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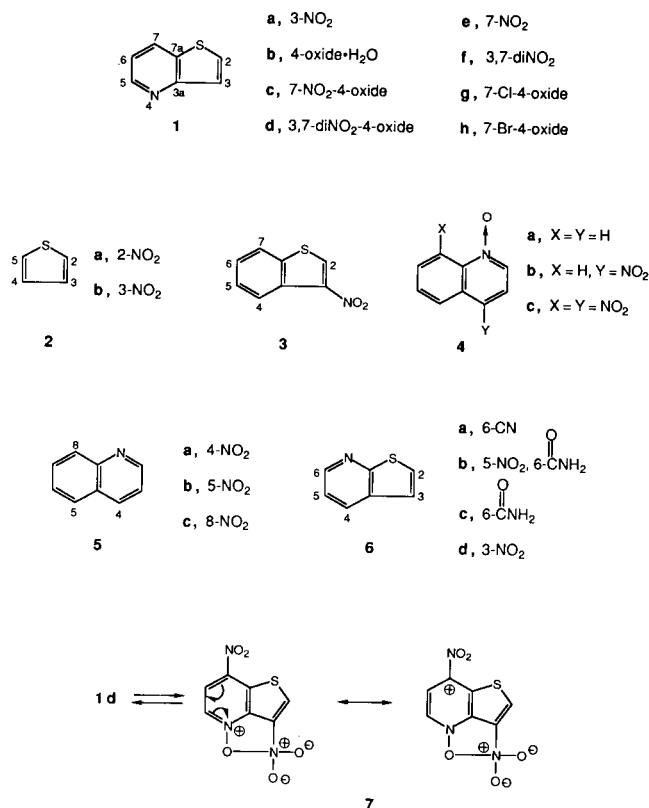
## Dedicated to Professor Ernest Campaigne on the occasion of his 75th birthday

Three compounds, thieno[3,2-*b*]pyridine 4-oxide, 7-nitrothieno[3,2-*b*]pyridine 4-oxide (**1c**), and 6-cyanothieno[2,3-*b*]pyridine, undergo nitration by means of a mixture of nitric and sulfuric acids to yield 3,7-dinitrothieno[3,2-*b*]pyridine (3%), 3,7-dinitrothieno[3,2-*b*]pyridine 4-oxide (**1d**) (26%), and 6-carbamoyl-5-nitrothieno[2,3-*b*]pyridine (**6b**) (11%), respectively. Structures of the products were ascertained by spectral means, notably infrared, <sup>1</sup>H nmr, and <sup>13</sup>C nmr. It is proposed that **1d** exists (at least in part) as a tricyclic structure and that **6b** may result from an intramolecular mechanism of nitration. An attempt to de-*N*-oxygenate **1c** with excess triphenylphosphine removes more than one oxygen atom per molecule (as triphenylphosphine oxide) without producing an identified thienopyridine product.

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In previous studies we reported that thieno[3,2-*b*]pyridine (**1**) undergoes nitration with nitric and sulfuric acids at 65° to produce the 3-nitro derivative **1a** [4]. Similarly, thieno[2,3-*b*]pyridine (**6**) gives the 3-nitro product **6d** at a reaction temperature of 110° [4]. With thieno[3,2-*b*]pyridine 4-oxide monohydrate (**1b**) as substrate nitration at 125° occurs in the pyridine ring to form the 7-nitro-4-oxide derivative **1c** [5]. We now describe three related studies on nitration of thienopyridine compounds. First, use of a large excess of nitric acid with **1c** (molar ratio 28:1) at 100-105° introduces a second nitro group into the ring system to give a 26% yield of dinitro-4-oxide **1d**. However, treatment of **1b** with a smaller excess of nitric acid (molar ratio 2.8:1) but with rapid heating to a temperature > 125° gives both dinitration and de-*N*-oxygenation to produce **1f** in small yield (3%). Last of all reaction of 6-cyanothieno[2,3-*b*]pyridine (**6a**) under conditions which effected the conversion **6** → **6d** gives both hydration of the cyano group plus nitration to yield **6b** (11%). This paper is concerned largely with structural studies on the new nitration products **1d**, **1f** and **6b** and correlation of the results with analogous examples from the literature.

