NMR SPECTROSCOPIC AND X-RAY STRUCTURAL CHARACTERIZATION OF TWO DIARYL DERIVATIVES OF (4-CYANO-6-METHYL-3,8-DIOXO-2,3,5,6,7,8-HEXAHYDROPYRIDO[3,4-c]PYRIDAZIN-6-YL)HYDRAZONO-ACETIC ACID ETHYL ESTER

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Abstract: ^{1}H, ^{13}C and ^{15}N NMR chemical shifts have been measured and assigned for [4-cyano-2-(3,4-dimethylphenyl)-6-methyl-3,8-dioxo-2,3,5,6,7,8-hexahydropyrido[3,4-c]pyridazin-6-yl-(3,4-dimethylphenyl)-hydrazono]- and [4-cyano-2-(3-chloro,4-methylphenyl)-6-methyl-3,8-dioxo-2,3,5,6,7,8-hexahydropyrido[3,4-c]-pyridazin-6-yl-(3-chloro,4-methylphenyl)hydrazono]-acetic acid ethyl esters. The structure of the first compound was also verified by a single crystal X-ray analysis.

Introduction

Substituted heterocycles such as pyrimidines and piperazines have been largely synthesized using various nitriles as starting compounds (1-4). Ibrahim *et al* .(1) used crotononitriles and arene diazonium salts to prepare pyridazine derivatives. Depending on the structure of the starting nitrile, the reaction products were either acyclic mono- or dihydrazones, which were cyclized to the corresponding pyridazine derivatives. In the present work the starting compound was ethylcyanoacetate, which in a reaction with a phenylhydrazono derivative gave in addition to the expected pyridazine derivative also an other reaction product, which proved to be a substituted pyrido[3,4-c]pyridazine. The pyrido[3,4-c]pyridazine was born, when the main reaction product reacted with a second phenylhydrazono molecule. In this paper we report the ^{1}H, ^{13}C and ^{15}N NMR spectral data for two pyrido[3,4-c]pyridazine derivatives. The single crystal X-ray structure for one compound is also presented.

Experimental

[4-cyano-2-(3,4-dimethylphenyl)-6-methyl-3,8.dioxo-2,3,5,6,7,8-hexahydropyrido[3,4-c]pyridazin-6-yl-(3,4-dimethylphenyl)-hydrazono]-acetic acid ethyl ester **1** and [4-cyano-2-(3-chloro,4-methylphenyl)-6-methyl-3,8.dioxo-2,3,5,6,7,8-hexahydropyrido[3,4-c]pyridazin-6-yl-(3-chloro,4-methylphenyl)-hydrazono]-acetic acid ethyl ester **2** were prepared as an ca. 10 % yield in an equimolar reaction both ethylcyanoacetate and 2-(3,4-dimethylphenylhydrazono)-3-oxobutyrate (**A**) and 2-(3-chloro,4-methyl-phenylhydrazono)-3-oxobutyrate (**B**) with ethylcyanoacetate (**C**) in the presence of ammonium acetate 160 °C for 1 hour. The main product were the expected 1-(3,4-substituted)-3-carbethoxy-4-methyl-5-cyano-6-oxo-1,6-dihydropyridazines in ca. 70 % yield (**D/E**). The synthesis reaction and the structures of starting compounds are presented in Figure 1. The numbering and the structures of the derivatives **1** and **2** are presented in Figure 2.

The ^{1}H, ^{13}C and ^{15}N NMR spectra were recorded for about 0.5 M DMSO-d_6 solution in a 5-mm sample tube at 30 °C on a Bruker Avance 500 MHz spectrometer equipped with an inverse detection probehead and z-gradient accessory and working at 500.13, 125.77 and 50.69 MHz respectively. The ^{1}H, ^{13}C and ^{15}N NMR chemical shifts of com-

