The Chemistry of Pyridine. VIII. The Sterochemistry of Tetrahydropyridines Isolated from the Reaction of Pyridine N-Oxides with Mercaptans in Acetic Anhydride[1]

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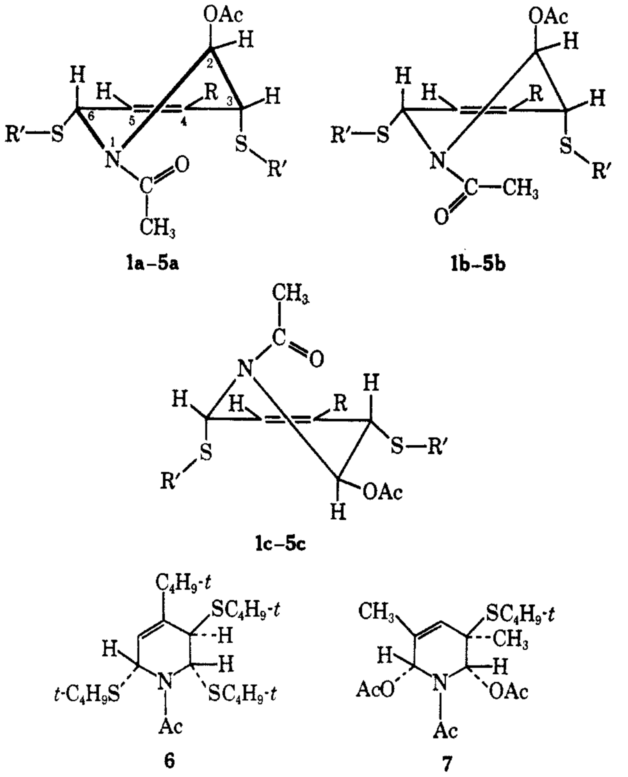
The complexity of the 100-MHz spectra of five 1-acetyl-2-acetoxy-3,6-(dialkylmercapto)-1,2,3,6-tetrahydropyridines produced from the reaction of pyridine, 4-picoline, and 4-phenyl- and 4-*t*-butylpyridine 1-oxides with mercaptans in acetic anhydride[3] is attributed to restricted rotation of the N-acetyl group. It was possible to obtain pmr parameters associated with two rotamers in solution. The α ring protons in these N-acetylpiperideines exhibited the greatest chemical-shift differences, of the order of 1 ppm. The pmr spectra also substantiated the structures of 1-acetyl-2,3,6-tri-*t*-butylmercapto-4-*t*-butyl-1,2,3,6-tetrahydropyridine and 1-acetyl-2,6-diacetoxy-3,5-dimethyl-3-*t*-butylmercapto-1,2,3,6-tetrahydropyridine, which had been isolated previously.[3] An interesting chemical-shift difference for a *methine proton* was observed (~1.5 ppm downfield) in two of the above compounds, when only part of their structure was changed from –**C**H(SR)CH(SR)– to –**C**H(SR)CH(OAc)–.

Analyses of the proton magnetic resonance (pmr) spectra of the N-acetylpiperideines isolated previously,[3,4] not only substantiated their gross structures, **1**–**7** (Chart I), but also served to establish their stereochemistry. The spectra of **1**–**6** suffered reversible changes with temperature which suggested the presence of magnetically nonequivalent species in solution. From an examination of the relative intensities of well separated signals, it was quite apparent that, on the pmr time scale, two magnetically different isomers in varying proportion could be observed for **1**–**6**.

