Nuclear Magnetic Resonance Studies of Bicyclic Thiophene Derivatives. II. Through Space H-F Coupling in *o*-Fluorophenyl Derivatives of Benzoylthiophene, Thienopyrimidine and Thienodiazepine Derivatives

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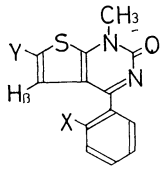
Proton–fluorine coupling over six bonds has been observed between fluorine and H_β of the thiophene ring in *ortho* fluorophenyl derivatives of 4-phenylthienopyrimidines (**1**), 2-acetylamino-3-benzoylthiophenes (**2**), 5-phenyl-1,4-thienodiazepines (**3**) and 5-phenyl-1,4-thienodiazepine-4-oxides (**4**). The solvent effect and the *N*-methylation effect on the coupling constant can be explained by considering that the H–F coupling is a through space coupling. The value of coupling constant (J_{HF}: 0.5 Hz to 4.1 Hz) depends upon the geometry of the ring system condensed at 2-C and 3-C of thiophene ring, decreasing in the order of **1**>**2**>**3**>**4**. A discussion is given on the manner of steric repulsion between the benzene ring and some atoms on the other moiety of these compounds.

In a previous paper,[1] we reported on the ring current effect of the benzene ring on H_β and H_α (when Y=H_α) of the thiophene ring in 4-phenylthienopyrimidines (**1**), 2-acetylamino-3-benzoylthiophenes (**2**), 5-phenyl-1,4-thienodiazepines (**3**) and 5-phenyl-1,4-thienodiazepine-4-oxides (**4**).



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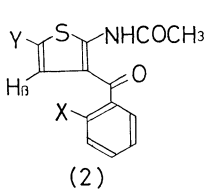

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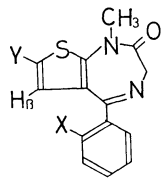

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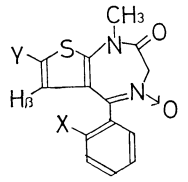

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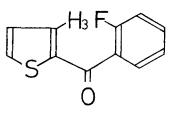
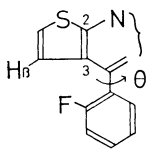
We have found that the H_β signal exhibits an extra splitting only when *ortho* substituent (X) of the benzene ring is fluorine, and that the amount of splitting is independent of the field. This indicates that there is a long range coupling over six bonds between H_β of the thiophene ring and fluorine on the benzene ring. Martin *et al.* did not mention such a H–F coupling between H_3 and fluorine in their NMR study of 2-(*o*-fluorobenzoyl)-thiophene (**5**).[2-3] The H–F coupling



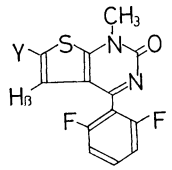
(5)

found in compounds (**1**)—(**4**) is considered to be a through space coupling. Compounds (**1**)—(**4**) are suitable for obtaining information on a H–F through space coupling, because each has a ring system condensed at 2-C and 3-C of the thiophene ring (*i.e.* compound (**2**) has a ring system by an intramolecular hydrogen bonding; see formula [IV] as well as Part I[1]) and has only one degree of freedom of internal rotation

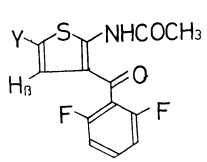


[I]

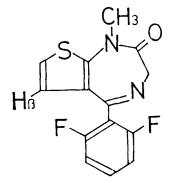
(*i.e.* torsional angle between the benzene ring plane and the thiophene ring plane; θ in formula [I]). The internuclear distance between H_β and fluorine in each of these compounds is simply related with θ, and the value of θ was estimated on the basis of ring current effect of the benzene ring on H_β.[1]



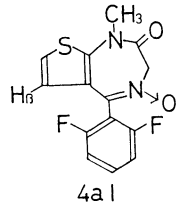
1a I (Y=H)
1b I (Y=Cl)



2a I (Y=H)
2b I (Y=Cl)

