Studies on Cardiotonic Agents. II.[1] Synthesis of Novel Phthalazine and 1,2,3-Benzotriazine Derivatives

Yuji NOMOTO,*[,a] Hiroyuki OBASE,[a] Haruki TAKAI,[a] Masayuki TERANISHI,[a] Joji NAKAMURA[b] and Kazuhiro KUBO[b]

Tokyo Research Laboratory, Kyowa Hakko Kogyo Co., Ltd.,[a] Asahimachi 3-6-6, Machidashi, Tokyo 194, Japan and Pharmaceutical Research Laboratory, Fuji, Kyowa Hakko Kogyo Co., Ltd.,[b] Shimotogari 1188, Nagaizumicho, Shizuoka 411, Japan. *Received January 12, 1990*

A series of phthalazine and 1,2,3-benzotriazine derivatives which have heterocyclylpiperidino groups was synthesized and tested for cardiotonic activity in anesthetized dogs. Several 6,7-dimethoxyphthalazine derivatives showed relatively potent cardiotonic activity comparable to that of amrinone.

Keywords positive inotropic activity; cardiotonic agent; structure–activity relationship; phthalazine; 1,2,3-benzotriazine; piperidine

Within the last decade a number of novel non-glycoside, non-catecholamine cardiotonic agents have been reported as potential replacements for digitalis in the treatment of congestive heart failure.[2] In a previous paper,[1] we described the synthesis and the cardiac stimulant activities of a series of quinazoline derivatives carrying various heterocyclylpiperidines. As a continuation of our investigation, we undertook further studies to prepare other azine derivatives. The Pfizer group reported the 6,7-dimethoxyphthalazine derivative carbazeran (**1**) (Chart 1) showed potent cardiotonic activity.[3] In order to define the structural requirements for cardiotonic activity of the series, we first attempted to carry out replacement of the ethyl carbamate moiety of **1** with various heterocyclic rings which we reported were intermediates of an antihypertensive agent.[4] We then replaced the 6,7-dimethoxyphthalazine nucleus of **1** with other azines. In this report, we wish to describe the synthesis and cardiotonic activity of various 6,7-dimethoxyphthalazine, 5,7-dimethyl-6-ethoxycarbonylphthalazine and 6,7-dimethoxy-1,2,3-benzotriazine derivatives as shown in Table I.

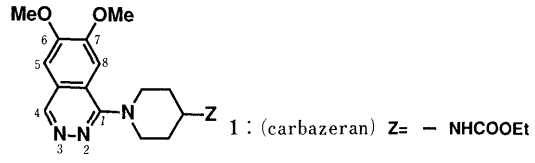


Chart 1

Chemistry The Pfizer group reported[3] that **1** was synthesized from 1-chloro-6,7-dimethoxyphtalazine (**25**) by treatment with the appropriate piperidine. But the reaction of **25** with 1-(4-piperidinyl)-1*H*-benzotriazole (Ia)[4] under similar reaction condition was very sluggish, and the desired **9** was obtained in poor yield. In order to activate the chlorine atom of **25** as a leaving group, we attempted to introduce