CHART I



1, $R = H, R' = t\text{-}C_4H_9$

2, $R = CH_3, R' = t\text{-}C_4H_9$

3, $R = C_6H_5, R' = t\text{-}C_4H_9$

4, $R = R' = t\text{-}C_4H_9$

5, $R = H, R' = CH_3$

To account for this phenomenon, a number of different equilibria were considered. These will be elaborated on briefly for **1** only. Although conformational equilibria between two half-chair forms of 1,2,3,6-tetrahydropyridine are expected to be relatively fast, it is possible that such a process, **1a** → **1c**, might well be slowed when substituted derivatives are considered. In such a case, two species might well be recorded on the pmr time scale. To diagnose for such an equilibrium, the pmr spectra of **1** were examined between −55 and 120°. No new signals appeared at low temperatures and the coupling constants remained constant which tends to rule out interconversions between **1a** and **1c**. In effect, this pointed to the presence of one fixed-ring conformer, and the data support this assumption. Although nitrogen inversion[5] could cause chemical-shift nonequivalence of the protons in **1** to **6**, for amides, this equilibrium is usually considered to be too rapid on the pmr time scale. Consequently, hindrance to rotation about the amide C–N bond[6] was considered to be responsible for the presence of two magnetically different isomers in solution and the data for **1**–**6** are compatible with such an interpretation. The pmr parameters are listed in Tables I and II. Coalescence

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[3] F. M. Hershenson and L. Bauer, *J. Org. Chem.*, **34**, 655 (1969).

[4] F. M. Hershenson and L. Bauer, *ibid.*, **34**, 660 (1969).

[5] Although originally proposed for amides by T. H. Siddall, III, and C. A. Prohaska [*Nature*, **208**, 582 (1965)], it was shown to be an erroneous interpretation of these data [Y. Shvo, E. C. Taylor, K. Mislow, and M. Raban, *J. Amer. Chem. Soc.*, **89**, 4910 (1967)]. The low barrier for nitrogen inversion in amides, ~2 kcal/mol suggests that at ambient temperatures the equilibrium is too fast on the pmr time scale [P. G. Lister and J. K. Tyler, *Chem. Comm.*, 152 (1966)]. However, nonequivalence of ring protons was observed for N-acylaziridines [F. A. L. Anet and J. M. Osyany, *J. Amer. Chem. Soc.*, **89**, 352 (1967)] and was interpreted in terms of nitrogen inversion. This is understandable that, unlike the six-membered N-acylpiperideines, the N-acylaziridine ring would not be expected to accommodate easily a partially planar sp^2-hybridized ring nitrogen, which would impose additional ring strain.

[6] For recent leading references, consult the interesting studies on N-acetylpiperidines by H. Paulsen and K. Todt [*Chem. Ber.*, **101**, 3385, 3397 (1967)] and those published after this work was completed by R. A. Johnson [*J. Org. Chem.*, **33**, 3627 (1968)].