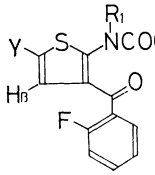


3a I



4a I

We have prepared *o,o'*-difluorophenyl derivatives (**1aI, 1bI, 2aI, 2bI, 3aI,** and **4aI**), and also 2-acetylamino-3-(*o*-fluorobenzoyl)thiophene derivatives (**2iB, 2jB,** and **2kB**). They also supply information on the H–F through space coupling. Long range proton-fluorine through space coupling over five bonds or more has been a subject of interest.[4-10] Investigations have



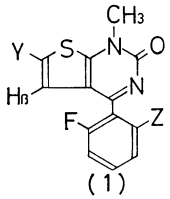
2i B (Y=NO_2, R_1=H)
2j B (Y=NO_2, R_1=CH_3)
2k B (Y=Cl, R_1=CH_3)

been made on the relation between J_{HF} and the spacial proximity of the coupled nuclei.[4,8–10] In this paper, we present our experimental results of these new compounds.

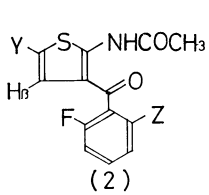
Results

NMR data for the fluorophenyl derivatives of compounds (**1**)—(**4**) are collected in Table 1. We see that the J_{HF} of *o*-fluorophenyl derivatives of compounds (**1**)—(**4**) is independent of substitution Y. The J_{HF} of compound (**3**) is also independent of the kind of substitution R_1. It depends, however, greatly upon the kind of ring system condensed at 2-C and 3-C of the thiophene ring. Thus, in the *o*-fluorophenyl derivatives, it is 0.5 Hz in compound (**4**), 1.2 Hz in compound (**3**), 2.7 Hz in compound (**2**) and 4.1 Hz in compound (**1**). In the *o*,*o*'-difluorophenyl derivatives, the H–F coupling is observed as a triplet. This may be explained by considering that H_β couples with two

Table 1. NMR data[a] for fluorine substituted compounds (**1**)—(**4**)



(1)



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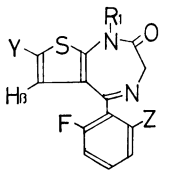

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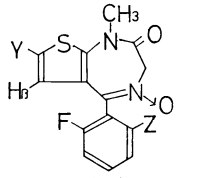
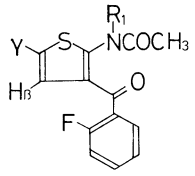


(4)

Compound	Y	Z	R_1	δ (ppm) H_α	δ (ppm) H_β	$J_{H_\beta, F}$ (Hz)
1aB	H	H	—	6.94[b]	7.07[b]	4.0 d[c]
1bB	Cl	H	—	—	6.93[b]	4.2 d
1aI	H	F	—	6.94	6.94	nv[d]
1bI	Cl	F	—	—	6.77	1.6 t[e]
2aB	H	H	—	6.66[b]	6.88[b]	2.6 d
2bB	Cl	H	—	—	6.74[b]	2.7 d[f]
2aI	H	F	—	6.67[g]	6.79[g]	1.3 t
2bI	Cl	F	—	—	6.63	1.5 t
3aB	H	H	CH_3	6.94[b]	6.68[b]	1.3 d[h]
3bB	Cl	H	CH_3	—	6.54[b]	1.2 d
3cB	H	H	H	6.83[b]	6.66[b]	1.2 d
3aI	H	F	CH_3	6.92[i]	6.65[i]	0.8 t
4aB	H	H	—	7.01[b]	6.52[b]	0.6 d
4bB	Cl	H	—	—	6.38[b]	0.5 d
4aI	H	F	—	7.03[i]	6.55[i]	bs[j]

a) See Experimental for protons not given here. b) Reported in Part I. c) Doublet. d) Not visible due to overlapping. e) Triplet. f) The observed splitting is field independent; J=2.7 Hz at 100 MHz ($CDCl_3$). g) J_{H_α, H_β}=5.8 Hz. h) The observed splitting is field independent; J=1.3 Hz at 100 MHz ($CDCl_3$). i) J_{H_α, H_β}=5.7 Hz. j) Broad singlet.

