Spectroscopic Identification of some Derivatives of 3,4-Diamino-4*H*-1,2,4-triazole and 3-Hydrazino-4*H*-1,2,4-triazole

Håkan Emilsson* and Hans Selander

Department of Organic Pharmaceutical Chemistry, Biomedical Center, University of Uppsala, Box 574, S-751 23 Uppsala, Sweden

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Spectroscopic methods (ir, ^{1}H- and ^{13}C-nmr, ms and uv) have been used for the structural elucidation and identification of different isomeric 1,2,4-triazole derivatives, obtained by cyclisation reactions from appropriate diaminoguanidines. The four compounds 3,4-diamino-4*H*-1,2,4-triazole, 3-hydrazino-4*H*-1,2,4-triazole, 3-amino-4-(2,6-dichlorobenzylideneamino)-4*H*-1,2,4-triazole and 3-(2,6-dichlorobenzylidenehydrazino)-4*H*-1,2,4-triazole, were chosen as representative structures to illustrate the general spectroscopic properties for 3,4-diamino- and 3-hydrazino-substituted 4*H*-1,2,4-triazoles and the corresponding hydrazones, with different substituents in the 5-position of the triazole ring (alkyl-, aralkyl-, mercapto-, hydroxy- and amino-groups). Nmr and uv spectroscopy were found to be the best methods for confirmation of the different series of hydrazones, while ir and nmr were found to be suitable for the structural elucidation of compounds in the series of 3,4-diamino- and 3-hydrazino-4*H*-1,2,4-triazoles, respectively.

