Nuclear Magnetic Resonance Studies of Bicyclic Thiophene Derivatives. I. Ring Current Effects of the Benzene Ring on the H_α and H_β Signals of the Thiophene Ring in Benzoylthiophene, Thienopyrimidine and Thienodiazepine Derivatives

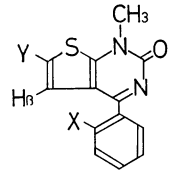
Toshiyuki HIROHASHI, Shigeho INABA, and Hisao YAMAMOTO

Takarazuka Research Laboratories, Sumitomo Chemical Co., Takatsukasa, Takarazuka, Hyogo 665

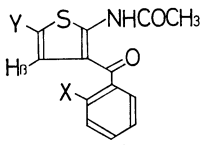
(Received March 14, 1974)

Various thiophene derivatives such as 4-phenylthienopyrimidines (**1**), 2-acetylamino-3-benzoylthiophenes (**2**), 5-phenyl-1,4-thienodiazepines (**3**) and 5-phenyl-1,4-thienodiazepine-4-oxides (**4**) have been prepared. Their proton magnetic resonance spectra show that H_α and H_β of the thiophene ring become more shielded with an increase in bulk of *ortho* substituent of the benzene ring. This is attributed to the shielding effect of the benzene ring; a steric repulsion between *ortho* substituent of the benzene ring and some atoms on another moiety of each molecule. Such a repulsion should bring the benzene ring out of the plane of the thiophene ring. The degree of shielding on H_β by the benzene ring is found to increase in the order **1**<**2**<**3**<**4**. This can be taken to indicate that the amount of steric repulsion depends not only on the bulk of *ortho* substituent of the benzene ring but also on the geometry of each ring system of **1**—**4**.

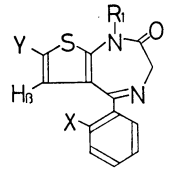
From pharmaceutical interest, we have prepared a number of thiophene derivatives including 4-phenylthienopyrimidines (**1**), 2-acetylamino-3-benzoylthiophenes (**2**), 5-phenyl-1,4-thienodiazepines (**3**), and 5-phenyl-1,4-thienodiazepine-4-oxides (**4**). In order to



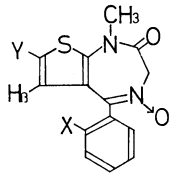
(1)



(2)

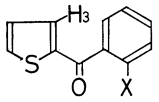


(3)



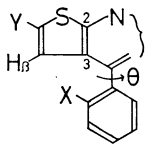
(4)

study the correlation between the biological activity and conformation of the molecules, we made studies by means of NMR spectroscopy. It was reported by Martin *et al.*[1-3] that H_3 in 2-benzoylthiophenes (**5**)



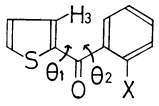
(5)

becomes more shielded with an increase in bulk of the *ortho* substituent (X) of the benzene ring. They found that, when a bulky substituent (X) is introduced, the dihedral angle between the thenoyl plane and benzene plane (*i.e.* θ_2 in formula [II]) is increased, and as a result, the shielding effect on H_3 by the benzene ring becomes more pronounced. H_β of **1**—**4** corresponds to H_3 of 2-benzoylthiophene **5**, since both protons are in close proximity with the benzene ring. However, compounds **1**—**4**, in which C=O or C=N moiety is fixed nearly co-planar with the thiophene plane by a ring formation as shown by formula [I], have a freedom of internal rotation (*i.e.* torsional angle between the

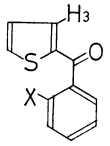


[I]

benzene and thiophene planes; θ in formula [I]). In **5**, there are two internal rotation axes (see θ_1 and θ_2 in formula [II]). Thus, there are two possible limiting



[II]

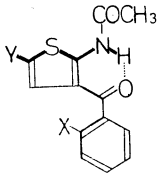


[III]

conformations of [II] and [III] for this type of compound.[2] In [III], it is apparent that the ring current effect of the benzene ring on H_3 should not be great. The chemical shifts of H_β in compounds **1**—**4** can therefore be correlated with the torsional angle θ more simply than the correlation between the chemical shifts of H_3 in compound **5** and the torsional angle θ_2. In this paper, the results of our proton-magnetic resonance measurement of compounds **1**—**4** are reported with interpretation in terms of the conformation of the compounds.

Results

NMR data for the thiophene derivatives are given in Tables 6—9. The signals of H_α and H_β of the thiophene ring show a simple AB type coupling. By substituting H_α with chlorine, we can easily tell which chemical shift is caused by H_β. High field shift of H_β by the chlorination is found to amount to 0.15 ppm. This assignment is supported by the fact that the H_α signal of the thiophene ring in compound **2** shows an extra doublet due to coupling with an amide proton (Table 7). The carbonyl oxygen of **2** is considered to form an intramolecular hydrogen bonding with an amide proton to form a six membered ring as represented by formula [IV]. This is judged from our


[IV]

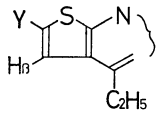
finding the amide proton signal at an extraordinarily low field (11.9±0.1 ppm). Gribble and Bousquet found the amide proton signal at about the same position in 2-acetylamino-benzophenone.[4] When Y is a hydrogen, H_α couples with the amide proton (J=0.8 Hz) through five zig-zag bonds (thick lines, [IV]). This supports the postulation of the intramolecular hydrogen bonding.[5,6] From Tables 6—9 it is evident that H_α and H_β are shielded increasingly by the benzene ring in the order X: H<F<Cl<Br<I for **1**—**4**. The amount of increase is greater for H_β than for H_α. However, the amount of increase in the series **1**—**4** seems to differ from one another.

Discussion

Shielding Effect of the Benzene Ring on H_α and H_β. Let us define the degree ($\Delta\delta$) of shielding on H_α and H_β caused by the benzene ring in compound **1**—**4** as

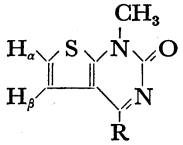
$$\Delta\delta = \delta_s - \delta$$

where δ is the chemical shift of H_α or H_β in each compound with the benzene ring, and δ_s is that in the corresponding compound in which the benzene ring is substituted by an ethyl group: Degrees of shielding


[V]

($\Delta\delta$) are listed in Tables 1—4. The $\Delta\delta$ value should include not only the ring current effect of the benzene ring, but also a through-space effect of C–X bond anisotropy and a through-bond effect of the halogen atom X. The benzene ring current itself is lowered by the inductive or mesomeric effect of the substituent X.[7] The amount of chemical shift caused by such effects, however, is considered to be sufficiently small in comparison with that caused by the benzene ring current on the basis of the following examinations.

TABLE 1. SHIELDING EFFECT ($\Delta\delta$) OF THE BENZENE RING ON H_α AND H_β OF COMPOUND **1**

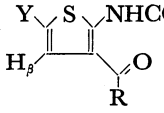

(**1a**)

	R	$\Delta\delta(H_\alpha)$ (ppm)[a]	$\Delta\delta(H_\beta)$ (ppm)[b]
A	Phenyl	−0.01	−0.13
B	*o*-Fluorophenyl	0.03	0.15
C	*o*-Chlorophenyl	0.05	0.30

a) $\Delta\delta(H_\alpha)=\delta_s(H_\alpha)-\delta(H_\alpha)$ b) $\Delta\delta(H_\beta)=\delta_s(H_\beta)-\delta(H_\beta)$

Bond Anisotropy Effect of C–X (Halogen) Bond. We prepared compounds **1**—**4** where the *ortho* substituent of benzene ring is a methyl group. The chemical shift of H_β was determined for each compound: $\delta H_\beta(X=CH_3)$, which was compared with the chemical shift of H_β of the corresponding compound, where X is chlorine: $\delta H_\beta(X=Cl)$ (Tables 6—9). The difference $[\delta H_\beta(X=CH_3)-\delta H_\beta(X=Cl)]$ was found to

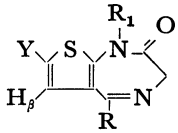
TABLE 2. SHIELDING EFFECT ($\Delta\delta$)[a] OF THE BENZENE RING ON H_α AND H_β OF COMPOUND **2**


(**2**)

	R	**2a**[b] $\Delta\delta(H_\alpha)$	**2a**[b] $\Delta\delta(H_\beta)$	**2b**[c] $\Delta\delta(H_\beta)$	av.[e] $\Delta\delta(H_\beta)$
A	Phenyl	−0.01	0.07	0.07	0.07
B	*o*-Fluorophenyl	0.05	0.31	0.28	0.30
C	*o*-Chlorophenyl	0.08	0.49	0.47	0.48
D	*o*-Bromophenyl	0.09	0.51	0.50	0.51
E	*o*-Iodophenyl	0.06	0.54	0.52	0.53

a) See Table 1. b) Y=H_α. c) Y=Cl. d) Average of **2a** and **2b**.

