

## IMINE-ENAMINE TAUTOMERISM IN HARMALINE

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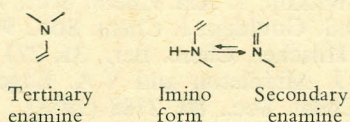
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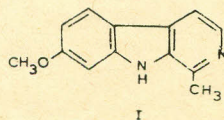
**Abstract.** The existence of an enamine tautomer of harmaline, in equilibrium with the imine form, has been demonstrated by NMR studies. Rapid deuteration of the exocyclic methyl group of harmaline in tetradeuteromethanol unambiguously established the existence of this equilibrium. The synthetic potentialities of these masked enamine systems has been discussed.

The tremendous synthetic potential of tertiary enamines was first recognized by Stork in 1954.<sup>1</sup> Since then, an intensive investigation has taken place to establish the breadth and limitations of these molecules for electrophilic substitution reactions. The less basic reaction conditions and the fact that enamines afford monoalkylated products only at the adjacent carbon give them a distinct advantage over the direct alkylation reactions of ketones via their enolates.

While some remarkably beautiful chemistry has been accomplished by utilizing the synthetic potential of tertiary enamines, hardly any work has been done on the chemistry of secondary enamines. This is primarily because secondary enamines predominantly exist in the imino form, both in aliphatic as well as cyclic compounds.<sup>2</sup> The possibility of a tautomeric equilibrium between the two forms has been recognized, though the equilibrium is invariably strongly displaced towards the imino form.<sup>3</sup>



During studies carried out on the enamine alkylations of *pyr-N*-methylharmaline with electrophilic olefins,<sup>4</sup> it was observed that when harmaline (I) was subjected to thin layer chromatography on silica gel GF-254 in 70% chloroform-30% methanol, it could be easily separated into two greenish fluorescent bands ( $R_f$  0.3 and 0.5). The slower moving component was the major one. The bands were scraped off separately, washed with methanol, and TLC on the methanolic washings from each eluate again afforded the same two spots. The IR, UV, NMR and mass spectroscopy on each eluate showed it to be identical with the original harmaline. Examination of the mass spectrum at 12 electron volts instead of



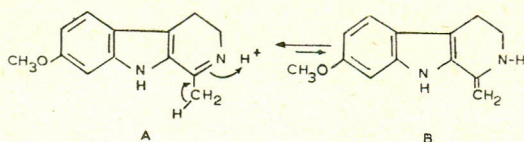
70 eV also failed to show up any subtle structural difference. It was evident that the two components of harmaline could only be separated in an adsorbed form on thin layer chromatography, but if any attempt was made to dissolve them, the same equilibrium mixture was obtained from each.

A cursory examination of the structure of harmaline shows that it is a conjugated ketimine, and that a possibility exists for the enamine tautomer with the exocyclic double bond to exist in mobile equilibrium with the imine tautomer. The lack of asymmetry in harmaline ruled out any diastereoisomers. Neither of the two spots in harmaline corresponded with the protonated species, the harmalinium cation, which was observed to have a distinctly different  $R_f$  value. It, therefore, appeared that harmaline existed in two rapidly equilibrating prototropic forms in solution which move as distinctly separable uniform chemical entities when adsorbed on silica gel but that the equilibrium is re-established in solution. A survey of the literature showed no known examples of imines in equilibrium with their enamine tautomers which were not stabilized by conjugation at the  $\beta$ -carbon to the nitrogen.\* However, the existence of such an equilibrium in cases where the conjugating group is situated at the  $\alpha$ -carbon had never been demonstrated. The existence of the enamine form has however been established for many compounds where the double bond is conjugated with a carbonyl group,<sup>6</sup> with esters,<sup>6,7</sup> and nitriles of  $\alpha$ - $\beta$ -unsaturated  $\beta$ -amino acids<sup>8,9,10</sup> and with  $\beta$ -amino ketones. In harmaline the conjugating indole nucleus is situated at the  $\alpha$ -carbon of the potential enamine system. There is no reason, however, why a conjugating group at this carbon should stabilize the enamine over the imine form since conjugative stabilization is available to both species.

