Synthesis and Spasmolytic Activity of 2-Substituted-3-(ω-dialkylamino-alkoxyphenyl)acrylonitriles and Related Compounds

Shunsuke Naruto,* Hiroyuki Mizuta, Toyokichi Yoshida, Hitoshi Uno, Katsuyoshi Kawashima, Toshiaki Kadokawa, and Haruki Nishimura

Research Laboratories, Dainippon Pharmaceutical Co., Ltd., 33-94, Enoki-cho, Suita, Osaka 564, Japan

Several analogs of (Z)-2-(1,2-benzisoxazol-3-yl)-3-[2-(2-piperidinoethoxy)phenyl]-acrylonitrile (1a), such as (Z)-2-(1,2-benzisothiazol-3-yl)-, (Z)-2-(1H-indol-3-yl)-, (E)-2-(2-thienyl)- and (E)-2-benzoyl-3-(ω-dialkylaminoalkoxyphenyl)acrylonitriles (2—5), were synthesized by means of the Knoevenagel condensation. The descyano analog (6) was prepared by means of the Wittig reaction. Triethylammonium formate reduction of 1 afforded the dihydro analog (7). The spasmolytic activities of these analogs were examined. Among these compounds, (Z)-2-(1,2-benzisothiazol-3-yl)-3-[2-(2-piperidinoethoxy)phenyl]-acrylonitrile (2a) and (Z)-2-(1,2-benzisothiazol-3-yl)-3-[2-(2-morpholinoethoxy)phenyl]-acrylonitrile (2b) showed potent antispasmodic activities in vitro and in vivo (in mice).

Keywords——acrylonitrile; ω-dialkylaminoalkoxybenzaldehyde; Knoevenagel reaction; Wittig reaction; triethylammonium formate; stereochemistry; photochemical isomerization; spasmolytic activity

In the previous paper,[1] we reported the synthesis and biological evaluation of 2-(1,2-benzisoxazol-3-yl)-3-(ω-dialkylaminoalkoxyphenyl)acrylonitriles (1) as a novel type of anti-spasmodic. Some of them, including trans[2]-2-(1,2-benzisoxazol-3-yl)-3-[2-(2-piperidino-ethoxy)phenyl]acrylonitrile (1a) and trans-2-(1,2-benzisoxazol-3-yl)-3-[2-(2-morpholinoethoxy)-phenyl]acrylonitrile (1b), showed a marked suppressive effect on spontaneous movement of the gastrointestinal tract, and lacked both musculotropic and competitive antimuscarinic actions. Mode-of-action studies suggested that 1a specifically inhibited acetylcholine release from the vagus nerve.[3] Encouraged by these results, we undertook further studies to prepare other analogs of 1 depicted in Chart 1, such as the benzisothiazole analog (2), indole analog (3), thiophene analog (4), benzoyl analog (5), descyano analog (6) and dihydro analog (7), in order to examine the effect of these structural modifications on the biological activity. This paper deals with the synthesis of these analogs of 1 and the results of biological evaluations.

Chemistry

The Knoevenagel condensation of 2-(1,2-benzisothiazol-3-yl)acetonitrile (8), 2-(1H-indol-3-yl)acetonitrile (9), 2-(2-thienyl)acetonitrile (10) and 2-benzoylacetonitrile (11) with an appropriate ω-dialkylaminoalkoxybenzaldehyde (12) gave the analogs, 2, 3, 4 and 5, respectively (Chart 2). These condensations gave predominantly the trans-products in which the two aromatic rings [phenyl and heterocyclic rings (or benzoyl group)] have a trans-stilbene like configuration. Stereochemical assignments were based on the following evidence.

As already reported,[1] the condensation of 2-(1,2-benzisoxazol-3-yl)acetonitrile with 12 in the presence of piperidine or acetic acid–ammonium acetate gave predominantly the trans-isomer (1). The stereochemistry of 1 was further confirmed by examination of trans-2-(5-chloro-1,2-benzisoxazol-3-yl)-3-(2,5-dimethoxyphenyl)acrylonitrile (15a), which was suitable for proton magnetic resonance (¹H-NMR) spectral analysis. Condensation of 2-(5-chloro-1,2-benzisoxazol-3-yl)acetonitrile (13) with 2,5-dimethoxybenzaldehyde (14) in the presence of acetic acid–ammonium acetate gave 15a. Photoirradiation of 15a in ethanol with a tungsten

1a : R^1 =H, position=2', n=2, NR^2R^3 =N

1b : R^1 =H, position=2', n=2, NR^2R^3 =N O

2 : R=

3 : R=

4 : R=

5 : R= —CO—

6

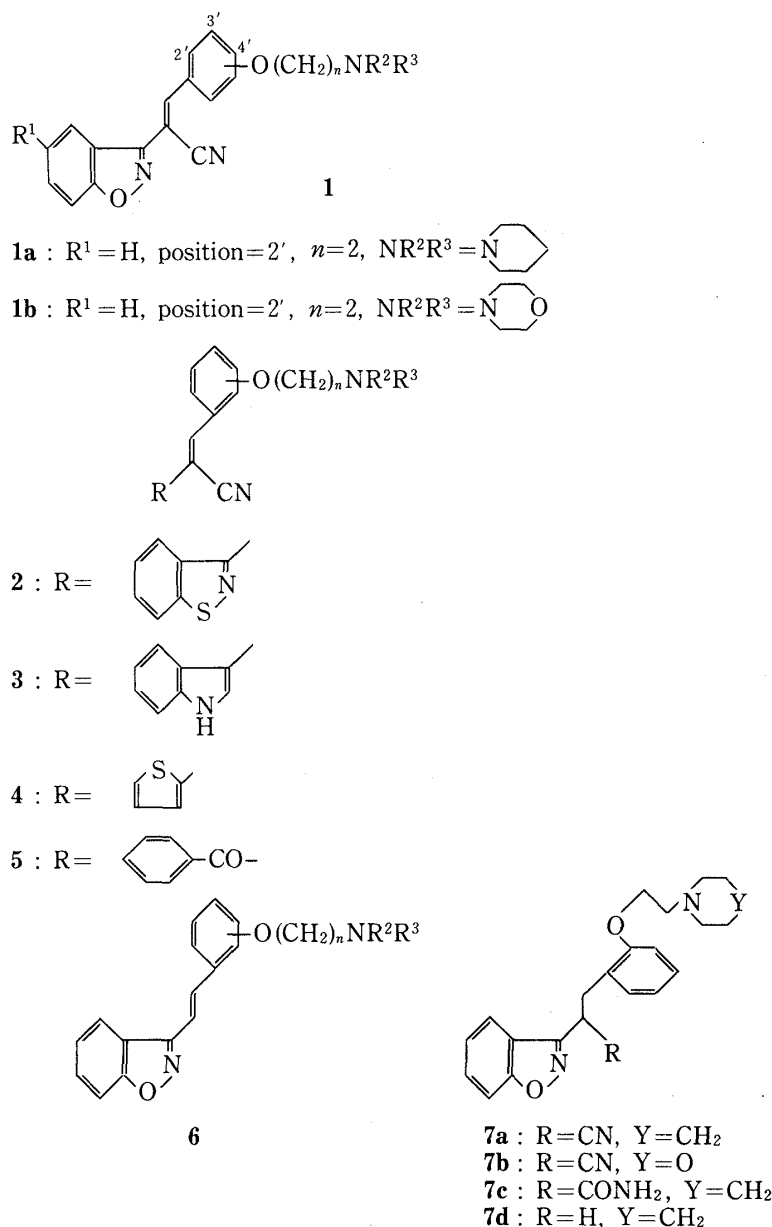7a : R=CN, Y=CH₂
7b : R=CN, Y=O
7c : R=CONH₂, Y=CH₂
7d : R=H, Y=CH₂

