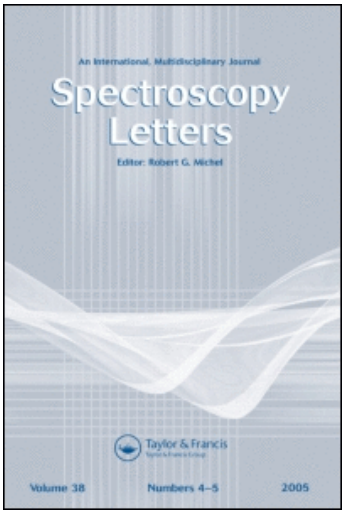

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Structural and Stereochemical Analysis of Some 9-Phenyl-8-N-substituted Thiocarbamoyl-7,8-Diazabicyclo [4.3.0]non-6-enes by NMR and Mass Spectrometric Techniques

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STRUCTURAL and STEREOCHEMICAL ANALYSIS OF SOME 9-PHENYL-8-N-SUBSTITUTED THIOCARBAMOYL-7,8-DIAZABICYCLO [4.3.0]NON-6-ENES BY NMR and MASS SPECTROMETRIC TECHNIQUES

KEY WORDS: 5-Methyl-9-phenyl-7,8-diazabicyclo[4.3.0]non-6-enes, Stereochemistry, Mass Spectra, NMR Spectra, Synthesis.

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ABSTRACT

In this study the structural and stereochemical analysis of some 9-Phenyl-8-N-Substituted thiocarbamoyl-7,8-diazabicyclo[4.-3.0] and the new synthesized 5-

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Methyl-9-phenyl-8-N-Substituted-thiocarbamoyl-7,8-diazabicyclo[4.-3.0]non-6-enes derivatives were studied by 2D NMR, 1D NOE experiments and electron impact mass spectrometry were reported. The N-substituted thiocarbamoyl compounds were mixtures of diastereomers as evidenced by differing Rf values on TLC plates. They were separated by successive applications of preparative TLC and structures were elucidated by IR, ^{1}H-NMR, ^{13}C-NMR, DEPT, 2D-NMR and EI-MASS techniques. The cis-trans isomerism of the compounds were determined by means of ^{1}H-NMR, ^{13}C-NMR and 1D NOE difference experiments. The conformation analysis of the bicyclic ring system was based on NOE difference experiments and NOESY spectra of compound-11. For the application of 1D NOE experiments, compound 11 was selected.

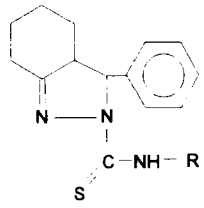
INTRODUCTION

The synthesis and stereochemistry of bicyclic dihydropyrazoles have been the subject of various studies due to the interesting pharmacological activity of these compounds [1-6].

Khalaf et al, prepared a series of compounds with the same ring system starting from 2,6-diarylidenecyclohexanones [4]. Lóránd and Szabó reported the synthesis and stereochemistry of the nonsubstituted 8-thiocarbamoyl and carbamoyl derivatives by reacting 2-benzylidene and 2,6-dibenzyldene-cyclohexanones with semicarbazide or thiosemicarbazide where only one diastereomer was obtained. X-ray crystallographic study of 2,6-dibenzylidene derivatives was performed but the stereochemistry of monobenzylidene derivatives was not thoroughly investigated [5].

We report here in addition to structural analysis by IR and mass spectra; the stereochemistry of the previously synthesized compounds (9-Phenyl-8-N-substitutedthiocarbamoyl-7,8-diazabicyclo[4.-3.0]) 9-11 (TABLE 1) were deter-

TABLE 1:



Compound No	R
9a	C_6H_5
9b	C_6H_5
10b	C_2H_5
11a	C_3H_5
11b	C_3H_5

a: trans, b: cis

mined by means of ^{1}H-NMR, 2D homonuclear and heteronuclear correlation spectra and NOE difference experiments. We also give the stereochemical properties of the newly synthesized 5-methylated derivatives on the basis of ^{1}H-NMR, ^{13}C-NMR, DEPT and homo and heteronuclear correlation spectra of representative derivatives (3a-b, 6a-b).

