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CONFORMATIONAL STUDIES OF 5-ACETYL-10-CYANO-10,11-DIHYDRO-5H-DIBENZ[b,f]AZEPINE†

C. R. ELLEFSON,* L. SWENTON, R. H. BIBLE, JR. and P. M. GREEN
Department of Chemical Research & Department of Analytical Resources and Methods, Searle Laboratories, Division of G. D. Searle & Co., P.O. Box 5110, Chicago, IL 60680, U.S.A.

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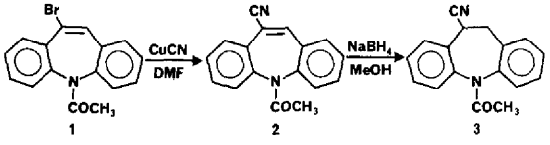
Abstract—5 - Acetyl - 10 - cyano - 10,11 - dihydro - 5H - dibenz[b,f]azepine, **3**, has been synthesized and its conformations in solution have been studied by variable temperature NMR. At −55° in $CDCl_3$ solution, **3** shows the signals due to four different conformational isomers. At 55°, signals due to only two conformers can be seen. The ABX pattern of each of the four conformers was analyzed using double resonance experiments and the LAOCN3 computer program. The relative abundances of the isomers in the mixtures were estimated by computer additions of different proportions of the spectra calculated for the separate isomers. These spectral observations are discussed in detail and interpreted in terms of slow inversion of the seven-membered ring by torsion of the 4a–5–5a bonds and restricted twisting of the C-10–C-11 ethylene bridge.

Although compounds having the dibenz[b,f]azepine ring system have been studied extensively in medicinal chemistry, only a few investigations of the conformations of this ring system have been reported. The conformational studies that have been reported were primarily concerned with the 5-alkyl or 5-acyl derivatives of the parent ring system.[1–6] We now report our observations on the conformational phenomena of the 10-substituted 5 - acetyl - 10,11 - dihydro - 5H - dibenz[b,f]azepine, **3**.

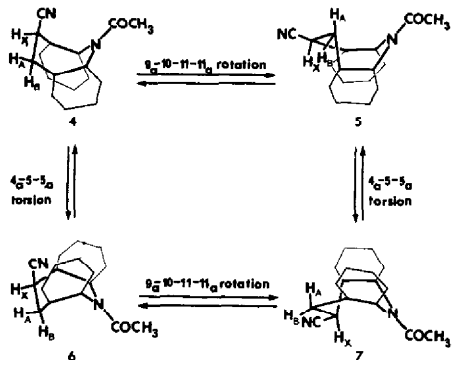
5 - Acetyl - 10 - cyano - 10,11 - dihydro - 5H - dibenz[b,f]azepine was prepared as outlined below. Treatment of 5 - acetyl - 10 - bromo - 5H - dibenz[b,f]azepine,[5] **1**, with cuprous cyanide in refluxing dimethylformamide afforded 5 - acetyl - 10 - cyano - 5H - dibenz[b,f]azepine, **2**. This α,β-unsaturated nitrile, **2**, was reduced with sodium borohydride in methanol, yielding the saturated nitrile, 5 - acetyl - 10 - cyano - 10,11 - dihydro - 5H - dibenz[b,f]azepine, **3**.



1 2 3

The conformational phenomena of **3** were studied by NMR in $CDCl_3$, pyridine-d_5 and DMSO-d_6 solutions at temperatures from −55° to +143°. At −55° in $CDCl_3$, signals due to four conformational isomers were identified. As the temperature was increased, coalescence of some of the signals occurred at about 20°. At 55°, signals due to only two conformational isomers were observed. These signals coalesced above 85°.

Our interpretation of the conformational phenomena as evidenced by the NMR data is depicted below. The two conformers observed at +55° are 7-membered ring inversion conformers. For these conformers the cyano group is either *syn* to the amide nitrogen bridge (as in **4** and **5**) or *anti* (as in **6** and **7**). At −55° two conformations of the C-10–C-11 ethylene bridge are observed for each of the ring inversion conformers. The cyano group has a pseudo-axial orientation in one of the ethylene bridge conformations (**4** and **6**) and a pseudo-equatorial orientation in the other (**5** and **7**).



