1,6-Dihydro-1,2,4,5-tetrazine, a Neutral Homoaromatic System[1,2]

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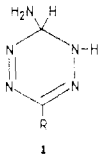
^{1}H NMR spectroscopy of some 1,6-dihydro-3-aryl(alkyl)-1,2,4,5-tetrazines and their conjugate bases and acids, at various temperatures, shows that these species are all homoaromatic. The hydrogens at position 6 have a different orientation toward the aromatic ring; one is oriented above and the other away from the aromatic ring, thus resulting in a large difference in chemical shift. The various parameters ($\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, and $\Delta G^{\ddagger}$) are determined by dynamic NMR measurements.

In a preceding paper[1] we described the formation of 6-amino-3-aryl(alkyl)-1,2,4,5-tetrazines by reaction of the appropriate 3-aryl(alkyl)-1,2,4,5-tetrazines with liquid ammonia and subsequent oxidation with potassium permanganate. As first step in this reaction sequence, the formation of a σ adduct between ammonia and the 1,2,4,5-tetrazine, i.e., 6-amino-1,6-dihydro-3-aryl(alkyl)-1,2,4,5-tetrazine (1) was proposed. In order to obtain some



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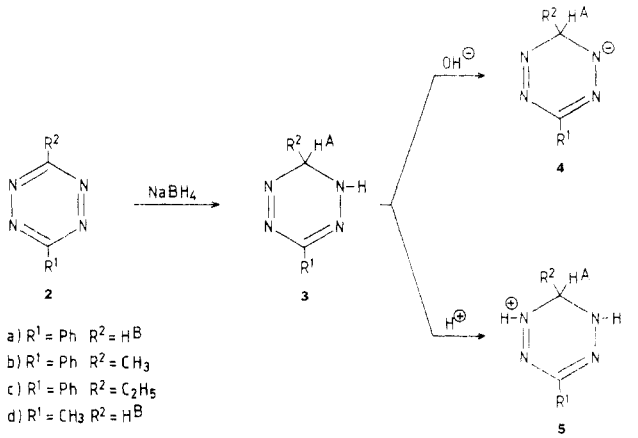
evidence for the intermediary existence of these σ adducts, the ^{1}H NMR spectrum of 3-phenyl-1,2,4,5-tetrazine in liquid ammonia was measured. We observed that the ring hydrogen appeared at 1.51 ppm. This means an upfield shift of 8.84 ppm when we compare this chemical shift value with the one found for the 6-hydrogen of 3-phenyl-1,2,4,5-tetrazine measured in deuteriomethanol (10.35 ppm). This upfield shift clearly points to the formation of 1 (R = Ph) in liquid ammonia.

However, it is very interesting that this chemical shift is observed at an unusually high field (1.51 ppm). The chemical shifts observed for adducts between pyrimidines,[3] 1,2,4-triazines,[4] pteridines,[5] and amide ion or ammonia are between 4 and 5.5 ppm. This seems to indicate that the change of hybridization of C_6 ($sp^2 \rightarrow sp^3$) which occurs on adduct formation is not the only factor responsible for this considerable upfield shift of 8.84 ppm. In order to obtain more insight into the structural features of adduct 1 (R = Ph), which could possibly explain this unexpected high upfield shift, we synthesized some 3-aryl(alkyl)-1,6-dihydro-1,2,4,5-tetrazines (**3a–d**) and studied the ^{1}H NMR spectra of these compounds, their conjugate bases **4**, and their conjugate acids **5** at various temperatures.

Results and Discussion

The compounds **3a–d** could be obtained in good yield by treatment of 1,2,4,5-tetrazines **2a–d** with sodium borohydride (Scheme I). The 1,6-dihydro structure was proven by the presence of N–H stretching vibrations at 3400 and 3200 cm^{-1} in the IR spectra and by the ^{1}H NMR spectra (Tables I and V).