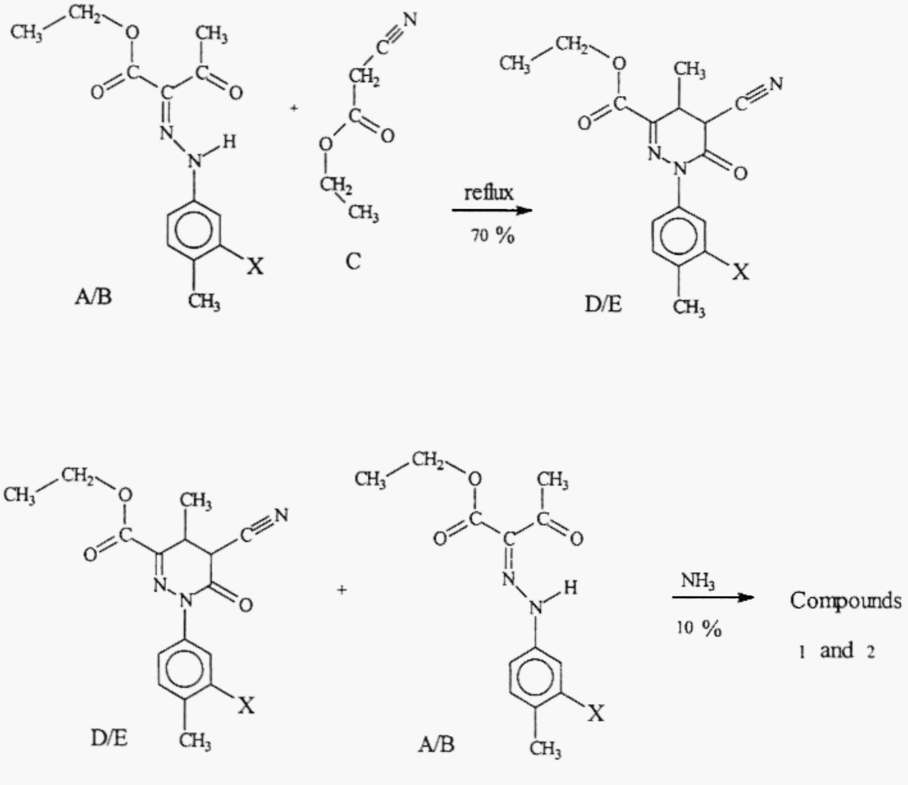

Figure 1. Synthesis reaction of compounds **1** and **2**.

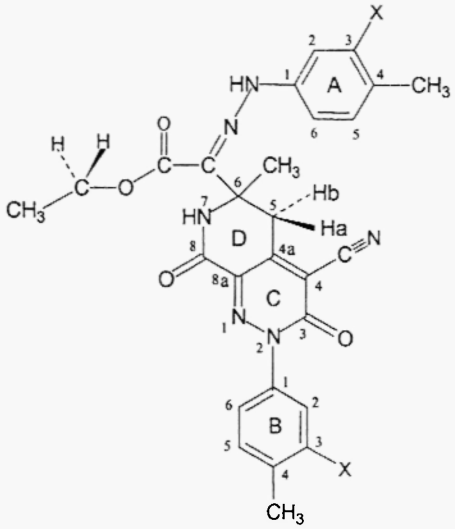

Figure 2. Compound **1**, X = CH_3, compound **2**, X = Cl.

pounds **1** and **2** have been solved based on PFG (5) $^1H,^{13}C$ HMQC (6,7) and HMBC (8) as well as PEG $^1H,^{15}N$ HMBC experiments. DQF $^1H,^1H$ COSY(9,10) was measured for compound **2**. The ^1H, ^{13}C and ^{15}N NMR chemical shifts are presented in Tables 1-3.

In ^1H NMR experiments the spectral width was 7000 Hz, the number of data points 64 K, which was zero filled to 128 K giving sa spectral resolution of 0.05 Hz, the number of scans was 8-32 and the flip angle 30°. An exponential window function of the spectral resolution was used prior to FT. The ^1H NMR chemical shifts are referenced to the residual signal of DMSO-d_6, d = 2.50 ppm from TMS (δ = 0.00 ppm).

Table 1. $\delta(^1H)$ (ppm from TMS) of **1** and **2** in 0.5 M DMSO-d_6 at 30 °C.

