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Spirocyclopropane Compounds. VI. Synthesis of Spiro[benzo[*b*]-thiophene-2(3*H*),1′-cyclopropan]-3-ones

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Spiro[benzo[*b*]thiophene-2(3*H*),1′-cyclopropan]-3-ones (IIIc-1—IIIc-11) and their aza analogs, such as spiro[cyclopropane-1,2′(3′*H*)-thieno[3,2-*c*]pyridin]-3′-one (IIIc-12) as well as spiro-[cyclopropane-1,2′(3′*H*)-thieno[2,3-*b*]pyridin]-3′-one (IIIc-13), were synthesized from thiosalicylic acids and from 4- and 2-mercaptonicotinic acids, respectively, in three steps. Decarboxylation of 4′,5′-dihydrospiro[benzo[*b*]thiophene-2(3*H*),3′(2′*H*)-furan]-2′,3-diones (IIc) gave 2,3-dihydrobenzo[*b*]thieno[3,2-*b*]furans (IVc) along with the desired spirocyclopropane compounds (IIIc). The ratios of IIIc to IVc were greatly influenced by the substituents on the benzene ring.

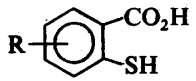
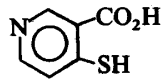
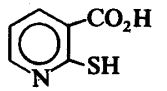
Keywords——spirocyclopropane; spiro[benzo[*b*]thiophene-2(3*H*), 1′-cyclopropan]-3-one; 2,3-dihydrobenzo[*b*]thienofuran; spiroannelation

Our previous reports described facile syntheses and the pharmacological activities (*e.g.*, anti-inflammatory, analgesic, gastric antisecretory and antiulcer activities) of spiro[cyclopropane-1,2′-[2*H*]indol]-3′(1′*H*)-ones (IIIa) and their 1′-oxa analogs (IIIa).[1-5] On the other hand, Okitsu *et al.*[6] reported that a novel ring contraction of 4-bromo-2,3-dihydrobenzo[*b*]thiepine-5(4*H*)-one gave a 1′-thia analog (IIIc-1), which inhibited platelet aggregation. In this report, we describe a convenient synthesis of the 1′-thia analogs by the decarboxylation of 4′,5′-dihydrospiro[benzo[*b*]thiophene-2(3*H*),3′(2′*H*)-furan]-2′,3-diones (IIc).

The substituted thiosalicylic acids and 2- or 4-mercaptonicotinic acids were allowed to react with α-bromo-γ-butyrolactone in the presence of base in an aqueous solution, and the corresponding 2-[(tetrahydro-2-oxo-3-furanyl)thio]benzoic acids or nicotinic acid derivatives (Ic) were obtained in good yields (Table I, Chart 1).

The resulting acids (Ic) were spiroannelated by heating with acetic anhydride and triethylamine to yield the corresponding 4′,5′-dihydrospiro[benzo[*b*]thiophene-2(3*H*),3′(2′*H*)-furan]-2′,3-diones (IIc-1—IIc-8), 4,5-dihydrospiro[furan-3(2*H*),2′(3′*H*)-thieno[3,2-*c*]pyridine]-2,3′-dione (IIc-12), and 4,5-dihydrospiro[furan-3(2*H*), 2′(3′*H*)-thieno-[2,3-*b*]pyridine]-2,3′-dione (IIc-13). The morpholinosulfonylspirolactone (IIc-9) was prepared from IIc-1 by chlorosulfonylation with chlorosulfonic acid, followed by treatment of the resulting 5-chlorosulfonylspirolactone with morpholine. This chlorosulfonylation was assumed to occur at the 5-position on the benzene ring, on the basis of the proton magnetic resonance (^{1}H-NMR) signals of the aromatic protons. The 5-amino spirolactone (IIc-10) was prepared by catalytic hydrogenation of the 5-nitro compound (IIc-5). Compound IIc-10 was subjected to usual acetylation using acetic anhydride and acetic acid to give the 5-acetylaminospirolactone (IIc-11) in 90% yield. The physicochemical properties of the spirolactones thus obtained are shown in Table I. The spirolactone (IIc-1) was subjected to decarboxylation by heating at 155—160 °C for 3.5 h in dimethylsulfoxide (DMSO) in the presence of sodium chloride to give the desired spirocyclopropane compound (IIIc-1, 79%) accompanied by a small amount of the rearranged compound, 2,3-dihydrobenzo[*b*]thieno[3,2-*b*]-

