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Stereochemistry of N-acyltetrahydro-1,5-benzodiazepines using NMR spectra, X-ray crystallography and semiempirical MO calculations

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The preferred conformations of N-acyl derivatives of 2,2,4-trimethyl-1*H*-tetrahydro-1,5-benzodiazepines **6-9** have been studied using NMR spectral techniques. In the case of N_1,N_5-diformyl derivative **9,** there is an equilibrium between the boat **BE** and chair **CE** conformations in which the two N-CO groups at N_1 and N_5 adopt *endo* and *exo* orientation, respectively. The average energy barrier for the interconversion between the *major* (**BE**) and *minor* (**CE**) conformers of **9** has been found to be 79.7 kJ/mol on the basis of the dynamic ^{1}H NMR spectral studies. The N_5-benzoyl- and N_5-phenylcarbamoyltetrahydrobenzodiazepines **6** and **7** prefer boat conformations **BE** with *exo* orientation of the N-CO groups. The X-ray crystal structure of **7** also shows the boat conformation **BE** with the *exo* orientation of the N-CO group. The diacetyl derivative **8** prefers a boat conformation **BE** in which the N-acetyl group at N_1 is predominantly at the *endo* position while that of N_5 is at *exo* orientation. The semiempirical molecular orbital calculations (**AM1** and **PM3**) support the conformational preferences derived from the NMR results.

Keywords: 1,5-Benzodiazepine, diformyl, major conformers, minor conformers, benzoyl, phenylcarbamoyl, diacetyl, interconversions, X-ray, energy barrier, semiempirical MO calculations

IPC Code: Int. Cl.[8] C07D

The N-acyl-*cis*-2,6-diarylpiperidines[1] **(***e.g.* **1a-e)**, *cis*-2,4-diphenyl-3-azabicyclo[3.3.1]-nonanes[2] **(***e.g.* **2a-c)** and hexahydro-1,4-diazepines[3] (*e.g.* **3a** and **3b**) prefer, in general, twist-chair/twist-boat/flattened boat, twin-chair and flattened boat conformations, respectively, with two rotameric states of the N-substituent group (*syn* and *anti*, **Figure 1**) in equilibrium. However, there is no equilibrium between two *ring* conformations at ambient temperature at any detectable levels.

While conformational analysis in medium sized rings is complicated by the flexibility exhibited by these compounds, the presence of a double bond as in cycloheptenes restricts the system to adopt a flexible boat or a rigid chair conformation[4]. The fusion of benzene ring with hexahydrodiazepines introduces a double bond in the diazepine ring and the resulting tetrahydrobenzodiazepines resemble cycloheptene and ε-caprolactam in their stereochemical properties[4]. With a view to studying the influences of the acyl functions at N_1 and N_5 over the conformational preferences of tetrahydrobenzodiazepines, the N_5-acyl- and N_1, N_5-diacyl 2,2,4-trimethyl-1*H*-tetrahydro-1,5-benzodiazepines **6-9** (**Scheme I**) were synthesized.

The predominance of equilibrium due to the *ring inversion* over the N-C=O rotation in the case of N-formyl derivative of tetrahydro-1,5-benzodiazepine **9** has now been observed. In this article the conformational preferences of N-acyl derivatives of 2,2,4-trimethyl-1*H*-tetrahydro-1,5-benzodiazepines **6-9** are discussed on the basis of ^{1}H and ^{13}C NMR data for solution state conformations, AM1 and PM3 semiempirical molecular orbital calculations for molecules in theoretical gaseous state as well as the X-ray methods for the solid state.

Results and Discussion

The preferred conformations of the N-acyltetrahydro-1,5-benzodiazepines **6-9** were derived

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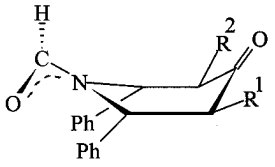
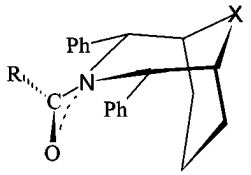


