# $^1H$ and $^{13}C$ Nuclear Magnetic Resonance Studies on the Tautomerism, Geometrical Isomerism, and Conformation of Some Cyclic Amidines, Guanidines, and Related Systems[1a]

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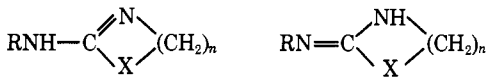
**Abstract:** A general method is developed using $^1H$ and $^{13}C$ NMR chemical shifts to determine unambiguously the predominant tautomeric form of many known aryl cyclic amidines and guanidines, 2-aminoimidazoles, 2-imino(amino)thiazines, and related tautomeric systems. In the case of 2-aryliminopyrrolidines, evidence for geometrical isomerism was found in both $^1H$ and $^{13}C$ NMR experiments. These results support the conclusion that, in all these potentially tautomeric systems under the present studies, the predominant tautomer is in the *imino* form [ArN=C(NHR)R′] rather than the *amino* form [ArNHC(=NR)R′].

Many compounds containing an amidine moiety[4] are known to possess interesting biological properties, particularly as antihypertensive agents.[5] Structures of these compounds have usually been presented in the literature as a presumed, predominant tautomer without supporting evidence and, in general, distinction between the two tautomers is difficult. Tautomerism in cyclic amidines (**1**) has been extensively studied.[6] In these systems, the problem is further complicated by the fact that the imino tautomer (**1b**)

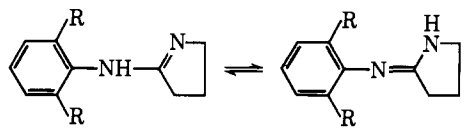


amino tautomer **1a** imino tautomer **1b**

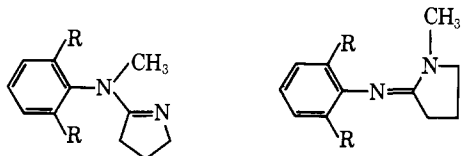
can exist as two geometrical isomers, the interconversion of which is related to processes similar to those studied for certain imines,[7] guanidines,[8] and hydrazones.[9]

In this paper, we describe NMR studies of some aspects of tautomerism, geometrical isomerism, and conformational change in systems of type **1**. In particular, we describe what appears to be a general method of distinguishing between **1a** and **1b** in the common and important cases where R is phenyl or substituted phenyl.

**Cyclic Amidines.** The 2-aminopyrroline-2-iminopyrrolidine tautomeric system was selected for investigation. The method of approach involved comparison of both $^1H$ and $^{13}C$ chemical shifts of the tautomeric system **2** with those of model compounds **3** and **4** in which the amino and imino



**2a** **2b**



**3** **4**

forms are established by appropriated N-methylation. The aromatic region of the proton spectra of models **8** and **9** are shown in Figure 1, together with that of the parent compound **7**, and chemical shift data are assembled in Table I. Two features of the spectra are particularly striking. First, the amino structure (e.g., **3**) is characterized by a substantial deshielding (0.3 ppm) of the protons of the 5 position relative to the imino isomer. Secondly, the para protons of the imino form are abnormally *shielded* (ca. 0.5 ppm) relative to the meta protons and to those of benzene itself. The first feature is attributed to the fact that the 5-methylene group in **3** is adjacent to an $sp^2$ hybridized nitrogen atom, and its protons will experience additional deshielding analogous to that observed for allylic protons in alkenes. The second effect indicates an increase of electron density at the para position in the tautomer **4**. Before considering the origin of this increased electron density, more direct evidence for its existence is presented from a consideration of $^{13}C$ chemical-shift data.

The $^{13}C$ chemical shifts for a series of cyclic amidines are presented in Table II. In the five-membered series, the assignments to the carbon atoms are straightforward. C(4), which experiences no serious perturbation of its charge density, is assigned to the resonance 18–22 ppm at highest field. It appears as a triplet in an off-resonance decoupled spectrum, as do the resonances in the region 28–30 and 44–56 ppm, the latter being assigned to C(5) since it is directly attached to a nitrogen atom. The resonances in the ranges 140–149 and 163–169 ppm are singlets in undecoupled spectra, and the latter is assigned to C(2) of the heterocyclic ring since oximes are known to absorb in the range 150–160 ppm,[10] whereas the former is nearer the range for aromatic carbon attached to an amino- or acetamidonitrogen (Table III). The assignments of the signals to the remaining five carbon atoms are mostly unambiguous, being based on considerations of intensities and on the existence or absence of spin–spin coupling to directly bonded protons. Only in the case of the phenyl derivative **5** is there an ambiguity, and here the assignment is based on the reasonable assumption that the ortho- and para-carbon atoms will have closely similar chemical shifts. In the six-membered series, all resonances except those of C(4) and C(5) can be uniquely assigned.