Chart 1

lamp afforded the cis-isomer (15b) (Chart 3). As shown in Table I, the ultraviolet (UV) spectrum of 15b showed hypsochromic shifts in comparison with that of 15a, indicating that the two aromatic rings of 15b have a cis-stilbene like configuration. In the ^{1}H-NMR spectra of 15a and 15b, all signals were assigned by means of spin decoupling experiments. There was an observable nuclear Overhauser effect (NOE) of 13% at the vinyl proton (H_V) (δ 8.55) of 15a when 4''-H (δ 8.09) was irradiated. A comparison of the ^{1}H-NMR data of 15a with those of 15b (Table I) revealed that the signals due to 6'-H (δ 6.65) and 5'-OCH₃ (5'-OMe, δ 3.42) of 15b appeared at higher field than those (6'-H at δ 7.89 and 5'-OMe at δ 3.86) of 15a. These facts were readily reconciled with cis-configuration of 15b, in which the 2',5'-dimethoxyphenyl ring is located above the benzisoxazole ring, having an anisotropic effect as shown in Chart 3. As already noted,[1] the chemical shift of the vinyl proton (H_V) of the trans-isomer (15a) is lower than that of the cis-isomer (15b) (Table I).

It was predicted that an analogous condensation of 8 with 12 in the presence of piperidine would afford the trans-isomer (2) (Table II). In fact, the singlet signal at δ 8.48 (in dimethyl-
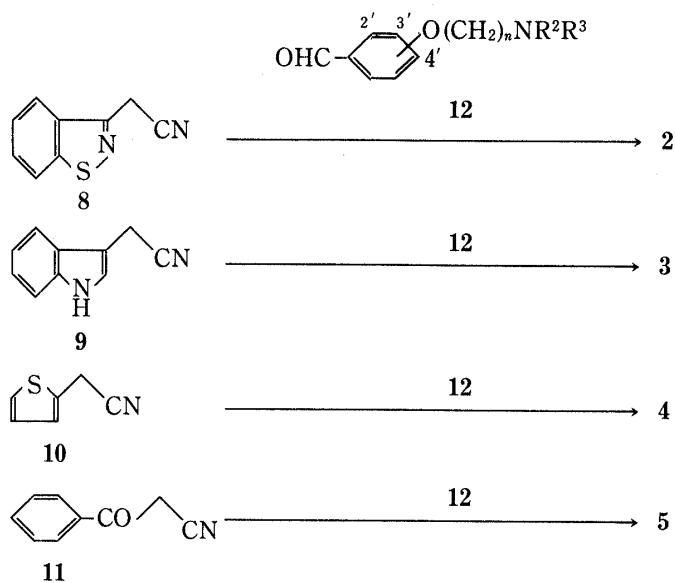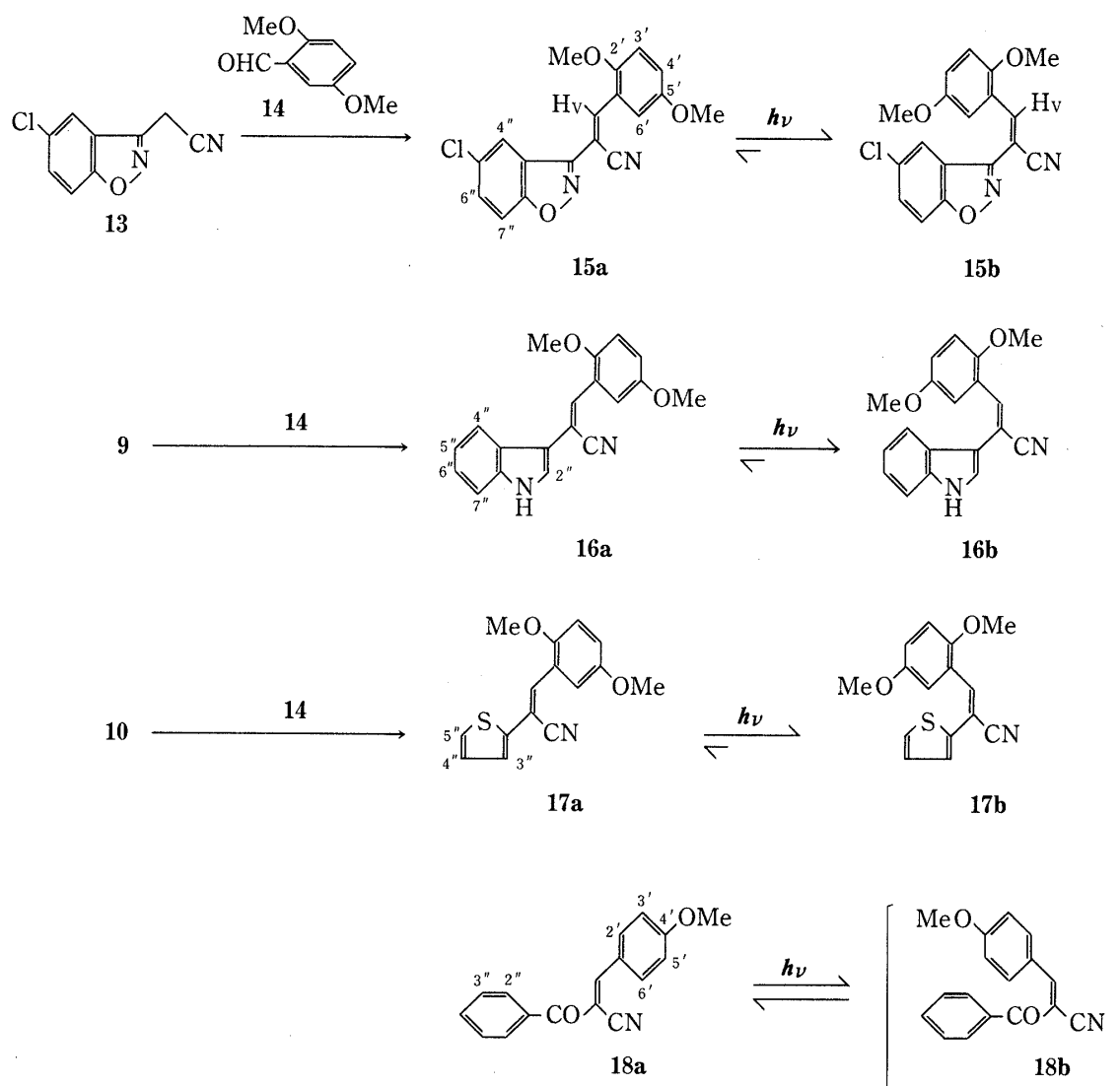
Chart 2

