

NOVEL PIPERIDONE DERIVATIVES: SYNTHESIS, SPECTRAL AND EVALUATION OF ANTIOXIDANT ACTIVITY

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Abstract

The present study was designed to synthesize isomeric alcohols from corresponding piperidone **1** by sodium ethoxide reduction and the alcohols were separated by column chromatography. The synthesized compounds were characterized by IR, ¹H & ¹³C spectral studies. In addition to that *in vitro* potential antioxidant activity of the compounds were analyzed via DPPH assay and compared with standard antioxidant such as α -tocopherol and proposed suitable mechanism of antiradical action. It has been found that piperidone **1** demonstrated excellent radical scavenging activity, much better than its isomeric alcohols **2** and **3**.

Key words:

Piperidone, Isomeric Alcohols, NMR, DPPH.

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1. INTRODUCTION

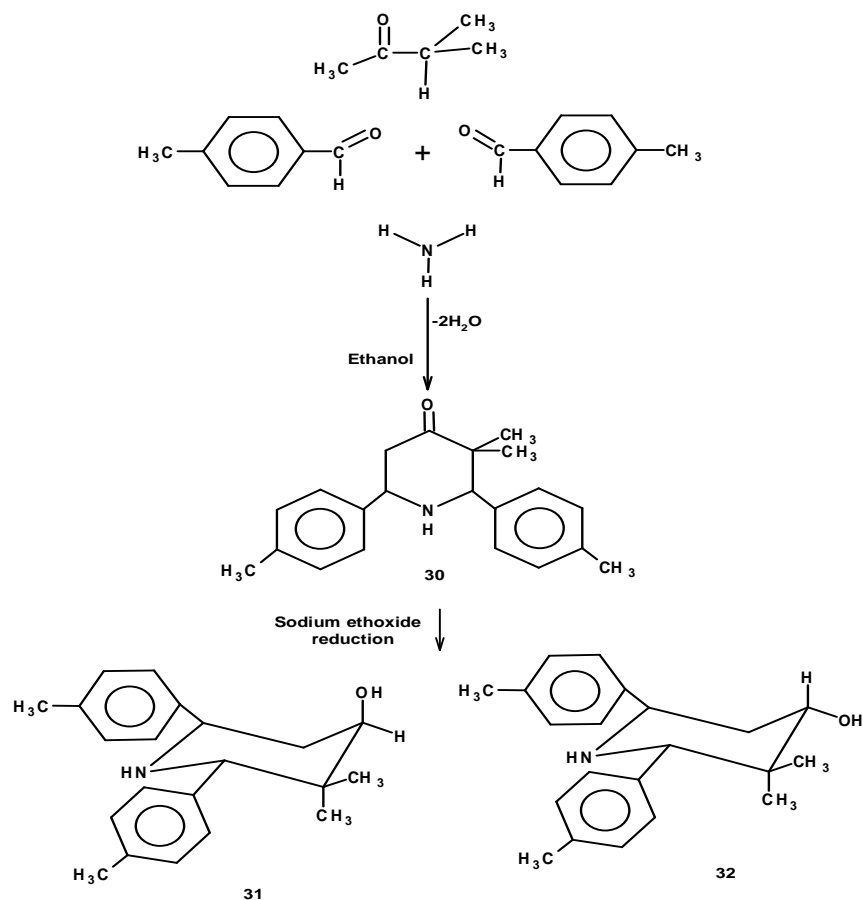
During a fairly recent 10-year period, several thousand piperidine compounds have been mentioned in clinical and preclinical studies [1]. Besides the interesting structural features, these compounds are also of pharmaceutical interest as they exhibit a wide range of biological activities [2]. Nevertheless, the variety of functionality and substitution patterns found in piperidine targets and the widely accepted concept that the biological properties of piperidines are highly dependent on the type and location of substituents on the heterocyclic ring [3]. Piperidine derivatives are found to possess pharmacological activity and form an essential part of the molecular structures of important drugs such as raloxifene and minoxidil [4]. Selective inhibition of

a number of enzymes involved in the binding and processing of glycoproteins has rendered piperidine alkaloids as important tools in the study of biochemical pathways [5]. Piperidones are somewhat less prominent, but often they serve a role as advanced intermediates prior to their conversion to piperidines [6]. Hydroxylated piperidine alkaloids are frequently found in living systems and display a wide range of biological activities due to their ability to imitate carbohydrates in a variety of enzymatic processes [7]. In many different disciplines antioxidants become more interested in new compounds, either synthesized or obtained from natural sources that could provide active components to prevent or reduce the impact of oxidative stress on cell [8]. Antioxidants are extensively studied for their capacity to protect organism and cell from damage that are induced by oxidative stress. Oxidative