The presence of two nitro groups in each of the products **1d** and **1f** is apparent from its infrared spectrum which exhibits four strong absorption bands (instead of the two present in **1c**) for non-equivalent nitro substituents. Moreover, each of these products loses both nitric oxide and nitrogen dioxide units on electron impact in mass spectrometry. Although neither product shows a positive Katritzky test [6,7] for the presence of the *N*-oxide function, **1d** does reveal the expected *N*-oxide band (albeit of only medium intensity) at 1256 cm<sup>-1</sup> (absent from **1f**). Moreover, this structural difference between the two products is corroborated by the mass spectra, which show a prominent peak at mass (*M* - 16) for **1d** but not for **1f** [8].



The <sup>1</sup>H nmr spectrum of either **1d** or **1f** consists of one singlet plus two doublets, consistent with either the location of (a) one nitro group in each ring or (b) both nitro groups in the pyridine ring. However, possibility (b) is considered unlikely due to the fact that the relative chemical shifts of the singlet and two doublets are markedly dependent on the solvent used. Thus, in hexadeuterioacetone or hexadeuteriodimethyl sulfoxide the singlet (for H-2) falls downfield of the pair of doublets (for H-5 and H-6), while

in hydrogen-bonding deuteriochloroform as solvent the singlet falls between the two doublets for **1f** and upfield of the two doublets for **1d**. If both nitro groups were in the pyridine ring (case b) one would expect the singlet to occur markedly downfield from the doublets in all solvents. Corroborating evidence is found in the magnitude of the coupling constant, 6.9-7.0 Hz for **1d** and 4.9-5.1 Hz for **1f**. In particular, reported coupling constants for the thieno[3,2-*b*]pyridine 4-oxide systems **1b**, **1c**, 7-chlorothiopheno[3,2-*b*]pyridine 4-oxide (**1g**), and 7-bromothiopheno[3,2-*b*]pyridine 4-oxide (**1h**) are  $J_{2,3} = 5.8 \pm 0.1$  Hz,  $J_{5,6} = 6.7 \pm 0.4$  Hz, and  $J_{6,7} = 8.2$  Hz (for **1b** only) [5]. Also reported coupling constants for the non-*N*-oxide systems **1**, **1a** and 7-nitrothiopheno[3,2-*b*]pyridine (**1e**) are  $J_{2,3} = 5.9 \pm 0.2$  Hz,  $J_{5,6} = 4.8 \pm 0.3$  Hz, and  $J_{6,7} = 8$  Hz [4,5,9]. Based on these data we conclude that **1d** is either the 3,7-dinitro-4-oxide (as shown) or its 2,7-dinitro-4-oxide isomer. Likewise, **1f** is either the 3,7-dinitro derivative (as shown) or its 2,7-dinitro isomer.

Finally, location of the nitro group in the thiophene ring was established as position 3 in both **1d** and **1f** by  $^{13}\text{C}$  nmr spectrometry. In each case the magnitude of  $^1J_{\text{CH}}$  for the unsubstituted position in the thiophene ring was compared with measured data for the reference compounds 2-nitrothiophene (**2a**), 3-nitrobenzo[*b*]thiophene (**3**), and **1c** and reported data for nitrothiophenes. A summary of pertinent one-bond C-H coupling constants is presented in Table I. From this table one notes that the  $^1J_{\text{CH}}$  value for an  $\alpha$  position (*i.e.* position 2 or 5) in the thiophene ring falls in the range of  $194 \pm 5$  Hz, while that of a  $\beta$  position

(*i.e.* position 3 or 4) is in the range of  $175.8 \pm 1.2$  Hz. Since the coupling constants for **1d** and **1f** fall near the middle of the former range one sees clearly that the nitro group in the thiophene ring of each of these compounds is not located at position 2 and, hence, must be at position 3 [11,12].

