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Is it possible to differentiate between 2-phenylaminodihydro-1,3-thiazine from 2-phenyliminotetrahydro-1,3-thiazine by spectral methods? New glance to the old problem

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ABSTRACT

Several studies have reported the presence of amine and imine tautomeric forms for hydrogenated 1,3-thiazine derivatives. However, identification of their tautomeric forms by UV, FTIR and mass-spectral methods does not yield expected results. Here, we report the synthesis of 2-phenylaminodihydro-1,3-thiazine and 2-phenyliminotetrahydro-1,3-thiazine and the analysis of their UV, FTIR and NMR (^{1}H and ^{13}C) spectral data. An identical picture of UV spectra was recorded for both compounds. However, distinctive characteristics were found in the FTIR, ^{1}H and ^{13}C NMR spectra. The C=N band of amine form was observed in higher frequency region relative to imine form. The signal of C2 carbon of amine form in ^{13}C NMR spectrum was occurred in more downfield (δ 165.3 ppm) relative to C2 signal of imine form (δ 152.1 ppm). In addition, the difference between C2 and C8 carbon signals of amine form was very high (Δδ = 30.6 ppm) relative to imine form (δ 5.4 ppm). The position of C2 and C8 signals and the difference between them in ^{13}C NMR spectrum was found to be more promising in identification of tautomeric forms in case of hydrogenated 1,3-thiazine derivatives.

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1. Introduction

2-Phenylaminodihydro-1,3-thiazine and 2-phenylimino tetrahydro-1,3-thiazine (Figure 1) have been the subjects of many discussions due to the presence of amine and imine tautomeric forms [1]. Some scientists have reported the formation of amine forms, while the others have reported the imine forms [1-5] as a result of cyclization of 1-(3-hydroxy propyl)-3-phenylthiourea in acidic medium. The C=N group wavenumber was undertaken as a key point to differ the tautomeric forms by Toldy [1] and others [2,3]. However, FTIR and UV-Vis and mass spectral methods did not give the expected results when identifying tautomeric forms [1]. The chemical shifts of the C(4) protons and ^{15}N nuclei chemical shifts were attempted to determine the most optimal tautomeric form [1,4,5]. However, only X-ray diffraction analysis played an important role to determine the tautomeric forms [6].

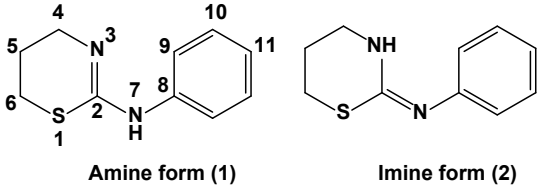

Figure 1. Tautomeric forms of 2-phenylaminodihydro-1,3-thiazine (1) and 2-phenyliminotetrahydro-1,3-thiazine (2).

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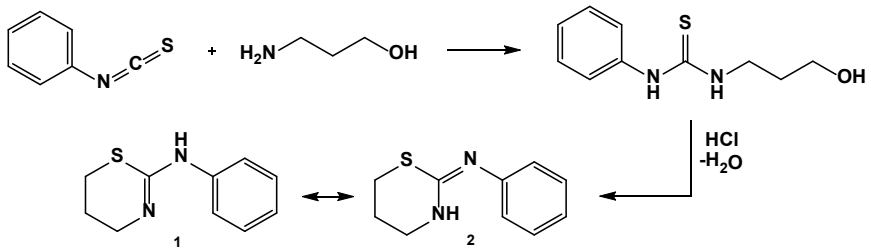

Scheme 1. The scheme of obtaining of 2-phenylaminodihydro-1,3-thiazine (**1**) or 2-phenyliminotetrahydro-1,3-thiazine (**2**).

On the other hand, these compounds contain an amidine group, which is relevant group of many biologically active compounds [1]. They are also considered as a biologically active heterocyclic analogue of thiourea [7,8]. The known veterinary preparation among 2-aryl(phenyl)substituted-1,3-thiazines is xylazine (2-(2,6-dimethylphenyl)amino-5,6-dihydro-4*H*-1,3-thiazine), which is used for sedation, anaesthesia, muscle relaxation, and analgesia in animals [9]. Recent paper showed [10], that 2-amino-5,6-dihydro-4*H*-1,3-thiazine may have great application potential in ameliorating the damage of radiotherapy. Besides, for new derivatives of 2-amino-5,6-dihydro-4*H*-1,3-thiazine antibacterial, antifungal, and NO synthase inhibiting activities were also found [11-16].

