21%; mp 44.0–46.0 °C; IR (cm^{-1}) 1640, 1590, 1560, 1140–1270; MS, m/z 395 (M^+); ^1H NMR ($CDCl_3$, δ) 2.4 (s, 3 H), 7.3 (m, 2 H), 8.0–8.1 (m, 2 H); ^{19}F NMR ($CDCl_3$, δ) −21.4 (qt, J = 11.3 Hz, J = 1.9 Hz, 2 F), −7.8 (ttq, J = 18.8 Hz, J = 11.3 Hz, 3 F), 18.0 (m, 3 F), 47.3 (qt, J = 18.8 Hz, J = 1.9 Hz, 2 F).

Anal. Calcd for $C_{14}H_7NOF_{10}$: C, 42.55; H, 1.79; N, 3.54. Found: C, 42.39; H, 1.89; N, 3.66.

6-(Pentafluoroethyl)-5-(trifluoromethyl)-2-phenyl-3-(dimethylamino)pyrimidin-4-one (5a). Excess 1,1-dimethylhydrazine was directly added to **3a** (0.5 g, 1.3 mmol) dissolved in ether at room temperature and heated to reflux over a period of 2 h. The ether insolubles were removed by filtration and the ether was evaporated from the filtrate to leave a yellow solid. The residue was extracted with hexane to give 0.2 g (25%) of a pale yellow solid: mp 140–142 °C; IR (cm^{-1}) 1140, 1160, 1210, 1240, 1530, 1580, 1720 ($\nu_{C=O}$); MS, m/z (relative intensity) 401 (M^+), 358 ($M^+ + 1 - N(CH_3)_2$, 100), 357 ($M^+ - N(CH_3)_2$, 67), 103 ($PhC{\equiv}N^+$, 69); ^1H NMR ($CDCl_3$, δ) 3.0 (s, 6 H), 7.59 (m, 5 H); ^{19}F NMR ($CDCl_3$, δ) −3.8 (t, J = 19.3 Hz, 3F), 17.0 (m, 3 F), 47.3 (q, J = 19.3 Hz, 2 F).

Anal. Calcd for $C_{15}H_{11}N_3OF_8$: C, 44.90; H, 2.76; N, 10.47. Found: C, 44.51; H, 2.87; N, 10.85.

2-(Trifluoromethyl)-1,1,1,3,3,4,4,5,5,5-decafluoropentane (6). Compound **6** was isolated as a THF solution by distillation of the reaction mixture of **1** and **2a**, at 66 °C under atmospheric pressure, and was characterized from ^{19}F NMR analysis which corresponded to that reported in literature.[12]

Registry No. **1**, 1584-03-8; **2a**, 55-21-0; **2b**, 619-80-7; **2c**, 3424-93-9; **2d**, 619-55-6; **3a**, 99838-04-7; **3b**, 99838-05-8; **3c**, 99883-78-0; **3d**, 99838-06-9; **5a**, 99838-07-0; **6**, 30320-28-6; H_2N-$N(CH_3)_2$, 57-14-7; *p*-toluoyl chloride, 874-60-2.

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Nuclear Magnetic Resonance Determination of the Site of Acylation of the Tautomeric Nucleophile 4-Thioxopyridine

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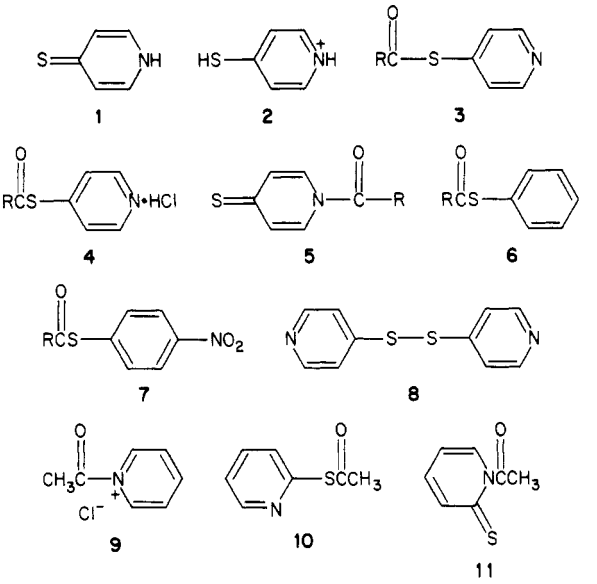
The tautomeric nucleophile 4-thioxopyridine (1) and the corresponding disulfide are useful mechanistic tools as electrophile and nucleophile traps, respectively.[1] We recently employed the title compound to elucidate the details of an enzymatic reaction mechanism, and it became imperative to unequivocally assign the site of acylation of this ambident nucleophile. While the ambiguity in the structure assignment was recognized before,[2,3] those assignments were based solely on UV–vis evidence and excellent chemical intuition. We have synthesized a number of derivatives and are now in a position to make unequivocal assignments based on ^{13}C and ^1H NMR spectroscopy. Conditions were found under which the *N*-acyl (amide) and *S*-acyl (thiol ester) derivatives could be interconverted reversibly. While most straight chain acyl derivatives can exist either as an *S*- or an *N*-acyl isomer, the pivaloyl and benzoyl derivatives exist exclusively as the thiol ester.

