NOTES

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Nuclear Magnetic Resonance Studies of Bicyclic Thiophene Derivatives. IV. Further Examples of Through-space H-F Coupling

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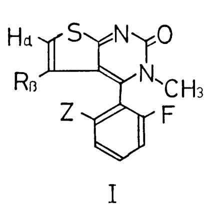
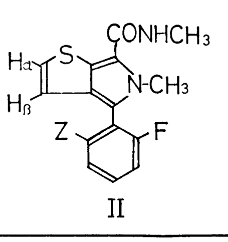
Synopsis. Bicyclic thiophene derivatives, 3-methyl-4-(*o*-fluorophenyl)-2,3-dihydrothieno[2,3-*d*]-pyrimidin-2-ones (I) and *N*,5-dimethyl-4-(*o*-fluorophenyl)-5*H*-thieno[2,3-*c*]-pyrrole-6-carboxamides (II), have been prepared. Two sorts of ^{1}H, ^{19}F spin coupling over six bonds attributable to a through-space mechanism have been observed in the ^{1}H NMR spectra of these compounds.

In previous papers,[1-2] we reported that long-range spin couplings over six or seven bonds are observed in various bicyclic thiophene derivatives; the coupling was considered to arise from a through-space mechanism. In the course of our synthetic studies of biologically active thiophenes, we have also found in the ^{1}H NMR spectra of other kinds of bicyclic thiophene derivatives, I and II, the presence of two long-range couplings, $^{6}J_{\mathrm{HF}}$, between *N*-methyl protons and fluorine as well as between the H_β of the thiophene ring and the fluorine; these are also considered to be through-space couplings. Myhre *et al.* have already reported through-space couplings between fluorine and two different protons in a molecule of 2,4,6-tri-*t*-butylfluorobenzene.[4] In this paper, we will present our observations of the $^{6}J_{\mathrm{HF}}$ in these new compounds. As is shown in Table 1, both *N*-methyl and H_β exhibit doublet signals in *o*-fluorophenyl-I and -II (Ia and IIa) and a triplet in 2,6-difluorophenyl-I and -II (Ib and IIb). These facts suggest the presence of a long-range coupling over six bonds between the *N*-methyl protons and fluorine as well as between the H_β of the thiophene ring and the fluorine. When the J_{HF} value of the *o*-fluorophenyl compound is compared with that of the corresponding 2,6-difluorophenyl compound, the $J(H_\beta, F)$ value is smaller for the former (Ia, 0.6 Hz; IIa, 0.8 Hz) than for the latter (Ib, 1.0 Hz; IIb, 1.0 Hz). On the contrary, the $J(CH_3, F)$ value is greater for the former (Ia, 1.2 Hz; IIa, 1.8 Hz) than for the latter (Ib, 0.8 Hz; IIb, 1.3 Hz). Since the torsional angle between the thiophene and the benzene-ring planes should be greater for the 2,6-difluorophenyl compound than for the *o*-fluorophenyl compound,[1] these facts reasonably suggest that, of the two possible conformers (A and B), the B conformer in which the fluorine atom is more proximate to the *N*-methyl group, is much predominant in the *o*-fluorophenyl compounds, I and II. When H_β is replaced by a methyl group, the $J(CH_3, F)$ value is decreased from 1.2 Hz (Ia) to 0.5 Hz (Ic). This phenomenon can easily be understood because the torsional angle between the thiophene and the benzene planes should be greater for Ic than for Ia as a result of the steric hindrance between the methyl group of the thiophene and the benzene rings in Ic. This greater torsional angle should lead to an increase in the internuclear distance between the *N*-methyl protons and fluorine.

Table 1. J_{HF} in compounds I and II



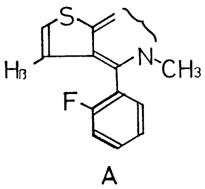
I



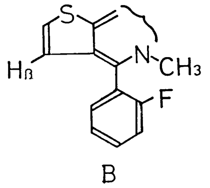
II

Compound	Z	R	$J_{H_\beta,F}$	$J(NCH_3,F)$
Ia[a]	H	H_β	0.6 d[b]	1.2 d
Ib[a]	F	H_β	1.0 t[c]	0.8 t
Ic	H	CH_3	—	0.5 d
IIa[a]	H	—	0.8 d	1.8 d
IIb[d]	F	—	1.0 t	1.3 t

a) $J_{H_\alpha,H_\beta}=6.3$ Hz, b) doublet, c) triplet, d) $J_{H_\alpha,H_\beta}=5.3$ Hz.



