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Nuclear Magnetic Resonance Studies of Heteroaromatic Systems. Methyl Coupling of 2-Substituted Picolines, 2-Pyridones and 2-Pyridthiones.

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The proton magnetic resonance spectra of all the 2-amino-, 2-chloro-, 2-nitropicolines were determined. Long-range coupling of the methyl groups to all available *ortho* (four bonds) and *para* (six bonds) ring protons was found in these picolines. The p.m.r. spectra of all of the ring methyl substituted 2-pyridones and 2-pyridthiones were analyzed. In 4- and 5-methyl-2-pyridones and the corresponding thiones, selective ring coupling was observed to only one *ortho* ring proton, *viz.*, to H-3 and H-6 respectively. However, in 3- and 6-methyl-2-pyridones and analogous thiones, long-range coupling was visible to both *ortho* and *para* ring protons. These long-range spin-spin interactions are interpreted in terms of the structures of 2-pyridones and their thione analogs.

In our investigation of 2-pyridones (1,2) we initiated a program of study of this molecule and its thione analog by means of nuclear magnetic resonance spectroscopy, anticipating that such a study might provide additional information on the aromatic character of 2-pyridone (3) and 2-pyridthione. Our approach consisted of studying the spin-spin coupling of the C-methyl protons to the ring protons in methyl substituted 2-pyridone and thione analogs. It was hoped that information on the delocalization of the π-electrons (4, 5) would be obtained through changes in this long-range coupling. Spin-spin coupling of protons on a benzyl carbon with those attached to an aromatic ring has been the subject of a number of recent studies (5-10).

Before analyzing the long-range methyl to ring proton coupling in 2-pyridones and thiones, we examined this effect in a series of 2-amino, 2-chloro and 2-nitropicolines. It was found that the presence of these groups on C-2 affected only the chemical shift of the ring protons, and to a lesser degree, the methyl protons. The amino and chloro groups shielded the ring protons, and the nitro group deshielding them with respect to the protons in pyridine itself. It is interesting to note that the presence of these quite different groups did not significantly alter the long-range methyl to ring spin-spin interactions either in pattern or in magnitude.

The chemical shifts and coupling constants of these picolines (Table I) agreed in general with those described for other pyridines (11). The signal furthest downfield was due to H-6 deshielded by the electronegative ring nitrogen and broadened by its electric quadrapole moment. The next signal arose from H-4, followed by the resonances due to the β-protons, much further upfield. The methyl resonance of the picolines appeared as expected of one attached to an aromatic sp^2 carbon atom. The signs of the coupling constants were not determined for this study.

2-Aminopicolines.

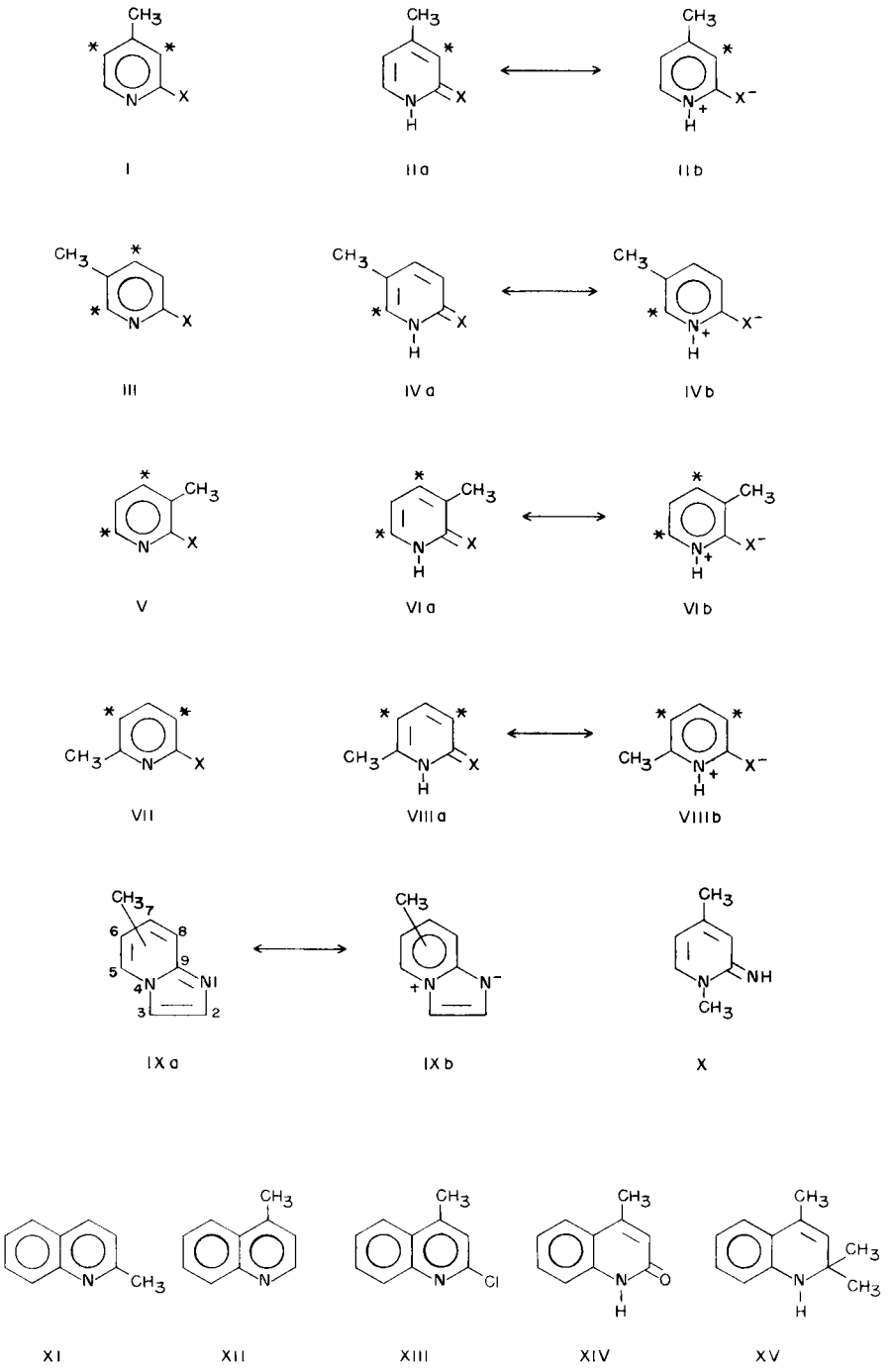
The n.m.r. spectra of the four isomeric 2-aminopicolines were examined in detail. The methyl and ring proton resonances are shown in Figures 1-4. A relatively broad band (2 protons), which was assigned to the amino group, is not shown. Only the chemical shifts and coupling constants of the ring protons were previously reported in detail; and this discussion will center around the pronounced methyl proton to various ring proton couplings.