Chart I[a]



[a] R = Me (**a**), Et (**b**), *t*-Bu (**c**), Ph (**d**), PhCH=CH (**e**), *p*-ClPhCH=CH (**f**), MeO (**g**), PhO (**h**).

Results and Discussion

The model compounds employed in our studies are listed in Chart I. Syntheses are discussed in the Experimental Section. Most relevant to our analysis are the ^{13}C and ^1H NMR data summarized in Table I. There are three types of structures evident in all these data: the *S*-acyl thiol ester hydrochloride **4**, the *S*-acyl thiol ester **3**, and the *N*-acyl (amide) compounds **5**. All the observed reactions and rearrangements are shown in Scheme I.

Salient features of the structure assignments follow. Reaction of pivaloic anhydride with **1** yielded a colorless liquid **3** [bp 95–100 °C (0.1 torr)] that according to ^{13}C NMR comparisons (the *tert*-butyl methyl and quaternary as well as the carbonyl chemical shifts) with **6c** and **7c**, exists as the thiol ester. While compound **3c** is a liquid (λ_{max} = 250 nm), reaction of **1** with acetic anhydride for 6 h at room temperature produces orange crystals of **5a**[2] (λ_{max} = 375 nm). By contrast reaction of **1** with acetyl chloride in acetone at room temperature produces **4a**[3] (λ_{max} = 276 nm). When a CD_3CN solution of **5a** was saturated with HCl gas, it yielded a product that was spectroscopically indistinguishable from **4a**. When a 0.5 M solution of **5a** dissolved in CD_3CN was incubated in the NMR probe at 22 °C, **5a** was converted to **3a** with a half-life of about 2 h. In water and in methanol at room temperature, **5a** was hydrolyzed (within hours) to **1** according to UV–vis spectroscopic measurements. When compounds **4a**,[2] **4b**, **4e**, **4f**, or **4g**[2] were neutralized with aqueous $NaHCO_3$ and extracted into ethyl ether, UV spectral features of **3** and **5** as well as of **1** could be observed. Therefore, the interconversion of **3** and **5** for certain R groups can be effected from either direction under certain conditions.

The thiol ester structure for **3a** is assigned by comparison of the acetyl methyl and carbonyl ^{13}C chemical shifts

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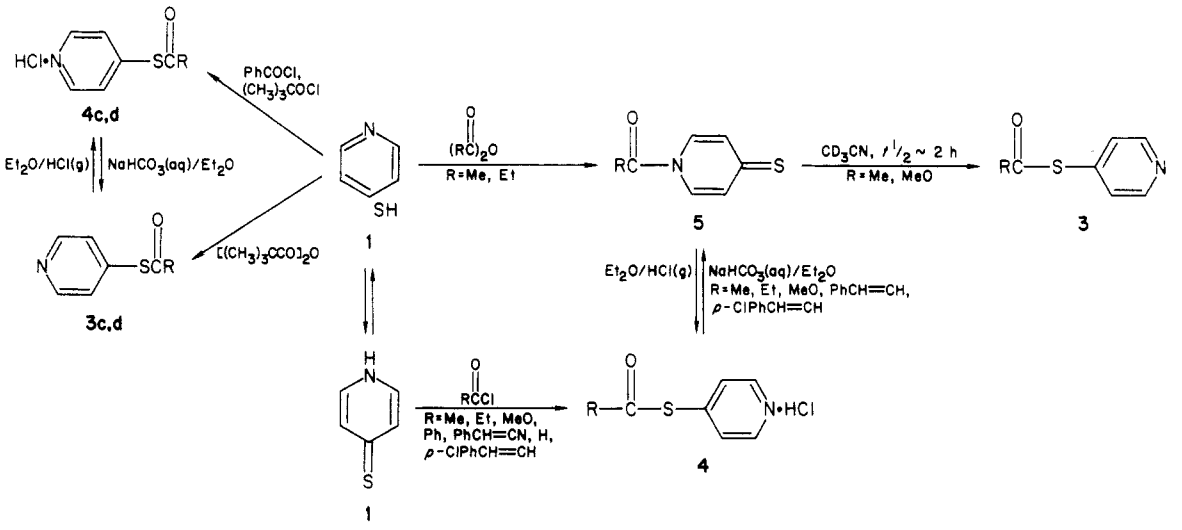
Table I. NMR Chemical Shifts (ppm) of Relevant Compounds