TABLE I. Physicochemical Data for Compounds Ic and IIc

Compd. No.	Starting material	Ic mp (°C)	Ic Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N	IIc mp (°C)	IIc Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N
													
1	R=H	180—182	85	$C_{11}H_{10}O_4S$	55.45 (55.24	4.23 4.02)		125—127	66	$C_{11}H_8O_3S$	59.99 (60.00	3.66 3.59)	
2	5-Cl	175—176	81	$C_{11}H_9ClO_4S$	48.44 (48.57	3.33 3.45)		143—143.5	28	$C_{11}H_7ClO_3S$	51.87 (51.87	2.77 2.56)	
3	5-CH_3	181.5—183	73	$C_{12}H_{12}O_4S$	57.12 (56.94	4.79 4.84)		122—124	55	$C_{12}H_{10}O_3S$	61.52 (61.45	4.30 4.36)	
4	4,5-$(CH_3O)_2$	240—242	51	$C_{13}H_{14}O_6S$	52.34 (52.09	4.73 4.61)		236—237	59	$C_{13}H_{12}O_5S$	55.70 (55.90	4.32 4.27)	
5	5-NO_2	150—152	78	$C_{11}H_9NO_6S \cdot 4/5C_2H_5OH$	47.27 (46.95	4.35 4.34	4.35 4.39)	190.5—193.5	66	$C_{13}H_{10}O_4S$	59.53 (59.15	3.84 4.14)	
6	5-$COCH_3$	216.5—218.5	79	$C_{12}H_{12}O_6S_2$	45.56 (45.80	4.83 3.86)		130—140.5	73	$C_{12}H_{10}O_3S_2$	54.11 (54.18	3.78 3.82)	
7	5-SCH_3	177.5—180	72	$C_{12}H_{12}O_4S_2$	50.68 (50.62	4.26 4.35)		92—93	86	$C_{12}H_{10}O_5S_2$	48.31 (48.22	3.38 3.32)	
8	5-SO_2CH_3	229—231	82	$C_{12}H_{12}O_6S_2$	45.56 (45.80	3.83 3.86)		146.5—149	77	$C_{15}H_{15}NO_6S_2$	48.77 (48.81	4.09 4.04	3.79 4.08)
9	5-SO_2N O							220—220.5	51	$C_{11}H_9NO_3S$	56.15 (56.61	3.86 3.73	5.96 5.96)
10	5-NH_2							187—190	82	$C_{13}H_{11}NO_4S$	56.30 (56.05	4.00 3.94	5.05 5.19)
11	5-$NHCOCH_3$							191.5—193	90	$C_{11}H_7NO_5S$	49.81 (49.82	2.66 2.83	5.28 5.02)
12								204—205	66[a]	$C_{10}H_7NO_3S$	54.28 (54.13	3.19 3.02	6.33 6.28)
13		199—201	53	$C_{10}H_8NO_4S$	50.20 (50.25	3.79 3.73	5.85 5.58)	106—107	64	$C_{10}H_7NO_3S$	54.28 (54.36	3.19 3.07	6.33 6.31)

a) Yield from 4-mercaptonicotinic acid is shown.