Proton	$\delta(^1H)$/ppm **1**	**2**
H-2 (ring A)	7.01	7.29
H-5	7.00	7.19
H-6	6.88	7.06
3-CH_3	2.16	-
4-CH_3	2.13	2.23
NH	11.46	11.32
H-2 (ring B)	7.13	7.49
H-5	7.22	7.47
H-6	7.15	7.37
3-CH_3	2.19	-
4-CH_3	2.24	2.37
Ha (CH_2, ring D)	3.38	3.42
Hb (CH_2, ring D)	3.86	3.87
CH_3 (ring D)	1.71	1.69
NH (ring D)	8.82	8.88
H (CH_2, ethoxy)	4.30	4.31
H (CH_2, ethoxy)	4.37	4.36
CH_3 (ethoxy)	1.36	1.35

In ^{13}C NMR experiments the spectral width was 31400 Hz (250 ppm), the number of data points 64 K giving a spectral resolution of 0.5 Hz, the number of scans was 624 – 2700 and the flip angle 30°. An exponential window function of the spectral resolution was used prior to FT. The ^{13}C NMR chemical shifts are referenced to the centre peak of the solvent DMSO-d_6, δ = 39.50 ppm from TMS (δ = 0.00 ppm).

In two dimensional PFG $^1H,^{13}C$ HMQC and HMBC measurements the matrix sizes were 1024 (f_2) x 256 (f_1), which were zero filled to 2048 x 512 and apodized by a shifted sine bell window function along both axes prior to FT. In PFG $^1H,^{13}C$ HMBC a 50 ms delay was inserted in the pulse program for evolution of long range couplings (optimum at 10 Hz). In addition, a low pass filter was used in the beginning of the HMBC pulse program to remove the correlations due to direct couplings. Similarly, in PFG $^1H,^{15}N$ HMBC experiments a 50 ms delay was used for evolution of long range couplings. The number of data points was 1024 (f_2) x 512 ($f_1 = {}^{15}N$). This matrix was zero filled to 1024 x 1024 and apodized by a shifted sine bell window function along both axes prior to FT. In ^{15}N NMR experiments the chemical shifts are referenced to the signal of external CH_3NO_2 in a 1 mm diameter capillary tube inserted coaxially in the 5 mm NMR tube, δ ($CH_3{}^{15}NO_2$) = 0.0 ppm.

In DQF $^1H,^1H$ COSY measurements the matrix size was 512 (f_1) x 2048 (f_2), which was zero filled to 1024 x 2048 and multiplied by sinebell window function prior to FT.

Table 2. $\delta(^{13}C)$ (ppm from TMS) of **1** and **2** in 0.5 M DMSO-d_6 at 30 °C

Carbon	$\delta(^{13}C)$/ppm 1	**2**
C-1 (ring A)	140.86	142.55
C-2	115.03	114.12
C-3	137.20	133.93
C-4	129.99	128.34
C-5	130.03	131.44
C-6	111.52	112.73
3-CH_3	19.43	-
4-CH_3	18.59	18.76
C-1 (ring B)	138.09	139.04
C-2	126.10	125.72
C-3	136.97	132.94
C-4	137.61	136.76
C-5	129.52	131.13
C-6	122.74	124.17
3-CH_3	19.15	-
4-CH_3	19.01	19.28
C-3 (ring C/D)	156.17	156.09
C-4	110.77	111.26
C-4a	150.13	149.82
C-5	38.26	38.08
C-6	57.28	57.34
C-8	159.40	159.55
C-8a	135.39	135.64
CN	112.97	112.77
6-CH_3	25.94	25.73
C=N	128.30	130.22
CO (ester)	161.90	161.63
CH_2	61.16	61.40
CH_3	13.89	13.83

Table 3. $\delta(^{15}N)$ (ppm from ext. CH_3NO_2) of 1 and **2** in 0.5 M DMSO-d_6 at 30 °C

Nitrogen	$-\delta(^{15}N)$/ppm 1	**2**
NH (ring A)	227.7	230.8
N-1 (ring C)	25.3	27.4
N-2 (ring C)	160.0	162.8
NH (ring D)	248.2	248.3
N=C	34.6	37.8
NC	not obs.	not obs.

