331. *Pteridine Studies. Part I. Nuclear Magnetic Resonance Studies of Pteridine and Methylpteridines.*

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The nuclear magnetic resonance spectra of pteridine, quinoxaline, and their monomethyl derivatives have been studied in chloroform solution. In all cases the spectra were simple patterns and were analysed by comparison with one another. The spectra of quinoxaline and 2-methylquinoxaline gave useful information for assignment of H-6 and H-7 of pteridine.

UP to the present, unsubstituted pyrrole,[1] imidazole,[2] pyridine,[3] pyrimidine,[2] and purine[4] have been studied by nuclear magnetic resonance, and some correlation between the electron densities of the ring and the magnitude of the chemical shifts of ring protons has been found.[5] We report here the results of a similar study of pteridine, quinoxaline, and their monomethyl derivatives.

[1] Schaeffer and Schneider, *J. Chem. Phys.*, 1960, **32**, 1224.
[2] Reddy, Hogbood, and Goldstein, *J. Amer. Chem. Soc.*, 1962, **84**, 336.
[3] Elvidge and Jackman, *J.*, 1961, 859.
[4] Jardetzky, *J. Amer. Chem. Soc.*, 1960, **82**, 222.
[5] Veillard and Pullman, *Compt. rend.*, 1961, **353**, 2418; also personal communication.

TABLE 1.

Nuclear magnetic resonance data (τ values) for pteridine and quinoxaline and some methyl derivatives at 60 Mc./sec.

Pteridine					Quinoxaline		
		Substitution				Substitution	
Parameter	None	2-Me	4-Me	7-Me	Parameter	None	2-Me
H-4	0·20	0·33	—	0·32	H-(2, 3)	1·17	1·28
H-2	0·35	—	0·57	0·43	CH_3	—	7·23
H-7	0·67 *	0·77 *	0·73 *	—			
H-6	0·85 *	0·97 *	0·92 *	1·02			
CH_3	—	6·97	6·87	7·04			
J (6, 7) (c./sec.)	1·7 ± 0·2	1·7 ± 0·2	1·7 ± 0·2	—			

* Doublet.

The parameters for the pteridines and quinoxalines are listed in Table 1. Pteridine has four signals, two singlets, τ 0·20 and 0·35, and two doublets, τ 0·67 and 0·85. Since pteridine, and 2- and 4-methylpteridine have a pair of doublets ($J = 1{\cdot}7 \pm 0{\cdot}2$ c./sec.) while 7-methylpteridine has no such doublet, it is reasonable to assign the pair of doublets to two protons of the pyrazine ring. Then it is clear that the singlet at τ 0·33 in the spectrum of 2-methylpteridine corresponds to the C-4-proton and the one at τ 0·57 in that of the 4-methyl derivative to the C-2-proton. Although Reddy *et al.*[2] observed that signals arising from the C-2-proton in pyrimidines are quite broad, owing to the influence of the two adjacent nitrogen atoms, no such broadening was observed in pteridines.

Assignment of the two singlets in pteridine was deduced as follows. The C-4-proton signal of 2-methylpteridine is 0·13 p.p.m. higher than the lower singlet of pteridine but 0·02 p.p.m. lower than the higher singlet. Since the introduction of a methyl group into an aromatic compound always shifts the signals of aromatic protons to higher field, the lowest signal (0·20) must be assigned to the proton at C-4. Consequently the higher singlet (0·35) is assigned to that at C-2. This is consistent with the observation that the C-14-proton signal of 2-methylpteridine (0·33) is lower than the C-2-proton signal of the 4-methyl derivative (0·57). Two lower signals of 7-methylpteridine, at τ 0·32 and 0·43, seem to correspond to the two singlets of pteridine at τ 0·20 (C-4–H) and 0·35 (C-2–H), respectively, since they deviate by 0·12 and 0·08 p.p.m. upfield from those of pteridine. The smaller magnitude of the shifts than in 2- and 4-methylpteridine is attributable to a larger distance between the methyl group and the proton.

Pteridine, and 2- and 4-methylpteridine have two doublet signals due to the pyrazine protons. The C-6-proton in 7-methylpteridine gives a signal at τ 1·02 which deviates by 0·17 p.p.m. from the higher doublet (0·85) and by 0·35 p.p.m. from the lower doublet (0·67) of the spectrum of pteridine. The difference value of 0·17 p.p.m. seems to be more likely than 0·35 p.p.m., since each ring-proton signal of methylpteridines deviates by 0·06—0·22 p.p.m. from the corresponding signal of pteridine. As 6-methylpteridine has not yet been synthesised, the spectra of quinoxaline and 2-methylquinoxaline were measured in order to determine the methyl substituent effect in the pyrazine ring. In this case, the introduction of a methyl group caused a shift of the C-3-proton signal upfield by 0·11 p.p.m. This suggests that a 7-methyl group on the pteridine ring would shift the signal of the C-6-proton upfield by about 0·1 p.p.m., and thus supports the above assignment. Thus the signal at τ 0·85 is assigned to the C-6-proton and the signal at τ 0·67 to the C-7-proton. In the spectra of 2- and 4-methylpteridine, the higher and lower doublets can also be assigned to the signals of the C-6- and the C-7-proton, respectively. These assignments are further supported by comparison of ring-proton and methyl-proton chemical shifts. In the case of pyrimidine and imidazole derivatives,[2] ring-proton shifts in unsubstituted compounds and the corresponding methyl-proton shifts in monomethyl derivatives move in parallel (Table 2). Since it would be reasonable

TABLE 2.