For the ring system of **3**, three restricted conformational processes should be considered: (1) rotation about the N–C(=O) amide bond; (2) twisting of the C-10–C-11 ethylene bridge; (3) ring inversion by torsion about the 4a–5–5a bonds. Our observation of four conformers at −55° indicates that at least two of the above processes must be slow at this temperature. For process (3) to be facile, the plane of the amide N–CO–Me group should be perpendicular to the plane of the 4a–5–5a bonds. In the preferred planar conformation of the amide acetyl group, the steric interaction between the acetyl Me group and aromatic protons *ortho* to the nitrogen hinder rapid ring inversion. Thus, slow rotation about the N–C(=O) amide bond, process (1), would preclude a rapid ring inversion, process (3). Indeed, in similar compounds with an N-alkyl substituent (and sp^3 configuration of the N), the barriers to ring inversion by torsion about the 4a–5–5a bonds are very low and ring inversion conformers have not been observed by us or others[4] even at −100°.[2] The barriers to twisting about the C-10–C-11 bond, i.e. process (2), are less severe and

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result from the normal rotational barriers and transannular proximity of the C-10 substituent and the amide group.

We believe that the four conformers observed at −55° are due to processes (2) and (3). Amide rotation may also be slow. However, it is likely that the amide rotational isomers are not observed in 100 MHz ^{1}H NMR spectra due to small differences in the chemical shifts of the acetyl methyl group of the rotamers. Observation of the chemical shifts of the aromatic protons *ortho* to the amide N was not possible due to the complexity of the aromatic proton signals.

Analysis of NMR spectra. NMR spectra were determined at temperatures from −55° to +55° in $CDCl_3$, from 40° to 100° in pyridine-d_5, and from 40° to 143° in DMSO-d_6. At +55° in $CDCl_3$, the coupling pattern of the C-10–C-11 ethylene bridge protons was confirmed by double resonance experiments. An ABX pattern was observed for the C-10 and C-11 proton signals of each conformer. (In the discussion below, H_X refers to the C-10 proton, H_A and H_B to the C-11 protons *cis* and *trans* respectively to the C-10 cyano substituent.) An iterative LAOCN3 computer program[7] was used to calculate the chemical shifts and coupling constants for each ABX pattern at +55° and −40°.

Figures 1 and 2 show the calculated and actual spectra of the C-10, C-11, and Me protons at −40° and +55° in $CDCl_3$. Table 1 lists the chemical shifts and coupling constants of the C-10, C-11 and acetyl Me protons in $CDCl_3$ at −40° and +55°, in pyridine at +51° and in DMSO at +55°.

At −40° in $CDCl_3$, only three Me signals are observed. However, the presence of four conformers is indicated by the four ABX patterns due to the C-10 and C-11 protons (Fig. 1 and Table 1). An estimate of the abundances of the conformers was made by matching the observed spectra with computer calculated spectra corresponding to various proportions of the conformers. The relative ratios of conformers **4**:**5**:**6**:**7** was estimated to be 0.35:0.47:1.00:0.80.

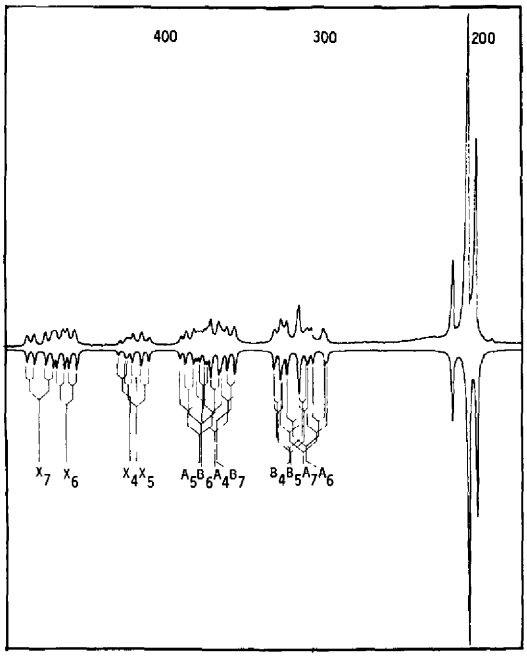


Fig. 1. Calculated and experimental 100 MHz NMR spectra of the C-10, C-11 and Me protons of **3** at −40° in $CDCl_3$.

