New cases of prototropic tautomerism in substituted pyridines

Research

V.P. Talsi, S.N. Evdokimov

Institute of Hydrocarbon Processing Problems, Siberian Branch, Russian Academy of Sciences,ul. Neftezavodskaya 54, Omsk, 644040 Russia

CORRESPONDENCE AUTHOR
V.P. Talsi
Email: vtalsi@ihcp.ru

ABSTRACT

When identifying newly synthesized heterocyclic compounds by the 13C NMR, broadening and disappearance of signals of most quaternary and some tertiary carbons were observed in a number of spectra, which was attributed to prototropic tautomerism. The schemes of tautomeric transformations are proposed and justified. The structural features and other conditions necessary for the occurrence and observability of tautomerism are determined. It is shown that the more informative spectra can be obtained by an increase of the analysis temperature.

KEYWORDS: NMR ^{13}C, ^{1}H, prototropic tautomerism, substituted pyridines

INTRODUCTION

Prototropic tautomerism is characteristic quality of some organic compounds to exist in the form of two or more structural modifications – tautomers which undergo mutual transformations as a result of proton transfer and redistribution of π-electrons [1]. Keto-enol tautomerism and various types of prototropic tautomerism of heterocyclic nitrogen compounds are particularly well-known [2]. The main method of tautomerism investigation is ^{1}H, ^{13}C, ^{15}N NMR spectroscopy, even ^{17}O, ^{31}P NMR being used in some cases.

So many articles devoted on identification of tautomers and the determination of the thermodynamic and kinetic parameters of the tautomeric reactions by NMR have been published, that, according to experts on the topic [2], the publication of one more paper on tautomerism should be justified either by the uniqueness of the systems involved or the method of their investigation.

Nevertheless we believe to be encountered with the deserving to be issued special cases of tautomerism when analyzing the ^{13}C NMR spectra of pyridine derivatives provided by the Omsk State University researchers [3].

RESULTS AND DISCUSSION

We have already observed the broadening and disappearance of signals in ^{13}C NMR spectra due to chemical exchange induced by hindered rotation around urethane bond or hindered pyramidal inversion of nitrogen [4, 5] but in our practice the analogous well known phenomenon associated with tautomerism [2] has been observed for the first time.

In the case of tautomerism, it is usually desirable to deal with fast or slow chemical exchange conditions when narrow (averaged or individual) NMR signals of the atoms of tautomers are observed. The intermediate ex-

change rate, when the lifetime of individual tautomers is comparable to the reciprocal of the difference in chemical shifts (expressed in Hz) of the corresponding atoms which belongs to different tautomers, leads to broadening and even complete disappearance in a case of ^{13}C NMR of the signals [4, 5].

It was disappearance of some signals of ^{13}C NMR spectra of DMSO-D$_6$ solutions of 6-oxo-4-phenyl-1,6-dihydro-2,2'-bipyridine-5-carboxamide (1) and 6-oxo-4-phenyl-1,6-dihydro-2,2'-bipyridine-5-carbonitrile (2) (Scheme 1) that we encountered with. The shown random carbon numbering of pyridine derivatives is used in the article for signal assignment in NMR spectra.
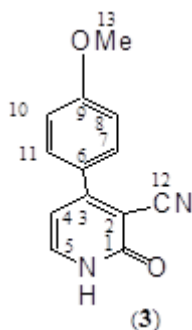
Scheme 1

$$R = C(=O)NH_2 \quad (1)$$
$$R = CN \quad (2)$$
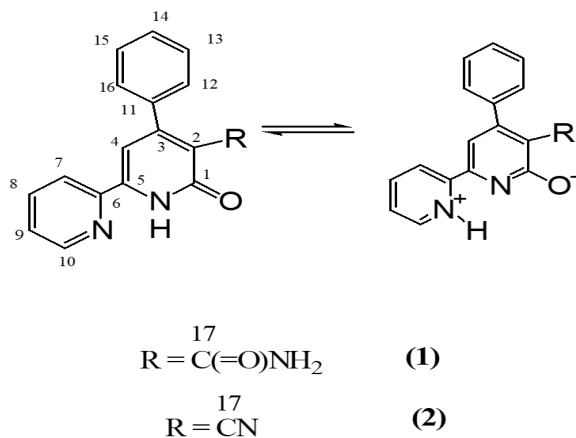
Figures 1, 2 contain the ^{1}H, ^{13}C NMR spectra of compound (1) and the assignment of signals made taking into account two-dimensional correlation spectra obtained with the help of pulse programs HSQC, HMBC, in view. All the protons of compound (1) signals fully correspond to the proposed structural formula (Fig. 1).

Initially, the signals of carbon 2 – 5 in the ^{13}C NMR spectrum of compound (1) (Fig. 2) were not found. Only after a long (18 h) acquisition it was possible to detect the missing, strongly broadened signals of the carbons. We consider the signals of carbon 2 - 5 to be broadened as a result of the chemical exchange shown in scheme 1 on a base of the following facts.

The phenomenon is not observed in a case of the large number of the similar hindered bulk pyridine derivatives available in the absence of NH protons in molecular structure.