damages play a significantly pathological role in human diseases. Cancer, emphysema, cirrhosis, atherosclerosis and arthritis have all been correlated with oxidative damage. Also, excessive generation of reactive oxygen species (ROS) induced by various stimuli and which exceeds the antioxidant capacity of the organism leads to variety of pathophysiological processes such as inflammation, diabetes, genotoxicity and cancer[9]. In the present study wide range applications of radical scavenging and antioxidant activities of newly synthesized compounds were investigated using DPPH method.

2. CHEMISTRY

Synthesis and isomerization of piperidine-4-ols have been described by Noller and Balasubramanian [10, 17].



3. BIOLOGY

The in vitro antioxidant activity of the synthesized compounds was evaluated by DPPH assay method. [11]

4. STATISTICAL ANALYSIS

Statistical significance of difference between the mean activities of the subgroups of compounds was determined by utilizing ANOVA for variables with normal distributions.

5. RESULT AND DISCUSSION

5.1 IR spectra

The prominent peaks around 3376, 3425 cm^{-1} in the IR spectra are attributed to ν_{OH} , mode in **2** and **3** respectively shows that C=O in piperidone **1** was reduced into secondary isomeric alcohols –CH-OH values are reproduced in Table 2.

5.1.1 ^1H NMR

The signals in the ^1H NMR spectra were assigned based on their positions, multiplicities and integrals. Due to syn-1,3-diaxial interaction with protons at C(2) and C(6) equatorial proton at C(4) in axial alcohol **2** resonated at 4.02 ppm whereas axial proton at C(4) in equatorial alcohol **3** resonated at 3.87 ppm. It confirms that H(4) in axial alcohol **2** gets deshielded than in equatorial alcohol **3**.

5.1.2 ^{13}C NMR

In ^{13}C NMR the above theme gets reversed chemical shift of C(4) in equatorial alcohol **3** shifted to downfield range than in axial alcohol **2**.

5.2 DPPH Radical scavenging activity

The model of scavenging the stable DPPH radical model is a widely used method to evaluate antioxidant activities in a relatively short time compared with other methods. The effect of antioxidants on DPPH radical scavenging was thought to be due to their hydrogen donating ability [12]. DPPH is a stable free radical and accepts an electron or hydrogen radical to become a stable diamagnetic molecule [13]. The reduction capability

of DPPH radicals was determined by decrease in its absorbance at 517 nm induced by antioxidants. The absorption maximum of a stable DPPH radical in ethanol was at 517 nm. The decrease in absorbance of DPPH radical caused by antioxidants, because of reaction between antioxidant molecules and radical, progresses, which result in the scavenging of the radical by hydrogen donation. It is visually noticeable as a discoloration from purple to yellow. Hence, DPPH is usually used as a substrate to evaluate antioxidative activity of antioxidants [14]. Data of antioxidant evaluation were expressed as mean \pm standard error of the mean ($n=3$) and independent student's t-test was used to determine the level of significance ($P < 0.05$). In this study antiradical activities of synthesized compounds **1-3** and standard antioxidant such as α -tocopherol were determined by using DPPH method.

Table 1: DPPH scavenging activity of compounds 1-3

COMPOUNDS	1	2	3
DPPH Scavenging activity(mg/ml)	44.25 \pm 0.94	30.82 \pm 2.16	32.62 \pm 1.71

The inhibitory effect of synthesized compounds **1-3** on DPPH radical was showed in figure 1. With the increase of concentration, the scavenging effect also increased. It was reported that reducing power serves as a significant indicator of antioxidant activity for a compound. The reducing properties are generally associated with the presence of reductones, which have been shown to exert antioxidant action by breaking the free radicals chain by donating a hydrogen atom [15]. Data reveal that the reducing power of piperidone **1** was stronger than its isomeric alcohols. Among the isomeric alcohols, equatorial alcohol **3** shows much better antiradical activity than axial alcohol **2**. As a result of 1,3-diaxial interaction axial alcohol **2** shows lower antiradical scavenging effect to DPPH radical. These results are evident from Table.1

6. EXPERIMENTAL

6.1. CHEMISTRY

IR spectra

Infrared spectra were recorded on a NICOLET AVATAR 360 FT-IR spectrometer. The sample was mixed with KBr and the pellet technique was adopted to record the spectra.