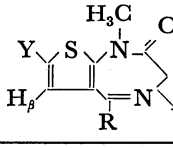
TABLE 3. SHIELDING EFFECT ($\Delta\delta$)[a] OF THE BENZENE RING ON H_α AND H_β OF COMPOUND **3**


(**3**)

	R	**3a**[b] $\Delta\delta(H_\alpha)$	**3a**[b] $\Delta\delta(H_\beta)$	**3b**[c] $\Delta\delta(H_\beta)$	**3c**[d] $\Delta\delta(H_\alpha)$	**3c**[d] $\Delta\delta(H_\beta)$	av.[e] $\Delta\delta(H_\beta)$
A	Phenyl	0.01	0.17	0.17	0.05	0.20	0.18
B	*o*-Fluorophenyl	0.06	0.32	0.31	0.08	0.34	0.32
C	*o*-Chlorophenyl	0.09	0.46	0.46	0.10	0.47	0.46
D	*o*-Bromophenyl	0.09	0.49	0.49	—	—	0.49
E	*o*-Iodophenyl	0.09	0.53	0.51	—	—	0.52

a) See Table 1. b) R_1=CH_3, Y=H_α. c) R_1=CH_3, Y=Cl. d) R_1=H, Y=H_α. e) Average of **3a**, **3b**, and **3c**.

TABLE 4. SHIELDING EFFECT ($\Delta\delta$)[a] OF THE BENZENE RING ON H_α AND H_β OF COMPOUND **4**


(**4**)

	R	**4a**[b] $\Delta\delta(H_\alpha)$	**4a**[b] $\Delta\delta(H_\beta)$	**4b**[c] $\Delta\delta(H_\beta)$	av.[d] $\Delta\delta(H_\beta)$
A	Phenyl	0.08	0.34	0.33	0.34
B	*o*-Fluorophenyl	0.13	0.45	0.43	0.44
C	*o*-Chlorophenyl	0.13	0.51	0.50	0.51
D	*o*-Bromophenyl	0.13	0.51	—	0.51
E	*o*-Iodophenyl	0.14	0.51	—	0.51

a) See Table 1. b) Y=H_α. c) Y=Cl. d) Average of **4a** and **4b**.

be −0.05 ppm for **1a**, −0.02 ppm for **1b**, 0.06 ppm for **2a**, −0.01 ppm for **3a** and −0.04 ppm for **4a**. Although the size of a methyl group is reported to be a little larger than that of the chlorine atom,[1,17] it is reasonable to consider that the torsional angle θ of the benzene ring with respect to the thiophene ring is nearly equal in the methyl-compound to that in the chloro-compound. The difference $[\delta H_\beta(X=CH_3)-\delta H_\beta(X=Cl)]$ might be attributed to the bond anisotropy effect of C–X (X=halogen) bond on H_β. Since the difference was found to be small, the bond anisotropy effect is considered to be very small. Nomura and Takeuchi[8] also provided an evidence that the bond anisotropy effect of C–X (halogen) must be small or nonexistent in aromatic systems.

Mesomeric and/or Inductive Effect of the ortho *Substituent X on the Benzene Ring Current.* We prepared compounds **2aF**, **2bF**, **3aF**, and **3bF**, where the *para* substituent of the benzene ring is chlorine. The chemical shift of H_β determined for each compound was δH_β-(Z=Cl), which was compared with the chemical shift of H_β of the corresponding compound where Z is a hydrogen: $\delta H_\beta(Z=H)$ (see Tables 7 and 8). The difference $[\delta H_\beta(Z=H)-\delta H_\beta(Z=Cl)]$ was found to be 0.07 ppm for **2a**, 0.03 ppm for **2b**, 0.02 ppm for **3a**, and 0.00 ppm for **3b**. The torsional angle of the benzene ring with respect to the thiophene ring should be nearly equal in the compound with Z=Cl to the corresponding compound with Z=H. The mesomeric and/or inductive effect of the *ortho* substituent (X=Cl) to the benzene ring current should be nearly equal to that of the *para* substituent (Z=Cl). The difference $[\delta H_\beta(Z=H)-\delta H_\beta(Z=Cl)]$ might be attributed to the mesomeric and/or inductive effect of the *ortho* substituent (X=Cl) on the benzene ring current. This effect was found to be very small. The above data seem to indicate that the through-bond effect of substituent X on the chemical shift of H_β is also very small. Martin *et al.* also examined the effect of *para* substituent Z(=H, F, Cl, Br, I, OCH_3, CH_3) in the benzene ring upon the chemical shift of H_3 in compound **5** (see formula [VI]).[1] They reported that the *para* substituent Z does not affect the chemical shift of H_3.

2aF(Y=H, Z=Cl) 3aF(Y=H, Z=Cl)
2bF(Y=Cl, Z=Cl) 3bF(Y=Cl, Z=Cl)

[VI]

Relative Amount of $\Delta\delta$ of H_α with Respect to That of H_β. We would like to show, by use of the Johnson and Bovey diagram (a figure of the isoshielding lines of benzene nucleus given by Johnson and Bovey[9]), that our observed relative amounts of $\Delta\delta$ of H_α with respect to that of H_β are explained by taking only the effect of benzene ring current into account. Let us take 2-acetamido-3-benzoylthiophene (**2a**) as an example. If we assume that the thiophene ring is in the same plane as the C–CO–C plane, the Dreiding models of this compound indicate that the center of the benzene ring and H_β and H_α come nearly on a straight line (formula [VII]). Here, the distance from the center of the benzene ring to H_β is 3.3 Å and to H_α 5.9 Å. The straight line and the distances are maintained even if the benzene ring rotates around the C–C bond by θ. In the Johnson and Bovey diagram, the position of H_β is expressed by a circle ($\mathbf{P}_\beta$) with its center at the origin and its radius of a length corresponding to 3.3 Å. The position of H_α is likewise expressed by a similar circle ($\mathbf{P}_\alpha$) whose radius has a length corresponding to 5.9 Å (Fig. 1). Here, the isoshielding lines of benzene nucleus are a modification of the figure given by Johnson and Bovey.[9] The observed shielding effect ($\Delta\delta$) of H_β of compound **2aA** is 0.07 ppm (Table 2). Therefore, the position of H_β should

[VII]

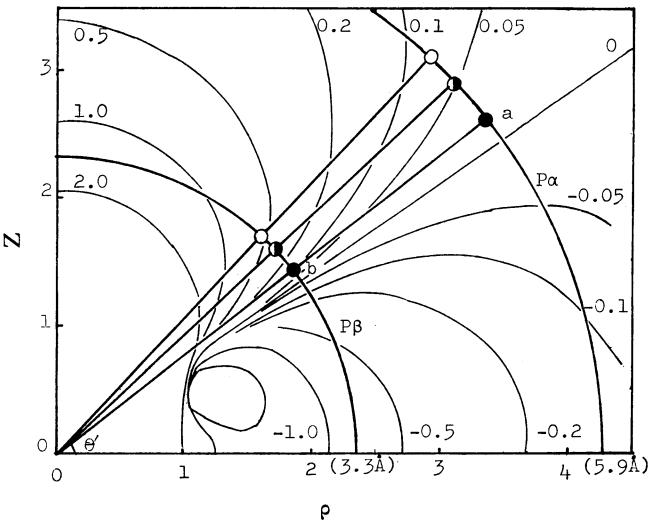


Fig. 1. Positions of H_α and H_β of compounds **2aA**—**2aC** as function of the isoshielding lines (expressed in ppm) of benzene nucleus; Z and ρ are expressed in ring radii (1.39 Å) according to Johnson and Bovey.[9] (●) Hα or H_β position of compound **2aA**, (◑) **2aB**, and (○) **2aC**. θ' is an angle between the benzene ring plane and the line which connect H_α, H_β, and center of the benzene ring. This is not the torsional angle (θ) between benzene ring plane and thiophene ring plane. When θ' is 60°, the torsional angle θ is nearly 90°.

be fixed at a point **b**. Connect point **b** with the origin. Since H_α is on the straight line connecting the center of the benzene ring and H_β in the molecule, the point representing H_α in the Johnson and Bovey diagram should also be on the straight line connecting the origin and point **b**. Let us denote the intersection of straight line **O–b** and circle $\mathbf{P}_\alpha$ by **a**. This corresponds to 0.01 ppm, which is almost equal to the observed value (−0.01 ppm) of $\Delta\delta$ for H_α (Table 2). In a similar way, the theoretical $\Delta\delta$ value for H_α derived from the observed $\Delta\delta$ value for H_β is nearly equal to the actually observed value for H_α in each compound **1a**, **2a**, **3a**, **3c**, and **4a** (Table 5).