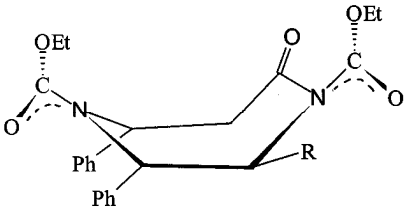
1a-e

	R^1	R^2
1a	H	H
1b	Me	H
1c	Et	H
1d	i-Pr	H
1e	Me	Me



2a-c

	R	X
2a	H	CO
2b	H	CH_2
2c	Me	CH_2



3a-b

	R
3a	H
3b	Me

syn *anti*

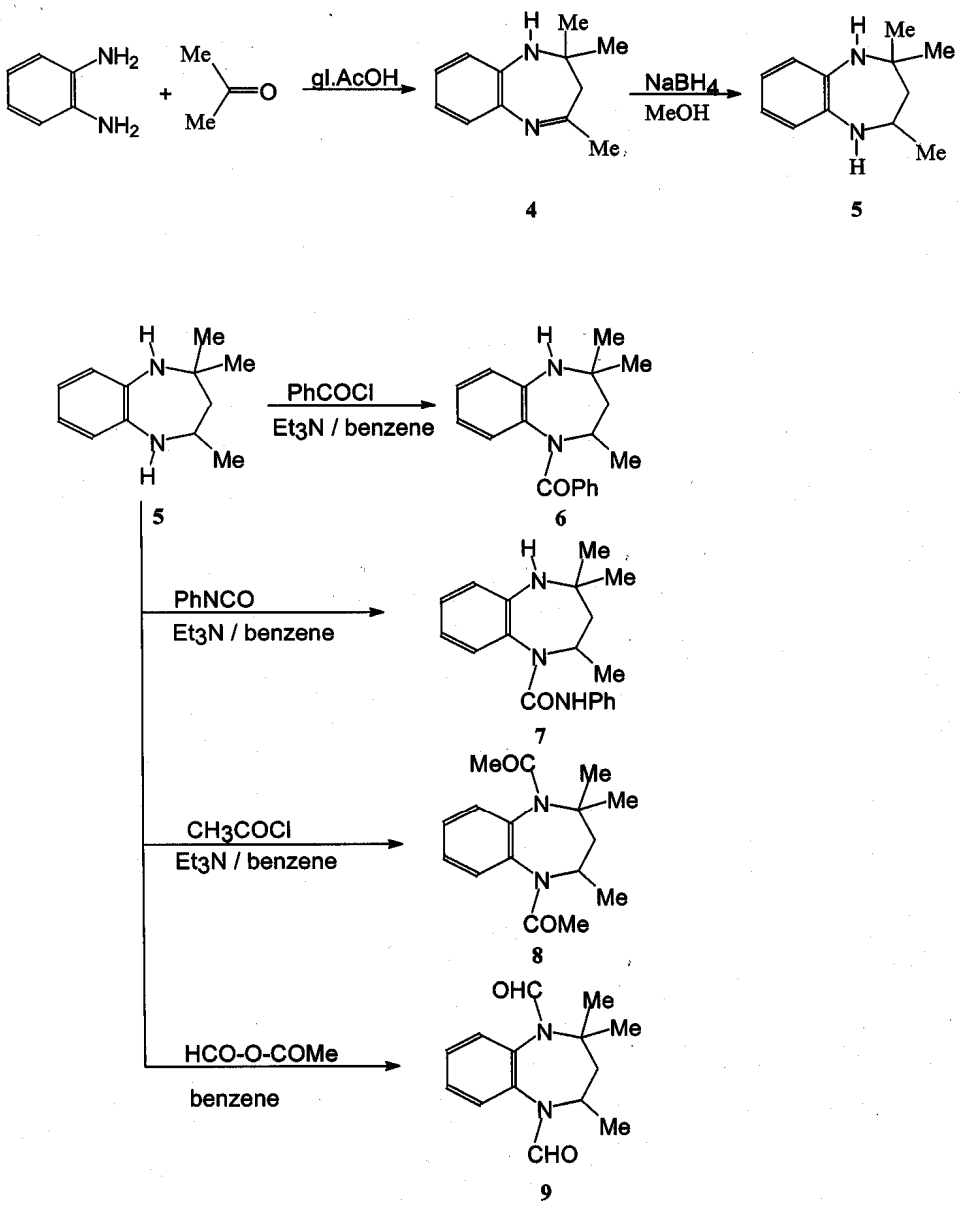
R, R^1, R^2 = alkyl or aryl

Figure 1—N-C Rotational equilibrium

from the ^1H and ^{13}C NMR spectral data in comparison with that of the parent amine **5**. The coupling constants ($J_{3a,4a}$ and $J_{3e,4a}$) were determined by irradiating the C4-methyl doublets and the corresponding dihedral angles were estimated using DAERM[5] (Dihedral angle estimation by ratio method). The parent benzodiazepine **5** has been reported to exist in a chair conformation[4].

N_5-Monoacyl derivatives of tetrahydro-1,5-benzodiazepines 6 and 7

The ^1H and ^{13}C NMR spectra of (**Table I**) the N_5-benzoyl and N_5-phenylcarbamoyl-tetrahydro-1,5-benzodiazepines **6** and **7** showed isochronous nature of the proton (as well as carbon) signals at RT indicating that either the rotation about N-CO bond may be fast or the N-CO group might be locked in one of the possible orientations *viz*., *exo* or *endo* [Between the two possible planar orientations of the N-C=O group, the one in which the oxygen is directed towards the benzene ring is designated as *endo* and the other in which oxygen is away from the benzene ring is *exo* (**Figures 2** and **3**)]. The shielding of α-carbon signals in the ^{13}C NMR spectra of the compounds **6** and **7** compared to that of the parent **5** was used to decide the orientation of the COPh and CONHPh groups, respectively. The *syn* orientation of C=O with reference to the α-carbon would result in an eclipsing interaction between N5-C4/N5-C11 and C-O bonds and the α-carbon is expected to be shielded[6]. Even if there



Scheme I

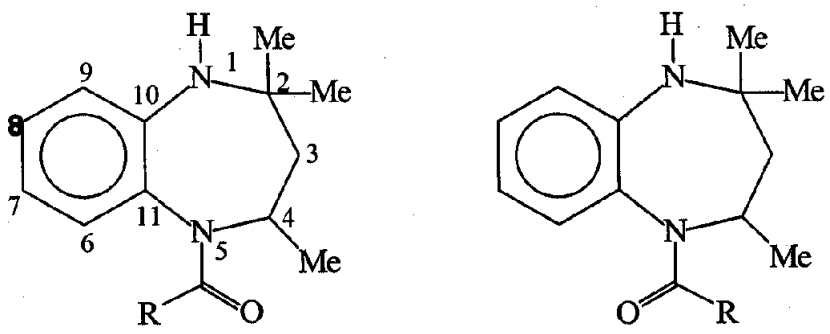
is a fast N-C rotation, the α-carbons are expected to be shielded[6]. It was observed that the *ipso* carbon signals C10 and C11 of **6** and **7** were deshielded (for **6**: 0.8 and 4.2 ppm; for **7**: 1.4 and 5.1 ppm, respectively) while the C4 carbon signals were shielded (0.8 and 2.1 ppm, respectively) with respect to those of the parent tetrahydrobenzodiazepine **5** (**Table I**). The deshielding of *ipso* carbons and shielding of C4 carbon eliminated both the possibilities of fast N-CO rotation and *endo* orientation of the N-CO group at N5. Hence, the N-CO group at N5 position adopts an *exo* orientation.

Ring conformations

The N-acyl derivatives **6** and **7** may prefer to adopt the chair conformations **CE** and **CA** or any of the boat conformations **BE** and **BA** (**Figure 4**), or twist forms. Flipping the C2-C3-C4 part of the ring or the aromatic part of the ring (*i.e.* N1-C10-C11-N5) from the parent chair leads to the boat forms **BA** and **BE**, respectively. In the boat form **BA**, the flipping of the C2-C3-C4 part of the ring would move the C2 and C4-equatorial methyl groups into the axial position resulting in 1, 3-diaxial interaction between the C2 and C4 axial methyl groups. The coupling constants

Table I—Spectral data of the N-acylbenzodiazepines **6-9** and the parent amine **5**