Table 2. Effect of *N*-methylation on $J_{H_\beta, F}$ (Hz)



Compound	R_1	Y	$J_{H_\beta, F}$	$J_{HF(N-CH_3)}/J_{HF(N-H)}$
2iB	H	NO_2	3.0	60%
2jB	CH_3	NO_2	1.8	
2bB	H	Cl	2.7	59%
2kB	CH_3	Cl	1.6	

Table 3. Solvent effect on $J_{H_\beta, F}$ (Hz)

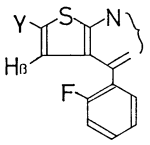
Compound	Solvent $CDCl_3$	Solvent DMSO-d_6
1bB	4.2	3.4
2aB[a]	2.6	2.1
3aB	1.3	1.2
4aB	0.6	0.5

a) J_{NH, H_α}=0.8 Hz in $CDCl_3$ and 0.7 Hz in DMSO-d_6.

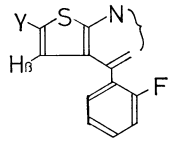
equivalent fluorine nuclei.[11] In compound **4aI**, H_β signal is observed as a broad singlet instead of a triplet. This suggests that the coupling constant is smaller than 0.5 Hz. In Table 2, the effect on J_{HF} by *N*-methylation of compound (**2**) is summarized. Each *N*-methyl compound (**2**) shows a smaller J_{HF} than the corresponding *N*-hydrogen compound. The solvent effect on J_{HF} of compounds (**1**)—(**4**) is summarized in Table 3. When the *o*-fluorophenyl derivatives of compounds (**1**)—(**4**) are measured in dimethylsulfoxide-d_6 solution, J_{HF} is found to be smaller than that in chloroform-*d* solution. In compound **2aB**, H_α couples with amide proton not only in chloroform-*d* but also in dimethylsulfoxide-d_6. This indicates that the carbonyl oxygen forms intramolecular hydrogen bonding with an amide proton to form a six membered ring also in dimethylsulfoxide-d_6, as well as in chloroform-*d* (see formula [IV] as well as Part I[1]).

Discussion

In order to explain the results of J_{HF}, let us assume as follows: of the two possible conformers [II] and [III], [II] is much more predominant in the *o*-fluorophenyl derivatives of Compounds (**1**)—(**4**). This is understandable, since [III] should be much less stable because of the Coulombic repulsion between the fluorine and imino nitrogen in compounds (**1**) and (**3**), carbonyl oxygen in compound (**2**), or oxygen atom of *N*-oxide in compound (**4**).[4] The assumption does not mean



[II]



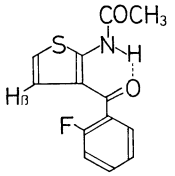
[III]

that the torsional angle θ between the benzene ring plane and thiophene ring plane is exactly zero degree in [II]. Let us define that [II] is a conformer in which $0° \leqq \theta < 90°$ and that [III] is a conformer in which $90° \leqq \theta < 180°$.

Proton-fluorine through Space Coupling. The observed proton-fluorine coupling is considered to be a through space coupling on the basis of the following observations.

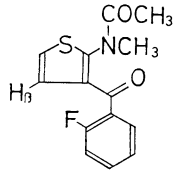
Solvent Effect on J_{HF}: We see from Table 3 that changing the solvent from chloroform-*d* to dimethylsulfoxide-d_6 causes a significant reduction in the J_{HF} of the *o*-fluorophenyl derivatives of compounds (**1**)—(**4**). According to Adcock *et al.*,[4] such a solvent effect can be taken as indicating that the proton-fluorine coupling is a through space coupling; changing the solvent from chloroform-*d* to dimethylsulfoxide-d_6 should cause an increase in the dielectric of the medium as well as dipole-dipole interaction, and therefore, should cause dampening of the intramolecular Coulombic repulsion which controls conformational preference. Thus, the population of conformer [III] should increase on changing the solvent. Since in [III], the internuclear distance between H_β and fluorine is much greater than that in [II], the J_{HF} value should decrease by changing the solvent, if the coupling takes place through space. This is what was actually found.

