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A ^{13}C NMR STUDY OF SOME DI-, TETRA-, AND HEXA-HYDROPYRIDAZINES

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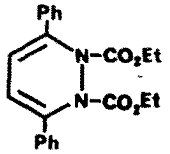
Abstract -- The room-temperature ^{13}C nmr spectra of ten hydropyridazines were analyzed in an attempt to determine the most stable conformations(s) of each. In contrast to earlier findings, dihydropyridazine 1 was found to be planar. The most stable conformations of tetrahydropyridazines 2b and 2d were found to be half-chairs, while tetrahydropyridazines 3b and 3c were most probably in boat configurations with both 3,6-substituents in pseudo-equatorial positions. The ^{13}C nmr spectra of 4,5-dibromohexahydropyridazines 4a and 4b were consistent with a mixture of three chair conformations formed by axial-equatorial nitrogen inversions.

When an azo group is bonded to two ester groups, as in diethyl azodicarboxylate, the resulting azo compound is a very reactive dienophile.[1] Diels-Alder reactions of such azo dienophiles with substituted butadienes result in 1,2-dicarbalkoxytetrahydropyridazines (2). The dicarbamate moeity, $-N(CO_2R)N(CO_2R)-$, in hydropyridazines of this sort provides a good stereochemical nmr probe for conformational studies. Several conformational processes are theoretically possible in them, namely: ring flip, hindered rotation about the carbamate N-CO bond, or nitrogen inversion. Breliere and Lehn[2], in a variable-temperature pmr study of hydropyridazine 2d, first noticed the presence of two conformational changes, a high-temperature process attributed to ring inversion and a low-temperature process assigned to hindered carbamate rotation. A controversy ensued over the nature of the low-temperature process with support given to hindered carbamate rotation[2-9], N-inversion[10-11], and both[12]. Most of these studies used variable-temperature ^{1}H or ^{19}F nmr.

4-Phenyl-1,2,4-triazoline-3,5-dione (PTAD) is one of the most reactive dienophiles known[13] and is now also commonly used to make Diels-Alder adducts. Recently, PTAD adducts have been found to be useful precursors in the synthesis of cyclic imide herbicides[14], of macrocyclic polyamine natural products[15], and of enantiomeric vic-dialkylidene-heterocycles[16]. The conformations of PTAD adducts are less complicated[17] than those of diethyl azodicarboxylate adducts because the former contain a five-membered triazoline ring.

In this work, the enhanced chemical shift range of ^{13}C nmr is used to investigate the stereochemistry of hydropyridazines 1 - 4.



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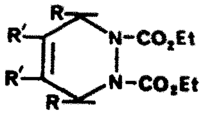
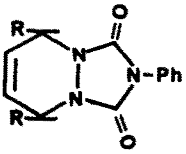
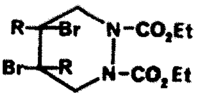


