NOE AND 2D-NOESY SPECTROSCOPIC STUDIES OF NAPHTHO[1,2-c]PYRAZOLINE DERIVATIVES

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تم تحضير مشتقات naphtho[1,2-c]pyrazoline بواسطة تكاثف 2-arylmethylidene-1-tetralones مع مشتقات الهيدرازين. تم توظيف أطياف nOe المطروحة لرنين البروتون النووي المغناطيسي و دراسات 2D-NOESY الطيفية للتمييز بين بروتوني البروكيرال ميثيلين الدياستيريومريين H_M و H_N في مركب 2-methyl-3-phenyl-3,3a,4,5-tetrahydronaphtho[1,2-c]pyrazole وأثبتت أن H_J و H_M تقعان تحت المستوى و H_H و H_N أعلى المستوى. هذه النتائج أظهرت علاقة متضادة بين البروتونين H_H و H_J المتجاورين وأكدت على الشكل والترتيب النسبي للمركزين الكيراليين في مشتقات البيرازولين.

The synthesis of naphtho[1,2-c]pyrazoline derivatives has been achieved *via* the condensation of 2-arylmethylidene-1-tetralones with hydrazine derivatives. ^{1}H NMR nOe difference spectra and 2D-NOESY spectroscopic studies were employed to distinguish between the diastereotopic prochiral methylene protons H_M and H_N in 2-methyl-3-phenyl-3,3a,4,5-tetrahydronaphtho[1,2-c]pyrazole and proved that H_J and H_M are down the plane and H_H and H_N are above the plane. These results revealed an *anti* relationship between the vicinal protons H_H and H_J and confirmed this relative configuration of the two chiral centers in pyrazoline derivatives.

INTRODUCTION

In the last decades the pyrazole derivatives had a considerable interest in the chemotherapeutic activity. The use of pyrazole derivatives in medicine is undoubtedly the principal practical application. Certain alkylpyrazoles have shown quite significant bacteriostatic [1-3], bacteriocidal and fungicidal actions [4-6]. Steroidal compounds whose structures include pyrazole rings are of interest as possible psychopharmacological agents [7,8]. Moreover, pyrimidinopyrazoles are being studied in the fight against cancer [9]. On the other hand, a wide variety of pharmacological properties are encountered with naphthalene derivatives [10]. Therefore, fused heterocyclic systems incorporating the naphthalene moiety and pyrazole ring were synthesized by Basaif *et al* [11] for the purpose of obtaining compounds of biologically importance.

EXPERIMENTAL

General procedure for preparation of naphtho[1,2-c]pyrazoline derivatives 2-8 [11]**.**

A mixture of the appropriate 2-arylmethylidene-1-tetralone **1** (0.001 mol) and the proper hydrazine derivative (0.0012 mol) in ethanol (30 ml) was heated under reflux for 3 hrs. Upon concentration and cooling, the pyrazoline derivative separated out and recrystallized from ethanol as needles.

Selected physical and spectroscopic data for 2-methyl-3-phenyl-3,3a,4,5-tetrahydronaphtho[1,2-c]pyrazole 2.

mp 136°C; FTIR (KBr) ν_{max} 3065(aromatic CH), 2950-2850(aliphatic CH), 1548(C=N) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (1H, dd, *J*=7.6, 2.3 Hz, Ar H_A), 7.48 (2H, d, *J*=7.3

Hz, Ar H_B), 7.39 (2H, t, J=7.1 Hz, Ar H_C), 7.32 (1H, d, J=7.1 Hz, Ar H_D), 7.23 (1H, dd, J=7.8, 3.6 Hz, Ar H_E), 7.21 (1H, dd, J=7.8, 3.4 Hz, Ar H_F), 7.14 (1H, dd, J=7.0, 2.1 Hz, Ar H_G), 3.68 (1H, d, J=13.5 Hz, H_H), 3.14 (1H, ddd, J=13.5, 13.5, 5.0 Hz, H_J), 2.78 (2H, dd, J=13.2, 5.0 Hz, H_K), 2.82 (1H, s, C$H_{3(L)}$), 2.17-2.11 (1H, m, H_M), 1.88-1.81 (1H, m, H_N) ppm; ^{13}C NMR (100.2 MHz, $CDCl_3$) δ 152.23 (C=N), 139.63 (Ar quat C), 138.16 (Ar quat C), 129.04 (Ar CH), 128.90 (Ar CH), 128.71 (2Ar CH), 128.3 (Ar quat C), 127.87 (Ar CH), 127.44 (2Ar CH), 126.62 (Ar CH), 124.13 (Ar CH), 80.50 (CH_H), 54.68 (CH_J), 42.07 ($CH_{3(L)}$), 29.28 ($CH_{2(K)}$), 26.83 ($CH_{2(M+N)}$) ppm; MS (EI) m/z (%) 51 (28), 65 (15), 77 (28), 91 (45), 115 (8), 116 (28), 118 (27), 144 (16), 185 (83), 262 (base, M^+); $C_{18}H_{18}N_2$ (262), Calcd.: C, 82.44; H, 6.87; N, 10.69. Found: C, 82.21; H, 6.56; N, 10.45.

