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Synthesis and ^{1}H and ^{13}C NMR spectral study of some *t*(3)-aryl-r(2),*c*(4)-dicarbalkoxy-*c*(5)-hydroxy-*t*(5)-methylcyclohexanones and their oximes

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Eight *t*(3)-aryl-r(2),*c*(4)-bis(carbalkoxy)-*c*(5)-hydroxy-*t*(5)-methylcyclohexanone oximes **4a** (Ar = Ph; R = Et), **5a** (Ar = *p*-$NO_2C_6H_4$; R = Et), **6a** (Ar = *p*-ClC_6H_4; R = Et), **7a** (Ar = Ph; R = Me), **8a** (Ar = *p*-$NMe_2C_6H_4$; R = Me), **9a** (Ar = *m*-$NO_2C_6H_4$; R = Me), **10a** (Ar = *p*-FC_6H_4; R = Me) and **11a** (Ar = *p*-$OMeC_6H_4$; R = Me) have been synthesized by treating the corresponding ketones with NH_2OH in the presence of sodium acetate. Ketones **8-11** have been newly synthesized by condensing methyl acetoacetate with the appropriate aromatic aldehyde in presence of methylamine. ^{1}H and ^{13}C NMR spectra of ketones **7**, **8**, **10** and **11** and oximes **4a**, **5a** and **6a** have been recorded in $CDCl_3$. ^{1}H and ^{13}C NMR spectra of ketone **9** and the other oximes **7a-11a** have been recorded in DMSO-d_6 since they are insoluble in $CDCl_3$. HOMOCOR spectrum has been recorded for **7** (in $CDCl_3$) and **7a**. NOESY spectrum has been recorded for **4a**, **7** (in $CDCl_3$ and DMSO-d_6), **7a** and **8a**. HSQC spectrum has been recorded for **7** (in $CDCl_3$) and **7a**. HMBC spectrum has been recorded for **5a** and **7a**. DEPT spectrum has been recorded for **4a**. The observed vicinal coupling constants suggest that all the compounds studied exist largely in chair conformation with axial orientations of the hydroxyl group at C-5 and equatorial orientations of all the other substituents. All the oximes have *E* configuration about C=N bond. The OH-proton at C-5 prefers to be *anti* to C(5)-C(6) bond in $CDCl_3$ but *anti* to C(4)-C(5) bond in DMSO-d_6. Change of solvent from $CDCl_3$ to DMSO-d_6 has a marked effect on the chemical shifts of the protons in the cyclohexane ring and OH proton. Among the two methylene protons at C-6 the equatorial proton has a higher chemical shift than the axial proton in $CDCl_3$ but a reverse trend is observed in DMSO-d_6. However,^{13}C chemical shifts are not influenced by the change of solvent. Oximation shields all the ring carbons of the cyclohexane ring except C-4. Oximation shields all the protons in the cyclohexane ring except H-6e, which is deshielded by about 0.9 to 1.0 ppm. Use of ^{1}H and ^{13}C chemical shifts for determining the configuration and conformation of oximes is also discussed.

Keywords: ^{1}H NMR, ^{13}C NMR, cyclohexanones, oximes, synthesis, configuration, conformation

Oximes and related compounds have been used as drugs and pesticides[1,2]. Cyclohexanone oxime and structurally related oximes have been shown to be animal carcinogens[3,4].

NMR spectral studies of oximes have been of constant interest[5-13]. Configuration of conformation of oximes have been assigned using NMR spectra. ^{1}H NMR spectral studies[9,10] of r(2),*c*(6)-diphenyl-1-heteracyclohexan-4-one oximes **1** have shown that these compounds adopt chair conformation **1C** with equatorial orientations of phenyl and alkyl groups. Oximes with alkyl groups at C-3 have *E*-configuration about the C=N bond.

It has been found that among the methylene protons, which are *syn* to NOH, the equatorial proton appears at a considerable higher frequency than the axial proton. Also, it has been found that the difference in the chemical shifts of the methylene protons *anti* to NOH is quite small.

Diaz *et al.*[12] have studied the conformations of 2,6-diaryl-1-hydroxypiperidin-4-one oximes **2** using ^{1}H and ^{13}C NMR spectra. Oximes can be easily synthesized by treating the corresponding ketone with hydroxylamine. Recently[14], it has been found that oximation of 2,6-diphenylcyclohexanone undergoes dehydrogenation also during oximation and gives (*E*)-2,6-diphenylcyclohex-2-enone oxime **3**. The structure of **3** has been elucidated by X-ray crystallographic study[14].

Hence, it is of interest to investigate the reaction of hydroxylamine with *t*(3)-aryl-r(2),*c*(4)-dicarbalkoxy-*c*(5)-hydroxy-*t*(5)-methylcyclohexanones **4-11**. ^{1}H and ^{13}C NMR spectra show that the products formed in the reaction of hydroxylamine with ketones **4-11** are the corresponding *E*-oximes **4a-11a**. The ketones **4-11** do not undergo dehydrogenation or dehydration during oximation.

^{1}H and ^{13}C NMR spectra of ketones **4-6** have been studied already[15]. ^{1}H and ^{13}C NMR spectra of ketones **7-**

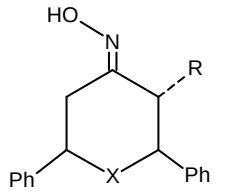
11 are included in the present study. In the earlier studies on oximes the signals were not assigned unambiguously by using two dimensional NMR techniques. In the present study the signals have been assigned unambiguously using two dimensional NMR techniques. The effects on the various chemical shifts and coupling constants due to oximation have been determined more precisely. Use of ^{1}H and ^{13}C chemical shifts in assigning the configuration of oximes is also discussed.