2 a: R=R′=H
b: R=Me R′=H
c: R=H R′=Me
d: R=Ph R′=H



3 a: R=H
b: R=Me
c: R=Ph



4 a: R=H
b: R=Me

Table 1. ^{13}C Chemical Shifts[a] for Hydropyridazines 1 - 4

Compound	Hydropyridazine		Carbethoxy			Aromatic		Other
	C(3,6)	C(4,5)	CO	OCH_2	CH_3			
1	139.67s[c]	112.37d[b]	154.51s	62.52t	13.73q	C(1) 135.18s[c]		
						C(2) 125.52d		
						C(3) 128.09d		
						C(4) 125.52d		
2a	43.17t	122.98d	154.57s	61.47t	13.66q			
2b	51.34d	129.73d	155.90s	61.88t	14.00q			C(3,6)CH_3 20.50q
	50.07d	128.56d	155.36s	61.00t				C(3,6)CH_3 17.52q
2c	47.03t	122.48s	154.91s	61.65t	14.03q			C(4,5)CH_3 14.93q
2d	59.80	130.37	157.02	62.95	14.19	C(1) 141.82, 139.91		
	57.83	128.92	155.56	61.33	13.86	C(2) 127.76, 127.04		
						C(3) 128.46, 128.37		
						C(4) 126.63, 125.14		
3a	43.17t	120.64d	152.22s			C(1) 131.14s		
						C(2) 125.17d		
						C(3) 128.81d		
						C(4) 127.81d		
3b	50.43d	126.26d	151.88s			C(1) 131.17s		C(3,6)CH_3 18.76q
						C(2) 125.23d		
						C(3) 128.79d		
						C(4) 127.70d		
						C(3,6)Ph	N-Ph	
3c	58.05d	128.35d[c]	151.64s			C(1) 137.04s	C(1) 131.03s	
						C(2) 127.58d[c]	C(2) 124.90d	
						C(3) 128.59d	C(3) 128.35d[c]	
						C(4) 128.35d[c]	C(4) 127.58d[c]	
4a	46.50t	52.25d	154.73s	62.88t	14.17q			
	46.00t	49.26d	154.59	62.44t				
	44.83t	47.25d	153.94s					
	44.31t	46.89d						
4b	54.64t	70.29s	154.64s	62.53t	14.20q			C(4,5)CH_3 26.88q
	54.09t	69.92s	154.46s	62.23t				C(4,5)CH_3 26.58q
	52.98t		154.29s					
	52.39t							

[a] ppm from TMS [b] multiplicity in off-resonance decoupled spectra [c] assignments less certain

RESULTS AND DISCUSSION

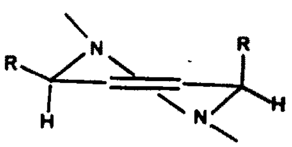
The chemical shift values of the ^{13}C nmr spectra of hydropyridazines 1 - 4 are given in Table 1. The assignments of these chemical shifts were greatly facilitated by use of the off-resonance decoupling multiplicities and by the fact that there were multiple examples of each kind of carbon atoms present in the ten compounds studied.

Diethyl 3,6-Diphenyl-1,2-pyridazinedicarboxylate(1). In a seminal study, Anderson and Lehn[4] postulated that 1 is in a dynamic cyclohexadiene-like ring inversion or ring-twist conformational process with $\Delta G^{\ddagger} = 23$ kcal/mol. This postulate was based on a variable-temperature pmr study where at room temperature the ethyl hydrogens of the CO_2Et groups have an ABC_3 pattern and this pattern changes to an A_2B_3 pattern at high temperature. The A and B methylene quartets of dihydropyridazine 1 were separated by 2.4 Hz, which is a very small separation compared to the 25 Hz separation found in the analogous AB quartets of 2d, the tetrahydropyridazine precursor of 1. This ten-fold difference is due to the fact that the two sides of the tetrahydropyridazine ring in 2d are vastly different magnetically because both of the *cis*-3,6-diphenyl groups are located on one side of the ring.

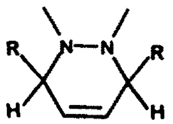
The proton-noise decoupled ^{13}C nmr spectrum of 1 at room temperature contains only 8 absorptions and is consistent with a symmetrical structure. The ester methylene carbons of 1 that contain the AB hydrogens just discussed have only one ^{13}C absorption located at 62.52 ppm. This is again very different from the situation found in the ^{13}C spectrum of 2d, where these same two methylene carbons are now separated by 1.62 ppm. The hybrid state of the ring nitrogen atoms in hydropyridazines 1 - 4 is normally sp^2 because of resonance stabilization between these nitrogen atoms and the adjacent carbonyl groups. The two carbamate groups of 1 are also twisted to help relieve the steric interaction between them. The high activation energy for the interconversion of the two twisted conformers of 1 is due to the highly congested planar transition state, where carbamate-phenyl steric eclipsing interactions are present in addition to carbamate-carbamate interactions. The simple ^{13}C nmr pattern observed for 1 is thus the result of internal symmetry present in each twisted conformation. An x-ray diffraction study of 1 is underway to determine its most stable solid state geometry.

