Total Assignment of the ^{1}H NMR Spectra of 5*H*-Indolo[1,7-*ab*][1]benzazepine, 6,7-Dihydro-5*H*-indolo[1,7-*ab*][1]benzazepine and Pyrrolo[3,2,1-*kl*]phenothiazine

Anders Hallberg, Torsten Dahlgren and Arnold Martin* (1)

Department of Pharmaceutical Sciences, College of Pharmacy, The Universtiy of Arizona, Tucson, AZ 85721

Kenner Christiansen

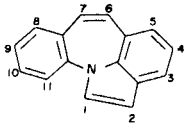
Department of Chemistry, The University of Arizona, Tucson, AZ 85721

Received August 24, 1981

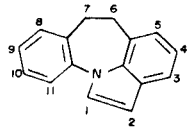
The total assignment of the ^{1}H nmr spectrum of the three tetracyclic compounds: 5*H*-indolo[1,7-*ab*][1]benzazepine, 6,7-dihydro-5*H*-indolo[1,7-*ab*][1]benzazepine and pyrrolo[3,2,1-*kl*]phenothiazine is described. Assignments were based on decoupling experiments and the spectrum of 1,10-dideuteriopyrrolo[3,2,1-*kl*]-phenothiazine and the spectral parameters were varified by spin-simulation techniques. A temperature study of 6,7-dihydro-5*H*-indolo[1,7-*ab*][1]benzazepine was also performed.

J. Heterocyclic Chem., **20**, 37 (1983).

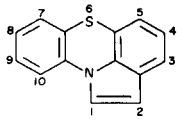
As a part of a systematic study of the structure-activity relationships of tricyclic compounds related to imipramine and promazine with restricted rotation in the side chain, we were interested in utilizing the tetracyclic systems **1, 2** and **3** as precursors. We have recently reported a convenient synthesis of the three systems (2).



1



2



3

In connection with a comparison study of the chemistry of these heterocycles, especially concerning sites of lithiation, we found it necessary to resolve their ^{1}H nmr spectra. We also hoped to obtain an estimate of the relative planarity of each of the systems in solution. The ^{1}H nmr spectra of 5*H*-dibenz[*b,f*]azepine (3,4), phenothiazine (5-10) and conformational studies of 10,11-dihydro-5*H*-dibenz-[*b,f*]azepine derivatives (3, 11-13) have been reported.

Presented here are the total assignment of the aromatic protons in **1, 2,** and **3** also the results of the temperature study of the ring inversion barrier in 6,7-dihydro-5*H*-indolo[1,7-*ab*][1]benzazepine.

Results and Discussion.

The proton chemical shift assignment were made from decoupling experiments in combination with comparison of coupling constants in indoles (14), dibenzazepines, 10,11-dihydrodibenzazepines and phenothiazines. The spectral parameters were varified by spin-simulation of separate 3- and 4-spin systems. The ^{1}H nmr spectra were recorded at 250 MHz in deuteriochloroform solution and are shown in figures 1, 2 and 3. Table 1 gives the chemical shift values of the aromatic protons and Table 2 the coupling contants.

The well separated doublets at the lowest and highest field in the spectra, with coupling constants 3.4-3.7 Hz, were readily assigned with decoupling experiments to be the 1- and 2-protons respectively (14). Decoupling of the 1-proton also sharpened up the broad high field doublet of doublets at 6.44 ppm (**1**), 6.99 ppm (**2**) and 6.56 ppm (**3**). The broadening of the doublet of doublets and of the 1-protons is due to a small long-range coupling, and the doublet of doublets was consequently assigned to the 5-protons. These assignments were confirmed by irradiation of the 5-protons, resulting in a sharp doublet from the 1-protons and the appearance of two distinct doublets at

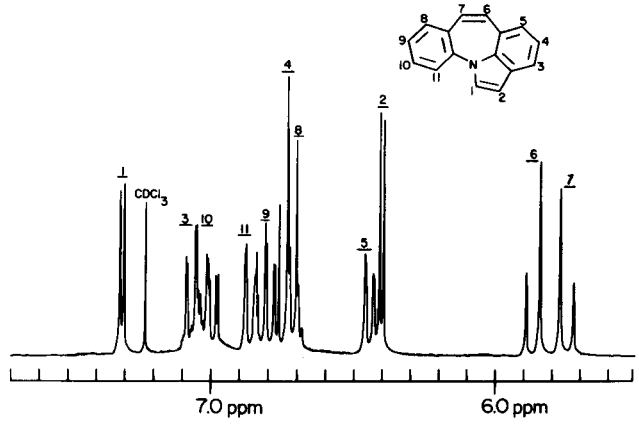


Figure 1. ^{1}H-nmr spectrum of 5*H*-indolo[1,7-*ab*][1]benzazepine (**1**) in deuteriochloroform.