Compd	^{1}H NMR ($CDCl_3$, δ, ppm)	^{13}C NMR ($CDCl_3$, δ, ppm)	MS (M^+)
6	1.23 (3H, d, Me at C4), 1.30 (3H, s, Me' at C2), 1.42 (3H, s, Me at C2), 1.62-1.69 (2H, m, H_a and H_e at C3), 3.42 (b, N1-H exchangable with D_2O), 4.84 (1H, m, C4-H), 6.45-8.77 (9H, m, aromatic)	18.4 (Me at C4), 29.4 (Me' at C2), 33.8 (Me at C2), 43.6 (C3), 47.0 (C4), 52.9 (C2), 118.4-131.4 (aromatic) 138.4, 144.4 (ipso), 170.2 (CO)	294
7	1.18 (3H, d, Me at C4), 1.23 (3H, s, Me' at C2), 1.34 (3H, s, Me at C2), 1.48 (1H, unsym dd, Hax at C3), 3.19 (b, N1-H, at C3), 1.62 (1H,dd, H_{eq} exchangable with D_2O), 4.80 (1H, m, C4-H), 6.09 (b, NH of NHCOPh exchangable with D_2O), 6.75 to 7.37 (9H, m, aromatic)	19.6 (Me at C4), 29.0 309 (Me' at C2), 33.4 (Me at C2), 43.8 (C3), 45.7 (C4), 53.0 (C2), 118.9-130.9 (aromatic), 139.0, 145.3 (ipso), 153.5 (CO)	309
8	1.00 (3H, d, Me at C4), 1.40-1.41 (5H, m, Me' at C2 and H_a and H_e at C4), 1.71 (3H, s, Me at C2), 1.82 and 1.90 (6H, 2×S, 2×$COCH_3$, at N1 and N5), 4.88 (1H, m, C4-H), 7.1-7.4 (4H, m, aromatic)	18.6 (Me at C4), 22.5(Me' at C2), 24.1 (Me at C2), 25.4 and 25.6 ($COCH_3$ at N1 and N5), 44.8 (C4), 46.8 (C3), 58.1 (C2), 128.4-129.9 (ipso), 168.3 & 170.2 (CO at N1 and N5)	274
9	*major* 1.08 (d, Me at C4), 1.48 (s, Me' at C2), 1.50 and 1.60 (m, H_{ax} and H_{eq} at C3), 1.78 (s, Me at C2), 4.78 (m, H4). *minor* 1.12 (d, Me at C4), 1.42 (s, Me' at C2), 1.72 (s, Me at C2) 4.74 (m, H4); 7.1-7.5 (m aromatic), 8.1 and 8.2 (2×CHO at N1 and N5)	*major* 18.7 (Me at C4), 23.5 (Me' at C2), 26.3 (Me at C2), 44.3 (C4), 45.9 (C3), 57.8 (C2); 132.5 & 138.3 (ipso) *minor*: 19.7 (Me at C4), 26.7 (Me' at C2), 31.7 (Me at C2), 44.7 (C4), 45.2 (C3), 56.2 (C2), 133.0 & 135.0 (ipso), 127.6-130.3 (aromatic) 161.3, 161.6, 161.9, 163.1 (*major* and *minor*, CHO at N1 and N5)	246
5	1.24 (3H, d, Me at C4), 1.08 (3H, s, Me' at C2), 1.33 (3H, s, Me at C2), 1.56-1.67 (2H, m, Ha & Hb at C3), 3.22 (1H, m, C4-H), 6.62-6.90 (9H, m, aromatic)	23.9 (Me at C4), 25.9 (Me' at C2), 32.8 (Me at C2), 51.2 (C3), 47.8 (C4), 51.7 (C2) 119.7-121.6 (aromatic), 137.6, 140.2 (ipso)	190



exo *endo*

R = Ph, NHPh

Figure 2—Relative orientations of the aryl groups in **b** and **7**

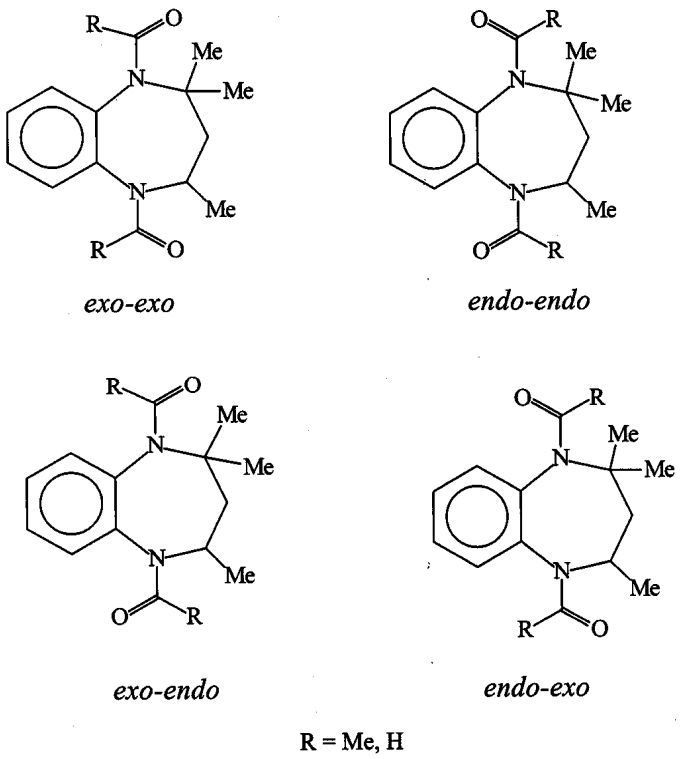


Figure 3—Relative orientations of the aryl groups in **8** and **9**

$^3J_{3a4e}$ and $^3J_{3e4e}$ are expected to be around 2-5 Hz for **BA** on the basis of the dihedral angles derived from Dreiding models [*cis* ($\phi_{3a,4e}$) and *trans* ($\phi_{3e,4e}$) angle of 60°)][7]. But one of the coupling constants of **6** and **7** was larger ($^3J_{3a4a}$ = 11.2, $^3J_{3e4a}$ = 5.9 and $^3J_{3a4a}$ = 11.9, $^3J_{3e4a}$ = 5.2 Hz, respectively, **Table II**). Hence, on the basis of the observed coupling constants and calculated dihedral angles (**Table II**), the possibilities of the boat conformation **BA** as well as the chair conformation **CA** were ruled out.

The coupling constants cannot be used to discriminate the conformations **CE** and **BE** since the C2-C3-C4 parts of them are similar. Analysis of the Dreiding models indicated that in the chair conformation **CE**, one of the methyl groups at C2 would fall into the periphery of the aromatic ring. But in the boat conformation **BE**, both the methyl groups are away from the ring. Hence, the difference in chemical shifts between the methyl carbons and protons at C2 may be expected to be smaller in the boat conformation **BE** compared to those of the parent chair **CE**. In the case of parent tetrahydrobenzodiazepine **5**, the chemical shift differences between the protons and carbons of the methyl groups at C2 were found to be 0.25 and 6.9 ppm, respectively. But the corresponding values were smaller in the compounds **6** and **7** (0.12 and 4.4 ppm and 0.11 and 4.4 ppm, respectively). Hence, it was concluded that the compounds **6** and **7** prefer to adopt boat conformation **BE** with *exo* orientation of the benzoyl and phenylcarbamoyl groups, respectively, at N5 position. The X-ray crystral structure of **7** and the AM1 calculations (**Table III**) also showed the preference for the boat conformation **BE**.