TABLE I

PMR PARAMETERS OF 1–7 IN C_5D_5N

Compound	Chemical shifts, δ, from internal TMS									Coupling constants, Hz							% of a and b
	H-2	H-3	H-4	H-5	H-6	NAc	OAc	t-C_4H_9S	Other	$J_{2,3}$	$J_{2,4}$	$J_{3,4}$	$J_{4,5}$	$J_{4,6}$	$J_{5,6}$	Other	
(i) At Ambient Temperature																	
1a	6.60	5.51	5.98	6.30	5.68	2.42	1.96	~1.4		2.0	1.0	6.0	10.0	2.0	3.5		64
1b	5.50	5.40	5.90	6.24	6.35	2.29	1.99										36
1a-2,6-d_2		5.51	5.99	6.31		2.41	1.95	~1.4				6.2	10.0				64
1b-2,6-d_2		5.40	5.91	6.25		2.28	1.98										36
2a	6.54	5.34		5.94	5.56	2.40	1.98	1.39, 1.43	1.78 (4-CH_3)	2.2					3.9	J_{3,CH_3} = 1.8 J_{5,CH_3} = 1.8	65
2b	5.46	5.27		5.91	6.26	2.23	2.04	1.40, 1.45	1.75 (4-CH_3)							J_{3,CH_3} = 2.0 J_{5,CH_3} = 2.0	35
3a	6.77	6.10		6.58	5.88	2.47	1.95	~1.4	7.2–7.6 (aromatic)	2.2					4.2		67
3b	5.65	6.03		6.58	6.50	2.29	1.98										33
4a	6.54	5.62		5.99	5.67	2.40	1.94	~1.4	1.04 (4-t-C_4H_9)	2.5					3.6	$J_{3,5}$ = 1.0	72
4b	5.41	5.52		5.98	6.30	2.37	2.00		1.04 (4-t-C_4H_9)								28
6a	6.53	3.92		5.84	5.57	2.45		~1.4	1.24 (4-t-C_4H_9)	2.4					3.2		85
6b	5.34	3.83		5.84	6.28	2.45			1.22 (4-t-C_4H_9)								15
7	6.49		6.06		6.25	2.49	1.64	1.39	1.85 (3-CH_3)		1.2			1.8		$J_{5\text{-}CH_3,6}$ = 0.8	
						2.12			1.86 (5-CH_3)							$J_{5\text{-}CH_3,4}$ = 1.5	
(ii) At Elevated Temperatures (115–120°)																	
1	[a]	5.39	5.86	6.21	[a]	2.29	1.93	1.37		2.0	1.0	6.0	10.0	2.0	3.5		
1-2,6-d_2	[a]	5.41	5.88	6.21	[a]	2.29	1.93	1.37				6.0	10.0				
2	[a]	5.27		5.87	[a]	2.26	1.94	1.38	1.75 (4-CH_3)	2.2					3.9	J_{3,CH_3} = 1.5 J_{5,CH_3} = 1.5	
3	[a]	5.99		6.50	[a]	2.33	1.92	1.42	7.2–7.7 (aromatic)	2.2					4.2		
4	[a]	5.60		6.03	[a]	2.31	1.97	1.53	1.13 (4-t-C_4H_9)	2.5					3.6	$J_{3,5}$ = 1.0	
5[b]	[a]	5.39	5.90	6.20	[a]	2.30	1.89		2.17, 2.23 (SCH_3)	1.6	1.0	5.5	9.6	2.2	3.7	$J_{3,6}$ = 0.8	
6	[a]	3.90		5.82	[a]	2.45		1.40	1.24 (4-t-C_4H_9)	2.4					3.2		

[a] Signals from H-2 and H-6 did not resharpen by 120°. [b] Ambient temperature parameters are not listed since many of the signals were broad and poorly resolved.

TABLE II

PMR PARAMETERS OF 1 IN C_6D_6

At Ambient Temperature

Compound	Chemical shifts, δ, from internal TMS[a]								Coupling constants, Hz[a]						% of a and b
	H-2	H-3	H-4	H-5	H-6	NAc	OAc	$t-C_4H_9S$	$J_{2,3}$	$J_{2,4}$	$J_{3,4}$	$J_{4,5}$	$J_{4,6}$	$J_{5,6}$	
1a	6.565	5.505	5.7475	5.942	4.930	2.00	1.70	1.04, 1.36	2.0	1.0	5.8	9.8	−2.25	3.65	54
1b	5.294	5.246	5.616	6.002	6.2875	2.00	1.54	1.24, 1.34							46
1a-2,6-d_2		5.4765	5.757	5.9575		2.04	1.72	1.09, 1.35			5.8	9.8			56
1b-2,6-d_2		5.230	5.626	6.0015		2.02	1.61	1.26, 1.34							44

[a] Chemical shifts and coupling constants of ring protons were obtained by fitting computer simulated spectrum with the experimental spectrum (See Experimental Section).

temperatures of cognate sets of signals varied considerably since this is a function of the chemical-shift difference between chemically identical nonexchanging protons.