Chart 3

TABLE I. Spectral Data for **15a,b**,**16a,b**, and **17a,b**

Compd. No.	Configuration[a]	^{1}H-NMR (δ in CDCl$_3$)[b]				UV (in EtOH)	
		2'-OCH$_3$	5'-OCH$_3$	6'-H	H$_v$	λ_{max}nm (log ϵ)	λ_{min}nm (log ϵ)
15a	*trans*	3.88	3.86	7.89	8.55	390 (3.96), 315 (4.15)	353 (3.72), 274 (3.83)
15b	*cis*	3.76	3.42	6.65	8.08	380 (3.83), 288 (4.03)	340 (3.54), 260 (3.94)
16a	*trans*	3.84	3.84	7.75	7.97	375 (4.26), 280 (3.98)	300 (3.72), 258 (3.88)
16b	*cis*	3.83	3.08	6.62	7.60	370 (4.02), 275 (4.12)	308 (3.61), 247 (4.02)
17a	*trans*	3.84	3.84	7.73	7.80	382 (4.16), 330 (4.11) 245 (3.85)	350 (4.08), 270 (3.69) 235 (3.84)
17b	*cis*	3.78	3.60	6.81	7.41	360 (3.83), 305 (3.84) 244 (4.03)	330 (3.81), 270 (3.79) 240 (4.03)

a) See note 2).
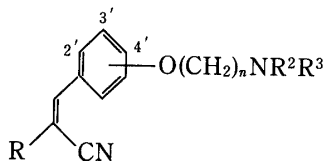b) Other ^{1}H-NMR data are collected in the experimental section.

sulfoxide (DMSO)-d_6) in the ^{1}H-NMR spectrum of 2-(1,2-benzisothiazol-3-yl)-3-[2-(2-morpholinoethoxy)phenyl]acrylonitrile hydrochloride (**2b**) was assigned as the vinyl proton of the *trans*-isomer by comparison with the signal at δ 8.68 (in DMSO-d_6) due to the vinyl proton of *trans*-**1a** hydrochloride.

Although syntheses of 2-(1H-indol-3-yl)-3-(substituted phenyl)acrylonitriles,[4] 2-(2-thienyl)-3-(substituted phenyl)acrylonitriles[5] and 2-benzoyl-3-(4-methoxyphenyl)acrylonitrile[6] (**18a**) have been reported, the stereochemistry was not specified. Since **1a** (*trans*-isomer) was about 300 times as active as the corresponding *cis*-isomer in terms of spasmolytic activity,[1] we examined the configuration about the double bond of the analogs, **3**—**5**. As shown in Chart 2 and 3, treatment of **9** with **12** and **14** in the presence of sodium ethoxide gave **3** (Table II) and **16a**, respectively, and condensation of **10** with **12** and **14** in the presence of potassium *tert*. butoxide[5b] afforded **4** (Table II) and **17a**, respectively. Photoirradiation of **16a** and **17a** under a tungsten lamp gave **16b** and **17b**, respectively. The *cis*-stilbene like configuration of **16b** and **17b** was deduced from the positions of the UV peaks, which showed hypsochromic shifts in comparison with those of **16a** and **17a** (Table I). Moreover, as shown in Table I, the signals due to 6'-H and 5'-OMe of the photoirradiated products (**16b** and **17b**) appeared at higher field, as in the case of **15b**. These results suggested that **3** and **4** obtained by similar condensation had a *trans*-stilbene like configuration. On the other hand, condensation of **11** with **12** was accomplished by treatment of **11** with the hydrochloride of **12** in the presence of a catalytic amount of **12** (Table II). Photoirradiation of **18a** in ethanol under a low pressure mercury lamp afforded an equilibrium mixture of **18a** and an isomer (**18b**). Several attempts to isolate **18b** from the reaction mixture were unsuccessful. However, comparison of the ^{1}H-NMR spectrum of the equilibrium mixture with that of **18a** proved that the mixture consisted of **18a** and **18b** in a ratio of about 1: 1. The ^{1}H-NMR spectrum of the mixture exhibited the following signals; two singlets of 4'-OMe at δ 3.90 (**18a**) and at δ 3.77 (**18b**) in a ratio of 1: 1, and two pairs of doublets of AA'BB' type due to the aromatic protons of the 4'-methoxyphenyl moiety at δ 7.80 (3'- and 5'-H) and 8.10 (2'- and 6'-H, $J=9$ Hz) (**18a**) and at δ 6.80 (3'- and 5'-H) and 7.35 (2'- and 6'-H, $J=9$ Hz) (**18b**) in a ratio of 1: 1 . As in the cases of **15b**, **16b** and **17b**, the high field shift of the 4'-OMe, 2'-H and 6'-H signals of **18b** could be explained by a *cis*-configuration of **18b**. Thus, it is suggested that **5** as well as **18a** has *trans*-configuration.

The descyano analog (**6**) was prepared by means of the Wittig reaction as shown in Chart 4. Treatment of 3-bromomethyl-1,2-benzisoxazole (**19**) with triphenylphosphine gave a phosphonium salt (**20**) which was, without further purification, treated with sodium hydride followed by **12** to afford *trans*-**6** (Table III) in which the coupling constant (J-value) between two vinyl protons was about 17 Hz.

Reduction of **1a** and **1b** with triethylammonium formate (TEAF)[7] in dimethylformamide (DMF) at 130°C for 22 h gave the dihydro analogs, **7a** and **7b**, in 62 and 72% yields, respec-

TABLE II. 2-Substituted-3-(ω-dialkylaminoalkoxyphenyl)acrylonitriles

$$\text{structure: 2'-3'-4'-phenyl ring}-O(CH_2)_nNR^2R^3,\ \ R-C(=CH\text{-aryl})-CN$$