The dihedral angles ϕ_{3a4a} and ϕ_{3e4a} were found to be decreased (**Table II**) for the compounds **6** (163 and 43°) and **7** (167 and 47°) compared to those of the diazepine **5** (182° and 62°, respectively) by 14-18° which is due to the *exo* orientation of acyl groups resulting in $A^{1,3}$-strain[8] between carbonyl group and equatorial methyl group at C4. In order to avoid the $A^{1,3}$-strain, the methyl group may deviate from the equatorial orientation. Analysis using Dreiding models indicated that the deviation would result in a decrease of both ϕ_{trans} and ϕ_{cis} angles. The deviation of methyl group from equatorial position would also move the $H4_{ax}$ proton towards the amide plane. Hence, the deshielding of $H4_{ax}$ proton in **6** and **7** (1.62 and 1.58 ppm, respectively) may be explained on the basis of Paulsen and Todt's model for the anisotropic effect of amides[9].

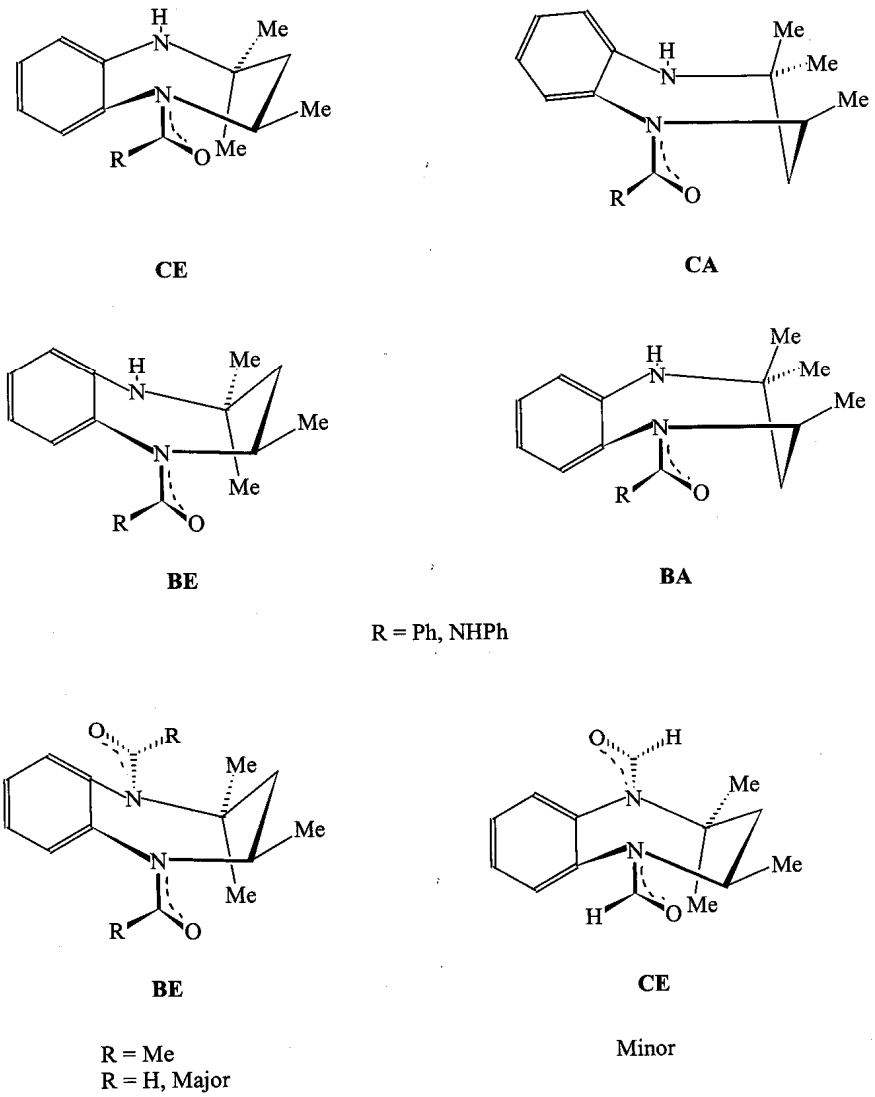


Figure 4

N_1,N_5-Diacyl derivatives of tetrahydro-1,5-benzodiazepines, 8 and 9

The N_1,N_5-diacetyl-2,2,4-trimethyl-1*H*-tetrahydro-1,5-benzodiazepine **8** also showed the isochronous nature of proton (as well as carbon) signals at RT. The deshielding of the C2 carbon by 6.4 ppm and the shielding of C4 carbon by 3.0 ppm indicate that the acetyl group at N_1 position preferentially adopts an *endo* orientation (*syn* to C10) while the acetyl group at N_5 prefers *exo* orientation (*syn* to C4).

The ^{1}H NMR spectrum of **8** recorded at -60°C showed broadening of all the signals indicating the possibility of an equilibrium with a second *ring* conformer at low temperatures. The coupling constants for the compound **8** could not be determined from the irradiation studies. The difference between the chemical shifts of the methyl groups at C2 was smaller ($\Delta\delta$ = 1.6 ppm) compared to that of the parent chair indicating a boat conformation **BE** for the compound **8**. Hence, it was concluded that the N_1,N_5-diacetyltetrahydrobenzodiazepine **8** prefers a boat conformation **BE** with *endo* and *exo* orientations of the acetyl groups at N1 and N5 positions, respectively.