The $^{13}C$ chemical shifts clearly show that the para position of **9** has an electron density significantly in excess of that for the carbon atoms of benzene itself ($\delta$ 128.5)[11] and the para position of **8**. When due allowance for substituent

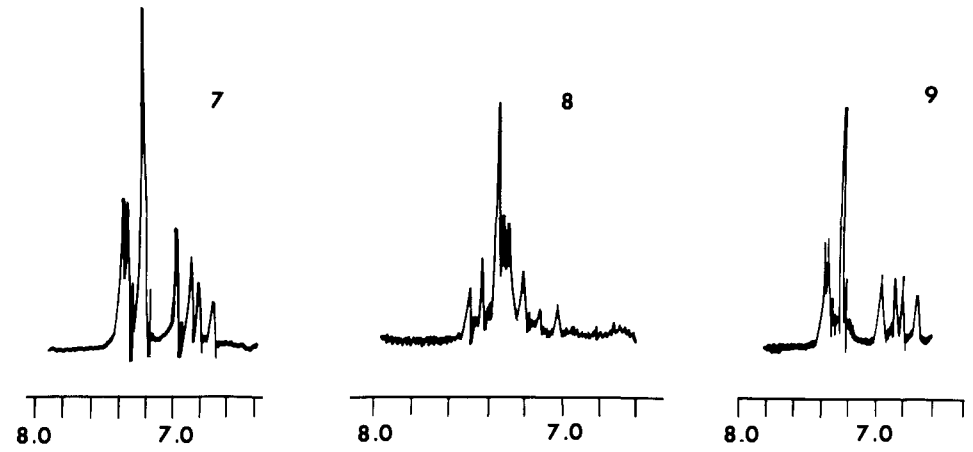
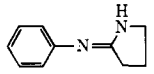
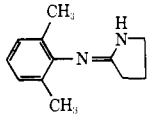
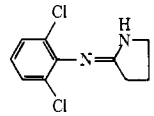
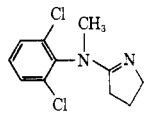
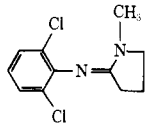


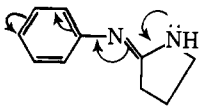

**Figure 1.** Partial $^1$H NMR spectra of compounds 7–9.

Table I. $^1$H NMR Spectral Data of Cyclic Amidines

| | | Solvent[a] | δ H-3 | H-4 | H-5 | $CH_3$ | $m^b$ | $p^b$ |
|---|---|---|---|---|---|---|---|---|
|  | (5) | A | 2.56 t | 2.04 m | 3.46 t | | | |
|  | (6) | A | 2.56 m | 2.05 m | 3.35 t | 2.10 | 6.97 | 6.81 |
| | (*anti*-6)[c] | A | 2.62 t | | | | | |
|  | (7) | A | (1.68–2.88)[d] | | 3.40 | | 7.22 | 6.80 |
| | | B | 2.50 m | 2.14 m | 3.43 t | | | |
| | | C | 2.04 t | 1.32 m | 2.80 t | | | |
| | (*anti*-7)[c] | A | 2.71 t | | | | | |
|  | (8) | A | (1.60–2.40)[d] | | 3.76 t | 3.23 | 7.42 | 7.24 |
|  | (9) | A | (1.58–2.44)[e] | | 3.43 t | 3.04 | 7.25 | 6.78 |

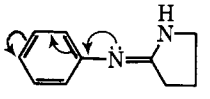
[a] A = $CDCl_3$; B = $CH_3OH$-$d_4$; C = $C_6D_6$. [b] Chemical shifts were determined by $AB_2$ analysis. [c] Determined at −40° on a Perkin-Elmer R-32 90 MHz instrument. [d] Unresolved multiplet. [e] Unresolved multiplet remained unchanged at −35 and 60°.

effects is made,[12,13] it is found that the ortho positions are similarly affected. This enhanced charge density could, in principle, arise from delocalization of the type shown in **13**,



**13**

but this is not feasible in the ortho,ortho′-disubstituted derivatives since the two participating π systems will be rendered orthogonal by steric effects. It is likely then that delocalization of the lone pair of the exocyclic nitrogen atom is responsible for the observed shieldings (cf. **14**) of the ortho

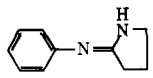
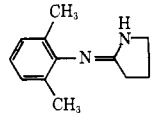
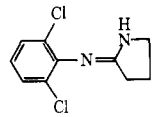
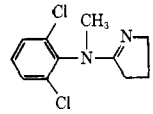
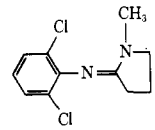
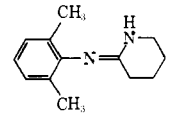
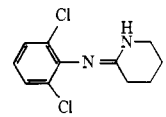


**14**

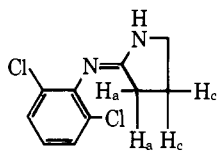
and para positions, and that the two rings are orthogonal even in the unsubstituted case, **5**. The hybridization of the exocyclic nitrogen atom must be between $sp^2$ and sp, although, as we shall see shortly, it certainly retains substantial $sp^2$ character. We conclude, therefore that shielding of the ortho and para carbon atoms results in the system Ar—N=C—N but not in Ar—N—C=N-. More convincing evidence in support of this statement is provided below where other classes of compounds are considered. Note that the use of this finding *as a means of establishing the tautomeric structures of N-arylamidines* does not require the presence of an unsubstituted para position, since the $^{13}$C chemical shift of this position can always be corrected for the presence of a directly attached substituent.[12]

Evidence for the existence of geometrical (syn and anti) isomers in most of the pyrrolidines is found in both the $^1$H and $^{13}$C spectra, and the rates of their interconversion are comparable with the NMR time scales at room temperature. Figure 2 illustrates the temperature dependence of the proton spectrum of **7**. The signals of $H_a$, $H_b$, and $H_c$ appear

