Indian Journal of Chemistry
Vol. 45B, August 2006, pp. 1887-1893

Synthesis of *N*-hydroxy-*r*-2,*c*-6-diphenylpiperidines using DMD and their stereochemical studies by NMR spectra and semiempirical MO calculations

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Received 12 August 2005; accepted (revised) 19 December 2005

r-2,*c*-6-Diphenylpiperidin-4-ones **2-6** and *r*-2,*c*-6-diphenylpiperidine **7** are treated with DMD and the reaction is found to yield only the corresponding *N*-hydroxy derivatives **8-13**. The preferred conformations of the *N*-hydroxy compounds **8-13** are analysed using the NMR spectra and semiempirical molecular orbital calculations. The *N*-hydroxy derivatives **8-13** are found to prefer distorted chair conformations.

Keywords: Dimethyldioxirane, diphenylpiperidine, conformation, MO calculation
IPC Code: Int. Cl.[8] C07D

Dimethyldioxirane (DMD, **1**) is an efficient and powerful electrophilic oxidant[1] and it is known to oxidise primary amines to nitro compounds[2], secondary amines to hydroxylamines (when the dioxirane is in equimolar quantity)[3], nitrones[4a] (when the dioxirane is in excess and the secondary amine has α-proton), nitroxyl radicals[4b] (when the secondary amine is without α-proton) and the tertiary amines to the corresponding *N*-oxides[4].

It is known that the *N*-hydroxy compounds are highly valuable synthetic intermediates widely used in organic synthesis[5]. They are used in the synthesis of nitrones, which are used commercially as spin traps[6], and nitroxides[7]. The hydroxylamines are used as polymerisation inhibitors[8] and they prevent the premature oxidation of leuco dyes in photoimaging compounds. *N*-Hydroxylamines are shown to be useful precursors to nitrenium ions[9]. Heterocyclic hydroxylamines are of much importance because of their pharmacological and physiological activity. Many potential central nervous system depressants exhibit more activity in their *N*-hydroxylamines form than in their amino or *N*-aryloxy derivatives[10]. Sterically hindered hydroxylamines are antioxidants[11] and used as suppressors for plant tumor growth[12].

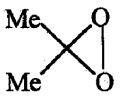
In this work, the oxidations of *r*-2,*c*-6-diphenylpiperidines **2-7** using excess dimethyldioxirane (*in situ*) were carried out with a view to studying the reaction of DMD with sterically hindered and stereochemically anchored *r*-2,*c*-6-diphenylpiperidines.

Results and Discussion

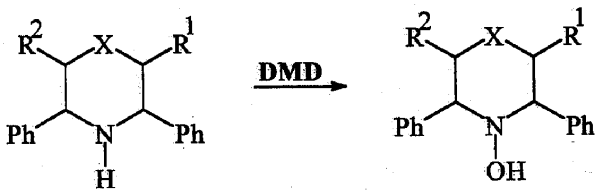
Reaction of the secondary amines **2-7** with excess of dimethyldioxirane resulted in the corresponding *N*-hydroxy products **8-13** in good yields (80-95%) (**Scheme I**). Even though dimethyldioxirane was used in large excess and the parent piperidines **2-7** possessed hydrogens at both the α positions, no α-hydroxylated product was formed. But the *N*-hydroxy derivatives **8-13**, which are the intermediates in the formation of nitrones, were obtained as the exclusive products.

The isolated and purified *N*-hydroxy derivatives **8-13** were treated again with excess dimethyldioxirane and the reaction did not yield the corresponding nitrones or the α-hydroxylated products.

The formation of nitrones might have been prevented in this reaction by the presence of bulky phenyl groups at both the α-positions of the nitrogen which might sterically hinder the approach of dimethyldioxirane for the introduction of the second oxygen atom thereby the reaction might have stopped at the stage of *N*-hydroxylamine formation. It is also interesting to note that quaternization with MeI also failed in the case of *r*-2,*c*-6-diphenylpiperidin-4-ones[13]. Considering the yield of the *N*-hydroxypiperidines and the ease of separation and purification, this reaction is useful to be a convenient route for the formation of *N*-hydroxy compounds from hindered secondary amines.