RESULT AND DISCUSSION

The title compounds were synthesized according to the method reported elsewhere [7]. The N-substituted thiocarbamoyl compounds thus formed were

mixtures of diastereomers as evidenced by differing Rf values on TLC plates. They were separated by successive applications of preparative TLC and structures were elucidated by IR, ^{1}H-NMR, ^{13}C-NMR, DEPT, 2D-NMR and EI-MASS techniques.

In the IR spectra the NH and C=S and amide II bands belonging to the thiocarbamoyl moiety appeared at the expected ranges; 3500-3100, 1275-1030 cm^{-1} respectively. Additionally the C=N band of the 2-pyrazoline ring were seen in the range 1591-1674 cm^{-1} for all the compounds.

In the mass spectra, molecular ion peaks were prominent for all the compounds. Two sets of fragments could be detected belonging to fragmentation of the thiocarbamoyl and bicyclic dihydropyrazole structure (Figure 1, TABLE 2).

Fragments resulting by loss of SH ion from thiocarbamoyl group were observed for all compounds, with 100 % abundance in the phenyl substituted derivatives (Compound 5a, 5b and 8a) due to resonance stabilization. On the other hand, α-cleavage adjacent to both sides of the C=S group have also been observed causing ejection of NHR"CS or CSNHR" type of ions characterizing thioamide bond and prolifering pyrazolium ions (6a).

As for the condensed ring, the 2-pyrazoline moiety have shown a fragmentation pattern giving rise to 3b and 4a type of ions, by loss of C_7H_{12} and N_2, for all the compounds, in accordance with literature data.These ions were further fragmented by loss of -SH, C_7H_{12} (3a) and -NHR" (3b) as expected [8].

In the ^{1}H-NMR spectra the aromatic and cyclohexane ring protons apppeared at the expected ranges. The doublet appearing in the range 5-6 ppm, due to H-1 and H-9 coupling, confirmed ring closure, while ^{13}C and DEPT spectra, revealed the bicyclic ring system (TABLE 3).

The cis-trans isomerism of the compounds 9-11 were determined by means of ^{1}H-NMR and 1D NOE difference experiments. For the complete

