

SCIENTIFIC PAPERS  
OF THE UNIVERSITY OF PARDUBICE  
Series A  
Faculty of Chemical Technology  
10 (2004)

**$^1\text{H}$ - $^{15}\text{N}$  NMR CORRELATION STUDY OF REACTION  
PRODUCTS OF SOME 3-AMINO-1*H*,3*H*-QUINOLINE-  
2,4-DIONES WITH UREA**

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Received July 8, 2004

*Considerably different reaction products in high yields were obtained by reaction of substituted 3-amino-1*H*,3*H*-quinoline-2,4-diones with urea in acetic acid depending on substituents in position 1 and positions 3.  $^1\text{H}$ - $^{15}\text{N}$  NMR correlation spectra were of prime importance in structure elucidation of reaction products formed. Gradient selected  $^1\text{H}$ - $^{15}\text{N}$ HMBC spectra of typical reaction products are shown and discussed.*

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## Introduction

There is a routine now to utilize  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra with the aim to characterize synthesized heterocyclic compounds. Nitrogen containing heterocycles are most frequently studied heterocycles. For these compounds, the measurement and analysis of  $^{15}\text{N}$  NMR data is of great importance. The reason for not so frequent utilization of  $^{15}\text{N}$  NMR data consists in low sensitivity of measurements [1] due to low natural abundance of  $^{15}\text{N}$  isotope (0.365%), low magnetogyric ratio and usually long relaxation times. The sensitivity can be considerably improved using indirect proton detection [2] provided appropriate  $^n\text{J}(^{15}\text{N}, ^1\text{H})$  coupling constants exist in compounds studied [3].

This article shows some applications of one- and two-dimensional  $^1\text{H}$ - $^{15}\text{N}$  NMR correlation spectra in structure elucidation of reaction products of substituted 3-amino-1*H*,3*H*-quinoline-2,4-diones with urea in acetic acid.

## Experimental

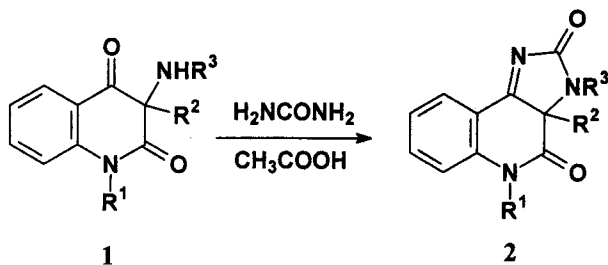
Syntheses of compounds studied are described in Refs. [4,5].

One- and two-dimensional gradient-selected  $^1\text{H}$ - $^{15}\text{N}$  (500.13 / 50.68 MHz) HMBC NMR spectra were recorded on a Bruker Avance spectrometer equipped with 5 mm tunable broadband probe. The compounds were dissolved in  $\text{DMSO}-d_6$ . The  $^1\text{H}$ - $^{15}\text{N}$  HMBC experiments were performed using the software given by Bruker.  $^{15}\text{N}$  chemical shifts were referred to the neat nitromethane placed in a coaxial capillary ( $\delta(^{15}\text{N}) = 0.0$ ). Positive values denote shifts to higher frequencies.

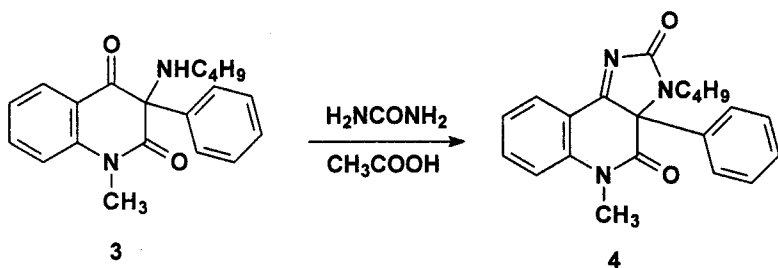
## Results and Discussion

The reactions of substituted compounds *1* with urea in boiling acetic acid were studied [4,5]. The starting compounds had different substituents in position  $\text{R}^1$  (H, Alk, Ar);  $\text{R}^2$  (Alk, Ar) and  $\text{R}^3$  (H, Alk, Ar). Originally it was expected that the structure of all reaction products would correspond to compound *2* (Scheme 1). After measuring the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra and MS [4,5], it was clear that the reaction products would have to be divided into several sub-groups according to types of substitution in positions  $\text{R}^1$ ,  $\text{R}^2$  and  $\text{R}^3$ . Typical representatives of these sub-groups will be shown.

