

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

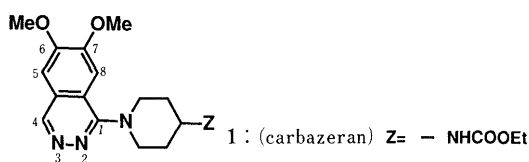


Chart 1

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.

Chemistry The Pfizer group reported³⁾ that **1** was synthesized from 1-chloro-6,7-dimethoxyphthalazine (**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

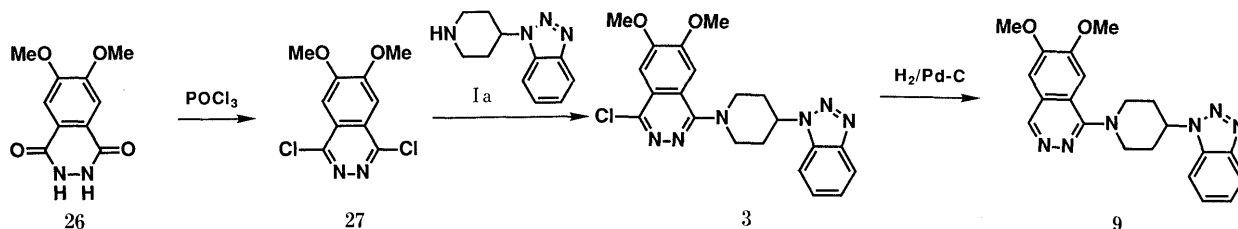


Chart 2

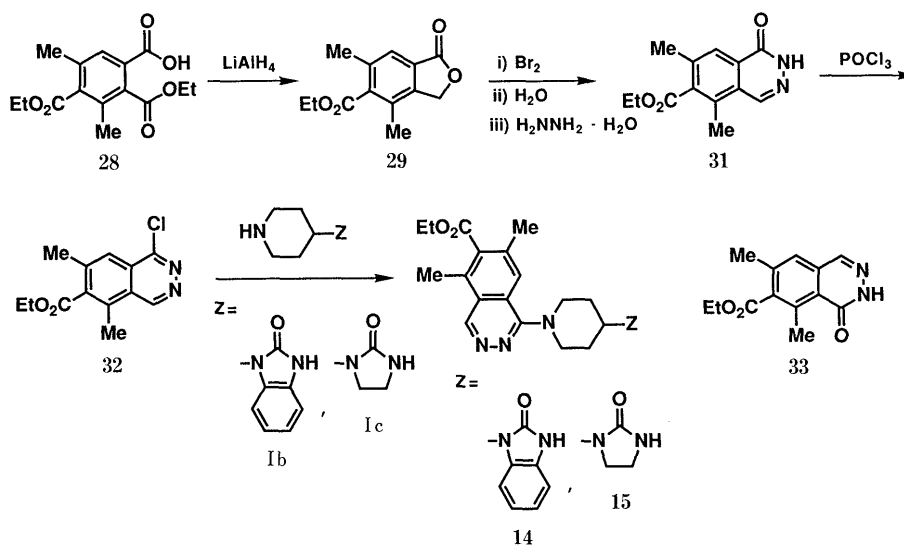


Chart 3

one more chlorine atom at the 4-position of **25**. Thus, treatment of the phthalazinedione (**26**)⁵ with POCl₃ 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-piperidiny)-1,3-dihydro-2(2*H*)-benzimidazolone (Ib), 1-(4-piperidiny)-2-imidazolidinone (Ic)}⁴ with the chloride (**32**) which was synthesized in 5 steps from **28**. Thus, reduction of **28**⁶ with LiAlH₄ gave the lactone (**29**). No further reduction occurred. Bromination of **29** with bromine in the presence of azobisisobutyronitrile (AIBN) in CCl₄ 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 (¹H-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 Miyazaki⁶ 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 POCl₃ and subsequent condensation with Ib in the presence of K₂CO₃ 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 reagent⁸ in toluene