The upfield singlets in **1** (δ 1.0–2.5) arose from S-*t*-butyl, acetoxy, and acetamido protons. The signals between δ 2.1 and 2.4 were assigned to the amide methyl protons on the basis that they tended to be somewhat broader (quadrupole coupling with N) than those from OAc groups (δ 1.9–2.0) and in **6** only NAc methyl resonances were present at δ 2.45. To simplify the analysis of the complex multiplets from the 5 ring protons from each of the two rotamers, **1a** and **1b**, the spectra of the 2,6-d_2 analog of **1** were examined in C_6D_6 and C_5D_5N. At 120°, in the 2,6-d_2 analog of **1**, the signals due to H-3, H-4, and H-5 could be resolved by first-order analysis. The alkene protons in this analog (H-3 and H-4) were expected to resonate furthest downfield and their chemical shifts and coupling constant are of the order reported for 1,2,3,6-tetrahydropyridines.[7] Hence, the signal furthest upfield in that region must be assigned to the H-3 resonance. One might have expected the chemical shift of a methine porton of the type –CHSR–, in the neighborhood of δ 4.0,[8] and it would appear that other factors affect its magnetic environment. Apparently, the anisotropy of the C=O of the vicinal acetoxy group[9] deshields H-3 of **1** by some 1.5 ppm, when compared with **6**, in which a sulfide instead of an acetoxy group is attached to the neighboring C-2 (also, note difference of $\delta_{H\text{-}3}$ in **4** and **6**). On cooling, twice as many signals appeared in the spectrum of the 2,6-d_2 analog of **1**. These were identified from their relative intensities and characteristic coupling constants as being derived from the two rotamers. This part of the study then established the chemical shifts of H-3, H-4, and H-5 and the respective coupling constants and this information was applied to the analysis of the considerably more complex multiplets in the spectra of **1**, in both C_6D_6 and C_5D_5N.

In studies involving rotamers of N-acylpiperidines, it had been shown that the signal furthest downfield stemmed from that α ring proton in which the amide C=O group is on the same side of it. The resonance of the other α ring proton in that particular rotamer might be as far as 1 ppm upfield from that most de-

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[7] (a) In 1,2,3,6-tetrahydropyridine, $\delta_{H\text{-}4}$ and $\delta_{H\text{-}5}$ are at 5.27 and 5.77 (unspecified) [N. S. Baccha, *et. al.*, NMR Spectra Catalog, Vol. I, Varian Associates, Palo Alto, Calif., 1962, No. 115]. (b) In 1,5-dimethyl-6-(*p*-methoxybenzyl)-1,2,3,6-tetrahydropyridine, $\delta_{H\text{-}4}$ is at 5.65 [A. E. Jacobson and R. T. Parfitt, *J. Org. Chem.*, **32**, 1894 (1967)]. (c) The olefinic protons in a number of 1-(β-3-indolylethyl)-1,2,3,6-tetrahydropyridines are observed between δ 5.6 and 5.7 [E. Wenkert, *et. al.*, *ibid.*, **33**, 747 (1968)]. (d) The most closely related model was 1-(3,4,5-trimethoxycinnamoyl)-1,2,3,6-tetrahydropyridine with $\delta_{H\text{-}3,H\text{-}4}$ (unresolved) at 5.85. It might be noted that in this 1-acyl-3-piperideine the two α-CH_2 groups absorbed at $\delta_{H\text{-}2}$ 3.8 and $\delta_{H\text{-}6}$ 4.2 [B. S. Joshi, V. N. Kamat and A. K. Saksena, *Tetrahedron Lett.*, 2395 (1968)].

[8] Chemical shifts for methine protons in similar magnetic environment as H-3 in **1** have been reported. (a) For $ClCH_2CH(SCH_3)CH{=}CH_2$, **CHS** is part of an ABC system, δ 3.2–3.9 [W. H. Mueller and P. E. Butler, *J. Org. Chem.*, **33**, 2642 (1968)]. (b) For

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CHS is buried in a multiplet centered at δ 3.40 [F. Lautenschlaeger, *ibid.*, **33**, 2627 (1968)].