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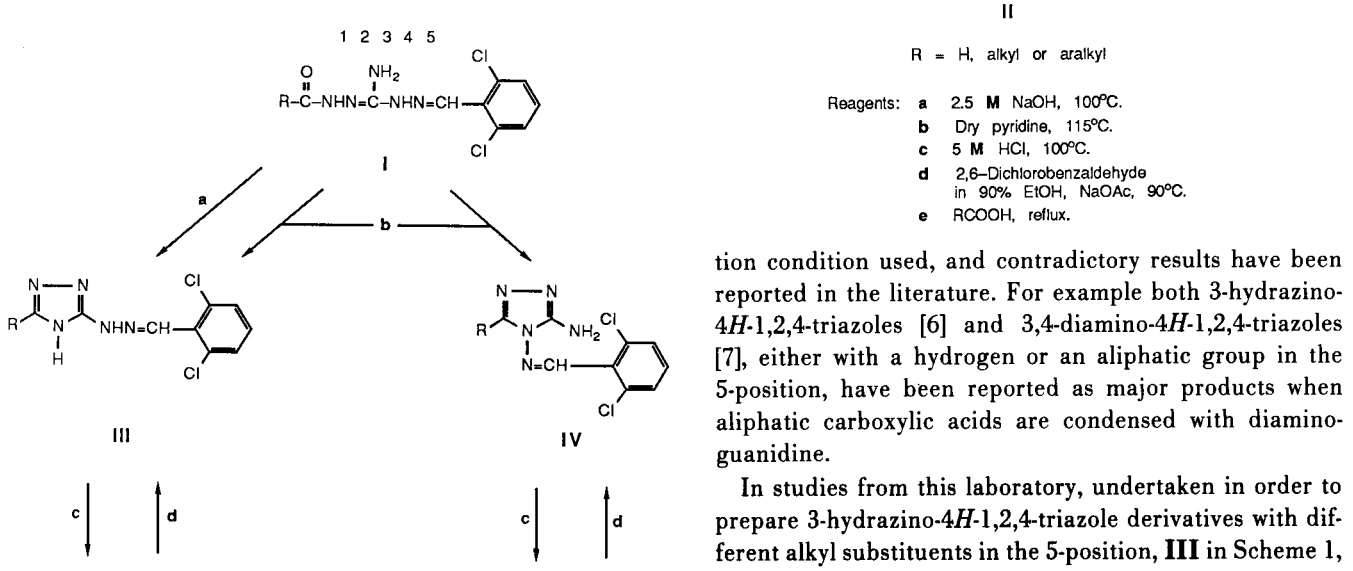
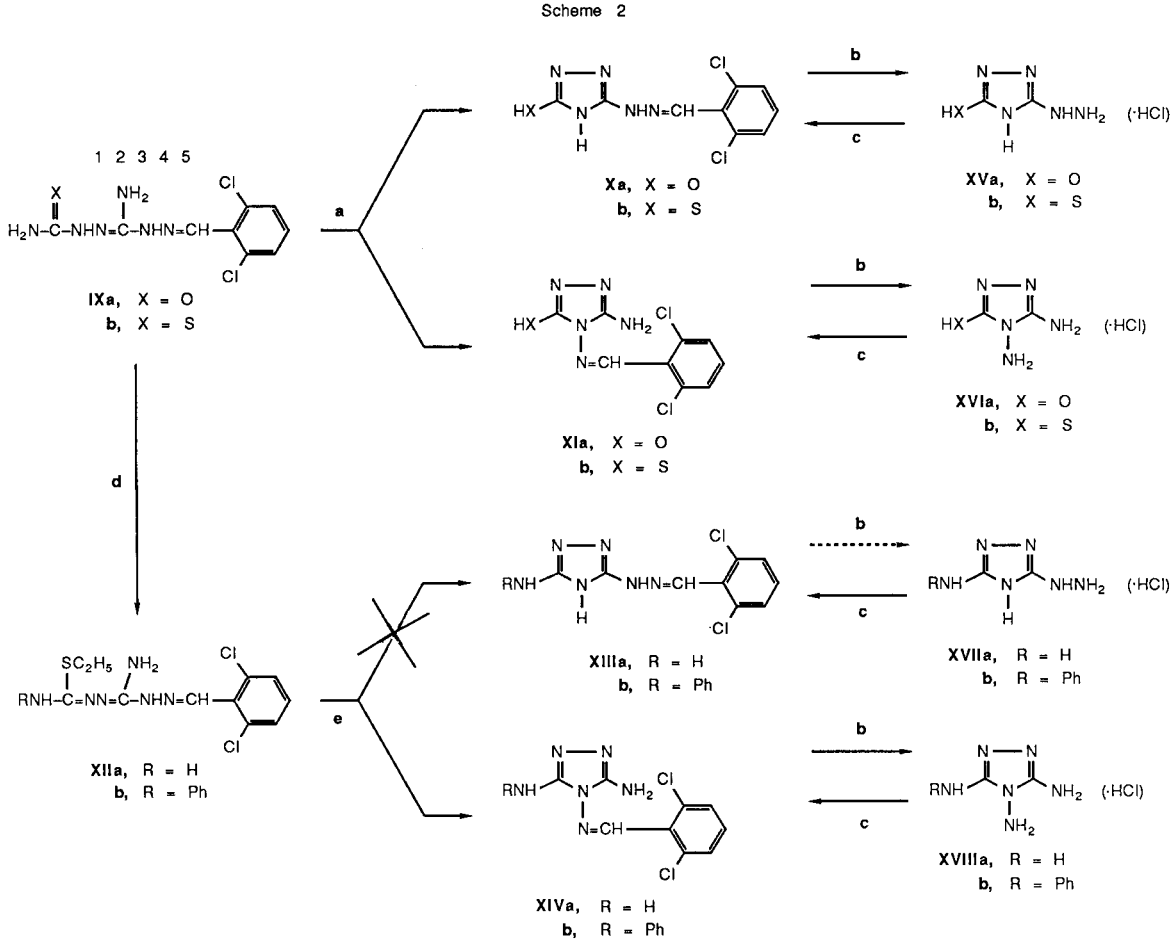
In our search for new antihypertensive agents, different series of substituted 4*H*-1,2,4-triazoles like 3-hydrazino-4*H*-1,2,4-triazoles, 3,4-diamino-4*H*-1,2,4-triazoles and the corresponding hydrazones, have been prepared and tested for antihypertensive properties in spontaneously hypertensive rats [1-5]. Several of these compounds have been obtained *via* different cyclization reactions of the appropriate diaminoguanidine derivatives. When, for example, 1-acyldiaminoguanidine or symetric 1,5-diacyldiaminoguanidine derivatives **I** and **II**, respectively, in Scheme 1 are cyclised, different isomeric 1,2,4-triazoles can theoretically be obtained, **III-IV** and **V-VI**, depending on which nitrogen (N-3 or N-4) is responsible for the nucleophilic attack on the carbonyl group. The yields of the ratios between the two isomeric triazole derivatives in the cyclisation reactions will, however, vary with respect to the reaction condition used, and contradictory results have been reported in the literature. For example both 3-hydrazino-4*H*-1,2,4-triazoles [6] and 3,4-diamino-4*H*-1,2,4-triazoles [7], either with a hydrogen or an aliphatic group in the 5-position, have been reported as major products when aliphatic carboxylic acids are condensed with diaminoguanidine.