Effect of N-Methylation on J_{HF}: *N*-Methylation of every compound in the series of compound (**2**) causes a lowering of the J_{HF} value to 60%. On the other hand, *N*-methylation of compound (**3**) causes no change in the J_{HF} value (*i.e.* compound **3cB**, $J=1.2$ Hz; compound **3aB**, $J=1.3$ Hz; see Table 1). The NH group of compound (**2**) forms an intramolecular hydrogen bonding with the carbonyl oxygen, so that a six membered ring is formed, as shown in formula [IV].

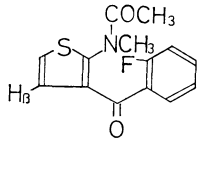


[IV]

On *N*-methylation, however, this hydrogen bonding is broken and there would be two possible conformers [V] and [VI]. In [VI], the internuclear distance



[V]



[VI]

between H_β and fluorine is much greater than in [V] or [IV]. In compound (**3**), on the other hand, no conformational change is expected by *N*-methylation. Thus it is understandable that no change in J_{HF} was observed.

Torsional Angle (θ) between the Benzene Ring Plane and Thiophene Ring Plane. The internuclear distance between H_β and fluorine in each of compounds (**1**)—(**4**) is considered to be related with the torsional angle between the thiophene and benzene ring planes (θ in formula [I]). The shielding effect of the benzene ring on H_β is also considered to be related with the torsional angle θ (see Part I[1]).

o-Fluorophenyl Derivatives of Compounds (1)—(4): As is seen from Table 1, J_{HF} of the *o*-fluorophenyl derivatives of compounds (**1**)—(**4**) decreases in the order of **1** ($J=4.1$ Hz)>**2** ($J=2.7$ Hz)>**3** ($J=1.2$ Hz)>**4** ($J=0.6$ Hz). As has been discussed in Part I,[1] the ring current effect of the benzene ring on H_β increases on going from compound (**1**) to compound (**4**) through compounds (**2**) and (**3**). It was thus assumed that the torsional angle θ increases in the order of **1**→**2**→**3**→**4**. Therefore, the internuclear distance between H_β and fluorine should increase in the order of **1**<**2**<**3**<**4**, and the J_{HF} value should decrease in this order, which is what was actually observed. This may be taken as an additional piece of evidence that the coupling between H_β and fluorine takes place through space. It also supports our previous conclusion that the torsional angle θ increases in the order of **1**<**2**<**3**<**4**.

TABLE 4. COMPARISON OF THE BENZENE RING CURRENT EFFECT ON H_β AND $J_{H_\beta,F}$ BETWEEN *o*-FLUOROPHENYL COMPOUND AND *o,o'*-DIFLUOROPHENYL COMPOUND

Compound	**1b**	**2**[a]	**3a**	**4a**
J_{HF}(F) (Hz)	4.2	2.7	1.3	0.6
J_{HF}(FF) (Hz)	1.6	1.4	0.8	—
$J_{HF}(FF)/J_{HF}(F)$	38%	52%	62%	—
$\Delta\delta'$ (ppm)	0.16	0.10	0.03	−0.03

a) Average value of compounds **2a** and **2b**.

o,o'-Difluorophenyl Compounds (1)—(4): Let us next compare the J_{HF} value of *o,o'*-difluorophenyl compounds (**1**)—(**4**) (*i.e.* J_{HF}(FF)) with the one of the corresponding *o*-fluorophenyl compounds (*i.e.* J_{HF}(F)) (Table 4). J_{HF}(FF) is always smaller than the corresponding J_{HF}(F). This can be explained by considering that the torsional angle θ in the *o,o'*-difluorophenyl compound is greater than that in the corresponding *o*-fluorophenyl compound. The greater θ causes greater internuclear distance between H_β and fluorine, and therefore should cause a smaller J_{HF} value. This phenomenon can be explained by considering that the steric and Coulombic repulsion should be greater in *o,o'*-difluorophenyl compound than in *o*-fluorophenyl compound.[4] Let us examine the amount of decrease in the J_{HF} value on going from a *o*-fluorophenyl compound to the corresponding *o,o'*-difluorophenyl compound. The $J_{HF}(FF)/J_{HF}(F)$ values are given in Table 4 for compounds (**1**)—(**3**). The value becomes greater in the order of **1** (38%)<**2** (52%)<**3** (62%). Let us define $\Delta\theta$ as the amount of increase in θ on going from a *o*-fluorophenyl compound to the corresponding *o,o'*-difluorophenyl compound. Then, what has just been observed may be taken as indicating that the $\Delta\theta$ value is the greatest for compound (**1**).