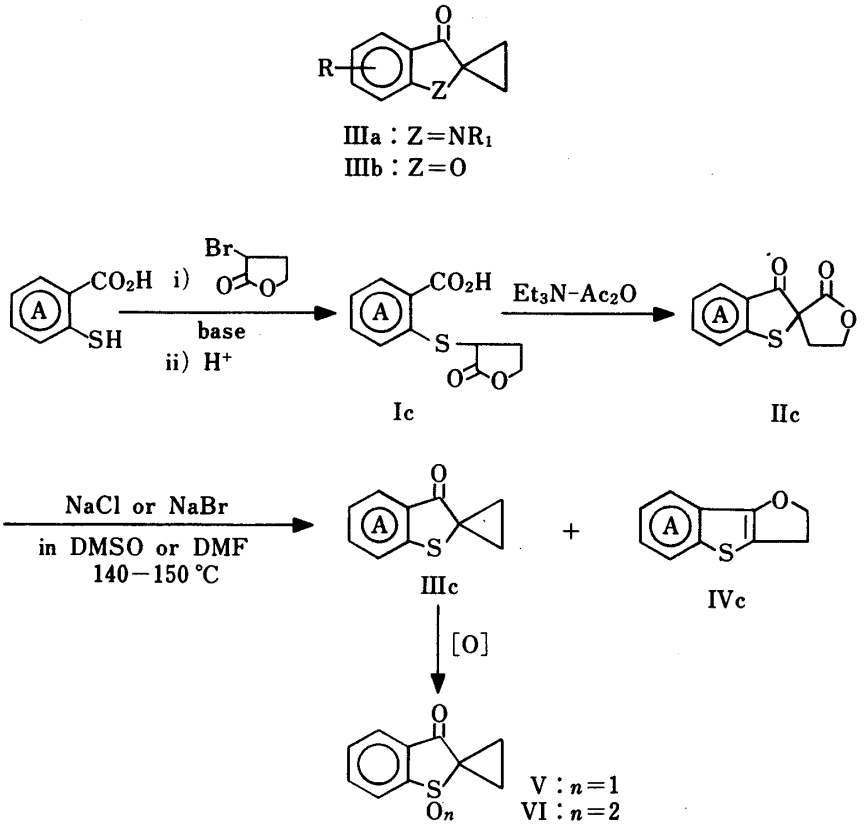
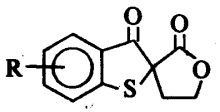
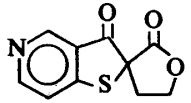
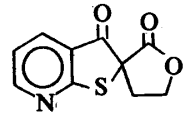


Chart 1

furan (IVc-1, 4.4%) as a by-product. The characteristic rearrangement of compound IIc-1 under the decarboxylation conditions may be attributable to stabilization of the intermediary carbanion owing to the *d*-orbitals of the adjacent sulfur atom. The structures of compounds IIIc-1 and IVc-1 were established by comparison of the spectral data and the melting points with those of the authentic compounds reported by Okitsu *et al.*[6] Compound IIIc-1 was readily converted to the sulfinyl (V) and sulfonyl (VI) derivatives (Chart 1) by usual oxidation using 1 and 2 eq of *m*-chloroperbenzoic acid, respectively. Substituted spirolactone derivatives (IIc-2—IIc-13) were subjected to decarboxylation under conditions similar to those described above to give the desired spirocyclopropane compounds (IIIc) and the corresponding rearranged products (IVc), respectively. The ratios of IIIc to IVc were greatly influenced by the kinds of substituents on the benzene ring or pyridine ring (Table II). The spirolactones (IIc) bearing electron-donating substituents on the benzene ring (*e.g.*, methyl, methoxy, methylthio and amino groups), when heated under decarboxylation conditions, predominantly gave the corresponding spirocyclopropane compounds (IIIc). On the other hand, decarboxylation of the spirolactone compounds (IIc-2, 5, 6, 8 and 9) having electron-withdrawing substituents on the benzene ring and the spirolactones, IIc-12 and IIc-13, favored the formation of the corresponding fused dihydrofuran compounds (IVc). Monitoring the decarboxylation by thin-layer chromatography (TLC) demonstrated that IIIc was the main product at the early stage of the decarboxylation, but the ratio of IVc to IIIc increased with lengthening of the reaction time, and finally the only products were the fused dihydrofuran compounds (IVc). Thus these compounds (IVc) seemed to have been formed not only by decarboxylation of the starting spirolactones (IIc) but also by rearrangement of the spirocyclopropane compounds (IIIc) initially formed under decarboxylation conditions.

In order to elucidate the mechanism of annelation of the spirocyclopropane compounds

TABLE II. Physicochemical Data for Compounds IIIc and IVc

Compd. No.	Starting material IIc	IIIc mp (°C)	IIIc Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N	IVc mp (°C)	IVc Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N
													