DMD
1



	X = CO	
2	$R^1 = R^2 = H$	8
3	R^1 = Me; R^2 = H	9
4	R^1 = Et; R^2 = H	10
5	R^1 = i-Pr; R^2 = H	11
6	$R^1 = R^2$ = Me	12
	X = CH_2	
7	$R^1 = R^2 = H$	13

Scheme I

The formation of *N*-hydroxy products **8-13** was confirmed by the absence of N-H stretching bands around 3300 cm^{-1} in the IR spectra and the appearance of singlets around 4.5-5.0 ppm, in the ^1H NMR spectra, exchangable with D_2O. The stereochemistry of the *N*-hydroxypiperidines was determined by the detailed analysis of their ^1H and ^{13}C NMR spectra (**Table I**) and semiempirical MO calculations.

The *N*-hydroxypiperidines **8-13** reported herein were found to have slightly distorted chair conformations. When the parent piperidines were converted to *N*-nitroso and *N*-acyl derivatives (**Figure 1**), drastic conformational changes were observed and they found to prefer twist-boat/twist-chair/flattened boat conformations[14]. The stereochemical influence exhibited by the *N*-hydroxy group on piperidines may be much less compared to their *N*-nitroso or *N*-acyl analogs since the destabilizing interactions like $A^{1,3}$-strain[15] and 1,3-diaxial phenyl-phenyl interaction etc, are dominant factors that determine the conformation of the *N*-nitroso and *N*-acyl derivatives while $A^{1,3}$ strain is absent in the *N*-hydroxypiperidines.

In the ^1H NMR spectrum of *N*-hydroxy-*r*-2,*c*-6-diphenylpiperidin-4-one **(8)** the benzylic proton signal was observed at δ 4.04 ppm as a doublet (**Table I**). When one of the C-3 protons was replaced by a methyl, ethyl, and isopropyl groups (**9-11**) the benzylic proton at C-2 appeared at δ 3.61, 3.74 and 3.95 ppm, respectively. Thus, the substitution at C-3 position by the alkyl groups shielded the axial C-2 proton by 0.43, 0.31 and 0.09 ppm, respectively. The magnitude of shielding was found to decrease as the bulkiness of the substituent increased which in turn increases the flattening of the ring as indicated from the decrease of coupling constants (J_{2H3a}) (**Table II**). The flattening along C2-C3 bond had arisen in these compounds in order to minimize the *gauche* interaction between the phenyl group at C-2 and the alkyl group at C-3. DAERM[16] (Dihedral Angle Estimation by Ratio Method) calculations were performed for these *N*-hydroxypiperidines (**8-11** and **13**) and the dihedral angles calculated (**Table II**) were found to explain the preference for distorted chair conformations (**Figure 2**).

In six-membered heterocycles a decrease in the electronegativity of a group in the ring skeleton shields the α-carbon and deshields the β and γ carbons[17]. The hydroxy group at ring nitrogen deshielded the α-carbons (C2 and C6) by 9.0-9.5 ppm and shielded the β and γ carbons by 1.5-3.0 ppm. Methyl substitution at C-3 caused a downfield shift of 0.4 ppm for the methyl bearing carbon instead of the anticipated 6.0 ppm. This decrease in deshielding may be accounted for by the presence of carbonyl group at C4 and N-OH group.

Semiempirical MO calculations

In order to compare the results obtained from solution state with those obtained from gaseous state semiempirical molecular orbital calculations[18] have been carried out for N-hydroxy derivatives. The heats of formation of various conformations of the *N*-hydroxy *r*-2,*c*-6-diphenylpiperidines **8-13** were calculated using AM1 method available in MOPAC 6 program. For each of the *N*-hydroxy derivatives all possible ring conformations (**Figure 3**), such as, a chair conformation (**CE**), a flipped chair form (**CA**), four boat forms (**B1-B4**) with C2 and C5 occupying prow and stern positions and two boat forms (**B5** and **B6**) with N1 and C4 occupying stern and prow positions, were considered as input structures. The optimization of these conformations was carried out by varying the torsion angle H-O-N-C2 within the possible range in

