Chemistry of Thienopyridines. XXVIII. Mass Spectra of Fourteen Substituted Thienopyridines and NMR Spectra of Four Picrates (1)

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Electron-impact mass spectra are presented for various substituted thieno[2,3-*b*]- and thieno[3,2-*b*]-pyridines. In particular, it is shown that chemical structures of alkylthienopyridines can be correlated (a) with their mass spectral fragmentation patterns and (b) with the proton magnetic resonance spectra of their picrate salts.

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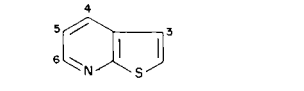
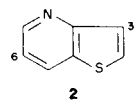
To aid in identifying thienopyridine derivatives synthesized in our laboratory we now report electron-impact mass spectral data for fourteen miscellaneous compounds (including seven with alkyl substituents) and the proton magnetic resonance spectra for four alkylthienopyridinium picrates. Compounds considered are **1a-1l** and **2a-2c**, for which syntheses and structural assignments of all but two (*i.e.*, **1c** and **1k**) have been reported previously (3-5).

Condensation of 1-penten-3-one (**3**) with bis(2-thienylammonium)hexachlorostannate(IV) (**4**) in the manner previously described for 1-buten-3-one with **4** (3) gave a mixture of **1c** and **1k**, liquids separable by gas chromatography on a stationary phase of silicone or Bentone-



1

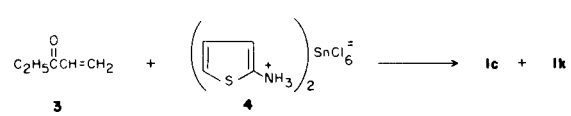
a, 3-NO_2
b, 4-Me
c, 4-Et
d, 4,6-DiMe
e, 5-Br
f, 5-CN
g, 5-Et
h, 5-$CH_2C(=S)N$(morpholine)
i, 5-CH_2CO_2Me
j, 6-Me
k, 6-Et
l, 6-n-Bu



2

a, 3-NO_2
b, 6-Et
c, 6-Ac

silicone (6). As with the corresponding 4- and 6-methylthieno[2,3-*b*]pyridine isomers (**1b** and **1j**) the 6-ethyl isomer is less strongly retained (6). Compounds **1c** and **1k** were purified further by conversion to crystalline picrates.



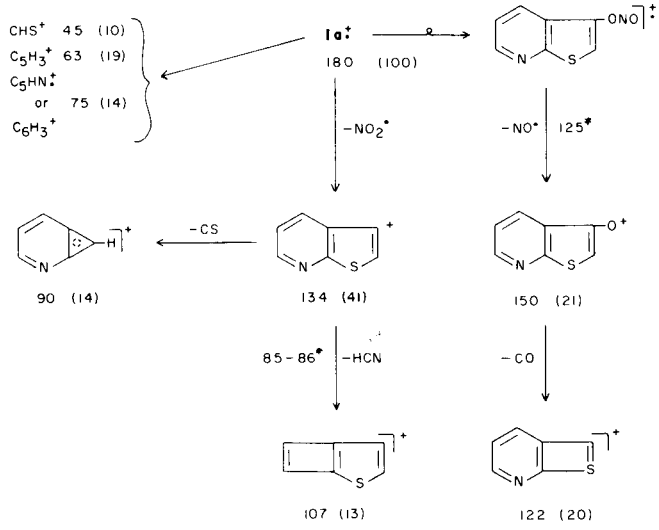
3 **4** **1c** + **1k**

The proton magnetic resonance spectrum of **1c** picrate clearly established the location of the ethyl group on the thienopyridine ring (*vide infra*) (7).