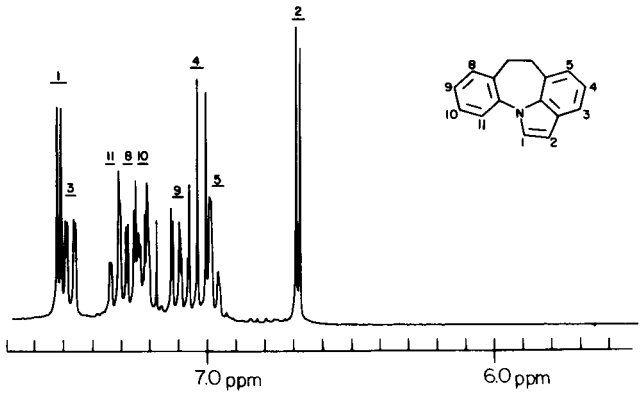


Figure 2. ^{1}H-nmr spectrum of 6,7-dihydro-5*H*-indolo-[1,7-*ab*][1]benzazepine (**2**, aromatic region only) in deuteriochloroform.

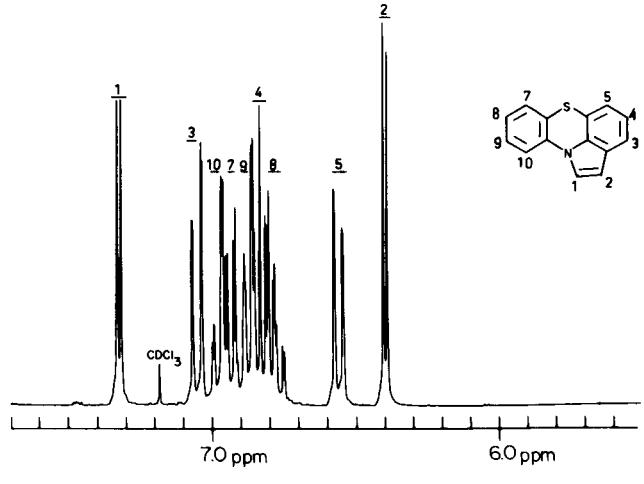


Figure 3. ^{1}H-nmr spectrum of pyrrolo[3,2,1-*kl*]phenothiazine (**3**) in deuteriochloroform.

6.73 ppm (**1**), 7.05 ppm (**2**) and 6.83 ppm (**3**) assigned to the 4-protons, and at lower field, 7.08 ppm (**1**), 7.49 ppm (**2**) and 7.04 ppm (**3**) assigned as the 3-protons. Separated irradiations of the doublet of triplets corresponding to the 4-protons, and the doublet of doublets corresponding to the 3-protons, confirmed our assignments. The H3, H4 coupling constants were in the range 7.5-8.0 Hz and the H4, H5 coupling constants in the range 7.2-7.4 Hz. In order to resolve the 4-spin-system, it was necessary to determine which of the coupled doublets that corresponded to the 8- and 11-protons of **1** and **2** or the 7- and 10-protons in **3**. The larger 3-bond coupling constants differed by more than 1 Hz and were assumed to be the 10,11 *ortho* coupling in **1** and **2** and the 9,10 *ortho* coupling in **3**. The *meta* couplings from the 11 protons in **1** and **2** and the 10 proton in **3** were also equal or smaller that the *meta* couplings from the 8-protons in **1** and **2** and the 7-proton in **3** as expected. Selective decoupling of all four protons gave approximate data for the coupling constants and the chemical shift for each of the separate protons (1,10-dideuteriopyrrolo[3,2,1-*kl*]phenothiazine). To confirm the assignments, we examined the spectrum of 1,10-dideuteriopyrrolo[3,2,1-*kl*]phenothiazine **4** (15) and also performed spin-simulations which provided us with the final parameters. Proof of the sites of deuterium substitution in **4** were obtained by comparison of the ^{13}C nmr spectra of **3** and **4** (16,17) which clearly distinguished C-7 (127.1 ppm) and C-10 (114.2 ppm). In the ^{1}H nmr spectrum of **1**, the 2-proton became a singlet, the 8-proton become a quartet with two ortho couplings ($J_{7,8}$ = 6.9 Hz; $J_{8,9}$ = 8.0 Hz), and the 9-proton became a quartet with a ortho coupling ($J_{8,9}$ = 8.0 Hz) and a meta coupling ($J_{7,9}$ = 1.7 Hz). The assignments of the 6- and 7-protons in

Table 1

^{1}H NMR Chemical Shifts (δ Values) in Deuteriochloroform at 27°C

Compound	1H	2H	3H	4H	5H	6H	7H	8H	9H	10H	11H
5*H*-Indolo[1,7-*ab*][1]-benzazepine (**1**)	7.31	6.40	7.08	6.73	6.44	5.86	5.75	6.71	6.81	7.01	6.86
6,7-Dihydro-5*H*-indolo-[1,7-*ab*][1]benzazepine (**2**)	7.53	6.70	7.49	7.05	6.99	3.20 (a)	3.20 (a)	7.28	7.10	7.24	7.33
Pyrrolo[3,2,1-*kl*]phenothiazine (**3**)	7.31	6.39	7.04	6.83	6.56		6.92	6.78	6.88	6.97	
1,10-Dideuteriopyrrolo-[3,2,1-*kl*]phenothiazine (**4**)		6.39	7.04	6.81	6.54		6.94	6.77	6.89		

(a) The four ethano-bridged protons appear as a singlet.