	^{1}H (CD_3CN/Me_4Si)			^{13}C (CD_3CN/Me_4Si)						
compd	CH_3 [or $(CH_3)_3C$]	α^a	β^a	$CH_3(S)$	C=O(S)	$CH_3(N)$	C=O(N)	α^a	β^a	γ^a
1		8.52	7.34					133.5	130.5	192.8
2		8.42	7.89					135.4	130.4	148.9
3a	2.45	8.61	7.40	30.0	191.7			151.0	128.0	138.9
3c	1.27	8.60	7.35	27.5[b]	203.1			149.9	128.8	139.2
				48.2[c]						
3d		8.66	7.51		188.5			151.0	128.3	139.1
3g	3.86	8.60	7.52	55.8				151.0	128.4	139.6
4a	2.56	8.65	8.07	30.2	188.4			139.8	128.3	151.6
4c	1.34	8.64	8.02	25.4	198.6			139.6	129.5	152.1
				47.2						
4g				56.8	192.1			141.6	128.8	153.5
4h								140.5	126.9	150.6
5a	2.57	7.94	7.15			21.2	168.7 (q)[d]	129.2	128.4	201.5 (t)[d]
5g	4.10	7.91	7.15			56.8	151.3	130.4	129.8	202.5 (t)[d]
6a				30.6	194.7					
6c	1.28			27.4[b]	204.1					
				47.3						
7a				30.9	192.9					
7c				27.4	203.2					
				48.1						
8								150.9	121.0	147.1
9						22.4	173.4	147.8	128.7	142.2
10	2.43	7.59-8.59[e]		30.8	193.4 (q)[d]	(124.3, 130.6, 137.8, 150.9, 152.3)[f]				

[a] Letters α, β, and γ refer to the ortho, meta, and para positions with respect to the pyridine nitrogen. [b] $(CH_3)_3C$. [c] $(CH_3)_3C$. [d] The ^{13}C-C-H multiplicities in parentheses were obtained from coupled spectra. [e] Chemical shift range. [f] No assignment was attempted for these chemical shifts.

Scheme I



to those in **6a** and **7a**, and of the carbonyl ^{13}C chemical shift to those in **3c**, **6c**, and **7c** when taking into account the *tert*-butyl alkyl shift in thiol esters.[4] The ^{1}H chemical shifts of the pyridine ring in **3a** are totally analogous to those of **3c**, a compound that exists as a thiol ester under all conditions examined by us. Compounds **5a** and **5g** have NMR (and UV[2]) spectral characteristics unexpected for a thiol ester. The carbonyl ^{13}C chemical shifts in **5a** and **5g** are similar to those in **9** and their pyridine ^{13}C chemical shifts to those in **1**. Assignment of the ^{13}C spectrum of **5a** to the *N*-acyl structure was strengthened by determination of the long-range two-bond ^{13}C-C-H J coupling multiplicities for the resonances at 168.7 (q, CH_3CO) and 201.5 ppm (t, C=S).

The method of choice (when feasible) for the synthesis of structures **5** is from the anhydride. It is also relevant to mention, however, that according to ^{13}C, ^{1}H, and UV spectroscopy, the acetyl derivative of the 2-thioxopyridine isomer is the thiol ester **10**, rather than **11**—perhaps due to the proximity of the N and S atoms.

