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IMINE–ENAMINE TAUTOMERISM OF TROPANONE SCHIFF'S BASES

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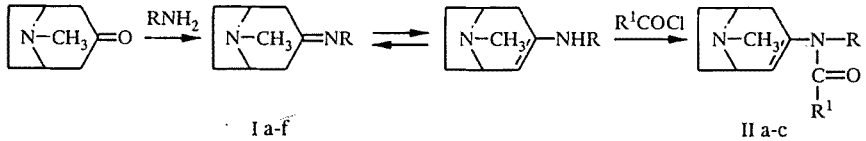
Using PMR spectroscopy, we have demonstrated the existence of an imine–enamine tautomerism and optically active forms in tropanone Schiff's bases. We have studied the effect of solvents and substituents on the tautomeric equilibrium of the system. By reaction with acid chlorides, we obtain the N-acylation products of the enamine form of the Schiff's bases.

Schiff's bases containing a mobile hydrogen atom in the α-position relative to the carbon–nitrogen double bond may display imine–enamine tautomerism [1].

We know that a shift of the tautomeric equilibrium toward the enamine is observed in polar solvents, capable of accepting a proton and forming an intermolecular hydrogen bond [1-4]. An analogous shift toward the enamine is observed in N-aryl-substituted systems as a result of conjugation of the electron pair of the nitrogen atom with the aromatic system [5-8]. Alkyl substituents at the nitrogen atom shift the equilibrium toward the imine form [6-8]. The imine–enamine tautomerism of tropanone Schiff's bases and their reactivity have not been studied.

Accordingly, it seemed expedient to determine the existence of imine–enamine tautomerism and to establish if it fits within the framework of ideas current in the literature on the effect of the above-indicated factors on the tautomeric equilibrium. In this case, we have in mind not only the theoretical but also the practical interest connected with synthesis of potential physiologically active compounds.

With this goal, we have synthesized a number of tropanone imines Ia-f by reaction of the corresponding amine with tropanone in benzene and toluene with azeotropic distilled water (Table 1).



I a-f II a-c

I a R = C_4H_9; b R = *cyclo*-C_6H_{11}; c R = $C_6H_5CH(CH_3)$; d R = $C_6H_5CH_2CH_2$; e R = C_6H_5; f R = *p*-$CH_3OC_6H_4$; II a R = C_4H_9, R^1 = CH_3; b R = C_6H_5, R^1 = C_3H_7; c R = C_6H_5, R^1 = *p*-ClC_6H_4

The tropane imines Ia-f were studied by PMR in three solvents ($CDCl_3$, C_5D_5N, $(CD_3)_2SO$), differing considerably in polarity and their ability to displace the equilibrium toward formation of the enamine form [3].

The signals in the PMR spectra were assigned based on literature data on tropane derivatives [10] and double resonance experiments (Table 2).

Analysis of the PMR spectra of compounds Ia-f showed that in $CDCl_3$, for all the studied compounds only the imine form is present with an accuracy to ±1%.

A different pattern is observed in $(CD_3)_2SO$. For tropanone derivatives Ia-f, along with the imine form we also detected the enamine form, the content of which fluctuates from 2.5% for compound Ib to 8% for Ie. The enamine form in the PMR

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TABLE 1. Characteristics and Tautomeric Composition of Compounds Ia-f

Compound	Empirical formula	T_{bp}, °C (mm Hg)	M^+	Content of enamine form in %		Yield, %
				C_5D_5N	$(CD_3)_2SO$	
Ia	$C_{12}H_{22}N_2$	105...108 (1)	194	10	5	78
Ib	$C_{14}H_{24}N_2$	112...115 (1)	220	10	2,5	77
Ic	$C_{16}H_{22}N_2$	134...136 (1)	242	22	6,5	69
Id	$C_{16}H_{22}N_2$	140...141 (1)	242	8	3	76
Ie	$C_{14}H_{18}N_2$	135...137 (1)	214	9	8	30
If	$C_{15}H_{20}N_2O$	170...173 (1)	244	15	5	40

spectra appears as a doublet signal from the vinyl proton at 4.1-5.0 ppm and a broadened signal from the NH proton at 3.8-5.0 ppm, the multiplicity of which depends on the substituent at the nitrogen atom.