2-Amino-4-picoline (see Figure 2) is discussed first. The doublet furthest downfield was assigned to H-6 and showed fine splitting due predominately to *para* coupling. The other signals showed considerable splitting which was attributed to coupling of H-5 and H-3 with the methyl group. From a simple first-order analysis of the spectrum, H-5 is coupled with H-3 and with the methyl protons and appears as a doublet with each arm consisting of a septet with relative intensities approximately in the ratios of 1:3:3:2:3:3:1 including in the analysis the weaker center band and the outer shoulders. Similarly, H-3 appears as a septet (1:4:7:8:7:4:1) when coupled with H-5, H-6 and C-methyl with the coupling constants indicated in Table I. The discrepencies in intensities is accounted for by the proximity of the 3 and 5 proton signals causing a "skewing" of the peaks. It is apparent that the methyl group couples with H-3 (J = 0.7 c.p.s.) and with H-5 (J = 0.6 c.p.s.) and this manifests itself by the methyl signal appearing broadened and indicating an unresolved multiplet of four lines. Thus, within the resolution capability of the instrument, the methyl group at C-4 couples with both H-3 and H-5 with about equal magnitude and to a considerably lesser degree with H-6. The magnitude of the coupling of the methyl protons to H-3 and H-5 compares well with that reported (11) for 4-picoline (J = 0.7 c.p.s.).

In the spectrum of 2-amino-5-picoline the methyl

group at C-5 couples strongly with both H-6 and H-4 as is evidenced when the signals for these two protons are examined (Figure 3). In contrast, the signal furthest upfield due to H-3 consists of an expected doublet showing fine *para* coupling but with little or no methyl coupling. Again, the methyl resonance shows breadth but individual lines are not resolved.

The spectra of 2-amino-3- and 6-picolines (Figures 1 and 4) show a unique feature found for methyl substituted pyridines. The pattern shown by their ring protons is interpreted readily if the methyl group couples with not only the adjacent *ortho* protons (4 bonds) but also with the far-removed *para* (6 bonds) protons. Such selective coupling has also been found recently in the benzene series (8). 2-Amino-3-picoline (Figure 1) gives a spectrum of the AMX type with the doublet furthest downfield assigned



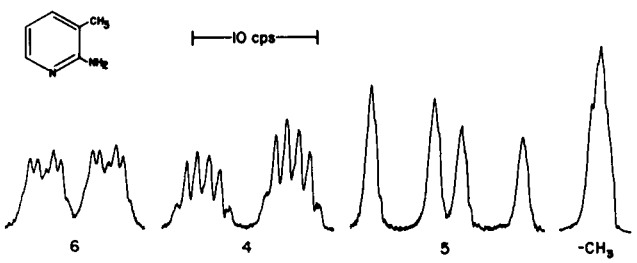


Figure 1. The spectrum of the aromatic and methyl protons in 2-amino-3-picoline at 60 Mc/s in $CDCl_3$ solution; the methyl spectrum was obtained at a different gain than that for the aromatic protons.

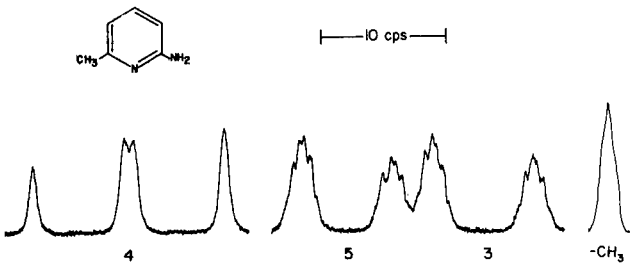


Figure 4. The spectrum of the aromatic and methyl protons in 2-amino-6-picoline at 60 Mc/s in $CDCl_3$ solution; the methyl spectrum was obtained at a different gain than that for the aromatic protons.

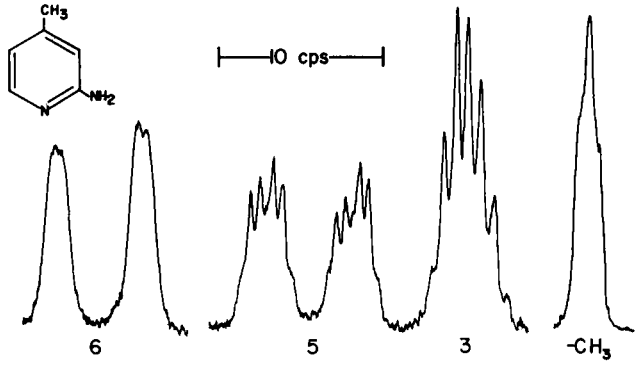


Figure 2. The spectrum of the aromatic and methyl protons in 2-amino-4-picoline at 60 Mc/s in $CDCl_3$ solution; the methyl spectrum was obtained at a different gain than that for the aromatic protons.

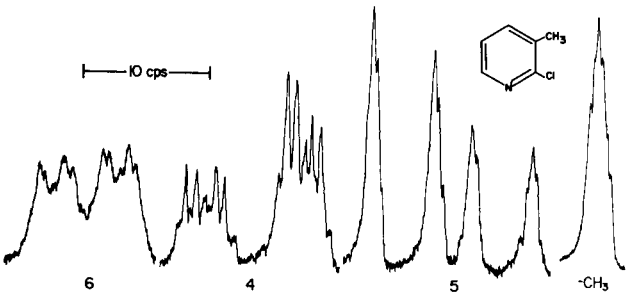


Figure 5. The spectrum of the aromatic and methyl protons in 2-chloro-3-picoline at 60 Mc/s in $CDCl_3$ solution; the methyl spectrum was obtained at a different gain than that for the aromatic protons.