1	R=H	69—70[a]	79	$C_{10}H_8OS$	68.15 (68.31	4.58 4.72)		57—58[a]	4.4	$C_{10}H_8OS$	68.15 (68.25	4.58 4.51)	
2	5-Cl	106—107	55	$C_{10}H_7ClOS$	57.01 (56.91	3.35 3.09)		83.5—84.5	6.4	$C_{10}H_7ClOS$	57.01 (56.98	3.35 3.28)	
3	5-CH_3	68—69.5	85	$C_{11}H_{10}OS$	69.44 (69.37	5.30 5.31)		83—85	1.9	$C_{11}H_{10}OS$	69.44 (69.17	5.30 5.50)	
4	4,5-$(CH_3O)_2$	167.5—169.5	89	$C_{12}H_{12}O_3S$	60.99 (61.10	5.12 5.04)		112—114	Trace	$C_{12}H_{12}O_3S$	60.99 (61.17	5.12 5.41)	
5	5-NO_2	126.5—127.5	9.7	$C_{10}H_7NO_3S$	54.29 (54.48	3.19 3.39	6.33 6.31)	168—169	40	$C_{10}H_7NO_3S$	54.29 (54.25	3.19 3.08	6.33 6.46)
6	5-$COCH_3$	128—129	60	$C_{12}H_{10}O_2S$	66.03 (66.01	4.62 4.42)		122—123	16	$C_{12}H_{10}O_2S$	66.03 (66.04	4.62 4.64)	
7	5-SCH_3	73—74	74	$C_{11}H_{10}OS_2$	59.42 (59.54	4.53 4.50)		56—57.5	14	$C_{11}H_{10}OS_2$	59.42 (59.54	4.53 4.68)	
8	5-SO_2CH_3	206.5—207	32	$C_{11}H_{10}O_3S_2$	51.94 (52.15	3.96 4.01)		125.5—127	16	$C_{11}H_{10}O_3S_2$	51.94 (51.84	3.96 4.01)	
9	5-SO_2N 	162.5—165	17	$C_{14}H_{15}NO_4S$	51.67 (51.45	4.65 4.55	4.31 4.31)	189—192	15	$C_{14}H_{15}NO_4S$	51.67 (51.43	4.65 4.61	4.31 4.58)
10	5-NH_2	147.5—149.5	61	$C_{10}H_9NOS$	62.80	4.74	7.33		Trace				
11	5-$NHCOCH_3$	205—208	14	$C_{12}H_{11}NO_2S$	61.78 (61.43	4.75 4.81	6.01 5.73)		[b]				
12		106—107	24	C_9H_7NOS	60.99 (61.02	3.98 3.90	7.90 7.99)	122—123.5	10	C_9H_7NOS	60.99 (60.80	3.98 3.81	7.90 8.18)
13		106—107	8.5	C_9H_7NOS	60.99 (60.93	3.98 3.89	7.90 7.82)	104—106	25	C_9H_7NOS	60.99 (61.12	3.98 3.96	7.90 7.84)

a) Reference 6. *b*) Major product, but could not be isolated.

(III) in the decarboxylation of spirolactones (II), we attempted to trap the intermediary carbanion in the presence of benzyl bromide in the medium, but we could not isolate any benzylated compounds under various conditions. When sodium azide, which is a good nucleophile but a poor leaving group, was used as a catalyst instead of alkali metal halides in an aprotic polar solvent [hexamethylphosphortriamide (HMPA)], the azidoethyl compound VIIc was isolated as a product in 35% yield. The structure of VIIc was established on the basis of the spectral data, showing a characteristic absorption band due to the azido group at 2100 cm^{-1} in the infrared (IR) spectrum and a molecular ion peak (M^+) at 219 (*m/e*) in the mass spectrum (MS). Thus, decarboxylation of the spirolactones (II) under almost neutral conditions appears to proceed through route b, *i.e.*, nucleophilic attack of halide anion at the 5′-C position of spirolactones (II), followed by decarboxylation and fast intramolecular cyclization of the resulting intermediary carbanion (Chart 2). Some of the spirocyclopropane