In the absence of the second pyridine cycle as the substitute and the second N-atom as a potential target of tautomeric proton transfer no broadening of the signals in the ^{13}C NMR spectrum occurs. For example ^{13}C NMR spectrum of 4-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (3) in DMSO-D$_6$ (Fig. 7, suppl. materials) contains no broadened signals, though lactam-lactim tautomerism is well known [2].

(3)

So it is the suggested tautomeric equilibrium (Scheme 1) that provides the conditions for the intermediate exchange rate and causes broadening of the carbons 2 -5 signals of compound (1).

Though we have no arguments based on spectroscopy (NMR) or mathematic modeling in favor of pictured zwitter ionic structures (scheme 1) they seems to be reasonable. At least the analogues polar structures are included in the published tautomeric equilibrium schemes [2].
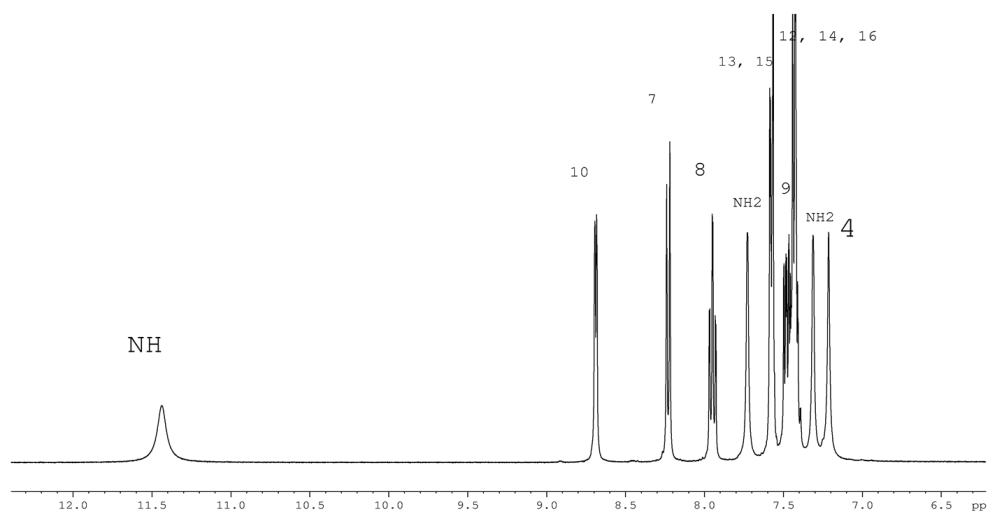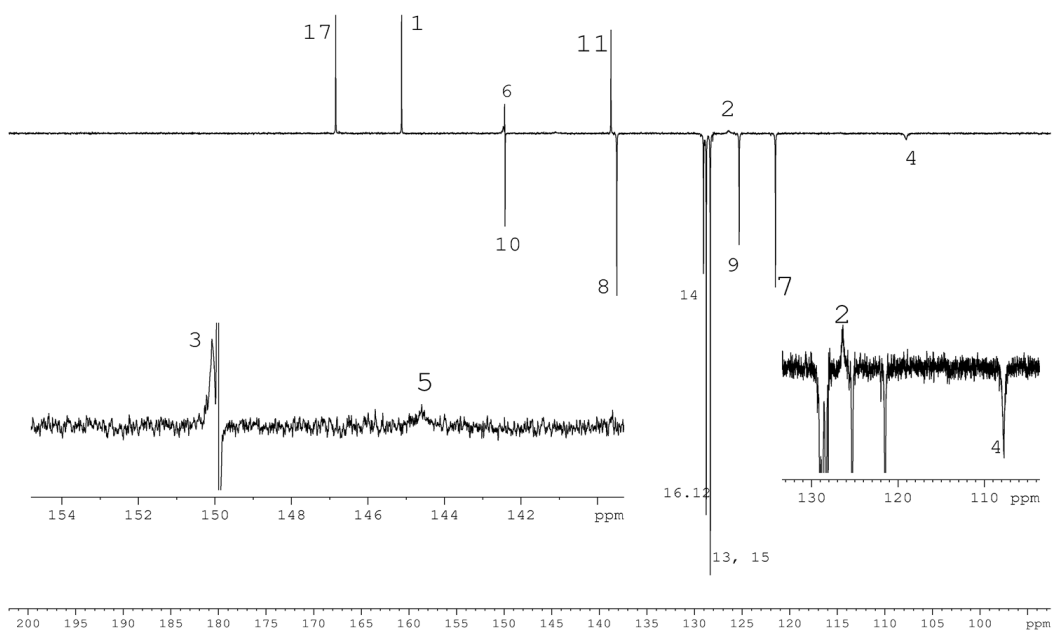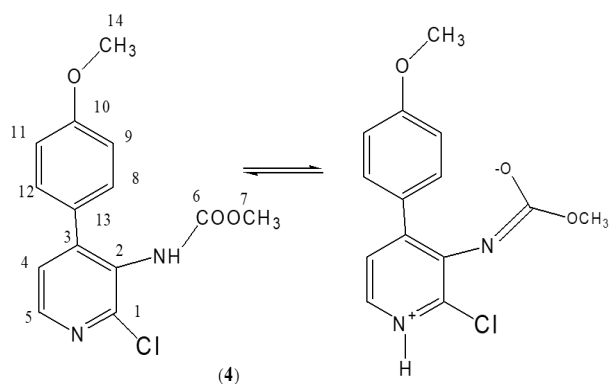
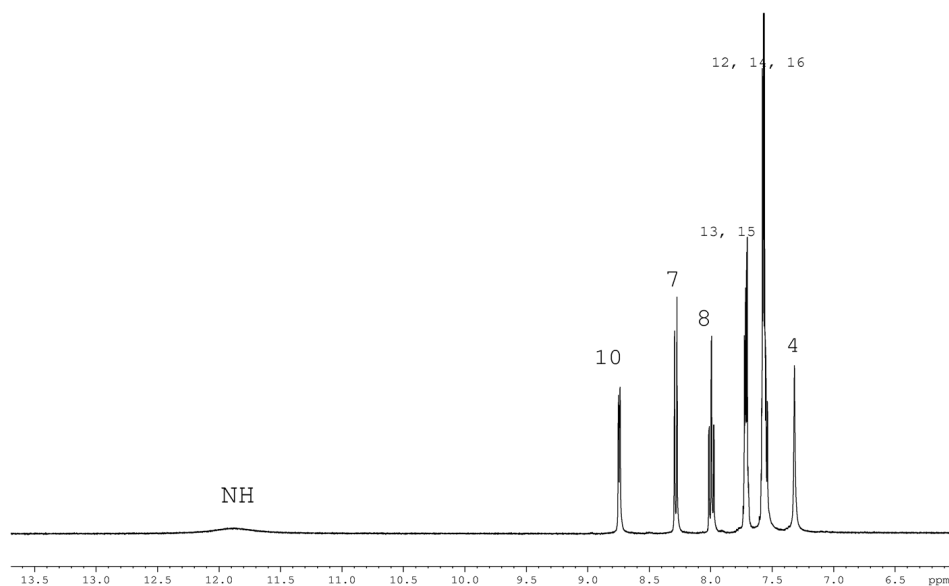**Fig. 1 :** ^{1}H NMR spectrum of compound (**1**).