Dihydropyridazine 1 is a diene and should undergo Diels-Alder reactions with reactive dienophiles. When 1 and PTAD were refluxed under nitrogen in toluene for 4 days, 1 was recovered unchanged. This unreactivity of diene 1 with PTAD probably reflects the high energy of the planar transition state needed for the Diels-Alder reaction to occur.

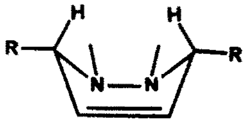
Diethyl 3,6-Dihydro-1,2-pyridazinedicarboxylates 2a-d. Tetrahydropyridazines 2 are structurally similar to cyclohexenes or 1,4-cyclohexadienes depending on the hybrid states of the two ring nitrogens. Cyclohexenes tend to prefer a half-chair conformation[18], while 1,4-cyclohexadienes prefer either a boat or a planar conformation depending on the substitution patterns[19]. The most stable conformations of *cis*-3,6-disubstituted-1,4-cyclohexadienes are normally boats with the two substituents in pseudoequatorial positions[20]. The three most probable conformations for tetrahydropyridazines 2 and 3 are:



Half-chair



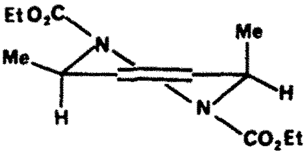
Planar



Boat

Internal symmetry elements in all three of the most probable conformations of tetrahydropyridazines 2a and 2c cause the number of different kinds of carbon atoms to be halved in each. This is experimentally verified by the ^{13}C nmr spectra of 2a and 2c where the former has only five peaks and the latter just six.

The situation is different in the cis-3,6-disubstitutedhydropyridazines 2b and 2d. The half-chair conformation of these two compounds contains all different carbon atoms in contrast to the planar and boat conformations each of which retains an internal plane of symmetry. The ^{13}C nmr spectrum of 2b shows the presence of 11 different carbons in a compound that contains only 12 total carbon atoms. This spectrum is only consistent with the half-chair conformation 5, in which



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one of the cis-3,6-dimethyl groups is pseudoaxial (17.52 ppm) and the other is pseudoequatorial (20.50 ppm). The upfield peak was assigned to the pseudoaxial methyl because of steric crowding[21,22], and because it lies in a shielding area of both the olefinic and carbonyl cones. The two C(3,6) carbons, C(4,5) carbons, carbonyl carbons, and O-CH_2-carbons are now magnetically nonequivalent and the upfield member of each pair is assigned to the carbon either on or near the pseudoaxial methyl group. The only magnetically equivalent carbons in 2b are the terminal methyls of the CO_2Et groups, which are now far enough removed from the 3,6-dimethyl groups to be unaffected by them.

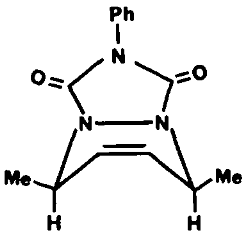
The ^{13}C nmr spectrum of 2d, the 3,6-diphenyl analogue of 2b, has 18 peaks. In addition to the hydropyridazine ring carbons, each of the three carbon atoms of the two CO_2Et groups are now different; the two carbonyl carbons and the two methylene carbons now differ by 1.5 ppm. These large chemical shift differences are the result of one of the CO_2Et groups being on the same side of the hydropyridazine ring as the two cis phenyl groups and its three carbons are shifted upfield. The upfield aryl carbons of 2d are assigned to the pseudoaxial phenyl group for the same reasons mentioned concerning 2b.

The fact that the two cis methyl groups of 2b and the two cis phenyl groups of 2d are magnetically nonequivalent is clear evidence that both of these compounds are present in their half-chair conformations. This finding is consistent with earlier ^{1}H nmr studies on 2d[2,4,6], 2c[3], and 2a[12].

