

Nuclear Magnetic Resonance Studies of Bicyclic Thiophene Derivatives. III. Through Space H-F Coupling over Seven Bonds

Toshiyuki HIROHASHI, Shigeho INABA, and Hisao YAMAMOTO

Institute for Biological Science, Sumitomo Chemical Co., Takatsukasa, Takarazuka, Hyogo 665

(Received October 18, 1974)

Synopsis. Bicyclic thiophene derivatives, 1,5-dimethyl-(**1**) and 3,5-dimethyl-4-(*o*-fluorophenyl)-1,2-dihydrothieno[2,3-*d*]-pyrimidin-2-ones (**3**), 2-acetylamino-3-(*o*-fluorobenzoyl)-4-methylthiophene (**5**), and some derivatives (**2**, **4**, **6**, **7**), have been prepared. ^1H , ^{19}F Spin couplings over seven bonds, $^7J_{\text{HF}}$, attributable to a through-space mechanism have been observed in the ^1H NMR spectra of these compounds.

In a previous paper,¹⁾ we reported that long-range spin couplings over six bonds were observed between the fluorine and H_β of the thiophene rings in 4-(*o*-fluorophenyl)thienopyrimidines, 2-acetylamino-3-(*o*-fluorobenzoyl)thiophenes, 5-(*o*-fluorophenyl)-1,4-thienodiazepines, and 5-(*o*-fluorophenyl)-1,4-thienodiazepine-4-oxides, the synthesis of all of which are of interest biologically. The coupling was considered to arise from a through-space mechanism.²⁾ Thus, we have examined the ^1H NMR spectra of other kinds of bicyclic thiophene derivatives, **1**—**7**, and discovered that there are long-range spin couplings between methyl or dichloromethyl

protons of the thiophene ring and the fluorine of the benzene ring over seven bonds, $^7J_{\text{HF}}$, which were also considered to be through-space couplings, as has hitherto been reported in a few papers.^{3–6)} In this paper, we will present our experimental results on the $^7J_{\text{HF}}$ found in these new compounds.

As is shown in Table 1, the β -methyl signals of the thiophene ring in **3** exhibited no detectable coupling with the fluorine. However, in **1** and **4**, which are isomers of **3**, $^7J_{\text{HF}}$ was observed (both 1.0 Hz). On the chlorination of the α -position of the thiophene ring, $^7J_{\text{HF}}$ was not practically influenced (in **2**, 1.1 Hz). The difference between the J_{HF} in **3** and those in **1**, **2**, and **4** should be due to the difference in steric hindrance; the torsional angle between the thiophene and the benzene planes should be greater for **3** than for **1**, **2**, and **4** as a result of the steric hindrance between the benzene and the *N*-methyl group in **3**. Accordingly, the internuclear distance between the fluorine and the methyl protons in **3** is so long that the through space coupling can not be detected. The dichloromethyl proton signal in **7** appears as a doublet ($J=0.7$ Hz), whose spacing is smaller than that of **2** ($J=1.1$ Hz). The difference might arise from the fact that, since the dichloromethyl group is bulkier than the methyl group, the torsional angle between the thiophene and the benzene planes should be greater for **7** than for **2**. Furthermore, $^7J_{\text{HF}}$ was also observed between the methyl protons of the thiophene ring and the fluorine in **5** and **6** ($J=0.5$ Hz). The difference between the $^7J_{\text{HF}}$ in **5** and **6** and those in **1** and **2** is probably due to the difference in the torsional angle between the thiophene and the benzene planes; the angle should be greater for **5** and **6** than for **1** and **2**, as has been reported in the case of $^6J_{\text{HF}}$ in the previous paper.¹⁾

Experimental

Measurements. The ^1H NMR spectra (δ , ppm) were recorded on a Hitachi R-20-B spectrometer at 60 MHz and at a probe temperature of 35 °C, using CDCl_3 solutions (about 10% w/v), with TMS as the internal reference. The chemical shifts are expressed in δ with a precision of ± 0.01 . The coupling constants were measured by several sweepings at an expanded sweep width (60 or 120 Hz) with an accuracy of ± 0.1 Hz. The IR spectra (wave number, cm^{-1}) were recorded as Nujol mulls on a Hitachi EPI-G-3 spectrophotometer. The UV spectra (wavelength, nm) were determined in 95% ethanol with a Hitachi-323 spectrophotometer. The melting points were measured on a Thomas-Hoover melting-point apparatus and are uncorrected.