Fig. 2 : ^{13}C NMR spectrum of compound (**1**).

NMR spectra of compound (**2**) with the assignment of signals are shown on figures 3, 4. The simple and informative ^{1}H NMR spectrum (Fig. 3) of the compound (**2**) fully corresponds to the proposed structure. Alongside with that, in ^{13}C NMR spectra of compound (**2**) the signal of carbons 1 - 6 were not observed at the temperature of 30 and 60 [0]C even after 30 hours of acquisition (Fig. 4). The spectra contain only two signals of the carbons 11, 17 of the compound (**2**). Consequently, the fast exchange (Scheme 1) conditions are realized only for these carbons due to the quite expected small chemical shifts difference in the tautomers. The temperature increase up to 90 °C made it possible to create conditions for rapid exchange for other carbons of the compound (**2**), except for carbons 2, 5. As a result, the signals of carbons 1, 3, 4, 6 broadened to a different degree in the spectrum become observed (Fig. 4).

Chemical exchange similar to that depicted in Scheme 1 made it possible to explain the difficulties in obtaining of an adequate ^{13}C NMR spectrum of methyl [2-chloro-4-(4-methoxyphenyl)pyridin-3-yl]carbamate (**4**) due to the broadening of several signals (see Scheme 2).

Scheme 2
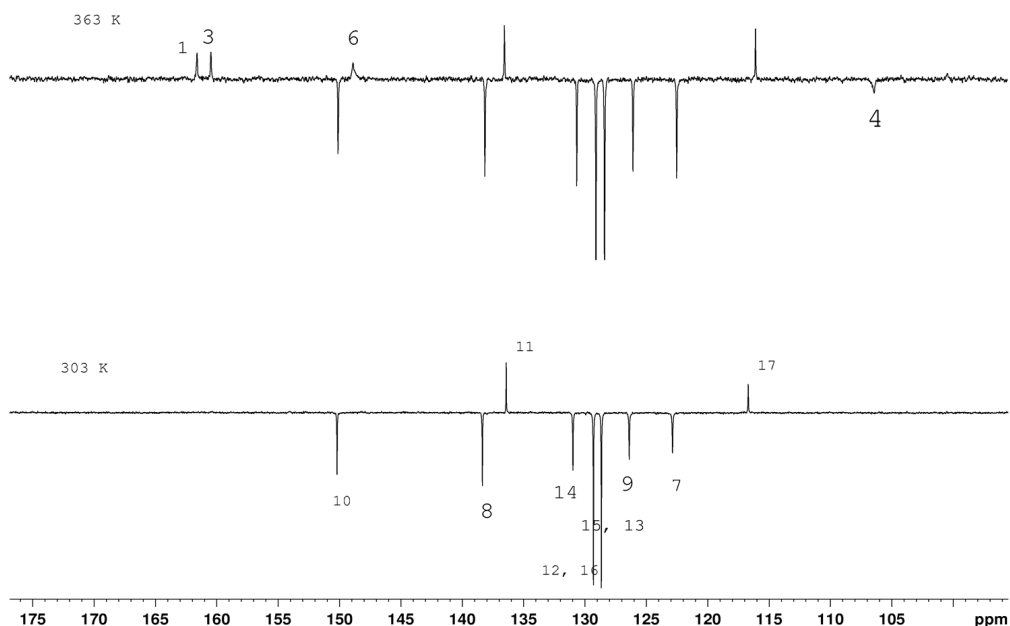

Fig. 3 : ^{1}H NMR spectrum of compound (**2**).