The correctness of the assignment of the signals in the region 3.8-5.0 ppm to the protons of the HC= and NH group of the enamine form in $(CD_3)_2SO$ is confirmed by double resonance experiments. In fact, in the case of compound Ia, irradiation at the resonance frequency of the 1-H, 5-H protons (3.19 ppm) leads to conversion of the doublet signal at 4.12 ppm to a singlet, which suggests the presence of interaction between the HC= protons and the 1-H, 5-H protons (J = 5.5 Hz) of the enamine form. Irradiation of the protons of the α-methylene group of the substituent at 3.20 ppm is accompanied by conversion of the triplet at 4.0 ppm (interaction of the protons of the CH_2 group with the NH proton of the enamine form, J = 4.9 Hz) to a singlet.

For compound Ib, irradiation at the resonance frequency of the 1-H, 5-H protons (3.19 ppm), and also the proton of the cyclohexane ring (3.28 ppm) is accompanied by transition of the doublet signals at 4.16 (HC=, J = 5.1 Hz) and 3.81 ppm (NH, J = 7.1 Hz) to singlets. For compound Id, in the spectrum we observed superposition of the triplet from the NH proton and the doublet from the HC= of the enamine form (4.20 and 4.22 ppm), which is also confirmed by double resonance experiments upon irradiation of the 1-H, 5-H protons (3.14 ppm) and protons of the NCH_2 group at 2.81 ppm. For the rest of the investigated compounds, the chemical shifts of the HC= and NH protons are also close, and for an estimate of the content of the enamine form in $(CD_3)_2SO$ solution we considered that the signal in the 4.2-5.0 ppm region is due to two protons (HC= and NH).

We should note that since differences in the chemical shifts of the rest of the protons of the two tautomeric forms are not great, the calculation of the content of the enamine form was done from comparison of the integrated intensity of the signal from HC=, NH, or both together and the overall intensity of the separated signals in the PMR spectra due to the contribution of both the imine and the enamine form.

A more complex pattern was observed in the case of C_5D_5N. Unfortunately, we could not completely avoid the presence of traces of water in the solvent, the signal from which overlaps with signals from the HC= and NH protons of the enamine form; therefore determination of the content of the enamine form was done indirectly, by subtracting the fraction of the integrated intensity of the water from the overall integrated intensity of the signal in the 4.9-5.0 ppm region.

However, we must note that although the solvents deuteropyridine and dimethylsulfoxide exert an effect on formation of the enamine form, nevertheless for all the investigated tropane derivatives Ia-f the content of the imine form in the indicated solvents predominated.

Known literature data on the fact that cyclohexane shifts the tautomeric equilibrium of Schiff's bases the most toward formation of the enamine form, thus surpassing deuteropyridine, DMSO, and DMF [3], was not confirmed in our case.

From data presented in Table 1 it follows that the content of the enamine form in pyridine on the whole exceeds its content in $(CD_3)_2SO$, although the latter is a more polar solvent than pyridine. This may be explained by steric hindrances caused by the structure of the tropane ring, upon formation of intermolecular hydrogen bonds in the case of the bulkier $(CD_3)_2SO$ compared with pyridine. We must note that the increase in the content of the enamine form can be affected also by the π-electron system of pyridine, which is missing in the case of $(CD_3)_2SO$.

Based on the data presented in Table 1, we cannot also clearly conclude that the aromatic substituents in compounds Ie,f substantially shift the equilibrium toward formation of the enamine form compared with alkyl substituents in compounds Ia-d. Thus compound Ic in pyridine surpasses all the compounds of this series in content of the enamine form, including their solutions in $(CD_3)_2SO$. This does not contradict known literature data on the displacement of the equilibrium toward the enamine form as a consequence of conjugation of the π-electrons of the aromatic ring with the p-electrons of the nitrogen