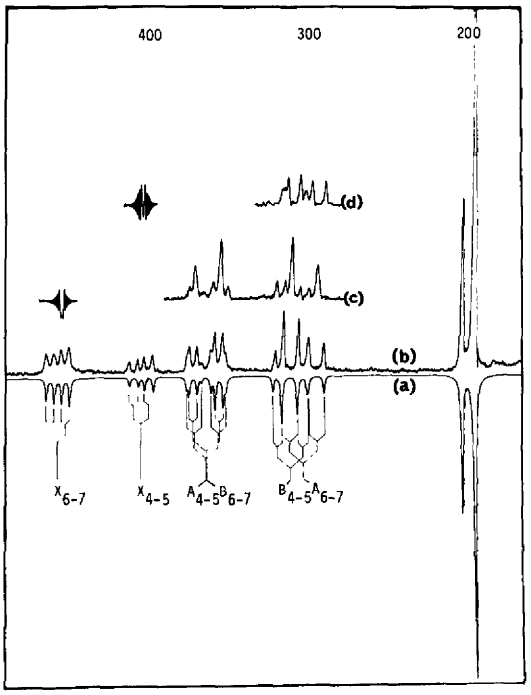


Fig. 2. Calculated (a) and experimental (b) 100 MHz NMR spectra of the C-10, C-11 and Me protons of **3** at +55° in $CDCl_3$. Tracings (c) and (d) show the results of irradiating the H_X protons of conformers **6**–**7** and **4**–**5** respectively.

The signals of the four conformers coalesce to two sets of signals at about 20° (Fig. 3). Because of the overlap of two of the Me signals and the complexity of the C-10 and C-11 proton signals, only approximate coalescence temperatures were determined. Coalescence of the H_X proton signals occurred at about 10° for **6** and **7** and at about 20° for **4** and **5**. The assignment of the proton signals at −40° to pairs of twist conformers about the C-10–C-11 ethylene bridge was based on the magnitudes of J_{AX}. In each of the pairs whose signals coalesce at 20°, namely **4** and **5**, **6** and **7**, one conformer has a large J_{AX}, the other a smaller J_{AX}. Such changes in vicinal coupling constants are best explained by changes in dihedral H–C–C–H angles caused by twisting of the ethylene bridge, with one conformer in each pair having a *pseudo* equatorial cyano conformation and a *pseudo* axial–axial coupling of H_A and H_X. The conformers **5** and **7** with large J_{AX} (10.0, 11.6 Hz), were assigned a *pseudo* equatorial cyano conformation in which the H_A–C–C–H_X dihedral angle is approximately 180°. Conformers **4** and **6** were assigned the *pseudo* axial cyano conformation (J_{AX} = 8.4, 7.4 Hz).

At −40°, assignments of the Me signals were based on their relative intensities compared to the H_X proton signals. Because of the overlap of two of the signals, Me peak assignments of conformers **6** and **7** may be reversed.

The two conformers observed at +55° must be due either to slow amide rotation or slow ring inversion by torsion about the 4a–5–5a bonds. The main difference between these conformers is in the chemical shifts of the C-10 and C-11 protons:

	ν_{4-5}	ν_{6-7}	$\Delta\nu$
H_A	363	303	−60
H_B	311	362	+51
H_X	403	455	+52

Table 1. NMR parameters of C-10 and C-11 protons

Temp. °C	Solvent	Conformer	Relative Ratio	ν_{CH_3}	ν_A	ν_B	ν_X	J_{AB}	J_{AX}	J_{BX}
-40[a]	$CDCl_3$	4	0.34	219[c]	367	323	421	-14.9	8.4	5.5
		5	0.47	209	377	323	416	-15.0	10.0	4.3
		6	1.00	204	313	376	463	-15.4	7.4	4.7
		7	0.80	209	315	366	479	-16.6	11.6	4.4
+55[a]	$CDCl_3$	4-5	0.45	202	363	311	403	-15.0	9.3	5.5
		6-7	1.00	194	303	362	456	-16.0	9.5	4.9
+51[d]	pyridine-d_5[e]	4-5	0.51	218	374	321	454	-15.7	7.7	5.5
		6-7	1.00	206	310	373	508	-16.0	8.8	4.5
+50[d]	DMSO-d_6[e]	4-5	0.89	192	354	-f	459	-15.5	7.0	6.0
		6-7	1.00	188	301	362	499	-15.9	7.7	5.0

a. Chemical shifts and coupling constants were calculated using the iterative LAOCN3 computer program[7].

b. Reference compound - internal TMS.

c. Chemical shifts and coupling constants are given in Hz.

d. Chemical shifts and coupling constants were estimated directly from spectra. Relative populations were obtained from heights of methyl signals.

e. Reference compound - internal HMDS.

f. Signal obscured by HDO peak.