TABLE 5. DIFFERENCE BETWEEN THE THEORETICAL AND OBSERVED VALUES FOR H_α

	R	Observed (ppm) $\Delta\delta(H_\beta)$	Observed (ppm) $\Delta\delta(H_\alpha)$	Theoretical (ppm) $\Delta\delta(H_\alpha)$	Difference[a] (ppm)
	Compound **1a**				
A	Phenyl	−0.13	−0.01	−0.02	0.01
B	*o*-Fluorophenyl	0.15	0.03	0.02	0.01
C	*o*-Chlorophenyl	0.30	0.05	0.05	0.00
	Compound **2a**				
A	Phenyl	0.07	−0.01	0.01	−0.02
B	*o*-Fluorophenyl	0.31	0.05	0.05	0.00
C	*o*-Chlorophenyl	0.49	0.08	0.08	0.00
D	*o*-Bromophenyl	0.51	0.09	0.08	0.01
E	*o*-Iodophenyl	0.54	0.06	0.08	−0.02
	Compound **3a**				
A	Phenyl	0.17	0.01	0.03	−0.02
B	*o*-Fluorophenyl	0.32	0.06	0.05	0.01
C	*o*-Chlorophenyl	0.46	0.09	0.07	0.02
D	*o*-Bromophenyl	0.49	0.09	0.08	0.01
E	*o*-Iodophenyl	0.53	0.09	0.08	0.01
	Compound **3c**				
A	Phenyl	0.20	0.05	0.03	0.02
B	*o*-Fluorophenyl	0.34	0.08	0.06	0.02
C	*o*-Chlorophenyl	0.47	0.10	0.08	0.02
	Compound **4a**				
A	Phenyl	0.34	0.08	0.06	0.02
B	*o*-Fluorophenyl	0.45	0.13	0.07	0.06
C	*o*-Chlorophenyl	0.51	0.13	0.08	0.05
D	*o*-Bromophenyl	0.51	0.13	0.08	0.05
E	*o*-Iodophenyl	0.51	0.14	0.08	0.06

a) Difference = $\Delta\delta(H_\alpha)$(observed) − $\Delta\delta(H_\alpha)$(theoretical).

Steric Effects. The correlation between the $\Delta\delta$ value (chemical shift caused by the ring current of the phenyl group) of H_β and the bulk of the *ortho* substituent X of phenyl group is shown in Fig. 2. We see that $\Delta\delta$ value increases with an increase of the bulk of X. This might be attributed to the steric repulsion between X of the phenyl ring and some atoms on another moiety of the molecule. Such a repulsion should bring the benzene ring out of the plane of thiophene ring. The $\Delta\delta$ value increases in going from compound **1** to compound **4** throgh compounds

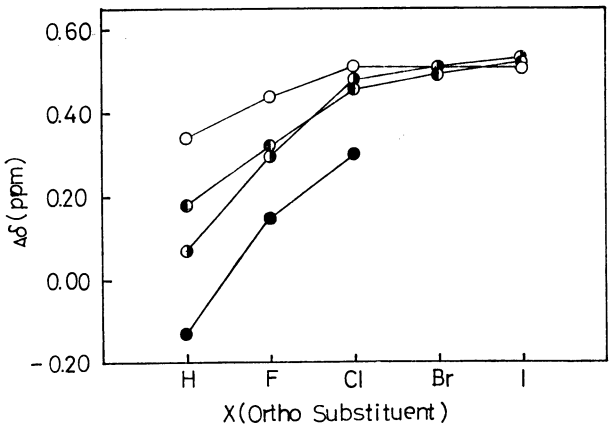
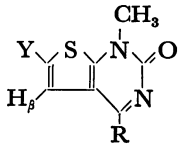


Fig. 2. Shielding effect ($\Delta\delta$) of benzene ring on H_β. (●) Compound **1**, (◑) compound 2, (◐) compound 3, and (○) compound **4**.

2 and **3**; *i.e.* **1**<**2**<**3**<**4**. This seems to indicate that the amount of steric repulsion depends not only on the bulk of X but also on the geometry and/or flexibility of the ring system condensed at 2-C and 3-C of the thiophene ring in each molecule (formula [I]). Such a steric repulsion is considered to be great even when X=H. Thus, the $\Delta\delta$ value markedly increases from compound **1** to compound **4** when X=H. This must mean that θ' greatly increases from compound **1**(X=H)→**2**(X=H)→**3**(X=H)→**4**(X=H). When X=F, on the other hand, the increase in the $\Delta\delta$ value (or the θ' value) in going from compound **1**(X=F)→**2**(X=F)→**3**(X=F)→**4**(X=F) is much smaller. When X=Cl, the corresponding increase in the $\Delta\delta$ value is even smaller. When X=Br or I, the $\Delta\delta$ value does not depend on the ring structure condensed at 2-C and 3-C of the thiophene ring. This might be explained by considering that the plane of the benzene ring is nearly perpendicular to the plane of the thiophene ring in compounds **2**—**4**, when X=Br or I.

TABLE 6. NMR DATA[a] FOR 1-METHYL-4-PHENYL (OR ETHYL)-1,2-DIHYDROTHIENO[2,3-*d*]-PYRIMIDIN-2-ONES (**1**)

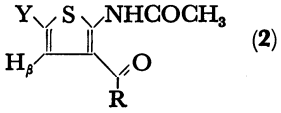


(**1**)

	R	Y	δ (ppm) H_α[b]	δ (ppm) H_β[b]
1aA	C_6H_5	H_α	6.98	7.35
1aB	*o*-F-C_6H_4	H_α	6.94	7.07
1aC	*o*-Cl-C_6H_4	H_α	6.92	6.92
1aG	*o*-Me-C_6H_4	H_α	6.93	6.87
1aH	C_2H_5	H_α	6.97	7.22
1bA	C_6H_5	Cl	—	7.19
1bB	*o*-F-C_6H_4	Cl	—	6.93
1bC	*o*-Cl-C_6H_4	Cl	—	6.77
1bG	*o*-Me-C_6H_4	Cl	—	6.75

a) See Experimental for other protons not given here.
b) $J(H_\alpha, H_\beta)$=5.8 Hz.

Table 7.[a] NMR data for 2-acetamido-3-benzoyl (or propionyl) thiophenes (2)

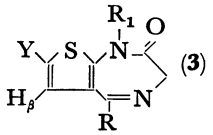


(2)

	R	Y	δ H_α[b]	δ H_β[b]	δ NH	(Hz) J_{NH,H_α}
2aA	C_6H_5	H_α	6.72	7.12	11.96	0.7
2aB	o-F-C_6H_4	H_α	6.66	6.88	11.94	0.8
2aC	o-Cl-C_6H_4	H_α	6.63	6.70	11.88	0.7
2aD	o-Br-C_6H_4	H_α	6.63	6.68	11.86	0.7
2aE	o-I-C_6H_4	H_α	6.65	6.65	11.85	nv[c]
2aF	p-Cl-C_6H_4	H_α	6.71	7.05	11.87	0.8
2aG	o-Me-C_6H_4	H_α	6.63	6.76	12.00	0.8
2aH	C_2H_5	H_α	6.71	7.19	11.90	0.8
2bA	C_6H_5	Cl	—	6.95	11.97	—
2bB	o-F-C_6H_4	Cl	—	6.74	11.92	—
2bC	o-Cl-C_6H_4	Cl	—	6.55	11.90	—
2bD	o-Br-C_6H_4	Cl	—	6.52	11.88	—
2bE	o-I-C_6H_4	Cl	—	6.50	11.85	—
2bF	p-Cl-C_6H_4	Cl	—	6.92	11.92	—
2bH	C_2H_5	Cl	—	7.02	11.87	—

a) Remarks and abbreviations as in Table 6. b) $J(H_\alpha,H_\beta)=5.8$ Hz. c) Not visible due to the overlapping of H_α and H_β signals.

Table 8.[a] NMR data for 5-phenyl (or ethyl)-1,3-dihydro-2*H*-thieno[2,3-*e*]-1,4-diazepin-2-ones (3)

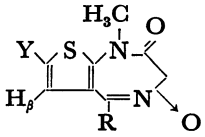


(3)

	R	R_1	Y	δ H_α[b]	δ H_β[b]
3aA	C_6H_5	CH_3	H_α	6.99	6.83
3aB	o-F-C_6H_4	CH_3	H_α	6.94	6.68
3aC	o-Cl-C_6H_4	CH_3	H_α	6.91	6.54
3aD	o-Br-C_6H_4	CH_3	H_α	6.91	6.51
3aE	o-I-C_6H_4	CH_3	H_α	6.91	6.47
3aF	p-Cl-C_6H_4	CH_3	H_α	7.01	6.81
3aG	o-Me-C_6H_4	CH_3	H_α	6.90	6.53
3aH	C_2H_5	CH_3	H_α	7.00	7.00
3bA	C_6H_5	CH_3	Cl	—	6.68
3bB	o-F-C_6H_4	CH_3	Cl	—	6.54
3bC	o-Cl-C_6H_4	CH_3	Cl	—	6.39
3bD	o-Br-C_6H_4	CH_3	Cl	—	6.36
3bE	o-I-C_6H_4	CH_3	Cl	—	6.34
3bF	p-Cl-C_6H_4	CH_3	Cl	—	6.68
3bH	C_2H_5	CH_3	Cl	—	6.85
3cA	C_6H_5	H	H_α	6.86	6.80
3cB	o-F-C_6H_4	H	H_α	6.83	6.66
3cC	o-Cl-C_6H_4	H	H_α	6.81	6.53
3cH	C_2H_5	H	H_α	6.91	7.00

a) Remarks and abbreviations as in Table 6. b) $J(H_\alpha,H_\beta)=5.8$ Hz.