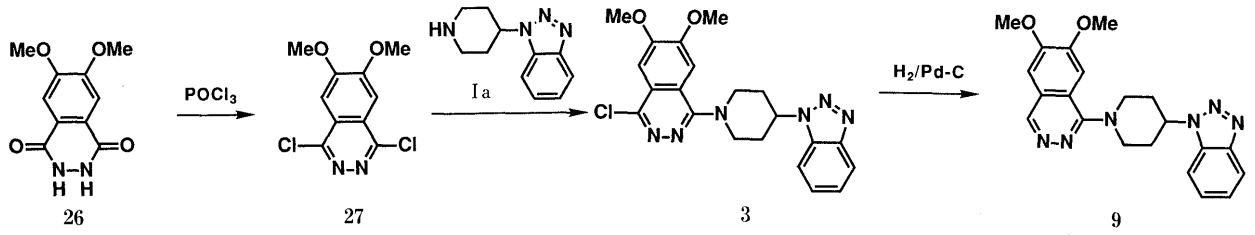


Chart 2

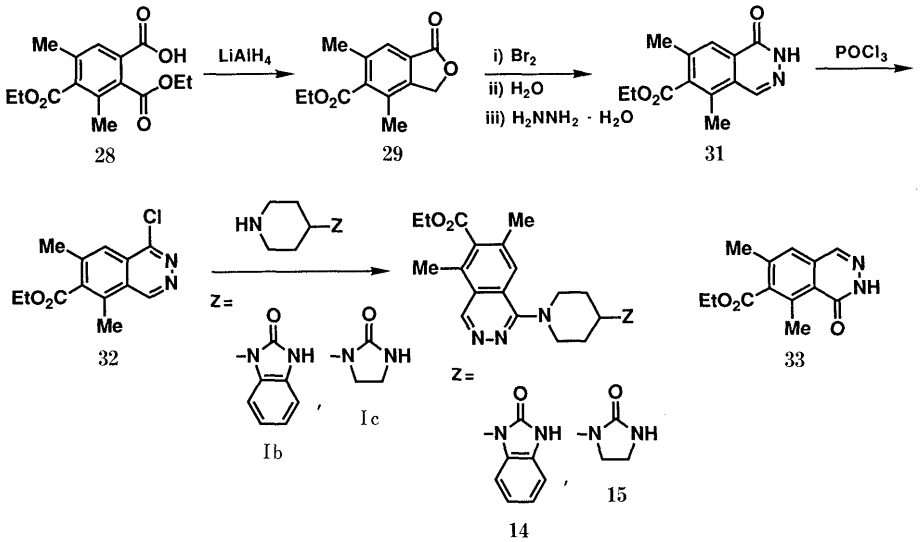


Chart 3

one more chlorine atom at the 4-position of **25**. Thus, treatment of the phthalazinedione (**26**)[5] with $POCl_3$ gave the dichloride (**27**) which reacted with Ia to afford **3** in 57% yield, followed by catalytic reduction to give **9** in 78% yield from **2** (Chart 2). The 6,7-dimethoxyphthalazine derivatives in Table I were prepared in the same manner.

The 5,7-dimethyl-6-ethoxycarbonylphthalazine derivatives (**14**, **15**) were prepared by reaction of the piperidines {1-(4-piperidinyl)-1,3-dihydro-2(2*H*)-benzimidazolone (Ib), 1-(4-piperidinyl)-2-imidazolidinone (Ic)}[4] with the chloride (**32**) which was synthesized in 5 steps from **28**. Thus, reduction of **28**[6] with $LiAlH_4$ gave the lactone (**29**). No further reduction occurred. Bromination of **29** with bromine in the presence of azobisisobutyronitrile (AIBN) in CCl_4 under reflux, and subsequent hydrolysis and ring closure with hydrazine hydrate gave the 1-phthalazinone **31**, probably *via* monobromide (**30**), in 15% yield from **29**. In proton nuclear magnetic resonance (^{1}H-NMR) spectrum, **31** showed signals of 4-H and 8-H of phthalazine ring at 8.33 and 8.14 ppm, respectively. On the other hand, Abuki and Miyazaki[6] reported the isomeric 4-phthalazinone **33** showed signals of 1-H and 8-H at 8.0 and 7.3 ppm, respectively. From these data, the structure of **31** was assigned as 1-phthalazinone. Chlorination of **31** with $POCl_3$ and subsequent condensation with Ib in the presence of K_2CO_3 and KI in dimethylformamide (DMF) at 100 °C afforded **14** (Chart 3).

The synthetic route to the 1,2,3-benzotriazine derivatives listed in Table II is outlined in Chart 4. The reaction of the benzotriazinone **34**[7] with Lawesson's reagent[8] in toluene

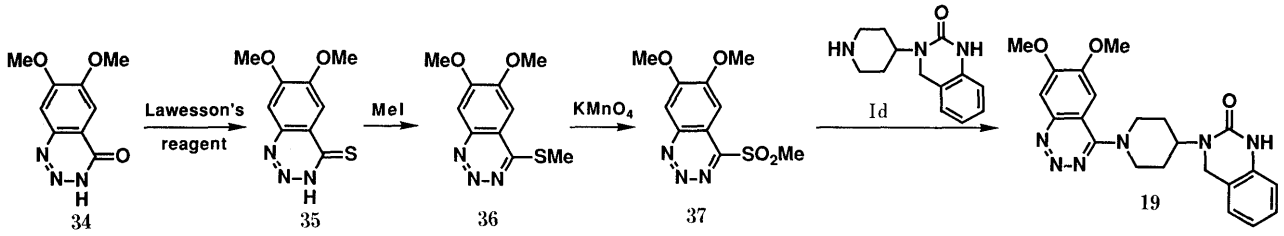
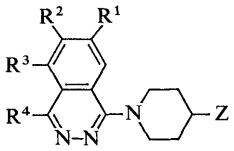