Scheme I



2 3 4 5

Table I. Chemical Shifts of the Ring Protons of Compounds 3a-d, 4a-c, and 5a at 306 K in CD_3OD/D_2O (4:1)

compd	H^A	H^B
3a	4.13 (s)	4.13 (s)
3b	2.22[a]	
3c	2.26[b]	
3d	3.94 (s)	3.94 (s)
4a	1.37 (d)	6.18 (d)
4b	1.18 (q)	
4c	1.02 (t)	
5a	4.55 (s)	4.55 (s)

[a] AB_3 system for H^A and CH_3. [b] Selective decoupling of CH_3 gives an A_2B spectrum for H^A and CH_2.

Table II. Chemical Shifts of Protons H^A and H^B below the Exchange Temperature in 1,6-Dihydro-1,2,4,5-tetrazines (in which $R_2 = H^B$) and in Homotropylium Cation (6)

compd	T_{coal}, K	$\delta(H^A)$	$\delta(H^B)$	$\Delta\delta$, ppm	J_{AB}, Hz
3a	243	2.13 (d)	6.13 (d)	4.00	7.5
3d	233	2.04 (d)	5.84 (d)	3.80	7.5
4a	318	1.37 (d)	6.18 (d)	4.81	6.6
5a	238	2.87 (d)	6.23 (d)	3.36	*a*
6		−0.73 (d)	5.13 (d)	5.86	7.2

[a] In this spectrum the signal remained broadened.

We observed that, whereas the ^{1}H NMR spectrum of **3a** measured at 306 K gave only one signal (4.13 ppm) for both hydrogens at position 6, at low temperature (199 K) these hydrogens gave rise to two doublets, one at 2.13 ppm and the other at 6.13 ppm (Table II). This phenomenon cannot be ascribed to the influence of the phenyl group at position 3, since 3-methyl-1,6-dihydro-1,2,4,5-tetrazine

(1) Part 3 on 1,2,4,5-tetrazine and its derivatives. For part 2 see A. Counotte-Potman and H. C. van der Plas, *J. Heterocycl. Chem.*, in press.
(2) Part 26 on NMR investigations of σ adducts of heterocyclic systems with nucleophiles. For part 25 see: H. J. W. van den Haak, H. C. van der Plas and A. van Veldhuizen, *J. Org. Chem.*, previous paper in this issue.
(3) J. Breuker and H. C. van der Plas, *J. Org. Chem.*, **44**, 4677 (1979).
(4) A. Rykowski, H. C. van der Plas, and A. van Veldhuizen, *Recl. Trav. Chim. Pays-Bas*, **97**, 273 (1978).
(5) A. Nagel, H. C. van der Plas, and A. van Veldhuizen, *Recl. Trav. Chim. Pays-Bas*, **94**, 95 (1975).

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Table III. Kinetic Parameters of Some 1,6-Dihydro-1,2,4,5-tetrazines Obtained by Dynamic NMR Measurements

compd	T_{coal},[a] K	n[b]	r	$\Delta H^{\ddagger}$, kJ/mol	$\Delta S^{\ddagger}$, J/mol K	$\Delta G^{\ddagger}$, kJ/mol
3a	243	8	−0.997	25.1 ± 0.8	−110 ± 3	51.9 ± 1.5
3d	233	9	−0.990	20.4 ± 1.1	−125 ± 4	49.5 ± 1.9
4a	318	6	−0.992	37.1 ± 2.4	−98 ± 9	68.1 ± 3.8
5a	238	9	−0.997	21.7 ± 0.7	−123 ± 3	51.1 ± 1.6

[a] The accuracy of the determination of the coalescence temperature was about 10 K. [b] n is the number of temperatures used for the calculation.

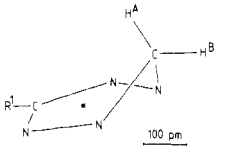


Figure 1. Perspective drawing of 1,6-dihydro-1,2,4,5-tetrazine.

(**3d**) gave analogous results: at 306 K both hydrogens at position 6 have the same chemical shift (3.94 ppm), while at about 199 K both hydrogens appear as doublets with different chemical shifts (see Table II). Dissimilarity of both hydrogens at position 6 is also found in the conjugate base of **3a**, i.e., **4a**, obtained on treatment of **3a** with sodium hydroxide.[6] The ^{1}H NMR spectrum of **4a** shows already at 306 K two absorptions, at 1.37 ppm and 6.18 ppm (Table I); at lower temperature sharp doublets appear. When **3a** is protonated (see Experimental Section) the 3-phenyl-1,6-dihydro-1,2,4,5-tetrazinium ion (**5a**) also shows dissimilarity of the hydrogens at position 6: at 306 K the ^{1}H NMR spectrum shows only a singlet at 4.55 ppm, whereas two doublets at 2.87 and 6.23 ppm occur at about 200 K.