Table I—Spectral data of compounds prepared **8-13**

Compd	^{1}H NMR($CDCl_3$, δ, ppm)	^{13}C NMR($CDCl_3$, δ, ppm)	Mass (M^+)
8	2.62 (d, 2H), 2.88 (t, 2H) H3 & H5-eq and H3 & H5-ax 4.04 (d, 2H, *J* = 11.9 Hz, H2 & H6), 4.45 (s, 1H, NOH), 7.21-7.56 (m, 10H, aromatic)	48.8 (C3 & C5), 70.4 (C2 & C6) 126.9-128.8 (aromatic), 141.6 (ipso), 205.0 (C4)	267
9	0.82 (d, 3H, Me at C3), 2.63 (dd, 1H, H5-eq), 2.88 (m, 2H, H3 & H5-ax), 3.61 (d, 1H, *J* = 11.4 Hz, H2), 4.01 (dd, 1H, dd, *J* = 12.9 & 3.3 Hz, H6), 4.4 (s, 1H, NOH), 7.21-7.51 (m, 10H, aromatic)	10.8 (Me at C3), 48.5 (C5), 49.6 (C3), 70.8 (C6), 76.7 (C2), 126.9-128.8 (aromatic), 140.8, 141.7 (ipso), 206.7 (C4)	281
10	0.76 (t, 3H, Me of ethyl), 1.46 (m, 2H, CH_2 of ethyl), 2.64 (dd, 1H, H5-eq), 2.76 (t, 1H H3-ax), 2.91 (t, 1H, H5-ax), 3.74 (d, 1H, *J* = 11.6 Hz, H2), 4.01 (dd, 1H, *J* = 12.9 & 3.3 Hz H6), 4.33 (s, 1H, NOH), 7.21-7.51 (m, 10H, aromatic)	11.7 (Me at C3), 18.4 (CH_2 at C3), 49.0 (C5), 55.8 (C3), 70.8 (C6), 75.6 (C2), 126.8-128.7 (aromatic), 140.8, 141.8 (ipso), 206.3 (C4)	295
11	0.91 (d, 3H, Me of i-Pr), 1.01 (d, 3H, Me of i-pr), 1.52 (m, 1H, CH of i-Pr), 2.56 (dd, 1H, H5-eq), 2.82 (m, merged, 2H, H3 & H5-ax) 3.95 (d, 1H, *J* = 11.4 Hz, H2), 4.01 (t, 1H, *J* = 10.1 & 2.4 Hz, H6), 4.31 (s, 1H, NOH), 7.21-7.54 (m, 10H, aromatic)	16.8, 20.9 (Me's of i-Pr), 26.3 (CH of i-Pr), 49.4 (C5), 58.7 (C3), 70.4 (C6), 74.2 (C2), 126.9-128.7 (aromatic), 141.0, 141.8 (ipso), 206.1 (C4)	309
12	0.81 (d, 6H, Me at C3 & C5), 2.91 (m, 2H, H3 & H5-ax), 3.59 (d, 2H, *J* = 11.5 Hz, H2 & H6), 4.73 (s, 1H, NOH), 7.21-7.52 (m, 10H, aromatic)	10.9 (Me at C3 & C5), 49.0 (C3 & C5), 76.7 (C2 & C6), 127.7-128.5 (aromatic), 140.9 (ipso), 208.5 (C4)	295
13	1.55 (m, 2H, C4-ax & eq), 1.67 (m, 2H, C3 & C5-eq), 1.82 (m, 2H, C3 & C5-ax), 3.69 (dd, 2H, *J* = 11.8 & 2.0 Hz C2 & C6), 4.79 (s, 1H, NOH) 7.22-7.35 (m, 10H, aromatic)	24.4 (C4), 36.0 (C3 & C5), 72.5 (C2 & C6), 126.9-128.4 (aromatic), 144.2 (ipso)	253

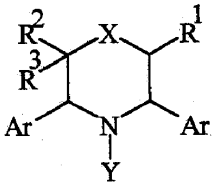
30° increments and the results are summarized in **Table III**.

The relative enthalpies of formation of various conformations of the N-hydroxy-*r*-2,*c*-6-diphenylpiperidines **8-13** indicate that the *N*-hydroxy derivatives **8-10, 12** and **13** prefer distorted chair conformations **CE** while the *N*-hydroxy derivative **11** prefers boat conformation **B3**. AM1 optimized structures for various conformations of **9** are given in **Figure 4** as a representative example.

Thus, it was concluded that the *N*-hydroxy-*r*-2,*c*-6-diphenylipiperidines **8-13** prefer distorted chair conformations (**Figure 2**) in solution and in gaseous states.