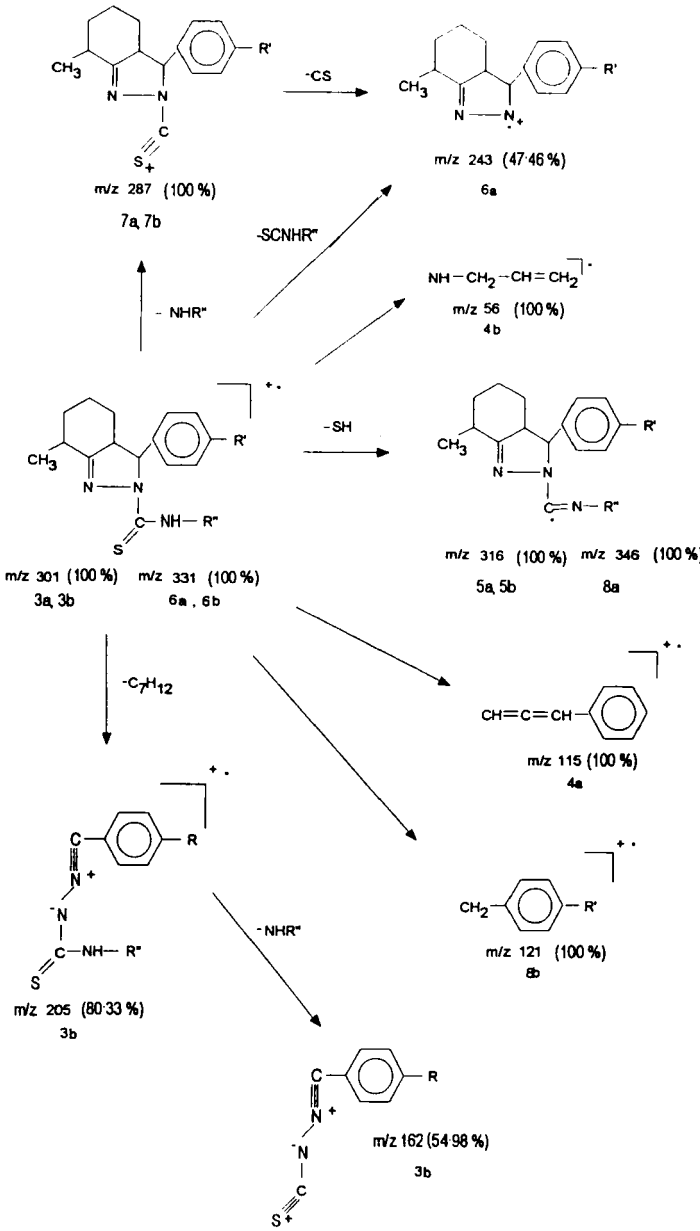


FIG 1: Fragmentation pathway of compounds 3-8(a-b)

TABLE 2: MASS FRAGMENTATION OF THE COMPOUNDS

3a, b: 301 (M^+, 100 %), 268 (M-SH), 205 (M-C_7H_{12}), 213 (M-CSNHR), 162 (M-$C_9H_{18}N$), 91 (M-$C_{10}H_{16}N_3S$), 115 (M-$C_8H_{16}N_3S$), 303 (M+2).

4a, b: 313 (M^+), 298 (M-15), 257 (M-NHR), 217 (M-C_7H_{12}), 213 (M-CSNHR), 56 (NHR, 100% *for 4b*). 115 (M-$C_9H_{16}N_3S$, 100 %), 162 (M-$C_{10}H_{17}N$), 91 (M-$C_{11}H_{16}N_3S$), 315 (M+2).

5a, b: 349 (M^+), 316 (M-SH, 100 %) 257 (M-NHR), 253 (M-C_7H_{12}), 213 (M-CSNHR), 91 (M-$C_{14}H_{16}N_3S$), 115 (M-$C_{12}H_{16}N_3S$), 162 (M-$C_{13}H_{17}N$), 351 (M+2).

6a, b: 331(M^+, 100 %), 298 (M-SH), 235 (M-C_7H_{12}), 243 (M-CSNHR), 84 (M-$C_{14}H_{17}$S for *6a*), 121 (M-$C_{10}H_{16}N_3S$), 192 (M-$C_9H_{16}N_3S$), 221 (M-C_8H_{14}), 145 (M-$C_8H_{16}N_3S$), 333 (M+2).

7a, b: 343 (M^+), 310 (M-SH), 287 (M-NHR, 100%), 247 (M-C_7H_{12}), 243 (M-CSNHR), 56 (NHR), 328 (M-15), 121 (M-$C_{11}H_{16}N_3S$), 145 (M-$C_9H_{16}N_3S$), 345 (M+2).

8a, b: 379 (M^+), 346 (M-SH, 100 %), 287 (M-NHR), 283 (M-C_7H_{12}), 243 (M-CSNHR), 121 (M-$C_{14}H_{16}N_3S$), 145 (M-$C_{12}H_{16}N_3S$), 381 (M+2).

assignment of cyclohexane ring protons, H-H COSY, LR COSY homonuclear correlation spectra and ^{13}C-H COSY heteronuclear correlation spectra were utilized. Conformational analysis was performed by NOE difference experiments and NOESY correlation spectra.

Assignment of the cis and trans isomers:

In accordance with the previous repots [2,3], H-9 proton coupled with H-1 appears at 0.5-0.7 ppm higher field in cis isomers than trans as a resolved

TABLE 3: ^{1}H-NMR (300 MHz) chemical shifts (δ/ppm) and characteristic coupling constants (J/Hz) for compounds 9a-b, 10b,11a-b

