

Conformations of Monoacyl and 1,3-Diacylbenzimidazoline-2-thiones and Dihydrobenzimidazoles

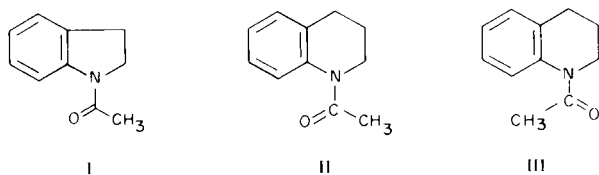
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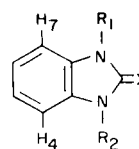
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The *endo* conformation of monoacyl and 1,3-diacylbenzimidazoline-2-thiones is predominant at ambient temperatures. Nmr temperature-dependent studies suggest that this is also true over a wide range of temperatures. In agreement with previous results (6) the *exo-endo* conformation in 1,3-diacyl-1,2-dihydrobenzimidazoles is generally the predominant one.

Assignment of conformations of rotamers in amides has been reported by Monro and Swell (1) using nmr and confirmed by Jones, Katritzky and Shapiro (2) through dipole measurements. Both teams concluded that, at ambient temperature, 1-acetylidoline exists almost entirely in the *endo* conformation I, whereas 1-acetyl-1,2,3,4-tetrahydroquinoline consists of about equal quantities of the *endo* II and the *exo* III conformers.



The assignment of conformations of 1,3-diacyl and 1,3-diaroylbenzimidazolones IV ($X = O$) has recently been reported using nmr (3). It was found that an *endo* conformation is predominant when either R_1 or R_2 or both



IV

were acetyl, propionyl or isobutryl groups. The resulting orientation of the carbonyl groups was reflected in a considerable deshielding of H_4 and/or H_7 amounting to about 1.3 ppm compared with the chemical shift of the same proton(s) of the parent compound ($R_1 = R_2 = H$). The predominance of the *endo* conformation was attributed to the dipole-dipole interaction between the acyl carbonyl and the carbonyl at position 2.

The purpose of the present work was to investigate the conformations of analogous amides (IV) in which X is sulfur or H_2 . It is proposed that the reduced dipole-dipole interaction in the case of the thiocarbonyl group, or the

Table I

Nmr Data for Compounds IV: Parent and Acylated Derivatives

No.	R_1	R_2	Chemical shift (δ) for H_4 and/or H_7	Δ (a)	
				$X = S$	$X = O^3$
IVa	H	H	7.22	0	0
IVb	H	CHO	7.23	0.01	- (b)
IVc	H	CH_3CO	8.08	0.86	-
IVd	H	C_2H_5CO	8.08	0.86	-
IVe	H	$(CH_3)_2CHCO$	7.93	0.71	1.3 (c)
IVf	CH_3CO	CH_3CO	8.02	0.80	1.25
IVg	PhCO	PhCO	7.93	0.71	0.90
IVh	$O-NO_2C_6H_4CO$	$O-NO_2C_6H_4CO$	8.40	1.18	1.45
IVi	$O-CH_3OC_6H_4CO$	$O-CH_3OC_6H_4CO$	7.65	0.43	1.26

(a) Δ : Difference in chemical shift between H_4 and/or H_7 of the substituted compound and that of the unsubstituted one (Compound IVa). (b) No monoacylbenzimidazolones were studied. (c) For $R_1 = R_2 (CH_3)_2CHCO$.

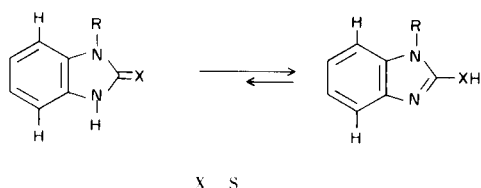
absence of such interaction in the case of the methylene group would affect both the value of deshielding of protons 4 and 7 and the degree of predominance of some conformers.

Results and Discussion.

Reference is made to Table I in the following discussion:

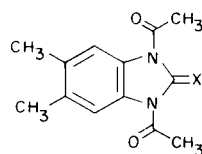
Except for IVb, the *endo* conformation is predominant at the probe temperature (35°) as shown by the value of Δ corresponding to a deshielding of one or two protons (mono or disubstituted). The results in the last column show, however, that the value of Δ is generally smaller in the present series of compounds than in the analogous benzimidazolones. This is assumed to be the result of a conformation in which the acyl carbonyl is slightly twisted, out of the planar *endo* conformation, to relieve the steric interaction between the alkyl or aryl substituent and the thiocarbonyl group. The twisting is possible because of the smaller dipole-dipole interaction offered by the thiocarbonyl group. As a result of such twisting, the maximum deshielding effect of the acyl carbonyl group is not observed.

In the monosubstituted compounds IVb to IVe, the following tautomerism can take place, which is consistent with the small tendency of sulfur to form double bonds (4).



This leads to a reduced dipole-dipole interaction between the thiocarbonyl and the acyl carbonyl group. The conformation adopted by any particular compound would be decided by the steric requirement of the acyl substituent. The *exo* conformation is predominant in IVb ($\Delta \sim 0$) due to the small interaction between the formyl hydrogen and H₇. In the others, the *endo* conformation is the predominant one because it will relieve the steric interaction between H₇ and the large alkyl group. This phenomenon is similar to that observed in *N*-acylindolines (1).

When both R₁ and R₂ are acyl groups (IVf), there is no possibility of tautomerism and the dipole-dipole interaction between the thiocarbonyl and the acyl carbonyl is severe, forcing the molecule to adopt the *di-endo* conformation.