RESULTS AND DISCUSSION

Condensation of 2-arylmethylidene-1-tetralones **1**, which prepared *via* condensation of 1-tetralone with aromatic aldehydes in presence of 10% aqueous sodium hydroxide solution, with hydrazine derivatives in boiling ethanol yielded the corresponding naphtho[1,2-c]pyrazoline derivatives **2**-**8** in good yields [11] (Scheme 1).

An X-ray crystal structure of pyrazoline derivative **2** which obtained by Basaif *et al* [11] showed an *anti* relationship between neighboring protons H_H and H_J. Therefore, pyrazoline derivative **2** was adopted for 1D ^{1}H NMR, nOe and 2D-NOESY spectroscopic studies to confirm this relative configuration of the two chiral centers in pyrazoline derivatives. The ^{1}H NMR spectrum of pyrazoline derivative **2** showed a doublet at δ 3.68 ppm for proton H_H with coupling constant J_{H_H/H_J} of 13.5 Hz indicating that vicinal protons H_H and H_J are in diaxial configurations. There is a doublet of doublet of doublet (ddd) at δ 3.14 ppm for proton H_J, which couples with the axial proton H_H (J_{H_J/H_H} =13.5 Hz) to split to two lines which each of

them split again to another two lines after coupling with the axial proton H_M (JH_J/H_M =13.5 Hz) to give four lines. Because of the coupling constant of H_J with H_H almost equals the coupling constant of H_J with H_M, the inner two lines coincide to give only three lines, which each of them split to two lines to give six lines after coupling with the equatorial proton H_N (JH_J/H_N =5.0 Hz). There is a doublet of doublet for two equivalent protons H_K at δ 2.78 ppm which couple with H_M (JH_K/H_M =13.2 Hz) and then couple with H_N (JH_K/H_N =5.0 Hz). There are two multiplets at δ 2.17-2.11 and 1.88-1.81 ppm for the axial proton H_M and the equatorial proton H_N, respectively.

Attempts to confirm the relationship between the vicinal protons H_H and H_J, and to distinguish between the diastereotopic methylene protons H_M and H_N in the pyrazoline derivative **2** were carried out by using nuclear Overhauser effect (nOe) and 2D-NOESY spectroscopic studies. ^{1}H NMR nOe difference spectra of the pyrazoline derivative **2** are accumulated in Table 1 and in particular show that irradiation of H_A, H_B, H_F, H_J, methyl L protons and H_N, individually, gave 20.8%, 19.6%, 21.3%, 21.3%, 21.3% and 21.3% enhancement of signal, respectively, for H_M, whereas, all of these irradiations did not give any enhancement for H_N. Irradiation of H_E, H_H, methylene K protons and H_M, individually, caused 15.4%, 20%, 21.3% and 21.3% enhancement of the signal, respectively, due to H_N, whereas, irradiation of these protons did not affect H_M. These results prove that H_M is close in space to H_A, H_B, H_F, H_J, methyl L protons and H_N, whilst, H_N is close in space to H_E, H_H, methylene K protons and H_M. All of these results confirm that the diastereotopic prochiral methylene protons H_M and H_N are distinguishable.

Irradiation of H_M caused 7.9% enhancement of the signal due to H_J, but did not affect H_H, whilst, irradiation of H_N gave 7.5% enhancement of signal for H_H, but did not affect H_J. These results prove that H_J and H_M are close to each other in space, whereas, H_H and H_N are close to each other in space, and hence, one can conclude that H_J and H_M are in the same

direction which is down of the plane, whilst, H_H and H_N are in the same direction which is above the plane.