Table 9.[a] NMR data for 1-methyl-5-phenyl(or ethyl)-1,3-dihydro-2*H*-thieno[2,3-*e*]-1,4-diazepin-2-one-4-oxides (4)



(4)

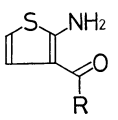
	R	Y	δ H_α[b]	δ H_β[b]
4aA	C_6H_5	H_α	7.06	6.63
4aB	o-F-C_6H_4	H_α	7.01	6.52
4aC	o-Cl-C_6H_4	H_α	7.01	6.46
4aD	o-Br-C_6H_4	H_α	7.01	6.46
4aE	o-I-C_6H_4	H_α	7.00	6.46
4aG	o-Me-C_6H_4	H_α	6.98	6.42
4aH	C_2H_5	H_α	7.14	6.97
4bA	C_6H_5	Cl	—	6.48
4bB	o-F-C_6H_4	Cl	—	6.38
4bC	o-Cl-C_6H_4	Cl	—	6.31
4bH	C_2H_5	Cl	—	6.82

a) Remarks and abbreviations as in Table 6.
b) $J(H_\alpha,H_\beta)=5.8$ Hz.

Experimental

^1H NMR spectra were recorded at 60 MHz on a Hitachi NMR spectrometer R-20-B in dilute deuteriochloroform solution (about 10% w/v). The probe temperature was 35 °C. TMS was used as an internal reference standard. The chemical shifts expressed in δ-values (ppm) downfield from TMS were measured directly from the spectra or from a frequency counter with a precision of ±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 ±0.1 Hz. IR spectra were recorded as nujol mulls on a Hitachi Infrared Spectrophotometer, EPI-G-3, being expressed in terms of wave numbers. UV spectra were determined in 95% ethanol with an ultraviolet spectrophotometer, Hitachi-323 or Shimadzu D-40-R, being expressed as λ_{max} nm(ε). Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Solvents for recrystallization are abbreviated as follows; ethanol (EtOH), 2-propanol (IPA), and dimethylformamide (DMF).

1) 2-Amino-3-benzoyl(or propionyl)-thiophenes.



Method A: *A–G.* The compounds were prepared by the method of Gewald[10] from appropriate ω-cyanoacetophenones and mercaptoacetaldehyde.

A (*R*: *phenyl*). Yield 32.9%: mp 152—153 °C (from EtOH) (lit,[11] 147 °C).

B (*R*: o-*fluorophenyl*). Yield 60.0%: mp 145—146.5 °C (from IPA). IR: 3350, 3230, 3130, 1610.

C (*R*: o-*chlorophenyl*). Yield 47.0%: mp 137—139 °C (from IPA). IR: 3380, 3275, 1597, 1522.

D (*R*: o-*bromophenyl*). Yield 34.0%: mp 152—152.5 °C (from IPA). IR: 3350, 3230, 3100, 1590.

E (*R*: o-*iodophenyl*). Yield 27.6%: mp 162—165 °C

(from IPA). IR: 3350, 3230, 3100, 1590.

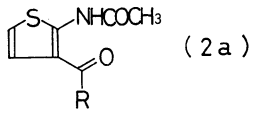
F *(R: p-chlorophenyl).* Yield 27.6%: mp 180—181.5 °C (from EtOH). IR: 3320, 3200, 3100, 1595.

G *(R: o-methylphenyl).* Yield 63.8%: mp 158—159 °C (from EtOH). IR: 3320, 3200, 3100, 1590.

*Method B: 2-Amino-3-proprionylthiophene (**H**).* This was prepared by the hydrolysis of 2-acetamido-3-propionylthiophene (**2aH**) with potassium hydroxide in aqueous ethanol at 95 °C for 10 min.

H *(R: ethyl).* Yield 87.7%: mp 140—142 °C (from Ether). IR: 3370, 3250, 3130, 1600, 1570.

*2) 2-Acetamido-3-benzoyl(or propionyl)-thiophenes (**2a**).*



(2a)

*Method A: **2aA—2aG**.* The compounds were prepared by the method of Gewald[10] from 2-amino-3-benzoylthiophenes with acetylchloride.

2aA *(R: phenyl).* Yield 67.6%: mp 115.5—116.5 °C (from Ether). IR: 3200, 3100, 3085, 1687, 1610. NMR: 2.31 (3H, s, $COCH_3$). UV: 248.5 (14400), 270 (12700), 343 (9200). Found: C, 63.54; H, 4.58; N, 5.70%. Calcd for $C_{13}H_{11}NO_2S$: C, 63.65; H, 4.52; N, 5.71%.

2aB *(R: o-fluorophenyl).* Yield 83.5%: mp 143.5—144.5 °C (from Ether). IR: 3235, 3100, 1698, 1622, 1618. NMR: 2.34 (3H, s, $COCH_3$). UV: 239 (13700), 276 (11900), 345 (9600). Found: C, 59.04; H, 4.01; N, 5.26%. Calcd for $C_{13}H_{10}NO_2SF$: C, 59.30; H, 3.83; N, 5.32%.

2aC *(R: o-chlorophenyl).* Yield 68.9%: mp 132—132.5 °C (from Ether). IR: 3225, 3075, 1682, 1618. NMR: 2.34 (3H, s, $COCH_3$). UV: 236 (14300), 275 (10800), 343 (9600). Found: C, 55.90; H, 3.80; N, 5.00%. Calcd for $C_{13}H_{10}NO_2SCl$: C, 55.82; H, 3.60; N, 5.01%.

2aD *(R: o-bromophenyl).* Yield 76.2%: mp 122.5—123.5 °C (from Ether). IR: 3215, 3075, 3055, 1691, 1618. NMR: 2.34 (3H, s, $COCH_3$). UV: 236 (14800), 276 (10600), 343 (9500). Found: C, 48.22; H, 3.04; N, 4.24%. Calcd for $C_{13}H_{10}NO_2SBr$: C, 48.16; H, 3.11; N, 4.32%.

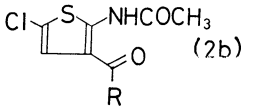
2aE *(R: o-iodophenyl).* Yield 26.1%: mp 125.5—127 °C (from Ether). IR: 3225, 3100, 3070, 1697, 1622. NMR: 2.33 (3H, s, $COCH_3$). UV: 232 (21800), 276 (10900), 344 (10100). Found: C, 42.37; H, 2.64; N, 3.77%. Calcd for $C_{13}H_{10}NO_2SI$: C, 42.07; H, 2.72; N, 3.77%.

2aF *(R: p-chlorophenyl).* Yield 23.6%: mp 107—108.5 °C (from Ether). IR: 3220, 3100, 1706, 1611. NMR: 2.32 (3H, s, $COCH_3$). UV: 268 (16100), 348 (9400). Found: C, 56.01; H, 3.62; N, 5.04%. Calcd for $C_{13}H_{10}NO_2SCl$: C, 55.82; H, 3.60; N, 5.01%.

2aG *(R: o-methylphenyl).* Yield 41.9%: mp 90—91.5 °C (from Ether). IR: 3235, 3105, 3087, 1695, 1623. NMR: 2.34 (3H, s, ϕ-CH_3), 2.35 (3H, s, $COCH_3$). UV: 237 (14200), 271 (10900), 338 (9700). Found: C, 64.86; H, 5.07; N, 5.34%. Calcd for $C_{14}H_{13}NO_2S$: C, 64.84; H, 5.05; N, 5.40%.

*Method B: 2-Acetamido-3-propionylthiophene (R: ethyl) (**2aH**).* To a suspension of 2-methyl-4*H*-thieno[2,3-*d*]-[1,3]oxazin-4-one (21.9 g) in dry ether (500 ml) was added dropwise a Grignard solution prepared from ethyl bromide (24.3 g), metallic magnesium (4.77 g) and ether (110 ml) at 15—20 °C. The mixture was stirred at room temperature overnight. First, water (500 ml), then conc, hydrochloric acid (120 ml) were added dropwise thereto under ice-cooling. The organic layer was separated and washed with 28% ammonia water, then condensed *in vacuo* and the residue crystallized to give 2-acetamido-α,α-diethyl-3-thiophenemethanol (8.6 g) as a by-product, mp 138—140 °C. The condensed filtrate was purified over a column of silica gel (240 g) and eluted with chloroform. Concentration of the chloroform elution gave the product (**2aH**) (3.13 g) as crystals. Recrystallization from ether gave colorless prisms, mp 73.5—74.0 °C. IR: 3220, 3100, 1665, 1640. NMR: 1.20 (3H, t, $CH_2\underline{CH_3}$), 2.26 (3H, s, $COCH_3$), 2.86 (2H, q, CH_2). UV: 236 (16600), 260 (7500), 267 (7100), 323 (8600). Found: C, 54.81; H, 5.52; N, 7.13%. Calcd for $C_9H_{11}NO_2S$: C, 54.80; H, 5.62; N. 7.10%.

*3) 2-Acetamido-3-benzoyl(or propionyl)-5-chlorothiophenes (**2b**)*



(2b)

These were prepared by the method of Hromatka *et al.*[12] from 2-acetamido-3-benzoyl (or propionyl)-thiophene (**2a**) with sulfurylchloride.