Crystals for single crystal X-ray analysis of compound **1** were obtained by slow evaporation from DMSO-d_6 solution in sealed NMR tube. The X-ray structural data were collected with a Nonius Kappa CCD diffractometer at 173.0 ± 0.1 K using graphite monochromatised MoK$_\alpha$ radiation (λ = 0.71073 Å). Data were processed with DENZO-SMN (11), the structure was solved by direct methods (SHELXS-97) (12) and refined on F^2 (SHELXL-97) (13).The reflections were corrected for Lorenz polarisation effects, absorption correction was not used. The hydrogen atoms were calculated to their idealised positions and refined with isotropic temperature factors (1.2 or 1.5 times the C temperature factor). No hydrogens were determined to a water molecule. Three of the sulphurs of the DMSO molecules are disordered over two positions. In addition one oxygen of a DMSO molecule is disordered over two positions. Other experimental X-ray data are shown in Table 4 and the ORTEP of **1** is illustrated in Figure 3.

Crystallographic data (excluding structure factors) for the structure has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-201440. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ UK.

Table 4. Experimental data for single crystal X-ray diffraction studies

Formula	$2\ C_{29}H_{30}N_6O_4 \cdot 8\ (CH_3)_2SO \cdot H_2O$
Formula weight (g·mol^{-1})	1694.3
Crystal system	Monoclinic
Space group	P 2_1 (No. 4)
Crystal size (mm)	0.15 x 0.20 x 0.40
a (Å)	11.5122 (2)
b (Å)	32.0092 (7)
c (Å)	11.9449 (2)
β (°)	95.101 (2)
V (Å^3)	4384.2 (1)
Z	2
D(calc.) (g·cm^{-1})	1.283
μ(MoK$_\alpha$) (mm^{-1})	0.272
θ range for data collection (°)	2.65 – 25.04
No. of reflections measured	17677
No. of reflections observed ($I > 2\sigma(I)$)	9974
No. of parameters	1052
R / R$_w$ for unique data with $I > 2\sigma(I)$ (%)	5.35 / 12.20
GoF	1.091

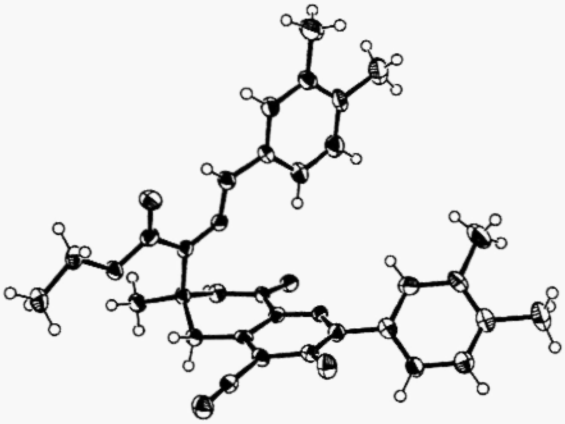

Figure 3. The ORTEP of compound 1.

ESI-TOF mass spectral studies gave the molecular formula of $C_{29}H_{30}N_6O_4$ for compound **1** and $C_{27}H_{24}N_6O_4Cl_2$ for compound **2**.

Results and discussion

The synthesis reaction and the structures of the starting compounds are presented in Figure 1. The numbering and the structures of the two derivatives 1 and **2** are presented in Figure 2.

NMR: The assignment of the NMR chemical shifts was started from the ^1H chemical shifts of 1 (Figure 2), because its single crystal X-ray structure was available. The $\delta(^1H)$ of the ethoxy-group are at 1.36 ppm (triplet) and at 4.30 and 4.37 ppm (AB-quartet because these methylene protons are diastereotopic) showing $^3J(H,H)$ = 7.1 Hz and $^2J(H,H)$ = -10.7 Hz. coupling constants.