Compound *3* having substituted nitrogen in position 1 and one substituent on nitrogen atom in position 3 gave reaction product *4*. MS and  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were in line with structure *4*, except for rather unusual  $^{13}\text{C}$  chemical shift of  $\text{C}=\text{N}$  carbon (183.3 ppm) [4]. Such a value is, e.g., typical of quinones. Since



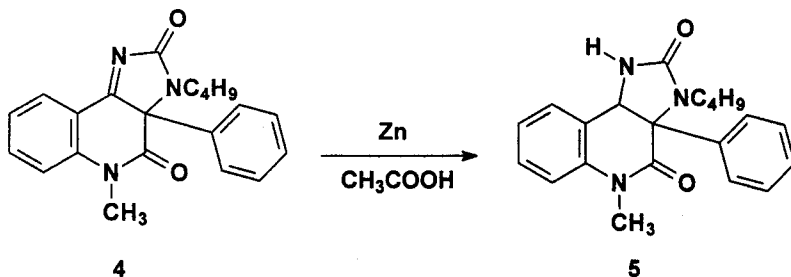
Scheme 1



Scheme 2

we were unable to find any suitable model compounds for comparison of  $^{13}\text{C}$  chemical shift, we decided to measure the  $^1\text{H}$ - $^{15}\text{N}$  HMBC spectrum[3,4]. This spectrum is shown in Fig. 1.

Correlations of  $\text{C}=\text{N}$  nitrogen with appropriate aromatic protons *via*  $^4J(^{15}\text{N}, ^1\text{H})$  and  $^5J(^{15}\text{N}, ^1\text{H})$  are clearly visible ( $\delta(^{15}\text{N}) = -72.7$  ( $\text{C}=\text{N}$ )), in addition to correlations of two other nitrogens with protons of methyl group ( $\delta(^{15}\text{N}) = -253.7$  ( $\text{N}-\text{CH}_3$ ) and butyl group ( $\delta(^{15}\text{N}) = -259.5$  ( $\text{N}-\text{C}_4\text{H}_9$ )).



Scheme 3

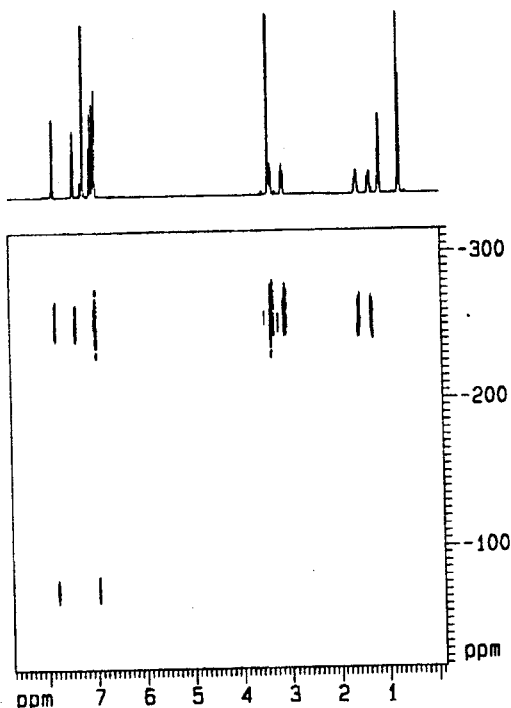


Fig. 1 Two-dimensional (2D) gradient selected (gs)  $^1\text{H}$ - $^{15}\text{N}$  HMBC spectrum of compound 4 in  $\text{DMSO}-\text{D}_6$  optimized for 7 Hz.