The ^{1}H and ^{13}C NMR spectra of the N_1,N_5-diformyl-2, 2, 4-trimethyl-1*H*-tetrahydro-1, 5-benzodiazepine **9** showed two sets of proton (as well as carbon) signals (3:1) corresponding to *major* and *minor* conformers. The doubling of signals could be due to the existence of two conformers in equilibrium and it was supported by the dynamic ^{1}H NMR spectra[10] recorded up to 94°C where the signals due to the *minor*

Table II—The Vicinal coupling constant data (in Hz) and the corresponding dihedral angles (in degrees) estimated using DAERM of the N-acyltetrahydrobenzodiazepines **6, 7** and **9** and parent amine **5**

Compd	J_{3e4a}	J_{3a4a}	ϕ_{3e4a}	ϕ_{3a4a}
6	5.9	11.2	43	163
7	5.2	11.9	47	167
9 *major*	4.4	12.2	50	170
minor	3.9	11.7	52	172
5	2.0	11.2	62	182

Table III—Calculated relative formation energies (ΔH_f in kcal/mol) of various ring conformations of the N-acyltetrahydrobenzodiazepines (**6** and **7**) by the AM1 and PM3 methods*

Compd		AM1 PM3 Rotamers			
		endo	*exo*	*endo*	*exo*
6	CE	5.13	0.39	3.18	0.00
	CA	7.51	2.11	3.79	0.55
	BE	5.31	0.00	2.91	0.11
	BA	8.87	8.35	6.72	4.64
	B2	5.92	7.76	5.76	4.44
7	CE	4.50	0.73	0.82	0.20
	CA	4.26	2.20	0.88	0.68
	BE	1.85	0.00	0.00	0.04
	BA	5.80	4.18	5.51	4.63
	B2	4.90	2.79	5.13	3.20

isomer started broadening and merged with those of the *major* isomer (**Chart 1**). The energy barrier for the interconversion of these two conformers was estimated using the modified Eyring equation derived by Shanon-Atidi and Bar-Eli[11] from the dynamic ^{1}H NMR spectra. The change in shapes of the signals of the H4 proton was followed. The T_c and $\Delta\delta$ were found to be 367 K and 23Hz, respectively. The calculated energy barriers $\Delta G_{AB}^{\#}$ and $\Delta G_{BA}^{\#}$ were 81.3 and 78.1 kJ mol^{-1}, respectively, with an average energy barrier of 79.7 kJ mol^{-1}.

In both the conformers the C2 carbon was found to be deshielded (*major* δ = 6.1 ppm, *minor* δ = 4.5 ppm) while the C4 carbon was found to be shielded (*major* δ = 3.5 and *minor* δ = 3.1 ppm), indicating that in both the forms the orientation of formyl function was *endo* at N1 position and *exo* at N5 position. Hence, the existence of equilibrium between the two conformers due to N-CO rotation was ruled out. The vicinal coupling constants ($^3J_{3a,4a}$ and $^3J_{3e,4a}$) for the major and minor conformers were found to be 12.2 and 4.4 and 11.7 and 3.9 Hz, respectively, and the corresponding dihedral angles were estimated to be 170° and 50° and 172° and 52°. The observation of almost similar dihedral angles between the protons in both the conformers would be possible only if the N1-C2-C3-C4-N5 part of the ring does not undergo flipping or twisting leading to a change in the orientations of the substituents.

The chemical shift difference between the methyl carbons at C2 in the *major* form was smaller ($\Delta\delta$ = 2.8 ppm) compared to that of the *minor* form ($\Delta\delta$ = 5.0 ppm) suggesting the boat conformation **BE** for the *major* conformer and the chair conformation **CE** for the *minor* conformer. In both the cases, the orientation of N_1 and N_5 formyl groups are *endo* and *exo*, respectively.

X-ray crystallography

The ORTEP[12] diagram of **7 (Figure 5)** shows a boat conformation **BE** for the tetrahydrobenzodiazepine ring, where C3 is the *prow* and C10 and C11 constitute the *stern*. The prow angle (the angle between the planes through N1, C2 , C4, N5 and C2, C3, C4) is 54.2 (2)°. The stern angle (the angle between the planes through N1, C2, C4, N5 and N1, C10, C11, N5) is 49 (1)°. The displacements of N1, C2, C3, C4, N5, C11, C10 from the least-squares plane defined by N1, C2, C4 and N5 are 0.085(1), -0.091 (1), 0.643 (3), 0.091 (1), -0.084 (1), 0.895 (3), and 0.947 (3) Å respectively.

The methyl group at C4 occupies equatorial orientation [the torsion angle C2-C3-C4-C41 = 174.7(2)°]. The torsion angles (C4-N5-C5-O5 = -4.1(3)° and C11-N5-C5-O5 = -174.1(2)° indicate that the phenylcarbamoyl group is in coplanar orientation with reference to C4-N5-C11 plane of the tetrahydrobenzodiazepine ring. In addition, these torsion angles support the *exo* orientation of the phenylcarbamoyl group (*syn* to C4) predicted on the basis of ^{1}H and ^{13}C NMR spectral data. The bond angles around nitrogen N5 (C4-N5-C11 =118.6(2)°, C4-N5-C5 = 118.6 (2)° and C5-N5-C11 = 122.1(2)° indicate a planar configuration of N5. The N5-C5 and C5-N51 bond lengths (1.366(3) Å and 1.367(3) Å respectively) are consistent with the partial double bond character.

The N1, C2, C4 and N5 atoms are in one plane which makes an angle of 44.2(1)° with the plane of the benzene ring. The sum of the bond angles around