TABLE 2. PMR Spectra of Tropanone Schiff's Bases Ia-f

Compound	Solvent	Isomer	Chemical shifts, δ, ppm
1	2	3	4
Ia	$CDCl_3$		0,85...1,70 & 3,25 (9H, m, C_4H_9); 1,25...1,70 & 2,04 (4H, m, 6-H, 7-H); 2,15...2,75 (4H, m, 2-H, 4-H); 2,41 (3H, s, NCH_3); 3,32 (2H, m, 1-H, 5-H)
	C_6D_{12}		0,90...1,70 & 3,20 (9H, m, C_4H_9); 1,25...1,65 & 1,92 (4H, m, 6-H, 7-H); 2,10...2,60 (4H, m, 2-H, 4-H); 2,31 (3H, s, NCH_3); 3,14 (2H, m, 1-H, 5-H)
	$(CD_3)_2SO$		0,87...1,55 & 3,20 (9H, m, C_4H_9); 1,20...1,50 & 1,90 (4H, m, 6-H, 7-H); 1,92...2,15 & 2,37...2,56 (4H, m, 2-H, 4-H); 2,27 (3H, s, NCH_3); 3,19 (2H, m, 1-H, 5-H); 4,00 (1H, t, J = 4,9 Hz, NH, enamine); 4,12 (1H, d, J = 5,5 Hz, HC=, enamine)
	C_5D_5N		0,90...1,75 & 3,20...3,45 (9H, m, C_4H_9); 1,25...1,75 & 1,88 (4H, m, 6-H, 7-H); 2,10...2,79 (4H, m, 2-H, 4-H); 2,28 (3H, s, NCH_3); 3,17 (2H, m, 1-H, 5-H); 4,96 (avg. signal HC=, NH, enamine)
Ib	$CDCl_3$		1,20...1,70 & 3,30 (11H, m, cyclo); 1,15...1,80 & 2,04 (4H, m, 6-H, 7-H); 2,10...2,75 (4H, m, 2-H, 4-H); 2,42 (3H, s, NCH3); 3,30 (2H, m, 1-H, 5-H)
	$(CD_3)_2SO$		1,05...1,75 & 3,28 (11H, m, cyclo); 1,15...1,80 & 1,90 (4H, m, 6-H, 7-H); 1,90...2,55 (4H, m, 2-H, 4-H); 2,27 (3H, s, NCH_3); 3,19 (2H, m, 1-H, 5-H); 3,81 (1H, d, J = 7,1 Hz, NH, enamine); 4,16 (1H, d, J = 5,1 Hz, HC=, enamine)
	C_5D_5N		1,10...1,80 & 3,39 (11H, m, cyclo); 1,10...2,00 (4H, m, 6-H, 7-H); 2,10...2,75 (4H, m, 2-H, 4-H); 2,29 (3H, s, NCH_3); 3,17 (2H, m, 1-H, 5-H); 4,90 (avg. signal HC=, NH, enamine)
Ic	$CDCl_3$	I	0,8...2,80 (8H, m, 2-H, 4-H, 6-H, 7-H); 1,46 (3H, d, J = 6,6 Hz, CH_3); 2,37 (3H, s, NCH_3); 3,32 (2H, m, 1-H, 5-H); 4,63 (2H, q, CH); 7,20...7,35 (5H, m, ArH)
		II	0,80...2,80 (8H, m, 2-H, 4-H, 6-H, 7-H); 1,50 (3H, d, J = 6,6 Hz, CH_3); 2,38 (3H, s, NCH_3); 3,20 (2H, m, 1-H, 5-H); 4,68 (2H, q, CH); 7,10...7,30 (5H, m, ArH)
	$(CD_3)_2SO$	I	0,72...2,70 (8H, m, 2-H, 4-H, 6-H, 7-H); 1,28 (3H, d, J = 6,6 Hz, CH_3); 2,25 (3H, s, NCH_3); 3,20 (2H, m, 1-H, 5-H); 4,66 (2H, q, CH); 3,88 (1H, d, HC=, enamine); 4,12 (1H, m, NH, enamine); 7,25...7,40 (5H, m, ArH)
		II	0,72...2,70 (8H, m, 2-H, 4-H, 6-H, 7-H); 1,33 (3H, d, J = 6,6 Hz, CH_3); 2,27 (3H, s, NCH_3); 3,11 (2H, m, 1-H, 5-H); 4,68 (2H, q, CH); 3,88 (1H, d, HC=, enamine); 4,12 (1H, m, NH, enamine); 7,10...7,30 (5H, m, ArH)
	C_5D_5N	I	0,86...2,82 (8H, m, 2-H, 4-H, 6-H, 7-H); 1,46 (3H, d, J = 6,60 Hz, CH_3); 2,26 (3H, s, NCH_3); 3,16 (2H, m, 1-H, 5-H); 4,78 (2H, q, CH); 4,97 (avg. signal HC=, NH, enamine); 7,15...7,64 (5H, m, ArH)
		II	0,86...2,82 (8H, m, 2-H, 4-H, 6-H, 7-H); 1,51 (3H, d, J = 6,6 Hz, CH_3); 2,26 (3H, s, NCH_3); 3,09 (2H, m, 1-H, 5-H); 4,76 (2H, q, CH); 4,97 (avg. signal HC=, NH, enamine); 7,15...7,64 (5H, m, ArH)
Id	$CDCl_3$		1,05...1,60 & 1,94 (4H, m, 6-H, 7-H); 2,00...2,75 (4H, m, 2-H, 4-H); 2,36 (3H, s, NCH3); 2,95...3,55 (4H, m, $(CH_2)_2$); 3,20 & 3,28 (2H, m, 1-H, 5-H); 7,10...7,30 (5H, m, ArH)
	C_6D_{12}		0,90...1,58 & 1,82 (4H, m, 6-H, 7-H); 1,85...2,60 (4H, m, 2-H, 4-H); 2,25 (3H, s, NCH_3); 2,86 и 3,40 (4H, m, $(CH_2)_2$); 3,01...3,10 (2H, m, 1-H, 5-H); 7,00...7,20 (5H, m, ArH)
	$(CD_3)_2SO$		0,97...1,49 & 1,83 (4H, m, 6-H, 7-H); 1,89...2,57 (4H, m, 2-H, 4-H); 2,23 (3H, s, NCH_3); 2,81 (2H, t, CH_2N); 3,14 (2H, m, 1-H, 5-H); 3,30...3,60 (2H, m, CH_2); 4,20 (1H, br. t, NH, enamine); 4,22 (1H, d, HC=, enamine); 7,10...7,37 (5H, m, ArH)
	C_5D_5N		1,05...1,55 & 1,82 (4H, m, 6-H, 7-H); 1,95...2,75 (4H, m, 2-H, 4-H); 2,25 (3H, s, NCH_3); 3,06...3,20 (2H, m, 1-H, 5-H); 3,00 and 3,42...3,75 (4H, m, $(CH_2)_2$); 4,88 (2H, avg. signal HC=, NH, enamine); 7,12...7,43 (5H, m, ArH)
Ie	$CDCl_3$		1,35...1,83 & 2,02 (4H, m, 6-H, 7-H); 2,20...2,90 (4H, m, 2-H, 4-H); 2,42 (3H, s, NCH_3); 3,20 & 3,40 (2H, m, 1-H, 5-H); 3,78 (3H, s, OCH_3); 6,64 & 6,84 (4H, m, ArH)