Fig. 4. ^{13}C NMR spectrum of compound (**2**).

The ^{1}H NMR spectrum (Fig. 5) of the compound (**4**) corresponds to its structural formula. In accordance with the proposed scheme 2, the signals of carbons 1, 2, 3, 5, 6 of the compound (**4**) in Fig. 6 are several times wider than the signals of carbon 10, 13 of phenyl substitute hardly influenced by suggested tautomerism. It took 12 hours to obtain the spectrum shown in Fig. 6. At the same time, an hour was enough to record the full spectrum of 2-chloro-4-(4-methoxyphenyl) nicotinamide (**5**) and 4-(4-methoxyphenyl)-2-methylnicotinamide (**6**), which did not contain any broadened signals (Fig. 8, 9 Suppl. materials).

R = Cl (**5**)

R = CH$_3$ (**6**)
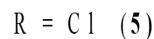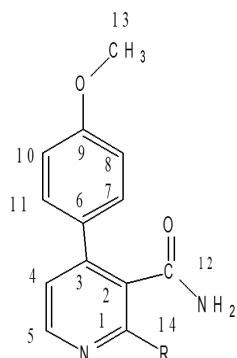
Chemical exchange depicted in Schemes 1 and 2 is probably facilitated when the negative charge which arises at the removing of NH proton during its transfer is stabilized by delocalization. In the case of the compound (**4**) this delocalization is provided by the carboxylic substitute and in the case of the compounds (**1**), (**2**) by the formation of an aromatic system.

It could also be necessary that both nitrogen atoms between which the proton moves during tautomeric transformation are in the single conjugation chain and can freely exchange not only protons, but also π-electrons. This condition is satisfied for the compound (**4**) and is violated in a case of pyridines (**5**), (**6**) which gives no broadened signals in ^{13}C NMR spectra.

 Another condition for the manifestation of tautomerism depictured on scheme 2 requires the application of prototropic polar solvent (DMSO-D$_6$ in our case).
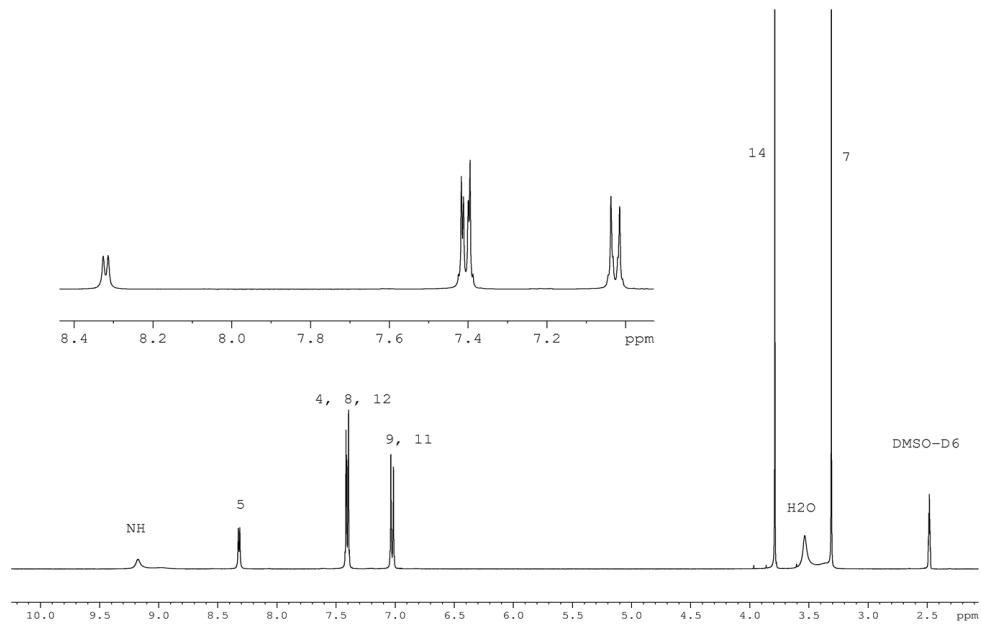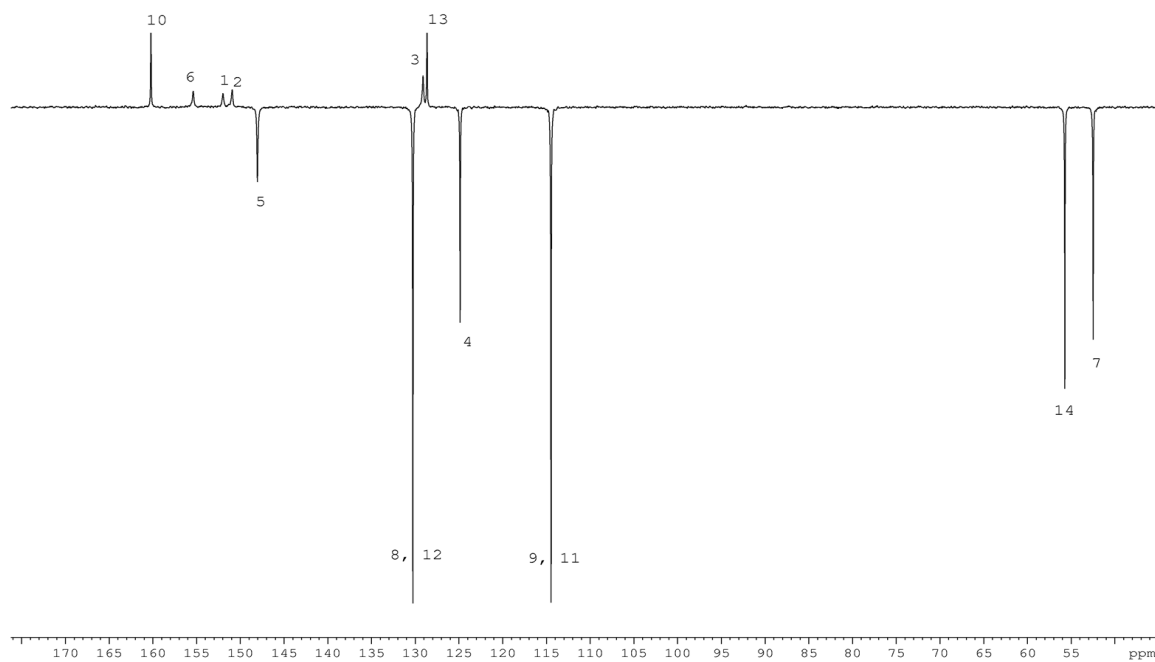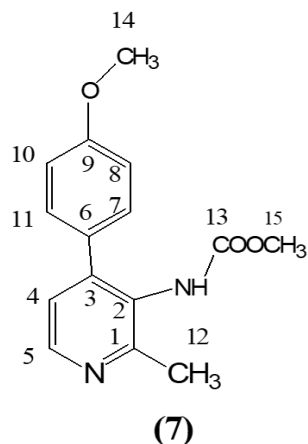
Fig. 5. ^{1}H NMR spectrum of compound (**4**).