Examination of the literature shows that there is precedent for the behavior of **1c** in further nitration. Ishikawa [13] reported that 4-nitroquinoline 1-oxide (**4b**) undergoes nitration by means of nitric and sulfuric acids to yield 4,8-dinitroquinoline 1-oxide (**4c**), isosteric with structure **1d** [14]. De-*N*-oxygenation during nitration of quinoline 1-oxide (**4a**) at elevated temperature ( $> 120^\circ$ ) led to 5- (**5b**) and 8-nitroquinolines (**5c**) [15,16]. Other cases of de-*N*-oxygenation during the process of nitration have been reported by Kröhnke and Schäfer [17] who found that pyridine 1-oxide yields 4-nitropyridine on reaction with nitric/sulfuric acids at  $240^\circ$  and **4b** yields 4-nitroquinoline (**5a**) on reaction with nitric oxide in sulfuric acid at  $100\text{-}150^\circ$ . It was suggested that the nitric oxide present in the reaction mixture serves to effect de-*N*-oxygenation with the formation of nitrogen dioxide.

It was noted previously that **1d** shows unexpected behavior in that it gives a negative Katritzky test and shows only a weak infrared absorption band for the presence of an *N*-oxide function. Additionally the  $^{13}\text{C}$  nmr spectrum of **1d** shows marked downfield shifts of signals for two of the quaternary carbon atoms. Thus, in the 7-nitro-*N*-oxide **1c** the signals for the quaternary carbons fall in the range of 128-134 ppm and in the 3,7-dinitro de-

Table I

Comparative One-Bond C-H Coupling Constants for Unsubstituted Positions on the Thiophene Ring in Selected Nitro-Substituted Compounds

Compound No.	Substituents (s)	Unsubstituted position	$^1J_{\text{CH}}$ value in Hz	Solvent used [a]	References
<b>1c</b>	7-nitro- <i>N</i> -oxide	2	190.6	A	[b]
		3	174.7		
<b>1d</b>	3,7-dinitro- <i>N</i> -oxide	2	195.6	B	[b]
<b>1f</b>	3,7-dinitro	2	194.1	A	[b]
<b>2a</b>	2-nitro	3	176.3	C	[b]
		4	176.9		
		5	189.1		
<b>2a</b>	2-nitro	3	177	A	[c]
		4	176		
		5	191		
<b>2b</b>	3-nitro	2	199	A	[c]
		4	177		
		5	194		
<b>3</b>	3-nitro	2	192.80	C	[b]

[a] A is hexadeuterioacetone; B is DMSO- $d_6$ ; C is deuteriochloroform. [b] Data from the present study. [c] See reference [10].

rivative **1f**, in the range of 132-149 ppm. However, in **1d** two shifts appear normal at 130-139 ppm, but the other two occur at 193.31 and 203.47 ppm, respectively. We suggest that these chemical and spectral irregularities may be ascribed to interaction between the *N*-oxygen and the 3-nitro group to form a cyclic structure, as shown in formula 7. Drain of electronic charge from C-3 and C-7 in this molecule could then account for the downfield chemical shifts [18].

In an effort to prepare 7-nitrothieno[3,2-*b*]pyridine (**1e**) as a reference compound we attempted to effect de-*N*-oxygenation of **1c** directly [19] by heating with excess triphenylphosphine until all **1c** was gone [20]. Column chromatography of the product mixture yielded 1.8 moles of triphenylphosphine oxide per mole of **1c** used and no **1e** was found. Thus, it is clear that triphenylphosphine can effect deoxygenation of a nitro group as well as an *N*-oxide group.