1H[1,2,4] Triazolo [1,2-a]pyridazine-1,3-(2H)diones 3a-c. The Diels-Alder adducts of dienes and PTAD are called 1H[1,2,4] triazolo[1,2-a]pyridazine-1,3-(2H)diones. Many derivatives of this heterocyclic ring system have recently been shown to possess herbicidal activity and phytotoxicity[14,23]. The low-temperature carbamate rotation process mentioned earlier is not possible in these compounds because the two carbonyls are now joined to a third nitrogen atom forming a five-membered triazoline ring.

The ^{13}C nmr spectra of 3a,b,c each contain only one carbonyl, one vinyl, and one C(3,6) peak consistent with the presence of a horizontal plane of symmetry in structure 3. This symmetry observation rules out a half-chair conformation for hydropyridazines 3b and 3c, which is not surprising since all five of the atoms in the triazoline ring probably lie near, if not in, a common plane, and a half-chair conformation would introduce large torsional strain into the five-membered ring. The N-phenyl carbons in 3a,b,c, also all come at similar chemical shift values of 131, 125, 128.7, and 127.7 ppm for the aromatic C-1, C-2, C-3, and C-4 positions, respectively. The ^{13}C spectrum of PTAD, the precursor of 3a,b,c, was taken as the N-phenyl model system; PTAD has a 5 peak specturm: 157.7 (CO), 129.5(C-1), 124.0(C-2), 128.6(C-3), and 128.2(C-4). From this data it can be concluded that only one conformation is present in 3a,b,c and that it has either a planar or boat geometry.

The ^{1}H nmr spectrum of 3c was also analyzed in a further effort to determine whether its conformation was planar or boat-shaped. The Garbisch equation[4,12,24] has been successfully used to determine the dihedral angle between vicinal vinyl and allyl hydrogens from their proton-proton coupling constants. The coupling constant $J_{H_3-H_4}$ for 3c was found to be 1.8 Hz, which corresponds to a dihedral angle of about 90°. The corresponding dihedral angle for the boat conformation is 98°, while that of the planar conformation is 55°. This finding is taken as evidence that the most stable conformation of 3c is the boat conformation 6. By implication, 3a and 3b are probably in similar conformations. An x-ray diffraction study of 3a,b,c is also underway.



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4,5-Dibromohexahydropyridazines 4a,b. The two dibromohexahydropyridazines 4a and 4b were chosen for this study because, despite several studies[3,25], the conformational nature of these compounds is still in question. These two compounds were synthesized by bromination of 2a and 2c, respectively, in CCl_4. Price[3] originally postulated that 4b has a 19.8 kcal/mole barrier to hindered carbamate rotation, but later suggested that a chair-boat equilibrium was more likely[25]. Hindered carbamate rotation barriers greater than 15 kcal/mole are highly suspect in hydropyridazines.

The ^{13}C spectrum of 4b is nice because all of its peaks are clearly separated and unique assignments can be made for each different carbon atom using off-resonance decoupling patterns. The key feature of this spectrum is the presence of four different C(3,6) carbon absorptions and two different C(4,5) carbons, see Figure 1b, indicating the presence of a mixture of several stable conformations. The ^{13}C spectrum of 4a is even more complicated than that of 4b because the chemical shift values of the C(4,5) carbon in 4a are now in the same region of its spectrum as the C(3,6) methylene carbons, see Figure 1a. The same cluster of four C(3,6) peaks found in 4b is also found in 4a but now shifted upfield by 8 ppm. There are also four C(4,5) absorptions in 4a instead of the two found in 4b. The fact that the same four cluster of peaks for the C(3,6) carbons is found in both 4a and 4b is evidence that a similar mixture of conformers is found in each compound, whatever its ultimate composition.