	9a	9b	10b	11a	11b
1-H	2.87	3.37	3.29	2.79	3.30
2eq-H	1.70-1.36	1.77-1.58	1.57	1.63-1.36	1.15-1.6
2ax-H	2.35-2.24	0.67	0.61	2.30-2.20	0.55-0.7
3eq-H	1.90	1.77-1.58	1.72	1.87	1.65-1.75
3ax-H	1.70-1.36	1.45-1.17	1.40-1.13	1.63-1.36	1.15-1.45
4eq-H	1.90	1.99	1.95	2.08	1.9-2.0
4ax-H	1.70-1.36	1.45-1.17	1.40-1.13	1.63-1.36	1.15-1.45
5eq-H	2.72	2.72	2.71	2.65	2.55-2.65
5ax-H	2.35-2.24	2.27	2.20	2.30-2.20	2.15-2.25
9-H	5.45	6.052	5.94	5.34	5.9-6.0
J_{1-9}	4.16	11.19	11.27	5.22	10.71
Phenyl	7.10-7.70	7.0-7.5	7.2-7.35	7.15-7.40	7.0-7.4
CH_2	-	-	3.60-3.75	-	-
CH_3	-	-	1.20-1.30	-	-
CH_2	-	-	-	4.25-4.35	4.15-4.40
CH=	-	-	-	5.90-6.00	5.9-6.0
$=CH_2$	-	-	-	5.15-5.25	5.15-5.30

doublet in compounds 9 and 10, but overlapping with the allylic proton signals in compound 11 as shown in TABLE 3. Addition of C_6H_6 to the solution of compound 11a in $CDCl_3$, caused a 0.9 ppm downfield shift of the signal allowing to precise assignment and ease in NOE difference experiments. For the application of 1D NOE experiments, compound 11 was selected. Irradiation of H-9 proton showed a 2.34 % NOE at H-1 proton in compound 11a and 5.88 % in compound 11b, confirming the cis-trans isomerism. On the other hand in the NOESY correlation maps of cis compounds, a correlation was observed between H-9 and H-1 which was not observed in trans compounds. For all the compounds, the J_{1-9} (cis) values were greater than J_{1-9} (trans) in the expected ranges (8-13 Hz) and (3-5 Hz) respectively.

Chemical shifts of the cyclohexane ring protons also showed characteristic differences in cis and trans isomers, such that, H-2ax protons shifted to considerably higher field in cis isomers due to the shielding effect of the 9-phenyl ring which is oriented close to this proton, while in the trans isomers it overlapped with H-3e and H-4ax protons in the range 2.35-2.20 ppm (TABLE 3).

Comparison of ^{13}C NMR spectra of two forms of all the compounds showed marked chemical shift differences at C-1, C-2, C-4 carbons (TABLE 4). In all the compounds the chemical shifts of these carbons were observed 3-9 ppm upfield in cis isomers relative to trans resulting from the preferential orientation of the phenyl ring towards the cyclohexane ring giving rise to a shielding effect.

Conformational Analysis:

The conformation analysis of the bicyclic ring system was based on NOE difference experiments and NOESY spectra of compound-11. The existence of NOE (TABLE 5) between H-3ax-H-5ax and H-4ax-H-2ax proton pairs showed that the chair conformation of cyclohexane ring is dominant in both cis and trans

TABLE 4: ^{13}C NMR (75 MHz) chemical shifts (δ/ppm) for compounds 9a-b, 10b,11a-b

	9a	9b	10b	11a	11b
C-1	58.07	49.74	49.51	57.87	49.53
C-2	33.82	28.23	28.15	33.76	28.15
C-3	24.74	24.03	24.05	24.74	24.04
C-4	27.98	25.24	25.24	27.93	25.22
C-5	28.14	27.76	27.68	28.05	27.69
C-6	162.98	162.34	161.51	162.44	161.77
C-9	69.07	66.09	66.16	69.34	66.31
C=S	174.74	-	175.73	176.95	175.86
C-1'	142.73	138.96	39.32	47.10	46.94
C-2'	123.85	123.92	14.63	134.25	134.33
C-3'	125.24	-	-	116.64	116.43
C-4'	125.05	125.05	-	-	-
C-9 phenyl C-1	138.95	137.69	138.21	143.09	138.96

forms. But the expected NOE between H-1ax and H-3ax-H-5ax could not be observed clearly in the trans form because of the overlap between H-5ax and H-2e protons and existence of water in the solvent forming hydrogen bonds with N-H group to bring about erroneous results.

For the unambiguous assingment of the NOE, the experiment was repeated with 600 MHz NMR, with addition of D_2O, in order to achieve a better resolution and eliminate the effect of the NH bond by deuterium exchange.