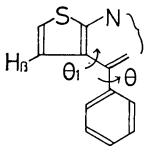
For a comparison of the chemical shift of H_β of *o,o'*-difluorophenyl compounds (**1**)—(**4**) (*i.e.* δH_β(FF)) with that of the corresponding *o*-fluorophenyl com-

pounds (*i.e.* $\delta H_\beta(F)$), let us define $\Delta\delta'$ as $\Delta\delta' = \delta H_\beta(F) - \delta H_\beta(FF)$. As may be seen from Table 4, the $\Delta\delta'$ value becomes smaller in the order of **1**>**2**>**3**>**4**. This order of the $\Delta\delta'$ value must mean that the $\Delta\theta$ value becomes smaller in this order. Thus, the result is in accordance with that obtained from the $[J_{HF}(FF)/J_{HF}(F)]$ value.

The Steric Effect by the Ring System Condensed at 2-C and 3-C of the Thiophene Ring. It has become clear that the torsional angle between the benzene ring plane and thiophene ring plane increases in the order of **1**<**2**<**3**<**4**. This fact should be taken as indicating that the amount of steric hindrance depends on the geometry of the ring system condensed at 2-C and 3-C of the thiophene ring in each molecule.

The difference in steric hindrance between compounds (**3**) and (**4**) can be explained as follows. From a comparison of 5-phenyl-1,4-thienodiazepine (**3**) with the corresponding *N*-oxide compound (*i.e.* compound (**4**)), we see that the torsional angle between the benzene and thiophene ring planes should be greater for (**4**), since in compound (**4**) the steric hindrance exists between the benzene ring and oxygen atom of *N*-oxide, which is near the benzene ring. This extra steric repulsion forces the benzene ring out of the plane of the thiophene ring. An analogous steric hindrance was reported in the case of *p*-bromobenzophenone oxime *o*-picrylethers.[12]

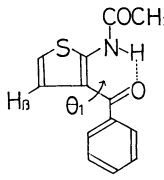
It should be mentioned that in the preceding discussion we assumed that the ring system condensed at 2-C and 3-C of the thiophene ring is in the same plane as the thiophene ring plane in each series of compounds (**1**)—(**4**) (see Part I[1]). On the basis of this assumption, we have defined the torsional angle between the benzene ring plane and the thiophene ring plane as θ (see formula [I]). This assumption should be true for compound (**1**); the thienopyrimidine ring is considered to be flat. However, in compounds (**2**)—(**4**), it seems that the ring system condensed at 2-C and 3-C of the thiophene ring is not completely flat and that the thiophene ring plane is to some extent twisted out of the C–CO–C or C–(C=N)–C plane. Thus in order to discuss the degrees of the torsional angle between the benzene ring plane and the thiophene ring plane in more detail, it is necessary to define the torsional angle more correctly. Let us define the torsional angle between the thiophene ring plane and C–CO–C or C–(C=N)–C plane as θ_1 and the torsional angle between the benzene ring plane and C–CO–C or C–(C=N)–C plane as θ (see formula [VII] as well as formula [I]).