Materials. The Synthetic Procedures for 4-(*o*-Fluorophenyl)-1,5-dimethyl-1,2-dihydrothieno[2,3-*d*]-pyrimidin-2-one (**1**), 4-(*o*-

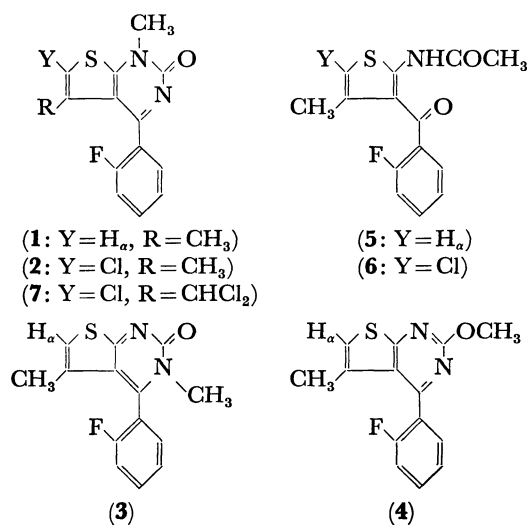


TABLE 1. NMR DATA ON BICYCLIC THIOPHENE DERIVATIVES

Compound	$^7J_{\text{HF}}$ (Hz)	δ (β - CH_3)	δ (H_α)	δ (NH)
1	1.0	1.85 ^{a)}	6.55	—
2	1.1	1.81	—	—
3	b)	1.50 ^{c)}	6.55	—
4	1.0	1.94 ^{d)}	6.86	—
5	0.5	1.73 ^{e)}	6.33	11.92
6	0.5	1.69	—	11.90
7	0.7	6.09 ^{f)}	—	—

a) $^4J(\text{H}_\alpha, 5-\text{CH}_3)=1.1$ Hz. b) Not detectable. c) $^4J(\text{H}_\alpha, 5-\text{CH}_3)=1.4$ Hz. d) $^4J(\text{H}_\alpha, 5-\text{CH}_3)=1.1$ Hz. e) $^4J(\text{H}_\alpha, 4-\text{CH}_3)=1.0$ Hz. f) Chemical shift of the dichloromethyl proton.

Fluorophenyl)-3,5-dimethyl-2,3-dihydrothieno[2,3-d]-pyrimidin-2-one (3), and 4-(*o*-Fluorophenyl)-2-methoxy-5-methylthieno[2,3-d]-pyrimidine (4): 2-Amino-3-(*o*-fluorobenzoyl)-4-methylthiophene was prepared from ω -cyano-*o*-fluoroacetophenone and mercaptoacetone as reported in a previous paper.⁷⁾ It was then heated with ethyl cabamate to give 4-(*o*-fluorophenyl)-5-methyl-1,2-dihydrothieno[2,3-d]-pyrimidin-2-one, which was methylated with methyl iodide to afford Compounds 1, 3, and 4.

2-Amino-3-(*o*-fluorobenzoyl)-4-methylthiophene. Yield, 35.5%, mp 163–164 °C (from ethanol). IR: 3320, 3200, 3100, 1590, and 1560.

4-(*o*-Fluorophenyl)-5-methyl-1,2-dihydrothieno[2,3-d]-pyrimidin-2-one. Yield, 76.1%, it was used the next step without any further purification.

Compound 1. Yield, 18.0%, mp 275–277 °C (from CHCl₃-ethanol). IR: 3050, 1658, 1643, and 1608. NMR: 1.85 (3H, d-d, 5-CH₃), 3.75 (3H, s, *N*-CH₃) and 6.55 (1H, q, H_a). UV: 251 (26100) and 346 (5100). Found: C, 61.30; H, 4.17; N, 10.24%. Calcd for C₁₄H₁₁N₂OSF: C, 61.30; H, 4.04; N, 10.21%.