To be absolutely sure about the skeleton of compound 4, we performed reduction with zinc dust in acetic acid and obtained compound 5 (Scheme 3). In two-dimensional (2D) gradient-selected (gs)  $^1\text{H}$ - $^{15}\text{N}$  HMBC spectrum of compound 5 (Fig. 2) optimized for 90 Hz, a doublet correlating with proton resonating at 5.22 ppm due to the existence of  $^1J(^{15}\text{N}, ^1\text{H})$  coupling constant was detected to give the evidence for N-H bond existence.

In 2D gs  $^1\text{H}$ - $^{15}\text{N}$  HMBC spectrum of the same compound optimized for 7 Hz (Fig. 3), the signals due to the existence of  $^nJ(^{15}\text{N}, ^1\text{H})$  coupling constants allowed us to determine all three  $^{15}\text{N}$  chemical shifts ( $(\delta(^{15}\text{N})) = -290.7$  (N-H),  $-251.1$ , (N- $\text{CH}_3$ ) and  $-275.0$  (N- $\text{C}_4\text{H}_9$ )).

Compound 6 possesses  $\text{NH}_2$  group in position 3 and differs from compound 4 having  $\text{NH}-\text{C}_4\text{H}_9$  group there. The consequence of this difference is that substance 7 was the reaction product of compound 6 with urea (Scheme 4).

The 1D gradient selected  $^1\text{H}$ - $^{15}\text{N}$  HMBC spectrum of compound 7 was measured using  $^{15}\text{N}$  hard pulse (Fig. 4). The middle and bottom traces belong to the same 1D  $^1\text{H}$ - $^{15}\text{N}$  HMBC spectrum and traces differ only in phasing performed with aim to correct different off-resonance effects of  $^{15}\text{N}$  hard pulse on

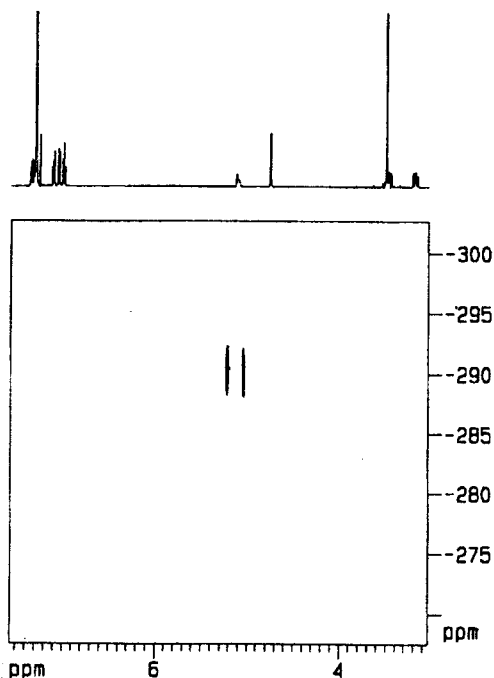
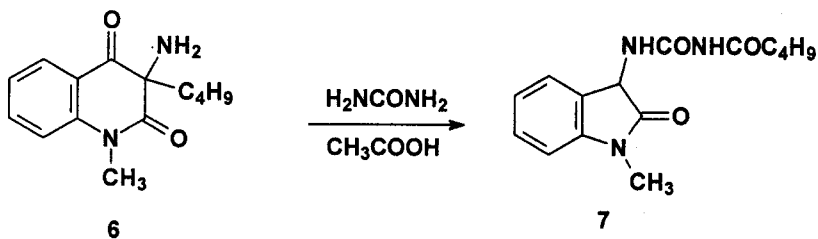


Fig. 2 2D gs  $^1\text{H}$ - $^{15}\text{N}$  HMBC spectrum of compound 5 in  $\text{DMSO-D}_6$  optimized for 90 Hz



Scheme 4

appropriate nitrogens. The conclusion following from this spectrum is that there are two NH groups in compound 7.