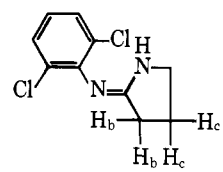
Table II. $^{13}C$ Chemical Shifts[a] for Cyclic Amidines

| | | s | o | m | p | 2 | 3 | 4 | 5 | 6 | $CH_3$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
|  | 5 | 149.0 | 121.2 | 129.0 | 122.0 | 163.9 | 30.4 | 22.2 | 47.2 | | |
|  | 6[b] | 147.8 | 129.3 | 127.9 | 122.3 | *c* | 29.6[d] | 22.2 | 44.5 | | 18.0 |
|  | 7[b] | 146.1[b] | 128.3 | 128.9 | 122.8 | 167.5[d] | 28.4[d] | 21.9 | 44.4 | | |
| *syn*-7[e] | | 145.9 | 128.6 | 127.9 | 122.7 | 168.5 | 28.7 | 21.6 | 44.5 | | |
| *anti*-7[e] | | 144.6 | 127.7 | 127.9 | 122.7 | 163.4 | 30.7 | 21.6 | 44.5 | | |
|  | 8 | 140.5 | 136.1 | 128.5 | 128.5 | 166.6 | 32.0 | 24.1 | 57.1 | | 36.3 |
|  | 9 | 147.3 | 128.3 | 127.8 | 122.2 | 163.5 | 28.7 | 19.4 | 51.7 | | 31.4 |
| 9·HCl | 10 | 133.4 | 131.0 | 128.2 | 129.2 | 167.1 | 30.5 | 18.1 | 56.2 | | 34.6 |
|  | 11 | *c* | 129.3 | 127.9 | 122.1 | *c* | 30.7[d] | (23.3, 21.6)[f] | | 42.5 | 17.9 |
|  | 12 | *c* | 128.5 | 128.0 | 122.7 | *c* | 28[d] | (22.7, 20.6)[f] | | 42.1 | |
| *syn*-12[g] | | 144.5 | 128.5 | 127.9 | 122.6 | 160.9 | 26.3 | (22.2, 20.1)[f] | | 42.3 | |
| *anti*-12[g] | | 142.9 | 128.2 | 127.8 | 123.4 | 157.0 | 30.2 | (22.2, 20.6)[f] | | 41.6 | |

[a] In parts per million from internal $Me_4Si$ in $CDCl_3$ at 31°. [b] Data for equilibrating mixture of syn and anti isomers. [c] Unobservable presumably because of exchange broadening. [d] Exchange broadened. [e] Determined at −60°. [f] Individual assignments cannot be made. [g] Determined at −70°.



*syn*-7



*anti*-7

as an unresolved multiplet at 37° in $CDCl_3$ solution. At 60°, this band is partially resolved into a broad singlet (two protons) overlapping with a two-proton multiplet at higher field (Figure 2a). The broad singlet corresponds to the coalesced $H_a$ and $H_b$ signals and the multiplet to the $H_c$ signal. At −40°, the spectrum (Figure 2c) shows a new triplet at lower field ($\delta$ 2.80, $J$ = 6 Hz) which integrates for 20% of a methylene group. This signal is assigned to $H_b$ of the anti isomer which therefore constitutes 20% of the mixture. This assignment is based on the following considerations. The aromatic ring in the syn isomer must assume a conformation perpendicular to the plane of the pyrrolidine ring in order to minimize the steric interactions of the chlorine atoms with $H_a$. In this conformation, $H_a$ is expected to be shielded by the aromatic ring current and therefore shifted to higher field. The observed downfield triplet ($\delta$ 2.80) is not consistent with this expectation and must therefore arise from $H_b$ of the anti isomer. The triplet (at 60°) near $\delta$ 3.50 becomes overlapping triplets at −40° indicating a small difference in the chemical shift of the C(5) protons in the two isomers. It was found that the population of isomers was influenced by solvent effects. In methanol-$d_4$ solution at −55°, the anti isomer constitutes 90% of the mixture and, in methanol-$d_4$–$CDCl_3$ (1:15), the two isomers exist in equal proportions.

Table III. $^{13}C$ Chemical Shifts[a] for Some Anilines and Acetanilides

| | s | o | m | p | $ArCH_3$ |
|---|---|---|---|---|---|
| $C_6H_5NH_2$ | 147.9 | 116.3 | 130.0 | 119.2 | |
| $C_6H_5NHCOCH_3$ | 138.0 | 120.4 | 128.7 | 124.1 | |
| 2,6-$(CH_3)_2C_6H_3NH_2$ | 142.7 | 121.4 | 128.1 | 117.8 | 17.4 |
| 2,6-$(CH_3)_2C_6H_3NHCOCH_3$ | 135.5 | 128.5 | 128.0 | 127.2 | 18.3 |
| 2,6-$Cl_2C_6H_3NH_2$ | 140.0 | 119.5 | 127.7 | 118.0 | |
| 2,6-$Cl_2C_6H_3NHCOCH_3$ | 135.0 | 130.6 | 128.8 | 128.8 | |

[a] See footnote *a*, Table II.