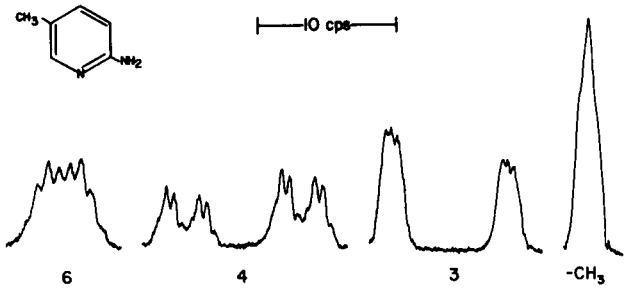


Figure 3. The spectrum of the aromatic and methyl protons in 2-amino-5-picoline at 60 Mc/s in $CDCl_3$ solution; the methyl spectrum was obtained at a different gain than that for the aromatic protons.

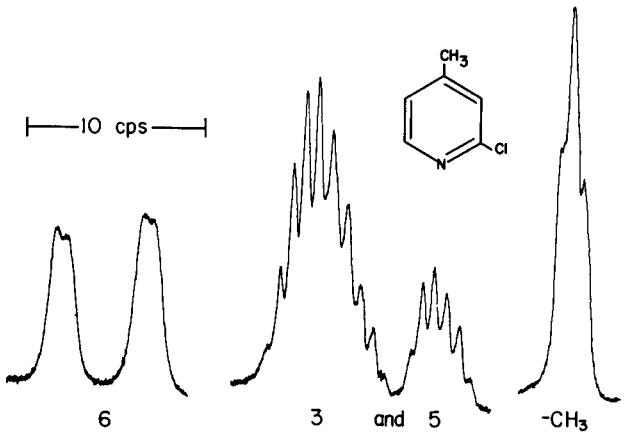


Figure 6. The spectrum of the aromatic and methyl protons in 2-chloro-4-picoline at 60 Mc/s; the methyl spectrum, obtained in $CDCl_3$ solution, was recorded at a different gain than that for the aromatic spectrum, obtained in a DMSO solution.

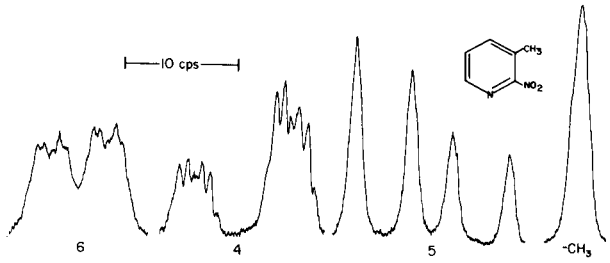


Figure 7. The spectrum of the aromatic and methyl protons in 2-nitro-3-picoline at 60 Mc/s in $CDCl_3$ solution; the methyl spectrum was obtained at a different gain than that for the aromatic protons.

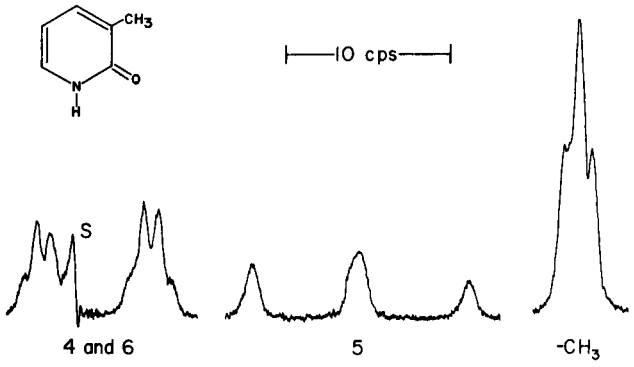


Figure 10. The spectrum of the ring and methyl protons in 3-methyl-2-pyridone at 60 Mc/s in $CDCl_3$ solution; the methyl spectrum was obtained at a different gain than that for the ring protons. The signal marked *S* is due to a chloroform impurity in the solvent.

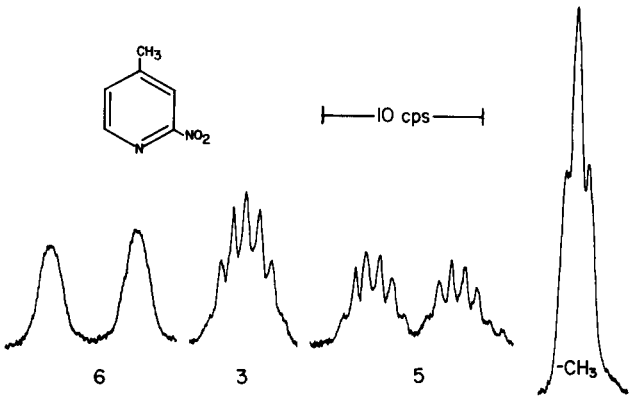


Figure 8. The spectrum of the aromatic and methyl protons in 2-nitro-4-picoline at 60 Mc/s in $CDCl_3$ solution; the methyl spectrum was obtained at a different gain than that for the aromatic protons.

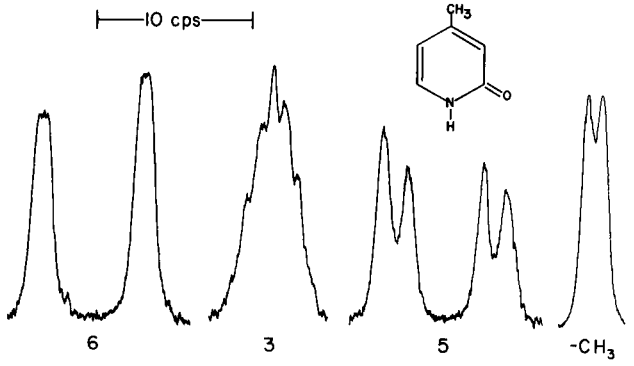


Figure 11. The spectrum of the ring and methyl protons in 4-methyl-2-pyridone at 60 Mc/s in $CDCl_3$ solution; the methyl spectrum was obtained at a different gain than that for the ring protons.

