A New Nonsteroidal Analgesic–Antiinflammatory Agent. Synthesis and Activity of 4-Ethoxy-2-methyl-5-morpholino-3(2*H*)-pyridazinone and Related Compounds

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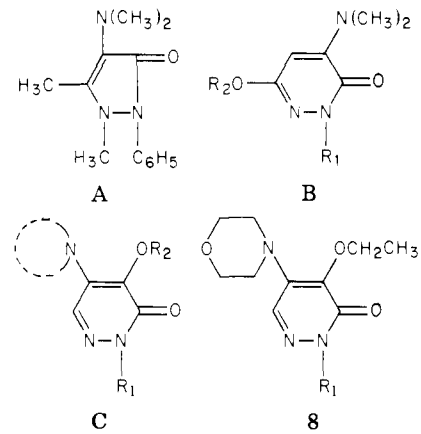
In order to examine analgesic and antiinflammatory activities, various 2-alkyl- or 2-alkenyl-4-alkoxy-5-(substituted amino)-3(2*H*)-pyridazinones were prepared. Among the compounds prepared, 4-ethoxy-2-methyl-5-morpholino-3(2*H*)-pyridazinone (**8**) was evaluated to be the most attractive compound as an analgesic–antiinflammatory agent. Compound **8** was shown to be more potent in analgesic and antiinflammatory activities and less potent in toxicity than aminopyrine and phenylbutazone. Some pyridazinone derivatives in which possible active sites of **8** are eliminated and altered were prepared, and their activities were evaluated by means of analogous assays. On the basis of available data, the structure–activity relationship in a series of 4-alkoxy-2-substituted-5-(substituted amino)-3(2*H*)-pyridazinones was also discussed.

Previous papers[1] have described the preparation and analgesic activity of 6-alkoxy-4-(dimethylamino)-2-phenyl- or -2-methyl-3(2*H*)-pyridazinones (B) closely related to the structure of aminopyrine (A) in view of the ring enlargement of pyrazolone to pyridazinone (Chart I).

In continuation of our investigations on the structure–pharmacological activity relationship in the pyridazinone derivatives, we were particularly interested in the modification of B based on the positional alteration of functional groups on the 3(2*H*)-pyridazinone skeleton. This paper deals with the synthesis and the analgesic–antiinflammatory activity of 4-alkoxy-2-substituted-5-(substituted amino)-3(2*H*)-pyridazinones (C). The present work led us to discover 4-ethoxy-2-methyl-5-morpholino-3(2*H*)-pyridazinone (**8**) as a potential analgesic–antiinflammatory agent which may be used clinically.

Chart I



R_1 = alkyl or aryl; R_2 = alkyl

Chemistry. Upon treatment of 4,5-dichloro-2-methyl-3(2*H*)-pyridazinone (**1**)[2] with morpholine, 4-chloro-2-methyl-5-morpholino-3(2*H*)-pyridazinone (**2**) and its isomeric 5-chloro-2-methyl-4-morpholino-3(2*H*)-pyridazinone (**3**) were obtained in 80 and 6% yields, respectively. Preferential formation of **3** was observed upon employment of toluene instead of water as a solvent; i.e., reaction of **1** with morpholine in toluene gave **2** and **3** in 25 and 50% yields, respectively.

The structures of **2** and **3** were confirmed as shown in Scheme I. Catalytic dehalogenation of **2** and **3** led to the formation of 2-methyl-5-morpholino-3(2*H*)-pyridazinone (**4**) and 2-methyl-4-morpholino-3(2*H*)-pyridazinone (**5**). The former compound, **4**, was identical in every respect with a sample prepared by reaction of 5,6-dichloro-2-methyl-3(2*H*)-pyridazinone (**6**)[2b] with morpholine, followed by catalytic reduction.[3]

A solution of **2** in ethanol containing sodium ethoxide was heated for 5 h. Careful posttreatment of the reaction mixture allowed isolation of 4-ethoxy-2-methyl-5-morpholino-3(2*H*)-pyridazinone (**8**), 4-hydroxy-2-methyl-5-morpholino-3(2*H*)-pyridazinone (**9**), 4-chloro-5-hydroxy-2-methyl-3(2*H*)-pyridazinone (**10**), and **4** in 80, 5, 2, and 0.05% yields, respectively (Scheme II).

Upon treatment with aqueous sodium hydroxide, the major product, **8**, was easily converted to **9**, which reverted to **8** by ethylation using diethyl sulfate. The minor products, **4** and **10**,[2a] were identical in every respect with authentic samples.

The formation of **4** appears to involve reductive dechlorination of **2** by sodium alkoxide. Occurrence of analogous reductive dechlorination by sodium alkoxide was frequently observed in various extents in 4-chloro-2-substituted-5-(substituted amino)-3(2*H*)-pyridazinones. Thus, the present result provides a novel example of reductive dechlorination in halogeno heterocycles.

Analogously, a series of compounds (**11**–**30**) which have close structural similarity with **8** were prepared from the corresponding 4-chloro-2-alkyl-5-(substituted amino)-3-(2*H*)-pyridazinones. Table I summarizes some synthetic data for these compounds.