2bA *(R: phenyl).* Yield 66.6%: mp 102.5—103.5 °C (from Ether). IR: 3220, 1698, 1610, 1600. NMR: 2.28 (3H, s, $COCH_3$). UV: 253 (18300), 353 (9200). Found: C, 55.69; H, 3.52; N, 4.94%. Calcd for $C_{13}H_{10}NO_2SCl$: C, 55.82; H, 3.60; N, 5.01%.

2bB *(R: o-fluorophenyl).* Yield 62%: mp 159—160.5 °C (from EtOH). IR: 3220, 3080, 1682, 1608. NMR: 2.31 (3H, s, $COCH_3$). UV: 256 (17400), 354 (9200). Found: C, 52.28; H, 3.09; N, 4.57%. Calcd for $C_{13}H_9NO_2SClF$: C, 52.45; H, 3.05; N, 4.71%.

2bC *(R: o-chlorophenyl).* Yield 77.3%: mp 180—181 °C (from EtOH). IR: 3230, 3075, 1682, 1613. NMR: 2.32 (3H, s, $COCH_3$). UV: 242 (19600), 350 (9500). Found: C, 49.93; H, 2.85; N, 4.45%. Calcd for $C_{13}H_9NO_2SCl_2$: C, 49.70; H, 2.89; N, 4.46%.

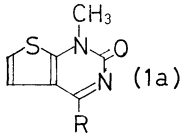
2bD *(R: o-bromophenyl).* Yield 75.9%: mp 162—163 °C (from EtOH). IR: 3225, 3065, 1688, 1612. NMR: 2.33 (3H, s, $COCH_3$). UV: 244 (19400), 350 (9400). Found: C, 43.56; H, 2.51; N, 3.87%. Calcd for $C_{13}H_9NO_2SBrCl$: C, 43.54; H, 2.53; N, 3.91%.

2bE *(R: o-iodophenyl).* Yield 48.5%: mp 124—126 °C (from Ether). IR: 3220, 3070, 1681, 1610. NMR: 2.35 (3H, s, $COCH_3$). UV: 232 (22200), 349 (9500). Found: C, 38.47; H, 2.26; N, 3.46%. Calcd for $C_{13}H_9NO_2SClI$: C, 38.50; H, 2.24; N, 3.45%.

2bF *(R: p-chlorophenyl).* Yield 40.9%: mp 119—121 °C (from Ether). IR: 3250, 1705, 1605. NMR: 2.31 (3H, s, $COCH_3$). UV: 263 (20300), 355 (9400). Found: C, 49.71; H, 2.87; N, 4.42%. Calcd for $C_{13}H_9NO_2SCl_2$: C, 49.70; H, 2.89; N, 4.46%.

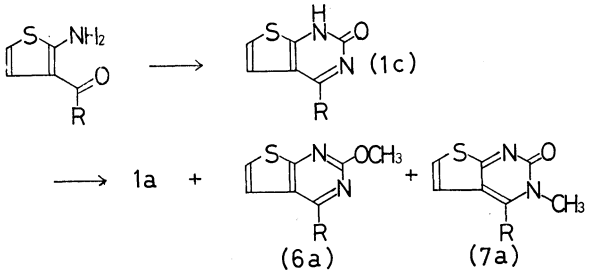
2bH *(R: ethyl).* Yield 17.2%: mp 156.5—157.5 °C (from Ether). IR: 3215, 3075, 1684, 1642. NMR: 1.19 (3H, t, J=7.1, $CH_2\underline{CH_3}$), 2.27 (3H, s, $COCH_3$), 2.78 (2H, q, J=7.1, CH_2). UV: 240 (19200), 331 (8000). Found: C, 46.70; H, 4.40; N, 5.97%. Calcd for $C_9H_{10}NO_2SCl$: C, 46.66; H, 4.35; N, 6.05%.

*4) 1-Methyl-4-phenyl(or ethyl)-1,2-dihydrothieno[2,3-d]-pyrimidin-2-ones (**1a**).*



(1a)

*Method A: **1aA—1aC**.*



A mixture of 2-amino-3-benzoyl-thiophene and ethyl carbamate was heated at 200 °C for one hour in the presence of zinc chloride to give 4-phenyl-1,2-dihydrothieno[2,3-*d*]-pyrimidin-2-one (**1c**), which was methylated with methyl-iodide in the presence of sodium hydride to afford **1a**, 2-methoxy-4-phenylthieno[2,3-*d*]-pyrimidine (**6a**) and 3-methyl-4-phenyl-2,3-dihydrothieno[2,3-*d*]-pyrimidin-2-one (**7a**). The procedure was applied to the synthesis of 1-alkyl-4-phenyl-1,2-dihydroquinazolin-2-one.[13]

1cA *(R: phenyl).* Yield 100%: mp 247—249 °C (from EtOH–DMF). IR: 3050, 1630 (broad).

1aA *(R: phenyl).* Yield 27.6%: mp 256—257.5 °C (from EtOH). IR: 3040, 1642, 1630. NMR: 3.78 (3H, s, N-CH_3). UV: 248.5 (29800), 349 (6000). Found: C, 64.44; H, 4.15; N, 11.48%. Calcd for $C_{13}H_{10}N_2OS$: C, 64.44; H, 4.16; N, 11.56%.

6aA *(R: phenyl).* Yield 5.8%: mp 160—161.5 °C (from EtOH). IR: 3050, 1580.

7aA *(R: phenyl).* Yield 1.5%: mp 175—181 °C (from EtOH). IR: 3065, 3050, 1660. UV: 251 (26900), 276 (6400), 366 (5500). Found: C, 63.27; H, 4.34; N, 10.81%. Calcd for $C_{13}H_{10}N_2OS$: C, 64.44; H, 4.16; N, 11.56%.

1cB *(R: o-fluorophenyl).* Yield 30.5%: mp 278—279 °C (from Acetone). IR: 3100, 3050, 1600 (broad).

1aB *(R: o-fluorophenyl).* Yield 13.2%: mp 222—223 °C (from EtOH). IR: 3055, 1660, 1618. NMR: 3.75 (3H, s, N-CH_3). UV: 247 (31000), 348.5 (6200). Found: C, 60.36; H, 3.42; N, 10.76%. Calcd for $C_{13}H_9N_2OSF$: C, 59.99; H, 3.49; N, 10.76%.

6aB *(R: o-fluorophenyl).* Yield 1.7%: mp 175—176.5 °C (from EtOH). IR: 3040, 1610.

7aB *(R: o-fluorophenyl).* Yield 3.6%: mp 191—192.5 °C (from EtOH–$CHCl_3$). IR: 3090, 3050, 1660, 1650, 1615. UV: 252 (26600), 276 (5600), 370 (5500). Found: C, 59.75; H, 3.46; N, 10.77%. Calcd for $C_{13}H_9N_2OSF$: C, 59.99; H, 3.49; N, 10.76%.

1cC *(R: o-chlorophenyl).* Yield 36%: This was used in the next step without further purification.

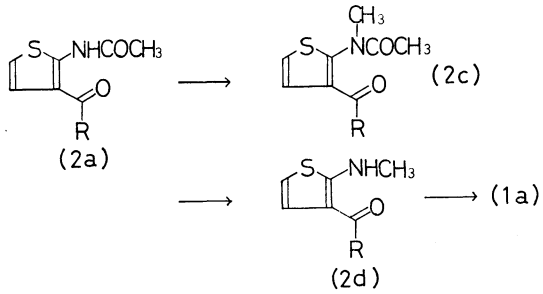
1aC *(R: o-chlorophenyl).* Yield 13.7%: mp 225—226 °C (from EtOH–$CHCl_3$). IR: 3080, 1660, 1645. NMR: 3.78 (3H, s, N-CH_3). UV: 245 (28000), 343 (6000). Found: C, 56.56; H, 3.14; N, 9.93%. Calcd for $C_{13}H_9N_2OSCl$: C, 56.42; H, 3.28; N, 10.12%.

6aC *(R: o-chlorophenyl).* Yield 3.6%: mp 172.5—174.5 °C (from Ether). IR: 3050, 1590, 1570, 1540.

7aC *(R: o-chlorophenyl).* Yield 8.3%: mp 190—192 °C (from EtOH–Ether). IR: 3075, 3060, 1660. UV: 252 (24900), 277 (5300), 366 (5200). Found: C, 56.61; H, 3.35; N, 9.82%. Calcd for $C_{13}H_9N_2OSCl$: C, 56.42; H, 3.28; N, 10.12%.

Method B: ***1aG, 1aH.***

2a was treated with sodium hydride and methyl iodide in the usual manner[13] to afford *N*-methyl-2-acetamido-3-benzoyl (or propionyl)-thiophene (**2c**), which was hydrolyzed with potassium hydroxide by the same method as for 2-amino-3-propionylthiophene (1, method B) to give 2-methylamino-3-



benzoyl(or propionyl)thiophene (**2d**). **2d** was then treated with ethyl carbamate by the same method as for **1aA—1aC** (4, method A) to afford **1a**.

2cG *(R: o-methylphenyl).* Yield 100% (oil). This was used in the next step without further purification.

2dG *(R: o-methylphenyl).* Yield 52.2%: mp 78—79.5 °C (from isopropyl ether). IR: 3250, 1610.