TABLE 5:

Compound	Proton irradiated	NOE observed (%)
trans 11	phenyl ortho protons	H-9 (8.034 %), H-1 (2.54 %)
	H-9	H-1 (2.34 %)
	H-1	H-5ax, H-2e (2.34 %) overlapp, H-3ax NOE is not observed because of H_2O
	H-5e	H-4ax (2.47 %)
	H-2e, H-5ax	H-1 (5.63 %), H-5e (19.35 %), H-3e (1.0 %)
	H-4e	H-4ax, H-2ax (7.0 %)
	H-3e	H-3ax (gem 8.19 %), H-2ax, H-4ax (1.69 %) H-4e (1.63 %).
	H-2ax	H-9 (4.02 %), H-2ax-H-5ax (7.4 % H-2-2 gem.), H-3e (2.2 %)
	H-4ax	H-4e (11.2 %), H-3e (5.01 %), H-2ax-H-5ax 83.390 %)*
	H-3ax	H-3e (10.3 %), H-5ax-2ax (2 %), H-1 (4.7 %)
cis 11	phenyl ortho protons	H-2ax (2.87 %), H-9 (3.29 %)
	H-9	H-1 (5.88 %)
	H-1	H-9 (3.68 %), phenyl meta protons (2.13 %)*, H-3ax (1.85 %)
	H-5e	H-5ax (gem 13.13 %), H-4e (1.75 %), H-3ax (2.094 %)
	H-5ax	H-5e (gem. 14.64 %)
	H-4e	H-5ax (3.29 %), 3ax (5.84 %), 4ax (9.88 %)
	H-3e	H-3ax (9.79 %), H-4ax (2.71 %), H-2ax (5.41 %)
	H-2e	H-3ax (5.36 %), H-2ax (15.92 % gem)
	H-3ax	H-5ax (3.12 %), H-4e (6.51 %), H-3e (9.77 % gem)
	H-4ax	H-2ax (3.07 %), 4e (12.67 %), 5e (1.97 %), H-1 (1.97 %)
	H-2ax	H-4ax (1.83 %), 2e (3.73 %), 3e (2.30 %)

* unexpected results.

This experiments revealed the existence of 2.866 % NOE between H-1 and H-3ax. On the other hand better resolution achieved by addition of a few drops acetone-d_6 to the $CDCl_3$ solution helped to observe a 2.93 % NOE between H-1 and H-5ax and confirmed the chair conformation for the cyclohexane ring in both cis and trans forms (Figure 2).