The three conformational processes that need to be considered for hexahydropyridazines 4a and 4b are hindered carbamate rotation, ring flip, and nitrogen inversion, see Figure 2. Ring flip is considered highly unlikely in 4b because the two methyl groups at C(4,5) strongly prefer the diequatorial positions leaving the two bromo atoms at the same two carbons in diaxial positions. The A values for $-CH_3$, $-CO_2Et$, and -Br are 2.74, 1.15, and

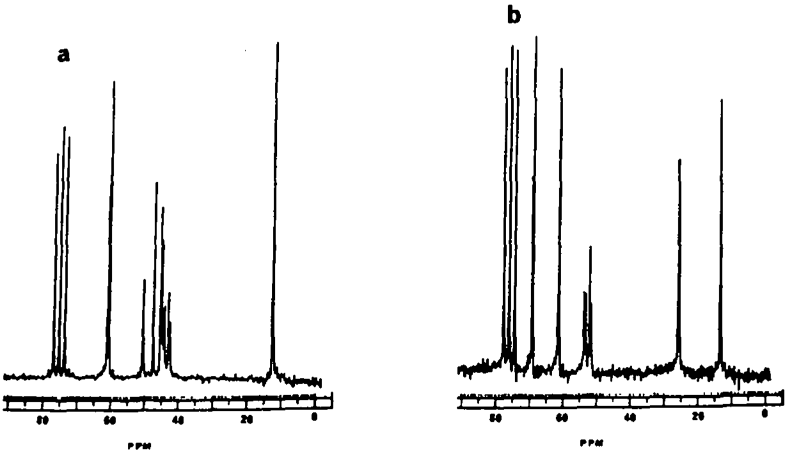

Figure 1. ^{13}C nmr spectra of (a) 4a and (b) 4b.

0.55 kcal/mole, respectively[26]. An equilibrium between the chair and boat conformers of 4b (7a,b,c,) is also considered unlikely because only two C(4,5) peaks were found in the ^{13}C spectrum of 4b, and such an equilibrium would produce more than two C(4,5) carbons. It is more difficult to estimate the expected chemical shift values for a mixture of the three hindered carbamate conformers 7g,h,i since no suitable model compounds are available.

A consistent, but not conclusive, interpretation of the ^{13}C nmr spectrum found for 4b (also 4a) involves a mixture of three stable nitrogen inversion conformers. Using the empirical parameters given in Wehrli and Wirthlin[22], the theoretically expected chemical shift values for a mixture of the three cyclohexane analogues of 4b were calculated. The results of this calculation was that the three component mixture should have two C(4,5) carbon absorptions, at 78.2 and 71.8 ppm, and four different C(3,6) carbon peaks located at 49.3, 45.7, 42.9, and 39.3 ppm. While the chemical shift values of hexahydropyridazine 4b would obviously be different from those of the cyclohexane model compound, the same general pattern of absorptions would probably be found. If this interpretation is correct, the high-field C(3,6) peak in 4b comes from conformer 7f (see Figure 2), the low-field peak from conformer 7d and the two intermediate peaks from the two different C(3,6) carbons in conformer 7e. The same interpretation can be applied to hexahydropyridazine 4a, but now the lack of the two C(4,5) methyl groups allows a mixture of conformers with the two C(4,5) bromo atoms in the diaxal as well as the diequatorial conformations. This would account for the presence of four C(4,5) carbon absorptions in 4a. An x-ray diffraction study of crystalline 4b is also underway.