In studies from this laboratory, undertaken in order to prepare 3-hydrazino-4*H*-1,2,4-triazole derivatives with different alkyl substituents in the 5-position, **III** in Scheme 1,

Scheme 1



Scheme 2



Reagents: **a** Dry pyridine, 115°C.
b 5 **M** HCl, 100°C.
c 2,6-Dichlorobenzaldehyde in 90% EtOH, NaOAc, 90°C.
d C_2H_5Br, NaOH, 20°C.
e Dry pyridine, 90°C.

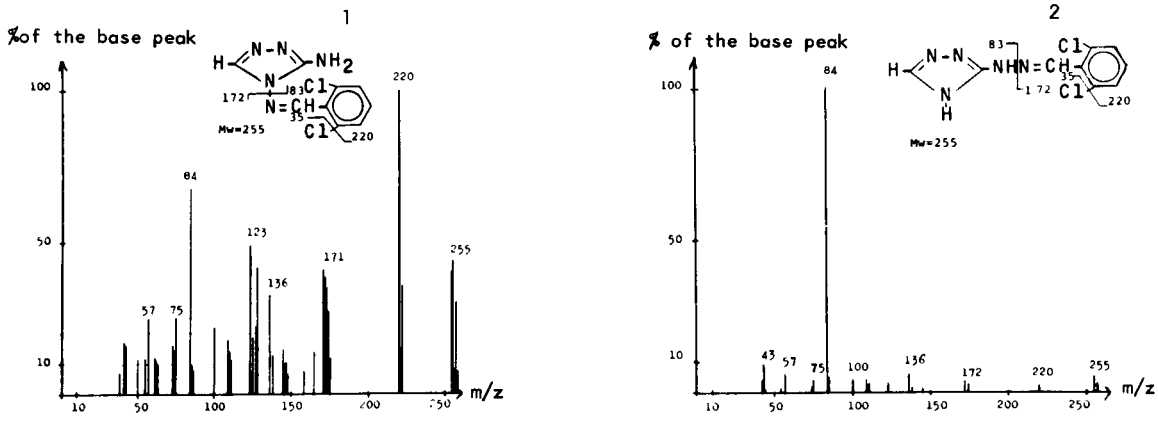
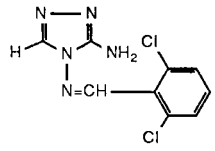
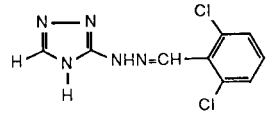
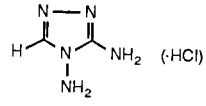
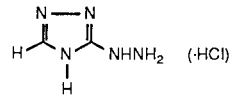


Figure 1. Mass spectra of compounds **1** and **2** (electron impact at 70 eV).

Table 1

Spectroscopic Properties of the Substituted 4*H*-1,2,4-Triazoles **1-4**

	 **1**	 **2**	 **3**	 **4**
Infrared spectroscopy [a]				
ν max (cm^{-1})	3420 (m), 3100 (m), 3015 (s), 1630 (s), 1560 (m), 1525 (m), 1495 (s), 1380 (m), 1195 (s), 1100 (m), 940 (m), 765 (s), 710 (m)	3400 (w), 3180 (m), 2900 (m), 2820 (m), 1640 (s), 1540 (s), 1190 (m), 1035 (m), 680 (m)	3350 (s), 3240 (s), 3150 (s), 3100-2500 (s-m), 1685 (s), 1630 (s), 1570 (m), 1550 (m), 1200 (s), 1010 (s)	3305 (m), 3200 (m), 3140 (m), 2970-2400 (s-m), 1600 (m), 1570 (s), 1550 (s), 1520 (m), 1435 (m), 1150 (s), 715 (s)
Ultraviolet spectroscopy [b]				
λ max (nm)	266	240 298		
ϵ	13635	8600 13525		
Mass spectroscopy [c]				
m/z (%)	257 (30), 255 (45) M^+, 222 (35), 220 (100), 175 (13), 174 (28), 173 (35), 172 (29), 171 (41), 165 (14), 147 (11), 146 (10), 145 (14), 138 (13), 136 (33) 128 (43), 127 (22), 125 (19), 123 (50), 111 (12), 110 (14), 109 (18), 100 (22), 85 (10), 84 (68), 75 (25), 57 (25), 42 (16), 41 (17)	255 (5) M^+, 220 (2), 172 (4), 145 (2), 136 (6), 84 (100), 43 (9)	99 (100) M^+, 84 (6), 44 (8), 43 (60) [d]	99 (100) M^+, 84 (6), 70 (8), 69 (9), 43 (71), 42 (11) [d]