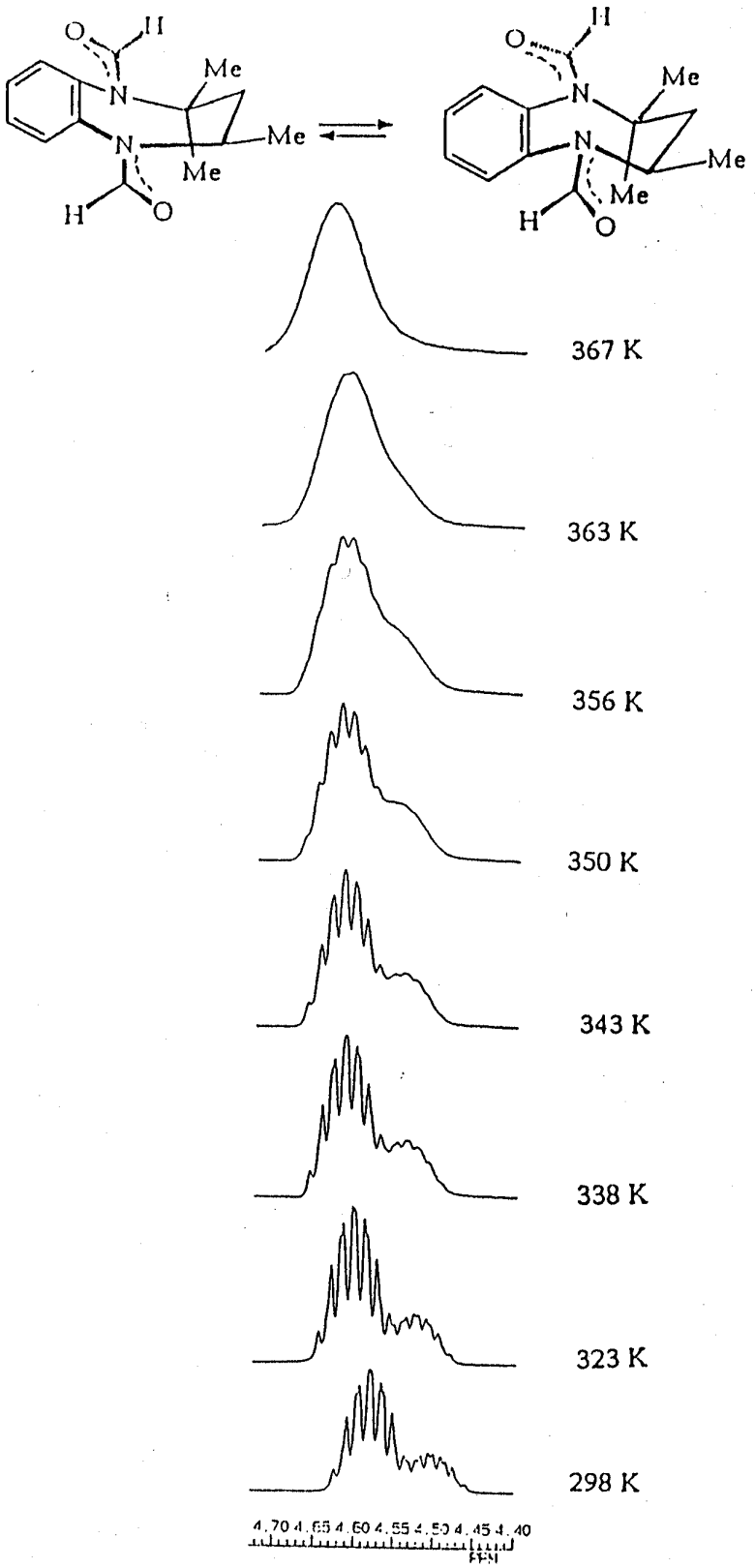


Chart 1 - Dynamic ^{1}H NMR spectra of **9**

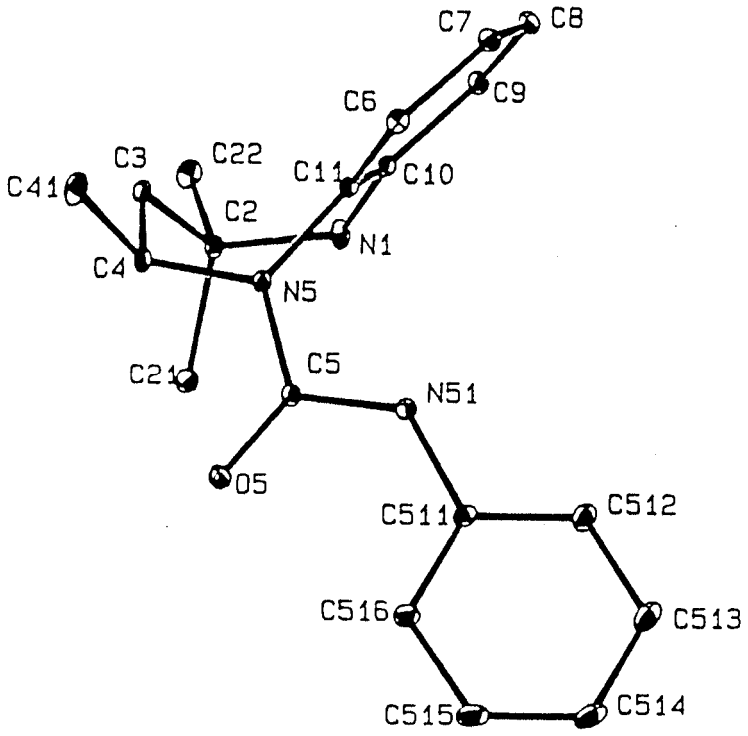


Figure 5 — X-ray structure of **7**

the nitrogen N1 is 349.7(2)°, indicating a pyramidal geometry at N1. It was found that a N-H....O intermolecular hydrogen bond exists between the proton H1 on N1 of the tetrahydrobenzodiazepine ring and atom $O5^{(i)}$ of the phenylcarbamoyl moiety. The hydrogen bond parameters are N1-H1 = 0.853(2) Å, N1...$O5^{(i)}$ = 3.021(3) Å, H1...$O5^{(i)}$ =2.178(2) Å and the angle N1-H1...$O5^{(i)}$ = 169.5(1)° [(i) = -x+1/2, y+1/2, z]. In addition, the estimated angles using DAERM (ϕ_{3a4a}=167° and ϕ_{3e4a} = 47°) agree with the angles found in the crystal structure of **7** (H3a-C3-C4-H4 = 168.1(2)° and H3e-C3-C4-H4 = 53.0(2)°. Hence, it was concluded that the molecule **7** adopts boat conformation **BE** both in solution and solid states.

Semiempirical MO calculations

The heats of formation of various *ring* conformations of the N-acyltetrahydrobenzodiazepines **6-9** obtained by semiempirical molecular orbital calculations using the AM1 and PM3 methods available in MOPAC-6 (ref. 13) were used to derive the relative stability of the conformations. For each of the N-acyltetrahydrobenzodiazepines **6-9** all possible *ring* conformations (**Figure 4**), such as a chair (**CE**), a flipped chair in which the methyl groups occupy axial positions (**CA**), a boat form with the methyl groups occupying equatorial orientations (**BE**), boat conformation with methyl groups occupying axial orientations (**BA**) and twist forms (**B1** and **B2**) were considered. The optimization of these conformations was carried out by varying specific torsion angles (C2-N1-C=O, C4-N5-C=O, N1-C2-C3-C4, C2-C3-C4-N5 *etc*.,), one at a time, within the possible ranges in 10° increments.

Orientation of N-C=O groups

A plot of AM1 energies against C2-N1-C=O, C4-N5-C=O torsion angles indicated that the energy minima occur, in general, at 0±10° and 180±10° while the energy maxima appear at 90±20° and 270±20°. These results show a strong conformational preference for the coplanar orientation of the N-C=O group with respect to the C2-N1-C10/C4-N5-C11 plane over the alternate perpendicular orientation. The calculated N-C bond lengths were found to be around 1.39 Å, which are close to the average sp^2 N-C bond length (1.38 Å) rather than the sp^3 N-C bond length (1.47 Å). The shortening of N-C bond showed the presence of a double bond character for N-C bond in the coplanar orientation. The hybridization of the nitrogen was found to be close to sp^2 when the N-C=O group adopts coplanar orientation, and to sp^3 when it adopts

perpendicular orientation.