Compd. No.	R[a]	Position	n	NR²R³	Salt	mp °C (recryst. solvent[b])	Yield (%)	Formula	C	H	Cl	N	S
2a	Bt	2'	2	(azepan-1-yl)	HCl	185—187 (A-E)	61	$C_{23}H_{23}N_3OS \cdot HCl \cdot 0.33H_2O$[c]	63.96 (63.97)	5.75 (5.88)	8.21 (8.43)	9.73 (9.61)	7.42 (7.66)
2b	Bt	2'	2	(morpholino)	HCl	194—196 (A-E)	85	$C_{22}H_{21}N_3O_2S \cdot HCl \cdot H_2O$	59.25 (59.18)	5.42 (5.27)	7.95 (8.17)	9.42 (9.45)	7.19 (7.21)
2c	Bt	2'	2	$N(C_2H_5)_2$	HCl	191—193 (A-E)	79	$C_{22}H_{23}N_3OS \cdot HCl$	63.83 (63.71)	5.84 (5.92)	8.56 (8.62)	10.15 (9.99)	7.75 (7.93)
2d	Bt	3'	2	$N(C_2H_5)_2$	HCl	176—178 (IP—E)	71	$C_{22}H_{23}N_3OS \cdot HCl$	63.83 (63.51)	5.84 (5.99)	8.56 (8.81)	10.15 (10.02)	7.75 (7.46)
2e	Bt	4'	2	$N(C_2H_5)_2$	HCl	178—180 (A-E)	67	$C_{22}H_{23}N_3OS \cdot HCl$	63.83 (63.67)	5.84 (5.79)	8.56 (8.86)	10.15 (10.22)	7.75 (7.78)
3a	In	2'	2	(azepan-1-yl)	HCl	236—238 (A)	18	$C_{24}H_{25}N_3OS \cdot HCl \cdot 0.33H_2O$	69.65 (69.79)	6.49 (6.22)	8.57 (8.66)	10.15 (10.10)	
3b	In	2'	2	$N(CH_3)_2$	—	127—128 (A)	55	$C_{21}H_{21}N_3O$	76.11 (75.90)	6.39 (6.53)		12.68 (12.58)	
3c	In	4'	3	$N(CH_3)_2$	—	140—141 (A)	23	$C_{22}H_{23}N_3O$	76.49 (76.28)	6.71 (6.88)		12.16 (11.99)	
3d	In	3'	3	$N(CH_3)_2$	—	185—187 (A)	24	$C_{22}H_{23}N_3O \cdot HCl$	69.19 (68.88)	6.33 (6.57)	9.28 (9.36)	11.00 (10.96)	
4a	Th	2'	2	(azepan-1-yl)	HCl	237—240 (A-E)	40	$C_{20}H_{22}N_2OS \cdot HCl$	64.07 (64.07)	6.18 (6.08)	9.46 (9.69)	7.47 (7.57)	8.55 (8.41)
4b	Th	2'	2	(morpholino)	HCl	216—218 (M)	54	$C_{19}H_{20}N_2O_2S \cdot HCl$	60.55 (60.74)	5.62 (5.53)	9.41 (9.45)	7.43 (7.41)	8.51 (8.60)
4c	Th	2'	2	$N(CH_3)_2$	HCl	155—157 (A-E)	44	$C_{17}H_{18}N_2OS \cdot HCl \cdot 0.33H_2O$	59.91 (59.79)	5.81 (5.70)	10.40 (10.29)	8.21 (8.14)	9.41 (9.60)
4d	Th	4'	2	$N(C_2H_5)_2$	HCl	147—149 (IP—E)	48	$C_{19}H_{22}N_2OS \cdot HCl$	62.88 (62.66)	6.39 (6.23)	9.77 (9.78)	7.72 (7.67)	8.83 (9.04)
4e	Th	3'	2	$N(C_2H_5)_2$	HCl	178—181 (IP—E)	77	$C_{19}H_{22}N_2OS \cdot HCl$	62.88 (62.63)	6.39 (6.24)	9.77 (9.83)	7.72 (7.54)	8.83 (8.90)
4f	Th	4'	2	$N(C_2H_5)_2$	HCl	147—149 (IP—E)	51	$C_{19}H_{22}N_2OS \cdot HCl$	62.88 (63.01)	6.39 (6.47)	9.77 (9.96)	7.72 (7.84)	8.83 (8.90)
5a	Bz	2'	2	(morpholino)	HCl	199—207 (A)	21	$C_{22}H_{22}N_2O_3 \cdot HCl$	66.24 (66.01)	5.81 (5.87)	8.89 (9.06)	7.02 (7.11)	
5b	Bz	2'	2	(pyrrolidin-1-yl)	HCl	176—180 (A)	35	$C_{22}H_{22}N_2O_2 \cdot HCl$	69.01 (69.07)	6.05 (6.02)	9.26 (9.48)	7.32 (7.24)	
5c	Bz	2'	2	$N(CH_3)_2$	HCl	194—197 (A)	49	$C_{20}H_{20}N_2O_2 \cdot HCl$	67.32 (67.16)	5.93 (6.06)	9.93 (10.01)	7.85 (7.80)	
5d	Bz	2'	2	$N(C_2H_5)_2$	HCl	157—162 (A)	33	$C_{22}H_{24}N_2O_2 \cdot HCl$	68.65 (68.80)	6.55 (6.63)	9.21 (9.34)	7.28 (7.27)	
5e	Bz	4'	2	(morpholino)	Ox.[d]	166—168 (A)	35	$C_{22}H_{22}N_2O_3 \cdot C_2H_2O_4$	63.71 (63.49)	5.35 (5.39)		6.19 (6.09)	
5f	Bz	4'	3	(morpholino)	Ox.	181—189 (IP)	45	$C_{23}H_{24}N_2O_3 \cdot C_2H_2O_4 \cdot 0.33H_2O$	63.56 (63.45)	5.69 (5.43)		5.93 (5.83)	
5g	Bz	4'	2	$N(CH_3)_2$	HCl	180—182 (A)	25	$C_{20}H_{20}N_2O_2 \cdot CHl$	67.32 (67.02)	5.93 (5.91)	9.93 (10.16)	7.85 (7.68)	

a) Bt=1,2-benzisothiazol-3-yl, In=1H-indol-3-yl, Th=2-thienyl, Bz=benzoyl.
b) A=EtOH, E=ether, IP=iso-PrOH, M=MeOH.
c) Compounds obtained as hydrates showed the presence of water in their IR and ¹H-NMR spectra even after being dried at 80—90 °C for 6—8 h under reduced pressure.
d) Ox.=oxalate.

tively. On the other hand, treatment of **1a** with TEAF at 180°C for 21 h afforded **7c** and **7d** in 35 and 31% yields, respectively, accompanied with hydrolysis and/or decarboxylation due to the high reaction temperature.[7c] The structural assignment of these products was based on their elemental analyses and spectral data.
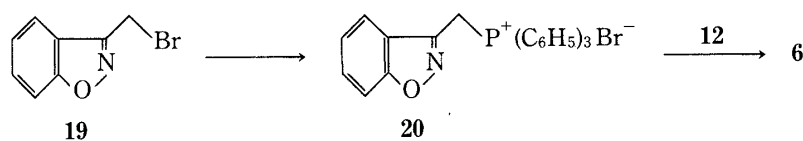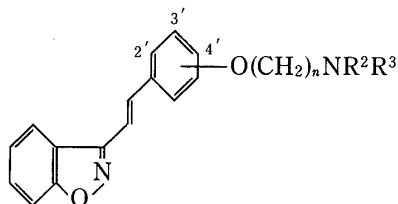
Chart 4