Fig. 6. ^{13}C NMR spectrum of compound (**4**).

Comple... yphenyl)-2-

methylpyridin-3-yl] carbamate (**7**) in CDCl$_3$ (Fig. 10, suppl. materials) which differs from compound (**4**) only by exchange of Cl to CH$_3$ in its molecule have no broadened signals.

(7)

It should be noted that the considered tautomerism is manifested in ^{1}H NMR spectra either. For example, similar proton signals are on average twice more broad in compound (**4**) than in (**5**) or (**6**). But this fact is usually ignored, since there are no problems with identification.
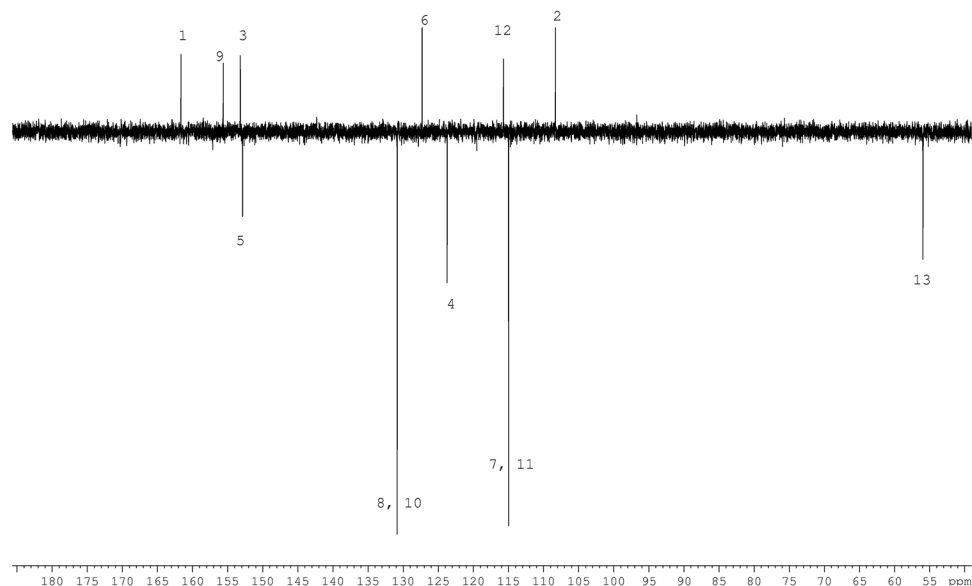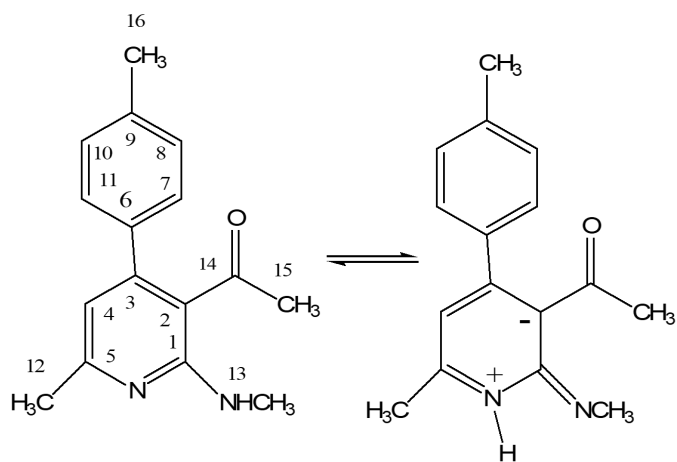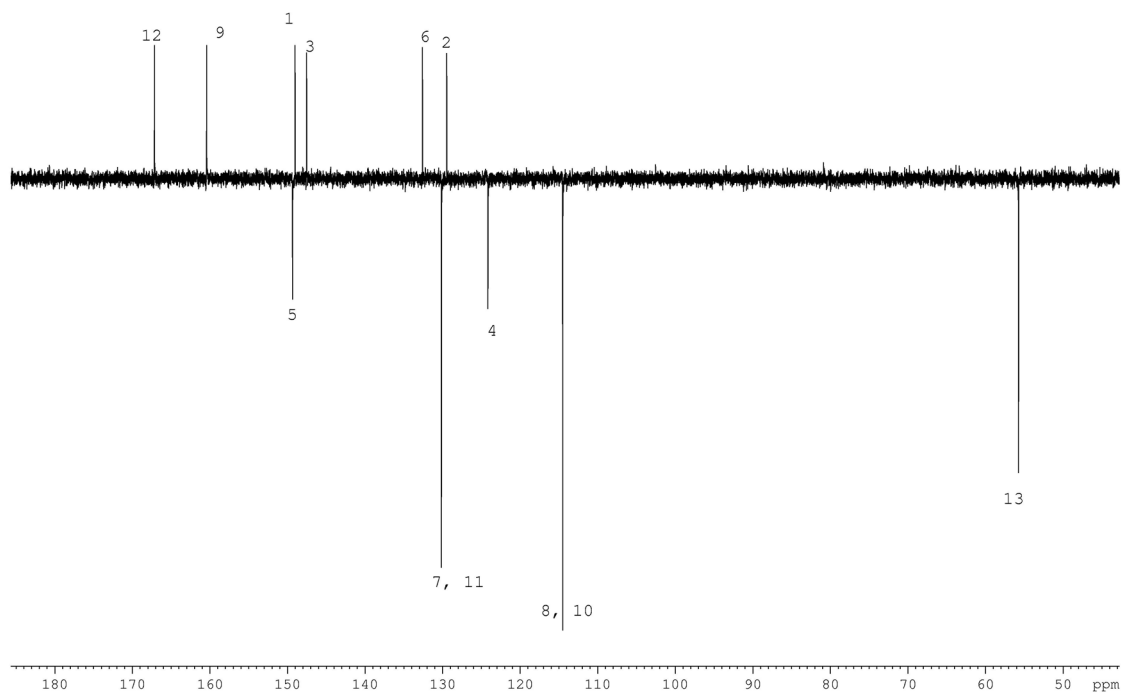

Fig. 7 (suppl. mat.) ^{13}C NMR spectrum of pyridine (**3**) in DMSO-D$_6$

The especially demonstrative case of tautomerism has been detected in a case of ^{1}H, ^{13}C NMR spectra of CDCl$_3$ solution of 1-[6-methyl-2-(methylamino)-4-(4-methylphenyl)pyridin-3-yl]ethanone (**8**). There are spectra of compound (**8**) and signal assignment in Fig. 11, 12. Essential broadening of several signals in ^{1}H, ^{13}C NMR spectra of pyridine (**8**) is explained reasonably by the suggested scheme 3 of chemical exchange. Close vicinity of N-atoms participating in tautomeric proton transfer in compound (**8**) can explain its occurrence in not prototropic CDCl$_3$.