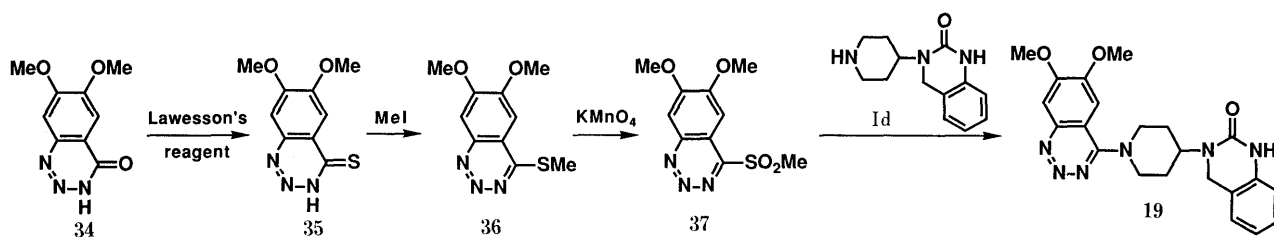
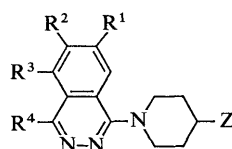


Chart 4

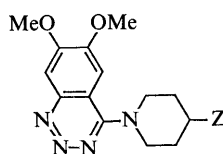
TABLE I



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 <i>H</i> -benzimidazol-1-yl	52	272—275 (DMF-H ₂ O)	C ₂₂ H ₂₂ ClN ₅ O ₃ ·1/4H ₂ O	59.46 (59.35)	5.10 (5.05)	15.76 (15.55)
3	MeO	MeO	H	Cl	1 <i>H</i> -Benzotriazol-1-yl	57	244—245 (DMF-H ₂ O)	C ₂₁ H ₂₁ ClN ₆ O 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-quinazoliny	79	267—270 (dec.) (DMF-H ₂ O)	C ₂₃ H ₂₄ ClN ₅ O ₃ ·H ₂ O	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-quinazoliny	81	224—225 (DMF-H ₂ O)	C ₂₃ H ₂₄ ClN ₅ O ₃ ·H ₂ O	58.53 (58.43)	5.55 (5.71)	14.84 (14.99)
6	MeO	MeO	H	Cl	3,4-Dihydro-2-oxo-2 <i>H</i> -1,3-benzoxazin-3-yl	49	247—249 (DMF-H ₂ O)	C ₂₃ H ₂₃ ClN ₄ O ₄ ·1/2H ₂ O	59.55 (59.61)	5.21 (5.03)	12.08 (11.95)
7	MeO	MeO	H	Cl	2-Oxo-1-imidazolidiny	43	220 (dec.) (DMF-H ₂ O)	C ₁₈ H ₂₂ ClN ₅ O ₃	55.17 (55.30)	5.66 (5.80)	17.87 (17.65)
8	MeO	MeO	H	H	1,3-Dihydro-2-oxo-2 <i>H</i> -benzimidazol-1-yl	76 ^{a)}	173—175 (dec.) (DMF-H ₂ O)	C ₂₂ H ₂₃ N ₅ O ₃ ·H ₂ O	62.40 (62.68)	5.95 (5.83)	16.54 (16.71)
9	MeO	MeO	H	H	1 <i>H</i> -Benzotriazol-1-yl	78 ^{a)}	221 (DMF-H ₂ O)	C ₂₁ H ₂₂ N ₆ O 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-quinazoliny	30 ^{a)}	147—148 (DMF-H ₂ O)	C ₂₃ H ₂₅ N ₅ O 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-quinazoliny	73 ^{a)}	200—203 (DMF-H ₂ O)	C ₂₃ H ₂₅ N ₅ O ₃ ·H ₂ O	63.14 (63.25)	6.22 (6.20)	16.01 (16.01)
12	MeO	MeO	H	H	3,4-Dihydro-2-oxo-2 <i>H</i> -1,3-benzoxazin-3-yl	78 ^{a)}	221 (DMF-H ₂ O)	C ₂₃ H ₂₄ N ₄ O ₄	65.70 (65.53)	5.75 (5.83)	13.32 (13.34)
13	MeO	MeO	H	H	2-Oxo-1-imidazolidiny	72 ^{a)}	148—152 (MeOH)	C ₁₈ H ₂₃ N ₅ O ₃ ·H ₂ O	57.59 (57.83)	6.71 (6.65)	18.65 (18.32)
14	Me	EtCO ₂	Me	H	1,3-Dihydro-2-oxo-2 <i>H</i> -benzimidazol-1-yl	63	196 (dec.) (DMF-H ₂ O)	C ₂₅ H ₂₇ N ₅ O ₃ ·3/4H ₂ O	65.42 (65.40)	6.26 (6.15)	15.26 (15.01)