TABLE III.　3-2-(ω-Dialkylaminoalkoxyphenyl)vinyl-1,2-benzisoxazole (6)

Compd. No.	Position	n	NR^2R^3	Salt	mp°C (recryst. solvent)[a]	Yield (%)	Formula	Analysils (%) Calcd (Found)			
								C	H	Cl	N
6a	2'	2	N⟩	HCl	219—222 (A)	41	$C_{22}H_{24}N_2O_2 \cdot HCl$	68.65 (68.53)	6.55 6.30	9.21 9.53	7.28 7.45)
6b	2'	2	N O	HCl	235—240 (M-E)	54	$C_{21}H_{22}N_2O_3 \cdot HCl$	65.20 (65.04)	5.99 5.98	9.16 9.41	7.24 7.34)
6c	2'	2	$N(C_2H_5)_2$	Ox.[b]	129—130 (AC-E)	63	$C_{21}H_{24}N_2O_2 \cdot C_2H_2O_4$	64.78 (64.50)	6.15 6.02		6.57 6.53)
6d	4'	2	$N(C_2H_5)_2$	HCl	176—179 (A-E)	42	$C_{21}H_{24}N_2O_2 \cdot HCl$	67.64 (67.40)	6.76 6.71	9.51 9.80	7.51 7.55)
6e	2'	3	$N(CH_3)_2$	HCl	177—179 (A-E)	58	$C_{20}H_{22}N_2O_2 \cdot HCl \cdot 0.33H_2O^{c)}$	65.85 (66.03)	6.54 6.43	9.72 10.01	7.68 7.70)

　　a)　AC=acetone; see also note *b*) in Table II.
　　b)　Ox.=oxalate.
　　c)　See note *c*) in Table II.

Pharmacological Results

　　Spasmolytic activities of the analogs of **1** were examined by measuring the inhibitory effect on the response of isolated ileum from guinea pig to transmural electrical stimulation (anti-TMS activity) and by means of the charcoal meal test in mice according to the methods previously reported.[1]　The results are compiled in Table IV.

　　From the viewpoint of structure–activity relationships, it has been noted that benzisoxazole derivatives (**1**) having a 2-(2-morpholinoethoxy)- or 2-(2-piperidinoethoxy)- side chain, such as **1b** and **1a**, show potent spasmolytic activity.[1]　As shown in Table IV, the benzisothiazole analogs (**2a** and **2b**), thiophene analogs (**4a** and **4b**) and descyano analogs (**6a** and **6b**) having these side chains exhibited potent anti-TMS activity.　Replacement of the benzisoxazole ring of **1** by a benzisothiazole ring resulted in a marked increase of anti-TMS activity (compare **2a** and **2b** with **1a** and **1b**, respectively), whereas replacement by a benzoyl group produced a decrease of the activity.　The anti-TMS activities of the thiophene and descyano analogs (**4** and **6**) were similar to those of **1**.　Reduction of the conjugated double bond of **1**, giving the dihydro analog **7**, caused a decrease of the activity, indicating that the stereochemical requirement (*trans*-configuration) for the anti-TMS activity[1] was not satisfied in the various dihydro analogs.　Among indole analogs, **3b** [having a 2-(2-dimethylaminoethoxy) side chain] showed a potent anti-TMS activity, whereas **3a** [having a 2-(2-piperidinoethoxy) side chain] was less active than **1a** and **3b**.

　　Some compounds exhibiting marked anti-TMS activity were administered orally to mice for the charcoal meal test.　Benzisothiazole analogs (**2a** and **2b**) showed marked activity

TABLE IV. Pharmacological Data

Compound No.	anti-TMS[a] ID_{50}, mM	anti-ACh[b] ID_{50}, mM	Charcoal meal test[c] % inhibition (dose, mg/kg)
2a	2.3×10^{-6}	3.5×10^{-3}	61 (30)
2b	6.3×10^{-7}	1.1×10^{-2}	69 (30)
2c	4.3×10^{-5}	4.3×10^{-3}	
2d	1.6×10^{-3}	6.7×10^{-3}	
2e	2.4×10^{-3}	3.1×10^{-3}	
3a	1.7×10^{-3}	4.7×10^{-3}	
3b	6.6×10^{-5}	8.8×10^{-3}	
3c	7.8×10^{-4}	4.1×10^{-3}	
3d	1.7×10^{-3}	7.4×10^{-3}	
4a	2.3×10^{-4}	1.5×10^{-2}	
4b	4.0×10^{-4}	1.5×10^{-2}	
4c	1.9×10^{-3}	5.6×10^{-3}	
4d	8.8×10^{-4}	4.1×10^{-3}	
4e	2.3×10^{-3}	7.2×10^{-3}	
4f	1.9×10^{-3}	4.7×10^{-3}	
5a	7.5×10^{-3}		
5b	8.4×10^{-3}		
5c	1.5×10^{-2}		
5d	9.1×10^{-3}		
5e	$>4.4 \times 10^{-2}$		
5f	2.1×10^{-2}		
5g	$>5.6 \times 10^{-2}$		
6a	1.7×10^{-4}	6.8×10^{-3}	17 (30)
6b	2.3×10^{-4}	6.8×10^{-2}	32 (30)
6c	3.0×10^{-4}	6.6×10^{-3}	20 (100)
6d	2.2×10^{-3}	5.4×10^{-3}	
6e	1.3×10^{-3}	4.1×10^{-3}	
7a	1.3×10^{-3}	5.0×10^{-3}	
7b	3.5×10^{-2}		
7c	3.0×10^{-2}		
7d	1.6×10^{-3}	3.0×10^{-3}	
1a	2.4×10^{-4}	8.7×10^{-3}	45 (30)
1b	1.3×10^{-5}	2.2×10^{-2}	55 (30)
Atropine sulfate	5.0×10^{-5}	7.6×10^{-6}	27 (100)
Scopolamine-N-butyl bromide	1.0×10^{-3}	7.5×10^{-5}	19 (100)

a) Concentration required for 50% inhibition of the response induced by transmural electrical stimulation (5Hz,0.1ms).[1]

b) Concentration required to produce 50% inhilbition of the response induced by acetylcholine (1.1× 10^{-4} mM).[1]

c) Percent inhibition of the charcoal meal transfer in mice (30 or 100 mg/kg,$p.o.$).[1]

(Table IV). However, the descyano analogs (6a and 6b) were less active than 1a and 1b in the *in vivo* test in mice, whereas they showed potent activity in the *in vitro* anti-TMS method.

The antimuscarinic activity of several compounds was examined by measuring the inhibitory effect on the response of isolated ileum from guinea pig to acetylcholine according to the method previously reported.[1] The results are compiled in Table IV. These compounds blocked the muscle response induced by acetylcholine chloride (1.1×10^{-4} mM) only at high concentrations of 10^{-2}—10^{-3} mM, and their activities were weak or negligible in comparison with those of atropine sulfate and scopolamine-N-butyl bromide.