Therefore, the erroneous assignment of the imino forms to the amino form is still ongoing [17]. In this regard, the main goal of this work was to synthesize amino and imino tautomeric forms of hydrogenated 1,3-thiazine, regardless of the product yield, and to analyse their UV-Vis, FTIR, ^{1}H, and ^{13}C spectral data for more accurate determination of their tautomeric forms.

2. Experimental

2.1. Materials and apparatus

Initial compounds phenyl isothiocyanate and 3-aminopropanol-1 were purchased from Sigma-Aldrich and used without any purification. The UV/Vis spectra of samples were recorded on Cary-5000 UV-Vis-NIR spectrophotometer (Agilent) in ethanol (95 %) solvent using 10 mm (1 mL) Micro Quartz Cuvettes. The FTIR spectra of the obtained compounds in KBr pellets were recorded on a Nicolet iS10 FT-IR spectrometer (4000-400 cm^{-1}). ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ (internal standard TMS) on a Bruker 400 MHz NMR Spectrometer (Avance II) at SAIF of Panjab University, Chandigarh, India.

2.2. Synthesis of 1-(3-hydroxypropyl)-3-phenylthiourea

1-(3-Hydroxypropyl)-3-phenylthiourea was synthesized by interaction of phenyl isothiocyanate with 3-aminopropanol-1 according to previous methods [1-5]. To a solution of 7.51 g (0.1 mol) of 3-aminopropanol-1 in 25 mL of THF was added 0.1 mol (13.5 g) of phenyl isothiocyanate in 15 mL of THF drop wise with stirring at a temperature of 15 to 20 °C. The reaction mixture was left to stand for 24 h at room temperature. Then, the obtained white mass was purified by recrystallization from aqueous ethanol (50 %). FTIR and ^{1}H NMR data were identical with literature data [1,18] (Scheme 1).

1-(3-Hydroxypropyl)-3-phenylthiourea: Color: White. Yield: 90%. M.p.: 122-124 °C. FT-IR (KBr, ν, cm^{-1}): 3400-3100 (OH, NH), 3000 (CH) (Aromatic), 2879, 2933 (CH_2), 1594, 1556 (Ar), 1441 (C=S), 1180, 1259 (C-N) 1051 (C-O) (alcohol). ^{1}H NMR (400 MHz, DMSO-d_6, δ, ppm): 1.69 (m, 2H, CH_2), 3.39-3.53 (m, 4H, N-CH_2, CH_2-O), 4.58 (br s, 1H, OH), 7.1 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.2 (t, *J* = 8.0 Hz, 2H, Ar-H), 7.4 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.74 (br s, 1H, Ar-NH), 9.52 (br s, 1H, C(S)-NH-C).

2.3. Synthesis of 2-phenylaminodihydro-1,3-thiazine

Cyclization of 1-(3-hydroxypropyl)-3-phenylthiourea has been achieved in concentrated acid (HCl) according to the method described in [1,2,19]. To a 0.05 mol of thiourea was added 300 mL of concentrated acid (HCl) and boiled for 5 h. To the evaporated half-reaction mixture was added 100 mL of water and, upon cooling, neutralized with an alkali solution (0.1 N $NaHCO_3$). Yellow oily product was separated from the reaction mixture. Further, it was dissolved in chloroform and put on the day in a dark place for evaporation of chloroform (Scheme 1).

2-Phenylaminodihydro-1,3-thiazine (**1**): Color: Yellow oil. Yield: 51%. FT-IR (KBr, ν, cm^{-1}): 3241 (NH), 3154, 3001 (CH) (Aromatic), 2931 (CH_2), 1620 (C=N), 1495, 1551, 1589 (Ar), 1181 (C-N). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.12-2.20 (m, 2H, CH_2), 3.11 (t, *J* = 6.0 Hz, 2H, CH_2), 3.59 (t, *J* = 6.0 Hz, 2H, CH_2), 7.25 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.31 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.37 (t, *J* = 8.0 Hz, 2H, Ar-H), 8.08 (s, 1H, N-H). ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 20.46 (1C, CH_2), 26.54 (1C, CH_2-S), 41.06 (1C, CH_2-N), 125.66 (2C, Ar-C), 127.70 (1C, Ar-C), 129.21 (2C, Ar-C), 134.79 (1C, Ar-C), 165.38 (1C, C=N).

2.4. Synthesis of 2-phenyliminotetrahydro-1,3-thiazine

Cyclization of 1-(3-hydroxypropyl)-3-phenylthiourea has been achieved in concentrated acid (HCl) as previously described [1,2,19]. To a 0.05 mol of thiourea was added 300 mL of concentrated acid (HCl) and boiled for 5 h. To the evaporated half-reaction mixture was added 100 mL of water and, upon cooling, neutralized with an alkali solution (0.1 N $NaHCO_3$). Oily product was separated from the reaction mixture. From the rest part of the reaction mixture, white powders were filtered and it was dissolved in chloroform and put for the day in a dark place for evaporation of chloroform. The product crystallized on standing. Yield of the product was 10%. A suitable colorless crystal was obtained for single crystal XRD analysis and it was identified as 2-phenyliminotetrahydro-1,3-thiazine, which was described in reference [6] (Scheme 1).