[VII]

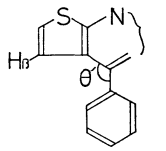
In the subsequent discussion, the following point is tacitly assumed. Conformations where the benzene ring and the carbonyl group or imino group are coplanar (maximum π-π overlap) become strongly preferred whenever structurally possible.[17]

In compound (**2**), the thiophene ring plane is considered to be to some extent twisted out of the C–CO–C plane by a steric hindrance between H_β of the thiophene ring and the benzene ring, because the six membered ring by the intramolecular hydrogen bonding may not be so rigid. An analogous steric hindrance was reported in the case of 2-amino-*p*-bromobenzophenone.[13] Thus, there may be some freedom of rotation around C–C bond (expressed as θ_1 in formula [VIII]). Ac-



[VIII]

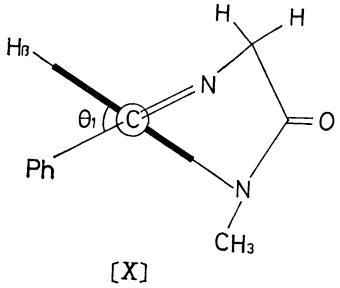
cordingly, in compound (**2**), the torsional angle between the benzene and thiophene ring planes can be expressed as θ_1 plus θ. In compound (**1**), θ_1 (see formula [VII]) is considered to be zero and thus the torsional angle can be expressed as θ (see formula [VII]). From experimental results, we can state that θ_1 plus θ in compound (**2**) is greater than θ in compound (**1**). The reason for this is as follows. Dreiding models of compounds (**1**) and (**2**) indicate that the bond angle C–CO–C or C–(C=N)–C (expressed as θ' in formula



[IX]

[IX]) is a little smaller in compound (**2**). This should cause greater steric hindrance between H_β of the thiophene and benzene rings, thus causing a greater torsional angle between the benzene and thiophene ring planes in compound (**2**) than in compound (**1**).

Compound (**3**) is considered to take a boat form known in benzodiazepines.[14] In this conformation, the thiophene ring plane is considered to be to some extent twisted out of the C–(C=N)–C plane by θ_1 (see formula [X]). Accordingly, the torsional angle



[X]

between the benzene and thiophene ring planes can be expressed as θ_1 plus θ. Experimental results suggest that θ_1 plus θ in compound (**3**) is greater than θ in compound (**1**). Presumably, θ_1 in compound (**3**) may be greater than θ in compound (**1**), and therefore θ_1 plus θ in compound (**3**) is greater than θ in compound (**1**).

Experimental

^{1}H NMR spectra were recorded at 60 MHz on a Hitachi NMR spectrometer R-20-B or 100 MHz on a JNM-4H-100 (Japan Electron Optics Lab.) in dilute deutero chloroform solution (about 10% w/v). The probe temperature was 35 °C. TMS was used as an internal reference standard. The chemical shifts are expressed in δ-values (ppm) downfield from TMS, and were measured directly from the spectra or from a frequency counter with a precision of $\pm$0.01 ppm. The coupling constants, measured by repeated sweeping at an expanded width (60 or 120 Hz), are expressed numerically in Hz with an accuracy of $\pm$0.1 Hz. IR spectra were recorded as Nujol mulls on a Hitachi Infrared Spectrophotometer, EPI-G-3 and are expressed as wave numbers. UV spectra were determined in 95% ethanol with an ultraviolet spectrophotometer, Hitachi-323, being expressed as λ_{max} mμ (ε). Melting points were measured on a Thomas-Hoover melting point apparatus and are uncorrected.

The synthetic procedures for the following compounds were reported in Part I.[1] 4-(*o*-Fluorophenyl)-1-methyl-1,2-dihydrothieno[2,3-*d*]-pyrimidin-2-one (**1aB**). 6-Chloro-4-(*o*-fluorophenyl)-1-methyl-1,2-dihydrothieno[2,3-*d*]-pyrimidin-2-one (**1bB**). 2-Acetamido-3-(*o*-fluorobenzoyl)-thiophene (**2aB**). 2-Acetamido-5-chloro-3-(*o*-fluorobenzoyl)-thiophene (**2bB**). 5-(*o*-Fluorophenyl)-1-methyl-1,3-dihydro-2*H*-thieno[2,3-*e*]-1,4-diazepin-2-one (**3aB**). 7-Chloro-5-(*o*-fluorophenyl)-1-methyl-1,3-dihydro-2*H*-thieno[2,3-*e*]-1,4-diazepin-2-one (**3bB**). 5-(*o*-Fluorophenyl)-1,3-dihydro-2*H*-thieno[2,3-*e*]-1,4-diazepin-2-one (**3cB**). 5-(*o*-Fluorophenyl)-1-methyl-1,3-dihydro-2*H*-thieno[2,3-*e*]-1,4-diazepin-2-one-4-oxide (**4aB**). 7-Chloro-5-(*o*-fluorophenyl)-1-methyl-1,3-dihydro-2*H*-thieno-[2,3-*e*]-1,4-diazepin-2-one-4-oxide (**4bB**).