Chart 4

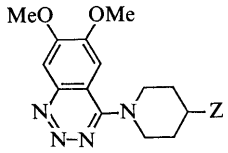
TABLE I



Compd. No.	R^1	R^2	R^3	R^4	Z	Yield (%)	mp (°C) (Crystn. solv.)	Formula	Analysis (%) Calcd (Found)		
									C	H	N
2	MeO	MeO	H	Cl	1,3-Dihydro-2-oxo-2*H*-benzimidazol-1-yl	52	272—275 (DMF–H_2O)	$C_{22}H_{22}ClN_5O_3 \cdot 1/4H_2O$	59.46 (59.35	5.10 5.05	15.76 15.55)
3	MeO	MeO	H	Cl	1*H*-Benzotriazol-1-yl	57	244—245 (DMF–H_2O)	$C_{21}H_{21}ClN_6O_2$	59.36 (59.26	4.98 5.10	19.78 19.70)
4	MeO	MeO	H	Cl	1,2,3,4-Tetrahydro-2-oxo-1-quinazolinyl	79	267—270 (dec.) (DMF–H_2O)	$C_{23}H_{24}ClN_5O_3 \cdot H_2O$	58.53 (58.26	5.55 5.31	14.84 14.73)
5	MeO	MeO	H	Cl	1,2,3,4-Tetrahydro-2-oxo-3-quinazolinyl	81	224—225 (DMF–H_2O)	$C_{23}H_{24}ClN_5O_3 \cdot H_2O$	58.53 (58.43	5.55 5.71	14.84 14.99)
6	MeO	MeO	H	Cl	3,4-Dihydro-2-oxo-2*H*-1,3-benzoxazin-3-yl	49	247—249 (DMF–H_2O)	$C_{23}H_{23}ClN_4O_4 \cdot 1/2H_2O$	59.55 (59.61	5.21 5.03	12.08 11.95)
7	MeO	MeO	H	Cl	2-Oxo-1-imidazolidinyl	43	220 (dec.) (DMF–H_2O)	$C_{18}H_{22}ClN_5O_3$	55.17 (55.30	5.66 5.80	17.87 17.65)
8	MeO	MeO	H	H	1,3-Dihydro-2-oxo-2*H*-benzimidazol-1-yl	76[a]	173—175 (dec.) (DMF–H_2O)	$C_{22}H_{23}N_5O_3 \cdot H_2O$	62.40 (62.68	5.95 5.83	16.54 16.71)
9	MeO	MeO	H	H	1*H*-Benzotriazol-1-yl	78[a]	221 (DMF–H_2O)	$C_{21}H_{22}N_6O_2$	64.60 (64.55	5.68 5.60	21.52 21.34)
10	MeO	MeO	H	H	1,2,3,4-Tetrahydro-2-oxo-1-quinazolinyl	30[a]	147—148 (DMF–H_2O)	$C_{23}H_{25}N_5O_3$	65.85 (65.68	6.01 5.73	16.70 16.84)
11	MeO	MeO	H	H	1,2,3,4-Tetrahydro-2-oxo-3-quinazolinyl	73[a]	200—203 (DMF–H_2O)	$C_{23}H_{25}N_5O_3 \cdot H_2O$	63.14 (63.25	6.22 6.20	16.01 16.01)
12	MeO	MeO	H	H	3,4-Dihydro-2-oxo-2*H*-1,3-benzoxazin-3-yl	78[a]	221 (DMF–H_2O)	$C_{23}H_{24}N_4O_4$	65.70 (65.53	5.75 5.83	13.32 13.34)
13	MeO	MeO	H	H	2-Oxo-1-imidazolidinyl	72[a]	148—152 (MeOH)	$C_{18}H_{23}N_5O_3 \cdot H_2O$	57.59 (57.83	6.71 6.65	18.65 18.32)
14	Me	$EtCO_2$	Me	H	1,3-Dihydro-2-oxo-2*H*-benzimidazol-1-yl	63	196 (dec.) (DMF–H_2O)	$C_{25}H_{27}N_5O_3 \cdot 3/4H_2O$	65.42 (65.40	6.26 6.15	15.26 15.01)
15	Me	$EtCO_2$	Me	H	2-Oxo-1-imidazolidinyl	54	220—221 (AcOEt–Et_2O)	$C_{21}H_{27}N_5O_3$	63.45 (63.39	6.84 6.87	17.61 17.46)

a) Dechlorination step.