[a] Potassium bromide pellets; w = weak, m = medium and s = strong. [b] In absolute ethanol at 20°C. [c] 70 eV; intensity ≧ 10%, except for M^+ and some of the important fragments. [d] 20 eV: intensity ≧ 6%.

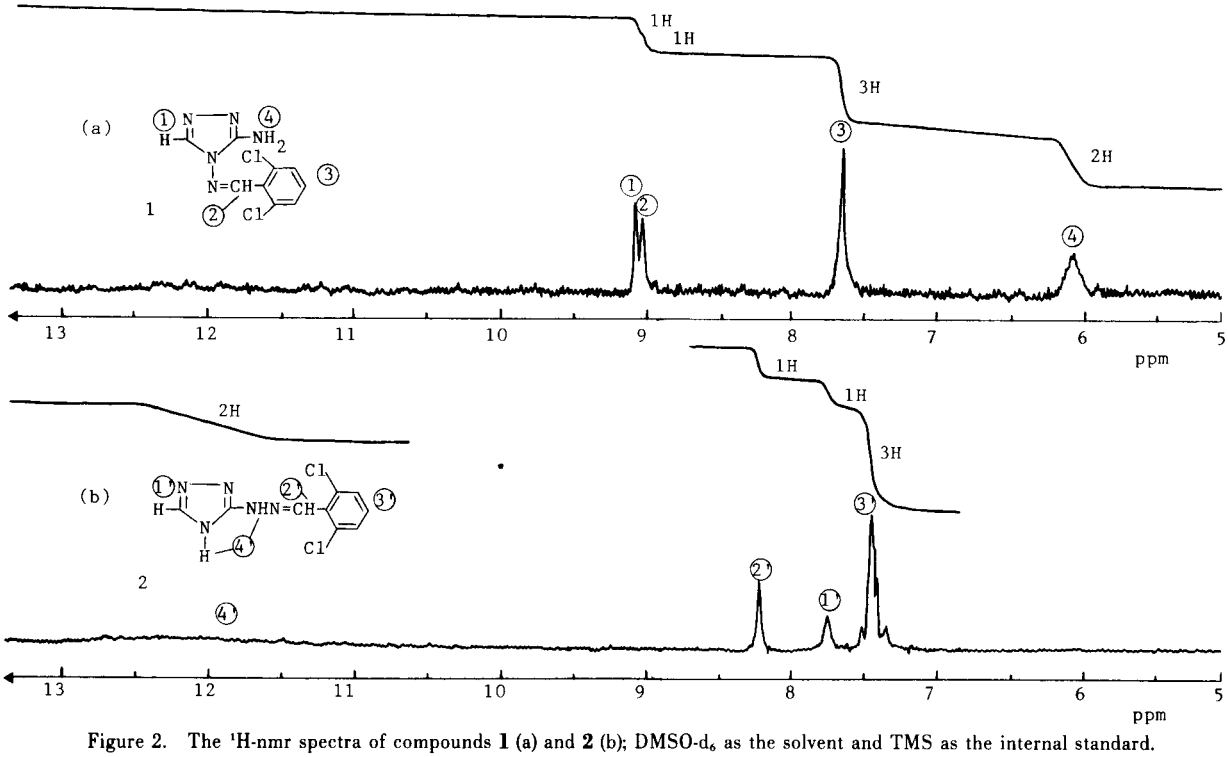


Figure 2. The ^{1}H-nmr spectra of compounds **1** (a) and **2** (b); DMSO-d_6 as the solvent and TMS as the internal standard.