Va, X = O
Vb, X = S

The lower value of deshielding in compound IVg might be attributed to cross conjugation between the acyl phenyl and its carbonyl group. This reduces the interaction of the nitrogen lone pair and the carbonyl group, and would cause some rotation around the N-CO bond of the amide.

An *ortho* substituent on the acyl phenyl was thought to interact sterically and prevent the above mentioned cross conjugation and thus restore the high value of deshielding. However, the effect was found to depend totally on the electronic nature of the substituent. An *ortho* electron-withdrawing substituent (-NO₂, compound IVh), by its electronic interaction with the acyl phenyl,

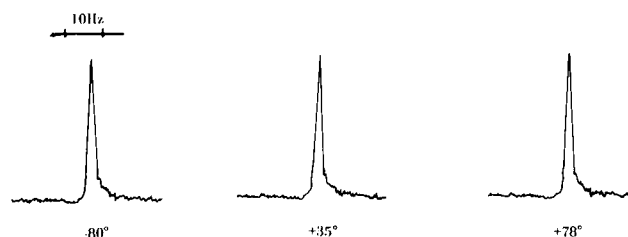


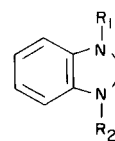
Fig. 1. The nmr spectra of aromatic protons in Va at various temperatures.

will prevent the above cross conjugation leading to a high value of deshielding. On the other hand, an *ortho* electron-donating substituent (-OMe, compound IVi) will enhance the above mentioned cross conjugation leading to a very low value of Δ .

The nmr spectra of compounds Va and Vb (5) were recorded over a wide range of temperature (-100 to $+80^\circ$) in an attempt to detect equilibria between different conformers.

Table II

The Chemical Shifts of the Aromatic Protons in Some 2,3-Dihydrobenzimidazole Derivatives



VI

No.	R ₁	R ₂	δ (ppm)	No. of Protons
VIa	CH ₃ CO	CH ₃ CO	7.18	3
			8.18	1
VIb	C ₂ H ₅ CO	C ₂ H ₅ CO	7.15	3
			8.18	1
VIc	H	PhCO	7.84	9

This study shows that, in both the benzimidazolone and the thio analogue, the *endo* conformer is the favored one, since no other signals corresponding to the *exo* or *endo-exo* conformers were detected (Fig. 1).

Table II shows the data for acyl derivatives of dihydrobenzimidazole. The down field aromatic signal (compounds VIa and VIb) integrates for one proton thus indicating the predominance of the *endo-exo* conformation at 35°. The absence of dipole-dipole interaction in these compounds made it possible for one of the groups to assume the *exo* conformation. No deshielding was observed for compound VIc with a monobenzoyl substituent indicating the predominance of the *exo* conformation. This is in agreement with the explanation offered above for the behaviour of a benzoyl substituent.

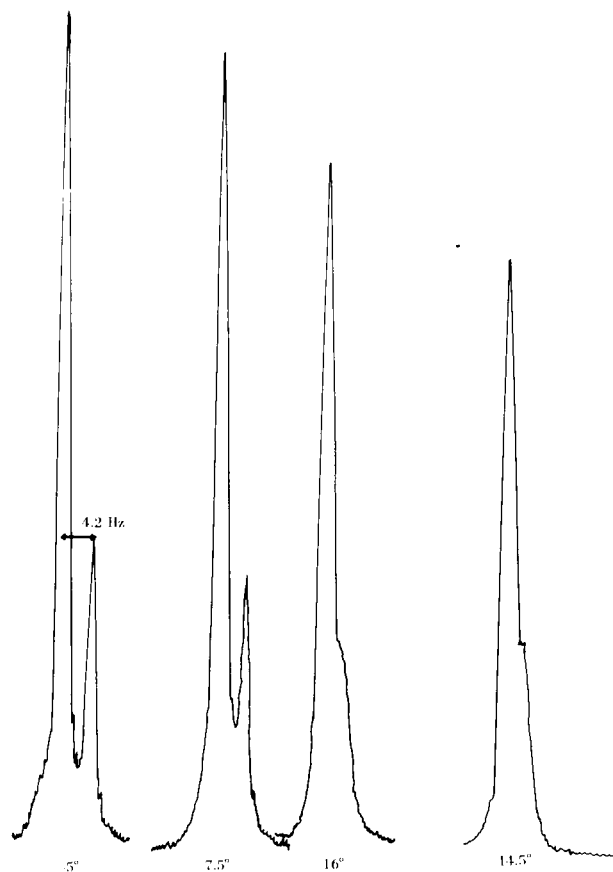


Fig. 2. The nmr temperature-dependent spectra of the methylene protons in VIa.

The study of the nmr spectra of VIa and VIb at different temperatures show that below 14.5°, (the coalescence temperature), the methylene protons appear as 2 signals (75:25) (Fig. 2). The low field signal (75%) might be due to the *endo-exo* or both the *endo-exo* and the *di-exo* conformations. The methylene protons will be under the same influence of the carbonyl group in both of them. The high field signal (25%) might be due to the *di-endo* conformation. It is believed, however, that the *exo-endo* conformation, in which the dipole-dipole interaction is minimal, accounts for most of the low field signal.

Calculation of ΔG for both VIa and VIb gave a value of about 15.5 Kcal/mole which is in agreement with the results obtained by Garner, Meth-Cohn and Suschitzky following the methyl signal of the acetyl groups of VIa (6).

EXPERIMENTAL

Compounds IVb to IVi and Va and Vb were prepared by the acylation of the corresponding parent compound using the acid chloride or anhydride in pyridine.

Compounds VIa through VIc were prepared by the catalytic hydrogenation (palladium/barium sulfate) of benzimidazole in the presence of the acid anhydride using an H. C. Brown hydrogenator.

The nmr spectra were recorded on a Varian NV-14 spectrometer.

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