Two possible mechanisms for geometrical isomerization involving a doubly bonded nitrogen atom have been considered.[7-9] One is referred to as the "lateral shift" mechanism involving a linear transition state. The second is termed the "internal rotation" mechanism and involves a rotation, of one-half of the molecule with respect to the other half, about an axis through the doubly bonded carbon and nitrogen atoms. In amidines, a third possibility, involving tautomerism, exists and may be referred to as the "tautomeric

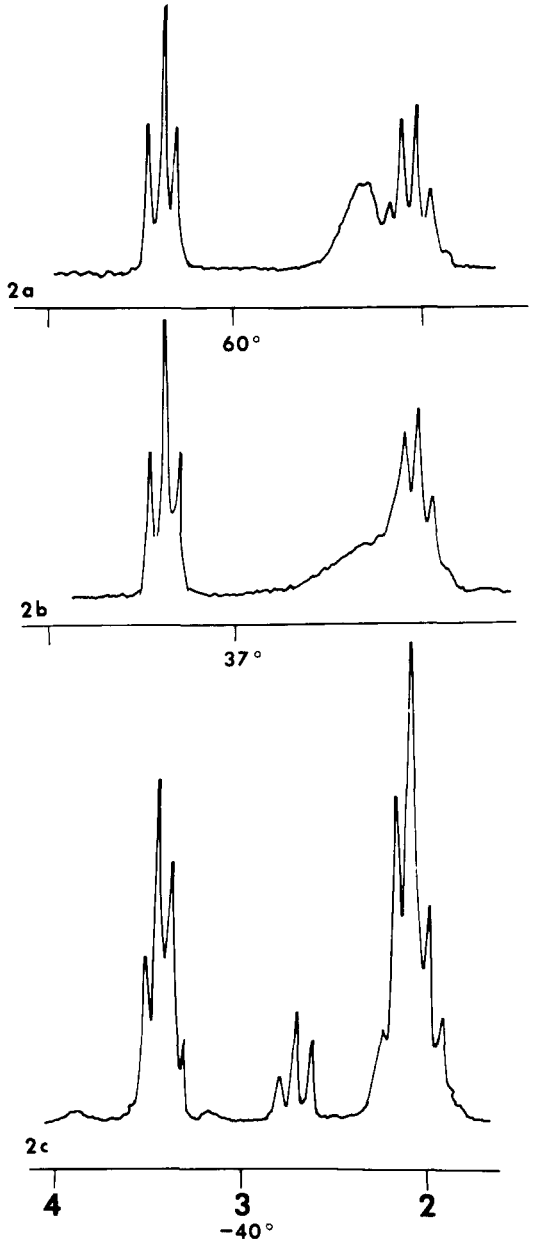
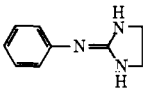
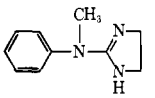
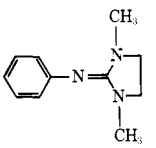
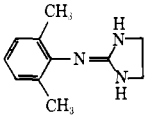
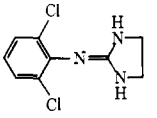
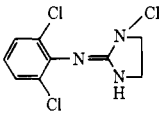
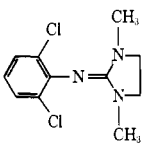



**Figure 2.** Partial $^1$H NMR spectra of compound **7** at various temperatures determined on a Perkin-Elmer R-32 90 MHz spectrometer.

rotation" mechanism. This process would involve prototropic tautomerization to the amino form **1a,** rotation of the pyrroline ring about the exocyclic C–N bond, and a retrograde tautomerization to the other geometrical isomer, **1b.** The first mechanism has been generally considered to be more favorable than the second for isomerization of the C=N—R moiety. The energetics of the third mechanism which we propose have not yet been defined. The second mechanism may be subject to acid catalysis and the third mechanism, depending as it does on a prototropic rearrangement, can involve either acid or base catalysis. In practice, the measurements were carried out in carefully purified chloroform, and we do not believe that acid catalysis is occurring. Although we have not carried out detailed line-shape analysis, it is clear that, at room temperature, the rate constants for isomerization are of the order of $10^2$ $sec^{-1}$ corresponding a free energy of activation of 15 kcal $mol^{-1}$ at room temperature. Such a low barrier is consistent with the lateral shift mechanism particularly in ortho,ortho'-disubstituted phenyl derivatives in which we have clear evi-

Table IV. $^1$H NMR Spectral Data of Cyclic Guanidines[a]

| | | δ | | | |
|---|---|---|---|---|---|
| | | H-4, H-5 | $CH_3$ | *m*[b] | *p*[b] |
|  | (15) | 3.45 s | | | |
|  | (16) | 3.64 s | 3.38 | | |
|  | (17) | 3.25 s | 2.65 | 7.11[c] | 6.78[c] |
|  | (18) | 3.41 s | 2.16 | 7.00 | 6.83 |
|  | (19) | 3.49 s | | 7.23 | 6.80 |
|  | (20) | 3.41 s | 3.00[d] | 7.28 | 6.82 |
|  | (21) | 3.34 s | 2.66 | 7.20 | 6.76 |

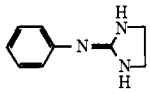
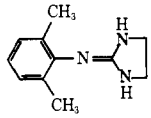
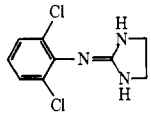
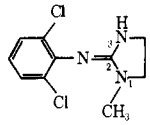
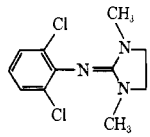
[a] All spectra were determined in $CDCl_3$. [b] Chemical shifts were determined by $AB_2$ analysis. [c] Determined at 300 MHz. δ = 6.83 ppm for ortho H. [d] Unchanged at −40°.

dence for delocalization of the imino nitrogen lone pair into the aromatic ring. Such delocalization will be more highly developed in the linear transition state which will consequently be of lower energy. No evidence for the coexistence of both isomers was found in the spectra of 2-phenyliminopyrrolidine (**5**) itself. The chemical shift of the C(3) protons is 2.50 compared with 2.62 for the anti isomer of the *o,o'*-dimethyl derivative. Absence of apparent isomerism in the phenyl system down to −30° could be a reflection of an extremely lower barrier, or merely because the anti isomer overwhelmingly predominates. The second alternative is at least plausible since the ratio of syn to anti changes from 4:1 in the dichloro derivative to 1:12 in the dimethyl system.