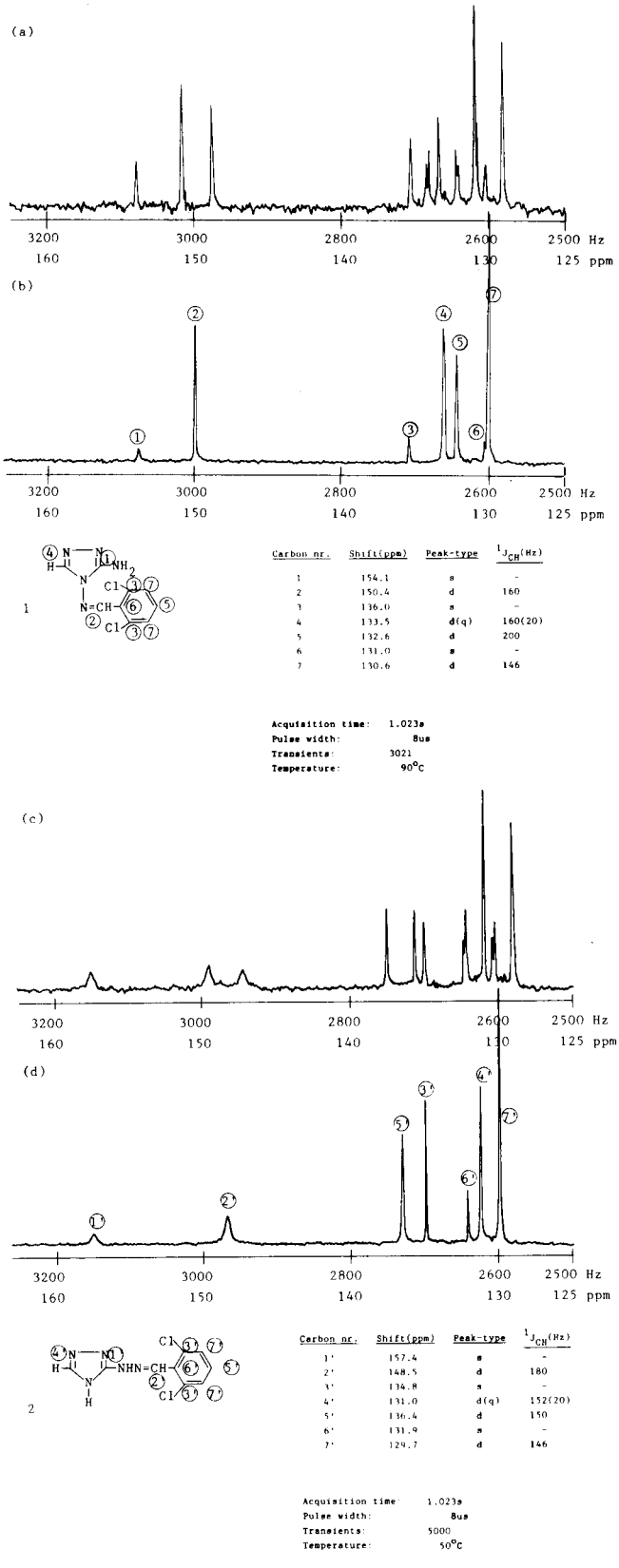


Figure 3. 25.2 MHz ^{13}C-nmr spectra of compounds **1** (a) off resonance decoupled, (b) proton noise decoupled, and **2** (c) off resonance decoupled, (d) proton noise decoupled; DMSO-d_6 as the solvent and dioxane as the internal standard.

it was found that the concomitant formation of the isomeric triazoles **IV** limited the yields of the desired products [1]. Similarly, isomeric triazoles, **X**, **XIa** and **b** in Scheme 2, were formed when the 1-carbamoyl- and 1-thiocarbamoyldiaminoguanidines, **IXa** and **b** in Scheme 2, were cyclised [1,4]. When the *S*-ethyl derivatives, **XIIa** and **b** in Scheme 2, were heated in pyridine, however, only 3,4-diamino derivatives, **XIVa** and **b** were formed.

The fact that isomeric 1,2,4-triazoles can be obtained in the cyclisation reactions used, prompted us to use several spectroscopic methods fully to confirm the correct structures of the products formed. Since detailed spectroscopic data for substituted 1,2,4-triazoles have not been reported in the literature to any great degree, we have decided to present some spectral data for 3-amino-4-(2,6-dichlorobenzylideneamino)-4*H*-1,2,4-triazole, 3-(2,6-dichlorobenzylidenehydrazino)-4*H*-1,2,4-triazole, 3,4-diamino-4*H*-1,2,4-triazole and 3-hydrazino-4*H*-1,2,4-triazole, **1-4** (Table 1). These compounds were chosen as representative structures to illustrate the general spectroscopic properties not only for the parent compounds, but also for structure analogues with various alkyl-, aralkyl-, mercapto-, hydroxy- or amino-substituents in the 5-position of the triazole rings, as shown in Schemes 1 and 2.

