *J*-modulated spin-echo technique [27], on selective heteronuclear decoupling experiments irradiating unambiguously assigned ^{1}H-NMR signals as well as on coupling information obtained from fully ^{1}H-coupled ^{13}C-NMR spectra. From a comparison of the chemical shift values for

the benzene C-1 and the N=CH atoms of all compounds investigated (except pyridine derivative **15**) a marked dependence upon the substitution pattern as well as on salt formation can be deduced. Thus, based on these chemical shift values, no decision (*E*) versus (*Z*) can be made when only one isomeric form is at hand.

A well established method for the discrimination of isomeric hydrazones, oximes and related compounds is based on the γ-effect: carbon atoms being in γ-position (α to C=N) to a *syn* located oxime-oxygen (or a *syn* hydrazone N-2 atom) suffer an upfield shift of 3 – 6 ppm compared to the γ-atoms in *anti*-position due to steric compression [28]. However, this effect is reported to be not universally applicable to phenyl ketones as phenyl carbons α to the C=N bond are shielded considerably less than aliphatic or vinyl carbon atoms [29]. A comparison of the benzene C-1 chemical shifts of (*Z*)-**4** · *Ac*OH and **4** · *Ac*OH reveals that in (*Z*)-**4** · *Ac*OH the benzene C-1 signal (δ 134.1 ppm) is shifted 3.6 ppm downfield compared to the corresponding C-1 signal (δ 130.5 ppm) in the (*E*)-configurated compound **4** · *Ac*OH – this is just the opposite trend as expected considering a "normal" γ-effect. However, the ^{13}C chemical shifts of the benzene carbons and that of N=CH in **4** · *Ac*OH (Table 2) agree well with the corresponding signals of the closely related compound 4-amino-3-[(2,6-dichlorobenzylidene)hydrazino]-4*H*-1,2,4-triazole hydrochloride (nebidrazine hydrochloride) [δ 142.3 (N=CH), 134.4 (benzene C-2,6), 131.3 (benzene C-4), 129.8 (benzene C-1), 128.8 (benzene C-3,5)] [30]. (*E*)-Configuration of this compound and its free base was unequivocally proved by means of X-ray analysis [31], which also revealed a distorsion between benzene ring and CH=N-N system causing a decreased conjugation of aromatic system and "side-chain".

In summary, all compounds investigated, except (*Z*)-**4** · *Ac*OH, were found to be the less crowded (*E*)-isomers, which are assumed to be more stable than their (*Z*)-analogues [32]. NOE difference spectroscopy turned out to be the method of choice for configurational assignments for compounds **11** – **14**, carrying a methyl group on the guanidine N^1 nitrogen, as well as with compounds **16** and **17** characterized by a "fixed" hydrogen atom attached to the guanidine N^1. Guanylhydrazones with no substituent on the guanidine N^1 nitrogen (compounds **1** – **10**) are assumed to prefer tautomeric form B in *DMSO-d*$_6$ solution. With the latter compounds configurational assignments were achieved using NOE considerations together with comparison of chemical shifts (^1H and ^{13}C) and of coupling constants [^1J (^{13}C, ^1H) of N=**C-H**] with the data of corresponding, unambiguously assigned (*E*)-configurated congeners **11** – **14**.

Experimental Part

Melting points (uncorrected) were determined on a Boetius hot-stage microscope. Elemental analyses were carried out by Mikroanalytisches Laboratorium, Institute of Physical Chemistry, University of Vienna. IR spectra (KBr disks) were recorded on a Perkin-Elmer FT-IR 16 PC spectrometer. Mass spectra were obtained either on a Varian MAT 311 A or on a Finnigan MAT 8230 instrument (both EI, 70 eV). NMR spectra were recorded on a Bruker AC 80 spectrometer (spectrometer frequency for ^1H: 80.13 MHz, for ^{13}C: 20.15 MHz) equipped with an Aspect 3000 computer and standard software. The ^{13}C-NMR spectra of some compounds with low solubility were obtained on a Bruker AM 400 WB instrument (spectrometer frequency for ^{13}C: 100.61 MHz). All NMR spectra were recorded from *DMSO-d*$_6$ solutions at 30°C in order to obtain sufficient solubility; the centre of the