Comparison of the chemical shifts of ring-protons and methyl-protons (τ values).

	Pyrimidine [2]			Imidazole [2]		Imidazole [2]		
Position	2	4	5	2	4	2	4	7
Ring-proton	0·75	1·23	2·64	2·30	2·87	0·35	0·20	0·67
Methyl-proton ...	7·25	7·47	7·70	7·58	7·73	6·97	6·87	7·05

to assume that this relationship holds good in the case of pteridines, the observed order C-4–Me < C-2–Me < C-7–Me from the lower field supports the above assignment.

If the ring-current anisotropy effects in various positions in pteridine do not differ substantially,[5] the order of electron density of carbon atoms should be the same as the above sequence: C-4 < C-2 < C-7 < C-6. Electron density calculation * of pteridine by Veillard and Pullman,[5] however, leads to the different sequence C-2 < C-4 < C-6 < C-7, and his correction for ring-current anisotropy to the experimental values did not bring satisfactory results. Indeed, in the case of pyrimidine [2] and purine,[4] the signal of the C-2-proton is always in a lower field than that of the C-4-proton. However, direct comparison of this observation with the corresponding proton shifts in pteridine would not be proper, since pyrimidine lacks a nitrogen atom at C-5, which would affect strongly the C-4-proton signal in pteridine, and since the spectrum of purine [4] was measured in aqueous alkali, in which it exists as an anion.

TABLE 3.

Methyl-substituent effects in pteridine.*

	Position				
Substituent	2	4	6	7	Sum
2-Methyl	—	0·13	0·12	0·10	0·35
4-Methyl	0·22	—	0·06	0·07	0·35
7-Methyl	0·12	0·08	0·17	—	0·37

* All values are the displacements (p.p.m.) of the proton shifts relative to the same position in the unsubstituted ring.

In an aromatic nucleus, replacement of a ring-proton by a methyl group always shifts the remaining ring-proton signals upfield, possibly because of hyperconjugation. Although an individual shift in methylpyrimidines has a different magnitude, Reddy *et al.*[2] observed that the sum of the ring-proton shifts is almost the same (0·50 p.p.m.) in various monomethyl derivatives. This value is significantly below the value of 1·00 p.p.m. observed for toluene, and they inferred that some of the charge transferred from a methyl group to the pyrimidine ring is localised on the nitrogen atoms. In the methylpteridine series, the sum of the ring-proton shifts falls surprisingly close to a constant value (0·35 p.p.m.) as shown in Table 3. Now, if we assume that the charge transferred from a methyl group is

TABLE 4.

Calculation of total effect of a methyl substituent on the chemical shift of aromatic ring.

	Total effect of methyl group (p.p.m.)
Toluene *	1·00 × 6/5 = 1·20
Methylpyrimidine †	0·54 × 6/3 = 1·08
Methylimidazole †	0·45 × 5/2 = 1·13
Methylpteridine	0·35 × 10/3 = 1·17

* "NMR spectra catalogue," Varian Associates, Pala Alto, Calif., 1962. † Average values obtained from the Table in ref. 2.

* By the self-consistent field method in the Pariser–Parr approximation (SCFPP method).

distributed equally on the carbon and nitrogen atoms in the ring, the total magnitude of methyl-substituent effect (shown in Table 4) would be calculated from the equation:

$$\text{Total effect of methyl group} = \frac{\text{Sum of ring-proton shifts} \times \text{Number of ring atoms}}{\text{Number of ring carbon atoms bearing hydrogen}} \sim 1{\cdot}1 \text{ p.p.m.}$$

Coupling constant $J(6, 7)$ in pteridines is surprisingly small (1·7 c./sec.) compared with that of the *ortho*-position in an aromatic nucleus (J = 7—10 c./sec.).[6] The electronegativities of the adjacent atoms (nitrogen) would account for this small coupling constant.[7]

Experimental

Materials.—Pteridine,[8] 2-methylpteridine,[9] 4-methylpteridine,[9] 7-methylpteridine,[9] quinoxaline,[10] and 2-methylquinoxaline [10] have been prepared by known methods.

Spectra.—The spectra were determined at 60 Mc./sec. with a Nihondenshi model JNM-3 spectrometer equipped with a flux stabiliser. Calibrations were performed by the usual sideband technique.[11] The peak frequencies were obtained by averaging measurements taken on several successive forward and reverse sweeps. The typical mean deviation of chemical shifts was 1·0 c./sec. or less, and of coupling constants ±0·2 c./sec. The solvent was chloroform, with tetramethylsilane as internal reference. All measurements were done at the same concentration (10·0%).

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