Table 2

^{1}H NMR Coupling Constants (Hz) in Deuteriochloroform at 27°C

Compound	J_{12}	J_{34}	J_{35}	J_{45}	J_{67}	J_{68}	J_{78}	J_{79}	J_{89}	J_{810}	J_{910}	J_{911}	J_{1011}
5*H*-Indolo[1,7-*ab*][1]benzazepine (**1**)	3.7	8.0	1.2	7.2	11.8				7.2	1.2	7.0	0.5	9.2
6,7-Dihydro-5*H*-indolo[1,7-*ab*][1]benzazepine (**2**)	3.5	7.5	1.5	7.2					7.0	1.6	7.4	1.2	8.0
Pyrrolo[3,2,1-*kl*]phenothiazine (**3**)	3.4	8.0	0.9	7.4			6.6	1.7	7.9	1.7	8.1		
1,10-Dideuteriopyrrolo[3,2,1-*kl*]phenothiazine (**4**)		7.9	0.8	7.3			6.9	1.7	8.0				

Table 3

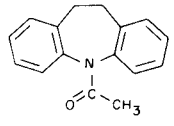
Temperature Effects on the Chemical Shifts (δ Values) of the Aromatic Protons of 6,7-Dihydro-5*H*-indolo[1,7-*ab*][1]benzazepine in Deuterioacetone

°C	1H	2H	3H	4H	5H	8H	9H	10H	11H
+20	7.75	6.72	7.47	7.01	6.98	7.35	7.16	7.32	7.50
0	7.78	6.74	7.48	7.02	7.00	7.36	7.17	7.33	7.51
−10	7.81	6.75	7.49	7.03	7.00	7.36	7.18	7.33	7.52
−20	7.82	6.76	7.49	7.03	7.01	7.37	7.18	7.34	7.52
−40	7.85	6.78	7.51	7.05	7.02	7.38	7.20	7.36	7.55
−60	7.90	6.80	7.53	7.06	7.03	7.40	7.21	7.38	7.56
−80	7.95	6.84	7.56	7.08	7.05	7.42	7.24	7.40	7.58
−100	8.00	6.88	7.58	7.10	7.08	7.44	7.26	7.42	7.60

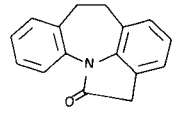
5*H*-indole[1,7-*ab*][1]-benzazepine were made by decoupling of the 5-proton, which sharpened the low field doublet at 5.85 ppm. Irradiation of the 8-proton, analogously caused the high field doublet at 5.75 ppm to sharpen.

Noteworthy is the fact that the 1- and 3-protons at low field and the 2- and 5-protons at high field are well separated and easily distinguished from the lines of the rest of the protons in all three systems. The main difference between **1, 2** and **3** is the approximately 0.3 ppm lower field position of each of the protons in the dihydro compound **2** compared to **1** and **3**. We interpret this fact by the assumption that 6,7-dihydro-5*H*-indole[1,7-*ab*]-[1]benzazepine (**2**) is a more planar system with delocalization between the indole and benzene moieties of the molecule. Comparison of Dreiding molecular models of the three systems support this idea. The chemical shift of the vinylic protons in **1** at 5.75 ppm 5.86 ppm appear at high field compared to the vinylic protons in the non cyclized compounds; 5*H*-dibenz[*b,f*]azepine 6.32 ppm, 5*H*-dibenz[*b,f*]azepine-5-acetaldehyde diethylacetal 6.70 ppm and 5*H*-dibenz[*b,f*]azepine-5-acetaldehyde 6.77 ppm. This behavior indicates that 5*H*-indole[1,7-*ab*][1]benzazepine is very rigid and more than slightly bent. From the similarity in chemical shifts and comparison with Dreiding models, pyrrolo[3,2,1-*kl*]phenothiazine (**3**) could be assumed to have nearly the same rigidity. A recent ^{13}C nmr relaxation study on this compound (17) supports this conclusion.