Experimental Section

General. All the melting points were determined using an electrically heated block with a calibrated thermometer and are uncorrected. Infrared spectra were recorded on Shimadzu IR-435 spectrophotometer as

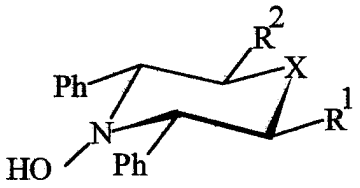


X = CO, CH_2
Y = NO, CHO, COMe, COOEt, COPh, CONHPh etc
Ar = Aryl
R^1, R^2, R^3 = H, alkyl

Figure 1

Table II—Vicinal coupling constants (in Hz) and dihedral angles of the *N*-hydroxy-*r*-2,*c*-6-diphenylpiperidines **8-13** compared with *r*-2,*c*-6-diphenylpiperidines **2-7**

Compd	$^3J_{2H3a}$	$^3J_{2H3e}$	$^3J_{6H5a}$	$^3J_{6H5e}$	ϕ_{cis} (H6-C6-C5-H5e)	ϕ_{trans} (H6-C6-C5-H5ax)
8	11.9	0.0	11.9	0.0	81	159
2	9.9	4.5	9.9	4.5		
9	11.4	—	12.9	3.3	57	177
3	10.3	—	11.4	3.2		
10	11.6	—	12.9	3.3	57	177
4	10.4	—	11.8	2.8		
11	11.4	—	10.1	2.4	58	178
5	10.5	—	11.3	3.4		
12	11.5	—	11.5	—		
6	10.3	—	10.3	—		
13	11.8	2.0	11.8	2.0	63	183
7	9.6	2.2	9.6	2.2		



R^1, R^2 = H, Me, Et, i-Pr
X = CO, CH_2

Figure 2

KBr pellets. The ^1H and ^{13}C NMR spectra were recorded on a Jeol GSX-400 MHz and Bruker AMX-400 MHz in $CDCl_3$ solution using TMS as internal reference. Mass spectra were recorded on a Jeol JMS-D 300 spectrometer operating at 70 eV.

Computational details

The AM1 methods available in MOPAC 6.1 version were used to perform the calculations on Pentium personal computers. The optimization of the conformations was performed by using an analytic gradient minimization method (BFGS, Precise option). Furthermore, Eigenvector Following (EF option) procedure was used to lower the mean gradient up to values below 0.01.

***N*-Hydroxy derivatives 8-13: General procedure**. *r*-2,*c*-6-Diphenylpiperidin-4-one (5.0 mmole) in dichloromethane (40 mL) and acetone (80 mL) was kept at 0°C in an ice bath and freshly prepared solution of oxone (6.14 g, 100 mmole) in water (25 mL) was added in drops for the period of 1 h with constant stirring. The *p*H was maintained between 7.0 and 8.0 by adding drops of potassium hydroxide solution. The reaction mixture was allowed to stir vigorously for about 40 min. After the separation of dichloromethane layer, the aqueous layer was extracted with two 50 mL portions of methylene chloride, the combined methylene chloride extract was washed with water, dried over anhydrous Na_2SO_4, filtered and evaporated. The solid left

