Synthesis of Mannich Bases of 8-Hydroxyquinoline

Humaira Siddiqi[b,*], Shaheen Faizi[a], Shaista Naz[b] and Erum Zahir[b]

[a]*H.E.J. Research Institute of Chemistry, International Centre for Chemical and Biological Sciences (ICCBS), University of Karachi, Karachi, Pakistan*

[b]*Department of Chemistry, University of Karachi, Karachi, Pakistan*

Abstract: In search of new potential therapeutic agents, 8-Hydroxyquinoline which is a highly active antifungal and antibacterial agent was subjected to Mannich reaction. Different combinations of aromatic aldehyde and aromatic amines were used for Mannich reaction on 8-Hydroxyquinoline from which one new 7-[α-(anilino)-3',4'-dimethoxybenzyl]-8-hydroxyquinoline (**3**) and two known Mannich bases (**1,2**) were obtained.

Keywords: 8-Hydroxyquinoline, Oxine, Mannich Base, Mannich Reaction.

1. INTRODUCTION

8-Hydroxyquinoline is an organic compound with the formula C_9H_7NO. It is a derivative of the heterocyclicquinoline. It is usually prepared from quinoline-8-sulfonic acid and through Skraup synthesis from 2-aminophenol [1-4]. Oxine and its derivatives have in the past received considerable attention for their biological activity. 8-Hydroxyquinoline has a wide variety of uses because of its metal chelating properties. It has been used extensively to construct highly sensitive fluorescent chemo sensors for sensing and imaging of metal ions of important biological and environmental significance [5]. 8-Hydroxyquinoline and its derivatives have been found to show diverse biological activities such as antibacterial [6], antimalarial [7], fungicidal [8], antitumor [9], insecticidal [10] and anti HIV [11].

The Mannich reaction is enormously useful for the construction of nitrogenous molecules. In this transformation, three components, a ketone, an aldehyde, and an amine, react to form an amino-ketone. This reaction has very much importance in organic synthesis for preparation of peptides-nucleotides, antibiotic and alkaloids and medicinal compounds *e.g.* rolitetracycline (Mannich base of tetracycline), fluoxetine (antidepressant) and tolmetin (anti-inflammatory drug) [12]. The reactivity of the bases accounts for several interesting properties (mainly pharmacological). Since 1989 our research group had been engaged in carrying out chemical reactions on oxine and synthesized a number of Mannich bases, imines, ethers and esters to study their biological activity [13, 14]. They were found to possess significant antibacterial, anticandidal and analgesic activities [13, 14]. In view of these facts further work on 8-Hydroxyquinoline was carried out and presented herein.

2. EXPERIMENTAL

2.1. General Note

UV (in methanol) and IR spectra (in $CHCl_3$ and KBr disc) were measured on U-3200 (Hitachi, Japan) and FTIR-8900 (Shimadzu, Japan) spectro-photometers, respectively. The EI-MS, FAB positive, FAB negative and HR-EI-MS spectra were recorded on MAT 312 (Finnigan, Germany) and JMS HX-110 spectrometer (Jeol, Japan). The ^{1}H NMR spectra were measured inDMSO-d_6, using Bruker Aspect AM-300 AM-400 and AM-500 spectrometers operating at 300, 400 and 500 MHz respectively, with spectra referenced to residual protiodeuterio solvent signals. Assignment of proton chemical shifts is based on COSY 45^0, NOESY and HMQC spectroscopy. The ^{13}C NMR spectra (Broad Band decoupled and DEPT) were run on a Bruker Aspect AM-300, AM-400 and AM-500 operating at 75, 100 and 125 MHz respectively. The chemical shifts are in ppm (δ) and coupling constants (*J*) are in Hz. The ^{13}C NMR spectral assignments have been made partly through DEPT, HMQC and HMBC spectra and partly through the comparison with the reported values of similar compounds.