In summary, Scheme I describes all the reactions and rearrangements observed in our study. ^{13}C and ^{1}H NMR of appropriate model compounds proved to be indispensible for the unambiguous assignment of the site of acylation of the title compound just as it was in the assignment of the site of alkylation of **1**.[5,6] In addition, we have elucidated the fate of pivaloylation of **1** and have also found conditions for the interconversion of **5a** and **5g** with the thiol ester derivatives, rather than with the thiol ester hydrochlorides previously reported.[2]

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Table II. Yields and Physical Properties of Acylated (Aroylated) 4-Thioxopyridine

compd	synthetic method[a] yields,[b] % A	B	C	D	mp,[d] °C	bp, °C (torr)	TLC,[e] R_f	UV-vis,[f] λ_{max}, nm
3c			70[c]	70		98–101 (0.5)	0.51	250
3d				70	70–72 (76[2])		0.45	292
4a	88	90					0.61	278
4b	80	85					0.57	276
4c	90	85					0.48	280
4d	70						0.44	250, 288
4e	71						0.42	315
4f	79						0.39	292
5a			50	45	86–87 (89[2])	79–81 (0.5)	0.62	376
5b			50	51	80–82	82–83 (0.5)	0.58	378
5e			70	70	113–115		0.42	308, 400
5f			85	85	101–103		0.38	305, 390

[a] A, **1** (RCOCl) → **4**; B, **5** (Et_2O–HCl) → **4**; C, **1** [$(RCO)_2O$] **5**; D, **4** ($NaHCO_3$–Et_2O) → **5**. [b] Yield based on compound depicted. [c] Obtained by refluxing **1** in 10-fold excess of pivaloic anhydride for 24 h. [d] Melting points of hydrochlorides **4** could not be determined due to decomposition. [e] Whatman MK $C_{18}F$ reverse-phase plates, CH_3CN solvent. [f] All in spectrograde CH_3CN.

Experimental Section

General. The melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Proton and carbon magnetic resonance spectra were recorded on an IBM WP-200SY Fourier transform instrument at 200.13 MHz (^1H) and 50.31 MHz (^{13}C). All chemical shifts are quoted in ppm downfield from internal tetramethylsilane (Me_4Si). Most ^{13}C spectra were collected under broad band decoupling conditions except where specifically noted. UV–vis spectra were recorded on a Cary 219 spectrophotometer.

4-Thioxopyridine (**1**) and 4,4′-dipyridinyldisulfide (**8**) were from Aldrich. Other compounds were of the highest purity commercially available. Thiol esters **6** and **7** were synthesized according to published procedures[7,8] and compounds **3g,h**, **4a,b,g**, and **5a** according to Comrie.[2]

The purity of compounds **3–10** was determined by integration of ^1H NMR spectra, according to which all had greater than 95% purity. The elemental analyses of new compounds **3c**, **4b–f**, **5b,e,f**, and **7c** indicated that several are hygroscopic. The amount of water adsorbed varies with the time between synthesis and analysis: **3c** (C, H); **4b**(C, H); **4c**, 0.6 H_2O (C, H, N, S); **4d**, 0.8 H_2O (C, H, N); **4e**, 0.5 H_2O (C, H, N); **4f** (C, H, N, S, Cl); **5b**, (C, H, N, S); **5e**, 0.25 H_2O (C, H, N, S); **5f**, 0.06 HCl (C, H, N, S, Cl); **7c** (C, H, N, S).

Synthesis of 4-Acyl(aroyl)thiopyridine Hydrochloride (Method A). 4-Thioxopyridine **1** (1.11 g, 0.01 mol) was suspended in a solution of acyl (aroyl) chlorides (0.05 mol) dissolved in 20 mL acetone, and the mixture was stirred under argon for three h. The resulting crystals of **4** were isolated by filtration, washed with acetone (2 × 5 mL), then with ethyl ether (2 × 5 mL), and dried in a vacuum desiccator over P_2O_5.

Conversion of *N*-Acyl Derivatives (5) to *S*-Acylhydrochlorides (4) (Method B). A solution of **5** (0.01 mol) in anhydrous diethyl ether (25 mL) was saturated with dry HCl gas. The suspension was stirred for 30 min, the crystals of **4** were filtered, washed with ether (3 × 5 mL) and dried in a vacuum desiccator over P_2O_5.

Conversion of 4-Acyl(aroyl)thiopyridine Hydrochloride 4 to 1-Acyl-4-thioxopyridine 5 (Method D). Compound **4** (0.01 mol) was stirred in cold 10% aqueous $NaHCO_3$ (20 mL) for 5 min. The liberated thiol ester **3** was extracted into ether (3 × 50 mL). The combined ether layer was dried (Na_2SO_4), the solvent was removed at reduced pressure, and the residue was kept under high vacuum at room temperature for 1 h. The residue was purified by vacuum distillation (**5a–c**) or recrystallization from ether–petroleum ether (**5d–f**).

Table II summarizes the physical and UV–vis spectroscopic properties of some of the compounds studied.

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