Results and Discussion

Synthesis and characterization of compounds

The oximes were synthesized following **Scheme I**. Kingsbury *et al.*[16] have prepared **7** by condensing methyl acetoacetate with benzaldehyde in the presence of piperidine. They have reported that two more stereoisomers are formed as minor products. In the present study methylamine was used as the catalyst. Under these conditions only **7** was formed.

All compounds were purified by recrystallisation from ethanol. Their homogeneity was checked on TLC. In the IR spectra of the oximes the band due to ketonic carbonyl stretching vibration was absent. Furthermore, the ^{1}H and ^{13}C NMR spectra of ketones **7-11** and oximes **4a-11a** confirmed their purity.



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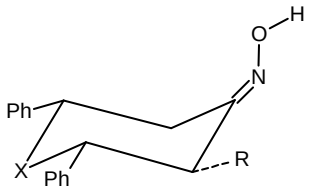
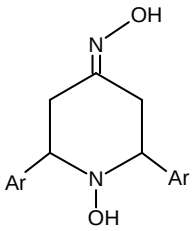


1C



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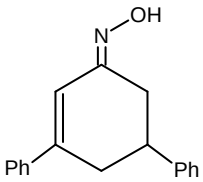

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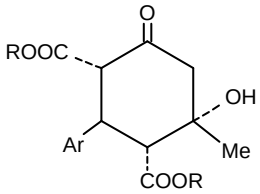
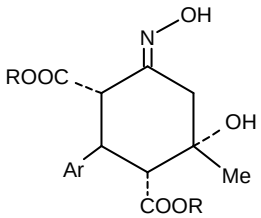


4-11



4a-11a

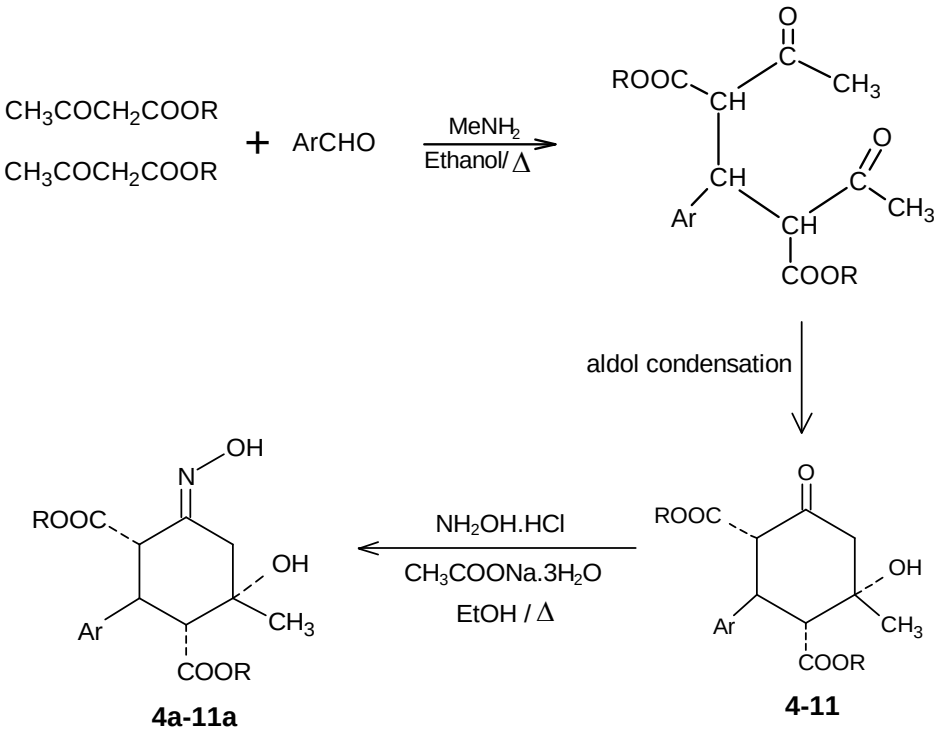
Compd	Ar	R
4 & **4a**	C_6H_5	COOEt
5 & **5a**	*p*-NO_2-C_6H_4	COOEt
6 & **6a**	*p*-Cl-C_6H_4	COOEt
7 & **7a**	C_6H_5	COOMe
8 & **8a**	*p*-$N(CH_3)_2$-C_6H_4	COOMe
9 & **9a**	*m*-NO_2-C_6H_4	COOMe
10 & **10a**	*p*-F-C_6H_4	COOMe
11 & **11a**	*p*-OMe-C_6H_4	COOMe

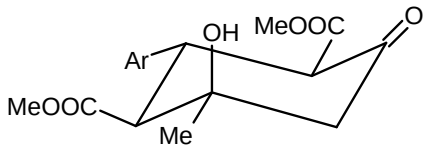
^{1}H NMR spectra

Kingsbury *et al.*[16] confirmed the structure of **7** using ^{1}H NMR spectrum at 100 MHz and one dimensional NOE measurements. Chair conformation **7C** was proposed for **7** based on the observed ^{1}H NMR spectral data. In the present study ^{1}H NMR spectrum of **7** was recorded at 400 MHz in $CDCl_3$. The signals were assigned by comparing with the previous reported spectral parameters of **7** (Ref. 16). These assignments were confirmed by HOMOCOR and NOESY spectra of **7**.

^{1}H NMR spectra of **8**, **10** and **11** were recorded in $CDCl_3$. These spectra were similar to that of **7** except for the aromatic protons. The extracted ^{1}H chemical shifts of **7**, **8**, **10** and **11** are listed in **Table I**. The extracted *J* values are given in **Table II**. The observed *J* values are in accordance with chair conformation **7C**, **8C**, **10C** and **11C** for these compounds. Since long-range coupling was observed between OH proton and H-6a in all these cases the OH proton should be *anti* to C(5)-C(6) bond as shown in **Figure 1**.