2.2. General Procedure for the Preparation of Mannish Bases

The products **1-2** were obtained on reaction of 8-Hydroxyquinoline and benzaldehyde with *o*-toluidine and 4-methoxyaniline, while 3 was obtained by reaction of 8-Hydroxyquinoline and aniline/3,4-dimethoxy benzaldehyde. In each case measured quantities of

*Address correspondence to this author at the Department of Chemistry, University of Karachi, Karachi-75270 Pakistan; Tel: +923332277606;
E-mail: chem_75@hotmail.com

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amines, aldehydes and 8-Hydroxyquinoline were mixed together in absolute ethanol. The reaction mixture was kept at room temperature and the course of the reaction was monitored with TLC, by visualized under UV light (254 and 366 nm). Compounds **1, 3** was separated out from their respective reaction mixture which were filtered and washed with methanol. Thick layer chromatography (silica gel, $CHCl_3$) of reaction mixture afforded pure compound (**2**) in an amorphous form.

Characterization of 7-[α-(2-Methyl anilino) benzyl]-8-hydroxyquinoline (1)

White crystals

Yield= 2.0g

m.p = 140-141^oC (solvent for recrystallization: MeOH).

R_f = 0.61(P.E:E.A:CH_3CN=5:5:1) Silica gel

UV λ_{max} nm (MeOH): 248 and 203

IR ν_{max} (KBr) cm^{-1}= 3410, 3254, 1595, 820

EI MS *m/z* (%) 340.1591 ($M^{\cdot+}$) (Calc. For $C_{23}H_{20}N_2O$ 340.1575) (17), 263 (M-77) (2), 249 (fragment a) (1), 234.0906 (fragment b, $C_{16}H_{12}$ NO) (100), 216 (fragment h) (20), 195 (fragment c, $C_{14}H_{13}N$) (2), 106.0656 (fragment d, C_7H_8N) (98), 91.0531 (fragment e,C_7H_7) (6).

^{1}H NMR data: Table **1**

Characterization of 7-[α-(4′′- Methoxyanilino)-benzy]-8-hydroxyquinoline (2)

Amorphous form

Yield= 2.0g

m.p =130^oC(solvent for recrystallization:MeOH)

R_f = 0.52 (P.E:E.A:CH_3CN=5:5:1) Silica gel

UV λ_{max} nm (MeOH): 248 and 203

IR ν_{max} (KBr) cm^{-1}= 3395, 3250, 1595, 820

^{1}H NMR: Table **1**

Characterization of 7-[α-(Anilino) 3′-4′-dimethoxy-benzyl]-8-hydroxyqionoline (3):

Amorphous

Yield= 1.5 g

m.p = 198^oC(solvent for recrystallization:MeOH)

R_f = 0.51(P.E:E.A:CH_3CN=6.5:3.5:1) Silica gel

IR ν_{max} ($CHCl_3$) cm^{-1}: 3325-3275 (OH), 2850 (Ar-OCH_3), 2890 (Ar-OCH_3), 1538-1608 (aromatic ring) and 1642 (NH).

EI MS *m/z* (%): 386 ($M^{\cdot+}$) (3.56%), 294 (fragment a, $C_{18}H_{16}NO_3$) (17.15%), 242 (fragment b, $C_{15}H_{16}NO_2$) (1.72%), and 93 (fragment C, C_6H_6N) (100%).

^{1}HNMR and ^{13}CNMR: Table **2**

3. RESULT AND DISCUSSION

Mannich base **1** was obtained as white crystals, on reaction of 8-Hydroxyquinoline with benzaldehyde and 2-methyl aniline. It showed molecular ion peak at *m/z* 340.1591 in HREI mass spectrum corresponding to the molecular formula $C_{23}H_{20}N_2O$. Its infrared spectrum displayed absorbance at 3410 cm^{-1} for secondary amine and at 820, 1595 and 3254 cm^{-1} for aromatic ring.