Reaction of 4-chloro-5-morpholino-3(2*H*)-pyridazinone (**37**)[4] with allyl chloride in acetone in the presence of potassium carbonate gave 2-allyl-4-chloro-5-morpholino-3(2*H*)-pyridazinone (**31**) in 84% yield (Scheme III). Upon heating **31** with sodium ethoxide in benzene, 2-allyl-4-ethoxy-5-morpholino-3(2*H*)-pyridazinone (**34**) was obtained in 50% yield together with 4-ethoxy-5-morpholino-2-propenyl-3(2*H*)-pyridazinone (**32**, 2%), 4-chloro-5-morpholino-2-propenyl-3(2*H*)-pyridazinone (**33**, 8%), and 2-allyl-5-morpholino-3(2*H*)-pyridazinone (**35**, 4%) which are isolable by column chromatography. The dechlorinated product **35** was alternately prepared by means of catalytic reduction of **37**, followed by allylation. When the analogous reaction was conducted in ethanol, two products, **32** and 2-propenyl-5-morpholino-3(2*H*)-pyridazinone (**36**), were isolated in 25 and 10% yields, respectively.

The presence of the 2-propenyl group in **32**, **33**, and **36**, which arises from base-catalyzed isomerization of the allyl grouping, was confirmed by their NMR spectra. A vicinal coupling constant between vinyl protons in the 2-propenyl group of **32**, **33**, and **36** is 14 Hz in every case, indicating a trans configuration of the 2-propenyl moiety.

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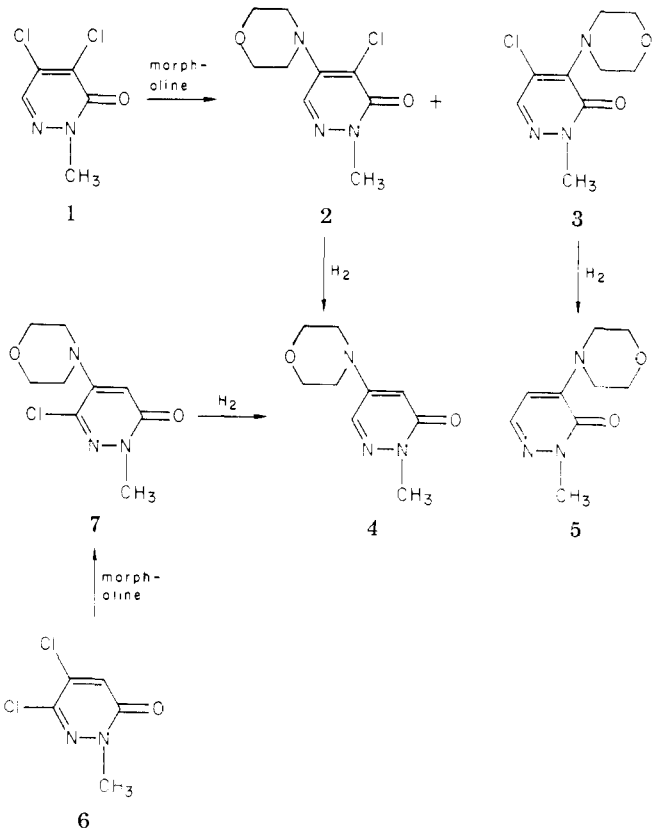
Scheme I



Scheme II

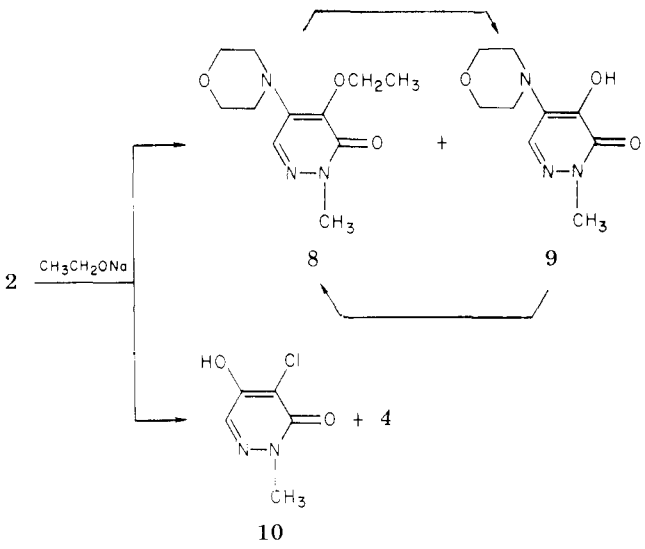
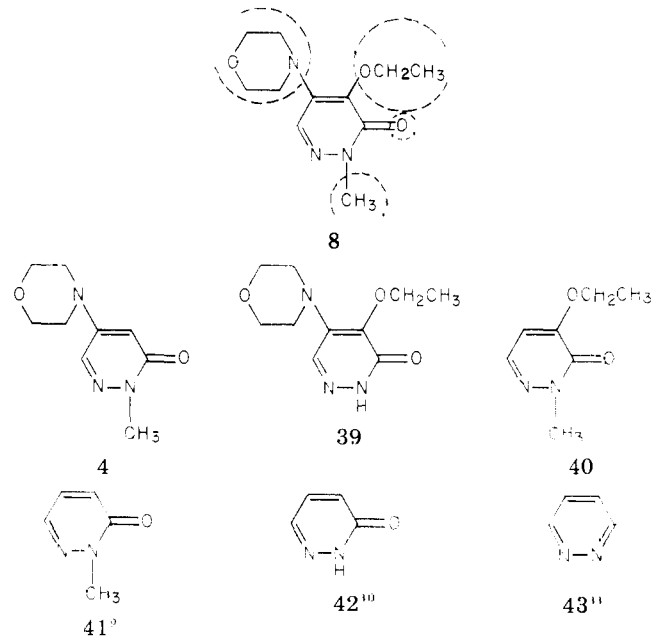


Chart II



flammatory activities. Among the 5-(substituted amino) derivatives tested, compounds **8**, **11**, **14**, and **20** showed analgesic activities comparable to aminopyrine; however, their antiinflammatory activities were weak in comparison with phenylbutazone except for 4-ethoxy-2-methyl-5-morpholino-3(2*H*)-pyridazinone (**8**, see Table I).