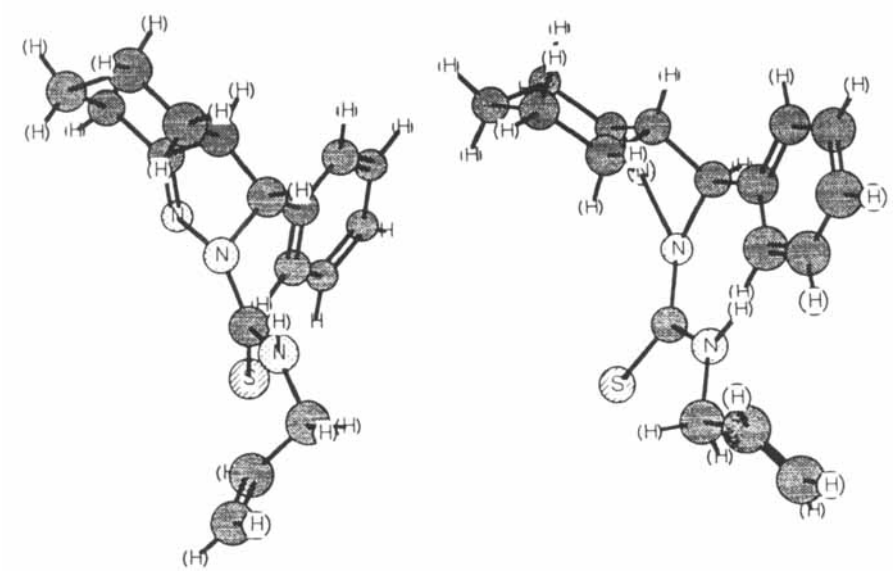
5-Methylated Derivatives

The ^{1}H-NMR of the newly synthesized 5-methylated compounds showed similar chemical shift and J values (TABLE 6). The H-4ax proton appeared upperfield due to the negative inductive effect of the vicinal methyl group. On the other hand, the H-9 proton appeared at the expected chemical shift values in both isomers, but gave two doublets differing~0.1 ppm indicating the existence of another isomer originating from the axial and equatorial orientation of the methyl group. This was supported by observation of two doublets (CH_3eq 1.18-1.35 ppm, CH_3ax 1.01-1.27 ppm) for the methyl group and the double integral values of the other protons. The ratio of the conformers with respect to the equatorial to axial position of the methyl group, was 3:1 in cis isomers and 1.5:1 in trans.

In the ^{13}C-NMR (TABLE 7) and DEPT spectra of selected compounds (3a-b, 4a-b, 5a-b, 6a-b) two peaks were clearly observed at the ppm values corresponding to CH_3, C-1, C-3, C-4, C-5 carbons (TABLE 8). For the methyl carbons, the upperfield peak was assigned for the equatorial position. The lower ppm value (~ 6 ppm) observed for the methyl group in comparison with the expected values [9] was explained with the shielding effect of the neighbouring C=N bond. The chemical shifts of the C-1, C-3, C-4 and C-5 carbons were in accordance with the known additivity rules [9].

EXPERIMENTAL

IR spectra were taken with Perkin Elmer FT IR 1720 X Infrared Spectrometers. NMR spectra were recorded on JEOL JNM-FX 200 Bruker AC-300, Bruker AM-600. Samples were dissolved in $CDCl_3$ containing tetramethylsilane as internal



trans 11 *cis 11*

FIG 2: 3D Molecular Modelles of cis and trans forms of Compound 11

standard. Chemical shifts δ are given in ppm and coupling constants (J) in Hz. EI-MS was performed on a JEOL JMS-DX-300 (30eV) and VG Zab Spec.(70 eV). Analytical TLC was carried on silica gel (Kieselgel HF 254, Merck, 0.25 mm) preparative TLC on 0.5 mm plates. Plates were scanned under ultraviolet light λ=254 nm.

Synthetic Procedures

Starting materials

2-Methyl-5-benzylidenecyclohexanone (m.p:108-110°C) and 2-methyl-5-(4-methoxybenzylidene)cyclohexanone (m.p: 62-4°C) were prepared by condensing 2-methylcyclohexanone with benzaldehyde or 4-methoxybenzaldehyde according to methods published earlier [2].

TABLE 6: 1H-NMR (300-600 Mhz) chemical shifts (/ppm) and characteristic coupling constants (J/Hz) for compounds 3-8(a,b)