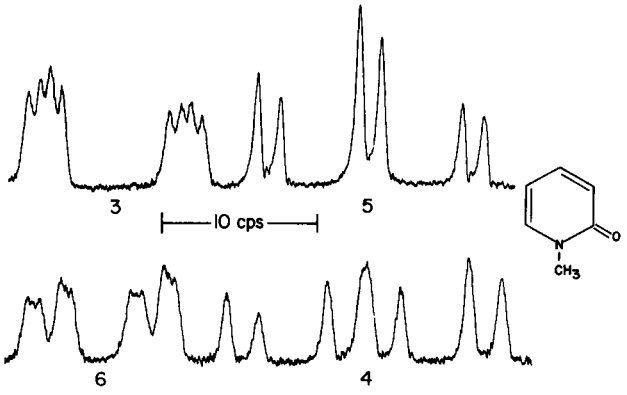


Figure 9. The spectrum of the ring protons in 1-methyl-2-pyridone at 60 Mc/s in $CDCl_3$ solution.

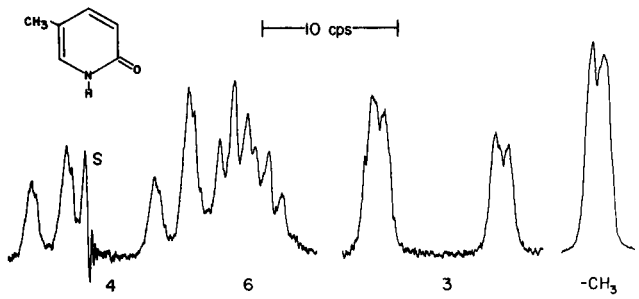


Figure 12. The spectrum of the ring and methyl protons in 5-methyl-2-pyridone at 60 Mc/s in $CDCl_3$ solution; the methyl spectrum was obtained at a different gain than that for the ring protons. The signal marked *S* is due to a chloroform impurity in the solvent.

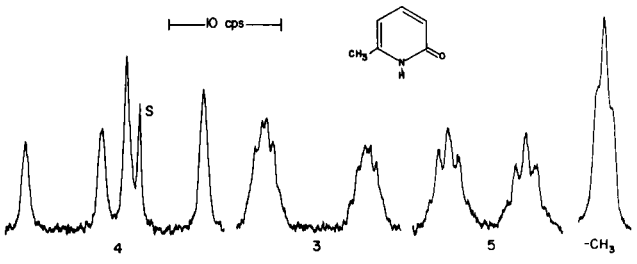


Figure 13. The spectrum of the ring and methyl protons in 6-methyl-2-pyridone at 60 Mc/s in $CDCl_3$ solution; the methyl spectrum was obtained at a different gain than that for the ring protons. The signal marked *S* is due to a chloroform impurity in the solvent.

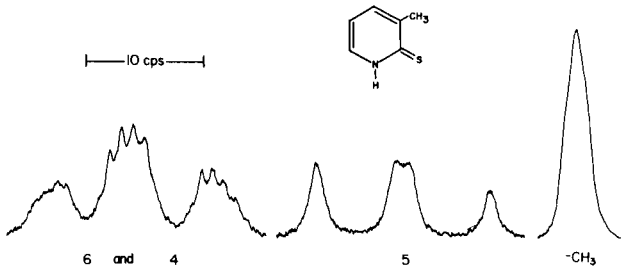


Figure 14. The spectrum of the ring and methyl protons in 3-methyl-2-pyridthione at 60 Mc/s in DMSO solution; the methyl spectrum was obtained at a different gain than that for the ring protons.

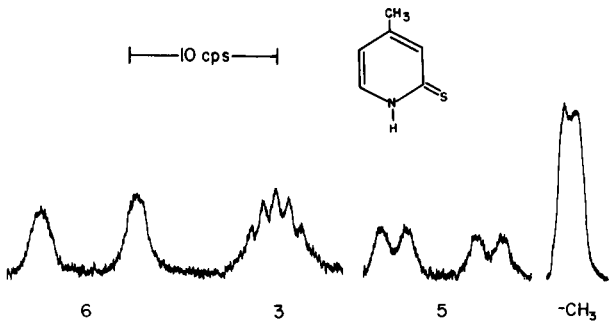


Figure 15. The spectrum of the ring and methyl protons in 4-methyl-2-pyridthione at 60 Mc/s in $CDCl_3$-DMSO (4:1) solution; the methyl spectrum was obtained at a different gain than that for the ring protons.

to H-6, showing 14 lines due to coupling with H-5, H-4 and methyl at the 3 position. A cognate situation can be ascribed to H-4, the complex doublet appearing next upfield (12). In contrast, the quartet due to H-5 is indeed relatively sharp, indicative of little or no coupling to the methyl protons. Again, the methyl peak showed up as an unresolved multiplet.

It was of interest to see if such long-range coupling to *ortho* (4 bonds) and *para* (6 bonds) protons was visible in 2-amino-6-picolines (Figure 4). Indeed, this was observed. The signal furthest downfield was assigned to H-4 in accordance to previous findings (11) and is recorded as a relatively sharp quartet while the signals due to H-3 and H-5 reveal obvious long-range coupling with the methyl group. The methyl signal here did not show much structure but its width at half-height (1.5 c.p.s.) compared to that of TMS (0.4 c.p.s.) suggested multiple coupling to ring protons.

From these observations it was clear that in the four isomeric 2-aminopicolines, the methyl protons coupled noticeably with every available *ortho* and *para* ring proton and to a much smaller extent with the *meta* ring protons. A simple first-order analysis of the multiplet structures gave the constants reported in Table I. It was of interest to ascertain if similar couplings would be found in 2-chloro and 2-nitropicolines and these data are presented next.

2-Chloropicolines.