In the third investigation of the nitration of a substituted thienopyridine, 6-cyanothieno[2,3-*b*]pyridine (**6a**) was heated with a mixture of nitric and sulfuric acids at 110°. Isolated was an 11% yield of 6-carbamoyl-5-nitro derivative **6b**. The presence of the carbamoyl and nitro functions in the molecule is readily apparent from the infrared spectrum. As in compounds **1d** and **1f** the <sup>1</sup>H nmr spectrum in deuteriochloroform consists of a singlet and two doublets, but the singlet is downfield (δ 8.46) of the doublets and the coupling constant is 6 Hz. Both of these features indicate that nitration must have occurred in the pyridine ring, at either C-4 or C-5. The possibility that the nitro group is located at C-4 is rejected on the basis of the comparison of the chemical shift for H-3 in **6b** with that formerly reported for H-3 in 6-carbamoylthieno[2,3-*b*]pyridine (**6c**) in the same solvent [21]. Thus, the change in chemical shift for H-3 from the hypothetical transformation **6c** → **6b** is only +0.02 ppm. Incidentally, the same numerical shift is also noted in the signal for H-2. If the nitro group were located at the 4-position the shift in H-3 should be considerably larger [22]. Hence, the nitro group is assigned to the 5-position.

The transformation **6a** → **6b** occurs under the same conditions as used for converting parent molecule **6** to the 3-nitro derivative **6d**. In fact, we had expected **6a** to give nitration in the thiophene ring. To account for nitration at position 5, instead, we suggest that reaction occurs intramolecularly *via* a complex or intermediate involving the amide group and nitric acid, *e.g.* an amide hydronitrate salt [23].

#### EXPERIMENTAL [24]

##### <sup>1</sup>H and <sup>13</sup>C NMR Spectra.

The <sup>1</sup>H nmr spectrum of carbamoyl compound **6b** was determined by means of a Varian Associates XL-100 instrument. All

other nmr spectra were obtained by means of a General Electric QE-300 or a Nicolet NT-360 Fourier transform spectrometer with TMS as an internal standard. Broad-band noise-decoupled <sup>13</sup>C nmr spectra were recorded over spectral widths of both 20 and 5 kHz, with a pulse width of 17 microseconds, 16K data points, and post-acquisition delay of 1.5 seconds. Undecoupled <sup>13</sup>C spectra used nuclear Overhauser enhancement. Selective low-power heteronuclear and homonuclear proton decouplings were used to obtain <sup>13</sup>C-<sup>1</sup>H and <sup>1</sup>H-<sup>1</sup>H coupling networks. For each individual case where an nmr connectivity has been established between a <sup>13</sup>C and a <sup>1</sup>H signal the one-bond coupling constant is shown as <sup>1</sup>J<sub>C,H<sub>r</sub>, where r is the position occupied by the proton in the structural formula.</sub>

2-Nitrothiophene (**2a**), 3-nitrobenzo[*b*]thiophene (**3**) [25], and 7-nitrothieno[3,2-*b*]pyridine 4-oxide (**1c**) [5] were used as reference compounds, especially to establish numerical values for <sup>1</sup>J<sub>CH</sub> in the thiophene ring. Data found for the <sup>13</sup>C nmr spectrum (deuteriochloroform) of **2a** are: δ 152.49 (s, C-2), 133.19 (d, <sup>1</sup>J<sub>CH</sub> = 189.1 Hz, C-5), 128.89 (d, <sup>1</sup>J<sub>CH</sub> = 176.3 Hz, C-3), 127.31 (d, <sup>1</sup>J<sub>CH</sub> = 176.9 Hz, C-4) [26], and of **3** are: 132.60 (d, <sup>1</sup>J<sub>CH</sub> = 192.80 Hz, C-2), 127.07, 126.42, 124.09, 122.99 (C-4 to C-7) [27]. Both <sup>1</sup>H and <sup>13</sup>C nmr spectra (hexadeuterioacetone) of **1c** were measured, thus: δ 8.40 (dd, AB system, J<sub>5,6</sub> = 7.0 Hz, Δδ = 35.3 Hz, H-5, H-6), 8.21 (d, J<sub>2,3</sub> = 5.8 Hz, H-2), 7.81 (d, H-3); δ 136.59 (d, <sup>1</sup>J<sub>CH</sub> = 195.7 Hz, C-5), 135.82 (dd, <sup>1</sup>J<sub>CH</sub> = 190.6 Hz, <sup>2</sup>J<sub>CH</sub> = 6.6 Hz, C-2), 133.31, 130.35, 128.34 (3 s, C-3a, C-7, C-7a), 119.12 (dd, <sup>1</sup>J<sub>C,H-6</sub> = 180.8 Hz, <sup>2</sup>J<sub>CH</sub> = 4.3 Hz, C-6), 118.04 (dd, <sup>1</sup>J<sub>C,H-3</sub> = 174.7 Hz, <sup>2</sup>J<sub>CH</sub> = 3.5 Hz, C-3).