From the results of the present studies, it appears that the structure-activity relationships in regard to the side chain, ω-dialkylaminoalkoxy moiety, of the benzisothiazole, thiophene and descyano analogs (2, 4 and 6) were similar to those which were previously determined for benzisoxazole derivatives (1). The antimuscarinic activity of the compounds exhibiting potent anti-TMS activity was weak or negligible, as was the case for 1a and 1b. As shown in

Table IV, the spasmolytic activities of **2a** and **2b**, in which the oxygen atom of the benzisoxazole ring of **1a** and **1b** is replaced by the bioisosteric sulfur atom, were more potent than those of **1a** and **1b** both *in vitro* and *in vivo*. Thus, the benzisothiazole analogs, **2a** and **2b**, as well as **1a** and **1b**, might be of practical interest as potent inhibitors of acetylcholine release from the vagus nerve.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H-NMR spectra were taken in $CDCl_3$ or DMSO-d_6 solution with a Varian HA-100 or Varian EM-360 spectrometer using tetramethylsilane as an internal standard. The following abbreviations are used; s=singlet, d=doublet, t=triplet, m=multiplet and br=broad. The coupling constants were determined from ^{1}H-NMR spectra taken with an expansion of the sweep width. Infrared (IR) spectra were taken in KBr disks with a Hitachi EPI-G3 or a Hitachi 260-10 spectrometer. UV spectra were recorded with a Shimadzu UV-240 spectrophotometer. Mass spectra (MS) were recorded with a Hitachi RMU-6L spectrometer. Organic extracts were dried over anhydrous Na_2SO_4.

(*Z*)-2-(1,2-Benzisothiazol-3-yl)-3-(ω-dialkylaminoethoxyphenyl)acrylonitriles (2a—e)——General Procedure: A mixture of **8** (3 mmol), an appropriate **12** (3 mmol), two drops of piperidine and toluene (20 ml) was refluxed for 5 h. After being cooled, the reaction mixture was made acidic (pH <1) by addition of ethanolic HCl. The resulting precipitate was collected and recrystallized from the solvent shown in Table II to give **2a—e**. The results are summarized in Table II.

(*Z*)-2-(1*H*-Indol-3-yl)-3-(ω-dialkylaminoalkoxyphenyl)acrylonitriles (3a—d)——General Procedure: **9** (0.01 mol) was added to a solution of sodium ethoxide [prepared from Na (0.011 mol) and abs. EtOH (20 ml)]. The mixture was stirred for 0.5 h at room temperature. A solution of an appropriate **12** (0.01 mol) in abs. EtOH (10 ml) was added to the mixture. The whole was stirred for 4 d at room temperature, then the solvent was evaporated off to give a residue, which was recrystallized from EtOH to give **3b, c**. In the case of **3a, d**, the residue was converted to the hydrochloride, which was recrystallized from EtOH. The results are summarized in Table II.

(*E*)-2-(2-Thienyl)-3-(ω-dialkylaminoethoxyphenyl)acrylonitriles (4a—f)——General Procedure: Potassium *tert.* butoxide (50 mg) was added to a solution of **10** (6 mmol) and an appropriate **12** (6 mmol) in EtOH (15 ml), and the mixture was stirred for 15 min at room temperature. The reaction mixture was diluted with toluene, and EtOH was distilled off. The toluene solution thus obtained was extracted with 5% HCl. The aqueous layer was made alkaline with conc. NH_4OH, and extracted with toluene. After removal of the solvent, the residue was converted to the hydrochloride, which was recrystallized from the solvent shown in Table II to give **4a—f**. The results are summarized in Table II.

(*E*)-2-Benzoyl-3-(ω-dialkylaminoalkoxyphenyl)acrylonitriles (5a—g)——General Procedure: A mixture of **11** (10 mmol), an appropriate hydrochloride of **12** (10 mmol), two drops of the same **12**, and EtOH (10 ml) was allowed to stand for 18 h at room temperature. The resulting precipitate was collected and recrystallized from the solvent shown in Table II to give the hydrochloride, **5a—d** or **5g**. In the case of **5e, f**, the resulting precipitate was converted to the oxalate, which was recrystallized from the solvent shown in Table II. The results are summarized in Table II.

3-[(*E*)-2-(ω-Dialkylaminoalkoxyphenyl)vinyl]-1,2-benzisoxazole (6a—e)——General Procedure: A mixture of **19** (20 g, 0.094 mol), triphenylphosphine (26 g, 0.1 mol) and toluene (200 ml) was heated at 90°C for 8 h, then cooled. The resulting precipitate was collected to give a phosphonium salt, mp 245—255°C (dec.), (**20**) (39.7 g, 89%), which was used without further purification. In an atmosphere of nitrogen, sodium hydride (0.01 mol) was added to a solution of **20** (0.01 mol) in dry tetrahydrofuran (THF) (40 ml), and the mixture was stirred for 1 h at room temperature. A solution of an appropriate **12** (0.009 mol) in dry THF (5 ml) was added to the mixture. After being stirred for 3 h at room temperature, the reaction mixture was filtered, and the filtrate was evaporated. The residue was extracted with a mixture of ether and 5% HCl. The aqueous layer was made alkaline with 5% K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ layer was dried and evaporated. The residue was converted to the hydrochloride, which was recrystallized from the solvent shown in Table III to give **6a, b, d, e**. In the case of **6c**, the hydrochloride was converted to the oxalate which was recrystallized from acetone–ether to give the oxalate. The results are summarized in Table III.

3-[1-Cyano-2-[2-(2-piperidinoethoxy)phenyl]ethyl]-1,2-benzisoxazole Hydrobromide (7a)——A mixture of (*Z*)-2-(1,2-benzisoxazol-3-yl)-3-[2-(2-piperidinoethoxy)phenyl]acrylonitrile (**1a**) (1.5 g, 4 mmol), TEAF[7] (5 ml) and DMF (6 ml) was heated at 130°C for 22 h. The reaction mixture was diluted with toluene and 5% Na_2CO_3. The organic layer was dried and evaporated to give a residue, which was purified by means of silica gel column chromatography. The first fraction of 3% MeOH–$CHCl_3$ eluate gave the free base of **7a** as an oil, which was converted to the hydrobromide, and the salt was recrystallized from EtOH–ether to

give **7a** (1.13 g, 62%), mp 182—184°C. *Anal.* Calcd for $C_{23}H_{25}N_3O_2 \cdot HBr$: C, 60.53; H, 5.74; Br, 17.51; N, 9.21. Found: C, 60.43; H, 5.81; Br, 17.31; N,9.00. IR: ν_{CN} 2220 cm^{-1}. MS: M$^+$ m/z 375. ^{1}H-NMR (δ in CDCl$_3$) of the oily free base of **7a**: piperidine moiety (1.43, 6H, br s and 2.45, 4H, m), $-CH_2-N=$ (2.70, 2H, t, $J = 6$ Hz), $-OCH_2-$ (4.13, 2H, t, $J = 6$ Hz), $-CH_2-CHCN-$ (3.45, 2H, m), $-CH_2-CHCN-$ (5.27, 1H, dd, $J = 6$ and 8 Hz), arom. protons (6.8—7.9, 8H, m).