The $\delta(^1H)$ assignments of two ABC-spin systems in the rings A and B are based on the characteristic $^3J(H,H)$ and $^4J(H,H)$ coupling constants as well as PFG DQF $^1H,^1H$ COSY measurements. After that PFG $^1H,^{13}C$ HMQC gave unambiguous ^{13}C assignments for the corresponding protonated carbons. The final step in the assignment of the ring A was PFG $^1H,^{13}C$ HMBC cross peak (evolution delay 50 ms) between NH proton at 11.46 ppm and a carbon at 111.52 ppm, which is C-6 bound to H-6 at 6.88 ppm. This was they key observation, which helped to solve all the $\delta(^1H)$ and $\delta(^{13}C)$ shifts of rings A and B.

There exist only two NH-protons as revealed by PFG $^1H,^{15}N$ HMBC, when the low-pass filter was miss-set to give these cross-peaks as doublets (in inv4gslplrnd pulse program the proton decoupler is off during the acquisition). The other amino proton at 8.82 ppm, which can't show cross-peaks with aromatic carbons is N-7.

The $\delta(^1H)$ of the methyls in the rings A and B resonating from 2.13 to 2.24 ppm were assigned based on PFG $^1H,^{13}C$ HMBC cross peaks. Their $\delta(^{13}C)$ are correlated with the following protons in the ring A: 18.59 ppm (4-CH_3) with 7.00 ppm (H-5); 19.43 ppm (3-CH_3) with 7.01 ppm (H-2). Similarly in the ring B: 19.01 ppm (4-CH_3) with 7.22 ppm (H-5) and 19.15 ppm (3-CH_3) with 7.13 ppm (H-2). The singlet of three protons at 1.71 ppm, belongs to the methyl group on sp^3-hybridized C-6, in the ring D.

An other AB-quartet at $\delta(^1H)$ = 3.38 and 3.86 ppm must belong to the geminal protons at C-5 (ring D), which also is ascertained by a PFG $^1H,^{13}C$ HMBC cross-peak between 7-NH and C-5 at 38.26 ppm.

As stated before the assignments of the $\delta(^1H)$ of the amino protons at 8.82 ppm and 11.46 ppm are based on PFG $^1H,^{15}N$ HMBC. Among them $\delta(^1H)$ at 8.82 ppm shows PFG $^1H,^{13}C$ HMBC cross peak with C-5 at 38.26 ppm and C-6 (methyl) at 25.94 ppm in the ring D whereas the amino proton resonating at $\delta(^1H)$ at 11.46 ppm is too far from the D-ring to show any cross-peaks transmitted by long-range couplings.

The assignments of the fifteen non-protonated $\delta(^{13}C)$ as well as $\delta(^{15}N)$ are all based on the PFG $^1H,^{13}C$ and $^1H,^{15}N$ HMBC experiments. The *ipso*-carbons of the aromatic rings were elucidated as follows: $\delta(^{13}C)$ 129.99 ppm is strongly correlated with the 2.16 ppm (3-CH_3), 2.13 ppm (4-CH_3), 7.01 ppm (H-2, ring A) and 6.88 ppm (H-6, ring A) and thus belongs to C-4 of the ring A. $\delta(^{13}C)$ shift of 137.20 ppm, which is correlated with the protons 7.00 ppm (H-5, ring A) and 2.16 ppm (4-CH_3) belongs to C-3 (ring A). $\delta(^{13}C)$ shift of C-1 (ring A) has shift value of 140.86 ppm, because that carbon shift is correlated with 11.46 ppm (NH) and 7.00 ppm (H-5, ring A).

The assignment of ^1H and ^{13}C chemical shifts in ring B was similarly based on the PFG $^1H,^{13}C$ HMQC and HMBC experiments. The $\delta(^{13}C)$ = 57.28 ppm belongs to the sp^3-hybridized C-6 (ring D). This is proved by its correlation with 8.82 ppm (N^1H), 3.86 ppm, 3.38 ppm (5-CH_2) and 1.17 ppm (6-CH_3).