Comp. No	1-H (1H,t)	2eq-H (1H,m)	2ax-H (1H,m)	3eq-H (1H,m)	3ax-H (1H,m)	4eq-H (1H,m)	4ax-H (1H,m)	5ax-H (1H,m)	9-H (1H,d)
3a	2.70-2.80	1.20-1.40	2.15-2.30	1.75-1.85	1.55-1.65	2.00-2.10	1.10-1.20	2.40-2.50	5.35-5.50 J1-9 3.75
3b	3.25-3.40	1.45-1.55	1.10-1.25	1.70-1.85	1.60-1.70	2.05-2.10	0.8-1.00	2.35-3.50	5.90-6.00 J1-9 11.25
4a	2.70-2.85	1.35-1.60	2.15-2.30	1.80-1.90	1.35-1.60	2.00-2.15	1.25-1.30	2.40-2.55	5.35-5.40 J1-9 4.41
4b	3.20-3.40	1.45-1.60	0.50-0.70	1.65-1.70	1.15-1.35	1.90-2.00	0.80-1.00	2.30-2.45	5.85-6.00 J1-9 13.23
5a	2.80-2.90	1.50-1.70	2.15-2.35	1.75-1.90	1.50-1.70	2.00-2.15	0.90-1.00	2.40-2.60	5.40-5.50 J1-9 4.05
5b	3.30-3.45	1.50-1.65	0.55-0.75	1.75-1.80	1.40-1.50	1.90-2.00	0.85-1.05	2.35-2.50	6.00-6.10 J1-9 8.91
6a	2.70-2.80	1.40-1.60	2.15-2.25	1.40-1.60	2.10-2.20	1.70-1.80	1.10-1.25	2.45-2.55	5.25-5.35 J1-9 4.16
6b	3.30-3.40	1.60-1.70	0.50-0.75	1.60-1.70	1.40-1.50	1.50-1.65	1.05-1.20	2.40-2.50	5.80-5.90 J1-9 9.16
7a	2.80-3.10	1.50-1.70	2.05-2.20	1.60-1.80	1.40-1.50	1.50-1.80	1.10-1.30	2.40-2.50	5.25-5.40 J1-9 4.00
7b	3.20-3.60	1.40-1.70	0.60-0.70	1.70-1.90	1.10-1.30	1.40-1.70	0.80-1.00	2.20-2.50	5.80-5.90 J1-9 10.0
8a	2.85-3.00	1.55-1.70	1.90-2.00	1.65-1.75	1.55-1.70	1.80-1.90	1.10-1.20	2.35-2.45	5.35-5.50 J1-9 4.00
8b	3.20-3.40	1.50-1.60	0.90-1.00	1.60-1.70	1.50-1.60	1.90-2.00	1.10-1.30	2.20-2.30	5.90-6.10 J1-9 10.43

TABLE 7: ^{13}C-NMR (75 Mhz) chemical shifts (δ/ppm) for compounds 3-8(a,b)

	3a	3b	4a	4b	5a	5b	6a	6b
C-1	58.18	50.00	58.17	50.00	58.75	50.00	58.57	46.44
C-2	34.00	28.70	34.50	29.75	34.00	28.75	34.28	30.00
C-3	24.80	25.00	25.00	24.78	24.75	24.25	25.32	25.00
C-4	39.48	36.50	37.56	35.21	37.25	34.25	37.25	31.78
C-5	34.80	34.80	34.39	30.00	34.75	34.25	34.25	30.82
C-6	165.84	166.10	166.15	170.75	166.25	166.00	166.00	165.00
C-9	69.22	69.22	69.39	69.40	69.25	67.25	68.57	66.00
CH-CH_3	16.62	16.10	16.64	16.66	16.50	16.30	17.40	18.44
C-9 phenyl C-1	143.12	143.12	143.05	139.70	139.00	138.00	136.00	135.75
OCH_3	-	-	-	-	-	-	55.42	55.56

TABLE 8 : ^{13}C-NMR chemical shifts (δ/ppm) for compounds 3a and 3b with respect to the axial and equatorial of 5-methyl group

		CH_3	C-1	C-2	C-3	C-4	C-5
3a	CH_{3eq}	17.25	58.18	34.00	24.80	39.48	34.80
	CH_{3ax}	16.62	54.00	34.50	20.00	37.40	31.50
3b	CH_{3eq}	17.50	50.00	28.70	25.00	36.50	34.80
	CH_{3ax}	16.10	46.25	30.00	24.54	34.00	31.75

7,8-Diazobicyclo[4.3.0] non-6-enes (2)

Hydrazine hydrate (0.03 mole) was added to an ethanolic solution of α,β-unsaturated ketone (0.01 mole) and refluxed for two hours. The resulting mixture was evaporated to dryness under vacuum and dissolved in ether. The etheric solution was washed 2 or 3 times with water and dried over Na_2SO_4.

5-Methyl-9-phenyl-8-N-substituted thiocarbamoyl-7,8-diazobicyclo[4.3.0]non-6-en derivatives (3)

To a solution of 2 (0.01 mole) in dry ether, ethyl-, allyl-, or phenylisothiocyanate (0.02 mole) and four drops of triethylamine were added and stirred for 5h at room temperature. The mixture was evaporated to dryness and the residue was purified and seperated to the diastereomers by repeated preparative thin layer chromatography on silicagel coated plates, with the solvent system, $CHCl_3$-MeOH (99:1).

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