3-[1-Cyano-2-[2-(2-morpholinoethoxy)phenyl]ethyl]-1,2-benzisoxazole Hydrobromide (7b)——A mixture of (Z)-2-(1,2-benzisoxazol-3-yl)-3-[2-(2-morpholinoethoxy)phenyl]acrylonitrile (**1b**) (1.7 g, 4.5 mmol), TEAF$^{7)}$ (6 ml) and DMF (6 ml) was worked up according to the procedure described for the preparation of **7a** to give **7b** (1.5 g, 72%), mp 168—170°C (EtOH–ether). *Anal.* Calcd for $C_{22}H_{23}N_3O_3 \cdot HBr$: C, 57.65; H, 5.28; Br, 17.43, N, 9.17. Found: C, 57.78; H, 5.28; Br, 17.30, N, 9.09.

3-[1-Carbamoyl-2-[2-(2-piperidinoethoxy)phenyl]ethyl]-1,2-benzisoxazole (7c) and 3-[2-[2-(2-Piperidino-ethoxy)phenyl]ethyl]-1,2-benzisoxazole Hydrochloride (7d)——A mixture of **1a** (1.5 g, 4 mmol) and TEAF$^{7)}$ was heated at 180°C for 21 h. The reaction mixture was diluted with toluene and 5% Na$_2$CO$_3$. The oragnic layer was dried and evaporated to give a residue, which was recrystallized from CH$_2$Cl$_2$–ether to give **7c** (0.55 g, 35%), mp 141—143°C. *Anal.* Calcd for $C_{23}H_{27}N_3O_3$: C, 70.21; H, 6.92; N, 10.68. Found: C, 70.41; H, 6.76; N, 10.63. MS m/z: M$^+$ 393. IR: $\nu_{C=O}$ 1660 cm^{-1}. ^{1}H-NMR (δ in CDCl$_3$): piperidine moiety (1.52, 6H, br s and 2.52, 4H, m), $-CH_2-N=$ (2.80, 2H, m), $-OCH_2-$ (4.14, 2H, m), $-CH_2-CHCONH_2$ (3.53, 2H, m), $-CH_2-CHCONH_2-$ (4.63, 1H, dd, $J = 6$ and 8 Hz), arom. protons (6.7—8.2, 8H, m). The mother liquor of **7c** was evaporated to give a residue, which was purified by means of silica gel column chromatography. The first fraction of CHCl$_3$ eluate gave an oil, which was converted to the hydrochloride, and the salt was recrystallized from iso-PrOH–ether to give **7d** (0.5 g, 31%), mp 134—135°C. *Anal.* Calcd for $C_{22}H_{26}N_2O_2 \cdot HCl \cdot 0.5$ H$_2$O: C, 66.74; H, 7.13; Cl, 8.95; N, 7.08. Found: C, 66.94; H, 6.86; Cl, 9.07; N, 7.18. MS m/z: M$^+$ 350.

(Z)-2-(5-Chloro-1,2-benzisoxazol-3-yl)-3-(2,5-dimethoxyphenyl)acrylonitrile (15a)——A mixture of **13** (2 g, 0.01 mol), **14** (1.6 g, 0.01 mol), glacial AcOH (0.4 ml), AcONH$_4$ (1 g) and toluene (200 ml) was refluxed for 5 h in a Dean–Stark apparatus. The reaction mixture was washed with water, dried and evaporated. The residue was recrystallized from AcOEt–ether to give **15a** (3.1 g, 89%), mp 142—144°C. *Anal.* Calcd for $C_{18}H_{13}ClN_2O_3$: C, 63.44; H, 3.85; Cl, 10.40; N, 8.22. Found: C, 63.55; H, 3.93; Cl, 10.44; N, 8.12. IR: ν_{CN} 2220 cm^{-1}. ^{1}H-NMR (δ in CDCl$_3$): 2'-OMe (3.88, 3H, s), 5'-OMe (3.86, 3H, s), H$_V$ (8.55, 1H, s), H$_{3'}$ (6.96, 1H, d), H$_{4'}$ (7.07, 1H, dd), H$_{6'}$ (7.89, 1H, d), H$_{4''}$ (8.09, 1H, m), H$_{6''}$ and H$_{7''}$ (7.57—7.59, 2H, m); $J_{3',4'} = 8.7$ Hz, $J_{4',6'} = 3.0$ Hz, $J_{3',6'} = 0.6$ Hz, $J_{V,4'} = 0.2$ Hz, $J_{V,6'} = 0.6$ Hz.

(E)-2-(5-Chloro-1,2-benzisoxazol-3-yl)-3-(2,5-dimethoxyphenyl)acrylonitrile (15b)——In a flask attached with a reflux condenser, a solution of **15a** (0.5 g) in EtOH (500 ml) was irradiated with 375 W tungsten lamp (Toshiba) for 10 h. After removal of the solvent, the residue was purified by means of silica gel column chromatography. Elution with toluene gave **15b** (0.1 g), mp 98—100°C. *Anal.* Calcd for $C_{18}H_{13}ClN_2O_3$: C, 63.44; H, 3.85; Cl, 10.40; N, 8.22. Found: C, 63.67; H, 3.81; Cl, 10.58; N, 8.18. IR: ν_{CN} 2210 cm^{-1}. ^{1}H-NMR (δ in CDCl$_3$): 2'-OMe (3.76, 3H, s), 5'-OMe (3.42, 3H, s), H$_V$ (8.08, 1H, s), H$_{3'}$ (6.92, 1H, d), H$_{4'}$ (6.86, 1H, dd), H$_{6'}$ (6.65, 1H, d), H$_{4''}$, H$_{6''}$ and H$_{7''}$ (7.22—7.53, 3H, m); $J_{3',4'} = 9.0$ Hz, $J_{4',6'} = 2.8$ Hz, $J_{3',6'} = 0.6$ Hz, $J_{V,4'} = 0.3$ Hz, $J_{V,6'} = 0.6$ Hz.