The relatively complex mass spectral fragmentation pattern of 3-nitrothieno[2,3-*b*]pyridine (**1a**) is presented in Scheme 1, where one notes the loss of the small molecules NO, NO_2, CO, CS, and HCN. Two of the dissociation steps

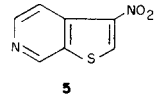
Scheme 1 (a)

Mass Spectral Fragmentation Pattern for 3-Nitrothieno[2,3-*b*]pyridine, **1a** (b)



(a) Includes all peaks of relative abundance ≥ 10%, except for 181 (10). (b) Ion source at 160°.

are corroborated by the presence of metastable peaks, at m/e 85-86 and 125. Consistent with earlier studies (8-13), ejection of HCN and CS (or CHS radical) as well as the formation of the thioformyl cation (m/e 45) characterize the mass spectral patterns of many thienopyridines. The mass spectra of the isomeric nitrothienopyridines **1a**, **2a**, **5**, and **6** (13,14) are similar in most respects, but there are some



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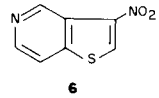

6

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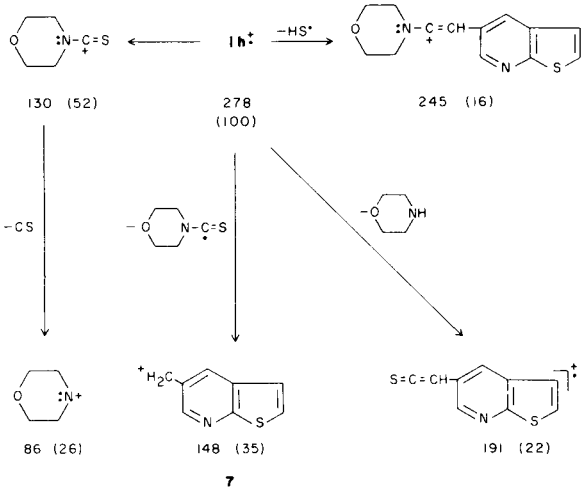
notable differences in relative intensities of certain peaks. While the ratio of intensitites of the peaks at 134 and 122 is approximately 2:1 for the [2,3-*x*] compounds **1a** and **5**, it is closely 1:2 for the [3,2-*x*] compounds **2a** and **6** (where *x* = *b* or *c*). Also the [*c*] compounds **5** and **6** show much more intense peaks (*ca.* 50%) at m/e 63 than do the [*b*] compounds **1a** and **2a** (*ca.* 17%), while **2a** has a particularly strong peak (41%) at m/e 39.

Scheme 2 depicts the fragmentation pattern of α-(5--thieno[2,3-*b*]pyridine)acetothiomorpholide (**1h**), wherein the molecular ion is the most abundant one. Fission of this ion occurs predominantly at one of the bonds to the carbon atom located β to the ring. In contrast, the thienopyridine nucleus remains largely intact. Somewhat analogously the molecular ion **1i**$^{+\cdot}$, which forms in the ion chamber after loss of HCl from the parent salt methyl α-(5-thieno[2,3-*b*]pyridine)acetate hydrochloride, undergoes

Scheme 2 (a)

Side-Chain Fragmentation in the Mass Spectrum of Thiomorpholide **1h** (b)



(a) Includes all peaks of relative abundance ≥10%, except for 280 (11), 279 (18), 192 (14), 149 (20), and 112 (10). (b) Ion source at 190°.

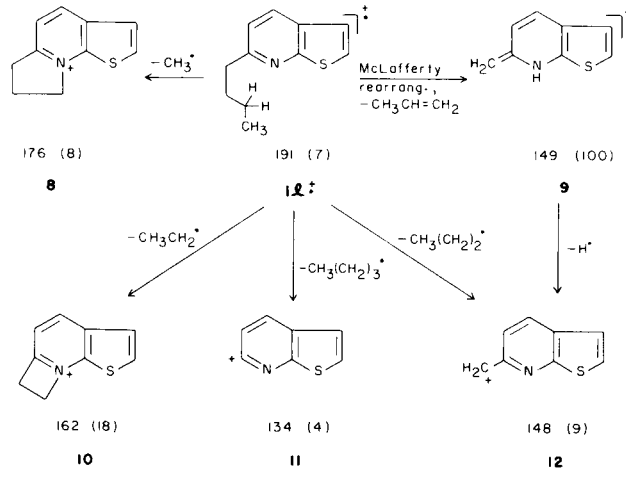
splitting principally at the β-carbon but to give almost exclusively the 5-thienopyridylmethyl carbonium ion (**7**, 100% abundance).