Pharmacological activities of **8** were also compared with those of 2-methyl-5-morpholino-3(2*H*)-pyridazinones **21**–**26** possessing various alkoxy groups (except ethoxy) and an allyloxy group at the 4 position. 4-*n*-Propoxy, 4-*n*-butoxy, and 4-(*n*-pentyloxy) derivatives (**22**, **25**, and **26**) showed stronger analgesic activity than **8** and aminopyrine. However, the antiinflammatory activity of these compounds (**22**, **25**, and **26**) was evaluated to be weaker than that of **8**. Replacement of the 2-methyl group in **8** with an ethyl group (**27**), *n*- and isopropyl groups (**28** and **29**), an *n*-butyl group (**30**), and a propenyl group (**32**) resulted in a marked decrease of the activities of the parent compound (**8**). On the other hand, replacment of the 2-methyl group in **8** with an allyl group (**34**) markedly increased the analgesic activity but decreased the antiinflammatory activity. Additionally, the assays of other related derivatives (**1**, **2**, **9**, and **10**) showed no significant effect except for **2**, which had stronger toxicity (see Table I).

On the basis of the above observations, it was concluded that the most interesting compound in a series of 2,4,5-trisubstituted 3(2*H*)-pyridazinones is **8** with respect to a balance of analgesic and antiinflammatory activities and toxicity (Chart II).

Table II lists the analgesic and antiinflammatory activities of compounds in which the functional groups in **8** are eliminated in various extents. These compounds, **4** and **39**–**43**, did not show appreciable activities, indicating that the nature and arrangement of functional groups in the molecule of **8** play a significant role in the receptor-site interactions for the exhibition of analgesic and antiinflammatory activities. The results of detailed pharmacological and clinical evaluation of **8** will be reported in the near future.

Pharmacology. The compounds synthesized by the methods described in the preceding section were tested for analgesic activity by the acetic acid induced stretching method,[5] for antiinflammatory activity using the carrageenan-induced paw edema method,[6] and for acute toxicity (see Experimental Section).

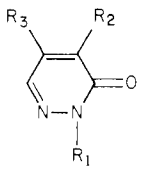
Discussion

Previously we have found that among various alkoxy groups an ethoxy group is the most effective for the exhibition of analgesic activity of 6-alkoxy-4-(dimethylamino)-2-phenyl-3(2*H*)-pyridazinones (B).[1a] On the basis of the above observation, 5-(substituted amino) derivatives **8** and **11**–**20** possessing an ethoxy function at the 4 position were first prepared in order to examine the influence of substituted amino groups on the analgesic and antiin-

Experimental Section

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. The IR (KBr, Nujol) and NMR ($CDCl_3$, Me_2SO-d_6) spectra of all new compounds

Table I. Some Synthetic and Pharmacological Data of 2-Alkyl- or 2-Alkenyl-4-alkoxy-5-(substituted amino)-3(2*H*)-pyridazinones