[9] (a) S. Takada, K. Yamada, S. Nakamura and Y. Hirata, *Chem. Comm.*, 538 (1967). (b) C. R. Narayanan and M. R. Sarma, *Tetrahedron Lett.*, 1553 (1968).

shielded signal.[6] When these considerations were applied to **1**, it seems reasonable that the most deshielded proton should be H-2 of the rotamer represented by **1a**. By a series of decoupling experiments, and in knowing $\delta_{H-3,H-4,H-5}$ for both rotamers, it was possible to find δ_{H-6} for **1a**. For rotamer **1b**, irradiation of H-5 helped to locate δ_{H-6}. However, δ_{H-2} in **1b** proved to be difficult to find with certainty by irradiation experiments, since H-2 and H-3 were part of an AB system. To establish δ_{H-2} of **1b** in C_6D_6 with certainty, the spectra the 5 spin system of **1a** and **1b** in C_6D_6 were calculated (Table II) and combined until the best fit was obtained (see Figure 1). The signs of all of the coupling constants were kept positive, except $J_{4,6}$, since the sign of allylic coupling constants have been reported to be negative.[10]

A temperature study of **1** in C_5D_5N (Figure 2) indicated that, by 115°, signals for H-3, H-4, and H-5 from **1a** and **1b** had coalesced. However, the chemical-shift differences of H-2 and H-6 in **1a** and **1b**, being 1.10 and 0.67 ppm, respectively, would dictate a higher coalescence temperature. At 115°, the signals from the α ring protons had broadened to the base line and appeared to have vanished. At this point, it is of interest to compare the spectrum of the S-methyl analog, **5**, with that of **1** in C_5D_5N at 120°. Although the pmr parameter of **5** at 35° could not be obtained by first-order analysis, at 120°, the signals from H-3, H-4, and H-5 are quite sharp. However, the signals from H-2 and H-6 have begun to coalesce as indicated by the broad hump around δ 5.7 (Figure 3). This does introduce the question as to whether or not the S-*t*-butyl at C-6 in **1** poses an additional barrier to rotation compared with the similarly placed S-methyl group in **5**. It is hoped that quantitative data will prove enlightening to this problem.

The pmr parameters of **2**–**7** are compiled in Table I. These were established in part by analogy to **1** and by a series of decoupling experiments. Temperature studies of **2**–**6** in C_5D_5N, up to 120°, again showed coalescence of the signals due to the β and γ ring protons while those of the α protons had flattened to the base line. It was rather surprising to find that **7** provided just a simple pmr spectrum. This compound possessed almost the least bulky α ring substituents of **1**–**6** (**5** being an exception, and it shows rotamers), but bore definitely the most electron-attracting groups (OAc) at those positions. It would then appear that a combination of these effects eliminated the barrier to rotation in **7** at 30° and a time-averaged spectrum resulted.

Stereochemistry.—Vicinal and long-range coupling constants for **1** to **7** agree with the conformational assignments. The constancy of the vicinal coupling constant, $J_{2,3}$ (~2 Hz) in **1**–**6**, would suggest a dihedral angle of ~60°, if the Karplus relationship[11] holds in these piperideines. On such a premise, H-2 and H-3 would be diequatorial[12] and the two bulky substituents would then be diaxial.[12] Such a *trans* arrangement of the