The parameters for these four isomers are listed in Table I from a first-order spectral analysis. The spectra of 2-chloro-3-picoline and 2-chloro-4-picoline are given in Figures 5 and 6 respectively. 2-Chloro-4-picoline (Figure 6) is discussed first. It revealed a doublet downfield (J = 4.8) assigned to H-6 with well resolved splitting due to *para* coupling and apparently no methyl coupling. It was apparent that H-3 was a multiplet superimposed on one arm of the doublet of multiplets arising from H-5. It was obvious that both H-3 and H-5 coupled with the methyl protons and the septets appeared quite like the ones shown for 2-amino-4-picoline (Figure 2). Furthermore, the methyl group showed up as a well-resolved, although distorted, triplet. In 2-chloro-5-picoline, it was equally easy to detect considerable coupling of the methyl protons with the adjacent protons, H-4 and H-6. Although H-6 appears as a very broad signal (width at half-height = 4.8 c.p.s. compared with 0.4 c.p.s. for TMS), it showed sufficient structure to allow estimation of the coupling constant of it to the methyl group. The doublet due to H-4 showed sufficient structure to permit determination of the long-range coupling constants. The proton furthest upfield was a broadened doublet, and besides the *para* coupling is involved in small undetermined methyl coupling. Thus, it was apparent that in the 2-chloro-4- and 5-picolines coupling with both available *ortho* protons occurred.

The analysis of the n.m.r. spectrum of 2-chloro-3-picoline (Figure 5) revealed coupling of the methyl group to H-4 and also over six bonds to H-6 and

TABLE I

N.m.r. Data

Substituted Picoline (a)	Chemical Shifts (p.p.m.)						Coupling Constants (c.p.s.) (d,e)									
	CH_3	H-3	H-4	H-5	H-6	Other	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{3,5}$	$J_{4,6}$	$J_{3,6}$	$J_{CH_3,3}$	$J_{CH_3,4}$	$J_{CH_3,5}$	$J_{CH_3,6}$
2-Amino-3-	1.98	-	7.18	6.53	7.98	NH_2-5.22	-	7.2	5.1	-	1.8	-	-	1.0	<0.2	0.6
2-Amino-4-	2.16	6.20	-	6.37	7.81	NH_2-4.68	-	-	5.2	1.5	-	0.6	0.7	-	0.6	<0.2
2-Amino-5-	2.12	6.32	7.12	-	7.79	NH_2-4.67	8.4	-	-	-	2.4	0.8	<0.2	0.6	-	0.8
2-Amino-6-	2.28	6.13	7.14	6.32	-	NH_2-5.23	8.1	7.3	-	1.2	-	-	0.6	<0.2	0.5	-
2-Chloro-3-	2.30	-	7.52	7.08	8.18		-	7.8	4.8	-	2.2	-	-	0.8	0.3	0.6
2-Chloro-4-	2.20	6.92	-	6.87	8.00		-	-	4.8	1.5	-	0.6	0.8	-	0.7	<0.2
2-Chloro-5-	2.27	7.13	7.45	-	8.18		8.5	-	-	-	2.5	~0.8	<0.2	0.7	-	~0.7
2-Chloro-6-	2.48	-	-	-	-		8.4	7.4	-	-	-	-	-	-	-	-
2-Nitro-3-	2.47	-	7.75	7.38	8.23		-	8.5	5.0	-	2.0	-	-	0.7	<0.2	0.6
2-Nitro-4-	2.52	7.73	-	7.37	8.33		-	-	5.4	1.6	-	0.8	0.8	-	0.8	<0.2
2-Nitro-5-	2.57	8.22	7.95	-	8.48		8.6	-	-	-	2.3	(f)	(f)	0.8	-	(f)
2-Nitro-6-	2.70	-	-	-	-		-	-	-	-	-	-	-	-	-	-
Substituted 2-Pyridone (a)																
1-Methyl-	-	6.26	7.19	5.99	7.47		9.1	6.6	6.6	1.5	2.1	0.8	-	-	-	-
3-Methyl-	2.16	-	7.25	6.13	7.25	NH-13.43	-	6.5	6.5	-	0	-	-	0.8	<<0.2	0.8
4-Methyl-	2.17	6.30	-	6.05	7.22	NH-13.17	-	-	6.5	1.5	-	0.8	0.8	-	<<0.2	<<0.2
5-Methyl-	2.06	6.45	7.23	-	6.93	NH-13.17	9.1	-	-	-	2.6	0.8	<<0.2	<<0.2	-	1.0
6-Methyl-	2.33	6.35	7.32	5.98	-	NH-13.28	9.1	6.9	-	1.0	-	-	0.5	<<0.2	1.0	-
1,4-Dimethyl-	2.10	6.18	-	5.92	7.23	NCH_3-3.43	-	-	6.8	1.9	-	0.8	0.8	-	<<0.2	<<0.2
3-Bromo-4-methyl	2.36	-	-	6.22	7.36		-	-	6.3	-	-	-	-	-	0	0
Substituted 2-Pyridthione (b)																
3-Methyl-	2.23	-	7.38	6.50	7.48		-	7.9	6.6	-	2.0	-	-	1.0	<<0.2	(f)
4-Methyl- (c)	1.98	6.82	-	6.25	7.20	NH-13.08	-	-	6.5	1.6	-	0.8	0.8	-	<<0.2	<<0.2
5-Methyl-	2.08	7.07	7.07	-	7.31	NH-14.08	-	-	-	-	-	-	<<0.2	<<0.2	-	1.0
6-Methyl-	2.02	7.10	7.33	6.52	-		9.0	6.6	-	1.9	-	-	(f)	<<0.2	0.7	-

(a) In $CDCl_3$. (b) In DMSO. (c) In $CDCl_3$-DMSO (4:1). (d) For 2-substituted pyridines, Brugel (Ref. 11) observed the following coupling constants: $J_{3,4} = 8.2 \pm 0.4$; $J_{4,5} = 7.6 \pm 0.4$; $J_{5,6} = 4.8 \pm 0.3$; $J_{4,6} = 2.0 \pm 0.3$; $J_{3,5} = 1.1 \pm 0.3$ and $J_{3,6} = 1.0 \pm 0.3$ c.p.s. (e) All coupling constants listed at less than 0.2 c.p.s. were estimated, since resolution was not sufficient to permit more accurate measurement. (f) Broad lines prevented determination.