Of course, the very existence of geometrical isomerism in these systems constitutes firm proof that they have the imino structure, **1b.**

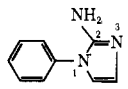
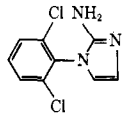
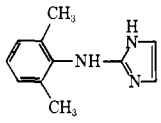
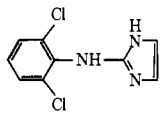
**Cyclic Guanidines.** Structures of potentially tautomeric cyclic guanidines have been generally expressed in the amino form as exemplified by the antihypertensive agent clonidine[14] (**19**). We now show that this compound exists predominantly in the imino form.[15] The proton chemical shifts for a series of cyclic guanidines are presented in Table IV. In the compounds **17** and **21,** which are fixed in the imino structure, the para protons are substantially more shielded than the meta protons, in contrast to the "fixed" model **16** for the amino tautomer in which all five aromatic protons absorb in a narrow range (7.20–7.53 ppm). Thus, on the basis of the chemical shifts of the para protons, clonidine (**19**) together with **15, 18,** and **20** is assigned the imino structure. These conclusions are confirmed by the $^{13}$C

Table V. $^{13}C$ Chemical Shifts[a] for Cyclic Guanidines

| | | s | o | m | p | 2 | 4 | 5 | $CCH_3$ or $NCH_3$ |
|---|---|---|---|---|---|---|---|---|---|
|  | (15) | 150.0 | 122.7 | 128.9 | 121.3 | 158.4 | 42.6 | 42.6 | |
|  | (18) | 147.6 | 130.9 | 127.7 | 121.7 | 156.2 | 42.4 | 42.4 | 18.2 |
|  | (19) | 145.2 | 129.7 | 128.2 | 122.5 | 157.8 | 42.5 | 42.5 | |
|  | (20) | 145.2 | 129.2 | 128.1 | 122.3 | 155.9 | 40.3 | 49.4 | 32.5 |
|  | (21) | 145.6 | 128.2 | 127.5 | 120.6 | 155.1 | 48.3 | 48.3 | 33.9 |

[a] See footnote *a*, Table II.

Table VI. $^{13}C$ Chemical Shifts[a] of 2-Amino-1-aryl- and 2-Arylaminoimidazoles

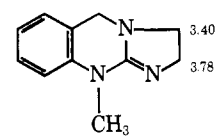
| | | s | o | m | p | 2 | 4 | 5 |
|---|---|---|---|---|---|---|---|---|
|  | (23) | 147.4 | 124.5 | 129.7 | 125.0 | 137.1 | 127.7 | 115.7 |
|  | (24) | 147.4 | 132.2 | 119.0 | 125.6 | 135.0 | 130.7 | 115.3 |
|  | (25)[c] | *b* | 135.6 | 128.9 | 126.4 | *b* | 117.8 | 117.8 |
|  | (26) | *b* | 129.6 | 128.9 | 125.3 | 135.7 | 118.5 | 118.5 |

[a] See footnote *a*, Table II. [b] Too weak for detection. [c] $CCH_3$, 18.2.

chemical shifts presented in Table V. As in the cyclic amidines, the imino tautomers are characterized by the shielded nature of the para carbon atom which fall in the same narrow range 120–123 ppm.

Further evidence for the predominant existence of the imino tautomer in this series is provided by a consideration of the chemical shifts of the methylene protons. In the imino forms, viz., **15, 18,** and **19,** these protons absorb as singlets near $\delta$ 3.45. In contrast, those of the amino model **16** are found at 3.64 again as a singlet. In all probability this latter system is undergoing a rapid, degenerate tautomerism since no coupling between the NH and the methylene protons is observed. Thus the observed shift of 3.64 for **16** is presumably the average of 3.45 found for **15** and approximately 3.83. These predicted chemical shifts are in reasonable agreement with those found in the fixed model compound **22.**[16]

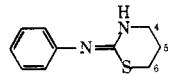
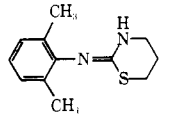
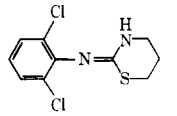
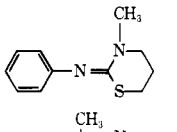
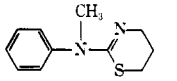
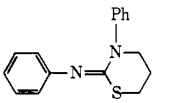
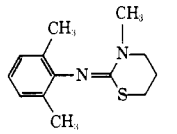
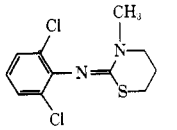
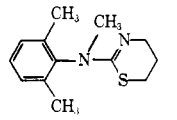
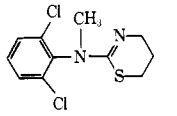
No evidence for geometrical isomerism has been observed in this series. It is known that the barriers to rotation about the C=N in guanidines are substantially lower than in simple amidines.