TABLE II



Compd. No.	Z	Yield (%)	mp (°C) (Crystn. solv.)	Formula	Analysis (%) Calcd (Found)		
					C	H	N
16	1,3-Dihydro-2-oxo-2*H*-benzimidazol-1-yl	79[a]	220—223 (MeOH)	$C_{21}H_{22}N_6O_3 \cdot HCl \cdot 1/2H_2O$	55.81 (55.93)	5.35 5.12	18.60 18.39)
17	1*H*-Benzotriazol-1-yl	61	201—203 (DMF–H_2O)	$C_{20}H_{21}N_7O_2 \cdot 1/2H_2O$	59.99 (60.31)	5.54 5.41	24.48 24.29)
18	1,2,3,4-Tetrahydro-2-oxo-1-quinazolinyl	76	239—241 (dec.) (DMF–H_2O)	$C_{22}H_{24}N_6O_3 \cdot 1/4H_2O$	62.18 (62.00)	5.81 5.84	19.78 19.62)
19	1,2,3,4-Tetrahydro-2-oxo-3-quinazolinyl	70	290—292 (dec.) (DMF–H_2O)	$C_{22}H_{24}N_6O_3$	62.84 (62.45)	5.75 5.60	19.99 19.61)
20	3,4-Dihydro-2-oxo-2*H*-1,3-benzoxazin-3-yl	76[a]	168—170 (MeOH)	$C_{22}H_{23}N_5O_4 \cdot HCl \cdot 1/2H_2O$	56.59 (56.45)	5.40 5.34	15.00 14.68)
21	2-Cyanoamino-3,4-dihydro-3-quinazolinyl	69	292—294 (dec.) (DMF–H_2O)	$C_{23}H_{24}N_8O_2$	62.15 (61.92)	5.44 5.36	25.21 25.00)
22	(1,3-Dihydro-2-oxo-1*H*-benzimidazol-1-yl)methyl	79	259—261 (DMF–H_2O)	$C_{22}H_{24}N_6O_3 \cdot 1/4H_2O$	62.18 (62.13)	5.81 5.84	19.78 19.57)
23	3,4-Dihydro-2,2-dioxido-1*H*-2,1,3-benzothiadiazin-1-yl	43[a]	210—211 (MeOH)	$C_{21}H_{24}N_6O_4S \cdot HCl \cdot 1/2H_2O$	50.25 (50.38)	5.22 5.30	16.74 16.50)
24	3,4-Dihydro-2,2-dioxido-1*H*-2,1,3-benzothiadiazin-3-yl	86	207—208 (DMF–H_2O)	$C_{21}H_{24}N_6O_4S \cdot H_2O$	53.15 (53.45)	5.52 5.30	17.71 17.60)

a) As HCl salt.

TABLE III. Biological Activity of Some Phthalazine and 1,2,3-Benzotriazine Derivatives in Anesthetized Dogs ($n=2$)

Compd. No.	Cardiotonic activity	
	LVdP/dt max (Δ%)	Relative potency[a]
2	NE	
3	7.8	0.13
4	35.3	0.63
5	10.0	0.16
6	5.2	0.09
8	18.6	0.64
9	NE	
10	NE	
11	27.4	0.95
12	14.8	0.51
15	15.8	0.51
16	NE	
17	NE	
18	NE	
19	28.2	1.01
20	4.2	0.40
21	30.4	0.59
22	12.0	0.45
23	13.1	0.59
24	NE	

a) Compared to the percent increase in LVdP/dt max observed with amrinone (1 mg/kg) in the same dogs. NE: no effect.

afforded the thione (**35**). Methylation of **35** with MeI in alkaline medium gave the methyl sulfide (**36**) which was oxidized to give the methyl sulfone (**37**) by treatment with $KMnO_4$ in a mixture of $CHCl_3$ and 70% AcOH. The compound **37** was immediately used in the next reaction without further purification because of its low stability. This compound was completely degraded at 40 °C within 1 h, even in the crystalline state. Reaction of **37** with 3-(4-piperidinyl)-1,2,3,4-tetrahydro-2-oxo-3-quinazoline (Id)[4] in dimethyl sulfoxide (DMSO) at room temperature afforded **19** in 70% yield.