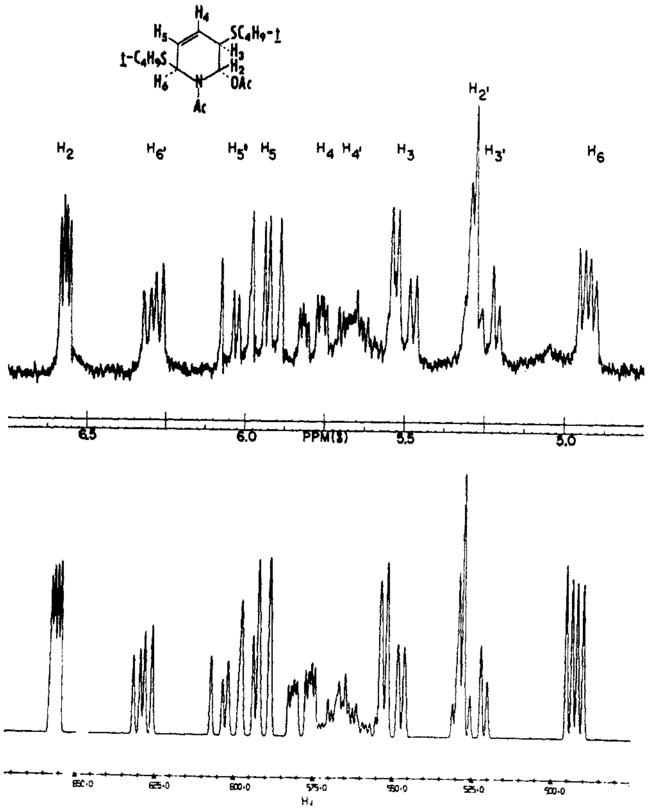

Figure 1.—Pmr spectrum of ring protons of **1a** (H-2 to H-6) and **1b** (H-2′ to H-6′) in C_6D_6—experimental spectrum on top, calculated one on bottom.

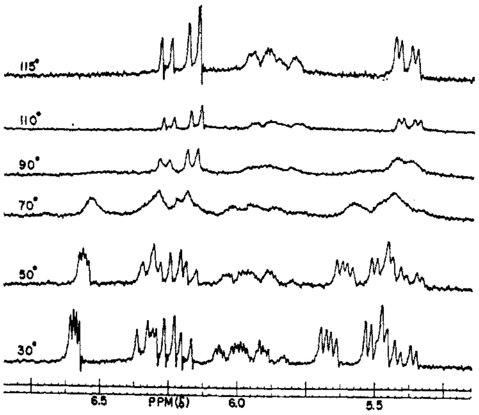

Figure 2.—Temperature study of pmr spectrum of ring protons (only) of **1** in C_5D_5N.

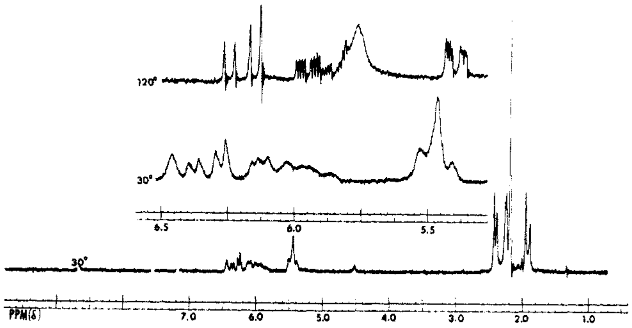

Figure 3.—Pmr spectrum of **5** in C_5D_5N.

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[10] N. S. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry," Holden Day, Inc., San Francisco, Calif., 1964, p 108.

[11] M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959), and **33**, 1842 (1960); *J. Amer. Chem. Soc.*, **85**, 2870 (1963).

[12] Although "equatorial" and "axial" are used, it is realized that perhaps quasiequatorial and quasiaxial would be a better description as suggested for allylic positions in cyclohexenes [R. J. Ferrier and N. Prasad, *J. Chem. Soc., C*, 1417 (1967)].

substituents should also be in agreement with *trans* opening of the episulfonium salt proposed in the mechanism of the formation of **1**–**7**.[3,4] Furthermore, the ready loss of acetic acid observed during the electron impact induced fragmentation of **1**–**5** is also favored, if such a process can take place by *cis* elimination.[13] Long-range coupling over four σ bonds (~1–2 Hz) was detected between H-2 and H-4 and this has been noted for other ring systems, provided an "M" or "W" arrangement of these bonds can be realized.[10,14,15] Since in **1**, **5**, and **7** the stereochemistry of the alkene protons, H-4, is fixed, such an arrangement of the bonds is feasible only if H-2 is equatorial.