15	Me	EtCO ₂	Me	H	2-Oxo-1-imidazolidiny	54	220—221 (AcOEt-Et ₂ O)	C ₂₁ H ₂₇ N ₅ O 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-2H-benzimidazol-1-yl	79 ^{a)}	220—223 (MeOH)	C ₂₁ H ₂₂ N ₆ O ₃ ·HCl·1/2H ₂ O	55.81 (55.93)	5.35 (5.12)	18.60 (18.39)
17	1H-Benzotriazol-1-yl	61	201—203 (DMF-H ₂ O)	C ₂₀ H ₂₁ N ₇ O ₂ ·1/2H ₂ O	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 ₂ O)	C ₂₂ H ₂₄ N ₆ O ₃ ·1/4H ₂ O	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 ₂ O)	C ₂₂ H ₂₄ N ₆ O ₃ (62.45)	62.84 (62.45)	5.75 (5.60)	19.99 (19.61)
20	3,4-Dihydro-2-oxo-2H-1,3-benzoxazin-3-yl	76 ^{a)}	168—170 (MeOH)	C ₂₂ H ₂₃ N ₅ O ₄ ·HCl·1/2H ₂ O	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 ₂ O)	C ₂₃ H ₂₄ N ₈ O ₂ (61.92)	62.15 (61.92)	5.44 (5.36)	25.21 (25.00)
22	(1,3-Dihydro-2-oxo-1H-benzimidazol-1-yl)methyl	79	259—261 (DMF-H ₂ O)	C ₂₂ H ₂₄ N ₆ O ₃ ·1/4H ₂ O	62.18 (62.13)	5.81 (5.84)	19.78 (19.57)
23	3,4-Dihydro-2,2-dioxido-1H-2,1,3-benzothiadiazin-1-yl	43 ^{a)}	210—211 (MeOH)	C ₂₁ H ₂₄ N ₆ O ₄ S ·HCl·1/2H ₂ O	50.25 (50.38)	5.22 (5.30)	16.74 (16.50)
24	3,4-Dihydro-2,2-dioxido-1H-2,1,3-benzothiadiazin-3-yl	86	207—208 (DMF-H ₂ O)	C ₂₁ H ₂₄ N ₆ O ₄ S ·H ₂ O	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 ($\Delta\%$)	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, $\Delta\%$) 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 amrinone⁹⁾ (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-one¹⁾ 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-ethoxy-carbonylphthalazine 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. ¹H-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 POCl₃ (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 C₁₀H₈Cl₂N₂O₂: 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 (CDCl₃) δ: 7.36 (2H, s, Ar-H), 3.95 (6H, s, CH₃O).