Compound 3. Yield, 10.0%, mp 178–181 °C (from CHCl₃-ethanol). IR: 3050 and 1655. NMR: 3.41 (3H, d, *N*-CH₃). UV: 220 (19700), 255 (23700), 295 (3000) and 373 (3900). Found: C, 61.33; H, 4.09; N, 10.10%. Calcd for C₁₄H₁₁N₂OSF: C, 61.30; H, 4.04; N, 10.21%.

Compound 4. Yield, 4.4%, mp 177–179 °C (from CHCl₃-ethanol). IR: 3065 and 1615. NMR: 1.94 (3H, d-d, 5-CH₃), 4.11 (3H, s, OCH₃) and 6.86 (1H, q, H_a). UV: 244 (34600) and 316 (3500). Found: C, 61.30; H, 4.17; N, 10.24%. Calcd for C₁₄H₁₁N₂OSF: C, 61.30; H, 4.04; N, 10.21%.

The other compounds were prepared according to the methods described previously.⁷⁾

2-Acetylmino-3-(*o*-fluorobenzoyl)-4-methylthiophene (5). Yield, 74.0%, mp 96–96.5 °C (from ether). IR: 3200, 3080, 1690, and 1600. UV: 244.5 (10300), 282.5 (10700), and 351 (6400). Found: C, 60.84; H, 4.32; N, 5.14%. Calcd for C₁₄H₁₂NO₂SF: C, 60.64; H, 4.36; N, 5.05%.

2-Acetylmino-5-chloro-3-(*o*-fluorobenzoyl)-4-methylthiophene (6). Yield, 82.4%, mp 140–140.5 °C (from ether). IR: 3180, 1695 and 1605. UV: 250 (14400) and 358 (6700). Found: C, 53.86; H, 3.43; N, 4.29%. Calcd for C₁₄H₁₁NO₂SClF: C, 53.94%; H, 3.56; N, 4.49%.

6-Chloro-1,5-dimethyl-4-(*o*-fluorophenyl)-1,2-dihydrothieno[2,3-d]-pyrimidin-2-one (2). Yield, 34.5%, mp 175–176 °C (from ethanol-ether). IR: 1660 and 1610. UV: 255 (26000) and 353 (5500). Found: C, 54.71; H, 3.44; N, 8.97%. Calcd for C₁₄H₁₀N₂OSClF: C, 54.46; H, 3.26; N, 9.07%.

6-Chloro-5-dichloromethyl-4-(*o*-fluorophenyl)-1-methyl-1,2-dihydrothieno[2,3-d]-pyrimidin-2-one (7). This was prepared from 1 with an excess of sulfurylchloride. Yield, 28.2%, mp 215–216 °C. IR: 1675 and 1610. UV: 219 (19300), 251 (16900), 282 (8000), and 347 (6000). Found: C, 44.46; H, 2.19; N, 7.55%. Calcd for C₁₄H₉N₂OSCl₃F: C, 44.52; H, 2.13; N, 7.42%.

The authors wish to thank Professor Masamichi Tsuboi, The University of Tokyo, and Dr. Makoto Sunagawa of this Institute for valuable suggestions, and Mr. Hiromi Sato for his cooperation in the synthetic experiments.

References

- 1) Part II: T. Hirohashi, S. Inaba, and H. Yamamoto, This Bulletin, **48**, 947 (1975).
- 2) See ref. 1 and references therein.
- 3) M. S. Newman, R. G. Mentzer, and G. Slomp, *J. Amer. Chem. Soc.*, **85**, 4018 (1963).
- 4) R. Filler and E. W. Choe, *ibid.*, **91**, 1862 (1969).
- 5) I. Agranat, M. Pabivovitz, I. Gosnay, and A. Weitzen-Dagan, *ibid.*, **94**, 2889 (1972).
- 6) R. J. Abraham, D. F. Wileman, G. R. Bedford, and D. Greatbanks, *Org. Magne. Resonance*, **4**, 343 (1972).
- 7) T. Hirohashi, S. Inaba, and H. Yamamoto, This Bulletin, **48**, 147 (1975).