solvent signal was used as internal standard which was related to tetramethylsilane with δ 2.49 ppm for ^1H and δ 39.50 ppm for ^{13}C. Acquisition parameters for the NOE difference spectra (recorded from approximately 0.2 *M*, non-degassed solutions) : 8 K data points; spectral width: 1 441 Hz; acquisition time: 2.84 s; digital resolution: 0.35 Hz/point; pulse width: 3 μs (90°); relaxation delay: 0.5 s; pre-irradiation time: 3 – 5 s; irradiation power: 45 – 50 dB below 0.2 W for single-frequency irradiation (Bruker-NOEDIFF), 55 – 59 dB below 0.2 W for multiplet-irradiation according to the method of Kinns and Sanders (Bruker-NOEMULT) [33]; number of scans: 80 – 400. ^1H-Decoupled ^{13}C-NMR spectra were obtained with the *J*-modulated spin-echo technique [27], for the acquisition of ^1H-coupled ^{13}C-NMR spectra the gated-decoupling mode was used.

The following known compounds were prepared according to reported procedures: **1** and **1** · HNO_3 [34], **2** [35], **3** [36], **4**, **4** · *Ac*OH and (*Z*)-**4** · *Ac*OH [18], **6** [3], **7** [37], **8** [14], **11** · HI [38], **14** [39], **15** [40], and **16** [2].

(E)-2-[(3,4,5-Trimethoxyphenyl)methylene]hydrazinecarboximidamide (**5**)

A mixture of 19.62 g (0.1 mol) 3,4,5-trimethoxybenzaldehyde and 11.0 g aminoguanidine hydrochloride (0.1 mol) in 80 ml methanol-water (1 : 1) were heated to reflux for some minutes. Upon cooling, colorless crystals separated which were collected and recrystallized from water (80 ml) to afford 23.2 g (80%) of **5** · HCl, m. p. 199 – 202°C. Anal. calcd. for $C_{11}H_{17}ClN_4O_3$ (288.74): Cl 12.28. Found: Cl 12.03. The free base **5** was obtained by treatment of an aqueous solution of **5** · HCl with an excess of 2 *N* NaOH. The precipitated material was filtered off, washed with water and dried to afford colorless crystals of m. p. 173 – 175°C. IR: 3 422, 3 348, 3 132 (NH), 3 004, 2 946 (CH), 1 678, 1 654, 1 626 cm^{-1}; MS (*m/z*): 252 (M^+, 100%), 251 (28), 165 (26), 163 (12), 150 (15), 87 (18), 81 (13), 43 (41). Anal. calcd. for $C_{11}H_{16}N_4O_3$ (252.27): C 52.37, H 6.39, N 22.21; found: C 52.67, H 6.24, N 22.10.

(E)-N-[(Phenylmethyleneamino)amidino]acetamide (**9**) [41]

A solution of 1.62 g (10 mmol) of **1** in 12 ml of dry pyridine was cooled to 0°C, then 2 ml (21 mmol) of acetic anhydride were added dropwise with stirring. After 16 h at room temperature the solvents were evaporated in vacuo and the residue was treated with excessive potassium bisulfate solution. The remaining solid was filtered off, washed with water followed by ether and recrystallized from ethanol to give 700 mg (24%) of **9** · 0.5 H_2SO_4 as colorless crystals, m. p. 211 – 212°C. IR: 3 330, 3 146 (NH), 3 054, 2 884 (CH), 1 726 (C=O), 1 678, 1 624, 1 614 cm^{-1}; MS (*m/z*): 204 (M^+, 64%), 161 (21), 127 (18), 91 (17), 87 (20), 43 (100). Anal. calcd. for $C_{10}H_{12}N_4O \cdot 0.5\ H_2SO_4$: C 47.42, H 5.17, N 22.12; found: C 46.70, H 4.94, N 21.64. The free base **9** was obtained upon treatment of an aqueous solution of **9** · 0.5 H_2SO_4 with basic ion exchange resin.