^{1}H NMR spectrum of **9** was recorded in DMSO-d_6. The signals were assigned based on their positions and multiplicities. The extracted coupling constants are given in **Table II**. The observed *vicinal* coupling constants of **9** are consistent with chair conformation **9C** for it. However, both the methylene protons at C-6 appeared only as doublets at δ 3.01 and 2.40. The OH proton appeared as a singlet at δ 5.15. These observations suggest that the long-range coupling between OH proton and H-6a is absent in **9**. This may be a solvent effect. Furthermore, due to the absence of long-range coupling between OH proton and H-6a it is not possible to assign the signals for the methylene protons unambiguously. In order to throw light into this problem ^{1}H NMR spectrum of **7** was recorded also in DMSO-d_6. NOESY spectrum of **7** also was recorded in DMSO-d_6.





Compd	Ar	R
7C	C_6H_5	COOMe
8C	*p*-$N(CH_3)_2$-C_6H_4	COOMe
9C	*m*-NO_2-C_6H_4	COOMe
10C	*p*-F-C_6H_4	COOMe
11C	*p*-OMe-C_6H_4	COOMe

Scheme I

In the ^{1}H NMR spectrum of **7** in DMSO-d_6, H-2 appeared as a doublet at δ 4.01 with a *J* value of 12.4 Hz. However, the signal for H-4 proton was merged with the signal for methyl protons of one of the carbomethoxy groups. Therefore, the vicinal coupling constant between H-2 and H-3 was determined from the signal for H-3 as 12.1 Hz. The observed vicinal coupling constants of **7** in DMSO-d_6 are consistent with chair conformation **7C**. The methyl protons at C-5 appeared as a singlet at δ 1.24.

However, the methylene protons at C-6 appeared only as doublets at δ 2.97 and 2.36. Also, the OH proton appeared as a singlet at δ 4.97. Hence, it is obvious that the long-range coupling due to -OH proton is not observed in DMSO-d_6. This suggests that the conformation of –OH group in DMSO-d_6 differs from that in $CDCl_3$. Probably in DMSO-d_6, OH proton prefers the conformation shown in **Figure 2** so as to form a strong hydrogen bond with DMSO-d_6. In such a conformation H-6a, C-6, C-5, O and OH proton do not form a **W** arrangement and long-range coupling between H-6a and OH proton is not possible.

In the NOESY spectrum of **7** the signal at δ 2.36 showed no NOE with H-2 and H-4. However, it showed NOE with the methyl proton at C-5 and OH proton. This suggests that among the methylene protons at C-6 the signal at δ 2.36 is due to the

Table I — ^{1}H Chemical shifts (δ, ppm) of ketones **7-11**[a]

Compd	H_{2a}	H_{3a}	H_{4a}	H_{6a}	H_{6e}	OH	CH_3 at C-5	CH_2 of COOR at C-2/C-4	CH_3 of COOR at C-2/C-4	Aromatic protons[g]
7	3.71	4.01	3.06	2.51	2.71	3.58	1.32	-	3.54/3.35[e]	7.22 (m)
7[b]	4.01	3.88	3.34	2.97	2.36	4.97	1.24	-	3.42/3.34[f]	7.25 (m)
8[c]	3.63	3.91	3.01	2.47	2.69	3.56	1.31	-	3.57/3.41[f]	6.62 (d, 3′, 5′); 7.05 (d, 2′, 6′)
9[b]	4.17	4.04	3.50	3.01	2.40	5.15	1.27	-	3.35/3.44[f]	7.61 (5′); 7.74 (6′) 8.11 (4′); 8.28 (2′)
10	3.63	4.01	3.02	2.51	2.72	3.51	1.33	-	3.57/3.40[f]	7.20 (2′, 6′); 6.99 (3′, 5′)
11[d]	3.63	3.97	3.02	2.49	2.71	3.54	1.32	-	3.56/3.40[f]	7.13 (2′, 6′); 6.82 (3′, 5′)

[a]$CDCl_3$ was used as solvent unless noted otherwise; [b]DMSO-d_6 was used as solvent; [c]NMe_2 protons appeared as a singlet at δ 2.91; [d]OMe protons appeared as a singlet at δ 3.77; [e]The signals were assigned using HSQC and HMBC spectra' [f]Assignments were made by comparison with **7** in $CDCl_3$; [g]Number in the parentheses indicate the number of carbon to which the proton is attached; *ipso* carbon is termed as C-1′.

Table II — ^{1}H–^{1}H coupling constants (Hz) of ketones **7-11**[a]

Compd	$J_{2a, 3a}$	$J_{3a,4a}$	$J_{OH,6a}$	$J_{6a,6e}$
7	12.3	12.2	2.5	14.3
7[b]	12.4	12.2	-	13.6
8	12.4	12.2	2.6	14.3
9[b]	12.3	12.1	-	14.0
10	12.5	12.2	2.8	14.4
11	12.5	12.3	2.7	14.3

[a]$CDCl_3$ was used as solvent unless noted otherwise; [b]DMSO-d_6 was used as solvent.

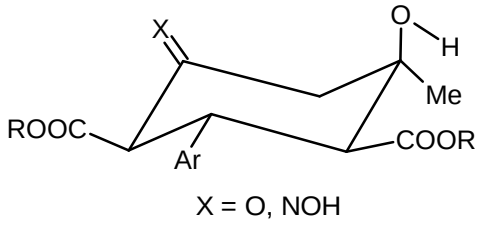


Figure 1 — Conformation of OH group in $CDCl_3$

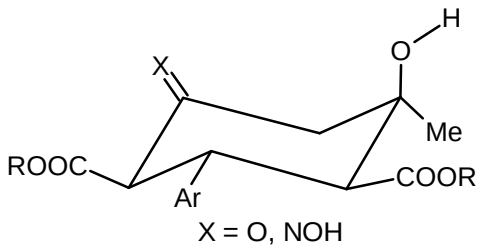


Figure 2 — Conformation of OH group in DMSO-d_6

equatorial methylene proton. Based on this observation, among the signals for the methylene protons of **9**, the signal at δ 3.01 was assigned to H-6a and that at δ 2.40 was assigned H-6e. It is interesting to note that no NOE was observed between the equatorial methylene proton and OH proton in ketones **4** and **5** whose spectra were recorded in $CDCl_3$[15]. No such NOE was observed in the NOESY spectrum of **7** in $CDCl_3$. Observation of such a NOE in **7** in DMSO-d_6 confirms that the OH group prefers conformation shown in **Figure 2** in DMSO-d_6. The observed chemical shifts of **7** and **9** in DMSO-d_6 are given in **Table I**. It is interesting to note that in DMSO-d_6 the axial methylene proton has a higher chemical shift than the equatorial methylene proton whereas the reverse trend is true in $CDCl_3$.