**22**

**2-Aminoimidazoles.** Because the aromatic nature of the imidazole ring, both 1-aryl and 2-arylamino derivatives serve as models for the amino tautomer **1.** In particular, the lone pair of electrons of the 1-nitrogen atom in **23** or **24** is a part of the aromatic $\pi$-electron system of the imidazole ring and is not expected to be available for delocalization into an 1-aryl substituent. $^{13}C$ data for four compounds are recorded in Table VI. In all cases, the ortho and para protons are less shielded than the carbon atoms of the analogously substituted arylimino compounds discussed above.

Table VII. $^1$H NMR and Uv Spectral Data of 2-Amino(imino)thiazines

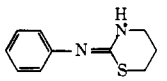
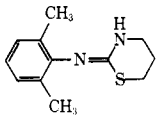
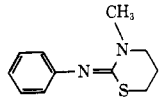
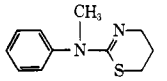
| | | NMR solvent[a] | δ H-4 | δ H-5 | δ H-6 | δ $CH_3$ | δ *m*[b] | δ *p*[b] | λ, mμ (ε) Observed[c] | λ, mμ (ε) Reported |
|---|---|---|---|---|---|---|---|---|---|---|
|  | (27) | A<br>B | 3.35 t<br>3.44 t | 2.00 m<br>2.02 m | 2.92 t<br>3.04 t | | | | 260 (9575) | 262 (8850)[d] |
|  | (28) | A<br>C | 3.35 t<br>3.20 t | 2.06 m<br>1.90 m | 2.92 t<br>2.85 t | 2.15<br>2.04 | 7.01 | 6.82 | 232 (13,830) | |
|  | (29) | C | 3.31 t | 2.00 m | 3.00 t | | 7.45 | 7.02 | | |
|  | (30) | A<br>B | 3.38 t<br>3.38 t | 2.18 m<br>2.13 m | 2.90 t<br>2.87 t | 3.17<br>3.12 | | | 232 (12,160)<br>270 (6040) | 233 (14,000)[d] |
|  | (31) | A | 3.73 t | 1.83 m | 2.92 t | 3.25 | | | 258 (5730) | 260 (5650)[e] |
|  | (32) | | | | | | | | | 264 (4516)<br>288 (4300)[e] |
|  | (33)[f] | A | 3.37 t | 2.12 m | 2.85 t | 2.12<br>3.20 | | | | |
|  | (34)[f] | A | 3.43 t | 2.15 m | 2.92 t | 3.25 | 7.28 | 6.85 | | |
|  | (35)[f] | A | 3.70 t | 1.78 m | 2.90 t | 2.22<br>3.12 | | | | |
|  | (36)[f] | A | 3.70 t | 1.80 m | 2.96 t | 3.14 | 7.36 | 7.18 | | |

[a] A = $CDCl_3$; B = $CH_3OH$-$d_4$; C = $Me_2SO$-$d_6$. [b] Chemical shifts were determined by $AB_2$ analysis. [c] Uv spectra were obtained in EtOH on a Cary Model 14 instrument. [d] Reference 19. [e] Reference 18. [f] $^1$H NMR data reported in ref 24.

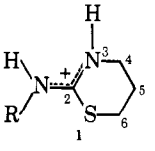
**2-Aryliminotetrahydro(arylaminodihydro)-1,3-thiazines.** There has been as much interest and confusion in the recent literature concerning the predominant tautomeric form of compounds of the type **27** (Table VII). Compound **27** was first synthesized by Tisler,[17] and the imino form was assigned to it on the basis of a comparison of its ir and uv spectral data with those of presumed **30** and **32.** However, it was later shown by Najer and coworkers,[18] by an unequivocal synthesis of **30,** that Tisler's assignment of structure **30** was incorrect and should have been **31** instead. These workers, on the basis of additional ir and uv spectral data, reversed Tisler's assignment of tautomeric structure **27.** They also reported[19] their interpretation of $pK_a$ determinations for a series of related compounds and claimed that these data supported the amino form as the predominant tautomer. More recently, Rabinowitz[20,21] described NMR studies which he claimed to concur with Tisler's assignment. Toldy and coworkers[22] also substantiated Rabinowitz's view.

A critical examination of these conflicting results and interpretations casts some doubt on the validity of the arguments in each case. Tisler's conclusion was apparently invalidated by the mistaken identity of the model compound **30.** The argument of Najer and coworkers[18] based on uv spectral data is inconsistent with other uv spectral data (Table VII). Although the uv absorption of **27** resembles that of the amino form **31** rather than the imino form **30,** the fact that there is a qualitative difference between the uv absorptions of the two imino structures **30** and **32** and the remarkable resemblance of uv spectra between **28** and the imino form **30** casts serious doubt on the validity of the use of uv spectral data for determination of tautomeric structures under present consideration. The interpretation of NMR spectral data by Rabinowitz is not convincing. First of all, a suitable model compound (e.g., **31**) to represent the amino form was not included. Secondly, the existence or absence of coupling between the C(4) methylene protons and an NH proton in the spectra of the *protonated* ions was unjustifiably claimed as a criterion for determining whether a free base exists in the imino form (i.e., coupling observed) or the amino form (i.e., coupling not observed). It is obvious

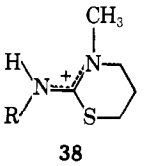
Table VIII. $^{13}C$ Chemical Shifts[a] of 2-Aminothiazines

| | | s | o | m | p | 2 | 4 | 5 | 6 | $CH_3$ |
|---|---|---|---|---|---|---|---|---|---|---|
|  | 27 | 146.7 | 122.1 | 128.6 | 122.5 | 152.0 | 27.1 | 22.7 | 42.9 | |
|  | 28 | 145.5 | 130.8 | 127.5 | 122.7 | 152.4 | 26.9 | 23.5 | 42.0 | 18.0 |
|  | 30 | 150.0 | 122.8 | 128.5 | 122.5 | 152.3 | 27.6 | 24.6 | 50.5 | 39.9 |
|  | 31 | 145.1 | 128.8[b] | 128.3[b] | 126.5 | 150.6 | 27.4 | 20.6 | 46.3 | 39.3 |

[a] See footnote *a*, Table II. [b] These assignments may be reversed.