As expected from results reported for mass spectral fragmentation of alkylquinolines (15), 6-*n*-butylthieno[2,3--*b*]pyridine (**1l**) undergoes carbon-carbon bond fission at all points along the alkyl chain (Scheme 3). The most abundant ion (at m/e 149) results from the loss of propene, probably via a McLafferty rearrangement to give **9**. Cleavage of alkyl groups from the molecular ion account for the formation of cations at 176, 162, 148 and 134 (corresponding to structures **8**, **10**, **12** and **11**, respectively). Structure **12** (isomeric with **7**) could also result from loss of a hydrogen atom from **9**.

A comparison of four of the significant mass spectral peaks for the five isomeric ethyl- and dimethylthienopyridines (C_9H_9NS) studied is presented in Table I. All of these isomers except **1g** and **2b** are easily distinguishable on the basis of the realtive abundances of the peaks. As for 2-ethylquinoline (16), the isosteric 6-ethylthieno[2,3-*b*]-pyridine (**1k**) is distinguished by the presence of an (M - 1) base peak, of likely structure **10** or **13** (15,17) and the probable loss of ethene to give **14** (m/e 135) or the thieno[2,3--*b*]pyridine cation radical (**15**). Compounds **1g** and **2b**, in which the ethyl group is in a β-position to the heteroatomic nitrogen, have base peaks at (M - 15) for loss of a methyl group. The resultant cations (**16** and **19**) may be stabilized largely in the thienoazatropylium forms **17** and **20** or, even more likely, as the thiaquinolinium structures **18** and **21** (17,18).

Scheme 3 (a)

Mass Spectral Fragmentation Pattern for 6-*n*-Butylthieno[2,3-*b*]pyridine, **1l** (b)



(a) Includes all peaks of relative abundance ≥4%, except for 163 (4), 151 (5), 150 (10). (b) Ion source at 160°.

Table I

Comparative Pertinent Mass Spectral Peaks for Four Ethyl- and One Dimethylthienopyridine Isomers

m/e	Chemical Assignment	Relative Abundance of Ion, % (a) For **1c**	For **1g**	For **1k**	For **2b**	For **1d**
163	M$^{+\cdot}$	100	60	78	61	100
162	(M-H)$^+$	34	15 (b)	100	14	18
148	(M-CH_3)$^+$	73	100	8	100	14
135	(M-C_2H_4)$^+$ or (M-[H + HCN])$^+$	8	6	21	4	4

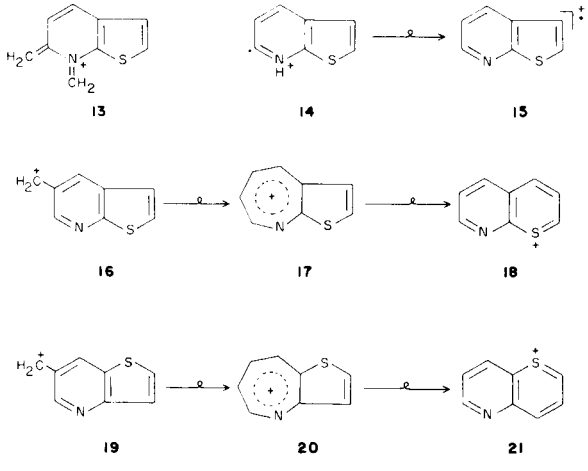
(a) See Experimental for the complete spectra. (b) Corroborated by the presence of a metastable peak.

Table 2

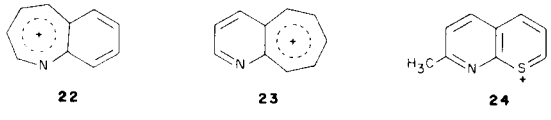
Comparative Chemical Shifts and Coupling Constants in the Proton NMR Spectra of Some Alkylthienopyridines and Their Picrates (TNP Derivatives)

		δ, ppm (b)						J, Hz	
Compound	Solvent (a)	H-2 and H-3	H-4	H-5	H-6 or H-7	CH_3	CH_2	2,3	Other Remarks
1b	A	7.12, 7.37		6.86	8.34	2.35		6.0	5,6 (4.5) reference 3
1b•TNP	B	7.65, 7.98		7.51	8.64	2.73		5.9	5,6 (5.4) (c)
1c•TNP	B	7.71, 8.01		7.55	8.70	1.33	3.11	6.0	5,6 (5.4), (c), Et (7.6)
1j	A	7.10, 7.33	7.80	7.12		2.60		6.0	4,5 (8.0) reference 3
1j•TNP	B	7.51, 7.89	8.43	7.51		2.72		5.7	4,5 (8.2) (d)
2b	A	7.59		8.60	7.86	1.16	2.62		5,7 (2), reference 3, Et (7.5)
2b•TNP	B	7.71, 8.53		9.05 (e)	8.90 (f)	1.32	2.91	5.7	5,7 (1.7), (g), Et (7.5)