Results and Discussion.

Spectroscopic data for compounds **1-4** are presented in Table 1 and in Figures 1-3. The hydrazones **1** and **2** were studied as free bases, while **3** and **4** were handled as the monohydrochloride salts.

Infrared Spectroscopy.

The most prominent absorption frequencies in the ir spectra for the four compounds are listed in Table 1. For the two hydrazone derivatives **1** and **2**, the characteristic N-H stretching and bending absorptions appear within the same frequency regions. The N-H stretching absorption bands are however, stronger for compound **1** than for compound **2**. Similarly, the ir spectra of structure analogues to **1** and **2** with other substituents in the 5-positions did not show any clear characteristic absorption bands that could be assigned to any of the two structure series.

The ir-spectroscopy, however, was more useful to distinguish the two series of triazoles represented by compounds **3** and **4**. In the spectra of **3** a strong absorption band from one of the amino groups appears at 1685 cm^{-1} (N-H bending). A similar strong absorption can be seen in the range of 1680-1730 cm^{-1} for all the studied 3,4-diamino-4*H*-1,2,4-triazoles with the 5-substituents mentioned above. For all the isomeric 3-hydrazino derivatives, including compound **4**, a strong absorption band from the hydrazino group appears in the region of 1570-1625 cm^{-1}. The NH-stretching absorption in com-

pound **3** give rise to three strong bands in the 3100-3350 cm^{-1} region, where compound **4** only shows weaker absorption bands.

Ultraviolet Spectroscopy.

A triazole ring in itself has a very weak uv absorption at 205 nm [8]. As expected substitution in the ring with two amino groups or a hydrazino group, as in compounds **3** and **4**, respectively, did not result in any significant change in the uv absorption spectra with respect to the parent compound.

The uv spectra of compounds **1** and **2** in ethanol solution, however, show strong absorption maxima at 266 and 298 nm, respectively. The absorption at a longer wavelength for compound **2** can be explained by the additional nitrogen in the linking chain between the two aromatic rings, affording an extended conjugated system. The strong uv-maximum around 300 nm was characteristic for all the studied derivatives of **2**, prepared with other 5-substituents as mentioned above. Similarly, the studied structure analogues to **1** showed a characteristic absorption maximum around 265 nm.

Mass Spectroscopy.

The electron impact mass spectra for compounds **1** and **2** at an ionization energy of 70 eV, are shown in Figure 1. Both compounds result in mass spectra with almost identical fragmentation patterns, but with differences in the intensities for the various fragments. When each pair of isomers of the structural analogues to **1** and **2** were compared one with the other, almost identical fragmentation patterns were found. This is most likely due to the rapid cleavage of the weak bond between the two nitrogens in the intermediate chain together with a hydrogen shift, resulting in the same triazole fragment from both series being formed. This nitrogen-nitrogen cleavage was also a dominant pathway in the fragmentations even when an ionization energy of 20 eV was used.

A cleavage of the nitrogen-nitrogen bond concomitant with a hydrogen shift is similarly dominant in all the tested free 3,4-diamino- and 3-hydrazino-4*H*-1,2,4-triazoles, exemplified by **3** and **4** (Table 1), resulting in almost identical fragmentation pathways also for these two series of compounds.

The continuing fragmentations of the triazole ring itself after cleavage of the side chain is in agreement with previously reported data [9].

Proton Nuclear Magnetic Resonance Spectroscopy.

The hydrazones **1** and **2** showed clear differences in the proton nmr spectra, when DMSO-d_6 was used as solvent (Figure 2). The benzylidene proton of **1** appears at 9.05 ppm, which is about 0.8 ppm downfield when compared with the corresponding proton in **2** (8.23 ppm). A possible explanation for this could be the anisotropy of the π-system in the triazole ring, which is closer to the benzylidene proton in **1** compared with **2**. The anisotropy of the triazole ring may also be the reason for the difference of 0.3 ppm, when the proton-shifts of the 2,6-dichlorophenyl groups in **1** and **2** are compared.