compd no.	R_1	R_2	R_3	reaction conditions: temp, °C	time, h	yield, %	mp or bp (mmHg), °C	cryst[a] solvent	formula[b]	analgesic act., ED_{50}, mg/kg sc[c]	antiinflam act., % inhibn of edema (mg/kg po): 100	50	25	acute toxicity, LD_{50}, mg/kg ip[c]
1[d]	CH_3	Cl	Cl	100	3	90	90-91	a	$C_7H_8N_2OCl_2$	>100	23.2	8.9[e]		
2	CH_3	Cl	morpholino	100	5	85	133-134	a	$C_9H_{12}N_3O_2Cl$	35 (22.4-54.7)	38.9	32.2	15.2	75 (68-83)
8	CH_3	OCH_2CH_3	morpholino	80	5	80	89-91	b	$C_{11}H_{17}N_3O_3$	41 (24.7-68.1)	55.0	38.8	20.2	700 (642-763)
9	CH_3	OH	morpholino				229-231	c	$C_9H_{13}N_3O_3$	>100	16.6	8.2		
10[f]	CH_3	Cl	OH				260-261	c	$C_5H_5N_2O_2Cl$	>100	5.8[c]			
11	CH_3	OCH_2CH_3	$NHCH_3$	150[g]	20	65	80-81	b	$C_8H_{14}N_2O_2$	55 (37.9-79.8)	31.1	4.5	1.1[e]	400 (353-452)
12	CH_3	OCH_2CH_3	$NH(CH_2)_2CH_3$	150[g]	20	72	105-108 (3)		$C_{10}H_{18}N_2O_2$	72 (40.4-128.2)	38.0	8.0	2.0	
13	CH_3	OCH_2CH_3	$N(CH_3)_2$	80	3	73	36-38	d	$C_9H_{16}N_2O_2$	86 (60.1-123.0)	49.5	30.7	27.5	305 (284-328)
14	CH_3	OCH_2CH_3	$N(CH_2CH_3)_2$	150[g]	24	65	144-149 (5)		$C_{11}H_{20}N_2O_2$	70 (32.4-151.1)	32.5	1.7		
15	CH_3	OCH_2CH_3	$N(CH_2CH{=}CH_2)_2$	80	12	35	130 (2)		$C_{13}H_{20}N_2O_2$	82 (73.7-91.2)	12.9	5.2[e]		
16	CH_3	OCH_2CH_3	thiomorpholino	80	4	92	194 (4)		$C_{11}H_{17}N_3O_2S$	>100	11.8	6.2		
17	CH_3	OCH_2CH_3	piperidino	80	4	90	140-141 (0.05)		$C_{12}H_{20}N_2O_2$	86 (60.1-123.0)	14.1	5.4[e]		
18	CH_3	OCH_2CH_3	1-pyrrolidinyl	150[g]	30	20	69-70	d	$C_{11}H_{18}N_2O_2$	>100	23.0	2.3[e]		
19	CH_3	OCH_2CH_3	*N*-methylpiperazinyl	150[g]	20	55	133-134	d	$C_{12}H_{21}N_3O_2$	82 (73.7-91.2)	12.3	10.2		
20	CH_3	OCH_2CH_3	anilino	150[g]	20	75	oil[h]		$C_{15}H_{18}N_2O_2$	36 (19.1-67.7)	4.9			
21	CH_3	OCH_3	morpholino	70	12	70	72-73	b	$C_{10}H_{16}N_2O_3$	72 (54.1-95.8)	43.4	23.2	11.0	600 (545-660)
22	CH_3	$O(CH_2)_2CH_3$	morpholino	100	2	91	87-89	b	$C_{12}H_{20}N_2O_3$	23 (13.6-38.9)	34.9	32.4	4.5	500 (417-600)
23	CH_3	$OCH(CH_3)_2$	morpholino	85	2	89	oil[h]		$C_{12}H_{20}N_2O_3$	86 (60.1-123.0)	7.2			
24	CH_3	$OCH_2CH{=}CH_2$	morpholino	100	1	80	60-61	d	$C_{12}H_{18}N_2O_3$	90 (62.1-130.5)	17.4	5.2		
25	CH_3	$O(CH_2)_3CH_3$	morpholino	125	1	82	oil[h]		$C_{13}H_{22}N_2O_3$	41 (24.7-68.1)	28.8	2.8[c]		440 (400-484)
26	CH_3	$O(CH_2)_4CH_3$	morpholino	150	1	80	oil[h]		$C_{14}H_{24}N_2O_3$	29 (16.4-49.4)	20.7	2.4		420 (353-500)
27	CH_2CH_3	OCH_2CH_3	morpholino	80	3	75	64-66	d	$C_{12}H_{20}N_2O_3$	95 (66.4 (135.9)	58.4	25.4	8.3	380 (330-437)
28	$(CH_2)_2CH_3$	OCH_2CH_3	morpholino	80	12	62	150-160 (0.46)		$C_{13}H_{24}N_2O_3$	>100	32.4	3.5		
29	$CH(CH_3)_2$	OCH_2CH_3	morpholino	80	12	80	147-149 (0.10)		$C_{13}H_{24}N_2O_3$	>100	22.2	2.1		
30	$(CH_2)_3CH_3$	OCH_2CH_3	morpholino	80	12	78	164-166 (0.15)		$C_{14}H_{26}N_2O_3$	>100	18.3			
32	$CH{=}CHCH_3$	OCH_2CH_3	morpholino	80	10	25	91-92	d	$C_{14}H_{22}N_2O_3$	>100	3.1			
34	$CH_2CH{-}CH_2$	OCH_2CH_3	morpholino	80	8	50	oil[h]	b	$C_{14}H_{22}N_2O_3$	18 (9.6-33.7)	23.5	1.2		550 (458-660)

[a] a = H_2O, b = MeOH-$(Me_2CH)_2O$, c = MeOH, d = $(Me_2CH)_2O$. [b] All compounds were analyzed for C, H, and N. [c] 95% confidence limits in parentheses. [d] Reference 2. [e] A negative number indicates an increased rate of edema compared with a control. [f] Reference 2a. [g] Reacted in a sealed tube. [h] Purified by silica gel column chromatography.