The other compounds were prepared by the following methods.

*2-Acetamido-3-(*o,o'*-difluorobenzoyl)-thiophene (**2aI**).* This was prepared from 2-methyl-4*H*-thieno[2,3-*d*][1,3]-oxazin-4-one and *m*-difluorobenzene with *n*-buthyllithium according to the procedure applied to the synthesis of 2-acetamido-5-chloro-2',6'-difluorobenzophenone reported by Lemke *et al.*,[15] Yield 7.4%: mp 129—130 °C (from ether). IR: 3250, 3100, 3050, 1686, 1624. NMR: 2.33 (3H, s, $COCH_3$). UV: 238 (14100), 276 (11700), 346 (9500). Found: C, 55.69; H, 3.26; N, 4.84%. Calcd for $C_{13}H_9NO_2SF_2$: C, 55.51; H, 3.22; N, 4.98%.

*2-Amino-3-(*o,o'*-difluorobenzoyl)-thiophene.* (Method: see Part I, Experimental part, Method 1B). Yield 39.9%: mp 128.5—129.5 °C (from IPA). IR: 3350, 3250, 3150, 1620, 1590.

*2-Acetamido-5-chloro-3-(*o,o'*-difluorobenzoyl)-thiophene (**2bI**).* (Method: see Part I, Method 3). Yield 25.9%: mp 135—137 °C (from *n*-hexane–ether). IR: 3260, 3120, 1697, 1640, 1633. NMR: 2.32 (3H, s, $COCH_3$). UV: 245 (19300), 335 (9400). Found: C, 49.31; H, 2.43; N, 4.20%. Calcd for $C_{13}H_8NO_2SClF_2$: C, 49.46; H, 2.55; N, 4.44%.

*4-(*o,o'*-Difluorophenyl)-1,2-dihydrothieno[3,2-*d*]-pyrimidin-2-one.* (Method: see Part I, Method 4A). Yield 44.4%: It was used to the next step without further purification.

*4-(*o,o'*-Difluorophenyl)-1-methyl-1,2-dihydrothieno[2,3-*d*]pyrimidin-2-one (**1aI**).* (Method: see Part 1, Method 4A). Yield 11.6%: mp 212—213 °C (from ether). IR: 3055, 1645. NMR: 3.79 (3H, s, *N*-CH_3). UV: 245 (31300), 347 (5800). Found: C, 56.09; H, 2.90; N, 10.12%. Calcd for $C_{13}H_8N_2OSF_2$: C, 56.11; H, 2.90; N, 10.07%.

*6-Chloro-4-(*o,o'*-difluorophenyl)-1-methyl-1,2-dihydrothieno[2,3-*d*]-pyrimidin-2-one (**1bI**).* (Method: see Part 1, Method 5) Yield 22.2%: mp 150.5—151.5 °C (from Ethanol–Ether). IR: 3080, 3050, 1670. NMR: 3.72 (3H, s, *N*-CH_3). UV: 250.5 (28600), 355 (6400). Found: C, 49.94; H, 2.17; N, 8.91%. Calcd for $C_{13}H_7N_2OSClF_2$: C, 49.93; H, 2.66; N, 8.96%.

*3-(*o,o'*-Difluorophenyl)-2-(*N*-phthalimidoacetyl)-aminothiophene.* (Method: see Part I, Method 7B). Yield 73.2%: mp 184—189 °C (from acetone). IR: 3200, 1775, 1620.