A



B

Experimental

Measurements. The ^{1}H NMR spectra were recorded on a Hitachi R-20-B spectrometer at 60 MHz, using $CDCl_3$ solutions (about 10%w/v) containing TMS as an internal reference at a probe temperature of 35 °C. The chemical shifts are expressed in δ (ppm) with a precision of ±0.01. The coupling constants were measured by several sweepings at an expanded width (60 or 120 Hz) with an accuracy of ±0.1 Hz. The IR spectra were recorded as Nujol mulls on a Hitachi EPI-G-3 spectrophotometer (wave number, cm^{-1}). The UV spectra (wavelength) 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 preparation of the following compounds has already been reported: 4-(*o*-fluorophenyl)-3-methyl-2,3-dihydrothieno[2,3-*d*]pyrimidin-2-one(Ia)[5] and

3,5-dimethyl-4-(*o*-fluorophenyl)-2,3-dihydrothieno[2,3-*d*]pyrimidin-2-one (Ic).[2] The other compounds were prepared by the following methods.

*4-(2,6-Difluorophenyl)-3-methyl-2,3-dihydrothieno[2,3-*d*]pyrimidin-2-one (Ib).* 2-Amino-3-(2,6-difluorobenzoyl)thiophene[1] and methyl isocyanate in benzene were heated under reflux to afford 4-(2,6-difluorophenyl)-4-hydroxy-3-methyl-1,2,3,4-tetrahydrothieno[2,3-*d*]-pyrimidin-2-one (yield, 36.9%; mp 212—217 °C), which was then heated at 240 °C to afford Ib. Yield, 11.0%; mp 188—190 °C (from ethanol-ether). IR: 3060, 1665, and 1620. NMR: 3.54 (3H, t, *N*-CH_3), 6.42 (1H, d-d, H_β) and 6.97 (1H, d, H_α). UV: 220.5 (19100), 251.5 (24300), 292 (2700) and 374 (5200). Found: C, 56.09; H, 3.09; N, 10.12%. Calcd for $C_{13}H_8N_2OSF_2$: C, 56.11; H, 2.90; N, 10.07%. The same procedure was applied to the synthesis of 3-methyl-4-phenyl-2,3-dihydroquinazolin-2-one by Metlesics *et al.*[6]

Compounds IIa and IIb. These compounds were prepared from 5-(*o*-fluorophenyl or 2,6-difluorophenyl)-1-methyl-1,3-dihydro-2*H*-thieno[2,3-*e*]-1,4-diazepin-2-one[1,5] with sodium hydride and methyl iodide. The same procedure was applied to the synthesis of 5-chloro-*N*, 2-dimethyl-3-phenyl-1-isoindolecarboxamide by Fryer *et al.*[7]

N,*5-Dimethyl-4-(*o*-fluorophenyl)-5*H*-thieno[2,3-*c*]pyrrole-6-carboxamide (IIa).* Yield, 31.1%; mp 131—132 °C (from ether). IR: 3300 and 1625. NMR: 3.04 (3H, d, J=4.9, $NH\underline{CH}_3$), 4.01 (3H, d, N^5-CH_3), 5.07 (1H, broad s, NH), 6.88 (1H, d-d, H_β) and 7.00 (1H, d, H_α). UV: 224 (14700), 251 (15800) and 324 (18900). Found: C, 62.60; H, 4.56; N, 9.92%. Calcd for $C_{15}H_{13}N_2OSF$: C, 62.49; H, 4.54; N, 9.71%.

*4-(2,6-Difluorophenyl)-*N*,5-dimethyl-5*H*-thieno[2,3-*c*]pyrrole-6-carboxamide (IIb).* Yield, 36.4%; mp 165—166 °C (from ethanol). IR: 3300 and 1627. NMR: 3.04 (3H, d, J=4.8, $NH\underline{CH}_3$), 4.00 (3H, t, N^5-CH_3), 5.67 (1H, broad s, NH), 6.83 (1H, d-t, H_β) and 7.03 (1H, d, H_α). UV: 221 (16200), 250.5 (15700) and 321 (18900). Found: C, 58.77; H, 4.05; N, 9.18%. Calcd for $C_{15}H_{12}N_2SOF_2$: C, 58.81; H, 3.95; N, 9.14%.

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