All these data strongly indicate that in the compound described above we deal with a species having a homoaromatic[7] system. The 1,6-dihydro-1,2,4,5-tetrazine ring can be considered as a monohomotetrazole, in which the tetrazole part of the molecule has a rather regular five-membered ring, allowing orbital overlap to form an aromatic 6π system (Hückel rule). Consequently, the methylene group has to point out of the plane of the ring, orienting one of the hydrogens, H^A, above the plane of the aromatic tetrazole ring and placing the other hydrogen, H^B, in an exo position (Figure 1).

The chemical shift difference between H^A and H^B in the neutral species **3a** and **3d** (3.80–4.00 ppm) is in good agreement with the expected shift difference of about 3–4 ppm, which is calculated by approximation from the ring-current effects in benzene.[8] From this result we concluded that there exists an induced ring current in **3a** and **3d**, which provides the explanation for the shift difference between H^A and H^B. From the results given in Table II it can be concluded that H^B is hardly affected by the charge in the ring; H^A, however, strongly experiences the influence of this charge through space, a negative charge causing an upfield shift (**4a**) and a positive charge causing a downfield shift (**5a**). This result is in accordance with the proposed conformation. For comparison the ^{1}H NMR data for H^A and H^B of the homotropylium cation

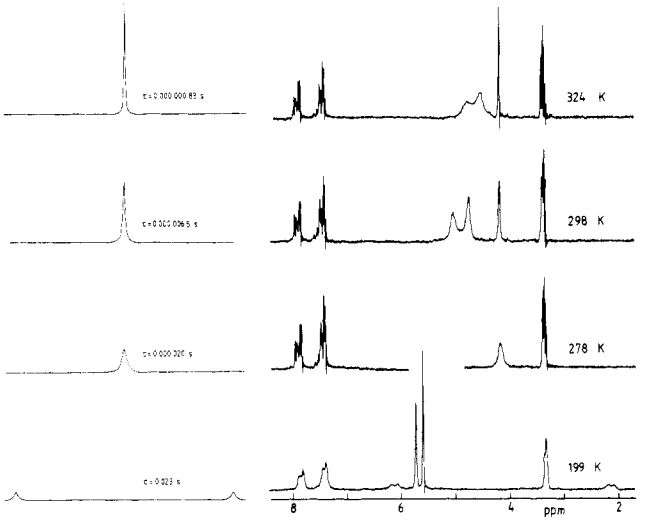
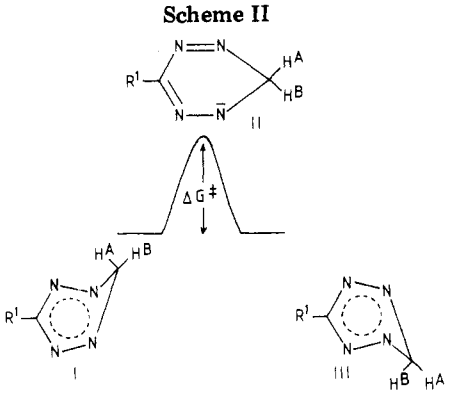


Figure 2. Measured (right) and calculated (left) line shape of H^A and H^B in 3-phenyl-1,6-dihydro-1,2,4,5-tetrazine (**3a**) in CD_3OD/D_2O (4:1) as a function of the temperature.

Scheme II



(**6**)[9,10] are included in Table II.

The coupling constant, $J_{A,B}$, of the homotropylium cation is of the same magnitude (7.2 Hz) as $J_{A,B}$ of the 1,6-dihydro-1,2,4,5-tetrazine system, thus indicating that the angle of N_1–C_6–N_5 is similar to that of C_1–C_8–C_7. Figure 2 shows some ^{1}H NMR spectra of **3a** at different temperatures. An increase in temperature (324 K) sharpens the singlet, a decrease (278 K) causes a broadening, and at very low temperature (199 K) two doublets appear.