Biological Results Cardiotonic activity of the compounds listed in Tables I and II was evaluated in anesthetized open chest dogs using procedures previously described.[1] The results of the test compounds were determined by measuring percent increase in maximum dP/dt of left ventricular pressure (LVdP/dt max, Δ%) after i.v. administration (1 mg/kg) in anesthetized mongrel dogs of either sex (8—15 kg, $n=2$). The potency of cardiotonic activity of the test compounds was compared with amrinone (1.0 mg/kg i.v.). Relative potency was calculated as the ratio of the LVdP/dt max of each compound to that of amrinone[9] (amrinone = 1) in the same dogs.

Results of the experiment are summarized in Table III. As regards effects of the substituents on piperidine ring, introduction of the 1,2,3,4-tetrahydro-2-oxo-3-quinazolinyl group (**11**, **19**) conferred relatively potent activity comparable to that of amrinone. We previously reported that 3-[1-(6,7-dimethoxy-4-quinazolinyl)-4-piperidinyl]-1,2,3,4-tetrahydroquinazolin-2-one[1] showed potent cardiotonic activity. These findings suggest that the 1,2,3,4-tetrahydro-2-oxo-3-quinazolinyl group was preferable for improved activity.

Other 6,7-dimethoxyphthalazine, 5,7-dimethyl-6-ethoxycarbonylphthalazine and 1,2,3-benzotriazine derivatives, however, were generally less potent than amrinone and the 6,7-dimethoxyquinazoline derivatives.[1]

Experimental

All melting points were determined on a micro melting point apparatus

(Yanagimoto) and are uncorrected. Infrared (IR) spectra were measured on a Shimadzu IR-27G spectrophotometer. ^{1}H-NMR spectra were measured on a Varian EM-390 and a JNM-PS-100 spectrometer using trimethylsilane (TMS) as an internal standard.

1,4-Dichloro-6,7-dimethoxyphthalazine (27) A solution of **26** (19.0 g, 86 mmol) in $POCl_3$ (45 ml) was refluxed for 2 h. The reaction mixture was evaporated under reduced pressure and the residue was poured into ice-water (150 ml). The precipitated crystals were collected by filtration, washed with water and dried to give crude **27** (16.0 g, 72%) which was used in the next reaction without further purification. An analytical sample was recrystallized from DMF–water, mp 195—200 °C (dec.). *Anal.* Calcd for $C_{10}H_8Cl_2N_2O_2$: C, 46.36; H, 3.11; N, 10.81. Found: C, 46.39; H, 3.23; N, 10.58. IR (KBr): 1600, 1510 cm^{-1}. NMR ($CDCl_3$) δ: 7.36 (2H, s, Ar-H), 3.95 (6H, s, CH_3O).

General Procedure for the Synthesis of 4-Chloro-6,7-dimethoxy-1-(4-heterocyclyl-1-piperidinyl)phthalazines. (1-[1-(4-Chloro-6,7-dimethoxyphthalazin-1-yl)-4-piperidinyl]-1*H*-benzotriazole (3) A mixture of **27** (2.0 g, 7.7 mmol), 1-(4-piperidinyl)-1*H*-benzotriazole (Id) (2.6 g, 9.9 mmol), K_2CO_3 (3.0 g) and KI (0.1 g) in DMF (10 ml) was stirred for 15 h at 100 °C. The reaction mixture was poured into water. The precipitates were collected by filtration, washed with water and dried to give crude crystals of **3** which were recrystallized from DMF–water to obtain 1.9 g (68%) of **3**. IR (KBr): 1600, 1500 cm^{-1}. NMR (DMSO-d_6) δ: 8.13 (2H, m, Ar-H), 7.55 (4H, m, Ar-H), 5.38 (1H, m, piperidine), 4.10 (6H, s, CH_3O), 3.80—1.60 (8H, m, piperidine). Compounds **2**, **4**—**7** were obtained in the same manner as described above. The yields, melting points and elemental analysis data are shown in Table I.