Its ^{1}H NMR spectrum (DMSO-d_6, 300MHz) showed three doublets at δ8.83 (dd, *J*=4.2, 1.6Hz, H-2), 7.51 (dd, *J*= 8.3, 4.2Hz, H-3), 8.27(dd, *J*= 8.3, 1.6Hz, H-4) and two doublets at 7.28(d, *J*=8.5Hz, H-5) and 7.69(d, *J*=8.5Hz, H-6) for oxine moiety. AA′ BB′C′ spin system for benzyl protons appeared as two, two protons broad doublet at δ 7.44 (*J*=7.1 Hz, H-2′, 6′) and a multiplet at δ 7.36 for H-3′, 5′ and a one proton broad triplet at δ 7.20(*J*=8.5) for H-4′. The benzyl CH (H-α) appeared as a one proton doublet at δ 6.20 (*J* =7.1 Hz). The presence of 2-methyl anilino group was evident from the chemical shifts at δ 6.49 (d, *J*= 6.5 Hz, H-3′′), 6.47 (dd, *J*=6.5 and 7.1 Hz, H-4′′), 6.85 (t, *J*=7.4 Hz, H-5′′), 6.97 (brd, *J*=7.1 Hz, H-6′′), and a doublet at δ 5.29 (*J*=7.1Hz) for NH proton. On shaking with D_2O the signal for NH proton disappeared while doublet of H-C at δ6.20 converted to a singlet, indicating both NH and H-C are adjacent to each other. The aromatic methyl group resonated at δ 2.49 as singlet. The ^{1}H NMR spectral data (Table **1**) and mass fragmentation pattern determined the structure of this Mannich base as 7-[α-(2′′-Methylanilino) benzyl]-8-hydroxyquinoline, (**1,** Figure **1**), the preparation of which has been reported earlier [15, 16].

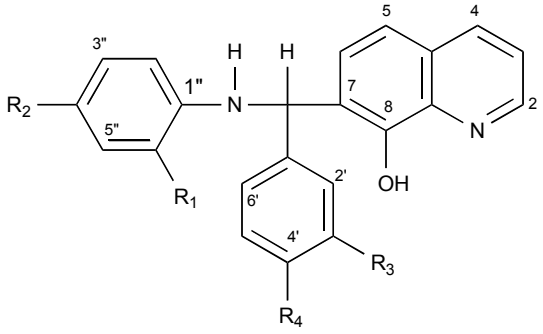
Mannich base **2** was obtained as brown crystals on reaction of 8-Hydroxyquinoline with benzaldehyde and 4-methoxy aniline. It showed molecular ion peak at *m/z* 356 in EI mass spectrum corresponding to the molecular formula $C_{23}H_{20}N_2O_2$. Its ^{1}H NMR spectrum showed the same signals for oxine and benzyl moiety as observed for those of **1** while 4-methoxy aniline part was evident by two multiplets at δ6.64(2H) and 6.57 (2H), and a singlet for methoxy group at δ3.93 in ^{1}H NMR spectrum (Table **1**). These spectroscopic data elucidated the structure of the base as 7-[α-(4′′-Methoxyanilino) benzyl]-8-hydroxyquinoline (**2,** Figure **1**), which has been prepared earlier [16].

In the third set oxine and 3,4-dimethoxy benaldehyde on reaction with aniline afforded the new

Table 1: ^{1}H -NMR Data (δ in ppm, *J* in Hz) of Compounds 1,2 in DMSO-d_6 at 300MHz

Assignments	1	2
2	8.83 dd (4.2, 1.6)	8.83 dd (3.9, 1.2)
3	7.51dd (8.3,4.2)	7.51dd (8.4,4.2)
4	8.27dd (8.3, 1.6)	8.25dd (8.4, 1.5)
5	7.28 d (8.5)	7.26 d (8.7)
6	7.69 d (8.5)	7.60 d (8.7)
2′,6′	7.44 brd (7.1)	7.42 brd (7.2)
3′,5′	7.36 m	7.31 m
4′	7.20 brt (8.5)	7.19 brt (7.2)
2′′	-	6.64m
3′′	6.49 d(6.5)	6.57 m
4′′	6.47 dd (7.1,6.5)	-
5′′	6.85 t (7.1)	6.57 m
6′′	6.97 brd (7.1)	6.64m
CH	6.20d (7.1)	6.07 brs*
NH	5.29 d (7.1)**	6.07 brs*
OCH_3	-	3.93s
CH_3	2.49 s	-
OH	9.98 (hump)**	9.97 (hump)**

*Integration decreased in D_2O.
**Disappeared in D_2O shake.



	R_1	R_2	R_3	R_4
1	CH_3	H	H	H
2	H	OCH_3	H	H
3	H	H	OCH_3	OCH_3

Figure 1: Structures of Mannich Bases **1-3**.