Table 2: IR stretching frequencies of compounds 1-3

Piperidone 1	Axial Alcohol 2	Equatorial Alcohol 3	Assignment
3441, 3318	-	-	ν_{N-H}
-	3376	3425	ν_{OH}
2974, 2923, 2804	2964, 2923	2924, 2860	ν_{C-H}
1699	-	-	$\nu_{C=O}$
-	1601	1635	ν_{C-OH} and ν_{N-H} in plane bending vibration
1413, 1459, 1512	1512, 1439	1430	$\nu_{C=C}$ stretching vibration of aromatic ring
1372	1379	1380	Symmetric bending vibration of methyl group
1025	1085, 1043	1000	ν_{C-N}
939, 816, 754, 727	928, 816, 746	874	Aromatic C-H out of plane bending vibrations
679, 513, 483	624, 562, 509	673, 539	Aromatic C-C out of plane bending vibrations

1H NMR spectra

Proton spectra were recorded on a AMX 400 NMR instrument operating at 400 MHz. Samples were prepared by dissolving 10 mg of the substance in 0.5 mL of $CDCl_3$ containing 1% TMS. The spectral parameters used are, number of transients, 32; number of data points, 32 K; spectral sweep width 4000 Hz.

^{13}C NMR spectra

Proton decoupled ^{13}C NMR spectra were recorded on a AMX 400 NMR instrument operating at 100 MHz. Solutions for the measurement of spectra were prepared by dissolving 0.5 g of the sample in 2.5 mL of $CDCl_3$ containing a few drops TMS as internal reference. The solvent chloroform-d also provided the internal field frequency lock signal. The spectral parameters used are, number of transients 5000;

number of data points 32K; pulse width 6 s (45°), spectral sweep width, 2200 Hz.

6.1.1 GENERAL PROCEDURE FOR SYNTHESIS OF COMPOUND 1

Dry ammonium acetate (0.5 mole) was dissolved in 50 ml of distilled ethanol was mixed with 4-methylbenzaldehyde (1 mole) and ethylisopropylketone (0.5mol) in distilled ethanol [10] was heated and cooled. After cooling the viscous liquid was dissolved in ether(50ml) and shaken with concentrated HCl (5ml)resulting the 3,3-dimethyl-*r*(2),*C*(6)-ditolylpiperdin-4-one was precipitated as its hydrochloride then the precipitate was filtered and washed with 50ml of Ether: Ethanol mixture(4:1) to remove colored impurities. By adding aqueous ammonia and acetone the base was liberated from ethanolic solution. It was recrystillized from ethanol.

1H NMR: 7.34[m,H(ortho)], 7.18[m,H(meta)], 3.80(s,H(6)), 3.79(s,H(2)),2.93(t,H5a), 2.46(d,H5e), 2.36(s,p-CH₃), 1.93(s,NH), 1.21(s,EqCH₃), 0.96(s,Ax CH₃).

^{13}C NMR:213.16(C(4)), 140.23(ipso), 137.32(Ph), 69.28(C(2)), 61.33(C(6)), 49.91(C(3)), 47.25(C(5)), 21.07(p-CH₃), 20.41(EqCH₃), 19.98(Ax CH₃).

6.1.2 GENERAL PROCEDURE FOR SYNTHESIS OF COMPOUNDS 2 AND 3.

The 4-hydroxy piperdines **2** and **3** were prepared from the corresponding piperdin-4-one **1** by adopting the general procedure [16, 17]. About (0.5mol) of Piperdin-4-one **1** in distilled ethanol was refluxed with (1mol) of liquid Na at 60°C for 7hrs.Reaction mixture was subjected to Co-TLC to check the formation of isomeric alcohols. After the formation reaction mixture was poured into acidified ice water. The crude was separated by ether separation and these isomeric alcohols were separated by column chromatography using neutral alumina as adsorbent and benzene: ethyl acetate (90:10) as eluent.

2. ¹HNMR: 7.38[m,H(ortho)], 7.18[m,H(meta)], 4.02(dd,H(4)), 3.80(s,H(6)), 3.78(s,H(2)), 2.92(t,H5a), 2.45(dd,H5e), 2.35(d,p-CH₃), 1.58(s,NH), 1.20(s,EqCH₃), 0.95(s,Ax CH₃).