At low temperature, the system is frozen to one conformation, and at higher temperatures there is a rapid exchange (ring inversion) between the two possible forms

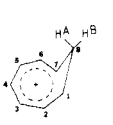
(6) The pK_a is about 10: W. Skorianetz and E. Kovacs, *Helv. Chim. Acta*, **54**, 1922 (1971); A. Counotte-Potman and H. C. van der Plas, unpublished results.

(7) (a) S. Winstein in "Carbonium Ions", Vol. III, G. A. Olah and P. v. R. Schleyer, Eds., Wiley-Interscience, New York, 1972, Chapter 22, p 965. According to Winstein a homoaromatic compound should obey the following conditions: (a) it has $4n + 2$ electrons (Hückel rule); (b) it has the ability to sustain an induced ring current; (c) there is an increased stability due to electron delocalization. (b) For a recent review, see L. A. Paquette, *Angew. Chem.*, **90**, 114 (1978).

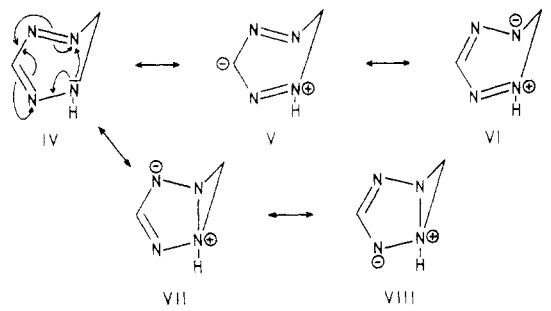
(8) F. A. Bovie in "Nuclear Magnetic Resonance Spectroscopy", Academic Press, New York, 1969, 265.

(9) W. J. Hehre, *J. Am. Chem. Soc.*, **96**, 5207 (1974).

(10) P. Warner, D. L. Harris, C. H. Bradley and S. Winstein, *Tetrahedron Lett.*, 4013 (1970).



Scheme III



I and III (Scheme II). This inversion is visualized to proceed through planar form II in which a considerable loss of delocalization energy appears.

The calculated spectra in Figure 2 were obtained with a programmable pocket calculator; from the lifetime, τ, the kinetic parameters were calculated[11] by means of the Eyring equation: $\log (k/T) = 10.32 - (\Delta H^{\ddagger}/4.57T) + (\Delta S^{\ddagger}/4.57)$. The plot of $\log (k/T)$ against $1/T$ was calculated with the least-squares method (Table III).[20]

The entropy of activation is strongly negative and not very different for all four compounds; in the transition state the system is more localized and needs more solvation, thus decreasing the degrees of freedom. Since $T\Delta S^{\ddagger}$ is almost constant for these four compounds (Table III), $\Delta H^{\ddagger}$ is linearly related to $\Delta G^{\ddagger}$; so it is reasonable to consider Scheme II to explain the differences in enthalpy of activation. These can be visualized by considering the possible resonance structures (Scheme III).

Besides the classical resonance structures IV–VI, the nonclassical resonance structures VII and VIII are possible. In the neutral compound **3a** the contribution of all these resonance structures is of less importance than in anion **4a**, due to separation of change in **3a** vs. delocalization of negative charge in **4a**. Therefore, ring inversion of **3a** requires less energy than the corresponding process of **4a**. In the protonated form **5a** there is even more separation of charge, resulting in a smaller $\Delta H^{\ddagger}$.

One of the possible resonance structures, V, has a negative charge on carbon. In **3a** (R^1 = Ph) this negative charge can easily be accommodated. In **3d** (R^1 = CH_3) this accomodation is impossible, resulting in a lower resonance stabilization in the forms I and III of **3d**, relative to that of **3a**. Consequently, the ring inversion of **3a** requires more energy due to more initial-state stabilization. The delocalization energy of the 1,6-dihydro-1,2,4,5-tetrazines is between 50 and 70 kJ/mol. For comparison, the homotropylium cation has a delocalization energy of 93 kJ/mol and is thus more stabilized than the 1,6-dihydro-1,2,4,5-tetrazines.