TABLE 2. (Continued)

1	2	3	4
	$(CD_3)_2SO$		1,10...1,70 & 1,91 (4H, m, 6-H, 7-H); 2,10...2,80 (4H, m, 2-H, 4-H); 2,30 (3H, s, NCH_3); 3,11 & 3,30 (2H, m, 1-H, 5-H); 3,62 (3H, s, OCH_3, enamine); 3,71 (3H, s, OCH_3); 4,61 (2H, br. s, HC=, NH, enamine); 6,52 & 6,65 (4H, m, ArH, enamine); 6,59 и 6,86 (4H, m, ArH)
	C_5D_5N		1,25...1,75 & 1,89 (4H, m, 6-H, 7-H); 2,25...2,50 & 2,86 (4H, m, 2-H, 4-H); 2,32 (3H, s, NCH_3); 3,11 & 3,28 (2H, m, 1-H, 5-H); 3,64 (3H, s, OCH_3, enamine); 3,71 (3H, s, OCH_3); 5,00 (br. signal, HC=, NH, enamine); 6,76...7,08 (4H, m, ArH)
I f	$CDCl_3$		1,30...1,85 & 2,03 (4H, m, 6-H, 7-H); 2,12...2,45 & 2,85 (4H, m, 2-H, 4-H); 2,42 (3H, s, NCH3); 3,12...3,31 (2H, m, 1-H, 5-H); 3,78 (3H, s, OCH_3); 6,65...7,85 (5H, m, ArH)
	$(CD_3)_2SO$		1,20...1,70 & 1,93 (4H, m, 6-H, 7-H); 1,93...2,80 (4H, m, 2-H, 4-H); 2,30 (3H, s, NCH_3); 3,12...3,31 (2H, m, 1-H, 5-H); 3,75 (3H, s, OCH_3); 5,00 (br. s, HC=, NH, enamine); 6,42...7,10 (5H, m, enamine); 6,50...7,43 (5H, m, ArH)
	C_5D_5N		1,25...1,75 & 1,88 (4H, m, 6-H, 7-H); 2,10...2,90 (4H, m, 2-H, 4-H); 2,28 (3H, s, NCH_3); 3,04 & 3,24 (2H, m, 1-H, 5-H); 3,70 (3H, s, OCH_3); 5,05 (br. signal, HC=, NH, enamine); 6,80...7,44 (5H, m, ArH)

atom, since in this case, in all likelihood as a result of steric hindrances connected with the spatial structure of the tropane ring, the aromatic ring in compounds Ie,f is oriented in space so that maximum overlap of the π- and p-orbitals is absent (and accordingly also conjugation). This hypothesis, along with the experimental data obtained, is quite consistent with an examination of Dreiding models, which shows that the position of the aromatic ring out of the plane of the piperidine moiety of the tropane ring is preferred.