^{1}H NMR spectra of oximes **4a, 5a** and **6a** were recorded in $CDCl_3$. All the signals in the ^{1}H NMR spectrum of **4a** were assigned by positions, multiplicities and the observed NOEs in the NOESY spectrum. ^{1}H NMR spectra of **5a** and **6a** resembled with that of **4a** except for the aromatic protons. However, in **5a** the –OH resonance merged with that for methylene protons of the COOEt group at C-4. ^{1}H NMR chemical shifts of **4a**, **5a** and **6a** are given in **Table III** and the coupling constants are given in **Table IV**. The coupling constants of the oximes are almost same as the corresponding values in the parent ketones[15]. This suggests that oximes **4a**, **5a** and **6a** should adopt chair conformation with axial orientation of the OH group at C-5 and equatorial orientations of all the other substituents.

Furthermore, in all cases the difference between the chemical shifts of H-6e and H-6a is quite large. Therefore, the methylene protons should be *syn* to NOH group. From the observed coupling constants and chemical shifts it is obvious that **4a**, **5a** and **6a** should adopt conformations **4aC**, **5aC** and **6aC,** respectively, with *E* configuration about the C=N bond. Furthermore, long range coupling between H-6a and OH proton suggests that the OH proton is *anti* to C(5)-C(6) bond as shown in **Figure 1** so that H-6a, C-6, C-5, O and OH proton are in **W** arrangement.

^{1}H NMR spectra of **7a-11a** were recorded in DMSO-d_6, since these compounds are insoluble in $CDCl_3$. In the ^{1}H NMR spectrum of **7a** there was a singlet at δ 10.69, corresponding to one proton, and this signal was assigned to the NOH proton. The aromatic protons appeared as a multiplet at δ 7.20. There was a singlet at δ 4.49, corresponding to one proton, which could be assigned to the OH proton at C-5. The benzylic proton (H-3) appeared as a triplet at δ 3.68. There were four doublets at δ 3.61, 3.30, 3.06 and 2.03, each corresponding to one proton. These doublets were assigned to H-2a, H-6e, H-4a and H-6a, respectively based on the correlations in the HOMOCOR and NOESY spectra of **7a**. The methyl protons of the carbomethoxy groups appeared as singlets at δ 3.34 and 3.66. The methyl protons of C-5 appeared as a singlet at δ 1.21.

The ^{1}H NMR spectra of oximes **8a**, **9a**, **10a** and **11a** were similar to the ^{1}H NMR spectrum of **7a** except for the aromatic protons. In all the cases the signals were assigned by comparison with **7a**. In the case of **8a** the assignments were confirmed by its NOESY spectrum.

The proton chemical shifts of **7a-11a** are given in **Table III** and the coupling constants are given in **Table IV**. It is seen that the difference between the chemical shifts of the methylene protons at C-6 is quite large. Based on this observation, and the observed *vicinal* coupling constants it is obvious that oximes **7a-11a** should adopt chair conformation **7aC-11aC** with NOH *syn* to C-6. However, long-range coupling between H-6a and OH proton was not observed. This is because the spectra of these compounds have been recorded in DMSO-d_6. In DMSO-d_6 the OH proton prefers conformation shown in **Figure 2**. The preference of this conformation was confirmed by the observation of NOE between H-6e and OH proton in **7a** and **8a**.

Generally, intramolecular hydrogen bond should be stronger than intermolecular hydrogen bond. However, in the present cases removal of the intramolecular

Table III —^{1}H Chemical shifts (δ, ppm) of oximes[a] **4a-11a**

Compd	H_{2a}	H_{3a}	H_{4a}	H_{6a}	H_{6e}	OH	CH_3 at C-5	CH_2 of COOR at C-2 & C-4	CH_3 of COOR at C-2 & C-4	Aromatic protons	>C=N-OH proton
4a[b]	3.51	3.82	2.80	1.82	3.76	3.64	1.33	3.84/3.97[d]	0.79/0.98[d]	7.24 (m)	8.06
5a[c]	3.49	3.89	2.85	1.85	3.54	3.74	1.26	3.76/3.83[e]	0.77/0.91[e]	7.41 (2′,6′); 8.05 (3′,5′)	10.46
6a[b]	3.45	3.82	2.76	1.81	3.68	3.57	1.33	3.80/3.99	0.85/1.09[f]	7.17 (d), 7.26 (d)	-
7a	3.61	3.67	3.05	2.02	3.29	4.49	1.20	-	3.34/3.26[g]	7.20 (m)	10.7
8a[i]	3.50	3.56	2.96	1.98	3.27	4.37	1.19	-	3.29/3.35[g]	6.5 (3′5′); 7.03 (2′,6′)	10.6
9a	3.87	3.79	3.26	2.08	3.37	4.70	1.26	-	3.32/3.38[h]	7.59 (5′); 7.74 (6′) 8.09 (4′); 8.21 (2′)	10.8
10a	3.51	3.81	2.88	1.89	3.62	5.07	1.31	-	3.37/3.42[h]	6.93 (3′,5′); 7.22 (2′,6′)	10.58
11a[j]	3.68	3.79	2.80	1.82	3.49	5.07	1.32	-	3.18/3.37[h]	6.79 (3′,5′); 7.09 (2′,6′)	10.20