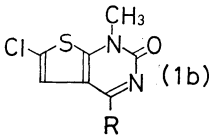
1aG *(R: o-methylphenyl).* Yield 31.7%: mp 193—199 °C (from EtOH). IR: 3040, 1638. NMR: 2.33 (3H, s, ϕ-CH_3), 3.77 (3H, s, N-CH_3). UV: 244.5 (26900), 340 (6000). Found: C, 65.55; H, 4.71; N, 11.05%. Calcd for $C_{14}H_{12}N_2OS$: C, 65.60; H, 4.72; N, 10.93%.

2cH *(R: ethyl).* Yield 65.4%: mp 78.5—79.5 °C (from Ether). IR: 3100, 1670.

2dH *(R: ethyl).* Yield 55.9% (oil). IR: 3300, 1615.

1aH *(R: ethyl).* Yield 10.9%: mp 155.5—157 °C (from EtOH). IR: 3055, 1640. NMR: 1.37 (3H, t, J=7.4, $CH_2\underline{CH_3}$), 2.91 (2H, q, J=7.4, CH_2), 3.70 (3H, s, N-CH_3). UV: 241 (28900), 327 (4900). Found: C, 55.45; H, 5.23; N, 14.34%. Calcd for $C_9H_{10}N_2OS$: C, 55.65; H, 5.19; N, 14.42%.

*5) 6-Chloro-1-methyl-4-phenyl-1,2-dihydrothieno[2,3-*d*]-pyrimidin-2-ones (**1b**).* ***1bA—1bC, 1bG.***



These were prepared by the method of Hromatka *et al.*[12] from 1-methyl-4-phenyl(or ethyl)-1,2-dihydrothieno[2,3-*d*] pyrimidin-2-one (**1a**) with sulfuryl chloride.

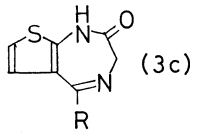
1bA *(R: phenyl).* Yield 64.8%: mp 136—140 °C (from EtOH). IR: 1673. NMR: 3.69 (3H, s, N-CH_3). UV: 252.5 (27100), 356 (6200). Found: C, 56.28; H, 3.72; N, 10.03%. Calcd for $C_{13}H_9N_2OSCl$: C, 56.42; H, 3.28; N, 10.12%.

1bB *(R: o-fluorophenyl).* Yield 24.0%: mp 192.5—194 °C (from EtOH). IR: 1677, 1622. NMR: 3.68 (3H, s, N-CH_3). UV: 251.5 (28300), 356 (6400). Found: C, 52.81; H, 2.65; N, 9.49%. Calcd for $C_{13}H_8N_2OSClF$: C, 52.98; H, 2.74; N, 9.50%.

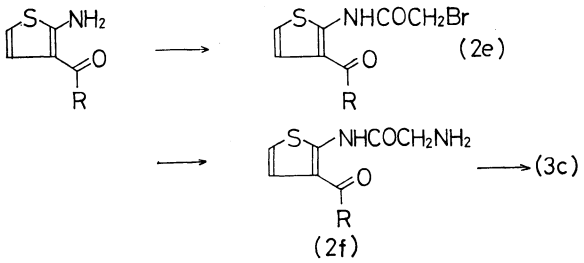
1bC *(R: o-chlorophenyl).* Yield 52.4%: mp 164—166 °C (from EtOH–Ether). IR: 1677, 1600. NMR: 3.73 (3H, s, N-CH_3). UV: 250 (25400), 352 (6300). Found: C, 50.13; H, 2.50; N, 9.00%. Calcd for $C_{13}H_8N_2OSCl_2$: C, 50.18; H, 2.59; N, 9.00%.

1bG *(R: o-methylphenyl).* Yield 14.4%: mp 139—140 °C (from EtOH). IR: 1661, 1601. NMR: 2.34 (3H, s, ϕ-CH_3), 3.72 (3H, s, N-CH_3). UV: 249 (26800), 347 (6700). Found: C, 57.91; H, 3.85; N, 9.65%. Calcd for $C_{14}H_{11}N_2OSCl$: C, 57.83; H, 3.81; N, 9.63%.

*6) 5-Phenyl(or ethyl)-1,3-dihydro-2H-thieno[2,3-*e*]-1,4-diazepin-2-ones (**3c**).* ***3cA—3cC, 3cH.***



Method:



3-Benzoyl(or propionyl)-2-bromoacetamido-thiophene (**2e**) was prepared from 2-amino-3-benzoyl(or propionyl)-thiophene with bromoacetylbromide. Ammonolysis of **2e** in chloroform saturated with gaseous ammonia afforded 2-aminoacetamido-3-benzoyl(or propionyl)-thiophene (**2f**), which was cyclized in dimethylsulfoxide at 100 °C to afford **3c**. The procedure was applied to the synthesis of benzodiazepine by Sternbach *et al.*[14]

2eA *(R: phenyl).* Yield 77.3%: mp 142—144 °C (from EtOH). IR: 3090, 3070, 1670, 1620.

2fA *(R: phenyl).* Yield 49.0%: mp 137.5—139 °C (lit[15], 145—147 °C).

3cA *(R: phenyl).* Yield 53.2%: mp 200.5—201.5 °C (lit[15], 203 °C).

2eB *(R: o-fluorophenyl).* Yield 77.1%: mp 101—102 °C (from Ether). IR: 3200, 1680, 1620.

2fB *(R: o-fluorophenyl).* Yield 79.1%: mp 127.5—129 °C (from CH_2Cl_2). IR: 3380, 3320, 3170, 3060, 1665, 1600.

3cB *(R: o-fluorophenyl).* Yield 75.4%: mp 201—201.5 °C from (EtOH). IR: 3060, 1685, 1615. NMR: 4.45 (2H, s, CH_2). UV: 242 (26600), 313 (2800). Found: C, 60.08; H, 3.43; N, 10.67%. Calcd for $C_{13}H_9N_2OSF$: C, 59.99; H, 3.49; N, 10.76%.

2eC *(R: o-chlorophenyl).* Yield 80.1%: mp 109—110 °C (from Ether). IR: 3060, 1670, 1600.

2fC *(R: o-chlorophenyl).* Yield 78.3%: mp 154—156 °C (from CH_2Cl_2). IR: 3390, 3320, 3220, 3050, 1685, 1635.

3cC *(R: o-chlorophenyl).* Yield 32.0%: mp 225—226 °C (from EtOH). IR: 3060, 1695, 1607. NMR: 4.47 (2H, s, CH_2). UV: 241 (22900), 311 (2900). Found: C, 56.68; H, 3.23; N, 10.04%. Calcd for $C_{13}H_9N_2OSCl$: C, 56.42; H, 3.28; N, 10.12%.

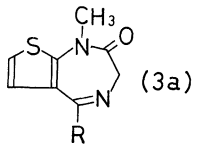
2eH *(R: ethyl).* Yield 68.7%: mp 107.5—108.5 °C (from Ether). IR: 3150, 3100, 1660, 1640.

2fH *(R: ethyl).* Yield 90.7%: mp 114—116 °C (from CH_2Cl_2). IR: 3400, 3340, 3150, 3080, 1640.

3cH *(R: ethyl).* Yield 17.0%: mp 137—140 °C (from Ether). IR: 3165, 3070, 1698, 1694, 1620. NMR: 1.16 (3H, t, $CH_2\underline{CH_3}$), 2.69 (2H, q, $CH_2\underline{CH_3}$), 4.19 (2H, s, $COCH_2N$)). UV: 233 (24200), 294 (3300). Found: C, 55.46; H, 5.08; N, 14.25%. Calcd for $C_9H_{10}N_2OS$: C, 55.65; H, 5.19; N, 14.42%.

7) 1-Methyl-5-phenyl(or ethyl)-1,3-dihydro-2H-thieno[2,3-e]-1,4-diazepin-2-ones (3a).

Method A: ***3aA—3aC, 3aH.*** These were prepared from 5-phenyl(or ethyl)-1,3-dihydro-2*H*-thieno[2,3-*e*]-1,4-diazepin-2-one (**3c**) with sodium hydride and methyliodide in the usual manner.[14]



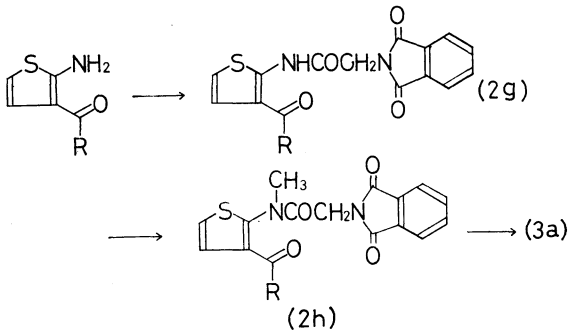
3aA *(R: phenyl).* Yield 86%: mp 134—135 °C (from (EtOH). (lit, 136—137.5 °C).[15]

3aB *(R: o-fluorophenyl).* Yield 84.3%: mp 115.5—117 °C (from EtOH). IR: 3040, 1680, 1600. NMR: 3.50 (3H, s, N-CH_3), 4.44 (2H, s, CH_2). UV: 243 (25300), 315 (2800). Found: C, 61.37; H, 4.12; N, 10.20%. Calcd for $C_{14}H_{11}N_2OSF$: C, 61.29; H, 4.04; N, 10.21%.