The ester carbonyl shift of 161.90 ppm, was assigned from its correlation with CH_2 protons (4.30 and 4.37 ppm). The two other carbonyl shifts, C-3 (ring C/D) of 156.17 ppm and C-8 (ring D) of 159.40 ppm were elucidated as follows. The $\delta(^{13}C)$ = 156.17 is correlated with $\delta(^{1}H)$ = 3.38 ppm, with one of the 5-CH_2 protons (ring D), while the $\delta(^{13}C)$ = 159.40 ppm is correlated with $\delta(^{1}H)$ = 1.71 ppm (6-CH_3 of ring D) and $\delta(N^{1}H)$ = 8.82 ppm. Only C-8 carbonyl can correlate with NH and 6-CH_3 protons of ring D.

The rest of the non protonated carbons C-4 (ring C), C-4a (ring C/D), C-8a (ring C/D), CN (ring C) and C=N (hydrazono group) have following $\delta(^{13}C)$: 110.77 ppm, 150.13 ppm, 135.39 ppm, 112.97 ppm and 128.30 ppm. From these only the $\delta(^{13}C)$ = 128.30 ppm is strongly correlated with the $\delta(N^{1}H)$ = 11.46 ppm and thus belongs to the hydrazono group. The $\delta(^{13}C)$ shifts of 110.77 ppm and 135.59 ppm are both strongly correlated with both methylene protons 3.38 ppm and 3.86 ppm in the ring D. The latter is also strongly correlated with NH proton (8.82 ppm) and thus belongs to C-8a, while the 110.77 ppm shift belongs to C-4. The $\delta(^{13}C)$ shift of 112.97 ppm is correlated with 3.38 ppm proton shift and very weakly with 3.86 ppm. These couplings are over four bonds, between the cyano carbon and the 5-CH_2 (ring D) protons. The typical shift area for cyano carbon is between 110.5 to 125.1 ppm (14).The last non protonated $\delta(^{13}C)$ = 150.13 ppm (C-4a) is correlated with the 5-CH_2 protons (3.38 and 3.86 ppm) and weakly with 6-CH_3 protons (1.71 ppm) and 7-NH (8.82 ppm).

The dihedral angle between C-8a and the 5-CH_2 proton Ha is 92.2° and between proton Hb, -150.4°. Because C-8a is more strongly correlated with the 3.86 ppm than with the 3.38 ppm proton shift, the former one must belong to Hb and the latter to Ha.

The $\delta(^{15}N)$ = -227.7 ppm and -248.2 ppm were assigned from the PFG $^{1}H,^{15}N$ HMBC spectrum, where their $^{1}J(^{1}H,^{15}N)$ with NH (11.46 ppm, ring A) and NH (8.82 ppm, ring D) were observed. The $\delta(^{15}N)$ = –248.2 ppm is also strongly correlated with 5-CH_2 (3.38 and 3.86 ppm) and 6-CH_3 (1.71 ppm) protons. The $\delta(^{15}N)$ = -227.7 ppm is correlated with the aromatic ring protons H-2 (7.01 ppm, ring A) and H-6 (6.88 ppm, ring A).

The most shielded non protonated $\delta(^{15}N)$ = -160.0 ppm, must belong to the sp^3-hybridized N-2 (ring C) (15). It is correlated with all the aromatic ring protons H-2, H-5 and H-6 (7.13, 7.22 and 7.15 ppm, ring B), which confirms the interpretation. The $\delta(^{15}N)$ = -34.6 ppm is correlated with NH proton shift of 11.46 ppm (ring A) and belongs to the hydrazono nitrogen C=N. Thus the $\delta(^{15}N)$ = -25.3 ppm belongs to the N-1 in ring C. It is weakly correlated with the NH proton of ring D (8.82 ppm).

The cyano nitrogen does not give any cross peak in the PFG $^{1}H,^{15}N$ HMBC measurement being five bonds away from the nearest protons.

After the assignment of all the ^{1}H, ^{13}C and ^{15}N NMR shifts of compound 1, those for compound 2 were much more straightforward. The aromatic ring $\delta(^{1}H)$ shifts deviated most from each other in compounds 1 and 2. The interpretation of the ^{1}H, ^{13}C and ^{15}N NMR shifts in compound 2 is based as above on the $^{n}J(H,H)$ values, DQF $^{1}H,^{1}H$ COSY, PFG $^{1}H,X$ ($X = {}^{13}C, {}^{15}N$) HMQC and HMBC experiments.

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