Ring conformations

Tables III-V show the relative formation energies obtained for various conformations of the tetrahydrobenzodiazepines **6-9** arrived at by the AM1 and PM3 methods. The calculations indicated that the boat conformation **BE** is the most favourable form in most of the cases in agreement with the NMR results. AM1 optimized structures of **9** are given as representative examples in **Figure 6**. The results of the calculations also indicated an equilibrium between the boat and chair conformations, in which the boat conformers **BE** dominate the equilibrium at RT over the chair conformers **CE**. The contribution from other conformers (**CA**, **B1** and **B2**) to the equilibrium is hardly significant as most of these conformers having the relative energies of more than 5 kcal/mol compared to the global minimum structures.

Table IV—Calculated relative formation energies (ΔH_f in kcal/mol) of various ring conformations of the N-acyltetrahydrobenzodiazepines (**8** and **9**) by the AM1 method*

Compd		AM1 Rotamers			
		endo-endo	*exo-endo*	*endo-exo*	*exo-exo*
8	CE	10.43	4.82	3.67	2.81
	CA	11.21	4.37	6.14	3.65
	BE	6.81	3.18	1.33	0.00
9	CE	5.19	2.80	2.87	2.96
	CA	7.80	5.50	4.02	3.87
	BE	3.69	0.60	1.52	0.00
	BA	7.49	5.32	4.97	4.24
	B1	7.73	5.14	6.65	4.79
	B2	5.55	4.28	4.63	4.26

Table V—Calculated relative formation energies(ΔH_f in kcal/mol) of various ring conformations of the N-acyltetrahydrobenzodiazepines (**8** and **9**) by the PM3 method*

Compd		PM3 Rotamers			
		endo-endo	*exo-endo*	*endo-exo*	*exo-exo*
8	CE	3.34	3.25	1.82	2.23
	CA	5.37	3.06	4.18	2.41
	BE	3.14	0.67	1.24	0.00
	BA	8.84	8.83	7.21	6.73
	B1	12.22	11.47	11.51	10.59
	B2	10.05	8.97	10.03	10.00
9	CE	2.41	0.89	2.07	3.93
	CA	4.10	4.36	1.30	3.62
	BE	2.35	0.00	2.45	2.55
	BA	5.41	6.05	4.66	6.07
	B1	8.93	6.56	9.85	8.15
	B2	5.32	6.33	5.21	6.98

*The *ring* conformation with relative energies of more than 5 kcal/mol for all its rotamers have not been included.

Conclusion

The N_1,N_5-diformyltetrahydrobenzodiazepine **9** was found to exist as a mixture of two conformers with unequal populations and the conformational equilibrium was found to exist between the boat **BE** and chair **CE** conformations in which the two N-CO groups occupy *endo-exo* orientation. The average energy barrier for the interconversion between the *major* and *minor* conformers of **9** was found to be 79.7 kJ/mol on the basis of the dynamic ^{1}H NMR spectral studies. The N_5-benzoyl- and N_5-phenylcarbamoyl-tetrahydrobenzodiazepines **6** and **7** prefer boat conformations **BE** with *exo* orientation of the acyl groups at N5. The X-ray crystal structure of **7** also showed the boat conformation **BE**. The diacetyl derivative **8** prefers a boat conformation **BE** in which the N-acetyl group at N1 adopts the *endo* orientation while that of at N5 *exo* orientation. The AM1 and PM3 calculations supported the conformational preferences derived from the NMR spectra.

Experimental Section

All the melting points were determined using an electrically heated block with a calibrated thermometer and are uncorrected. Infrared spectra were recorded using a Shimadzu IR-435 spectrophotometer using KBr pellets. The ^{1}H and ^{13}C NMR, HETCOR, COSY spectra and Dynamic ^{1}H NMR spectra were recorded in $CDCl_3$/DMSO-d_6 solutions with TMS as an internal standard using Bruker AMX-400, Bruker WH-270 and JEOL-GSX 400 spectrometers. Mass spectra were recorded on a Jeol JMS-D 300 spectrometer operating at 70 eV. The parent benzodiazepine 2,3-dihydro-2,2,4-trimethyl-1*H*-1,5-benzodiazepine **4**, was prepared by following the reported procedure[4].

Computational details: The AM1 and PM3 methods available in the MOPAC 6.1 PC version were used to perform the molecular orbital calculations on Pentium personal computers. The geometry of each of the conformations was optimized by using the key

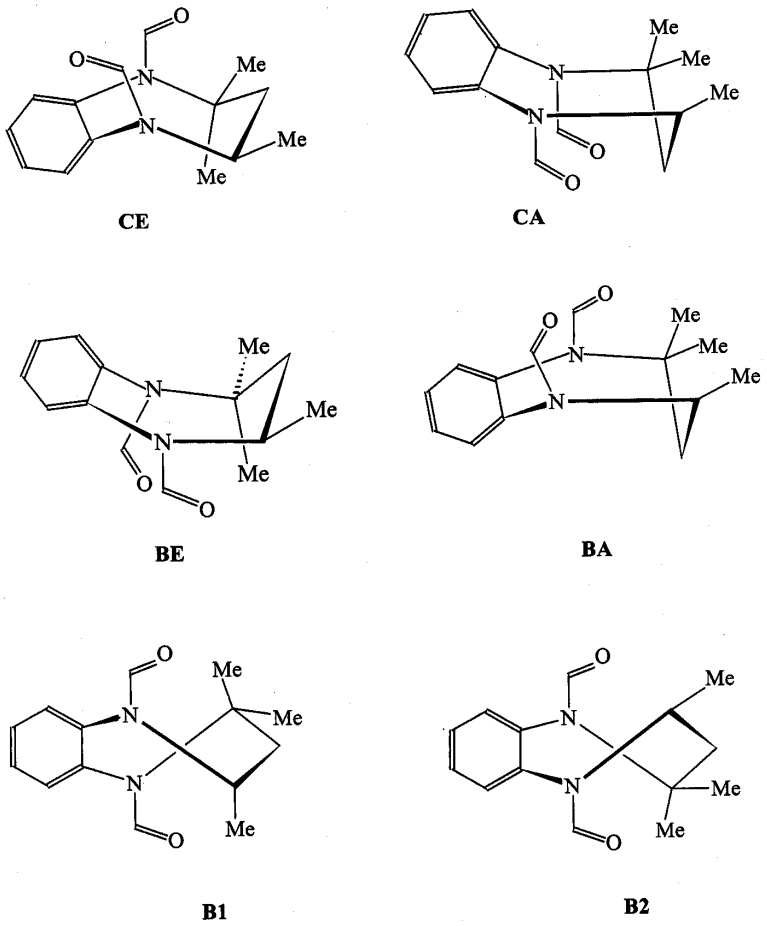


Figure 6—AM1 optimized structures of **9**

words AM1/PM3, PRECISE and EF. The gradients were maintained at 0.01 by using GNORM.