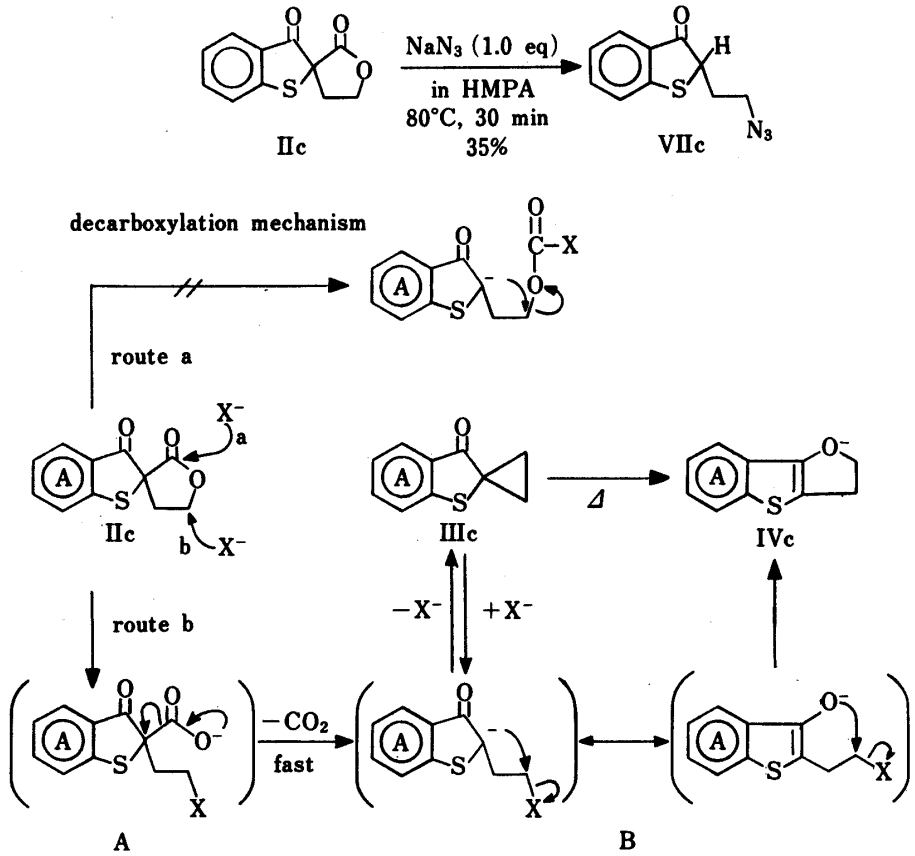


Chart 2

compounds (IIIc) showed inhibitory activities against platelet aggregation induced by adenosine diphosphate, collagen and arachidonic acid, similarly to IIIc-1.[6]

Experimental

All melting points were determined on a micro melting point apparatus (Yanagimoto) and are uncorrected. ^{1}H-NMR spectra were obtained with Varian A-60A and Varian HA-100 spectrometers, IR spectra with a Hitachi 215 grating infrared spectrophotometer, and MS with a Hitachi RMU-6D mass spectrometer.

2-[(Tetrahydro-2-oxo-3-furanyl)thio]benzoic Acid (Ic-1)——α-Bromo-γ-butyrolactone (38 g) was added to a solution of thiosalicylic acid (25 g) and Na_2CO_3 (60 g) in H_2O (250 ml) at 0 °C with stirring. After being stirred at room temperature for 3 h, the mixture was treated with conc. HCl (80 ml). The resulting precipitates were collected, washed with water, dried and recrystallized from EtOH, giving Ic-1 (32.5 g) as colorless prisms. IR ν_{max}^{KBr} cm^{-1}: 2750—2450, 1710.

2-[(Tetrahydro-2-oxo-3-furanyl)thio]benzoic acids (Ic-2—Ic-8) and nicotinic acid derivatives (Ic-12 and Ic-13) were also prepared from the corresponding substituted thiosalicylic acids, 4- and 2-mercaptonicotinic acids, respectively, according to the procedure for the synthesis of Ic-1.

4′,5′-Dihydrospiro[benzo[*b*]furan-2(3*H*),3′(2′*H*)-furan]-3,2′-dione (IIc-1)——A mixture of Ic-1 (15.9 g) in Ac_2O (100 ml) and Et_3N (20 ml) was heated at 140 °C for 3 h with stirring. After cooling, the mixture was concentrated *in vacuo*. Recrystallization of the resulting residue from EtOH gave IIc-1 (9.4 g) as pale yellow plates. IR ν_{max}^{KBr} cm^{-1}: 1775, 1710. ^{1}H-NMR ($CDCl_3$) δ: 2.4—3.5 (2H, m, CH_2CH_2O), 4.3—5.0 (2H, m, CH_2CH_2O), 7.2—8.0 (4H, m, aromatic H).