(a) A is carbon tetrachloride; B is moist hexadeuteriodimethyl sulfoxide. (b) All TNP derivatives also show a sharp singlet at 8.60 ±0.02 for 2 picrate ring protons. The δ values are given *vs.* TMS as an internal standard. (c) Assignments of H-5 and H-6 may be reversed, however coupling between H-5 and H-6 was confirmed by double irradiation. (d) Assignments of H-4 and H-5 may be reversed. (e) Broadened singlet. (f) Broadened doublet. (g) Assignments of H-5 and H-7 may be reversed.



Djerassi, *et.al.*, (17) noted a marked difference in the ratio of intensitites (M - [H + HCN])/(M - H) for the peaks in the spectra of the methylquinoline isomers depending upon whether the methyl group is substituted in the pyridine ring (ratio, 1.3) or in the benzene ring (ratio, 0.32). They ascribed the difference to a greater ease of losing HCN from the benzoazatropylium ion (**22**) than from the pyridotropylium ion (**23**) intermediates.



In contrast, the corresponding ratio of peak intensities for 6-methylthieno[2,3-*b*]pyridine (**1j**) is 0.33, instead of 1.3 (expected from isosterism). This result is readily interpretable if the (M - H) fragment from **1j** exists to an appreciable extent as the thiaquinolinium ion **18** and only to a smaller degree as the thienoazatropylium ion **17**. There is also a contrast in the ratios of intensities (M - [H + MeCN])/(M - (H + HCN) for the peaks from the isosteres 2,4-dimethylquinoline and 4,6-dimethylthieno[2,3-*b*]-pyridine (**1d**). The former shows a ratio of 2.7, with an intensity of *ca.* 15% for loss of (H + MeCN); while **1d** has a ratio of 1.0, with an intensity of only 4% for loss of (H + MeCN). Again thiaquinolinium ions, *e.g.* **24**, may be implicated in this thienopyridine case. Further evidence for or against the formation of thiaquinolinium ions needs to be sought by a study of the mass spectra of a variety of methylthienopyridines (19).

Comparison of the fragmentation patterns of the ethylthieno[2,3-*b*]pyridines **1c**, **1g** and **1k** with those of the respective isosteres 4-, 3- and 2-ethylquinolines (20) shows many similarities in the major peaks (relative abundances >40%), but the ethylthienopyridines give fewer peaks of relative intensities in the range of 10-40%. As with cases of isomeric compounds reported in the literature, bromothienopyridine **1e** shows abundant ions at M and (M -Br) values (9,14), cyano derivative **1f** has significant peaks at M and (M - HCN) (9), and acetyl compound **2c** gives the order of peaks of (M - CH_3) > M > (M - Ac) in relative intensities (10).

A search of the chemical literature, including catalogs of spectra, failed to reveal a single case where the nmr spectrum of an amine picrate had been reported, although spectra have been obtained on various other amine salts and the use of nmr studies to measure association constants for organic charge-transfer complexes is a well-documented method (21-24). We now report that proton nmr spectra of the picrates of the alkylthienopyridines **1b**, **1c**, **1j** and **2b** are readily obtainable in moist hexadeuteriodimethylsulfoxide solution. Under these circumstances one observes resonance peaks for all of the protons in the alkylthienopyridines and a sharp singlet at δ 8.60 ±0.02 for the two ring protons on the picric acid moiety. No phenolic proton signal is apparent. For cases