General Procedure for the Synthesis of 6,7-Dimethoxy-1-(4-heterocyclyl-1-piperidinyl)phthalazines. 1-[1-(6,7-Dimethoxyphthalazin-1-yl)-4-piperidinyl]-1*H*-benzotriazole (9) A suspension of **3** (1.4 g, 3.8 mmol) and 10% Pd on carbon (0.2 g) in AcOH (30 ml) was stirred under atmospheric pressure of H_2 for 3 h at 40 °C. The catalyst was filtered off and the filtrate was concentrated, then adjusted to pH 10 with 1 N NaOH. The precipitated crystals were collected by filtration, washed and dried to give crude crystals of **9** which were recrystallized from DMF–water afforded **9** (1.0 g, 67%). IR (KBr): 1600 cm^{-1}. NMR ($CDCl_3$) δ: 9.12 (1H, s, Ar-H), 8.10 (1H, m, Ar-H), 7.60—7.12 (5H, m, Ar-H), 4.90 (1H, m, piperidine), 4.10 (6H, s, CH_3O), 3.60—1.70 (8H, m, piperidine). Compounds **8**, **10**—**13** were obtained in the same manner as described above. The yields, melting points and elemental analysis data are shown in Table I.

5,7-Dimethyl-6-ethoxycarbonyl-1(2*H*)-phthalazinone (31) $LiAlH_4$ (5.7 g, 150 mmol) was added portionwise to a solution of **28** (40.0 g, 136 mmol) in tetrahydrofuran (THF) (200 ml) and the mixture was stirred for **30** min at room temperature. The reaction mixture was poured into ice-water, the whole was extracted with $CHCl_3$, and the organic layer was dried over $MgSO_4$ and evaporated to dryness. The residual oil was purified by column chromatography (SiO_2, 500 g, $CHCl_3$) to afford oily **29** (16.0 g, 48%). IR (KBr): 1770, 1745 cm^{-1}. NMR ($CDCl_3$) δ: 7.45 (1H, s, Ar-H), 5.21 (2H, s, $-CH_2-$), 4.45 (2H, q, J=6 Hz, $-OCH_2CH_3$), 2.36, 2.28 (3H, each, s, CH_3), 1.44 (3H, t, J=6 Hz, $-OCH_2CH_3$). Bromine (5.6 g, 70 mmol) was added dropwise to a boiling solution of **29** (16.0 g, 65 mmol) and AIBN (0.1 g) in CCl_4 (100 ml) with stirring over a 2 h period. The reaction mixture was concentrated and the residue was suspended in water (150 ml), then heated at 100 °C for 1 h. Hydrazine hydrate (8 ml) was added to the mixture and stirred for 1 h at 60 °C. The precipitates were collected by filtration, washed with water, dried to give crude crystals of **31** which were recrystallized with DMF–water to afford pure **31** (5.2 g, 31%), mp 190—192 °C. *Anal.* Calcd for $C_{13}H_{14}N_2O_3$: C, 63.39; H, 5.74; N, 11.37. Found: C, 63.22; H, 5.59; N, 11.40. IR (KBr): 1720, 1650 cm^{-1}. NMR ($CDCl_3$) δ: 10.92 (1H, br, NH), 8.33 (1H, s, Ar-H), 8.14 (1H, s, Ar-H), 4.48 (2H, q, J=6 Hz, $-OCH_2CH_3$), 2.55, 2.42 (3H, each, s, CH_3), 1.44 (3H, t, J=6 Hz, $-OCH_2CH_3$).