(Z)-2-(1H-Indol-3-yl)-3-(2,5-dimethoxyphenyl)acrylonitrile (16a)——**9** (7.8 g, 50 mmol) was added to a solution of sodium ethoxide [prepared from Na (1.3 g, 57 mmol) and EtOH (100 ml)]. The mixture was stirred for 1 h at room temperature, and **14** (8.3 g, 50 mmol) was added to the mixture. The whole was stirred for 16 h at room temperature, then the solvent was evaporated off to give a residue, which was recrystallized from EtOH to give **16a** (12 g, 79%), mp 126—127°C. *Anal.* Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20. Found: C, 75.16; H, 5.30; N, 9.00. IR: ν_{CN} 2220 cm^{-1}, ν_{NH} 3350 cm^{-1}. ^{1}H-NMR (δ in CDCl$_3$): 2'-OMe and 5'-OMe (3.84, 6H, s), H$_V$ (7.97, 1H, s), H$_{3'}$ and H$_{4'}$ (6.8—7.0, 2H, m), H$_{6'}$ (7.75, 1H, m), H$_{2''}$ (7.56, 1H, d, $J = 2.5$ Hz, s after deuteration with D$_2$O), H$_{4''}$ (8.0, 1H, m), H$_{5''}$, H$_{6''}$ and H$_{7''}$ (7.1—7.5, 3H, m), NH (8.45, 1H, br s, exchangeable with D$_2$O).

(E)-2-(1H-Indol-3-yl)-3-(2,5-dimethoxyphenyl)acrylonitrile (16b)——As in the case of photoisomerization of **15a** a solution of **16a** (100 mg) in EtOH (100 ml) was irradiated for 40 h. After removal of the solvent, the residue was recrystallized from ether–hexane to give **16b** (45 mg), mp 127—129°C. *Anal.* Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20. Found: C, 75.08; H, 5.15; N, 9.18. IR: ν_{CN} 2210 cm^{-1}, ν_{NH} 3350 cm^{-1}. ^{1}H-NMR (δ in CDCl$_3$): 2'-OMe (3.83, 3H, s), 5'-OMe (3.08, 3H, s), H$_V$ (7.60, 1H, s), H$_{3'}$ and H$_{4'}$ (6.86—6.90, 2H, m), H$_{6'}$ (6.62, 1H, m), H$_{2''}$ (7.38, 1H, d, $J = 2.5$ Hz, s after deuteration with D$_2$O), H$_{4''}$, H$_{5''}$, H$_{6''}$ and H$_{7''}$ (6.90—7.35, 4H, m), NH (8.4, 1H, br s, exchangeable with D$_2$O).

(E)-2-(2-Thienyl)-3-(2,5-dimethoxyphenyl)acrylonitrile (17a)——Potassium *tert*: butoxide (50 mg) was added to a solution of **10** (0.7 g, 5.7 mmol), and **14** (0.87 g, 5.7 mmol) in EtOH (14 ml), and the mixture was stirred for 10 min at room temperature. The resulting precipitate was collected and recrystallized from EtOH to give **17a** (1.25 g, 81%), mp 91—92°C. *Anal.* Calcd for $C_{15}H_{13}NO_2S$: C, 66.40; H, 4.83; N, 5.16; S, 11.82. Found: C, 66.53; H, 4.73; N, 5.06; S, 11.72. IR: ν_{CN} 2205 cm^{-1}. ^{1}H-NMR (δ in CDCl$_3$): 2'-OMe and 5'-OMe (3.84, 6H, s), H$_V$ (7.80, 1H, s), H$_{3'}$ (6.86, 1H, d), H$_{4'}$ (6.93, 1H, dd), H$_{6'}$ (7.73, 1H, d), H$_{3''}$ (7.37, 1H, dt), H$_{4''}$ (7.05, 1H, dd), H$_{5''}$ (7.29, 1H, dd); $J_{3',4'} = 9.1$ Hz, $J_{4',6'} = 2.7$ Hz, $J_{3',6'} = 0.8$ Hz, $J_{3'',4''} = 3.7$ Hz, $J_{3'',5''} = 1.3$ Hz, $J_{4'',5''} = 5.1$ Hz, $J_{V,4'} = 0.3$ Hz, $J_{V,6'} = 0.8$ Hz, $J_{V,3''} = 0.4$ Hz, $J_{V,5''} = 0.4$ Hz.

(Z)-2-(2-Thienyl)-3-(2,5-dimethoxyphenyl)acrylonitrile (17b)——As in the case of photoisomerization of

15a, a solution of **17a** (150 mg) in EtOH (150 ml) was irradiated for 25 h. After removal of the solvent, the residue was recrystallized from ether–hexane to give **17b** (60 mg), mp 63—64°C. *Anal*. Calcd for $C_{15}H_{13}$-NO_2S: C, 66.40; H, 4.83; N, 5.16; S, 11.82. Found: C, 66.22; H, 4.75; N, 4.94; S, 11.88. IR: ν_{CN} 2220 cm^{-1}. ^{1}H-NMR (δ in CDCl$_3$): 2′-OMe (3.78, 3H, s), 5′-OMe (3.60, 3H, s), H$_V$ (7.41, 1H, s), H$_{3'}$ and H$_{4'}$ (6.86, 2H, m), H$_{6'}$ (6.81, 1H, m), H$_{3''}$ (7.30, 1H, m), H$_{4''}$ (6.97, 1H, dd), H$_{5''}$ (7.28, 1H, m); $J_{3'',4''} = 3.7$ Hz, $J_{3'',5''} = 1.3$ Hz, $J_{4'',5''} = 5.1$ Hz.

Photoisomerization of (*E*)-2-Benzoyl-3-(4-methoxyphenyl)acrylonitrile (18a)——18a, mp 101—103°C.[6] IR: ν_{CN} 2225 cm^{-1}, $\nu_{C=O}$ 1645 cm^{-1}. ^{1}H-NMR (δ in CDCl$_3$): 4′-OMe (3.90, 3H, s), H$_V$ (8.07, 1H, s), H$_{2'}$ and H$_{6'}$ (8.10, 2H, d, $J = 9$ Hz), H$_{3'}$, and H$_{5'}$ (7.08, 2H, d, $J = 9$ Hz), H$_{2''}$ and H$_{6''}$ (7.7—8.1, 2H, m), H$_{3''}$, H$_{4''}$ and H$_{5''}$ (7.3—7.7, 3H, m). A solution of **18a** (0.2 g) in EtOH (200 ml) was irradiated by an Ishii Rika Kiki low pressure mercury lamp for 20 h at room temperature. After removal of the solvent, the ^{1}H-NMR spectrum of the residue was taken in CDCl$_3$ solution (see text).

References and Notes

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2) In the text (except in the summary and experimental sections), we have chosen to describe the configuration about the double bond of these compounds by the use of the descriptors *cis* and *trans*; *trans*-compounds are those in which the two aromatic rings [phenyl and heterocyclic rings (or benzoyl group)] have a *trans*-stilbene like configuration, and *cis*-compounds have the opposite configuration. If the configuration of these compounds is specified by use of the descriptors *E* and *Z*, compounds **4** (**4a**—**f**), **5** (**5a**—**g**), **6** (**6a**—**e**), **15b**, **16b**, **17a** and **18a** are of the *E* configuration and compounds **1a**, **1b**, **2** (**2a**—**e**), **3** (**3a**—**d**), **15a**, **16a**, **17b** and **18b** are of the *Z* configuration, as described in the summary and experimental sections.

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