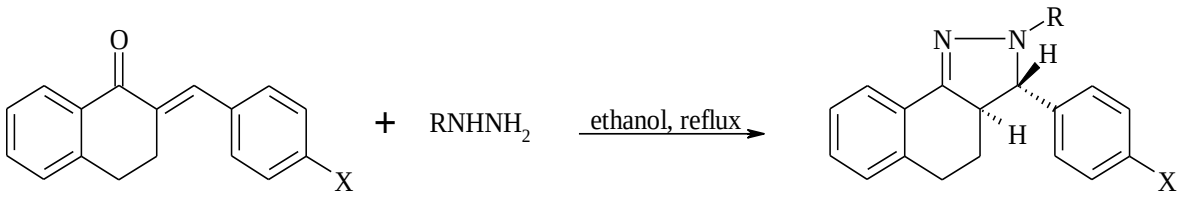
An X-ray crystal structure for compound **2**, which obtained by Basaif *et al* [11], confirmed these results that H_J and H_M are down of the plane, whereas, H_H and H_N are above the plane.

Fig. 1 illustrates the 2D-NOESY spectrum of the pyrazoline derivative **2**. The one-dimensional spectrum is reproduced along one axis of the two-dimensional contour plot. There are three correlation peaks at δ 2.15 and 7.48 ppm, 2.15 and 3.14 ppm and 2.15 and 2.82 ppm for H_M with H_B, H_M with H_J and H_M with methyl L protons, respectively. This proves that H_M is in close position to H_B, H_J and methyl L protons. There are two correlation peaks at δ 1.85 and 3.68 ppm and 1.85 and 2.87 ppm for H_N with H_H and H_N with methylene K protons, respectively and this proves that H_N is close in space to H_H and methylene K protons. These results confirm that the diastereotopic prochiral methylene protons H_M and H_N are distinguishable.

There are two correlation peaks at δ 2.15 and 3.14 ppm and 1.85 and 3.68 ppm for H_M with H_J and H_N with H_H, respectively, proving that H_M is in close position to H_J and H_N is in close position to H_H. These results confirm the previous result that H_M and H_J are in the same direction which is down of the plane, whereas, H_N and H_H are in the same direction *i.e.* above the plane.

By conclusion, all of these results determined by 2D-NOESY spectrum confirm all results determined by nOe difference spectra.

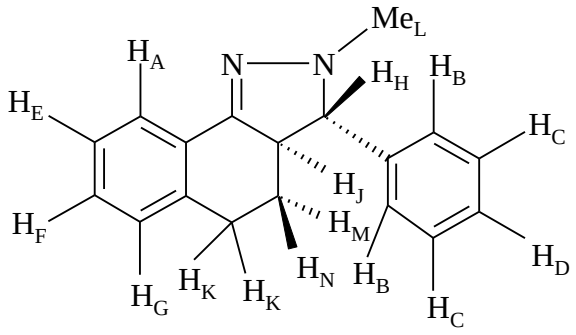
All the signals of the pyrazoline derivatives **2** were assigned by nOe and 2D-NOESY spectroscopic studies.



1

2 X=H, R=CH_3 **3** X=*p*-CH_3, R=CH_3
4 X=H, R=C_6H_5 **5** X=*p*-CH_3, R=C_6H_5
6 X=H, R=*p*-ClC_6H_4
7 X=*p*-CH_3, R=*p*-ClC_6H_4
8 X=*p*-CH_3, R=*p*-$NH_2SO_2C_6H_4$

Scheme 1



2

Table 1. ^{1}H NMR steady state nOe data for the naphtho[1,2-c]pyrazoline derivative **2**.

Irradiation Site	Signal enhancement (%)												
	H_A	H_B	H_C	H_D	H_E	H_F	H_G	H_H	H_J	H_K	H_L	H_M	H_N
H_A	-	-	-	-	3.8	14.6	-	4.6	12.5	-	-	20.8	-
H_B	-	-	7.1	-	2.9	5.8	12.5	10	20	-	-	19.6	-
H_C	-	-	-	-	-	-	-	20.8	-	-	-	-	-
H_D	-	-	-	-	-	-	-	16.3	21.3	-	-	-	-
H_E	16.7	-	-	-	-	-	11.3	6.3	21.3	-	-	-	15.4
H_F	11.7	-	-	-	-	-	-	8.3	-	-	-	21.3	-
H_G	-	-	-	-	-	-	-	6.7	13.3	16.7	-	-	-
H_H	-	13.8	-	-	-	-	-	-	8.3	-	-	-	20
H_J	-	4.2	-	-	-	-	6.7	6.3	-	-	-	21.3	-
H_K	-	-	-	-	-	-	12.1	2.5	13.8	-	-	-	21.3
H_L	-	-	-	-	-	-	-	20.4	-	-	-	21.3	-
H_M	-	-	-	-	-	-	-	-	7.9	-	-	-	21.3
H_N	-	-	-	-	-	-	-	7.2	-	7.1	-	21.3	-