[a]DMSO-d_6 uses as solvent unless noted otherwise; [b]$CDCl_3$ was used as solvent; [c]The spectrum was recorded in $CDCl_3$ after adding one drop of DMSO-d_6 so as to get a clear solution; [d]The signals were assigned using NOESY spectrum; [e]The signals were assigned using HMBC spectrum; [f]Assignments were made by comparison with **4a** and **5a**; [g]The signals were assigned by HSQC, HMBC, HOMOCOR and NOESY spectra; [h]Assignments were made by comparison with **8a**; [i]$N(CH_3)_2$ protons appeared as singlet at δ 2.83; [j]OMe protons appeared as singlet at δ 3.70.

hydrogen bonding between the carbonyl oxygen of the alkoxy group at C-4 and OH proton at C-5, perhaps, allows the alkoxy group to adopt a conformation minimising its steric interactions with the phenyl and methyl groups at the adjacent carbons.

^{13}C NMR spectra

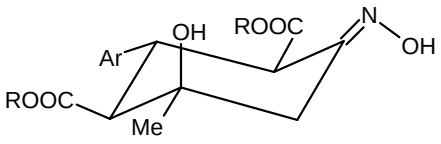
^{13}C NMR spectra of ketones **4-6** have been studied already[15]. In the present work ^{13}C NMR spectra of ketones **7, 8, 10** and **11** were recorded in $CDCl_3$. ^{13}C NMR spectrum of **9** was recorded in DMSO-d_6 since it is insoluble in $CDCl_3$.

For ketone **7**, the individual assignments of carbon chemical shifts were made on the basis of the correlations observed in the HMBC and HSQC spectra. ^{13}C NMR spectra of **8, 10** and **11** were similar to that of **7** except for the aromatic carbons. ^{13}C NMR spectrum of **9,** which was recorded in DMSO-d_6 also was similar to that of **7** except for the aromatic carbons. This shows that ^{13}C chemical shifts are independent of solvent.

Table IV — ^{1}H–^{1}H coupling constants (Hz) of oximes[a] **4a-11a**

Compd	$J_{2a,\ 3a}$	$J_{3a,4a}$	$J_{OH,6a}$	$J_{6a,6e}$
4a[b]	12.1	12.1	2.3	14.6
5a[c]	12.0	12.5	d	14.8
6a[b]	12.1	12.1	2.3	14.8
7a	12.0	11.5	-	14.3
8a	11.4	11.2	-	14.3
9a	12.0	11.5	-	14.2
10a	12.0	12.0	-	14.6
11a	12.3	12.0	-	14.7

[a]DMSO-d_6 uses as solvent unless noted otherwise; [b]$CDCl_3$ was used as solvent; [c]The spectrum was recorded in $CDCl_3$ after adding one drop of DMSO-d_6 so as to get a clear solution; [d]Long range coupling was not observed.



Compd	Ar	R
4aC	C_6H_5	COOEt
5aC	*p*-NO_2-C_6H_4	COOEt
6aC	*p*-Cl-C_6H_4	COOEt
7aC	C_6H_5	COOMe
8aC	*p*-$N(CH_3)_2$-C_6H_4	COOMe
9aC	*m*-NO_2-C_6H_4	COOMe
10aC	*p*-F-C_6H_4	COOMe
11aC	*p*-OMe-C_6H_4	COOMe

The assignments of the aromatic carbons in **8, 9, 10** and **11** were made by comparing the observed values with those calculated using the substituent effects for $-N(CH_3)_2$, NO_2, F and OCH_3 groups[17]. The other ^{13}C signals were assigned by comparison with **7**. ^{13}C chemical shifts of ketones **4-11** are given in **Table V**.

^{13}C NMR spectra of oximes **4a-6a** were recorded in $CDCl_3$ and **7a-11a** were recorded in DMSO-d_6. For all these oximes ^{13}C NMR spectra were similar except for the aromatic carbons and alkyl part of the alkoxycarbonyl group. The signals in **7a** were assigned using HMBC and HSQC spectra. The ^{13}C chemical shifts in the other oximes were assigned by comparison with **7a** and the corresponding ketones. For **5a** the assignments were confirmed by its HMBC spectrum. Furthermore, DEPT spectrum of **4a** was consistent with the assignments. ^{13}C chemical shifts of **4a-11a** are given in **Table VI**.

Analysis of chemical shifts

Comparison of the proton chemical shifts of **7** in $CDCl_3$ and DMSO-d_6 suggests that change of solvent from $CDCl_3$ to DMSO-d_6 shifts H-2a, H-3a, H-4a, H-6a and OH proton to higher frequencies but shifts H-3a and H-6e to lower frequencies. The magnitudes of the shifts are given below: H-2a (0.30 ppm); H-3a (-0.13 ppm); H-4a (0.28 ppm); H-6a (0.46 ppm); H-6e (-0.35 ppm); OH (1.39 ppm). These effects may be due to the change in the conformations of the substituents in the cyclohexane ring in DMSO-d_6. Already it has been shown that the conformation of OH group is changed by replacing $CDCl_3$ with DMSO-d_6. Change in the conformation of OH group probably modifies the conformation of the COOMe group at C-4. The conformation of the COOMe group at C-2 also may be modified in DMSO-d_6 since the dipole-dipole interaction between the ketonic carbonyl group and ester carbonyl group will be decreased in the more polar DMSO-d_6. Due to hydrogen bonding between OH group and DMSO-d_6 one molecule of DMSO-d_6 will be placed above the methylene protons. This solvent molecule also may influence the chemical shifts of the methylene protons by the magnetic anisotropic effect of the SO moiety. The observed changes in proton chemical shifts may be due to a combination of all these effects.