In compounds **3b** and **3c** as well as in **4b** and **4c** with a methyl or ethyl group next to the hydrogen at position 6, the δ value of H^A is found at high field (2.22, 2.26, 1.18, and 1.02 ppm, respectively). This result leads to the conclusion that in these compounds the hydrogen is oriented above the plane of the ring and that the large group is in the exo position. In the other form there will be an interaction between the van der Waals radii of the nitrogens and the hydrogens of the methyl group. A large substituent at the homotropylium cation is in the exo position too.[12] An increase in temperature in order to bring about a ring inversion was not successful since these species decompose on heating. This indicates that the other conformation cannot be obtained. To gain more certainty about the proposed structure (Figure 1), we have planned to obtain an X-ray analysis of compound **3b** or **3c**.

With these results in mind, the explanation of the high-field chemical shift of the H_6 on adduct formation between 3-phenyl-1,2,4,5-tetrazine and liquid ammonia—as discussed in the beginning of this paper—is evident. The molecule is in the homotetrazole conformation; the amino group, being large, is in the exo position, and the hydrogen is oriented above the plane of the ring and thus appears at high field in the ^1H NMR spectrum. To our knowledge the occurrence of homoaromaticity in 1,6-dihydro-1,2,4,5-tetrazines has never been found and is, in general, unknown for aza aromatic systems.[13,14] All adducts of amide to aza aromatics known so far[13] have no homoaromatic properties. The chemical shift of 4–5.5 ppm observed in these systems excludes an orientation of the hydrogen attached to the sp^3 carbon atom above the plane of an aromatic ring, since this should result in a shift at much higher field.

Experimental Section

Melting points are uncorrected. Mass spectra were determined on an AEI MS 902 mass spectrometer. ^1H NMR spectra were recorded on a Varian EM 390 spectrometer equipped with a Varian EM 3940 variable-temperature controller (temperature ±2 K) or on a Varian XL-100-15 spectrometer. Me_4Si was used as internal standard (δ 0). In liquid ammonia the solvent peak was used as the standard. The spectra were converted to the Me_4Si scale by addition of 0.95 ppm. The pocket calculator was a Texas Instruments Ti-59 programmable calculator. Column chromatography was carried out over Merck silica gel 60 (70–230 mesh).

Preparation of Starting Materials. 3-Phenyl-1,2,4,5-tetrazine (2a) and 3-Methyl-1,2,4,5-tetrzine (2d). These compounds were prepared as described before.[15,16]

6-Methyl-3-phenyl-1,2,4,5-tetrazine (2b). This compound was prepared analogous to the procedure of Lang et al.[15] Accordingly, 21.1 g of acetamidine hydrochloride,[17] 13.4 g of benzimido ethyl ether hydrochloride,[17] and 50 mL of absolute ethanol were cooled at −10 °C. Then, 51 mL of hydrazine hydrate was added, keeping the temperature below 5 °C. The mixture was stirred for 3 h at 25 °C and then poured into 370 mL of water. The crystals were filtered off, and the water layer was continuously extracted with boiling chloroform for 2 days. The crystals were dissolved in the chloroform, and oxygen was bubbled through this solution for 3 days. After column chromatography on silica gel with petroleum ether (60–80 °C)/dichloromethane as eluent, 1.38 g of **2b** (11%) was obtained: mp 74.5–76 °C (lit.[18] mp 75 °C); mass spectrum, m/e 172 (M^+); ^1H NMR ($CDCl_3$) δ 3.01 (3 H, s, CH_3), 7.38–7.54 (3 H, m, m/p-H), 8.36–8.55 (2 H, m, o-H). Anal. Calcd for $C_9H_8N_4$: C, 62.78; H, 4.68. Found: C, 62.60; H, 4.87.

6-Ethyl-3-phenyl-1,2,4,5-tetrazine (2c). This compound was prepared according to the same procedure as described for **2b**; from 24.2 g of propionamidine hydrochloride was obtained 1.74 g (13%) of a dark purple oil of **2c**: mass spectrum, m/e 186 (M^+); exact mass measurement $C_{10}H_{10}N_4$ (M^+), 186.0905 (theoretical 186.0905); ^1H NMR ($CDCl_3$) δ 1.54 (3 H, t, CH_3), 3.36 (2 H, q, CH_2), 7.39–7.63 (3 H, m, m/p-H), 8.40–8.60 (2 H, m, o-H). Anal. Calcd for $C_{10}H_{10}N_4$: C, 64.50; H, 5.41. Found: C, 64.29; H, 5.48.