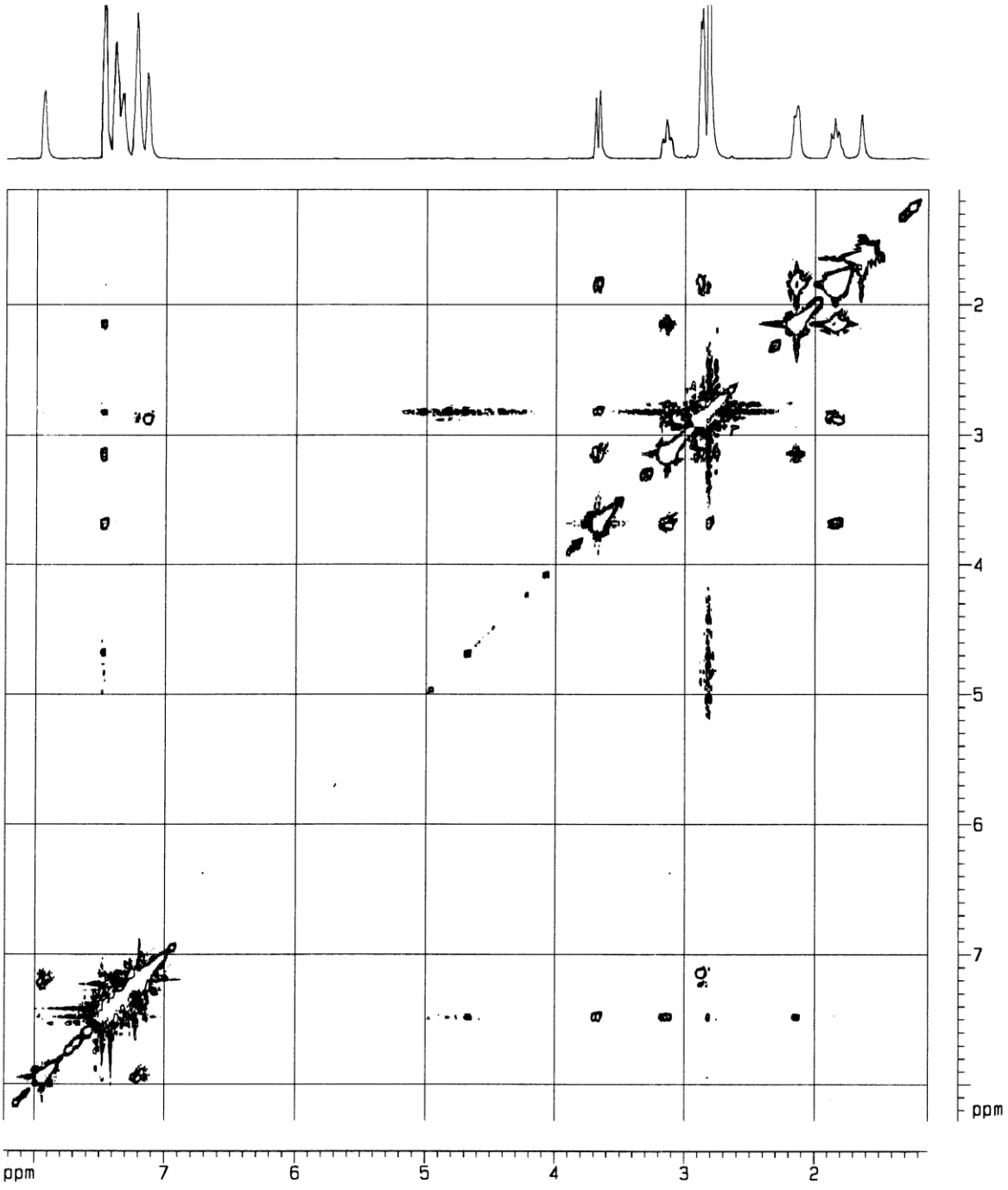


FIG 1. The 2D-NOESY 400 MHz NMR spectrum of the naphtho[1,2-c]pyrazoline derivative **2**.

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