Comparison of the proton chemical shifts of the oximes with those of the corresponding ketones in the same solvent reveals that oximation shields all the protons in the cyclohexane ring except H-6e. The observed effects in the various oximes are given in

Table V — ^{13}C Chemical shifts (δ, ppm) of ketones **7-11**

Carbons	Compd				
	7	**8**[a]	**9**	**10**	**11**[b]
C-1	201.1	201.6	202.3	200.8	201.3
C-2	62.4	62.8	61.0	62.5	62.7
C-3	45.1	44.3	43.5	44.3	44.4
C-4	57.3	57.5	55.8	57.2	57.3
C-5	73.0	72.9	72.4	72.9	72.9
C-6	52.7	52.7	53.9	52.7	52.7
CH_3 at C-5	28.7	28.7	28.0	28.6	28.7
C=O of COOR at C-2	168.1	168.4	168.3	168.2	168.3
C=O of COOR at C-4	174.1	174.4	170.4	174.0	174.2
CH_3 of COOR at C-2 and C-4	51.8/52.0	52.7/52.0	51.3/50.9	52.1/51.9	52.0/51.9
Aromatic carbons[c]	127.8 (others) 128.7 (3′,5′) 138.2 (1′)	112.6 (3′,5′) 125.6 (1′) 128.3 (2′,6′) 149.9 (4′)	122.0 (4′) 122.3 (2′) 129.6 (5′) 135.2 (6′) 142.4 (1′) 147.6 (3′)	115.8 (3′,5′) 129.5 (2′,6′) 134.1 (1′) 149.6 (4′)	114.1 (3′,5′) 128.8 (2′,6′) 130.2 (1′) 159.0 (4′)

[a]$N(CH_3)_2$ signal was observed at δ 40.4; [b]OCH_3 signal was observed at δ 55.2; [c]The numbers in the parentheses give the position of carbons.

Table VII. The causes of the shifts on protons of the α and β carbons (H-6a, H-6e, H-2a and H-3a in the present oximes) have been discussed already[9]. It is seen that proton H-4 (proton in the γ-carbon) is shielded in the oximes relative to the corresponding ketones. The reason for this is not clear.

Since the assignments of ^{13}C chemical shifts have been made for **7** and **7a** using HSQC and HMBC spectra, the effects of oximation on the chemical shifts of cyclohexanone ring carbons were obtained by comparing the ^{13}C chemical shifts of **7a** with those of **7**. These effects (ppm) are as follows: C-1, -47.9; C-2 (*anti* α-carbon) -9.1; C-3 (*anti* β-carbon) -1.6; C-4 (γ-carbon) -0.4; C-5 (*syn* β-carbon) -3.0; C-6 (*syn* α-carbon) -15.6.

The ^{13}C chemical shifts of the ring carbons in **4a, 5a, 6a, 7a, 8a, 9a, 10a** and **11a** were computed by adding these effects to the ^{13}C chemical shifts of the corresponding ketones. The calculated chemical shifts are given along with the observed chemical shifts in the parentheses in **Table VI**. It is seen that the calculated values are in good agreement with the experimental values though the ^{13}C NMR spectra of oximes have been recorded in two different solvents.

Use of NMR spectra in the stereochemical study of oximes

Unsymmetric ketones can give two isomeric oximes. It is worth examining the possibility of assigning the configuration of the oximes unambiguously using NMR spectra. Roberts and co-workers[6] assigned the configuration of several isomeric ketoximes using the fact that oximations shields the *syn*-α-carbon to a greater extent than the *anti*-α-carbon. Heinisch and Holzer[18] assigned the configuration of isomeric oximes from acetophenone and 2-acetylpyridine by NOE measurements. They have found that irradiation of the methyl protons enhances the intensity of the signal for OH proton only in the *E*-oxime. Heinisch and Holzer have stated that solubility problem limits the use of ^{13}C NMR spectroscopy in assigning the configuration of oximes.

In the present study no NOE was observed between the methylene protons at C-6 and the NOH proton in $CDCl_3$ and DMSO-d_6. However, C-6 suffers the greater shielding on oximation in all cases. Moreover, this study shows that ^{13}C chemical shifts of oximes and ketones are not affected by solvents significantly. Hence, it is now believed that ^{13}C NMR spectroscopy is probably the best method for assigning the configuration of ketoximes.

Roberts and co-workers[6] have reported the ^{13}C chemical shifts of several unsymmetric ketones and isomeric oximes obtained from them. The chemical shifts of the *syn*- and *anti*-α-carbons in the oximes were calculated by adding the oximation effects obtained from this study to the chemical shifts of the α-carbons in the ketones. In all cases the calculated values agreed well with the observed values.