TABLE II

2-Chloropicolines

Position of CH_3 Group	Yield %	B.p., °C (30 mm.)	n_D^{20}		Analyses C,%	H,%	N,%
				Calcd. for C_6H_6ClN:	56.49	4.74	10.98
3	30	93-94 (a)	1.5316	Found:	56.40	4.96	10.94
4	39	97-99 (b)	1.5283	Found:	56.59	4.88	11.05
5	28	97	1.5275	Found:	56.73	4.95	10.81
6	49	86-88 (c)	1.5271	Found:	56.44	5.03	10.75

(a) Reference 22 lists b.p. 192-193 at 751 mm.; (b) Reference 23 lists b.p. 194-195 at 760 mm.; n_D^8 1.5293; (c) O. Seide [*J. Russ. Phys. Chem. Soc.*, 46, 1220 (1915); *ibid.*, 50, 534 (1918); *Chem. Zentr.*, III, 1022 (1923)] lists b.p. 183.5-184° at 749 mm.

TABLE III

Methyl 2-Pyridthiones

Position of CH_3 Group	Yield %	M.p., °C		Analyses C,%	H,%	N,%
			Calcd. for C_6H_7NS:	57.56	5.64	11.19
3	43	172-173	Found:	57.64	5.90	11.07
4	9	175-178	Found:	57.49	5.75	11.09
5	50	199-200	Found:	57.43	5.80	11.08
6	51	152-154	Found:	57.82	5.65	11.02

to some degree to H-5. The resonance due to the latter was observed as a quartet, each arm showing hints at fine structure. Furthermore, the methyl signal appeared as a broad band with considerably more structure than expected of a triplet and suggesting coupling to all three-ring protons. Unfortunately, the analysis of the spectrum of 2-chloro-6-picoline was not a simple one, being of the type $ABMX_3$ where the X protons belonged to the methyl group, the M proton being H-6 and AB being strongly coupled together (H-3 and H-5). The signal furthest downfield was a quartet, yielding two approximate *ortho* coupling constants listed in Table I and clearly showing the absence of methyl coupling which was a sufficient analysis for this coupling pattern study. The multiplet due to H-3 and H-5 was coupled to the methyl protons as seen by extensive splitting. Furthermore, the methyl group appeared as a complex multiplet.

2-Nitropicolines.

It was of interest to establish if the nitro group would exert observable effects on the long-range coupling of the methyl groups to the *ortho* and *para* ring protons. The phenomena observed for 2-amino and 2-chloropicolines were repeated in this series. 2-Nitro-4-picoline (Figure 8) showed the methyl signal as a triplet suggesting coupling to both H-3 and H-5, which was substantiated when the absorption from these protons was examined. As expected, the resonance of H-3 occurred further downfield than H-5 due to the great deshielding effect of the nitro group on the adjacent carbon. This paramagnetic shift of H-3 is important in the analysis of 2-nitro-5-picoline. The latter showed a broad band (width at half-height = 5.0 c.p.s. compared to 0.4 c.p.s. for TMS) furthest downfield, assigned to H-6 and then two doublets, one broad but without structure, the other showing extensive structure in each arm. Normally, one would have assigned the signal next to that of H-6 to that arising from H-4 but in considering the tremendous deshielding influence of the nitro group on H-3, the signal devoid of splitting is assigned to H-3. Then the furthest upfield signal is attributed to H-4, being coupled, of course, with the methyl protons. That the methyl group couples with several ring protons is evidenced when its signal was found to be a broadened, unresolved multiplet. The spectrum of 2-nitro-3-picoline (Figure 7) was relatively self-explanatory and showed definite coupling of the methyl group to H-4 and H-6 and very little coupling to H-5. Unfortunately, the spectrum of 2-nitro-6-picoline showed the ring protons as an ABC pattern and no conclusions could be reached on the extent of methyl coupling.

It is evident from the n.m.r. spectra of these three series of 2-amino-, 2-chloro- and 2-nitropicolines, the methyl groups coupled with available *ortho* and *para* protons in the order of 0.8 to 0.5 c.p.s. and to *meta* protons, 0.2 c.p.s. or less. Furthermore, the magnitude of the coupling seemed independent of the type of substituent on the aromatic pyridine ring.

Methyl substituted 2-pyridones.

The n.m.r. spectra of the five isomers were examined. 1-Methyl-2-pyridone revealed a clear-cut spectrum (Figure 9) with no methyl to ring proton coupling. It afforded us a chance to establish the magnitude of the ring coupling (13). However, the methyl substituted 2-pyridones clearly indicated methyl to ring proton coupling and the following effects were established. The 3- and 6-methyl-2-pyridones exhibited the methyl signal as a triplet, thus suggesting, like the similarly constituted aromatic pyridines, that the methyl group is coupled with several ring protons. 3-Methyl-2-pyridone is discussed first (Figure 10). The signals due to H-4 and H-6 were coincident and if coupled to the methyl protons and H-5 would give rise to a doublet of quartets with the relative intensities of each quartet being 1:3:3:1. The signal due to H-5 appeared as a triplet with considerably less methyl coupling.

6-Methyl-2-pyridone (Figure 13) showed the H-4 resonance as the signal furthest downfield as a relatively sharp quartet indicative of little methyl coupling. This quartet yielded the two coupling constants to H-3 and H-5, and the problem was to decide which signals belonged to these two protons. When the chemical shifts of H-3 and H-5 of the 2-pyridones (Table I) are examined, the H-3 seemed more deshielded than H-5 and partly on that basis this assignment was made. In addition if one assumes that methyl coupling to the proton *ortho* to it (H-5) is larger than to the *para* one (H-3) and if the *meta* coupling constant ($J_{3,5}$) is 1.0 c.p.s., the pattern for H-5 would approximate to that observed with the relative intensities of 1:4:6:4:1. Now if $J_{3,5}$ is 1.0 c.p.s. and J_{CH_3, H_5} is 0.5 c.p.s., a sextet, 1:3:4:4:3:1, would be expected for each arm of the doublet of H-3 and this pattern was seen.

Apparent anomalies were observed when the spectra of 4- and 5-methyl-2-pyridones were analyzed. The methyl signal of 4-methyl-2-pyridone (Figure 11) was recorded as a distinct doublet and from the pattern of the ring protons, it was obvious that the methyl group couples predominantly to H-3. Since H-3 couples to H-5 and to the methyl protons, a septet showing intensities approaching the ratio of 1:4:7:8:7:4:1 was seen. From the appearance of the quartet due to H-5, coupling of it to the methyl group is considerably less and the relatively sharp downfield doublet (H-6) is broadened primarily by *para* coupling and the effect of nitrogen's electric quadrapole moment. This coupling of the methyl group predominantly to one *ortho* proton is also shown in 1,4-dimethyl-2-pyridone. Its spectrum exhibited relatively sharp signals due to H-6 and H-5 but that due to H-3 was observed as a septet similar to that of 4-methyl-2-pyridone (*cf.* Figure 11). It is of interest to note that no methyl to H-5 coupling occurred in 3-bromo-4-methyl-2-pyridone (14).