Figure 5 shows two-dimensional  $^1\text{H}$ - $^{15}\text{N}$  HMBC spectrum of compound 7 in  $\text{DMSO-D}_6$  optimized for 7 Hz. The nitrogen resonating at  $-252.2$  ppm correlates with methyl group protons as well as with aromatic proton at *peri* position and, thus, must belong to  $\text{N-CH}_3$ . For two NH groups the residual signals due to  $^1\text{J}(^{15}\text{N}, ^1\text{H})$  coupling constants are visible since no low pass filter was used in the pulse sequence. The resonances can be assigned undoubtedly

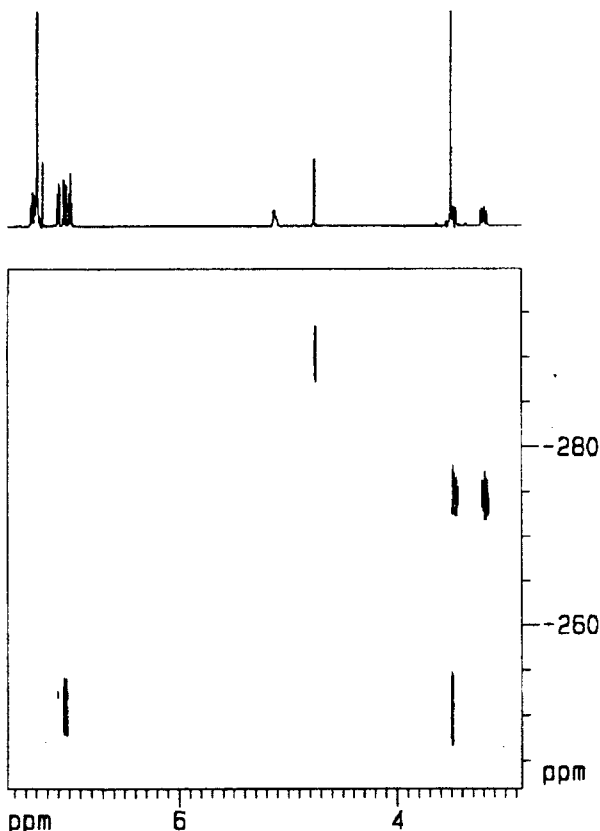


Fig. 3 2D gs  $^1\text{H}$ - $^{15}\text{N}$  HMBC spectrum of compound 5 in  $\text{DMSO}-\text{D}_6$  optimized for 7 Hz

using cross-peaks due  $^n\text{J}(^{15}\text{N}, ^1\text{H})$  coupling constants: the  $^{15}\text{N}$  signal at  $-298.0$  ppm correlating with CH proton of five-membered ring must belong to CH-NH, while the second one correlating with methylene protons of butyl group is from NH-COC<sub>4</sub>H<sub>9</sub> fragment ( $\delta(^{15}\text{N}) = -301.4$ ).

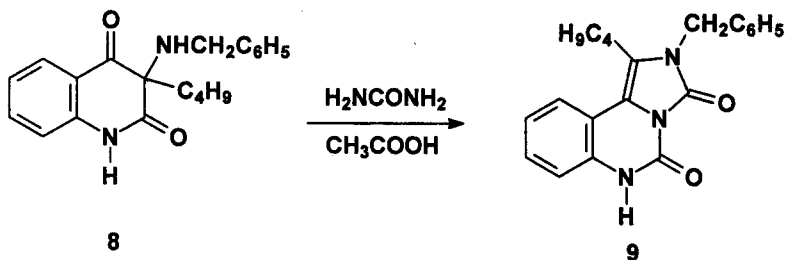
When nitrogen in position 1 possesses proton instead of alkyl or aryl group (compound 8) a different reaction product (substance 9) was prepared in a high yield again.

The NH proton correlates with both nitrogens of NH group (giving a doublet,  $\delta(^{15}\text{NH}) = -264.6$  and second nitrogen *via* HN-CO-N ( $\delta(^{15}\text{N}) = -232.0$ ). The last nitrogen correlates with methylene protons of butyl and benzyl groups ( $\delta(^{15}\text{N}) = -241.8$ , Fig. 6).

Compound 10 having two butyl groups in position 3 gave the reaction product 11. 2D gs  $^1\text{H}$ - $^{15}\text{N}$ HMBC spectrum of compound 11 optimized for 7 Hz is depicted in Fig. 7. There is the same structural motif NH-CO-N as that in compound 9.  $^{15}\text{N}$  chemical shifts in substance 11 are as follows:  $\delta(^{15}\text{N}-\text{C}_6\text{H}_5) = -193.2$ ,  $\delta(^{15}\text{N}-\text{H}) = -247.7$  and  $\delta(^{15}\text{N}-\text{C}_4\text{H}_9) = -227.5$ .