1b, **1j** and **2b**, proton nmr spectra of the parent free amines in carbon tetrachloride were reported earlier (3). Respective assignments of the resonances for the two aromatic protons in the thiophene ring of the picrates are uncertain. This is likewise the situation for the two protons in the alkyl-substituted pyridine rings (25). However, it appears that all signals for the picrates in hexadeuteriodimethylsulfoxide fall downfield ($\delta\Delta$ = 0.1-1.2 ppm) from the corresponding signals for the free amines in carbon tetrachloride (Table 2). For **2b**•TNP $\Delta\delta$ is particularly large (0.94 and 1.04 or 1.19) for one proton in each of the two heterocyclic rings. Moreover, line broadening is easily observed for both of the pyridine ring proton signals in this picrate. In general, coupling constants do not change significantly on going from the amine in carbon tetrachloride to its picrate in moist DMSO. However, $J_{5,6}$ changes from 4.5 to 5.4 for this transformation. Observation of a coupling constant of 5.4 Hz for the pyridine ring protons in **1c**•TNP clearly establishes this compound as the 4-ethyl derivative rather than the isomeric 6-ethyl compound (**1k**•TNP, expected $J_{4,5}$ = 8.2 Hz, see **1j**•TNP coupling constant). Compounds **1c** and **1k** were separated from a reaction mixture (*vide supra*), but only sufficient pure **1c**•TNP was available for nmr studies.

Several workers (22,23,26) have investigated the proton nmr spectra of pyridinium and substituted pyridinium salts in various solvents. Gowland and McClelland (23) proposed that the percentage of proton transfer from the acid to the base is dependent upon (a) the difference in pK_a's of the two components and (b) the solvent used. Assuming their results with trichloroacetic acid (pK_a 1) and pyridine (pK_a 5.2) are a suitable model for **1k**•TNP from picric acid (pK_a 0.4) and **1k** (pk_a estimated as 4.4, *i.e.*, the same as thieno[3,2-*b*]pyridine) (27), one would expect complete proton transfer in water and very little transfer in DMSO. Probably as a result of our use of moist DMSO the proton is both transferred to a large extent and undergoes such rapid exchange as to show no signal in the nmr spectrum. The downfield shifts ($\Delta\delta$) and the line broadening in the spectrum of **2b**•TNP seem consistent with these assumptions. A further investigation of the use of azinium picrates for structural studies on azines is clearly warranted (19).

EXPERIMENTAL (28)

4- and 6-Ethylthieno[2,3-*b*]pyridines (**1c** and **1k**).

Reaction of ethylvinyl ketone (**3**) (Aldrich) with bis(2-thienylammonium)hexachlorostannate(IV) (**4**) in absolute ethanol was conducted in the same manner as previously described for methyl vinyl ketone with **4** (3). The mixture of liquid products was purified and separated by vapor phase chromatography by means of a stationary phase of silicone fluid DC 550 (10%) on Chromosorb W at 170° to give the 6-ethyl compound (**1k**, relative yield 55%, relative retention V_R = 1.0) and the 4-isomer (**1c**, relative yield 45%, V_R = 1.5).

Anal. Calcd. for C_9H_9NS: C, 66.2; H, 5.6; N, 8.6. Found for **1c**: C, 65.9; H, 5.6; N, 8.6. Found for **1k**: N, 8.6.

These compounds were purified further by conversion to picrates, obtained as canary yellow needles from absolute ethanol.

Anal. Calcd. for $C_{15}H_{12}N_4O_7S$: C, 45.9; H, 3.1; N, 14.3; S, 8.2. Found for **1c** picrate, mp 177-178°: C, 45.8; H, 3.0; N, 14.4; S, 8.1. Found for **1k** picrate, mp 162-163.5°: C, 45.6; H, 3.1; N, 14.3; S, 8.0.

Mass Spectra.

Mass spectra were determined by Drs. Susan Rottschaefer and Richard Wielesek by means of a CEC model 21-110 double focusing instrument operated at 70 eV. In the following list of data are given the temperature of the ion source (°C), m/e values for all peaks of relative abundances (shown in parentheses) variously ≥4, 5 or 10% (as indicated by the minimal value shown for the compound) of the base peak, and any observed metastable peaks (indicated by asterisks) plus the corresponding ion decomposition pathways.

3-Nitrothieno[2,3-*b*]pyridine (**1a**).

See Scheme 1.

4-Ethylthieno[2,3-*b*]pyridine (**1c**).

This compound had ms: (160°) 165 (5), 164 (13), 163 (100) M$^+$, 162 (34), 149 (8), 148 (73), 135 (8), 121 (5).

4,6-Dimethylthieno[2,3-*b*]pyridine (**1d**).