We know that the tropinone oxime, due to the asymmetry of the tropane ring, may exist as two optically active forms, differing in the geometry of the =N−OH moiety [11]. The tropanone Schiff's bases Ia-f may also exist as two optically active forms due to disruption of the symmetry plane of the tropane ring of the =N−R moiety.

First we showed that in the PMR spectrum of compound Ic, containing (Ñ)-α-phenylethylamine as the second asymmetric center, we observe a double set of signals characteristic for the presence of two diastereomers (see Table 2). This phenomenon was characteristic for all the investigated solvents. For the rest of the Schiff's bases, the set of signals in the PMR spectrum corresponding to a pure compound.

The enamine form of the tropanone Schiff's bases Ia,e reacts in good yields with acid chlorides under standard conditions [12] with formation of the corresponding enamides, which is indicated by the presence in the PMR spectra of signals from the vinyl protons at 5.7-5.9 ppm with integrated intensity 1H.

EXPERIMENTAL

The PMR spectra of compounds Ia-f were taken on the Bruker AC-250 spectrometer at room temperature in $CDCl_3$, $(CD_3)_2SO$, C_5D_5N, C_6D_{12}, internal standard TMS. The tautomeric composition was determined by integration of the corresponding signals in the spectra. The imine−enamine equilibrium was established in the course of 30 min, monitored by recording the spectra over time. The PMR spectra of compounds IIa-f were taken on the Varian T-60 spectrometer.

The molecular masses of compounds Ia-f were determined mass spectrometrically on the Varian MAT-112 spectrometer with ionizing potential 70 eV. The purity of the compounds obtained was monitored using GLC on the Tsvet-152 chromatograph (column l = 0.7 m, d = 0.4 mm, solid support Chromaton NAW-0.16, liquid phase SE-30/5%. Conditions: T_{vap} 300°C, temperature programming 75-300°C/10°C per min, nitrogen flow rate 60 ml/min.

The melting points were determined on a Boetius stage.

The elemental analysis data for Compounds Ia-f and IIa-c correspond to the calculated values.

General Technique for Obtaining Tropanone Imines Ia-f. A solution of 35 g (0.25 moles) tropanone and 0.5 moles of the corresponding amine in 150 ml benzene for compounds Ia-d and in 150 ml toluene for Ie,f was boiled with a Dean and Stark attachment up to maximum liberation of water. The solvent was evaporated and the residue was distilled under vacuum. Compound If was synthesized earlier in [13].

3-(N-Butyl-N-acetyl)amino-8-methyl-8-azabicyclo[3,2,1]-oct-3-ene (IIa). Yield 50%, T_{bp} 165-168°C (1 mm). PMR spectrum ($CDCl_3$): 0.82-1.9 and 3.3 (9H, m, C_4H_9); 1.25-2.85 and 3.30 (8H, m, trop. ring); 2.05 (3H, s, $COCH_3$); 2.41 (3H, s, NCH_3); 5.70 ppm (1H, d, HC=).

3-(N-Aryl-N-butyryl)amino-8-methyl-8-azabicyclo[3,2,1]-oct-3-ene (IIb). Yield 69%, T_{mp} 175-178°C. PMR spectrum (CD_3OD): 0.70-3.0 (7H, m, C_3H_7); 1.30-3.20 and 4.15 (8H, m, trop. ring); 2.94 (3H, s, NCH_3); 5.90 (1H, d, HC=); 7.43 ppm (5H, m, ArH).

3(N-Aryl-N-*p*-chlorobenzoyl)amino-8-methyl-8-azabicyclo[3,2,1]-oct-3-ene (IIc). Yield 50%, T_{mp} 188-189°C. PMR spectrum (CD_3OD): 1.73-3.10 and 4.10 (8H, m, trop. ring); 2.85 (3H, s, NCH_3); 5.80 (1H, d, HC=); 7.10-7.55 ppm (9H, m, ArH).

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