2,3-Dihydro-2,2,4-Trimethyl-1*H*-tetrahydro-1,5-benzodiazepine, **4**. To an ice-cold solution of 1,2-diaminobenzene (10.8 g, 100 mmoles) in glacial acetic acid (30 mL), acetone (16 mL, 218 mmoles) was added while shaking and kept at 25°C for 16 h. Crushed ice was added to the reaction mixture and neutralized with ammonia. The precipitated solid was separated, washed thoroughly with water and dried. The solid was dissolved in ethanol, allowed to reflux with charcoal and filtered. Purification by recrystallisation from ethanol twice after treatment with charcoal afforded yellow crystals of **4**, Yield 9.9 g (53%), m.p. 123-24°C [lit[4]. m.p. 125-28°C].

2, 2, 4-Trimethyl-1*H*-tetrahydro-1, 5-benzodiazepine, **5**. Benzodiazepine **4** (1.71 g, 9.10 mmoles) was dissolved in methanol (75 mL) and stirred with a magnetic stirrer. Sodium borohydride[14] (0.31 g, 8.38 mmoles) was added in three portions over a period of 1 h while maintaining the temperature at 45°C. After the addition was over, the solution was maintained at 45°C for another 2 h. Methanol was evaporated partially and the reaction mass poured into water. The mixture was extracted with chloroform several times. The organic extractions were combined, dried with anhydrous Na_2SO_4 and evaporated. The yellow oil obtained was purified by recrystallization from aqueous ethanol to afford colorless crystals of **5** (yield 1.48 g, 86%). m.p. 56-7°C. Anal. Calcd. for $C_{12}H_{18}N_2$: C, 75.78; H, 9.47; N, 14.73. Found: C, 75.51; H, 9.22; N, 14.65%.

5-Benzoyl-2, 2, 4-trimethyl-1*H*-tetrahydro-1, 5-benzodiazepine, **6**. To an ice-cold solution of tetrahydrobenzodiazepine **5** (0.95 g, 5 mmoles) in anhydrous benzene (25 mL), triethylamine (2 mL, 14.4 mmoles) and benzoyl chloride (2.5 mL, 18 mmoles) were added. The reaction mixture was stirred at RT for 1 h. The precipitated ammonium salt was filtered off and the filtrate was washed with water (4×10 mL).

The benzene solution was dried over anhydrous Na_2SO_4 and passed through a short column of silica. A white solid was obtained upon concentration of the benzene solution and was purified by recrystallization from benzene:pet.ether (60-80°C) mixture (10:1) yielded colorless crystals of **6**, yield 0.89 g (60.5%), m.p. 128-30°C. Anal. Calcd. $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.38; H, 7.64; N, 9.31%.

5-Phenylcarbamoyl-2, 2, 4-trimethyl-1*H*-tetrahydro-1, 5-benzodiazepine, **7**. To a solution of tetrahydrobenzodiazepine **5** (0.95 g, 5 mmoles) in anhydrous benzene (25 mL), a catalytic amount of triethylamine and phenyl isocyanate (0.6 mL, 5 mmoles) were added. The reaction mixture was stirred at RT for 6 h. The benzene solution was washed with water (4×20 mL) and dried over anhydrous Na_2SO_4. The solution was passed through a short column of silica and concentrated. The resulting solid was purified by recrystallization from benzene to afford colorless crystals of **7**, yield 1.41g (91.3%), m.p. 167-68°C. Anal. Calcd. for $C_{19}H_{23}N_3O$: C, 73.75; H, 7.49; N,13.58. Found: C, 73.47; H, 7.62; N, 13.32%.

1, 5-Diacetyl-2, 2, 4-trimethyl-1*H*-tetrahydro-1, 5-benzodiazepine, **8**. To an ice-cold solution of tetrahydrobenzodiazepine **5** (0.95 g, 5 mmoles) in anhydrous benzene (25 mL), triethylamine (2 mL, 15 mmoles) and acetyl chloride (1.28 g, 15 mmoles) were added. The reaction mixture was stirred at RT for 2 h. The precipitated ammonium salt was filtered off and the filtrate was washed with water (4×20 mL). The benzene solution was dried over anhydrous Na_2SO_4 and concentrated after passing through a short column of silica. The resulting solid was purified by recrystallization from benzene to yield pale yellowish brown crystals of **8**, yield 1.06 g (77.4%), m.p. 199-200°C. Anal. Calcd. $C_{16}H_{22}N_2O_2$: C, 70.04; H, 8.09; N, 10.21. Found: C, 70.26; H, 8.41; 10.02%.

1,5-Diformyl-2,2,4-trimethyl-1*H*-tetrahydro-1,5-benzodiazepine, **9**. To ice-cold acetic anhydride (10 mL), 85% formic acid (5 mL) was added slowly while stirring and the resulting solution was heated to 60°C. Immediately, the temperature of the solution rose steeply to about 90-100°C on its own and the solution was externally cooled and then maintained at 50-60°C for 1.5 h. The resulting acetic-formic anhydride was cooled to 5°C and added slowly to a cold solution tetrahydrobenzodiazepine **5** (0.95, 5 mmoles) in anhydrous benzene (30 mL). The reaction mixture was stirred at RT for 5 h and the solution was poured into water (250 mL). The benzene layer was separated and the aqueous layer was extracted with chloroform (4×25 mL). The organic extracts were combined, dried (anhydrous Na_2SO_4), passed through a short column of silica and concentrated. Purification by crystallization from benzene:pet. ether (60-80°C) mixture (1:1) yielded colorless crystals of **9**, Yield 1.12 g (91.1%), m.p. 111-13°C. Anal. Calcd. $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.51; H, 7.15; N, 11.42%.

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