The most prominent differences in the spectra of compounds **1** and **2**, however, are the signals from the nitrogen protons in the two molecules. This large difference is unexpected, but a possible reason could be an increase in acidity of the nitrogen protons in **2** compared with **1**, due to the higher grade of conjugation in this molecule as mentioned above. This is supported also by the higher mobility of these protons in **2**, indicated by a broadening of the peak in the spectra. All the resonances from the nitrogen protons in **1** and **2** could be eliminated from the spectra by addition of a drop of deuterium oxide to the sample tube.

The structure analogues of **1**, with the substituents mentioned above in the 5-position, showed a characteristic resonance peak for the benzylidene proton at about 9.0-9.3 ppm, while the corresponding proton in the structure analogues of **2** appeared in the range of 8.2-8.3 ppm. The nitrogen protons in these two series appeared in the range of 4.8-6.3 ppm and 11.3-12.8 ppm respectively, similar to the unsubstituted compounds **1** and **2**.

The proton nmr spectrum for a DMSO-d_6 solution of **4**, showed a broad peak for the nitrogen protons in the range of 8.7-11.3 ppm. The nitrogen protons in the spectra of the 5-substituted analogues, however, resulted in more distinct peaks in the same region being found.

No spectrum of compound **3** was obtained due to its poor solubility in DMSO or any other solvent suitable for nmr studies. The structure analogues to **3** with other 5-substituents, however, were soluble in DMSO-d_6 and showed two broad peaks around 6 and 8 ppm, respectively, representing the two amino groups. Based on the signals for the protons of the 3-amino group in **1** it can be concluded that the peak at 8 ppm represents the protons in the 4-amino group in compound **3**.

Carbon-13 Nuclear Magnetic Resonance Spectroscopy.

The ^{13}C-nmr spectra of **1** and **2** in DMSO-d_6, are shown in Figure 3. Both the complete (proton noise decoupled) and off-resonance decoupled spectra are shown, and the ^{13}C-resonances are presented in ppm. Each carbon in the molecule has been assigned a number from 1 to 7, for **1** and 1'-7' for **2**.

In the spectrum of **2**, the carbon-1' signal appears at the lowest field of all the carbons in the molecule, and about 3 ppm more downfield compared with the corresponding signal in the spectrum of the isomer **1**. This finding is in agreement with literature data for an amino- or hydrazino-substituted aromatic carbon atom [10]. The benzylidene carbons of the two compounds appear at almost the same

frequency (2 and 2'). The carbons 5 (5') and 7 (7') in **1** and **2** are obtained as doublets, while the carbons 3 (3') and 6 (6') appear as singlets, in the off-resonance spectra, as expected. The carbons 4 in **1** and 4' in **2**, appear as double doublets, and a possible reason for this may be the occurrence of both syn- and anti-forms of the two hydrazones.

Carbon-13 nmr spectra were not performed for any of the other hydrazones prepared due to technical difficulties. The spectral data of **1** and **2**, however, indicate that this technique can be used to distinguish the two isomeric series of compounds from each other.

General Conclusions.

From the spectroscopic data presented above, it can be concluded that proton nmr spectroscopy is the most illustrative and general method to distinguish the two series of hydrazones, represented by **1** and **2**, from each other.

Besides nmr, uv spectroscopy was found to be the only useful technique to distinguish the two series from each other. Mass and infrared spectroscopy were, however, not suitable techniques due to the lack of structural characteristics in the spectra from these series.

The structures of the free amino- and hydrazinotriazoles, represented by **3** and **4**, can be confirmed and distinguished from each other by the use of ir and nmr spectroscopy, while ms and uv were less suitable.

EXPERIMENTAL

The uv spectra were recorded in ethanol solution at 20°C on a Pye Unicam SP 1800 spectrophotometer (190-360 nm). The ir spectra were run as potassium bromide pellets on a Perkin-Elmer 157 G spectrophotometer. The electron impact mass spectra were obtained at ionization energies of 20 or 70 eV, using an LKB 9000 instrument equipped with a direct inlet system for introducing the compounds. The ^{1}H-nmr spectra were recorded in DMSO-d_6 solution with TMS as internal standard, using a Perkin-Elmer R 12B spectrometer. The ^{13}C-nmr spectra were run in DMSO-d_6 solution with dioxane as internal standard on a JEOL FX 900 90 MHz instrument.

The compounds **1**, **2**, **3** and **4** were prepared as reported previously [1,3].

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* Correspondence should be addressed to: Ph.D. Håkan Emilsson, Research and Development Department, ACO Läkemedel AB, Box 3026, S-171 03 Solna, Sweden.

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