4′,5′-Dihydrospiro[benzo[*b*]thiophene-2(3*H*),3′(2′*H*)-furan]-3,2′-diones (IIc-2—IIc-8), 4,5-dihydrospiro[furan-3(2*H*),2′(3′*H*)-thieno[2,3-*c*]pyridine]-2,3′-dione (IIc-12) and 4,5-dihydrospiro[furan-3(2*H*),2′(3′*H*)-thieno[2,3-*b*]-pyridine]-2,3′-dione (IIc-13) were also prepared from the corresponding substituted 2-[(tetrahydro-2-oxo-3-furanyl)thio]benzoic acids (Ic-2—Ic-8) and nicotinic acid derivatives (Ic-12 and Ic-13), respectively, according to the procedure for the synthesis of IIc-1, except for IIc-9, 10 and 11.

5-Morpholinosulfonyl-4′,5′-dihydrospiro[benzo[*b*]thiophene-2(3*H*),3′(2′*H*)-furan]-3,2′-dione (IIc-9)——Compound IIc-1 (5.0 g) was added in small portions to $ClSO_3H$ (15 ml) at 0 °C with stirring. After being stirred at room temperature for 1.5 h, the mixture was poured carefully into ice-H_2O and extracted with AcOEt. The extract was washed with water, dried and extracted with a solution of morpholine (1.2 g) in AcOEt (50 ml) at 0 °C. The mixture was allowed to stand at 0 °C overnight and concentrated *in vacuo*. Recrystallization of the resulting residue from acetone–H_2O gave IIc-9 (4.3 g) as colorless needles.

5-Amino-4′,5′-dihydrospiro[benzo[*b*]thiophene-2(3*H*),3′(2′*H*)-furan]-3,2′-dione (IIc-10) and Its Acetyl Derivative (IIc-11)——The 5-nitrospirolactone (IIc-5, 1.02 g) was hydrogenated in AcOH (100 ml) in the presence of 5% Pd–C (wet, 352 mg) at room temperature under atmospheric pressure of H_2 gas with stirring. After the uptake of H_2 gas had ceased, the catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. Recrystallization of the resulting residue from benzene gave IIc-10 (723 mg) as pale yellow needles.

This 5-aminospirolactone (IIc-10) was converted to the 5-acetylamino derivative (IIc-11) by usual acetylation using Ac_2O and AcOH. Recrystallization from MeOH gave pale yellow needles.

Decarboxylation of 4′,5′-Dihydrospiro[benzo[*b*]thiophene-2(3*H*),3′(2′*H*)-furan]-2′,3-dione (IIc-1)——A mixture of IIc-1 (8.0 g) and NaCl (2.3 g) in DMSO (20 ml) was heated at 155—160 °C for 3.5 h with stirring. After cooling, the mixture was poured into ice-H_2O. The resulting precipitates were collected, washed with water, dried and subjected to column chromatography on silica gel (300 g) with *n*-hexane–AcOEt (5:1, v/v). Compound IVc-1 (278 mg) was obtained from the first fraction as colorless prisms (recrystallized from *n*-hexane). IR ν_{max}^{KBr} cm^{-1}: 1590, 1580, 1400. ^{1}H-NMR ($CDCl_3$) δ: 3.22 (2H, t, J=8 Hz, CH_2CH_2O), 4.98 (2H, t, J=8 Hz, CH_2CH_2O). Recrystallization from MeOH of the crystals obtained from the second fraction gave pure IIIc-1 (5.135 g) as colorless prisms. IR ν_{max}^{KBr} cm^{-1}: 1690, 1585. ^{1}H-NMR ($CDCl_3$) δ: 1.4—2.0 (4H, m, cyclopropane CH_2), 7.0—8.0 (4H, m, aromatic H).

The decarboxylation conditions (based on the results in Table II) of other 4′,5′-dihydrospiro[benzo[*b*]thiophene-2(3*H*),3′(2′*H*)-furan]-2′,3-diones (IIc-2—IIc-11) and the aza derivatives (IIc-12 and IIc-13) are summarized in Table III.