Mannich base **3**. Its EIMS spectrum has molecular ion peak at *m/z* 386 corresponding to the molecular formula $C_{24}H_{22}N_2O_3$. The IR spectrum showed peaks at 3325-3275 (OH), 2850 and 2890 (Ar-OCH_3) and 1642 (NH) cm^{-1}. The ^{1}H-NMR spectrum (DMSO-d_6, 300 MHz, Table **2**) displayed quinol signals at δ 8.74 (brd, *J*= 4.2 Hz, H-2), δ 7.39 (dd, *J*=8.3, 4.2 Hz, H-3), and 8.10 (brd, *J*=8.4 Hz, H-4). Two one-proton doublets at δ 7.36 (d, *J*= 8.5 Hz) and 7.60 (d, *J*=8.6 Hz) were attributed to H-5 and H-6 respectively. The exact attribution of the chemical shift of these two protons has been made through NOESY experiment which exhibited spatial connectivity of H-6 with H-5 and CH, H-4 with H-3 and H-5, H-2 with H-4 and H-3. The presence of anilino group was evident from the chemical shifts at δ 6.63 (dd, *J*= 8.5, 1.1 Hz, H-2′′, 6′′), 7.12 (t, *J*= 7. 4 Hz, H-3′′, 5′′) and 6.75 (t, *J*= 7.4 Hz, H-4′′) while 3,4-dimethoxy benzyl protons appeared at δ 7.04 (brs, H-2′), 6.95 (d, *J*=7.5 Hz, H-5′) and 6.78 (d, *J*=7.5 Hz. H-6′) while the two methoxy group protons resonated at δ 3.82. The CH and NH protons appeared at δ 6.06 (brs) and 4.41(brs). On shaking with D_2O the signal for NH proton disappeared while doublet of H-C at δ6.06 converted into a sharp singlet, indicating both NH and H-C are adjacent to each other. The structure of the compound was determined as 7-[α-(Anilino)-3',4'-dimethoxybenzyl]-8-hydroxyquinoline (**3**), which was corroborated by important mass fragments at *m/z* 386 (M^+), 294 (fragment a, $C_{18}H_{16}NO_3$), 242 (fragment b, $C_{15}H_{16}NO_2$) and 94 (fragment c, C_6H_6N) and comparison of these spectroscopic data with the reported data of similar compounds [16,17].

Table 2: ^{1}H -and ^{13}C-NMR Data (δ, Hz) of 3 in DMSO-d_6

HMQC ^{1}H x ^{1}H					
Assignements	**^{13}C**	**^{1}H**	**HMBC**	**COSY 45°**	**NOESY**
2	147.9	8.74 brd (4.2)	H-4, H-3	H-3,H-4	H-6′, H-3
3	121.5	7.39 dd (8.3, 4.2)	H-2	H-2,H-5	H-2, H-4
4	135.9	8.10 brd (8.4)	H-5	H-3,H-2	H-3, H-5
5	117.4	7.30 d (8.5)	H-4, H-6	H-6	H-6, H-4
6	126.2	7.60 d (8.6)	H-5	H-5	H-2, H-5, CH
7	125.6	-	H-5	-	-
8	149.5	-	H-6	-	-
9	138.1	-	H-5	-	-
10	127.4	-	H-4, H-6, H-3, H-5	-	-
1′	147.9	-	H-5′	-	-
2′	112.0	7.04 brs	H-6′	-	H-2, H-2′′, CH
3′	148.8	-	H-2′	-	-
4′	149.9	-	H-2′, H-6′, H-5′	-	-
5′	119.4	6.95d (7.5)		H-6′	H-2′′
6′	111.7	6.78d (7.4)	H-2′	H-5′	H-2, H-6, CH
1′′	149.9	-	H-3′′, H-2′′	-	-
2′′	112.9	6.63 d (8.5)	H-3′′	H-3′′	H-5′′, CH
3′′	128.2	7.12 t (7.4)	H-4′, H-2′′	H-2′′, H-4′′	H-2′, H-6′,
4′′	116.1	6.75 t (7.4)	H-5′	H-3′′,5′′	
5′′	128.2	7.12 t(7.4)	H-2′′	H-6′′, H-4′′	H-2′, H-6′,
6′′	112.9	6.63 d (8.5)	H-4′, H-5′, H-3′′	H-5′′	H-3′′,CH
H	54.0	6.06 brs	H-2′, H-6′, H-6	NH	H-2′, H-6′, H-6, H-2′′,6′′
OCH_3	55.6	3.82 s	-	-	-
OCH_3	55.6	3.82 s	-	-	-
NH	-	4.41brs		CH	

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