Scheme 3

(8)
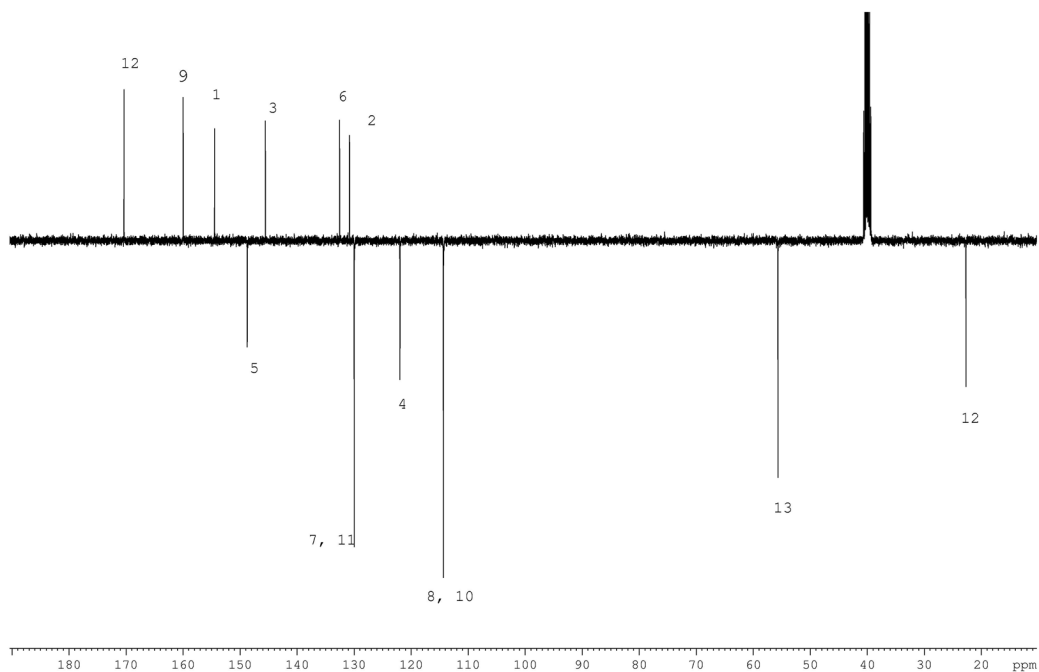

Fig. 8 (suppl. mat.) ^{13}C NMR spectra of pyridine (**5**) in DMSO-D$_6$

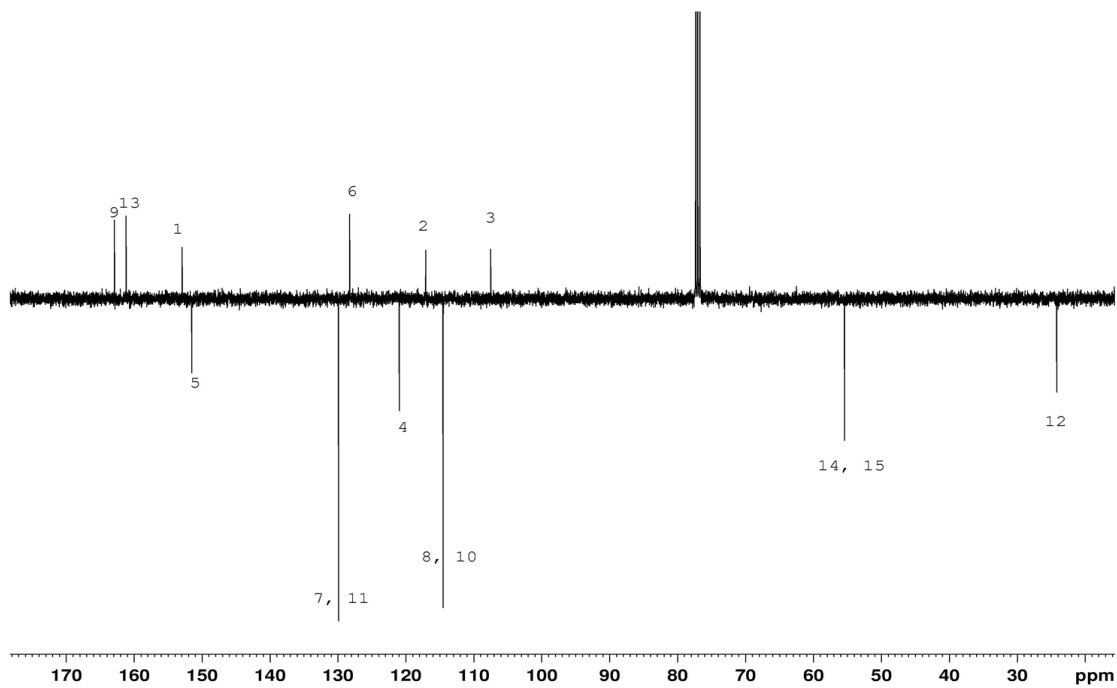Fig. 9 (suppl. mat.) ^{13}C NMR spectrum of pyridine (**6**) in DMSO-D$_6$