2-Phenyliminotetrahydro-1,3-thiazine (**2**): Color: White. Yield: 10%. M.p.: 125-127 °C. FT-IR (KBr, ν, cm^{-1}): 3217 (NH), 3095, (CH) (Aromatic), 2926, 2857 (CH_2), 1613 (C=N), 1493, 1580 (Ar), 1163 (C-N). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.90-2.05 (m, 2H, CH_2), 2.93 (t, *J* = 6.0 Hz, 2H, CH_2), 3.37 (t, *J* = 6.0 Hz, 2H, CH_2), 6.47 (b.s, 1H, N-H), 6.99 (t, *J* = 8.0 Hz, 1H, Ar-H), 7.03 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.24 (t, *J* = 8.0 Hz, 2H, Ar-H). ^{13}C NMR (101 MHz, $CDCl_3$, δ, ppm): 22.74 (1C, CH_2), 27.11 (1C, CH_2-S), 43.04 (1C, CH_2-N), 122.25 (2C, Ar-C), 122.72 (1C, Ar-C), 128.80 (2C, Ar-C), 146.73 (1C, Ar-C), 152.16 (1C, C=N).

3. Results and discussion

Previously published papers mention the *N*-phenyl-5,6-dihydro-4*H*-1,3-thiazin-2-amine and *N*-(1,3-thiazinan-2-ylide ne)benzenamine by their trivial names: 2-phenylaminodi hydro-1,3-thiazine (**1**) and 2-phenyliminotetrahydro-1,3-thiazine (**2**), respectively (Figure 1).

Table 1. Chemical shifts (δ, ppm) of ^{1}H and ^{13}C nuclei of amine and imine forms.

^{1}H NMR, ($CDCl_3$, 400 MHz)							
Sample	**NH**	**H (C4)**	**H (C5)**	**H (C6)**	***o*-H**	***m*-H**	***p*-H**
Powder (Imine)	6.47 (b.s)	3.37 (t)	1.98 (m)	2.93 (t)	7.03 (d)	7.24 (t)	6.97 (t)
Oily (Amine)	8.08 (s)	3.59 (t)	2.15 (m)	3.11 (t)	7.25 (d)	7.37 (t)	7.31 (t)
^{13}C NMR, ($CDCl_3$, 100 MHz)							
Sample	**C2/C8**	**C4**	**C5**	**C6**	**C9**	**C10**	**C11**
Powder (Imine)	152.1/146.7	43.0	22.7	27.1	122.2	128.8	122.7
Oily (Amine)	165.3/134.7	41.0	20.4	26.5	125.6	129.2	127.7

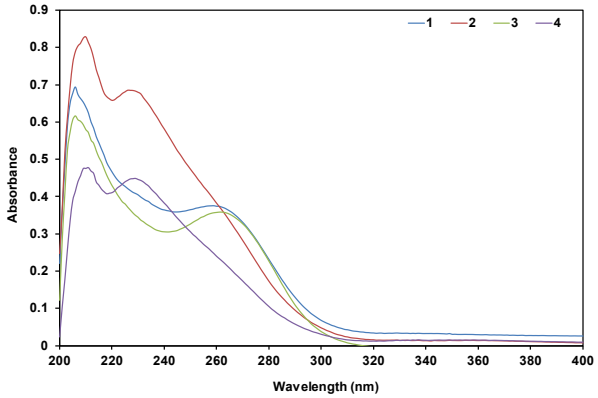

Figure 2. UV-spectra of amine (**1**, **2**), imine (**3**, **4**) in ethanol and acidic medium, respectively.

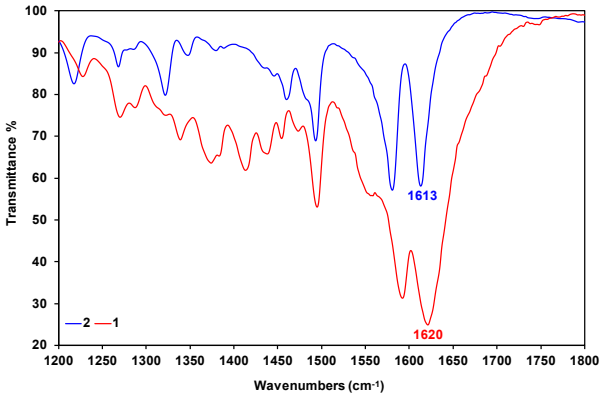

Figure 3. FTIR spectra of amine (**1**) and imine (**2**) forms in 1200-1800 cm^{-1} region.