behind

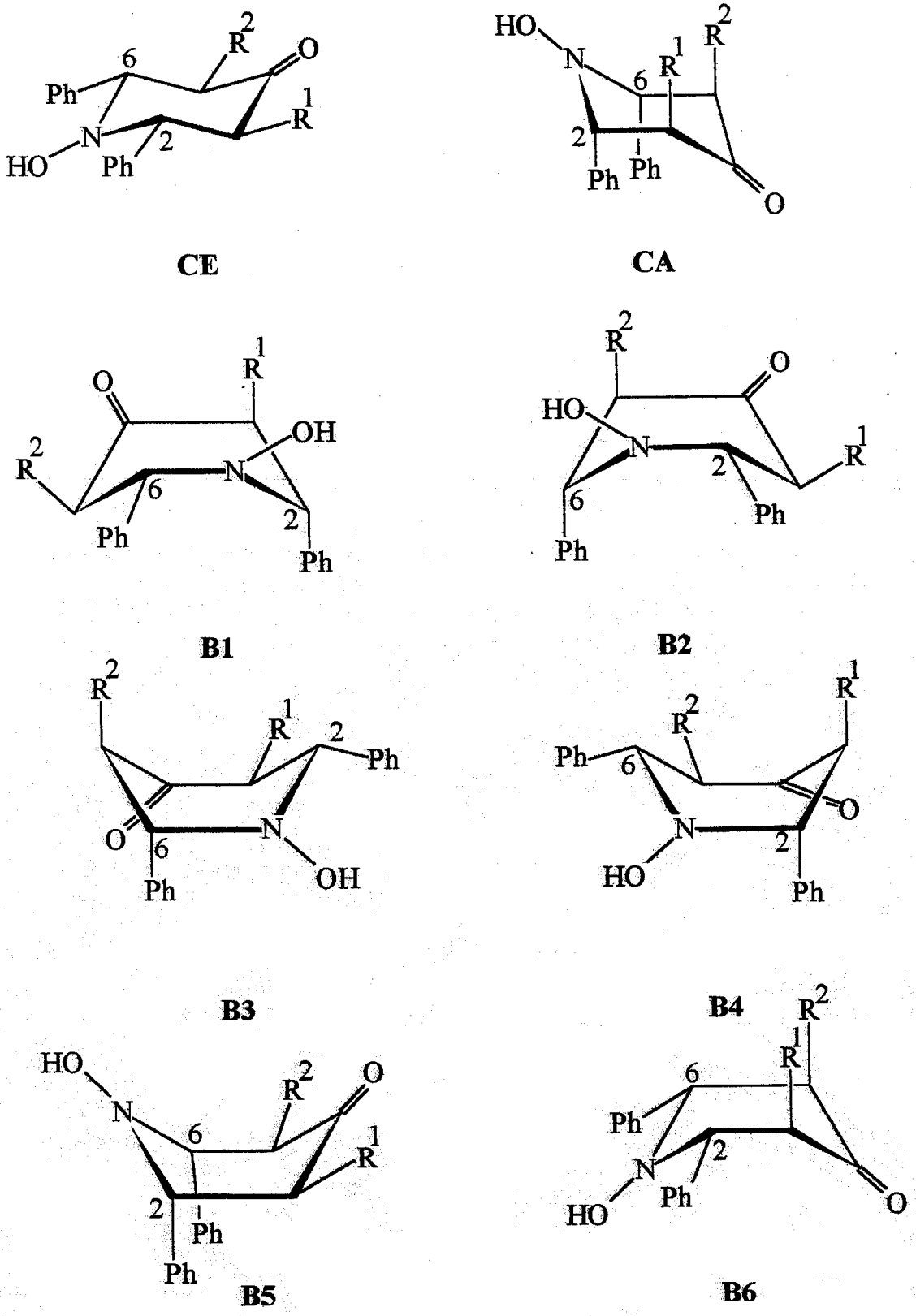


Figure 3—Possible conformations for N-hydroxy-r-2,c06-diphenylpiperidines 8-13

Table III—Calculated relative enthalpies of formation (kcal mol^{-1}) of various conformations of *N*-hydroxy-*r*-2,*c*-6-diphenylpiperidines **8-13** by AM1 method

Compd	Conformations					
	CE	CA	B1	B2	B3	B4
8	0.00	2.27	4.79	5.73	0.84	1.00
9	0.00	1.41	0.20	1.15	0.88	0.20
10	0.00	1.18	3.39	4.75	1.85	0.30
11	3.80	0.70	0.16	4.91	0.00	0.13
12	0.00	1.72	0.30	—	0.56	0.66
13	0.00	4.06	3.24	7.03	2.53	3.82

Table IV—Physical data of compounds prepared **8-13**

Compd	m.p. (°C)	Yield (%)	Mol. Formula	Calcd(Found) %		
				C	H	N
8	87-89	89	$C_{17}H_{17}NO_2$	76.38 (76.23	6.36 6.30	5.24 5.31)
9	198-200	85	$C_{18}H_{19}NO_2$	76.84 (76.64	6.76 6.71	4.58 4.66)
10	135-137	85	$C_{19}H_{21}NO_2$	77.28 (77.38	7.12 7.05	4.75 4.65)
11	175-177	91	$C_{20}H_{23}NO_2$	77.67 (77.48	7.44 7.40	4.53 4.60)
12	204-206	93	$C_{19}H_{21}NO_2$	77.28 (77.40	7.12 7.24	4.75 4.67)
13	79-81	78	$C_{17}H_{19}NO$	80.63 (80.82	7.59 7.64	5.53 5.45)