##### 3,7-Dinitrothieno[3,2-*b*]pyridine (**1f**).

To a stirred mixture of 7.2 ml (115 mmoles) of 71% nitric acid (density 1.42 g/ml) and 6.3 ml of 96% sulfuric acid at 0-5° was added 6.87 g (40.6 mmoles) of thieno[3,2-*b*]pyridine 4-oxide monohydrate (**1b**) [5] over a period of 25 minutes. The mixture was heated rapidly until vigorous evolution of nitrogen dioxide ensued and then allowed to cool to room temperature. Subsequently it was raised to 126 ± 5°, where it was maintained for 2.5 hours. The cooled mixture was poured into ice-water. The precipitate was washed successively with water, 5% aqueous sodium carbonate, and water and then dried in air. Recrystallization from acetone (charcoal) gave 258 mg (3%) of yellow prisms, mp 196-199° dec. An analytically pure sample (mp 197-199°) gave a negative Katritzky test [6]; ir: 1551, 1532, 1346, 1322 (nitro groups), 739 cm<sup>-1</sup>; <sup>1</sup>H nmr (deuteriochloroform): δ 9.32 (d, J<sub>5,6</sub> = 5.1 Hz, H-5), 9.12 (s, H-2), 8.31 (d, H-6); <sup>1</sup>H nmr (DMSO-*d*<sub>6</sub>): δ 9.58 (s, H-2), 9.23 (d, J<sub>5,6</sub> = 4.9 Hz, H-5), 8.41 (d, H-6); <sup>1</sup>H nmr (hexadeuterioacetone): δ 9.48 (s, H-2), 9.28 (d, J<sub>5,6</sub> = 5.1 Hz, H-5), 8.46 (d, H-6); <sup>13</sup>C nmr (hexadeuterioacetone/DMSO-*d*<sub>6</sub>): δ 152.83 (d, <sup>1</sup>J<sub>C,H-5</sub> = 189.0 Hz, C-5), 149.04 (d, J<sub>CH</sub> = 4.7 Hz), 146.88 (d, J<sub>CH</sub> = 4.8 Hz), and 141.38 (s, 3 quaternary carbons), 141.12 (d, <sup>1</sup>J<sub>C,H-2</sub> = 194.1 Hz, C-2), 132.75 (s, quaternary carbon), 115.46 (dd, <sup>1</sup>J<sub>C,H-6</sub> = 174.1 Hz, <sup>2</sup>J<sub>CH</sub> = 10.0 Hz, C-6); ms: *m/e* 226 (18), 225 (M<sup>+</sup>, 100), 195 (M<sup>+</sup> - NO, 68), 149 (M<sup>+</sup> - NO - NO<sub>2</sub>, 6), 121 (149<sup>+</sup> - CO, 17).