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]-1H-benzotriazole (3) A mixture of **27** (2.0 g, 7.7 mmol), 1-(4-piperidinyl)-1H-benzotriazole (**Id**) (2.6 g, 9.9 mmol), K₂CO₃ (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, CH₃O), 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]-1H-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 H₂ 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 (CDCl₃) 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, CH₃O), 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(2H)-phthalazinone (31) LiAlH₄ (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 CHCl₃, and the organic layer was dried over MgSO₄ and evaporated to dryness. The residual oil was purified by column chromatography (SiO₂, 500 g, CHCl₃) to afford oily **29** (16.0 g, 48%). IR (KBr): 1770, 1745 cm⁻¹. NMR (CDCl₃) δ: 7.45 (1H, s, Ar-H), 5.21 (2H, s, -CH₂-), 4.45 (2H, q, *J* = 6 Hz, -OCH₂CH₃), 2.36, 2.28 (3H, each, s, CH₃), 1.44 (3H, t, *J* = 6 Hz, -OCH₂CH₃). 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 CCl₄ (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 C₁₃H₁₄N₂O₃: 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 (CDCl₃) 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, -OCH₂CH₃), 2.55, 2.42 (3H, each, s, CH₃), 1.44 (3H, t, *J* = 6 Hz, -OCH₂CH₃).

1-Chloro-5,7-dimethyl-6-ethoxycarbonylphthalazine (32) A suspension of **31** (4.0 g, 16 mmol) in POCl₃ (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 MgSO₄ and evaporated to dryness. The oily residue was purified by column chromatography (SiO₂, 120 g, 0.5% MeOH-CHCl₃). The product was crystallized from iso-PrOH-hexane to afford **32** (3.0 g, 70%), mp 167 °C. *Anal.* Calcd for C₁₃H₁₃ClN₂O₃: 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 (CDCl₃) δ: 9.53 (1H, s, Ar-H), 7.98 (1H, s, Ar-H), 4.52 (2H, q, *J* = 6 Hz, -OCH₂CH₃), 2.72, 2.55 (3H, each, s, CH₃), 1.33 (3H, t, *J* = 6 Hz, -OCH₂CH₃).

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(2H)-benzimidazolone (14) A mixture of **32** (0.13 g, 0.50 mmol), **1b** (0.13 g, 0.50 mmol), K₂CO₃ (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 (SiO₂, 10 g, 4% MeOH-CHCl₃) to afford **14** (0.14 g, 63%) as crystals which were recrystallized from DMF-water. IR (KBr): 1730, 1690 cm⁻¹. NMR (CDCl₃) 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, -OCH₂CH₃), 4.22–1.80 (8H, m, piperidine), 2.62, 2.48 (3H, each, s, CH₃), 1.41 (3H, t, *J* = 7 Hz, -OCH₂CH₃). 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(3H)-1,2,3-benzotriazinethione (35) A suspension of **34** (25.0 g, 121 mmol) and Lawesson's reagent⁸⁾ (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 C₉H₉N₃O₂S: 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, CH₃O).

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 C₁₀H₁₁N₃O₂S: C, 50.62; H, 4.67; N, 17.71. Found: C, 50.24; H, 4.75; N, 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, CH₃O), 2.80 (3H, s, CH₃S).

6,7-Dimethoxy-4-methylsulfonyl-1,2,3-benzotriazine (37) KMnO₄ (5.0 g) was added portionwise to a mixture of **36** (3.0 g, 13 mmol) in 70% AcOH (150 ml) and CHCl₃ (60 ml) with ice-cooling and stirred for 30 min. To the reaction mixture was added 30% H₂O₂ until the mixture was clear. CHCl₃ was removed by evaporation under reduced pressure below 35 °C. The precipitates were collected by filtration, washed successively with water, MeOH and Et₂O 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(1H)-quinazolinone (19) A mixture of **37** (1.0 g, 3.7 mmol), **Id**·HCl (1.0 g, 3.7 mmol) and Et₃N (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, -CH₂-), 4.00 (6H, s, CH₃O), 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**, 114437t (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).