3aC *(R: o-chlorophenyl).* Yield 56.0%: mp 109.5—111.0 °C (from Ether). IR: 3080, 3070, 1682. NMR: 3.52 (3H, s, N-CH_3), 4.47 (2H, s, CH_2). UV: 212.5 (27700), 240.5 (21600), 311 (2800). Found: C, 57.68; H, 3.66; N, 9.46%. Calcd for $C_{14}H_{11}N_2OSCl$: C, 57.83; H, 3.81; N, 9.64%.

3aH *(R: ethyl).* Yield 18.1%: mp 82—83 °C (from Ether). IR: 3040, 1682, 1627. NMR: 1.17 (3H, t, J=7.4, $CH_2\underline{CH_3}$), 2.68 (2H, q, J=7.4, $\underline{CH_2}CH_3$), 3.44 (3H, s, N-CH_3), 4.21 (2H, s, $COCH_2N$). UV: 235 (22000), 295 (3200). Found: C, 57.64; H, 5.75; N, 13.30%. Calcd for $C_{10}H_{12}N_2OS$: C, 57.67; H, 5.81; N, 13.45%.

Method B: ***3aD—3aG.***



3-Benzoyl-2-(*N*-phthalimidoacetyl)amino-thiophene (**2g**) was prepared from 2-amino-3-benzoylthiophene with phthaloylimidoacetylchloride. Methylation of **2g** with sodium hydride and methyliodide in the usual manner afforded 3-benzoyl-2-(*N*-methyl-*N*-phthalimidoacetyl)amino-thiophene (**2h**), which was treated with hydrazine hydrate to afford **3a**.[16]

2gD *(R: o-bromophenyl).* Yield 69.3%: mp 205—208 °C (from Acetone). IR: 3200, 3100, 1780, 1720, 1705, 1615.

2hD *(R: o-bromophenyl).* Yield 58.4%: mp 170—172 °C (from Acetone). IR: 1765, 1725, 1690, 1650.

3aD *(R: o-bromophenyl).* Yield 31.7%: mp 109—113 °C (from EtOH). IR: 3080, 3060, 1677. NMR: 3.51 (3H, s, N-CH_3), 4.46 (2H, s, CH_2). UV: 215 (26200), 240 (20500), 312 (2700). Found: C, 49.85; H, 3.46; N, 8.51%. Calcd for $C_{14}H_{11}N_2OSBr$: C, 50.16; H, 3.31; N, 8.36%.

2gE *(R: o-iodophenyl).* Yield 50.2%: mp 206—208 °C (from Acetone). IR: 3230, 1775, 1720, 1690, 1610.

2hE *(R: o-iodophenyl).* Yield 71.1%: mp 167—175 °C (from Acetone). IR: 3110, 1770, 1725, 1695, 1650, 1620.

3aE *(R: o-iodophenyl).* Yield 45.4%: mp 136—137.5 °C (from EtOH). IR: 3045, 1679, 1669. NMR: 3.53 (3H, s, N-CH_3), 4.46 (2H, s, CH_2). UV: 220 (28000), 313 (2700). Found: C, 43.91; H, 2.84; N, 7.22%. Calcd for $C_{14}H_{11}N_2OSI$: C, 43.99; H, 2.90; N, 7.33%.

2gF *(R: p-chlorophenyl).* Yield 78.4%: mp 215—216 °C (from Acetone). IR: 3220, 1765, 1710, 1605.

2hF *(R: p-chlorophenyl).* Yield 78.5%: mp 211—212 °C (from Acetone). IR: 3080, 1765, 1720, 1680, 1660.

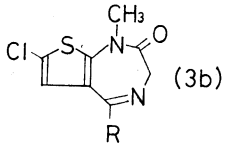
3aF *(R: p-chlorophenyl).* Yield 76.5%: mp 139.5—141 °C (from EtOH). IR: 3040, 1678. NMR: 3.49 (3H, s, N-CH_3), 4.40 (2H, s, CH_2). UV: 251 (30100), 317 (2900). Found: C, 57.77; H, 3.71; N, 9.60%. Calcd for $C_{14}H_{11}N_2OSCl$: C, 57.83; H, 3.81; N, 9.64%.

2gG *(R: o-methylphenyl).* Yield 42.6%: mp 211—213 °C (from Acetone). IR: 3250, 3050, 1775, 1720, 1690.

2hG *(R: o-methylphenyl).* Yield 78.0%: mp 153.5—155 °C (from Acetone). IR: 3100, 1765, 1720, 1690, 1640.

3aG *(R: o-methylphenyl).* Yield 74.0%: mp 125—127 °C (from EtOH). IR: 3075, 1675, 1612, 1605. NMR: 2.08 (3H, s, ϕ-CH_3), 3.53 (3H, s, N-CH_3), 4.45 (2H, s, CH_2). UV: 240 (24700), 307 (2900). Found: C, 66.64; H, 5.21; N, 10.28%. Calcd for $C_{15}H_{14}N_2OS$: C, 66.64; H, 5.22; N, 10.36%.

*8) 7-Chloro-1-methyl-5-phenyl(or ethyl)-1,3-dihydro-2H-thieno-[2,3-e]-1,4-diazepin-2-ones (**3b**), **3bA—3bF**, **3bH**.*



(3b)

These were prepared by the method of Hromatka *et al.*[12] from 1-methyl-5-phenyl(or ethyl)-1,3-dihydro-2*H*-thieno[2,3-*e*]-1,4-diazepin-2-one (**3a**) with sulfuryl chloride.

3bA *(R: phenyl).* Yield 80.0%: mp 117.5—119.0 °C (from EtOH), (lit[12], 120—122 °C).

3bB *(R: o-fluorophenyl).* Yield 73.5%: mp 101.5—103 °C (from IPA). IR: 1693, 1681, 1613. NMR: 3.43 (3H, s, N-CH_3), 4.44 (2H, s, CH_2). UV: 244 (24200), 320 (2900). Found: C, 54.25; H, 3.17; N, 8.81%. Calcd for $C_{14}H_{10}N_2OSClF$: C, 54.45; H, 3.26; N, 9.07%.

3bC *(R: o-chlorophenyl).* Yield 28.0%: mp 82.5—84 °C (from Ether). IR: 1692. NMR: 3.47 (3H, s, N-CH_3), 4.47 (2H, s, CH_2). UV: 243 (20800), 319 (2900). Found: C, 51.62; H, 3.22; N, 8.47%. Calcd for $C_{14}H_{10}N_2OSCl$: C, 51.70; H, 3.10; N, 8.62%.

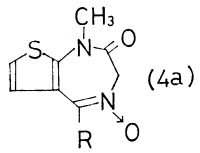
3bD *(R: o-bromophenyl).* Yield 49.2%: mp 86—89 °C (from Ether). IR: 1690. NMR: 3.46 (3H, s, N-CH_3), 4.46 (2H, s, CH_2). UV: 242 (20200), 319 (3000). Found: C, 45.95; H, 2.75; N, 7.60%. Calcd for $C_{14}H_{10}N_2OSBrCl$: C, 45.49; H, 2.73; N, 7.58%.

3bE *(R: o-iodophenyl).* Yield 32%: mp 217—221 °C (hydrochloride), (from EtOH). IR: 3110, 3035, 2350 (broad), 1905, 1720, 1633. NMR (Measured as a free base): 3.48 (3H, s, N-CH_3), 4.46 (2H, s, CH_2). Found: C, 36.98; H, 2.41; N, 6.10%. Calcd for $C_{14}H_{10}N_2OSClI \cdot HCl$: C, 37.11; H, 2.45; N, 6.18%.

3bF *(R: p-chlorophenyl).* Yield 83.5%: mp 212—213.5 °C (from $CHCl_3$–EtOH). IR: 1693, 1678. NMR: 3.44 (3H, s, N-CH_3), 4.42 (2H, s, CH_2). UV: 251 (27200), 323 (2900). Found: C, 51.58; H, 3.09; N, 8.43%. Calcd for $C_{14}H_{10}N_2OSCl_2$: C, 51.71; H, 3.10; N, 8.61%.

3bH *(R: ethyl).* Yield 16.0%: mp 76.5—77.5 °C (from Ether). IR: 1680, 1620. NMR: 1.18 (3H, t, J=7.3, $CH_2\underline{CH_3}$), 2.65 (2H, q, J=7.3, $\underline{CH_2}CH_3$), 3.40 (3H, s, N-CH_3), 4.24 (2H, s, CH_2). Found: C, 49.45; H, 4.45; N, 11.29%. Calcd for $C_{10}H_{11}N_2OSCl$: C, 49.49; H, 4.57; N, 11.54%.

*9) 1-Methyl-5-phenyl(or ethyl)-1,3-dihydro-2H-thieno[2,3-e]-1,4-diazepin-2-one-4-oxides (**4a**), **4aA—4aE**, **4aG**, **4aH**.*



(4a)

Method: These were prepared by the method of Hromatka *et al.*[15] from 1-methyl-5-phenyl(or ethyl)-1,3-dihydro-2*H*-thieno[2,3-*e*]-1,4-diazepin-2-one (**3a**) with *m*-chloroperbenzoic acid.