1-Chloro-5,7-dimethyl-6-ethoxycarbonylphthalazine (32) A suspension of **31** (4.0 g, 16 mmol) in $POCl_3$ (20 ml) was stirred for 15 min at 90 °C. The reaction mixture was evaporated under reduced pressure and the residue was poured into crushed ice and extracted with AcOEt. The organic layer was washed with water, dried over $MgSO_4$ and evaporated to dryness. The oily residue was purified by column chromatography (SiO_2, 120 g, 0.5% MeOH–$CHCl_3$). The product was crystallized from iso-PrOH–hexane to afford **32** (3.0 g, 70%), mp 167 °C. *Anal.* Calcd for $C_{13}H_{13}ClN_2O_2$: C, 58.99; H, 4.95; N, 10.58. Found: C, 58.78; H, 5.03; N, 10.60. IR (KBr): 1730 cm^{-1}. NMR ($CDCl_3$) δ: 9.53 (1H, s, Ar-H), 7.98 (1H, s, Ar-H), 4.52 (2H, q, J=6 Hz, $-OCH_2CH_3$), 2.72, 2.55 (3H, each, s, CH_3), 1.33 (3H, t, J=6 Hz, $-OCH_2CH_3$).

General Procedure for the Synthesis of 5,7-Dimethyl-6-ethoxycarbonyl-1-(4-heterocyclyl-1-piperidinyl)phthalazines. 1-[1-(5,7-Dimethyl-6-ethoxycarbonyl-1-phthalazinyl)-4-piperidinyl]-1,3-dihydro-2(2*H*)-benzimidazolone (14) A mixture of **32** (0.13 g, 0.50 mmol), Ib (0.13 g, 0.50 mmol), K_2CO_3 (70 mg) and KI (10 mg) in DMF (10 ml) was stirred for 15 h at 100 °C. The reaction mixture was concentrated under reduced pressure, then the residue was purified by column chromatography (SiO_2, 10 g, 4% MeOH–$CHCl_3$) to afford **14** (0.14 g, 63%) as crystals which were recrystallized from DMF–water. IR (KBr): 1730, 1690 cm^{-1}. NMR ($CDCl_3$) δ: 10.10 (1H, s, NH), 9.32 (1H, s, Ar-H), 7.70 (1H, s, Ar-H), 7.00 (4H, m, Ar-H), 4.60 (1H, m, piperidine), 4.42 (2H, q, J=7 Hz, $-OCH_2CH_3$), 4.22—1.80 (8H, m, piperidine), 2.62, 2.48 (3H, each, s, CH_3), 1.41 (3H, t, J=7 Hz, $-OCH_2CH_3$). Compound **15** was obtained in the same manner as described above. The yields, melting points and elemental analysis data are shown in Table I.

6,7-Dimethoxy-4-(3*H*)-1,2,3-benzotriazinethione (35) A suspension of **34** (25.0 g, 121 mmol) and Lawesson's reagent[8] (49.0 g, 122 mmol) in toluene (700 ml) was stirred for 4 h at 100 °C. The precipitates were collected by filtration and washed with MeOH to afford crude crystals of **35** (21.0 g, 78%). The crystals were used in the next reaction without further purification. An analytical sample was recrystallized from DMF–water, mp 255—256 °C. *Anal.* Calcd for $C_9H_9N_3O_2S$: C, 48.42; H, 4.06; N, 18.82. Found: C, 48.35; H, 4.22; N, 18.69. IR (KBr): 1505 cm^{-1}. NMR (DMSO-d_6) δ: 16.04 (1H, br s, NH), 7.83 (1H, s, Ar-H), 7.60 (1H, s, Ar-H), 4.03, 4.00 (2H, each, s, CH_3O).

6,7-Dimethoxy-4-methylthio-1,2,3-benzotriazine (36) MeI (6.0 ml, 96 mmol) was added dropwise to a stirred solution of **35** (21.0 g, 94 mmol) in 2 N NaOH (100 ml) and MeOH (200 ml), and the reaction mixture was stirred for 2 h at room temperature. The precipitated crystals were collected by filtration and washed with water to afford crude crystals of **36** (20.0 g, 89%). The crystals were used in the next reaction without further purification. An analytical sample was recrystallized from DMF–water, mp 171—173 °C (dec.). *Anal.* Calcd for $C_{10}H_{11}N_3O_2S$: C, 50.62; H, 4.67; N, 17.71. Found: C, 50.24; H, 4.75; 17.59. IR (KBr): 1600, 1515 cm^{-1}. NMR (DMSO-d_6) δ: 7.71 (1H, s, Ar-H), 7.17 (1H, s, Ar-H), 4.06, 4.03 (3H, each, s, CH_3O), 2.80 (3H, s, CH_3S).