Abraham, Kricka and Ledwith have performed a detailed analysis of the temperature dependent ^{1}H nmr spectrum of 5-acetyl-10,11-dihydro-5*H*-dibenz[*b,f*]azepine (**5**) and suggested that the occurrance of two conformational equilibria: rotation about the amide C-N bond and inversion of the central seven-membered ring (12). In the annelated compound **6** the amide group is held in a rigidly planar conformation and ring inversion involves mainly the ethano-bridge and the least substituted aromatic ring. The ^{1}H nmr spectra of **5** at 100 MHz showed the ethano-bridge protons as a single line down to -60°. In our ^{1}H nmr variable temperature investigation of **6** at 250 MHz in deuteroacetone, we observed a complex multiplet for the ethano protons below -40° (ABCD System) which collapsed into an apparent A_2B_2 system over the range -30 to +40°. We also observed coalescence of the amide methylene protons from an AB quartet below -40° to a sharp singlet above +30°C. In deuterochloroform the ethano protons collapsed from an ABCD system to an A_2B_2 system over the range −20 to +10° and the methylene protons collapsed from an AB quartet into a singlet in the range of -20° to 0°.



5



6

When a deuteroacetone solution of 6,7-dihydro-5*H*-indolo[1,7-*ab*][1]benzazepine (**2**) is cooled to -110°, all of the aromatic protons are shifted to lower field. At -60°, the ethano-bridge protons give rise to an ABCD spectrum consisting of two groups of peaks centered at 3.1 and 3.3 ppm. Increasing the temperature causes a broadening and collapse of this spectrum to a single peak at approximately -5°. This peak sharpens to a single slightly broadened peak at 40°.

Instrumentation.

Spectra were recorded on a Bruker WM-250 NMR spectrometer at a frequency of 250.13 MHz. The samples were run as 0.5 *M* solutions in deuterochloroform or deuteroacetone with TMS internal reference.

Spectra were recorded at a data point resolution of 0.18 Hz. Gaussian multiplication was used to increase the resolution for comparison with simulated spectra. Variable temperature studies were carried out using a BUT-1000 temperature controller.

Spin-simulation was carried out using the Bruker PANIC spin-simulation program on the Aspect 2000 computer. Spectra were simulated as independent three four spin systems.

Ackowledgement.

This work was supported in part by research grants Nos. MH 31184 and NSI4997 from the United States Public Health Service.

REFERENCES AND NOTES

(1) To whom inquiries should be addressed.

(2) A. Hallberg, D. R. Deardorff and A. R. Martin, *Heterocycles,* **19**, 75 (1982).

(3) L. J. Kricka and A. Ledwith, *Chem. Rev.,* **74**, 101 (1974 and references therein).

(4) J. A. G. Drake and D. W. Jones, "Nuclear Magnetic Resonance Spectroscopy in Molecular Biology" in Jerusalem Symposium on Quantum Chemistry and Biochemistry, Vol. II, B. Pullman, ed, D. Reidel Pub. Co., Dordrecht, Holland, 1978, p 493.

(5) J. Cymerman-Craig, D. E. Green, S. K. Roy, L. H. Piette and K. O. Loeffler, *J. Med. Chem.,* **8**, 392 (1965).

(6) N. E. Sharpless, R. B. Bradley and J. A. Ferretti, *Org. Magn. Reson.,* **6**, 115 (1974).

(7) M. Rouillard, N. Giulieri and M. Azzaro, Bull. Soc. Chim. France, 2141 (1974).

(8) R. L. Mital and R. C. Chaudhary, *J. Chem. Eng. Data,* **20**, 204 (1975).

(9) G. Fronza, R. Mondelli, G. Scapini, G. Ronsisvalle and F. Vittoro, *J. Magn. Reson.,* **23**, 437 (1976).

(10) I. C. Calder, R. B. Johns and J. M. Desmarchelier, *Aust. J. Chem.,* **24**, 325 (1971).

(11) R. J. Abraham, L. J. Kricka and A. Ledwith, *J. Chem. Soc., Chem. Commun.,* 282 (1973).

(12) R. J. Abraham, R. Robinson, L. J. Kricka and A. Ledwith, *J. Chem. Soc., Perkin Trans. II,* 1646 (1974).

(13) C. R. Ellefson, L. Swenton, R. H. Bible, Jr. and P. M. Green, *Tetrahedron,* **32**, 1081 (1976).

(14) S. P. Hiremath and R. S. Hosmane, *Adv. Heterocyclic Chem.,* **15**, 277 (1973).

(15) T. Dahlgren, A. Hallberg and A. R. Martin, *Heterocycles,* in press.

(16) L. C. Vishwakarma, A. Hallberg, T. Dahlgren and A. R. Martin, *J. Heterocyclic Chem.,* in press.

(17) R. T. Gampe, G. E. Martin, A. C. Pinto and R. A. Hollins, *J. Heterocyclic Chem.,* **18**, 155 (1981).