Table VI — ^{13}C Chemical shifts (δ, ppm) of oximes **4a-11a**

Carbons	Compd							
	4a	**5a**	**6a**	**7a**	**8a**[a]	**9a**	**10a**	**11a**[b]
C=N/C-1	154.1 153.9	151.6 152.2	154.1 152.3	153.2	153.5 153.7	152.8 154.4	152.5 152.9	149.5 153.4
C-2	54.1 53.8	53.7 52.7	54.1 52.6	53.4	53.7 53.8	52.9 52.0	54.0 53.5	54.1 53.7
C-3	45.1 42.1	44.1 43.2	44.5 42.3	43.6	43.5 42.8	43.5 42.0	43.9 42.8	44.1 42.9
C-4	57.5 56.9	56.4 56.1	57.4 55.7	56.9	57.2 57.1	56.3 55.4	57.5 56.8	57.7 56.9
C-5	70.8 70.5	70.2 70.2	70.9 69.4	70.0	70.0 69.9	70.1 69.4	70.6 69.9	70.8 69.9
C-6	36.0 37.5	36.0 37.2	36.0 36.4	37.1	37.0 37.1	37.2 38.3	36.2 37.1	35.9 37.1
CH_3 at C-5	28.7	28.2	28.7	28.6	28.7	28.6	28.7	28.7
C=O of COOR at C-2	169.1	168.7	168.9	170.1	170.2	169.9	170.0	168.4
C=O of COOR at C-4	173.9	172.1	173.7	171.5	171.7	171.0	173.6	168.4
CH_3 of COOR at C-2 and C-4	13.5/13.8	13.3/13.5	13.7/13.9	50.7/50.9	50.7/50.9	50.9/51.1	51.5/51.6	51.2
CH_2 of COOR at C-2 and C-4	60.7/60.8	59.9/60.1	61.0	-	-	-	-	-
Aromatic carbons[c]	127.5, 128.2, 128.4 (others) 138.4 (1′)	122.8 (3′, 5′) 129.1 (2′, 6′) 146.5 (4′) 147.0 (1′)	128.7 (3′, 5′) 129.7 (2′, 6′) 134.9 (4′) 137.4 (1′)	127.9, 128.2 (others) 140.7 (1′)	111.8 (3′, 5′) 127.9 (1′) 128.6 (2′, 6′) 149.0 (4′)	122.0, 122.6 (2′, 4′) 129.6 (5′) 135.5 (6′) 143.3 (′) 147.6 (3′)	115.1 (3′, 5′) 128.6 (2′, 6′) 135.0 (1′) 149.7 (4′)	113.5, 113.9 (3′, 5′) 127.7, 128.9 (2′, 6′) 138.1 (1′) 157.9 (4′)

[a]$N(CH_3)_2$ signal was observed at δ 42.5; [b]OCH_3 signal was observed at δ 55.1; [c]The numbers in the parentheses give the position of carbons; Calculated values are given in second row.

Table VII — Effect of oximation on ^{1}H chemical shifts

Oxime	Ketone	$\delta_{oxime} - \delta_{ketone}$ (ppm)				
		H-2a	H-3a	H-4a	H-6a	H-6e
4a	**4**	- 0.17	- 0.21	- 0.23	- 0.68	0.96
5a	**5**	- 0.19	- 0.28	- 0.24	- 0.68	0.99
6a	**6**	- 0.21	- 0.27	- 0.30	- 0.64	0.90
7a*	**7***	- 0.40	- 0.17	- 0.29	- 0.95	0.93
9a*	**9***	- 0.30	- 0.25	- 0.24	- 0.93	0.97

* Values in DMSO-d_6

Nowadays, ^{13}C NMR spectrum can be recorded quickly. The signals can be assigned unambiguously using HSQC and HMBC spectra. Hence, the following method is proposed for assigning the configuration of an oxime $C^aC(NOH)C^b$-unambiguously. Labelling is done so that C^a is *anti* to N-OH in the *E*-isomer. In the *E*-isomer C^b should be shielded to a greater extent than C^a whereas in *Z*-isomer C^a should be shielded to a greater extent than C^b. Due to this, the chemical shift difference of C^a and C^b ($\Delta\delta_{ab}$) in the *E*-isomer should be greater than that in the ketone whereas for the *Z*-isomer $\Delta\delta_{ab}$ should be less than that in the ketone. The calculated $\Delta\delta_{ab}$ values of several ketones and oximes from them are given in **Table VIII**. It is seen that in all cases configuration of oxime could be assigned unambiguously by using the above-cited rule.

In oximes from saturated six-membered cyclic ketones the equatorial α-proton in the *syn*-side has a greater chemical shift than that in the *anti*-side by about 0.9 to 1.0 ppm[9,19]. Hence, for such oximes the configuration can be assigned also by using proton chemical shifts. However, this method is not useful in compounds with conformational flexibility. For example, in O-vinyl derivative of acetone oxime the methyl protons in the *syn* and *anti* side have chemical shifts of δ 1.93 and 1.94, respectively[20]. However, the *syn* and *anti* methyl carbons have chemical shifts of δ 15.7 and 21.3, respectively. Similarly, in cyclohexanone oxime the α-methylene protons in both sides differ in their chemical shifts only by about 0.3 ppm[21]. However, the chemical shifts of the two α-carbons differ by 6.2 ppm[6].

This is because in the different conformations different C-H bonds interact with the NOH moiety. The proton on the interacting bond will be deshielded but the other protons are shielded. Thus, due to conformational equilibrium an average effect is obtained. However, in all the possible conformations the same carbon gets the negative charge and is shielded in all conformations to the same extent.

However, ^{1}H chemical shifts of the α-protons in oximes from saturated six-membered ketones can be used to detect conformational equilibrium. In case a conformation involving interaction with the axial methylene proton in the most stable chair conformation than the value of $\Delta\delta_{ea}$ will be reduced. By comparing the $\Delta\delta_{ea}$ values for the *syn* side α-protons in oximes from a series of saturated six-membered ketones one can detect whether a conformation other than the most stable one (with majority of the substituents in the equatorial position) contributes significantly to any compound.

Table VIII[†] — Values of $\Delta\delta_{ab}$ in isomeric oximes $C^aC(NOH)C^b$ and the corresponding ketones

Ketone	$\Delta\delta_{ab}$		
	Ketone	*E*-oxime	*Z*-oxime
Butanone	7.5	15.9	1.8
3-Methylbutanone	16.2	23.5	10.6
4,4-Dimethylpentan-2-one	23.5	32.8	17.3
Phenylacetone	21.7	28.6	15.4
2-Methylcyclohexanone	3.5	11.1	- 4.9
3-Methylcyclohexanone	8.9	14.3	2.5
Menthone	5.1	16.9*	4.8
Isomenthone	9.0	18.0*	1.7*

[†]Chemical shifts for the ketones and oximes were taken from Ref. 6; *Chemical shifts for the oximes were taken from Ref. 11.