*3-(*o,o'*-Difluorophenyl)-2-(*N*-methyl-*N*-phthalimidoacetyl)-aminothiophene.* (Method: see Part 1, Method 7B). Yield 54.7%: mp 192—193 °C (from acetone). IR: 3110, 3060, 1775, 1715, 1685, 1660, 1615.

*5-(*o,o'*-Difluorophenyl)-1-methyl-1,3-dihydro-2*H*-thieno[2,3-*e*]-1,4-diazepin-2-one (**3aI**).* (Method: see Part I, Method 7B). Yield 54.7%: mp 97.5—99.5 °C (from ether). IR: 3125, 3060, 1701, 1669, 1616. NMR: 3.54 (3H, s, *N*-CH_3), 4.52 (2H, s, CH_2). UV: 240 (22700), 315 (3000). Found: C, 57.50; H, 3.39; N, 9.69%. Calcd for $C_{14}H_{10}N_2OSF_2$: C, 57.53; H, 3.45; N, 9.58%.

*2-(*N*-Acetyl-*N*-methyl)-amino-3-(*o*-fluorobenzoyl)-thiophene.* (Method: see Part I, Method 4B). Yield 56.9%: mp 94—95 °C (from ether). IR: 3100, 1660, 1640, 1600.

*2-(*N*-Acetyl-*N*-methyl)-amino-5-chloro-3-(*o*-fluorobenzoyl)-thiophene (**2kB**).* (Method: see Part I, Method 3). Yield 71.4%: oil. IR: 1670, 1605. NMR: 1.98 (3H, s, $COCH_3$), 3.13 (3H, s, *N*-CH_3), 6.93 (1H, d, H_β).

*2-Acetamido-3-(*o*-fluorobenzoyl)-5-nitrothiophene (**2iB**).* This was prepared from 2-acetamido-3-(*o*-fluorobenzoyl)-thiophene (**2aB**) (already reported in Part I) with fuming nitric acid in the presence of acetic acid and acetic anhydride, according to the procedure applied to the synthesis of 2-nitrothiophene.[16] Yield 31.0%: mp 162—164 °C (from ethanol). IR: 3210, 3120, 1691, 1642, 1614. NMR: 2.39 (3H, s, $COCH_3$), 7.79 (1H, d, H_β), 12.12 (1H, s, NH). UV: 247 (15500), 343 (14400). Found: C, 50.35; H, 3.25; N, 8.93%. Calcd for $C_{13}H_9N_2O_4SF$: C, 50.65; H, 2.94; N, 9.09%.

*2-(*N*-Acetyl-*N*-methyl)-3-(*o*-fluorobenzoyl)-5-nitrothiophene (**2jB**).* This was prepared by the same method as that for **2iB** from 2-(*N*-acetyl-*N*-methyl)-amino-3-(*o*-fluorobenzoyl)-thiophene with fuming nitric acid. Yield 75.5%: mp 123—124.5 °C (from ethanol). IR: 3090, 1680, 1665, 1605. NMR: 2.11 (3H, s, $COCH_3$), 3.29 (3H, s, *N*-CH_3), 7.85 (1H, d, H_β). UV: 247 (16000), 323 (7100). Found: C, 52.02; H, 3.43; N, 8.62%. Calcd for $C_{14}H_{11}N_2O_4SF$: C, 52.17; H, 3.44; N, 8.69%.

*5-(*o,o'*-Difluorophenyl)-1-methyl-1,3-dihydro-2*H*-thieno[2,3-*e*]-1,4-diazepin-2-one-3-oxide (**4aI**).* (Method: see Part I, Method 9). Yield 54.9%: mp 104—107 °C (from ethanol). IR: 1682, 1627. NMR: 3.61 (3H, s, CH_3), 4.83 (2H, s, CH_2). UV: 248 (20500), 264 (17700), 310 (6400). Found: C, 54.60; H, 3.33; N, 8.92%. Calcd for $C_{14}H_{10}N_2O_2SF_2$: C, 54.54; H, 3.27; N, 9.09%.

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