Scheme III

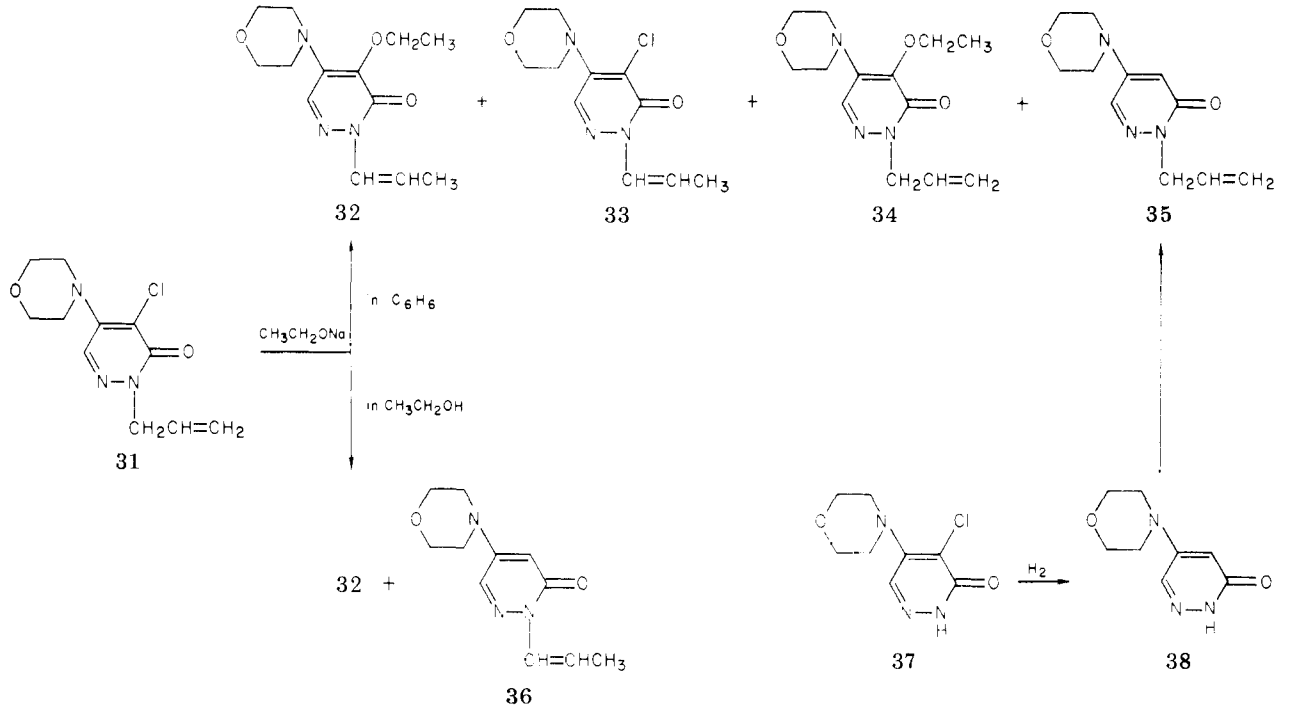
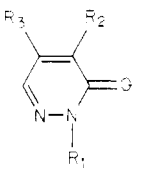


Table II



compd no.	R_1	R_2	R_3	analgesic act., ED_{50}, mg/kg sc[a]	antiinflam act., % inhibn of edema (mg/kg po) 100	50	25	acute toxicity, LD_{50}, mg/kg ip[a]
4	CH_3	H	morpholino	>100	5.6[c]			
39[b]	H	OCH_2CH_3	morpholino	>100	9.2			
40[b]	CH_3	OCH_2CH_3	H	>100	-12.2[c]			
41[d]	CH_3	H	H	65 (49.2-85.8)	4.5			
42[e]	H	H	H	>100	6.3			
43[f] (pyridazine)				>100	2.4[c]			
aminopyrine				46 (26.9-78.7)	48.2	25.0	11.0	420 (351-513)
phenylbutazone				>100	40.6	35.0	18.0	420 (378-467)

[a] 95% confidence limits in parentheses. [b] For synthesis see Experimental Section. [c] A negative number indicates an increased rate of edema compared with a control. [d] Reference 9. [e] Reference 10. [f] Reference 11.

described here were consistent with their structures. Microanalyses were indicated only by the symbols of the elements. Microanalytical results obtained for those elements were within ±0.4 of their theoretical values.

4-Chloro-2-methyl-5-morpholino-3(2*H*)-pyridazinone (2) and 5-Chloro-2-methyl-4-morpholino-3(2*H*)-pyridazinone (3). **A.** A solution of 4,5-dichloro-2-methyl-3(2*H*)-pyridazinone (**1**)[7] (179 g, 1.0 mol) and morpholine (217.5 g, 2.5 mol) in H_2O (1200 mL) was heated under reflux for 5 h and concentrated under reduced pressure. After cooling, the resulting precipitate was collected by filtration, washed with H_2O, and recrystallized from H_2O to give **2** (195 g, 80), mp 133-134 °C. Anal. ($C_9H_{12}N_3O_2Cl$) C, H, N. The filtrate was extracted with 500 mL of $CHCl_3$. After removal of the solvent, the residue was recrystallized from isopropyl ether to give **3** (13.7 g, 6%), mp 101-102 °C. Anal. ($C_9H_{12}N_3O_2Cl$) C, H, N.

B. A mixture of **1** (19.7 g, 0.1 mol), morpholine (21.8 g, 0.25 mol), and toluene (120 mL) was refluxed for 5 h and evaporated under reduced pressure to dryness. The residue was dissolved in H_2O (100 mL) and extracted with $CHCl_3$ (100 mL). After evaporation of the solvent, fractional recrystallization of the residue from isopropyl ether gave **3** (11.5 g, 50%) and **2** (5.7 g, 25%).

2-Methyl-5-morpholino-3(2*H*)-pyridazinone (4). A. A solution of **2** (1.0 g, 0.0044 mol) in EtOH (20 mL) was catalytically reduced in the presence of 10% Pd/C (0.8 g) for 2 h at room temperature. After removal of the catalyst by filtration, the filtrate was concentrated and diluted with H_2O (10 mL). The aqueous solution was made basic with 1 N $NaHCO_3$ and then extracted with $CHCl_3$ (15 mL). After evaporation of the solvent, the residue was recrystallized from isopropyl ether to give **4** (0.4 g, 47%), mp 154-155 °C. Anal. ($C_9H_{13}N_3O_2$) C, H, N.