4aA *(R: phenyl).* Yield 67.0%: mp 158—159 °C (from EtOH–CCl_4). IR: 3070, 1688. NMR: 3.53 (3H, s, N-CH_3), 4.73 (2H, s, CH_2). UV: 245 (20500), 313 (7700). Found: C, 61.26; H, 4.46; N, 9.96%. Calcd for $C_{14}H_{12}N_2O_2S$: C, 61.70; H, 4.40; N, 10.30%.

4aB *(R: o-fluorophenyl).* Yield 83.0%: mp 80.5—85 °C (from EtOH). IR: 3400, 3070, 3020, 1688, 1679, 1609. NMR (Measured after removal of crystalline ethanol): 3.57 (3H, s, N-CH_3), 4.78 (2H, s, CH_2). UV: 246 (20600), 267 (17200), 310 (6900). Found: C, 57.08; H, 5.19; N, 8.20%. Calcd for $C_{14}H_{11}N_2O_2SF \cdot C_2H_5OH$: C, 57.13; H, 5.10; N, 8.33%.

4aC *(R: o-chlorophenyl).* Yield 73.5%: mp 163—163.5 °C (from EtOH–CCl_4). IR: 3050, 1696. NMR: 3.57 (3H, s, N-CH_3), 4.77 (2H, s, CH_2). UV: 249 (19700), 310 (6400). Found: C, 54.77; H, 3.55; N, 8.93%. Calcd for $C_{14}H_{11}N_2O_2SCl$: C, 54.82; H, 3.62; N, 9.13%.

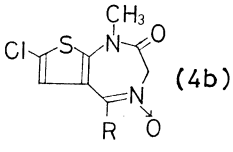
4aD *(R: o-bromophenyl).* Yield 61.0%: mp 162—163.5 °C (from EtOH–CCl_4). IR: 3100, 1685. NMR: 3.59 (3H, s, N-CH_3), 4.77 (2H, s, CH_2). UV: 254 (19400), 310 (5800). Found: C, 47.52; H, 3.03; N, 7.70%. Calcd for $C_{14}H_{11}N_2O_2SBr$: C, 47.88; H, 3.16; N, 7.98%.

4aE *(R: o-iodophenyl).* Yield 18.2%: mp 161 °C (decomp.) (from EtOH–CCl_4). IR: 3100, 3080, 1671. NMR: 3.60 (3H, s, N-CH_3), 4.78 (2H, s, CH_2). UV: 229.5 (24400), 252 (19800), 305 (sh) (6700). Found: C, 42.35; H, 2.66; N, 7.00%. Calcd for $C_{14}H_{11}N_2O_2SI$: C, 42.23; H, 2.78; N, 7.03%.

4aG *(R: o-methylphenyl).* Yield 54.7%: mp 149.5—150.5 °C (from EtOH). IR: 3115, 1687. NMR: 2.24 (3H, s, ϕ-CH_3), 3.61 (3H, s, N-CH_3), 4.78 (2H, s, CH_2). UV: 242.5 (21100), 275 (20400), 305 (7100). Found: C, 62.76; H, 5.14; N, 9.70%. Calcd for $C_{15}H_{14}N_2O_2S$: C, 62.92; H, 4.93; N, 9.78%.

4aH *(R: ethyl).* Yield 46.8%: mp 169—171.5 °C (from EtOH–Ether). IR: 3075, 3050, 1690. NMR: 1.20 (3H, t, $CH_2\underline{CH_3}$), 2.85 (2H, q, $\underline{CH_2}CH_3$), 3.54 (3H, s, N-CH_3), 4.62 (2H, s, CH_2). UV: 254.5 (22500), 298 (5800). Found: C, 53.61; H, 5.40; N, 12.52%. Calcd for $C_{10}H_{12}N_2O_2S$: C, 53.55; H, 5.40; N, 12.49%.

*10) 7-Chloro-1-methyl-5-phenyl(or ethyl)-1,3-dihydro-2H-thieno[2,3-e]-1,4-diazepin-2-one-4-oxides (**4b**).*



(4b)

Method A: ***4bA***, ***4bB***. These were prepared by the method of Hromatka *et al.*[12] from 1-methyl-5-phenyl-1,3-dihydro-2*H*-thieno-[2,3-*e*]-1,4-diazepin-2-one-4-oxide(**4a**) with sulfurylchloride.

4bA *(R: phenyl).* Yield 40.1%: mp 194—195 °C (from EtOH–CCl_4). IR: 3075, 1691. NMR: 3.48 (3H, s, N-CH_3), 4.74 (2H, s, CH_2). UV: 243 (23600), 275 (18100), 315 (sh) (6900). Found: C, 54.96; H, 3.64; N, 9.11%. Calcd for

$C_{14}H_{11}N_2O_2SCl$: C, 54.81; H, 3.61; N, 9.13%.

4bB *(R: o-fluorophenyl).* Yield 83.2%: mp 153—154 °C (from *n*-Hexane–Ether). IR: 1693, 1680. NMR: 3.50 (3H, s, N-CH_3), 4.78 (2H, s, CH_2). UV: 242.5 (23900), 269.5 (21800), 315 (sh) (6200). Found: C, 52.08; H, 3.08; N, 8.41%. Calcd for $C_{14}H_{10}N_2O_2SClF$: C, 51.78; H, 3.10; N, 8.62%.

Method B: ***4bC, 4bH.*** These were prepared by the method of Hromatka *et al.*[15] from 7-chloro-1-methyl-5-phenyl-(or ethyl)-1,3-dihydro-2*H*-thieno[2,3-*e*]-1,4-diazepin-2-ones (**3b**) with *m*-chloroperbenzoic acid.

4bC *(R: o-chlorophenyl).* Yield 54.3%: mp 95—97 °C (from CCl_4). IR: 1710, 1678. NMR: 3.51 (3H, s, N-CH_3), 4.79 (2H, s, CH_2). UV: 250 (21700), 265 (22000), 315 (sh) (5500). Found: C, 36.47; H, 2.09; N, 5.57%. Calcd for $C_{14}H_{10}N_2O_2SCl_2 \cdot CCl_4$: C, 36.39; H, 2.04; N, 5.66%.

4bH *(R: ethyl).* Yield 25.2%: mp 171—172 °C (from Ether). IR: 1689. NMR: 1.19 (3H, t, J=7.4, $CH_2\underline{CH_3}$), 2.78 (2H, q, J=7.4, $\underline{CH_2}CH_3$), 3.48 (3H, s, N-CH_3), 4.63 (2H, s, CH_2). Found: C, 46.52; H, 4.63; N, 10.88%. Calcd for $C_{10}H_{11}N_2O_2SCl$: C, 46.42; H, 4.29; N, 10.83%.

The authors express their deep gratitude to Prof. Masamichi Tsuboi, the University of Tokyo, and Dr. Makoto Sunagawa in this laboratory for their guidance and encouragement throughout this work. They are also indebted to Mr. Tadashi Doi and Miss Keiko Kawazoe for measurement of the UV spectra, and to Mr. Hiromi Sato for his co-operation in the synthetic experiments.

References

1) M. L. Martin, C. Andrieu, and G. J. Martin, *Tetrahedron Lett.*, **1966**, 921.
2) M. L. Martin, C. Andrieu, and G. J. Martin, *Bull. Soc. Chim. Fr.*, **1968**, 698.
3) C. Andrieu, M. L. Martin, and G. J. Martin, *ibid.*, **1968**, 703.
4) G. W. Gribble and F. P. Bousquet, *Tetrahedron*, **27**, 3785 (1971).
5) B. Roques, S. Combrisson, C. Riche, and C. Pascard-Billy, *ibid.*, **26**, 3555 (1970).
6) J. A. Weil, A. Blum, A. H. Heiss, and J. K. Kinnaird, *J. Chem. Phys.*, **46**, 3132 (1967).
7) H. P. Figeys and R. Flammang, *Mol. Phys.*, **12**, 581 (1967).
8) Y. Nomura and Y. Takeuchi, *Tetrahedron Lett.*, **1968**, 5585; *ibid.*, **1968**, 5665.
9) C. E. Johnson, Jr. and F. A. Bovey, *J. Chem. Phys.*, **29**, 1012 (1958).
10) K. Gewald, *Chem. Ber.*, **98**, 3571 (1965).
11) M. Robba, Jeanne-Merie Lecomte, and M. C. Sevricourt, *C. R. Acad. Sci. Paris*, **267**, 697 (1968).
12) O. Hromatka, D. Binder, C. R. Noe, P. Stanetty, and W. Veit, *Monats. Chem.*, **104**, 715 (1973).
13) H. Ott and M. Denzer, *J. Org. Chem.*, **33**, 4263 (1968).
14) L. H. Sternbach, R. I. Fryer, W. Metlesics, E. Reeder, G. Sach, G. Saucy, and A. Stempel, *J. Org. Chem.*, **27**, 3788 (1962).
15) O. Hromatka and D. Binder, *Monatsh. Chem.*, **104**, 704 (1973).
16) *Chem. Abstr.*, **64**, 5120h (1966).
17) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, New York (1960), p. 260.