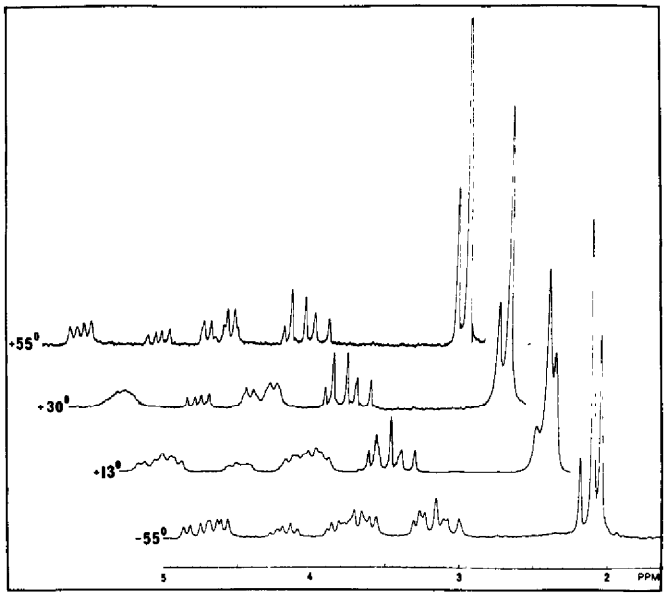


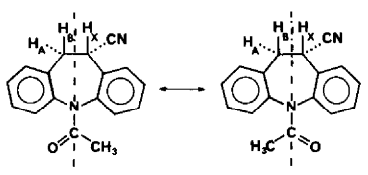
Fig. 3. 100 MHz NMR spectra of **3** in $CDCl_3$ soln at −55°, +13°, +30° and +55°.

If the conformers seen at +55° are due to slow amide rotation, the failure to observe ring inversion conformers could be explained either by assuming that only one ring conformer predominates, or that the chemical shifts of the C-10, C-11 and amide methyl protons of both ring conformers are very similar.

If only one ring conformer exists, it would be expected that on amide rotation the changes in the chemical shifts of H_B and H_X would be similar in magnitude but opposite in sign.

The effect of amide rotation on the positions of protons and amide carbonyl relative to plane bisecting 7-membered ring is as follows:

H_A: same side ⟶ opposite sides
H_B: same side ⟶ opposite sides
H_X: opposite sides ⟶ same side.



If the C-10 and C-11 protons in both ring conformations have the same chemical shifts, it would be expected that

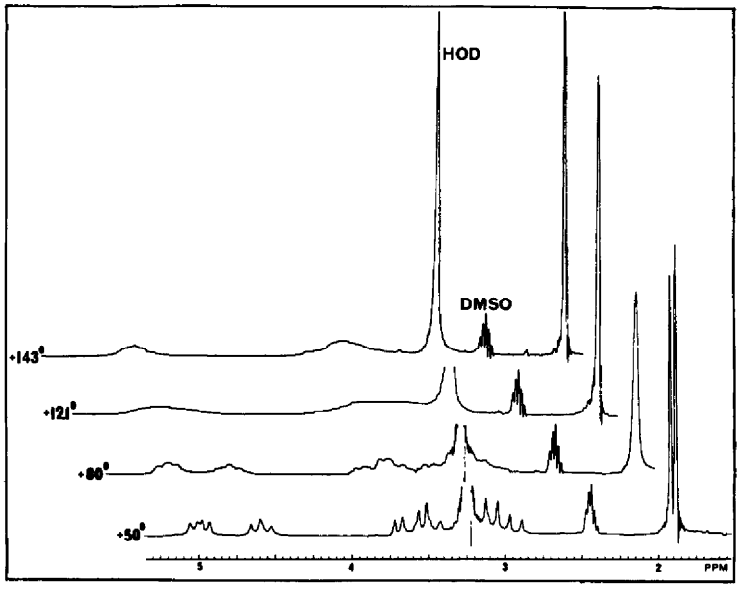


Fig. 4. 100 MHz NMR spectra of 3 in DMSO soln at 50°, 80°, 121° and 143°.