Spiro[benzo[*b*]thiophene-2(3*H*),1′-cyclopropan]-3-one 1-Oxide (Vc)——a) *m*-Chloroperbenzoic acid (1.4 g) was added in small portions to a solution of IIIc-1 (1.0 g) in CH_2Cl_2 (10 ml) at room temperature with stirring. After

Table III. Conditions for Decarboxylation of Spirolactones (IIc)

Starting material (g)	Catalyst (g)	Solvent (ml)	Reaction temperature (°C)	Reaction time (h or min)
IIc-1 (8.0)	NaCl (2.3)	DMSO (20)	155—160	3.5 h
IIc-2 (2.55)	NaCl (0.586)	DMSO (13)	150	0.5 h
IIc-3 (2.8)	NaBr (2.5)	DMF (30)	140	1.5 h
IIc-4 (2.8)	NaCl (0.657)	DMSO (30)	150	2.5 h
IIc-5 (3.0)	NaCl (1.4)	DMSO (60)	150	1.5 h
IIc-6 (2.0)	NaBr (2.0)	DMF (20)	140	1.0 h
IIc-7 (0.21)	NaBr (0.163)	DMF (4.0)	140	45 min
IIc-8 (0.6)	NaBr (0.4)	DMF (20)	140	15 min
IIc-9 (2.0)	NaBr (2.0)	DMF (40)	140	15 min
IIc-10 (0.0404)	NaCl (0.0206)	DMSO (2.0)	150	3.0 h
IIc-11 (0.2)	NaCl (0.112)	DMSO (5.0)	150	5.0 h
IIc-12 (0.753)	NaCl (0.224)	DMSO (4.0)	150	45 min
IIc-13 (6.0)	NaCl (1.7)	DMSO (30)	155—160	1.5 h

being stirred at room temperature for 2 h, the mixture was treated with aqueous $Na_2S_2O_4$ solution and extracted with CH_2Cl_2. The extract was washed with water, dried and concentrated *in vacuo*. Recrystallization of the resulting residue from iso-PrOH gave Vc (980 mg, 90%) as colorless needles, mp 88.5—89.5 °C. *Anal.* Calcd for $C_{10}H_8O_2S$: C, 62.48; H, 4.19. Found: C, 62.40; H, 4.02.

b) $Cu(NO_3)_2 \cdot 3H_2O$ (1.4 g) was added in small portions to a solution of IIIc-1 (1.0 g) in Ac_2O (20 ml) at 70 °C with stirring. After being stirred at 70 °C for 20 min, the mixture was cooled, poured into ice-H_2O and extracted with AcOEt. The extract was washed with water, dried and concentrated *in vacuo*. Recrystallization of the resulting residue from iso-Pr_2O gave Vc (803.6 mg, 74%).

c) The above oxidation of IIIc-1 with $Cu(NO_3)_2 \cdot 3H_2O$ could also be performed at room temperature to obtain Vc in 79% yield.

Spiro[benzo[*b*]thiophene-2(3*H*),1′-cyclopropan]-3-one 1,1-Dioxide (VIc)——*m*-Chloroperbenzoic acid (5.1 g) was added in small portions to a solution of IIIc-1 (2.2 g) in CH_2Cl_2 (20 ml) at room temperature with stirring. After being stirred at room temperature for 6 h, the mixture was treated with aqueous $Na_2S_2O_4$ solution and extracted with CH_2Cl_2. The extract was washed with water, dried and concentrated *in vacuo*. Recrystallization of the resulting residue from AcOEt gave VIc (1.775 g, 69%) as colorless prisms, mp 205—207 °C (lit.[6] 205—206 °C). *Anal.* Calcd for $C_{10}H_8O_3S$: C, 57.68; H, 3.87. Found: C, 57.81; H, 3.85.

2,3-Dihydro-2-(2-azidoethyl)benzo[*b*]thiophene-3-one (VIIc)——NaN_3 (60.9 mg) was added to a solution of IIc-1 (221.8 mg) in HMPA (2.0 ml) at room temperature with stirring. The mixture was heated at 80 °C for 30 min with stirring. After cooling, the mixture was poured into ice-H_2O and extracted with AcOEt. The extract was washed with water, dried and concentrated *in vacuo*. The resulting residue was subjected to column chromatography on silica gel (20 g) with benzene. Compound VIIc (77.3 mg, 35%) was obtained from the first fraction as a pale yellow oil. IR ν_{max}^{KBr} cm^{-1}: 2100, 1690. ^{1}H-NMR ($CDCl_3$) δ: 1.65—2.85 (2H, m, $CH_2CH_2N_3$), 3.53 (2H, t, J=7 Hz, $CH_2CH_2N_3$), 3.97 (1H, dd, J=7, 5 Hz, 2-position H), 6.9—7.75 (4H, m, aromatic H). MS *m/e*: 219 (M^+).

From the second fraction, IIIc-1 (95 mg, 43%) was recovered.

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