Fig. 10 (suppl. mat.) ^{13}C NMR spectrum of pyridine (**7**) in CDCl$_3$
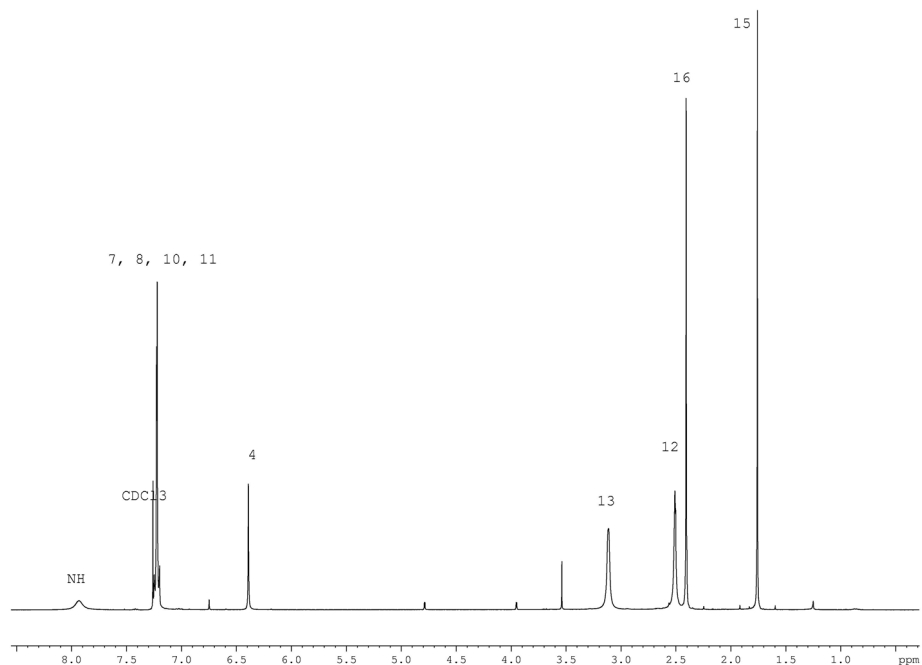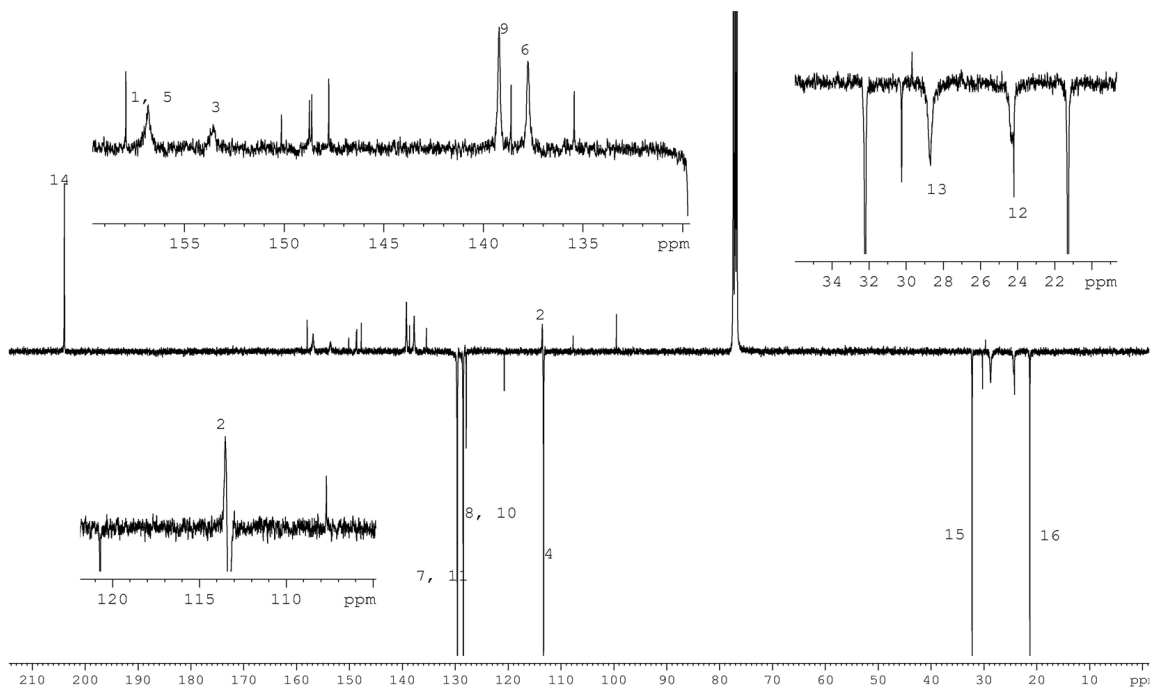
Fig.11 ^{1}H NMR spectrum of pyridine (**8**)

Fig.12. ^{13}C NMR spectrum of pyridine (**8**). Several unlabelled very narrow signals belong definitely as was shown experimentally to acquisition artifacts.

Conclusion

Serious problems of identification of some pyridine derivatives by NMR because of the broadening of signals can be reliably attributed to special cases of prototropic tautomerism.

Experimental

The ^{13}C, ^{1}H spectra of pyridine derivatives (**1**) - (**7**) were recorded on an Avance 400 (Bruker) NMR spectrometer using mainly DMSO-D_6 as a solvent and $CDCl_3$ for deuterium stabilization and as an external standard. To record ^{13}C NMR spectra, the APT pulse program was applied with a relaxation delay of 6 sec. To exclude saturation as a reason for reducing the intensity of the signals of the carbons, a large relaxation delay (40 s) was employed in a number of experiments. The durations of $\pi/2$ pulses were 3μc (^1H) and 7μc (^{13}C).

The pulse programs HSQC, HMBC (versions with gradient pulses) which are part of the program package of the spectrometer were used to record two-dimensional correlation spectra.

REFERENCES

1. Tautomerism: Methods and Theories, First Edition. Edited by L. Antonov. **2014** Wiley-VCH Verlag GmbH & Co.
2. R.M. Claramunt, C. Lоpez, M.D.Santa María, D. Sanz, J. Elguero, Progress in NMR Spectroscopy, **2006**, 49, 169-2006. DOI: 10.1002/chin.200711279
3. G.P.Sagitullina, Chem. Heterocycl. Compd. **2011**, 4, 635.
4. V.P Savin,., V.P. Talzi, N.O. Beck, N.O., *Zh. Org. Khim.*,**1984**, 20, 1842 - 1848.
5. V.P. Talsi., S.N. Evdokimov, *Zh. Org. Khim.* **2017** (in press).

Contact Us:

SIFT DESK
Deerpark Dr, #75, Fullerton,CA,92831,United States.
E-mail:
helpdesk@siftdesk.org
Visit us on the web at:
www.siftdesk.org