on amide rotation the changes in the chemical shifts of H_A and H_B would be similar. In fact, in going from conformer **4–5** to **6–7**, the changes in the chemical shifts of H_B and H_X are similar in magnitude and have the same sign, while the changes in the chemical shifts of H_A and H_B are similar in magnitude but opposite in sign. Thus the observed changes in chemical shifts are not consistent with the expected changes for amide rotation.

If the conformers at +55° are due to 7-membered ring inversion, the changes in the positions of H_A, H_B and H_X relative to the N bridge in going from **4–5** to **6–7** are:

H_A: *syn* → *anti*
H_B: *anti* → *syn*
H_X: *anti* → *syn*.

Thus, for ring inversion, the changes in chemical shifts would be expected to be similar for H_B and H_X, and of opposite sign for H_A. That is what is actually observed.

For the process involving ring inversion by torsion about the 4a–5–5a bonds, coalescence temperatures of the Me signals were determined in pyridine and DMSO (Fig. 4). The Me signals coalesced at 90° in pyridine and at 83° in DMSO. In DMSO, the signals of the two ABX patterns of the C-10–C-11 bridge protons merged at about 120° and were still broad at 143°.

EXPERIMENTAL

The NMR spectra were determined using either a Varian HA-100-15 or a Varian XL-100-15 instrument, IR spectra were determined using a Beckman IR-12, and UV spectra were determined using a Beckman DK2. M.ps were determined in open capillary tubes in a Melt-Temp apparatus and are uncorrected.

5 - *Acetyl* - 10 - *cyano* - 5H - *dibenz*[*b,f*]*apezine* (**2**). A mixture of 6.3 g (0.020 mole) 5 - acetyl - 10 - bromo - 5H - dibenz[b,f]apezine[5] and 3.6 g (0.040 mole) cuprous cyanide in 30 ml DMF was stirred at reflux for 2 hr. The mixture was partially cooled and then poured into 120 ml concd NH_4OH. The resultant mixture was extracted with CH_2Cl_2 and the extracts were washed with 3 × 50 ml of 2 N HCl and 3 × 50 ml water and dried over $MgSO_4$. Removal of the solvent left an oil that was crystallized from benzene–hexane, yielding 4.1 g (79%) off-white crystals, m.p. 146.5–147.5°; IR ν ($CHCl_3$) 2225 and 1684 cm^{-1}; NMR δ ($CDCl_3$) 1.9 (3H, s, CH_3), 7.3–7.9 ppm (9H, m, aromatic and vinylic); UV λ_{max}^{MeOH} (ϵ) 227.5 (20,300), 243 (12,500), 297 nm (13,500). (Found: C, 78.15; H, 4.55; N, 10.72. Calc. for $C_{17}H_{12}N_2O$: C, 78.44; H, 4.65; N, 10.76%).

5 - *Acetyl* - 10 - *cyano* - 10,11 - *dihydro* - 5H - *dibenz*[*b,f*]*azepine* (**3**). $NaBH_4$ (15.2 g, 0.040 mole) was added in portions over 15 min to a soln of 10.4 g (0.40 mole) **5** - acetyl - 10 - cyano - 5H - dibenz[b,f]azepine in 400 ml MeOH.† The solution became warm and was stirred until it returned to room temp. The solvent was removed under reduced pressure and the residual solid was washed with several portions of water and dried, yielding 9.0 g of white solid that was recrystallized from THF/hexane yielding 7.6 g (73%) of pure white crystals, m.p. 148–149°; IR ν ($CHCl_3$) 2228 and 1678 cm^{-1}; NMR (see text for detailed analysis); UV λ_{max}^{MeOH} (ϵ) 231.5[sh] nm (8400). (Found: C, 77.51; H, 5.48; N, 10.65. Calc. for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68%).

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†It is noteworthy that, when the $NaBH_4$ reduction of **2** was carried out using EtOH as the solvent at 45°, a considerable amount of cleavage of the acetyl group was observed.

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