Experimental Section

HOMOCOR, HSQC and HMBC spectra were recorded on a Bruker DRX 500 NMR spectrometer using standard parameters. Phase sensitive NOESY spectrum were recorded with a mixing time 1s.

For recording 2D NMR spectra solutions were made by dissolving 50 mg of the material in 0.5 mL of the solvent. The number of data points was 1K. All NMR measurements were made using 5 mm tubes.

Preparation of compounds

t(3)-Aryl-r(2),*c*(4)-biscarbethoxy-*c*(5)-hydroxy-*t*(5)-methylcyclohexanones (4-6)

All the *t*(3)-aryl-r(2),*c*(4)-biscarbethoxy-*c*(5)-hydroxy-*t*(5)-methylcyclohexanones were prepared by using the procedure of Pandiarajan *et al.*[15].

t(3)-Aryl-r(2),*c*(4)-biscarbomethoxy-*c*(5)-hydroxy-*t*(5)-methylcyclohexanones (7-11)

A mixture of methyl acetoacetate (100 mmoles), substituted benzaldehyde (50 mmoles) and methylamine (50 mmoles) in ethanol (50 mL) was warmed on a water bath for about 10 min. The reaction mixture was kept overnight. The separated solid was filtered and it was purified by recrystallisation from ethanol. The physical data for **7-11** are as follows: **7** (yield 85%, m.p. 171°C); **8** (yield 70%, m.p. 181°C); **9** (yield 75%, m.p. 202°C); **10** (yield 78%, m.p. 155°C); **11** (yield 75%, m.p. 172°C).

t(3)-Aryl-r(2),*c*(4)-dicarbalkoxy-*c*(5)-hydroxy-*t*(5)-methylcyclohexanone oximes (4a-11a)

All oximes were prepared by the following general procedure. Hydroxylamine hydrochloride (60 mmoles) and sodium acetate trihydrate (150 mmoles) were dissolved in warm ethanol (20 mL) and it was filtered to remove the sodium chloride. To the filtrate the ketone (50 mmoles) in warm ethanol (30 mL) was added and the mixture was refluxed for 20 min. Then it was allowed to cool. The cold solution was poured into ice. The separated solid was collected on a Büchner funnel and it was purified by recrystallization from ethanol. The physical data for **4a-11a** are as follow: **4a** (yield 80%, m.p. 178°C); **5a** (yield 70%, m.p. 218°C); **6a** (yield 68%, m.p. 206°C); **7a** (yield 85%, m.p. 204°C); **8a** (yield 69%, m.p. 221°C); **9a** (yield 72%, m.p. 222°C); **10a** (yield 78%, m.p. 188°C); **11a** (yield 80%, m.p. 130°C).

Elemental analysis

Elemental analyses were performed on a Perkin-Elmer CHN analyser. Elemental analysis was done for **7**. For **7** the observed percentages of C and H are 63.50 and 6.28, respectively. The percentage of C and H, calculated for the molecular formula $C_{17}H_{20}O_6$ are 63.72 and 6.30, respectively.

Elemental analysis was done for **7a**. For **7a** the observed percentage of C, H and N are 60.92, 6.38 and 4.16, respectively. The percentage of C, H and N calculated for the molecular formula $C_{17}H_{21}O_6N$ are 60.86, 6.32 and 4.18, respectively.

Recording of spectra

IR spectra

IR spectra were recorded on AVATAR 330 FT-IR Thermo Nicolet spectrometer in KBr pellets.

NMR spectra

1D NMR spectra of ketones **7-11** and oximes **6a-9a** were recorded on a Bruker AMX 400 NMR spectrometer operating at 400 MHz for ^{1}H and 100.6 MHz for ^{13}C. For oxime **5a** 1D NMR spectra were recorded on Bruker DRX 500 NMR spectrometer operating at 500 MHz for ^{1}H and 125.7 MHz for ^{13}C. For oximes **10a** and **11a** 1D NMR spectra were recorded on AV 300 NMR spectrometer operating at 300 MHz for ^{1}H and 75.4 MHz for ^{13}C. 1D NMR spectra of oxime **4a** were recorded on Bruker 200 MHz spectrometer operating at 200 MHz for ^{1}H and 50.3 MHz for ^{13}C. Thirty two FIDS were collected and the number of data points were 16 K.

For recording ^{1}H NMR spectra, **7-11**, **4a** and **6a** solutions were prepared by dissolving about 10 mg of the material in 0.5 mL of $CDCl_3$. ^{1}H NMR spectrum of **5a** was recorded after the addition of a drop of DMSO-d_6 to the solution prepared by dissolving about 10 mg of the material in 0.5 mL of $CDCl_3$. For ^{1}H NMR spectra of **7a-11a** and **7**, solutions were prepared by dissolving about 10 mg of the material in 0.5 mL of DMSO-d_6. For ^{13}C NMR spectra, solutions were prepared by dissolving about 50 mg of the compound 0.5 mL of solvent ($CDCl_3$ or DMSO-d_6). In all cases TMS was used as the internal standard.

Conclusion

Oximation of *t*(3)-aryl-r(2),*c*(4)-biscarbalkoxy-*c*(5)-hydroxy-*t*(5)-methylcyclohexanone give only *E* oximes on oximation. The other isomer (*Z*-oxime) is not formed. The ketones do not undergo dehydrogenation during oximation. All the oximes adopt chair conformation with axial orientation of hydroxy group at C-5 and equatorial orientation of all the other substituents. The OH proton prefers to be *anti* to C(5)-C(6) bond in $CDCl_3$ but prefers to be *anti* to C(4)-C(5) bond in DMSO-d_6. Change of solvent from $CDCl_3$ to DMSO-d_6 has a marked influence on proton chemical shifts. However, ^{13}C chemical shifts are not influenced by the change of solvent. Configuration of the oxime can be determined by comparing the chemical shift difference between the α-carbons in the oxime with that in the ketone.

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