Reductions with Sodium Borohydride. General Procedure. To a solution of 2 mmol of the 1,2,4,5-tetrazine (**2a–d**) in

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(14) J. Daunis, L. Djounaihifdi, and H. Lopez, *J. Heterocycl. Chem.*, **16**, 427 (1979).
(15) S. A. Lang, Jr., B. D. Johnson, E. Cohen, *J. Heterocycl. Chem.*, **12**, 1143 (1975).
(16) A. D. Counotte-Potman and H. C. van der Plas, *J. Heterocycl. Chem.*, **15**, 445 (1978).
(17) A. W. Dox, *Org. Synth.* **8**, 1 (1928).
(18) R. A. Bowie, M. D. Gardner, D. G. Neilson, K. M. Watson, S. Mahmood, and V. Ridd, *J. Chem. Soc., Perkin Trans. 1*, 2395 (1972).

Table IV. Physical Data of Compounds 3a-d Obtained by Sodium Borohydride Reduction

compd	yield, %	mp, °C	IR ($CHCl_3$),[b] cm^{-1}	analyses, % calcd C	calcd H	found C	found H
3a	80	83-85	3390, 3210	59.98	5.04	60.18	5.17
3b	68	106.5-108	3395, 3200	62.05	5.79	61.81	5.78
3c	55	95-96.5	3395, 3210	63.81	6.43	63.52	6.56
3d[a]	29	oil	3405, 3220	36.72	6.16	38.55	6.76

[a] This compound was found to be unstable. It was impossible to obtain reproducible microanalytical data because during weighing the compound evolved gas due to decomposition. Compound 3d was further identified by comparing its UV spectroscopic data [pH 7.5 λ_{max} (water) 421 nm (log ϵ 2.70), 306 (3.43); pH 12.9 λ_{max} (water) 339 (3.34)] with those of 3,6-dimethyl-1,6-dihydro-1,2,4,5-tetrazine[6] [pH 7.5 λ_{max} (water) 418 nm (log ϵ 2.66), 305 (3.43); pH 12.9 λ_{max} (water) 347 (3.33)]. [b] For NH in each case.

Table V. ^1H NMR Data of Compounds 3a-d, 4a-c, and 5a at 306 K in CD_3OD/D_2O (4:1)[a]

compd	6-CH_3	6-CH_2	CH_3	o-H	m/p-H	3-CH_3	NH[b]
3a				7.79-7.93 (m)	7.34-7.48 (m)		6.7 (br s)
3b	2.00 (m)			7.79-7.93 (m)	7.34-7.48 (m)		5.3 (br s)
3c		2.51 (m)	1.35 (t)	7.79-7.93 (m)	7.34-7.48 (m)		6.2 (br s)
3d						2.48 (s)	6.0 (br s)
4a				7.74-7.88 (m)	7.16-7.42 (m)		
4b	1.99 (d)			7.74-7.88 (m)	7.16-7.42 (m)		
4c		2.45[c]	1.33 (t)	7.74-7.88 (m)	7.16-7.42 (m)		
5a				7.81-7.95 (m)	7.43-7.55 (m)		

[a] The chemical shifts of the protons on position 6 are in Table I. [b] In $CDCl_3$; the other protons are in similar positions as in CD_3OD/D_2O. [c] Quintet.

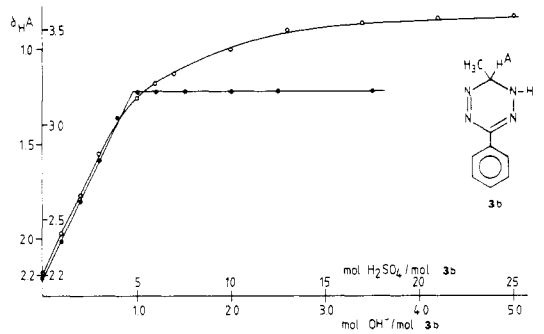

Figure 3. Chemical shifts of H^A of 3-phenyl-6-methyl-1,6-dihydro-1,2,4,5-tetrazine **3b** upon deprotonation (closed circles) and protonation (open circles) in CD_3OD/D_2O (4:1).