B. A mixture of 5,6-dichloro-2-methyl-3(2*H*)-pyridazinone (**6**)[2b] (1 g, 0.0056 mol) and morpholine (1.2 g, 0.0138 mol) in EtOH (15 mL) was heated in a sealed tube at 100 °C for 5 h. The reaction mixture was concentrated, diluted with H_2O (15 mL), and extracted with $CHCl_3$. After the solvent was evaporated, the residue was recrystallized from MeOH-isopropyl ether to give 6-chloro-2-methyl-5-morpholino-3(2*H*)-pyridazinone (**7**) (1 g, 78%), mp 127-128 °C. Anal. ($C_9H_{12}N_3O_2Cl$) C, H, N. In a manner similar to the case of method A, **4** was obtained by catalytic dehalogenation in good yield.

2-Methyl-4-morpholino-3(2*H*)-pyridazinone (5). In a manner similar to the preparation of **4**, catalytic dehalogenation of **3** (1 g, 0.0044 mol) gave **5** (0.5 g, 59%), mp 138-139 °C. Anal. ($C_9H_{13}N_3O_2$) C, H, N.

4-Ethoxy-2-methyl-5-morpholino-3(2*H*)-pyridazinone (8) and 4-Hydroxy-2-methyl-5-morpholino-3(2*H*)-pyridazinone (9). **A.** To a solution of Na (46 g, 2 mol) dissolved in EtOH (1600 mL), **2** (229 g, 1 mol) was added in portions. The mixture was refluxed for 5 h and concentrated under reduced pressure. The residue was dissolved in H_2O (1200 mL) and the resulting aqueous alkaline solution was extracted with $CHCl_3$ (1200 mL). The $CHCl_3$ layer was washed with 10% HCl (400 mL) and then H_2O (400 mL) and dried over anhydrous Na_2SO_4. After the solvent was removed by evaporation, the residue was recrystallized from MeOH–isopropyl ether to give **8** (167 g, 70%), mp 89–91 °C. Anal. ($C_{11}H_{17}N_3O_3$) C, H, N. The alkaline mother liquor was neutralized with 10% HCl and cooled at 5 °C. An insoluble substance was collected by filtration and recrystallized from EtOH to give **9** (10.55 g, 5%), mp 229–231 °C. Anal. ($C_9H_{13}N_3O_3$) C, H, N. After the neutral filtrate was acidified with 10% HCl the resulting precipitate was collected and washed with H_2O. Recrystallization from MeOH gave **10**[2a] (3.2 g, 2%). The acidic solution (400 mL), which was first obtained by washing the $CHCl_3$ layer with 10% HCl, was made basic with 20% NaOH (210 mL) and extracted with $CHCl_3$ (300 mL). The $CHCl_3$ solution thus obtained gave additional **8** (24 g, 10%). From the basic mother liquor (about 610 mL), **4** (0.097 g, 0.05%), mp 154–155 °C, was isolated by means of chromatography.

B. A mixture of **8** (10 g, 0.042 mol) and 5% NaOH (100 mL) was heated under reflux for 3 h. The reaction mixture was neutralized with 10% HCl and cooled at 5 °C. The precipitate was recrystallized from EtOH to give **9** (5 g, 57%). To a solution of **9** (1 g, 0.0047 mol) in H_2O (5 mL) containing KOH (0.31 g, 0.0055 mol) was added $(C_2H_5)_2SO_4$ (0.85 g, 0.0055 mol). The reaction mixture was stirred at room temperature for 12 h. An insoluble substance separated out on cooling and was removed by filtration, and the filtrate was concentrated. The residue was dissolved in H_2O (10 mL) and extracted with $CHCl_3$ (10 mL). After the solvent was evaporated, the residue was recrystallized from MeOH–isopropyl ether to give **8** (0.5 g, 44%).

4-Alkoxy-2-alkyl-5-(substituted amino)-3(2*H*)-pyridazinones 11–30. Analogously **11–30** were obtained from the corresponding starting materials under the reaction conditions described in Table I.

2-Allyl-4-chloro-5-morpholino-3(2*H*)-pyridazinone (31). A mixture of 4-chloro-5-morpholino-3(2*H*)-pyridazinone (**37**)[4] (3 g, 0.014 mol), allyl bromide (2.5 g, 0.021 mol), and K_2CO_3 (3.7 g, 0.028 mol) in acetone (50 mL) was refluxed for 4 h with stirring. After removal of the solvent, the residue was dissolved in H_2O (20 mL) and extracted with $CHCl_3$. The $CHCl_3$ layer was concentrated to leave a solid mass which was recrystallized from MeOH–isopropyl ether to give **31** (3 g, 84%), mp 104–105 °C. Anal. ($C_{11}H_{14}N_3O_2Cl$) C, H, N.

4-Ethoxy-5-morpholino-2-propenyl-3(2*H*)-pyridazinone (32), 4-Chloro-5-morpholino-2-propenyl-3(2*H*)-pyridazinone (33), 2-Allyl-4-ethoxy-5-morpholino-3(2*H*)-pyridazinone (34), and 2-Allyl-5-morpholino-3(2*H*)-pyridazinone (35). **A.** A mixture of **31** (1.0 g, 0.0039 mol) and NaOEt (0.1 g, 0.0044 mol) in absolute benzene (20 mL) was refluxed for 4 h. The reaction mixture was concentrated and the residue was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O. After removal of the solvent, an oily residue was chromatographed on silica gel [solvent $CHCl_3$–EtOH (25:1)]. An initial eluant gave **35** (0.04 g, 4%, from MeOH), mp 92–93 °C. Anal. ($C_{11}H_{15}N_3O_2$) C, H, N. The second eluant was further submitted to silica gel chromatography [solvent $CHCl_3$–CH_3COOEt (3:1)] to separate **33** (0.08 g, 8%), mp 111–112 °C, **32** (0.02 g, 2%), mp 91–92 °C, and **34** (0.5 g, 50%, oil).