Fig. 4 Part of  $^1\text{H}$  NMR spectrum of compound 7 in  $\text{DMSO}-\text{D}_6$  (top trace) and part 1D gradient selected  $^1\text{H}-^{15}\text{N}$  HMBC spectrum of compound 7 optimized for 90 Hz and measured using  $^{15}\text{N}$  hard pulse (middle and bottom traces). The middle and bottom traces belong to the same 1D  $^1\text{H}-^{15}\text{N}$  HMBC spectrum and traces differ only in phasing performed with aim to correct different off-resonance effects of  $^{15}\text{N}$  hard pulse on appropriate nitrogens



Scheme 5

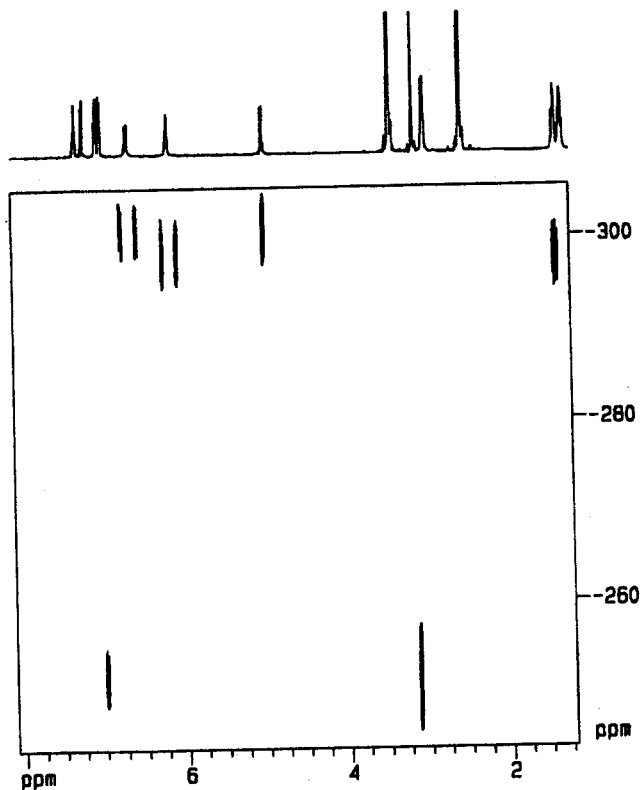
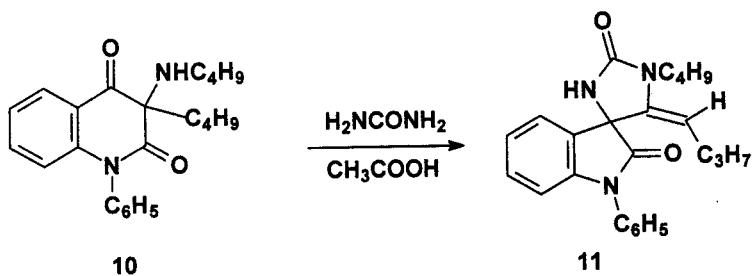


Fig. 5 2D  $^1\text{H}$ - $^{15}\text{N}$  HMBC spectrum of compound 7 in  $\text{DMSO}-\text{D}_6$  optimized for 7 Hz



Scheme 6

The existence of  $=\text{CHC}_3\text{H}_7$  was proved using  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra [4].

All synthetic details,  $^1\text{H}$  and  $^{13}\text{C}$  NMR data as well as proposals of reaction mechanisms, which are in accord with the proposed structures, can be found in Refs.[4,5].