This compound had ms: (150°) 165 (5), 164 (12), 163 (100) M$^+$, 162 (18), 148 (14), 135 (4), 122 (4), 121 (4).

5-Bromothieno[2,3-*b*]pyridine (**1e**).

This compound had ms: (80°) 217 (5), 216 (9), 215 (100) M$^+$, 214 (9), 213 (98) M$^+$, 134 (44) [M - Br]$^+$, 63 (7), $C_5H_3^+$.

5-Cyanothieno[2,3-*b*]pyridine (**1f**).

This compound had ms: (90°) 162 (5), 161 (11), 160 (100) M$^+$, 133 (7) [M - HCN]$^+$, 116 (6).

5-Ethylthieno[2,3-*b*]pyridine (**1g**).

This compound had ms: (170°) 164 (7), 163 (60) M$^+$, 162 (15), 150 (5), 149 (10), 148 (100), 135 (6), 121 (7), 104 (5), 77 (5), 69 (6), 63 (8) $C_5H_3^+$, 51 (7), 45 (10) CHS$^+$, 39 (8) $C_3H_3^+$, 161-162* (163→162).

α-(5-Thieno[2,3-*b*]pyridine)acetothiomorpholide (**1h**).

See Scheme 2.

Methyl α-(5-Thieno[2,3-*b*]pyridine)acetate Hydrochloride (**1i**•HCl).

This compound had ms: (190°) 208 (8), 207 (59) M$^+$ after loss of HCl, 150 (5), 149 (11), 148 (100) [M - CH_3OC=O]$^+$, 121 (6) [M - (CH_3OC=O + HCN)]$^+$.

6-Methylthieno[2,3-*b*]pyridine (**1j**).

This compound had ms: (160°), 151 (5), 150 (11), 149 (100) M$^+$, 148 (24), 134 (4) [M - CH_3]$^+$, 122 (8) [M - HCN]$^+$, 121 (8), 104 (4) [M - CHS]$^+$, 63 (5) $C_5H_3^+$.

6-Ethylthieno[2,3-*b*]pyridine (**1k**).

This compound had ms: (155°) 165 (4), 164 (13), 163 (78) M$^+$, 162 (100), 148 (8), 136 (9), 135 (21), 134 (8), 122 (4), 63 (4) $C_5H_3^+$.

6-*n*-Butylthieno[2,3-*b*]pyridine (**1l**).

See Scheme 3.

3-Nitrothieno[3,2-*b*]pyridine (**2a**).

This compound had ms: (170°) 181 (10), 180 (100) M$^+$, 150 (25) [M -NO]$^+$, 134 (27) [M - NO_2]$^+$, 122 (54), [M - (NO + CO)]$^+$, 107 (14) [M - (HCN + NO_2)]$^+$, 90 (12) [M - (CS + NO_2)]$^+$, 83 (13), 78 (10), 69 (10), 63 (15) $C_5H_3^+$, 45 (14) CHS$^+$, 39 (41) $C_3H_3^+$, 125* (180→150), 85-86* (134→107).

6-Ethylthieno[3,2-*b*]pyridine (**2b**).

This compound had ms: (150°) 164 (8), 163 (61) M$^+$, 162 (14), 149 (11), 148 (100), 122 (5), 121 (5).

6-Acetylthieno[3,2-*b*]pyridine (**2c**).

This compound had ms: (100°) 178 (8), 177 (69) M^{+}, 164 (6), 163 (11), 162 (100) $[M - CH_3]^{+}$, 135 (9), 134 (62) $[M - (CH_3 + CO)]^{+}$, 107 (5), 96 (7), 82 (8), 81 (5), 63 (13) $C_5H_3^{+}$, 43 (7) Ac^{+}, 110-111* (162→134).

Proton Magnetic Resonance Spectra.

Proton Magnetic Resonance spectra were obtained on 3.6-6.5 weight % solutions of crystalline picrates in hexadeuteriodimethylsulfoxide (Stohler, 99.5% D, with tetramethylsilane as internal reference) by means of a Varian XL-100A spectrometer operated in a continuous-wave mode. A sweep width of 1000 Hz was used to determine chemical shifts and integrations and an expanded spectrum of 100 or 250 Hz (full scale) was used to determine coupling constants. Each spectrum showed a strong peak for the presence of adventitious water in the solvent.

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