B. A solution of **37**[4] (1 g, 0.0046 mol) in EtOH (40 mL) was catalytically reduced in the presence of 10% Pd/C (1 g) for 4 h. After an insoluble substance was removed by filtration, the filtrate was concentrated and the residue was recrystallized from H_2O to give 5-morpholino-3(2*H*)-pyridazinone (**38**) (0.5 g, 60%), mp 267–268 °C. Anal. ($C_8H_{11}N_3O_2$) C, H, N. A mixture of **38** (0.5 g, 0.0028 mol), allyl bromide (0.7 g, 0.0058 mol), and K_2CO_3 (1.0 g, 0.0072 mol) in acetone (30 mL) was refluxed for 24 h, evaporated, and extracted with $CHCl_3$ (10 mL). After removal of the solvent, the resulting residue was purified by silica gel chromatography [solvent $CHCl_3$–EtOH (3:1)] to give **35** (0.35 g, 57%).

5-Morpholino-2-propenyl-3(2*H*)-pyridazinone (36) and 32. A solution of **31** (1.7 g, 0.0067 mol) in ethanolic sodium ethoxide [EtOH, 20 mL, and Na metal, 0.46 g (0.02 mol)] was refluxed for 3 h. After evaporation of the solvent, the residue was dissolved in isopropyl ether (20 mL) and cooled at 5 °C. The precipitate thus obtained was collected by filtration and recrystallized from EtOH–isopropyl ether to give **36** (0.14 g, 10%), mp 149–151 °C. Anal. ($C_{11}H_{15}N_3O_2$) C, H, N. The filtrate was concentrated and the residue was purified by means of silica gel chromatography [solvent $CHCl_3$–CH_3COOEt (3:1)] to isolate **32** (0.46 g, 25%).

4-Ethoxy-5-morpholino-3(2*H*)-pyridazinone (39). 2-Benzyl-4-ethoxy-5-morpholino-3(2*H*)-pyridazinone[7] [1.8 g, 0.0057 mol; bp 225–228 °C (3.5 mmHg). Anal. ($C_{20}H_{21}N_3O_3$) C, H, N] in AcOH (35 mL) was catalytically reduced in the presence of 10% Pd/C (2.0 g) under a pressure of 4.6 kg/cm^2 at 60 °C for 36 h. After the solvent was evaporated under reduced pressure, the residue was dissolved in H_2O (20 mL), made basic with 10% Na_2CO_3, and then extracted with $CHCl_3$ (60 mL). The $CHCl_3$ layer was further extracted with 10% aqueous NaOH (25 mL). The alkaline solution was made weakly basic with 20% HCl and then extracted with $CHCl_3$ (100 mL). After removal of the solvent, the residue was recrystallized from $CHCl_3$–isopropyl ether to give **39** (0.4 g, 31%), mp 185–187 °C. Anal. ($C_{10}H_{15}N_3O_3$) C, H, N.

4-Ethoxy-3(2*H*)-pyridazinone (40). A mixture of **1**[2] (18 g, 0.1 mol) and NaOEt (8.8 g, 0.13 mol) in benzene (200 mL) was refluxed for 3 h and evaporated. The residue was dissolved in H_2O (150 mL) and extracted with $CHCl_3$ (200 mL). After evaporation of $CHCl_3$, the oily residue was recrystallized from isopropyl ether to give 5-chloro-4-ethoxy-2-methyl-3(2*H*)-pyridazinone (9.5 g, 50%), mp 34–35 °C. Anal. ($C_7H_9N_2O_2Cl$) C, H, N. A solution of 5-chloro-4-ethoxy-2-methyl-3(2*H*)-pyridazinone (1.0 g, 0.0053 mol) or 6-chloro-4-ethoxy-2-methyl-3(2*H*)-pyridazinone[2b] (1.0 g, 0.0053 mol) in EtOH (20 mL) was catalytically reduced in the presence of 10% Pd/C at 20 °C for 3 h. After filtration of an insoluble substance, the filtrate was concentrated and recrystallized from isopropyl ether to give **40** (0.5 g, 61%), mp 77–78 °C. Anal. ($C_7H_{10}N_2O_2$) C, H, N.

Pharmacological Methods. Analgesic activity was evaluated by the acetic acid induced stretching method.[5] Eight male ddY mice weighing 18–22 g were used in each group. The test compound, suspended in a 1% gum arabic solution, was administered subcutaneously, and 30 min later each mouse received a 0.6% acetic acid solution in a volume of 0.1 mL/10 g of body weight intraperitoneally. The analgesic effect was considered to be positive when a mouse showed no stretching syndrome for the period from 5 to 20 min after the injection of acetic acid, and ED_{50} was calculated by the method of Litchfield and Wilcoxon.[8]

Antiinflammatory activity was examined by the method of Winter et al.[6] Six male Wistar rats weighing 120–150 g were used for each group. Carrageenan (0.1 mL, 1%) was injected subcutaneously into the plantar surface of the hind paw 30 min after oral administration of test compounds suspended in a 1% gum arabic solution. The edema formation was measured 3 h after the injection and compared with that of carrageenan alone and with the test compound for calculation of percent inhibition.