*Anal.* Calcd. for C<sub>7</sub>H<sub>3</sub>N<sub>3</sub>O<sub>4</sub>S: C, 37.33; H, 1.34. Found: C, 37.38; H, 1.15.

##### 3,7-Dinitrothieno[3,2-*b*]pyridine 4-Oxide (**1d**).

To a stirred mixture of 8.8 ml (141 mmoles) of 71% nitric acid and 10.8 ml of 96% sulfuric acid at 0-5° was added 1 g (5.1 mmoles) of 7-nitrothieno[3,2-*b*]pyridine 4-oxide (**1c**) [5]. The mixture was heated to 100° over 10 minutes and then maintained at

100-105° for 15 minutes longer, whereupon the amber solution had changed to bright yellow. The cooled solution was poured into ice-water. The yellow precipitate was washed with water until the washings were neutral and dried in air, yield 318.6 mg (26%), mp 228-234° dec. Recrystallization from acetone gave golden brown, fine needles, mp 238-239° dec, negative Katritzky test [6]; ir: 1549, 1518, 1334, 1294 (nitro groups), 1256 (medium, *N*-oxide), 1162, 695 cm<sup>-1</sup> [28]; <sup>1</sup>H nmr (deuteriochloroform): δ 8.34 (dd, AB system, J<sub>5,6</sub> = 7 Hz, Δδ = 19.8 Hz, H-5, H-6), 8.26 (s, H-2); <sup>1</sup>H nmr (DMSO-d<sub>6</sub>): δ 9.05 (s, H-2), 8.54 (dd, AB system, J<sub>5,6</sub> = 6.9 Hz, Δδ = 44.5 Hz, H-5, H-6); <sup>1</sup>H nmr (hexadeuterioacetone): δ 8.89 (s, H-2), 8.54 (dd, AB system, J<sub>5,6</sub> = 7.0 Hz, Δδ = 9.7 Hz, H-5, H-6); <sup>13</sup>C nmr (DMSO-d<sub>6</sub>): δ 203.47, 193.31, 138.29 (3 s, 3 quaternary carbons), 138.01 (d, <sup>1</sup>J<sub>C,H-5</sub> = 196.9 Hz, C-5), 133.86 (d, <sup>1</sup>J<sub>C,H-2</sub> = 195.6 Hz, C-2), 130.44 (s, quaternary carbon), 119.28 (dd, <sup>1</sup>J<sub>C,H-6</sub> = 176.7 Hz, <sup>2</sup>J<sub>CH</sub> = 3.3 Hz, C-6) [29]; ms: m/e 242 (10), 241 (M<sup>+</sup>, 100), 225 (M<sup>+</sup> - O, 64), 211 (M<sup>+</sup> - NO, 21), 195 (M<sup>+</sup> - NO<sub>2</sub>, 35), 179 (M<sup>+</sup> - NO<sub>3</sub>, 10), 165 (M<sup>+</sup> - N<sub>2</sub>O<sub>3</sub>, 13), 121 (165<sup>+</sup> - CO<sub>2</sub>, 14).

*Anal.* Calcd. for C<sub>7</sub>H<sub>5</sub>N<sub>3</sub>O<sub>3</sub>S: C, 34.86; H, 1.25. Found: C, 34.86; H, 1.26.

#### Deoxygenation of 7-Nitrothieno[3,2-*b*]pyridine 4-Oxide (**1c**).

A stirred mixture of 0.5 g (2.55 mmoles) of **1c** and 4 g (15.3 mmoles) of triphenylphosphine (Aldrich) was heated at 125-135° in an atmosphere of nitrogen gas for 40 minutes whereupon tlc (silica gel/acetone-chloroform) showed that all **1c** had reacted. The dark brown mixture was dissolved in chloroform and chromatographed on a column of silica gel (70 g), first with petroleum ether (35-60°) and then with chloroform as eluent, to give crude tan solid. Recrystallization of this solid from anhydrous ether gave colorless crystals of triphenylphosphine oxide, yield 1.27 g (4.57 mmoles), mp 141-148°. After further recrystallizations this product was shown to be identical with an authentic sample (Aldrich) by mixture melting point and <sup>1</sup>H nmr spectra.