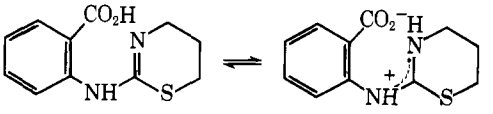


37



38

that, in the protonated ion of a 3-unsubstituted derivative **37,** each of the two nitrogen atoms is protonated permitting maximum delocalization of the positive charge. The protonated ions of the two tautomeric forms are therefore identical. However, in the protonated ion of the 3-*substituted* imino form **38,** the proton is attached only to the imino nitrogen for the same reason. The rationalization of Rabinowitz undoubtedly could lead to erroneous conclusions in structural assignments such as **39.** In contrast to the other

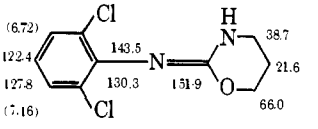


39

members of the series, the amino form was reportedly assigned, because no coupling between the C(4) protons and the NH proton was observed in the spectrum determined in TFA solution.[21] The absence of NH coupling (in the absence of NH signal) is a consequence of the rate of NH exchange in such a system and does not reflect the position of the imino bond. In the particular case of **39,** the molecule most likely exists in the zwitterion, and the question of tautomerism does not arise.

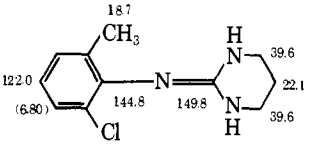
The various reasons stated above prompted us to extend our investigations to this series of compounds. Model compounds **30, 31,** and **40** were examined. Our uv spectral data for **27, 30,** and **31** (Table VII) confirm the reported values and also the vulnerability of this method. The NMR spectral data show that the chemical shifts of the C(4) protons of **27** and **28** are similar to those of the imino form **30.** Although the spectrum of **29** was determined in $Me_2SO$-$d_6$ rather than $CDCl_3$, the chemical shift of the C(4) protons is not expected to be greatly affected by solvents ($Me_2SO$ vs. $CHCl_3$) as indicated by the case of **28.** The NMR spectral data of additional model compounds[23] (**33–36**) are in agreement with the suggestion that the predominant tautomer is the imino form. Conformational differences between the endocyclic and exocyclic six-membered ring may affect the chemical shift of the C(4) protons (more likely than in the five-membered ring series) so that some uncertainty remains. $^{13}C$ chemical shifts, however (Table VIII), provide a definitive means of establishing structure. Again, it is found that the ortho and para carbon atoms of the imino model **30** are abnormally shielded in contrast to the amino structure **31.** Thus it is clear that both **27** and **28** are the predominant tautomers.

The oxa analog **40** evidently also exists as the imino tautomer. The chemical shifts of the corresponding aromatic protons are indicated in parentheses.



40

**Miscellaneous Amidines and Guanidines.** Although we have concentrated on cyclic systems, the data in Table IX indicate that simple tautomeric aryl amidines and guanidines exist predominantly as the imino isomers. Similarly, the six-membered guanidine **46,** for which a complete assignment of the aromatic carbon resonance was not possible, appears to be the imino isomer since at least one of the aromatic carbon atoms absorbs at 122.0 ppm.



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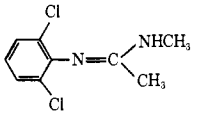
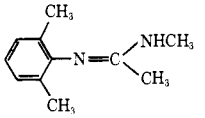
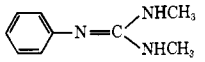
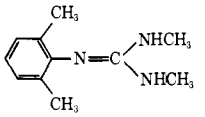
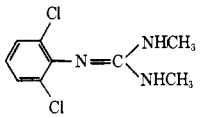
## Experimental Section

$^1H$ NMR spectra were determined on a Varian T-60 instrument at 37° unless otherwise noted. $^{13}C$ NMR spectral data were obtained with a JEOL PS-100-FT spectrometer. Chemical shifts are reported as parts per million from internal $Me_4Si$. Uv spectra were obtained on a Cary 14 spectrometer. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6E spectrometer. All NMR samples were free bases. Salts were converted to the corresponding free bases by basifying the aqueous solutions and extracting with $CH_2Cl_2$ or $Et_2O$ followed by evaporating the solvent and drying the residues.