The stereochemistry about C-6, for at least **1**, **5**, and **7**, is based on the angular dependence of the allylic coupling constant, $J_{4,6}$. It was established that the magnitude of these allylic coupling constants (0–3 Hz) reaches a maximum when the angle between the allylic protons and the plane of the alkene is 90°, and a minimum when it approaches 0 or 180°.[15,16] The size of $J_{4,6}$ in **1**, **5**, and **7** (~2.0 Hz) suggests that angle to be about 100°, which can be accommodated if H-6 is axial,[17] as can be visualized from models. If H-6 were equatorial, the angle would be 150–160°, and this would suggest J_{allylic} to approach 0 Hz. Since **2**, **3**, **4**, and **6** bore a substituent at C-4, allylic couplings were not available for these piperideines. However, the similarity of chemical shifts and coupling constants in this whole series suggest the same stereochemistry about C-6 as outlined above. One other allylic coupling, *viz.*, $J_{3,5}$, deserves brief mention. Although, attempts were made to find this coupling in **1**–**6**, it was only observed in the spectra of **4** (~1 Hz). This small coupling is not surprising since models indicate that the angle between an equatorial H-3 and the plane of the alkene approaches 180°, and this indeed also supports the stereochemistry of H-3.

Experimental Section

Pmr spectra were obtained with 10–15% solutions at 100 MHz using a Varian Associates HA-100 spectrometer. All spectra were recorded in the frequency sweep mode. Double-resonance experiments were conducted with the attached Hewlett–Packard audio oscillator Model 200AB. Unless otherwise noted, spectra were obtained at ambient probe temperature, 30.4°.

The data are presented in Tables I and II; chemical shifts are reported in parts per million (δ) from internal tetramethylsilane (TMS). Chemical shifts and coupling constants were obtained by first-order analysis. In general, the signs of the coupling constants were not determined. Assignments of chemical shifts were corroborated by as many decoupling experiments as possible.

Although $CDCl_3$, $CCl_2{=}CCl_2$, and $(CH_3CO)_2O$ proved to be satisfactory, C_5D_5N or C_6D_6 proved to be the most satisfactory solvents. The latter were void of acidic contaminants to which **1**–**7** were quite sensitive, particularly at elevated temperatures. C_5D_5N was useful for the temperature studies. The concentration of **1**–**7** in solution affected the pmr spectra to a negligible extent and was not taken into account. Temperature studies on **1**–**6** were repeated a number of times to ensure that no decomposition took place.

The theoretical spectrum for each of the two 5 spin systems belonging to the ring protons of the two isomers of **1** in C_6D_6 was calculated and then combined to compare with the experimentally observed spectrum. Computer calculations toward this end were performed on an IBM 1801 computer and calculated spectra were plotted by a Calcomp plotter. A noniterative LAOCOON II program was used and reported chemical shifts and coupling constants (Table II) were determined by direct comparison of experimental and theoretical spectra.

Registry No.—**1**, 18841-62-8; **1**-2,6-d_2, 18826-32-9; **2**, 18826-33-0; **3**, 18841-63-9; **4**, 18826-34-1; **5**, 18826-35-2; **6**, 18826-36-3; **7**, 18826-37-4; acetic anhydride, 108-24-7.

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[13] W. S. Briggs and C. Djerassi, *J. Org. Chem.*, **33**, 1612 (1968).

[14] L. D. Hall and L. Hough, *Proc. Chem. Soc.*, 382 (1962).

[15] S. Sternhell, *Rev. Pure Appl. Chem.*, **14**, 15 (1964).

[16] E. W. Garbish, *J. Amer. Chem. Soc.*, **86**, 5561 (1964).

[17] Other factors are in favor of such an arrangement. A sulfide group at C-6 in the equatorial position would encounter less steric crowding by 1,3 diaxial interactions. Also, if the mechanism of the addition of the elements of $RSCOCH_3$ across the imine at C-6=N holds,[3] attack by the thiol on an 1-acetyl-2,3-dihydropyridinium cation should occur from the least hindered side which would then introduct RS′ at C-6, equatorially.