6,7-Dimethoxy-4-methylsulfonyl-1,2,3-benzotriazine (37) $KMnO_4$ (5.0 g) was added portionwise to a mixture of **36** (3.0 g, 13 mmol) in 70% AcOH (150 ml) and $CHCl_3$ (60 ml) with ice-cooling and stirred for 30 min. To the reaction mixture was added 30% H_2O_2 until the mixture was clear. $CHCl_3$ was removed by evaporation under reduced pressure below 35 °C. The precipitates were collected by filtration, washed successively with water, MeOH and Et_2O and dried under reduced pressure at room temperature for 15 min to afford crude crystals of **37** (2.8 g, 83%). IR (KBr): 1500 cm^{-1}. The crude **37** was used immediately in the next reaction without further purification because of its low stability even in the crystalline state.

General Procedure for the Synthesis of 6,7-Dimethoxy-4-(4-heterocyclyl-1-piperidinyl)-1,2,3-benzotriazines. 3-[1-(6,7-Dimethoxy-1,2,3-benzotriazin-4-yl)-4-piperidinyl]-3,4-dihydro-2(1*H*)-quinazolinone (19) A mixture of **37** (1.0 g, 3.7 mmol), Id·HCl (1.0 g, 3.7 mmol) and Et_3N (1.1 ml, 8.0 mmol) in DMSO (7 ml) was stirred at room temperature for 18 h. The reaction mixture was poured into water and the precipitates were collected by filtration. Recrystallization from DMF–water afforded **19** (12.0 g, 70%). IR (KBr): 1660 cm^{-1}. NMR (DMSO-d_6) δ: 9.20 (1H, s, NH), 7.57—6.74 (6H, m, Ar-H), 4.50 (1H, m, piperidine), 4.34 (2H, s, $-CH_2-$), 4.00 (6H, s, CH_3O), 3.50—1.70 (8H, m, piperidine). Compounds **16**—**28**, **20**—**24** were obtained in the same manner as described above. The yields, melting points and elemental analysis data are shown in Table II.

References

1) Y. Nomoto, H. Obase, H. Takai, M. Teranishi, J. Nakamura and K. Kubo, *Chem. Pharm. Bull.*, **38**, 1591 (1990).
2) For a recent review; M. D. Taylor, I. Sircar and R. P. Steffen, *Annu. Rep. Med. Chem.*, **22**, 85 (1987).
3) F. Follath, F. Kersting, G. R. J. Lewis, R. J. Warden, N. M. Woolhouse and C. T. Dolley, *Clin. Pharmacol. Ther.*, **20**, 24 (1976); M. B. Fawzi, E. Davison and M. S. Tute, *J. Pharm. Sci.*, **69**, 104 (1980).
4) H. Obase, N. Nakamizo, H. Takai and M. Teranishi, *Bull. Chem. Soc. Jpn.*, **56**, 3189 (1983); *idem*, *J. Heterocycl. Chem.*, **20**, 565 (1983); H. Obase, N. Nakamizo, H. Takai, M. Teranishi, K. Kubo, K. Shuto, Y. Kasuya, K. Shigenobu and M. Hashikami, *Chem. Pharm. Bull.*, **31**, 3186 (1983); H. Takai, H. Obase, N. Nakamizo, M. Teranishi, K. Kubo, K. Shuto and T. Hashimoto, *ibid.*, **33**, 1104 (1985); H. Takai, H. Obase, M. Teranishi, A. Karasawa, K. Kubo, K. Shuto, Y. Kasuya and K. Shigenobu, *ibid.*, **34**, 1907 (1986).

5) O. Abou-Teim, R. B. Jansen, J. F. W. McOmie and D. H. Perry, *J. Chem. Soc., Perkin Trans. 1*, **1980**, 1841.
6) H. Abuki and H. Miyazaki, *J. Labelled Compd. Pharmacol.*, **6**, 889 (1980).
7) F. G. Kathawala, U. S. Patent 3678166 (1972) [*Chem. Abstr.*, **77**, 114437*t* (1972)].
8) B. S. Pedersen, S. Scheibye, N. H. Nilsson and S.-O. Lawesson, *Bull. Soc. Chim. Belg.*, **87**, 223 (1978).
9) R. E. Weishaar, M. H. Cain and J. A. Bristol, *J. Med. Chem.*, **28**, 537 (1985).