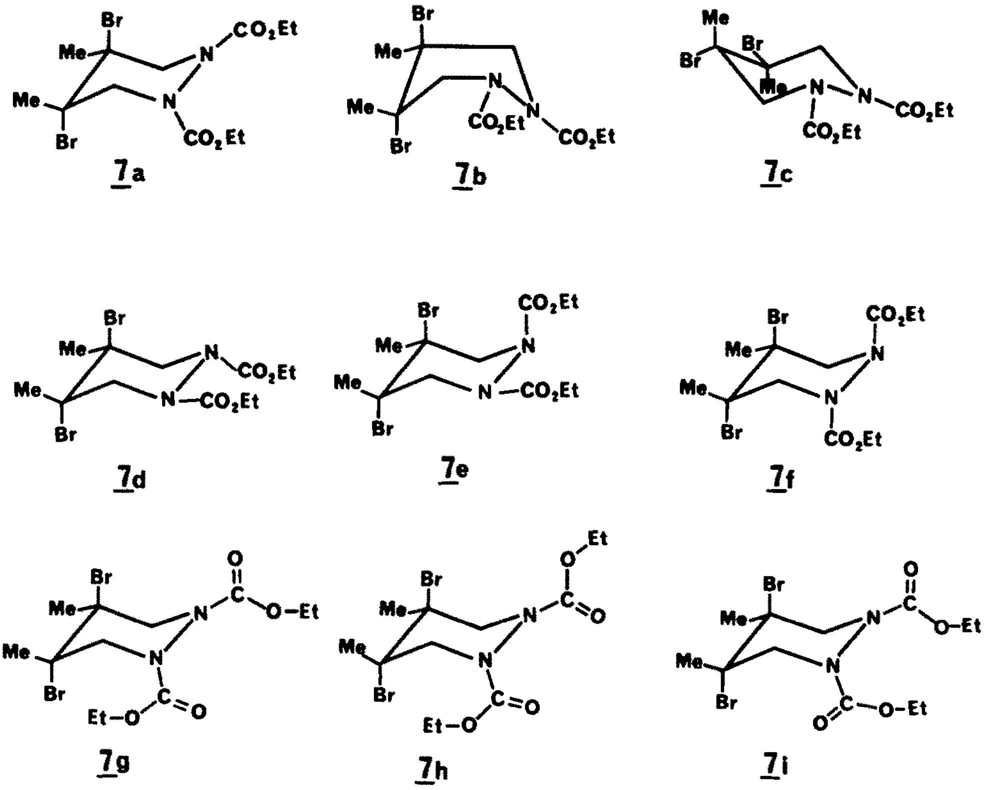

Figure 2. Possible stable conformers of 4b from ring flip (a-c), nitrogen inversion (d-f), and hindered carbamate rotation (g-i).

EXPERIMENTAL

Melting points were determined on a Mel-temp apparatus and are uncorrected. Infrared spectra were run on a Perkin-Elmer 283B spectrophotometer. Nmr spectra, both ^1H and ^{13}C, were run on a Varian CFT-20 instrument. The ^{13}C chemical shifts were referenced to the center peak of d-chloroform and reported as ppm from TMS. Elemental analysis was performed by Galbraith Laboratories.

Compounds $1^{4,27}$, $2a^{12}$, $2b^{28}$, $2c^{3,29}$, $2d^{4,30}$, $3a^{13a}$, $3c^{13b}$, $4a^{31}$, $4b^{29}$ were prepared by established literature procedures and their physical constants and spectral data were in agreement with previously assigned structures.

5,8-Dihydro-cis-5,8-dimethyl-2-phenyl-1H-[1,2,4]triazolo[1,2a]pyridazine-1,3(2H)-dione (3b). A solution of 3.05 g (0.0174 mole) PTAD in dry acetone was added to 1.43 g (0.0174 mole) of *trans*, *trans*-2,4-hexadiene in acetone. The deep red color disappeared immediately. After removal of solvent, recrystallization from carbon tetrachloride/petroleum ether gave 3.0g (68%) of a white solid mp 134.5-136°C. ^1H nmr ($CDCl_3$) 1.5 (d,6H,J=7 Hz), 4.4 (q,2H,J=7 Hz), 5.9 (s,2H), 7.4-7.6 ppm (m,5H); ir ($CHCl_3$) 3000, 1760, 1490, 1410, 1285 cm^{-1}. *Anal.* Calcd for $C_{14}H_{15}N_3O_2$: C, 65.35; H, 5.88; N, 16.33. Found: C, 65.15; H, 5.99; N, 16.28.

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