(E)-N,N'-[(2,4-Dichlorophenylmethylene)hydrazonomethylene]bis-(acetamide) (**10**)

A solution of 2.33 g (8 mmol) of **6** · *Ac*OH and 3.5 ml of acetic anhydride (37 mmol) were stirred at 100°C for 10 min. The separation of the reaction product (which began immediately after the educt dissolved) was completed by addition of ether and light petroleum; the crystals were collected by filtration and recrystallized from ethanol (30 ml). Yield: 1.32 g (52%) of colorless needles, m. p. 185 – 186°C. IR: 3 442, 3 320 (NH), 1 682, 1 638 (C=O); MS (*m/z*): 315/317 (M^+, 5/4%), 153 (16), 127 (13), 87 (16), 43 (100). Anal. calcd. for $C_{12}H_{12}Cl_2N_4O_2$ (315.16): C 45.73, H 3.84, N 17.78; found: C 46.00, H 3.69, N 17.81.

(E)-2-[(4-Methoxyphenyl)methylene]-1-methyl-hydrazinecarboximidamide (**12**) [42]

A solution of 1.92 g (10 mmol) of **2** in 20 ml of methanol was treated with 1.60 g (11 mmol) iodomethane and the mixture was kept at room temperature for 24 h. The crystals which had separated were filtered off and washed with some drops of methanol to afford 1.95 g (58%) of **12** · HI as colorless

crystals, m.p. 296–299°C. The free base **12** was obtained by treatment of a hot aqueous solution of **12** · HI with an excess of 40% KOH. The precipitated material was filtered off, washed with cold water and dried in vacuo to afford colorless crystals of m.p. 177–178°C. IR: 3480, 3370, 3330, 3154 (NH), 1604 cm^{-1}; MS (*m/z*): 207 (18), 206 (M^+, 100%), 164 (80), 149 (42), 134 (36), 108 (20), 105 (19), 99 (83), 91 (27), 73 (80), 72 (34), 43 (23). Anal. calcd. for $C_{10}H_{14}N_4O$ (206.25): C 58.24, H 6.84, N 27.16; found: C 58.47, H 6.64, N 26.93.

(E)-1,N-Dimethyl-2-[(phenyl)methylene]hydrazinecarboximidamide (**13**)

A solution of 0.70 g (4 mmol) of **11** in 10 ml of methanol was treated with 0.75 g (5.3 mmol) of iodomethane and the mixture was kept at room temperature for two days. After evporation of approx. 5 ml of methanol and addition of ether, crystals of **13** · HI separated, which were collected by filtration (1.09 g, 86%, m.p. 218–220°C). To obtain the free base, a solution of **13** · HI in hot water was treated with an excess of 2 *N* NaOH, then the water layer was exhaustively extracted with chloroform. The combined chloroform phases were dried ($MgSO_4$) and evaporated. The residue was recrystallized from benzene-hexane to afford **14** as colorless crystals, m.p. 102–103°C. IR: 3370, 3336 (NH), 3004, 2936 (CH), 1612 cm^{-1}; MS (*m/z*): 190 (M^+, 38%), 134 (43), 133 (44), 113 (100), 104 (13), 92 (23), 80 (19), 79 (14), 57 (94). Anal. calcd. for $C_{10}H_{14}N_4$ (190.25): C 63.13, H 7.42, N 29.45; found: C 63.30, H 7.40, N 29.67.

(E)-2,6-Dichlorobenzaldehyde 1 H-Tetrazol-5-ylhydrazone (**17**) [5]

The synthesis of compound **17** from 2,6-dichlorobenzaldehyde and 5-hydrazinotetrazole was carried out following the procedure given in Ref. [43]. Yield: 95% of colorless crystals, m.p. 229–231°C (ethanol). IR: 3428 (NH), 3022, 2958 (CH), 1636 cm^{-1}; MS (*m/z*): 256/258 (M^+, 14/9%), 221 (13), 174 (20), 173 (14), 172 (26), 160 (18), 158 (46), 125 (19), 123 (100), 87 (23). Anal. calcd. for $C_8H_6Cl_2N_6$ (257.08): C 37.38, H 2.35, N 32.69; found: C 37.62, H 2.46, N 32.42.

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