Acute toxicity was expressed as a LD_{50} value calculated by the method of Litchfield and Wilcoxon.[8] It was determined 72 h after an intraperitoneal injection to groups of eight male ddY mice.

Tables I and II summarize the pharmacological results in the above assays.

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Studies on Analgesic Agents. 1.[1a] Preparation of 1,2-Diphenyl-2-(4-substituted 1-piperazinyl)ethanol Derivatives and Structure–Activity Relationships

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The preparation and analgesic activity of a series of the title compounds (**8–55** and **57**) are described. The intermediates, 2-phenyl-2-(1-piperazinyl)acetophenones **5** and **6**, were prepared from benzyl phenyl ketones **3** via their bromides **4**. On reduction, compounds **5** afforded the titled compounds **8–12**, **16**, and **26–48**. Compounds **13–15** and **17–25** were obtained by alkylation or benzylation of 1,2-diphenyl-2-(1-piperazinyl)ethanols **7** derived from **6** by reduction. The reduction of **5** and **6** with metal hydrides predominantly gave the erythro isomers. The erythro isomers were remarkably more active than their threo isomers. The more active members in this series of compounds were **16** and derivatives **35** and **37–44** of *dl-erythro*-1-phenyl-2-(substituted phenyl)-2-[4-(*p*-methoxybenzyl)-1-piperazinyl]ethanol. Compounds **16**, **43**, and **44** were the most active with a potency of about two to three times that of codeine. Racemates **16** and **38** were resolved into their optical isomers and it was found that (−)-**16** and (+)-**38** were more potent than their antipodes. Structure–activity relationships are discussed.

The analgesic activity of lefetamine (**1**) is known to be about one-tenth as potent as that of (-)-morphine.[2] Recently Natsuka et al. reported that a related compound, (*S*)-(+)-1-cyclohexyl-4-(1,2-diphenylethyl)piperazine (**2**), is approximately equipotent to (−)-morphine as an analgesic and that the absolute configuration of its asymmetric carbon is opposite to that of both **1** and (−)-morphine (C^9).[3] It is notable that the replacement of the dimethylamino moiety of **1** by a cyclohexylpiperazinyl group caused such a significant increase in activity. On the other hand, it might be expected that the conformation of two phenyl rings in **1** and **2** also plays an important role for the appearance of the activity. It is assumed that **1** takes an eclipsed conformation in which two phenyl rings are perpendicular to each other.[4] Thus the introduction of a hydroxyl group at position C^2 of **2** to create a new asymmetric center adjacent to the original one might have effects on the conformation of the two phenyl rings leading to altered activity. In fact, Yamakawa had reported that *dl*-1,2-diphenyl-2-(dimethylamino)ethanol showed no analgesic activity by the Haffner method while only the levo form possessed weak activity and that, as a conclusion, the introduction of a hydroxyl group to **1** caused a marked decrease in activity.[5] Therefore, it was deemed of interest to synthesize new types of compounds containing both the piperazinyl and hydroxyl groups—1,2-diphenyl-2-piperazinylethanol derivatives. Based on the above considerations, a number of the title compounds were prepared and tested for analgesic activity in experimental animals. Some of these compounds were found to possess potent activity.

Chemistry. The titled compounds were prepared by the methods shown in Scheme I. Benzyl phenyl ketones **3** used as starting materials were prepared by Grignard reaction of benzyl halides with benzonitriles in ether or by Friedel–Crafts reaction of phenylacetyl chlorides with benzene, toluene, or phenol in good yields. Bromination of **3** with bromine in $CHCl_3$, followed by amination with N-substituted piperazines or piperazine, gave **5** or **6**, respectively, which was reduced by metal hydrides such as $NaBH_4$ and $LiAlH_4$ to give the amino alcohols **8–12**, **16**, and **26–48** or **7** (see Table I). Compounds **13–15** and **17–25** were obtained from **7** by alkylation with alkyl halides or by heating with benzaldehydes in the presence of formic acid.[6]

On acylation with the corresponding acid anhydrides in pyridine at room temperature, the amino alcohols **16** and **38** gave the acyl derivatives **49–51**. For comparison of the analgesic activity, the dehydroxylated compound **57** was prepared by reaction of *N*,*N*-bis(2-chloroethyl)(1,2-diphenylethyl)amine **56** with (*p*-methoxybenzyl)amine in DMF (see Scheme II).[3] On reduction of **5** or **6** with metal hydrides as described above, erythro isomers were obtained predominantly according to Cram's rule.[7] Diastereoisomers were separated by recrystallization of the dihydrochloride salts of the amino alcohol from 80% EtOH or by column chromatography of the free base on silica gel (3% MeOH-$CHCl_3$). The stereochemical assignments were confirmed by NMR and in particular by the chemical shift and the coupling constant of the C^1 proton (-OCH=). The erythro isomers showed a doublet at δ 5.25–5.35 (J = 4.4–5.0 Hz) and the threo isomers showed a doublet at δ 4.95–5.05 (J = 10.1–10.3 Hz) which corresponded with those reported by Munk et al.[8] for 1,2-diphenyl-2-aminoethanol derivatives. The total yield of the titled compounds from **3** was 30–40%.

Optical resolution of racemic compounds **16** and **38** was accomplished by the formation of salts with (+)-2'-

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