¹³CNMR: 140.25(*ipso*), 137.29(Ph), 69.29C(4), 61.32C(2), 59.92C(6), 49.90C(3), 47.25C(5), 21.01(p-CH₃), 20.38(EqCH₃), 19.96(Ax CH₃).

3. ¹HNMR: 7.36[m,H(ortho)], 7.15[m,H(meta)], 3.87(dd,H(4)), 3.62(s,H(6)), 3.54(t,H(2)), H(5a), 2.34(d,H5e), 1.80(t,p-CH₃), 1.42(s,NH), 0.94(s,EqCH₃), 0.88(s,Ax CH₃).

¹³CNMR: 141.65(*ipso*), 136.75(Ph), 76.72C(4), 69.24C(2), 60.10C(6), 39.65C(3), 39.48C(5), 23.97(p-CH₃), 21.02(EqCH₃), 19.98(Ax CH₃).

6.2 FREE RADICAL SCAVENGING ACTIVITY

Free radical scavenging activity of compounds was measured by DPPH, using the method of Blois [11]. Briefly, 0.1 mM solution of DPPH in ethanol was

prepared, and this solution (1 mL) was added to sample solutions in CHCl₃ (3 mL) at different concentrations (1-10 mg/mL). The mixture was shaken vigorously and allowed to stand at room temperature for 30 min. Then the absorbance was measured at 517 nm in a spectrophotometer. Lower absorbance of the reaction mixture indicated higher free radical scavenging activity. The DPPH Concentration (mM) in the reaction medium was calculated from the following calibration curve and determined by linear regression

$$(R: 0.997): \text{Absorbance} = 0.0003 \times \text{DPPH} - 0.0174.$$

The capability to scavenge the DPPH radical was calculated using the following equation:

$$\text{DPPH} \cdot \text{Scavenging effect (\%)} = (A_0 - A_1/A_0) \times 100$$

Where, A₀ is the absorbance of the control reaction and A₁ is the absorbance in the presence of the samples or standards.

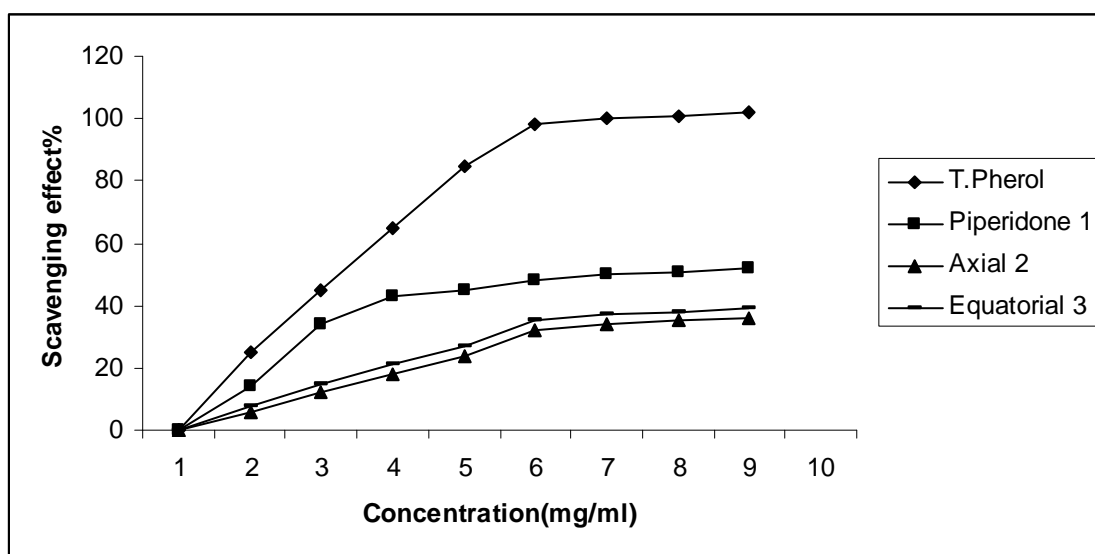


Figure 1: Scavenging effects of α-tocopherol and compounds 1-3

CONCLUSION

In vitro antioxidant evaluation by DPPH assay concludes that piperidone exhibit strong antioxidant activity by electron donating mechanism (i.e.) it donate unshared pair of electrons on carbonyl oxygen atom. Reduction of C=O into -OH resulted in a decreased scavenging activity of isomeric alcohols

compared to piperidone. Order of Antioxidant Activity: 1>3>2.

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