In the spectrum of 5-methyl-2-pyridone (Figure 12), the methyl signal appeared as a doublet, indicative of coupling with one adjacent ring proton and the question arose as to whether it was with H-6 or H-4. The signal furthest upfield was a clear quartet and was attributed to H-3, thus yielding the two coupling constants, $J_{3,4}$ and $J_{3,6}$. In knowing $J_{3,4}$, it became apparent that the furthest downfield signal (a quartet) was due to H-4 which coupled very little to the methyl protons. This was adjoined (upfield) by the signal due to H-6, which now appeared as a complex multiplet. It is understandable that H-6 is slightly more deshielded due to the adjacent methyl group, but the rather selective coupling of the methyl group predominantly to H-6 is an unexpected phenomenon.

For all the pyridones examined no N-H to C-H coupling was observed. The N-D analogs were prepared and showed no change in ring proton resonances.

It was now of interest to examine the thione analogs of the four pyridones discussed above and observe if similar selective couplings would be found.

Methyl substituted 2-pyridthiones.

Of the four isomeric methyl 2-pyridthiones, 4-methyl-2-pyridthione (Figure 15) presented a pattern quite analogous to its oxygen analog (see Figure 11). The methyl group was observed clearly as a doublet indicative of coupling predominantly to only one ring proton, *viz.*, to H-3 and very little coupling to H-5 or H-6.

When 3- and 6-methyl-2-pyridthiones were examined for long-range coupling to H-4 and H-6, we encountered problems due to lack of separation of signals, but some definite facts emerged. In 3-methyl-2-pyridthione (Figure 14), the methyl signal was a multiplet indicative of extensive coupling with ring protons. The signal furthest downfield was assigned to one-half of the doublet expected of H-6 and could not be resolved but was extremely broad (width at half-height = 4.0 compared to that of TMS at 0.4 c.p.s.) and this width is ascribed to methyl coupling. The next set of signals consisted of a doublet of sextets, one arm of which was superimposed on the upfield signal of H-6, the other separate and the pattern of the latter (1:3:4:4:3:1) is readily explained when based on the coupling constants listed in Table I. The signal due to H-5 consisted of a quartet showing little if any methyl coupling.

The analysis of the spectra of 6-methyl-2-pyridthione was not quite so simple. The signal furthest downfield consisted of a relatively sharp quartet and is attributed to H-4 which showed little or no coupling to the methyl protons. The problem arose to assign H-3 and H-5. The chemical shifts of this compound and the coupling constants suggest that the

signal furthest upfield be considered H-5 which was also strongly coupled to the methyl group, as expected. The remaining doublet is then attributed to H-3, but its diffuse pattern did not permit calculation of the long-range coupling constant, although the broadness of the band strongly suggested it.

The remaining isomer, 5-methyl-2-pyridthione presented the methyl peak as a doublet and the very broad signal due to H-6 suggesting coupling of the methyl group with that proton. Since H-3 and H-4 were strongly coupled (approaching the AB pattern), the chemical shifts could only be obtained approximately and no long-range coupling constants determined.

Thus in this series, it is apparent that in 4- and 5-methyl-2-pyridthiones, coupling occurs essentially only with one of the neighboring protons (H-3 and H-6 respectively) as witnessed by the appearance of the methyl group as a doublet. In the other two isomers, the 3- and 6-methyl signals appeared each as triplets suggesting coupling to both *ortho* and *para* protons, but the coupling constants to the *ortho* proton only could be calculated.

DISCUSSION

This study has shown that aromatic methyl groups in picolines couple with available *ortho* and *para* ring protons while in 2-pyridones and 2-pyridthiones selective coupling occurred as indicated by the starred positions in the formulas. Thus, in 2-substituted-4-picolines (I), the methyl protons couple with both H-3 and H-5 while in 4-methyl-2-pyridone and its thione analog (II) coupling is seen to H-3 only. Similarly, in 2-substituted-5-picolines (III), the methyl proton couples with both H-4 and H-6 with about the same magnitude while in 5-methyl-2-pyridone and its thione analog (IV), coupline was shown predominantly to H-6. In addition, methyl groups at 3 and 6 in *both* the 2-substituted picolines (V and VII), and 2-pyridones (and thiones) (VI and VIII) couple to *both* the available *ortho* (4 bonds) and *para* (6 bonds) protons.

It was also suggested (8) that the magnitude of this long-range coupling serves as a sensitive index of the bond order of the aromatic bond(s) involved and hence a measure of the π-electron delocalization. From this one might conclude that the selective coupling to only one *ortho*-proton in (II) and (IV) for example is an indication of the slightly more double bond character of C_3-C_4 and C_5-C_6 than the aromatic counterparts (I and III) and this manifests itself in this apparent selective coupling. Significantly, as bond length is a function of bond order, X-ray studies reveal the length of these two sides in 2-pyridone are considerably shorter than C_4-C_5 (15). This argument can be applied also where a methyl group is attached to what appears at the end of a conjugated diene in 3- and 6-methyl-2-pyridones (VI and VIII). Since the long-range methyl to ring proton coupling constants in the 2-pyridones and thiones are considerably smaller than expected for a comparable aliphatic system, considerable aromatic character must be associated with 2-pyridones and thiones (16). This picture might be considered adequate and would substantiate the premise that the methyl to ring proton coupling is π-electron transmitted.