Here, we also kept their trivial names according to the tendency. The general reaction scheme for the preparation of hydrogenated 1,3-thiazines is shown in Scheme 1 [1,2].

Almost 50 years ago, the question about the structure of 1-(3-hydroxypropyl)-3-phenylthiourea's cyclization products was started. Those times, some scientists have suggested the formation of an amino product based on the UV-spectral data. Whereas others suggested the formation of an imino product on the basis of IR and NMR spectral data [1-5]. However, ^{13}C NMR spectroscopy played decisive role, supplemented by the results of X-ray method in determination of the exact tautomer form. The structure of only imine form **2** was determined by Kalman and co-workers [6] using the single crystal X-ray diffraction method. As a result of our synthesis, we extracted two substances - a white powder and a yellow oily compound from the reaction mixture.

The ^{1}H and ^{13}C spectra of the samples are given in Table 1. The NMR spectra of the powder sample are identical with literature data [1,4,17]. However, in early work, NMR data were related to the imine form [4]. On the contrary to this, the structure was determined as amine form (white powder) by Corbett and Caille on the basis of NMR data in their recently work [17]. The ^{1}H and ^{13}C NMR data of the powder sample **2** are match with the results of Jackman and Jen [4], which supported by our single crystal XRD analyses and it was attributed to the imine structure.

However, the NMR spectral data of the oily sample differs from the imine form and literature data. It is similar to the 1,3-thiazine skeleton by the number of ^{1}H and ^{13}C signals. In the UV spectrum of both samples recorded in ethanol, an identical pattern of absorption bands was found (Figure 2). Adding a solution of 0.1 N hydrochloric acid to the ethanol solution led to a hypsochromic (blue) shift of the long-wavelength absorption band in both samples. Then, the addition of 0.1 N alkali (NaOH) to the acid-alcohol solution led to the initial position of the maximum. This allowed us to ignore the salt form of samples and it can be approved by the absence of bands in the 2500-2700 cm^{-1} region in their FTIR, characteristic to quaternary salts of nitrogen containing compounds [20]. According to above given data, we can attribute the oily sample to amine structure. It can be supported by FTIR spectra (Figure 3). The absorption band of the C=N bond is observed at 1620 and 1613 cm^{-1} for amine and imine forms, respectively. Moreover, we noticed that the presence of some bands in the fingerprint region in relatively intense form in imine and its low intensity in amine form or vice versa.

According to ^{13}C NMR data, the position of C2 and C8 signals and the difference between them can be played an important

role in identifying tautomeric forms. The C2 signal (δ 165.3 ppm) of amine form is in a more downfield relative to the C2 signal (δ 152.1 ppm) of imine. The difference between C2 and C8 signals of amine is very high (Δδ = 30.6 ppm) than the imine form: Δδ (C2-C8) = 5.4 ppm. This difference is more promising in the case of identifying tautomeric forms of 1,3-thiazine derivatives relatively to the C4 signal or the signal of C4 protons, which suggested in literatures [1,4].

The wavenumbers of C=N bonds of amine (**1**) and imine (**2**) forms were obtained and determined the detection of the band of the C=N group of amine form in the higher frequency region relative to the imine form. It is known that the amino-imino tautomeric conversion is not possible without external factors (temperature, hv, pH, and others).

4. Conclusion

2-Phenylaminodihydro-1,3-thiazine and 2-phenylimino tetrahydro-1,3-thiazine have been synthesized and analyzed using their UV, FTIR and NMR (^{1}H, ^{13}C) spectral data. NMR spectra of imine and amine forms clearly show the presence of only one tautomeric form in usual condition and amino-imino-tautomeric conversion in the case of the studied 1,3-thiazines can be possible only by external factors (temperature, hv, pH, etc.). Albeit, identical UV spectra were recorded in neutral, acidic and alkaline medium for both compounds, distinctive characteristics were found in FTIR, ^{1}H and ^{13}C spectra. Thus, we suggest the position of C2 and C8 signals and the difference between them in ^{13}C NMR spectrum could be more promising in identifying the tautomeric forms of 1,3-thiazine derivatives.

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Disclosure statement

Conflict of interests: The authors declare that they have no conflict of interest.
Author contributions: All authors contributed equally to this work.
Ethical approval: All ethical guidelines have been adhered.
Sample availability: Samples of the compounds are available from the author.

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