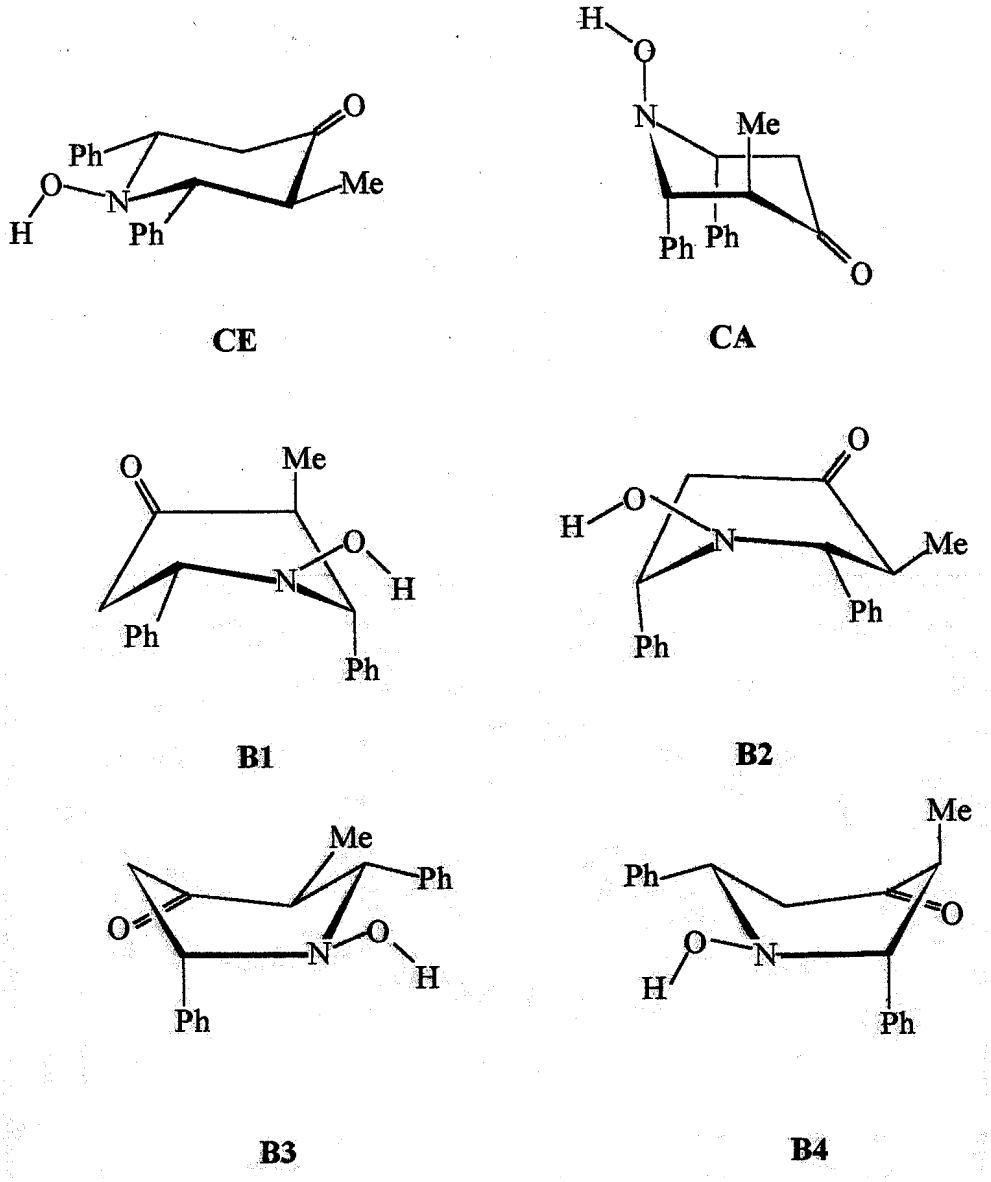


Figure 4—Am1 optimized structures of 9

was recrystallised from 1:2 mixture of benzene and petroleum ether (60-80 °C) to get colorless crystals of *N*-hydroxy derivative. The yields and melting points are given in **Table IV**.

Acknowledgement

The authors thank DST and CSIR for financial support and fellowship and RSIC, IIT, Chennai and SIF, IISC, Bangalore for the service in recording ^{1}H and ^{13}C NMR spectra and RSIC, CDRI, Lucknow for mass spectra.

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