8 mL of ethanol and 4 mL of chloroform was added a solution of 76 mg of $NaBH_4$ in 3 mL of ethanol and 1 mL of water dropwise. The color changed from red to yellow. After the mixture was stirred for 15 min, some solid $NaBH_4$ was added in order to complete the reaction. Then water and 1 g of NH_4Cl were added. After extraction of the water layer with chloroform, drying of the extract over $MgSO_4$, and evaporation of the chloroform, 1,6-dihydro-1,2,4,5-tetrazine was obtained and purified by recrystallization from ether–pentane or by preparative thin-layer chromotography over silica gel PF_{254} (2 mm) eluted with 5% ether in dichloromethane. The yields and physical data are summarized in Table IV. For ^1H NMR spectrocopic data see Tables I and V. The compounds were stored at −20 °C.

Protonation of 1,6-Dihydro-1,2,4,5-tetrazines 3a and 3b. Like tetrazoles,[19] 1,6-dihydro-1,2,4,5-tetrazines are easily protonated as can be seen in Figure 3. In Figure 3 the chemical shift of H^A of **3b** is plotted against the moles of sulfuric acid added per mole of **3b** (open circles). For comparison (closed circles) the deprotonation of **3b** to **4b** is also given. After addition of 1 mol of sodium hydroxyde/mol of **3b** the deprotonation is complete, and the chemical shift remains constant. The protonation of **3b** to **5b** gives about the same lineair *increase* in chemical shift as the *decrease* in deprotonation. After addition of 5 mol of sulfuric acid the linearity stops, and the curve slowly reaches a maximum. From anaology with the deprotonation we concluded that after addition of 5 mol of sulfuric acid, a monoprotonated dihydrotetrazine is obtained, **5b**. So the pK_a of **5b** is about 0.4.[19] In the same way 3-phenyl-1,6-dihydro-1,2,4,5-tetrazine (**3a**) was protonated to **5a**.

Acknowledgment. We thank Dr. M. J. A. de Bie (R. U. Utrecht) and Dr. J. F. J. Engbersen for valuable discussions, Mr. H. Jongejan for carrying out the microanalyses, and Dr. C. A. Landheer and Mr. W. P. Combé for the mass spectrometric data.

Registry No. 2a, 36022-11-4; **2b**, 38634-12-7; **2c**, 76630-73-4; **2d**, 67131-36-6; **3a**, 76630-74-5; **3b**, 76630-75-6; **3c**, 76630-76-7; **3d**, 76630-77-8; **4a**, 76630-78-9; **4b**, 76630-79-0; **4c**, 76630-80-3; **5a**, 76630-81-4; **5b**, 76630-82-5; **6**, 32731-02-5; acetamidine hydrochloride, 124-42-5; benzimido ethyl ether hydrochloride, 5333-86-8; propionamidine hydrochloride, 3599-89-1.

(19) The pK_a of 5-phenyltetrazole is −2.24. V. N. Strel'tsova, N. P. Shirokova, G. I. Koldobskii, and B. V. Gidaspov, *Zh. Org. Khim.*, **10**, 1081 (1974).

(20) The plots obtained from the Eyring equation gave the following for **3a**, **3d**, **4a**, **5a**, respectively. **3a**: $y = (-1311 \pm 39)x + (4.55 \pm 0.14)$; $r = -0.997$; $t_\alpha = -33.8$; $n = 8$. **3d**: $y = (-1066 \pm 57)x + (3.78 \pm 0.20)$; $r = -0.990$; $t_\alpha = -18.6$; $n = 9$. **4a**: $y = (-1938 \pm 123)x + (5.21 \pm 0.45)$; $r = -0.992$; $t_\alpha = -15.8$; $n = 6$. **5a**: $y = (-1137 \pm 35)x + (3.88 \pm 0.13)$; $r = -0.997$; $t_\alpha = -32.7$; $n = 9$.