Efforts to isolate a thienopyridine component from chromatographic fractions were unsuccessful.

#### 6-Carbamoyl-5-nitrothieno[2,3-*b*]pyridine (**6b**).

To 0.55 ml of 96% sulfuric acid (stirred and cooled in a water bath) was added 352 mg (2.2 mmoles) of 6-cyanothieno[2,3-*b*]pyridine (**6a**) [21] at such a rate as to maintain a temperature below 50°. Then 0.23 ml (3.7 mmoles) of 70% nitric acid was added dropwise, without cooling, so as to maintain a temperature of 105-115°. The mixture was cooled, poured onto ice, neutralized with sodium bicarbonate, and extracted with chloroform. The residue from evaporation of the extract was recrystallized from chloroform to give 52 mg (11%) of **6b**, mp 236-240°, raised to 262-264° dec on slow sublimation at 80-100° (0.005 mm); ir: 3430 and 3280 (N-H stretching), 1715 (strong, carbonyl), 1520 and 1330 cm<sup>-1</sup> (nitro group); <sup>1</sup>H nmr (deuteriochloroform): δ 8.46 (s, H-4), 7.73 (d, J<sub>2,3</sub> = 6 Hz, H-2), 7.38 (d, H-3); uv (ethanol): [30] λ max 229 nm (log ε 4.59), 268 (4.31), 314 (4.17); ms: m/e 223 (M<sup>+</sup>, 96), 180 (M<sup>+</sup> - HNCO, 100), 179 (M<sup>+</sup> - H<sub>2</sub>NCO, 32), 178 (21), 135 (27), 134 (31).

*Anal.* Calcd. for C<sub>6</sub>H<sub>5</sub>N<sub>3</sub>O<sub>3</sub>S: C, 43.05; H, 2.26; N, 18.83; exact mass, 223.003. Found: C, 43.32; H, 1.96; N, 18.71; exact mass, 223.003.

Processing of the foregoing mother liquor from recrystallization gave 120 mg of recovered **6a**.

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- [23] W. J. Hickinbottom, "Reactions of Organic Compounds", 3rd Ed, John Wiley and Sons, Inc, New York, NY, 1962, p 335.
- [24] Infrared spectra were determined on potassium bromide wafers by means of a Beckman IR-10 instrument or by Long K. Tran with a Nicolet 5-DXB FTIR instrument. Electron-impact mass spectra at 70 eV were obtained by Dr. Richard Wielesek of this laboratory on a CEC model 21-110 or a VG 12-250 instrument. Elemental analyses were conducted by Desert Analytics, Tucson, Arizona.
- [25] K. Fries and E. Hemmecke, *Ann. Chem.*, **470**, 1 (1929).
- [26] Compare data for **2a** in hexadeuterioacetone [10].
- [27] No effort was made to assign the four signals in the range δ

128-122 to specific carbon atoms. Note that the resonance for C-2 falls further downfield than  $\delta$  128.

[28] Relative  $R_f$  values (silica gel/acetone-chloroform, 1:3): **1c**, 0.28; **1f**, 0.41; **1d**, 0.62.

[29] Since protons H-5 and H-6 are not clearly distinguished in the nmr spectrum the assignments of the  $^{13}\text{C}$  nmr signals to C-5 and C-6 are

based on the relative sizes of (a) the chemical shifts and (b) the one-bond C-H coupling constants. Both of these values should be larger for C-5. Compare data for C-2 and C-3, respectively, in quinoline. See J. B. Stothers, "Carbon-13 NMR Spectroscopy", Academic Press, New York, NY, 1972, pp 262, 343.

[30] The spectrum was obtained by means of a Cary 15 instrument.