Except for compound **16,** the preparations, biological activities, and literature references of the compounds described in this paper are reported elsewhere.[2]

Table IX. $^{13}C$ Chemical Shifts[a] of Acetamidines and Guanidines

| | | s | o | m | p | 1 | $NCH_3$ | $CCH_3$ | $ARCH_3$ |
|---|---|---|---|---|---|---|---|---|---|
|  | 41 | 146.2 | 128.2 | 127.9 | 122.6 | 158.6 | 28.5 | 18.2 | |
|  | 42 | 149.0 | 128.9 | 127.7 | 121.5 | 155.5 | 28.4 | 17.2 | 18.2 |
|  | 43 | 144.7 | 123.8 | 129.3 | 121.6 | 152.5 | 28.5 | | |
|  | 44 | 146.8 | 130.9 | 127.9 | 121.6 | 150.7 | 28.7 | | 18.1 |
|  | 45 | 144.2 | 129.7 | 128.2 | 122.1 | 152.9 | 28.7 | | |

[a] See footnote *a*, Table II.

**2-(*N*-Methyl)phenylamino-2-imidazoline (16).** (a) To a stirred mixture of *N*-methylaniline (53.5 g, 0.5 mol) and NaSCN (81 g, 1.0 mol) in benzene (500 ml) at 35–40° was added dropwise a solution of trifluoroacetic acid (85.5 g) in benzene (250 ml). After refluxing the solution for 4 hr and stirring at 25° for 18 hr, the solid material was dissolved by stirring with water. The benzene solution was washed with water, dried, and evaporated to dryness. The solid residue was recrystallized from benzene–cyclohexane to give 1-methyl-1-phenylthiourea (62.2 g), mp 99–103°.

Anal. Calcd for $C_8H_{10}N_2S$: C, 57.80; H, 6.06; N, 16.85. Found: C, 57.48; H, 6.14; N, 16.79.

A solution of the thiourea (25 g, 0.157 mol) and $CH_3I$ (32 g, 0.226 mol) in $CH_3OH$ (50 ml) was refluxed for 18 hr. The solvent was evaporated to dryness to give the corresponding *S*-methylthiuronium iodide (43.4 g).

The thiuronium salt (15 g, 0.049 mol) was dissolved in $CH_3OH$ (90 ml). The solution was refluxed with ethylenediamine (5.85 g, 0.097 mol) for 48 hr. After evaporation of the solvent, the residue was stirred with water. The mixture was basified with 10% NaOH solution and extracted with $CH_2Cl_2$. The $CH_2Cl_2$ solution was washed with brine and evaporated to an oil. The product (**16**)[24] was isolated by distillation as an oil (0.3 g): bp 114° (0.25 mm); mass spectrum *m/e* 175 ($M^+$); NMR (Table IV) consistent with assigned structure.

(b) A mixture of **15** (0.32 g, 2 mmol) and dimethyl sulfate (1.26 g, 10 mmol) in $C_6H_6$ (10 ml) was refluxed for 4 hr. After cooling, the solvent was separated from the oil. The aqueous solution of the oil was basified (10 *N* NaOH) and extracted with $CH_2Cl_2$. The extract was washed with brine and dried ($MgSO_4$). Evaporation of the solvent gave the product as an oil. The NMR and mass spectral data are in agreement with those of **16** prepared by the previous method.

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## References and Notes

(1) (a) This paper is Part VII in the series Amidines[2] and Part XIII in the series Studies in Nuclear Magnetic Resonance Spectroscopy.[3] (b) The Pennsylvania State University; (c) Smith Kline & French Laboratories.
(2) Part VI: T. Jen, H. Van Hoeven, W. Groves, R. A. McLean, and B. Loev, *J. Med. Chem.*, **18**, 90 (1975).
(3) Part XIII: V. R. Haddon and L. M. Jackman, *Org. Magn. Reson.*, **12**, 333 (1973).
(4) The term "amidine moiety" is used here to include those compounds containing the potentially tautomeric system –NH—C(X)=N– in which X = C, N, O, or S.
(5) For reviews, see (a) W. T. Comer and A. W. Gomoll, "Medicinal Chemistry", 3rd ed, Part II, A. Burger, Ed., Wiley-Interscience, New York, N.Y., 1970, Chapter 39, p 1019; (b) A. Kreutzberger, *Prog. Drug Res.*, **11**, 356 (1968), Birkhäuser, Ver. ag.
(6) For reviews, see (a) A. R. Katritzky and J. M. Lagowski, "Advances in Heterocyclic Chemistry", Academic Press, New York, N.Y., 1963: Vol. 1, p 312; Vol. 2, p 3; (b) G. Schwenker and K. Bösl, *Pharmazie*, **24**, 653 (1969).
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(15) Preliminary conclusion of this study was disclosed: T. Jen, B. Dienel, H. Bowman, J. Petta, A. Helt, and B. Loev. *J. Med. Chem.*, **15**, 727 (1972).
(16) See ref 15.
(17) M. Tisler, *Arch. Pharm. (Weinheim, Ger.)*, **65**, 621 (1960); *Tetrahedron Lett.*, 12 (1959).
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(20) E. Cherbuliez, Br. Baekler, O. Espejo, H. Jindra, B. Willhalm, and J. Rabinowitz, *Helv. Chim. Acta*, **50**, 331 (1967).
(21) J. Rabinowitz, *Helv. Chim. Acta*, **52**, 255 (1969).
(22) L. Toldy, P. Sohar, K. Farago, I. Toth, and L. Bartalits, *Tetrahedron Lett.*, 2167 (1970).
(23) P. Sohar and L. Toldy, *Magy. Kem. Foly.*, **78**, 535 (1972).
(24) A different preparation of **16** was claimed in British Patent 310,534 [*Chem. Abstr.*, **24**, 732[2] (1934)]. The compound was described as a solid (mp 131°) without supporting data for its structure.