This selective methyl to ring proton coupling has recently been reported in a number of related systems. In a paper on the n.m.r. spectra of a number of methyl substituted imidazo[1,2-a]pyridines (IX), selective splitting of the methyl groups with only one *ortho* ring proton was observed when the methyl group was at position C-6, 7 or 8, being coupled only to H-5 (J = 1.1 c.p.s.), H-8 (J = 0.8 c.p.s.) and to H-7 (J = 1.0 c.p.s.) respectively. Although the authors state that a methyl group at C-5 does not couple to H-6, the broadness of their bands at H-6 in their published spectrum suggests some coupling (17). It was concluded from another study of the n.m.r. spectra of the imidazo[1,2-a]-pyridines (18) that these compounds are essentially aromatic, just as pyridones and their thione analogs were considered to be. Although the spectrum of 1,4-dimethylpyridoneimine (X) was published (18), no long-range coupling was reported, but judging from the broad 4-CH_3 and H-3 signals, considerably methyl to H-3 coupling would be expected.

Selective coupling of methyl groups in 10 π-electron systems are available. For example, the methyl group at C-1 in naphthalene couples to H-2 (J = 0.7 c.p.s.) (10). Strangely enough, 2-methylnaphthalene shows only significant coupling to H-1 (J = 0.7 c.p.s.) and not to H-3 (10). In quinaldine (XI), little coupling (<0.4 c.p.s.) (8) was observed to H-3 while in lepidine (XII) $J_{CH_3,\ H_3}$ was found to be 0.93 c.p.s. (10). Thus, even in these "aromatic" quinolines, selective methyl to *ortho* proton coupling appeared. We observed that in 2-chloro-4-lepidine (XIII) in deuterochloroform showed the methyl group at δ 2.25, coupled to H-3 (J = 1.0 c.p.s.) while in 4-methylcarbostyryl (XIV), the methyl signal appeared as a doublet at δ 2.53 (J = 1.3 c.p.s. in deuterochloroform). It seems in the less aromatic quinolone, the long-range coupling of the methyl group to the *ortho* proton is larger than in the more aromatic quinoline counterparts. In a recent paper, in the non-aromatic 1,2-dihydroquinolines (XV), the coupling of the methyl to H-3 was of the order of 1.5 c.p.s. (10).

EXPERIMENTAL (20)

2-Aminopicolines.

All of these compounds were obtained from Reilly Tar and Chemical Co., Indianapolis, Indiana. 2-Amino-3- and 6-picolines were purified by distillation *in vacuo*, the 4- and 5-isomers crystallized from carbon tetrachloride prior to use.

2-Nitropicolines.

2-Nitro-3-, 4-, 5- and 6-picolines were synthesized by the oxidation of the corresponding amines by persulfuric acid (21).

Methyl 2-pyridones.

The 3-, 4-, 5- and 6-methyl-2-pyridones were prepared by the diazotization of the aminopicolines according to the method of Seide (22) and crystallized to literature m.p. from benzene.

2-Chloropicolines.

Their preparation was adapted from the one published by Seide (23) and is described in full for the synthesis of 2-chloro-5-picoline: A solution of 2-amino-5-picoline (10.8 g., 0.1 mole) in concentrated hydrochloric acid (188 ml., d = 1.19) was saturated with hydrogen chloride gas at 5° to 0° (ice and acetone bath). To this stirred solution, with hydrogen chloride still bubbling through, was added sodium nitrite (20.7 g., 0.3 mole) in small portions, keeping the temperature below 5°, and then stirring was continued for 1 hour longer at 0°. The stirred mixture was allowed to warm to room temperature during 12 hours and then made basic with 20% sodium hydroxide solution (500 ml.). Extraction with methylene chloride (300 ml.) afforded a slightly colored oil. This product was placed on activated alumina (90 g., Alcoa, grade F-20) with petroleum ether, b.p. 30-60°. Elution with the same solvent furnished the pure product listed in Table II.

Methyl 2-pyridthiones.

These were made in several ways (24).

3-Methyl-2-pyridthione.

A stirred mixture of 3-methyl-2-pyridone (1.09 g., 0.01 mole), phosphorus pentasulfide (3.34 g., 0.015 mole) was boiled under reflux in pyridine (25 ml., dried by distillation from barium monoxide) for 24 hours. The mixture was decomposed by adding water (25 ml.) and warming the solution on the steam bath for 3 hours. Solvents were then removed *in vacuo* and the residue was dissolved in 50 ml. warm water and the *p*H adjusted to 7.0 by means of sodium carbonate.

A small dark precipitate was filtered off and discarded. The filtrate was extracted with methylene chloride (400 ml.) from which, on evaporation the product was obtained. It was crystallized from benzene and is listed in Table III.

5-Methyl-2-pyridthione.

This compound was prepared in this fashion from the corresponding pyridone (see Table III).

6-Methyl-2-pyridthione.

Anhydrous sodium hydrogen sulfide (8.41 g., 0.15 mole) was prepared by saturating an ethanol solution of sodium ethoxide with hydrogen sulfide and removing the solvents *in vacuo*. The salt was dissolved in freshly distilled propylene glycol (b.p. 185°) and to it was added 2-chloro-6-picoline (3.52 g., 0.03 mole). The mixture was boiled for 20 hours. Solvents were removed *in vacuo* and the residue dissolved in 50 ml. of water. On adjusting the *p*H to 7 with acetic acid, a precipitate was filtered off. The aqueous solution was extracted with chloroform (200 ml.) and gave the product which was crystallized from benzene (see Table III). When commercial hydrated sodium hydrosulfide was used in this preparation, the only product isolated was 6-methyl-2-pyridone.

4-Methyl-2-pyridthione.

This compound was prepared from 2-chloro-4-picoline with commercial hydrated sodium hydrosulfide as described for the last preparation. It was crystallized from 95% ethanol (see Table III).

3-Bromo-4-methyl-2-pyridone.

A solution of bromine (5.23 g., 0.031 mole) in acetic acid (75%, 50 ml.) was added dropwise to a stirred solution of 4-methyl-2-pyridone (3.52 g., 0.031 mole) in glacial acetic acid (75 ml.). The mixture was heated on a steam bath for 25 minutes, and poured over crushed ice. After standing for 12 hours, the solvents were removed *in vacuo*, yielding a slightly colored oil which solidified upon addition of water (25 ml.). Crystallization from absolute ethanol furnished the pure product (1.57 g., 37%), m.p. 195-197° (14).

Anal. Calcd. for C_6H_6BrNO: C, 38.34; H, 3.22; N, 7.45. Found: C, 38.18; H, 3.31; N, 7.49.

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