To verify this hypothesis of an imine-enamine equilibrium in harmaline, the NMR spectra of a pure specimen of harmaline were recorded in  $\text{CH}_3\text{OH}$  and  $\text{CD}_3\text{OD}$ . An immediate collapse of the  $C$ -methyl signals present at 2.25 in  $\text{CH}_3\text{OH}$  was observed showing the exchange of the  $C$ -methyl protons with deuterium. This unambiguously proved the existence

\*After this work was complete, a report appeared of the existence of an imine-enamine equilibrium between isopropylidene isopropylamine and its enamine tautomer.<sup>5</sup>





of an enamine form (B) of harmaline in equilibrium with the imino form (A). In spite of intensive attempts to observe the olefinic protons in the NMR spectrum of a solution of harmaline in deuterated benzene, deuterated methanol, carbon tetrachloride etc. (including the use of a computer of average transients) no such signals were detectable. This is indicative of the very small contribution of this form to the equilibrium mixture and of the rapidity of interconversion. Robinson and his coworkers have previously anticipated the possibility of such an equilibrium<sup>11</sup> and evidence for it also comes from the synthesis of harmaline by Spencer,<sup>12</sup> though Spencer and Abramovitch have later contended that such an equilibrium need not be invoked.<sup>13</sup> Our results help to clarify the situation and positively establish the existence of such an equilibrium.

An interesting feature of the behaviour of harmaline when subjected to chromatography on silica gel is that when it is applied on a TLC plate from its solution in benzene or carbon tetrachloride and subjected to ascending chromatography in 70%  $\text{CHCl}_3$ -30% MeOH, only the faster running component is discernible. In contrast when harmaline is dissolved in a more polar solvent system such as MeOH or DMSO and applied to a plate, both components are separated with the slower running spot as the major one. Thus there is a distinct proclivity for the faster running component to be adsorbed from solutions of harmaline in benzene or carbon tetrachloride and for the slower running component to be adsorbed from solutions of harmaline in solvents of greater polarity. The rapid interconversion between the two species in solution would allow the adsorption of harmaline as one or the other form when such a preference existed. It is interesting that the NMR spectra of harmaline in both  $\text{CD}_3\text{OD}$  and  $\text{C}_6\text{D}_6$  correspond only to the imino form. This suggests that even when a tautomer is present in insufficient quantity to be detectable by NMR spectroscopy, the parent compound may be completely adsorbed in this minor form with the proviso that (a) there was a rapid interconversion between the two forms contributing to the equilibrium and (b) there was a distinct preference for adsorption of the minor form from a solvent of suitable polarity.

On repeated crystallisation of pure harmaline (which was obtained as a microcrystalline material m.p. 235°C, from the seeds of *Peganum harmala*) in methanol/benzene, higher melting (m.p. 258°C) rhombic crystals

were obtainable. Since the melting point of these crystals corresponded to that of 'harmidine' reported by Siddiqui,<sup>14</sup> a detailed examination of these crystals was made. IR, UV, NMR and mass spectrometry unambiguously established the identity of these crystals with harmaline. The difference in melting point may, therefore, be attributed to the different crystalline state of the higher melting crystals, and not to the differences in methods of measurement as previously suggested.<sup>15</sup> Further confirmation for the structure of the higher melting crystals came from X-ray crystallography.<sup>16</sup>

We have subsequently investigated the reactivity of the exocyclic carbon of harmaline with various electrophilic species and have found that the typical enamine alkylation reactions of tertiary enamines are affected easily and in good yields with harmaline.<sup>17</sup> The applications of this discovery appear tremendous since the possibility of enamine reactions from these masked substances, imines, has not previously been exploited. Such possibilities are being vigorously pursued and the syntheses of *Strychnos* and *Hunteria* alkaloidal systems are at hand.

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