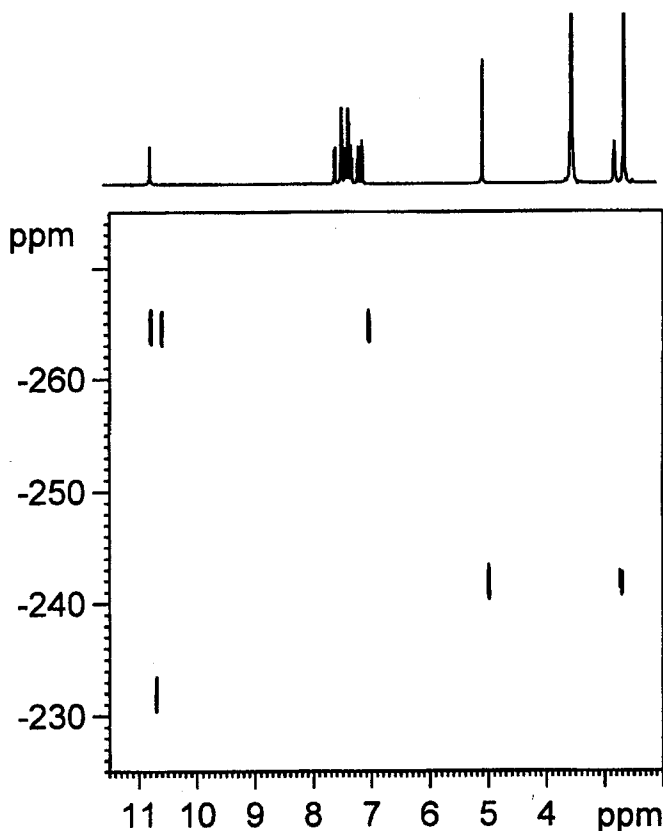


Fig. 6 2D gs  $^1\text{H}$ - $^{15}\text{N}$  HMBC spectrum of compound 9 in  $\text{DMSO}-\text{D}_6$  optimized for 7 Hz

## Conclusion

It is apparent that — at first glance — a very simple reaction of  $\alpha$ -aminoketones 1 with urea proceeds in a very complex manner and offers great surprises in variability of reaction product structures. The described reactions are not only interesting from a theoretical point of view but, owing to the simple reaction protocol, they provide an easy pathway to prepare novel heterocyclic systems in high yields that might be interesting structures for studying biological activity. 1D and 2D gs  $^1\text{H}$ - $^{15}\text{N}$  correlation spectroscopy experiments are very useful to characterise heterocycles containing nitrogen atoms, however, in case of rearrangement of nitrogen containing heterocyclic compounds  $^1\text{H}$ - $^{15}\text{N}$  correlation techniques are of key importance in structure elucidation.

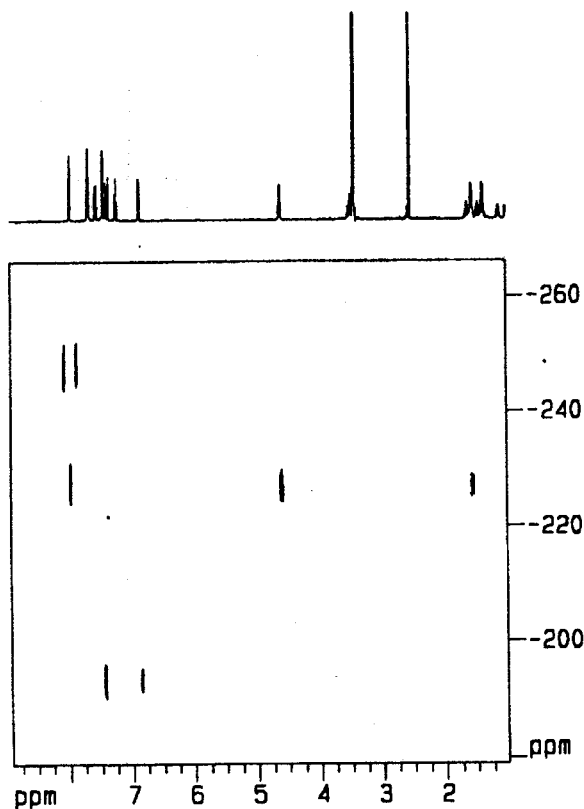


Fig. 7 2D  $^1\text{H}$ - $^{15}\text{N}$  HMBC spectrum of compound *11* in  $\text{DMSO}-\text{D}_6$  optimized for 7 Hz

## Acknowledgements

M.H. acknowledges the support of the grant project No. 203/02/0023 sponsored by the Grant Agency of the Czech Republic.

## References

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