= 9 Hz, H-12), 9.31 (s, 1, H-7). Anal. ($C_{20}H_{15}N_2ClO_4 \cdot 0.5H_2O$) C, H, N. Cl.

10-Methyl-20(*RS*)-camptothecin (32). 5-Methyl-2-nitrobenzaldehyde (**14c**) was prepared by the oxidation of 5-methyl-2-nitrobenzyl alcohol.[23] The reduction of **14c** using $FeSO_4$ and NH_4OH in hot aqueous EtOH yielded the unstable amino aldehyde **14d**, which was used as such in the Friedlander condensation.

The oxytricyclic ketone **5** (130 mg, 0.5 mmol) and the 5-methyl-2-aminobenzaldehyde (**14d**) (560 mg) in toluene (60 mL) were refluxed for 0.5 h. Acetic acid (1 mL) and *p*-TsOH·H_2O (35 mg) were added, and refluxing was continued for an additional 5 h. The solvent was removed in vacuo, and warm Et_2O (30 mL) was added. The collected residue was recrystallized from $CHCl_3$/MeOH/EtOAC to yield **32** (102 mg, 57%); mp 278–281 °C; IR (KBr) 3460, 2980, 1740 (lactone), 1655 (pyridone), 1590, 1550, 1470, 1450, 1370, 1260, 1240, 1160, 1050 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 0.89 (t, 3, J = 7 Hz, H-18), 1.87 (q, 2, H-19), 2.54 (s, 3, 10-CH_3), 5.24 (s, 2, H-17), 5.42 (s, 1, H-5), 7.31 (s, 1, H-14), 7.69 (d, 1, J = 8.6 Hz, H-11), 7.86 (s, 1, H-9), 8.05 (d, 1, J = 8.6 Hz, H-12), 8.55 (s, 1, H-7). Anal. ($C_{21}H_{18}N_2O_4 \cdot 0.25H_2O$) C, H, N.

10,11-Dihydroxy-20(*RS*)-camptothecin Hydrobromide (34) and 10,11-Dihydroxy-20(*RS*)-camptothecin (35). 4,5-Bis(benzyloxy)-2-nitrobenzaldehyde (**15a**) was converted to the nitro acetal **15b**, which was then reduced to the amino acetal **15c** with Na_2S by well-established procedures. Both of these intermediates could not be purified and were used as such for further reactions.

A solution of the crude bis(benzyloxy) amino acetal **15c** (400 mg) and oxytricyclic ketone **5** (132 mg, 0.5 mmol) in toluene (60 mL) was refluxed for 8 h. The mixture was filtered and the intermediate 10,11-bis(benzyloxy) product **33** was collected as pure material (220 mg, 81%): mp 276 °C; IR (KBr) 3440, 1740 (lactone), 1650 (pyridone), 1590, 1490, 1440, 1380, 1250, 1140, 1100 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 0.88 (t, 3, J = 7 Hz, H-18), 1.86 (m, 2, H-19), 5.22 (s, 2, H-17), 5.34 (s, 2, 10-OC$H_2C_5H_5$), 5.39 (s, 2, 11-OC$H_2C_6H_5$), 5.41 (s, 2, H-5), 6.50 (s, 1, OH), 7.25 (s, 1, H-14), 7.35-7.65 (m, 12, H-9, H-12, 10- and 11-OC$H_2C_6H_5$), 8.44 (s, 1, H-7).

The bis(benzyloxy)camptothecin derivative **33** (130 mg, 0.23 mmol) was gently refluxed for 2 h in 24% aqueous HBr (50 mL). The acid was removed in vacuo and the residue was dissolved in hot MeOH (50 mL). Ether (50 mL) was added and the powdery yellow 10,11-dihydroxy-20(*RS*)-camptothecin hydrobromide (**34**) was collected (122 mg, 77%): mp >300 °C. Anal. ($C_{20}H_{17}N_2O_6Br \cdot 0.5H_2O$) C, H, N, Br.

The dihydroxy hydrobromide salt **34** (110 mg, 0.23 mmol) was suspended in water (10 mL). Sodium hydroxide (0.1 N, 7.2 mL) was added, and the mixture was stirred until a clear solution resulted. Acidification to slightly acid pH using 5 *N* HCl gave a suspension, which was centrifuged after 1 h. The supernatant liquid was decanted and the process repeated with additional water (20 mL). The residue was dried to give free base **35** (78 mg, 74%): mp >300 °C; IR (KBr) 3490, 3000 (b), 1740 (lactone), 1645 (pyridone), 1590, 1460, 1385, 1265, 1190, 1150 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 0.88 (t, 3, J = 7 Hz, H-18), 1.87 (q, 2, H-19), 5.20 (s, 2, H-17), 5.42 (s, 2, H-5), 7.35 (s, 1, H-14), 7.44 (s, 1, H-9), 7.52 (s, 1, H-12), 8.51 (s, 1, H-7). Anal. Calcd for $C_{20}H_{16}N_2O_6$: 380.1008. Found: 380.1007. ($C_{20}H_{16}N_2O_6 \cdot 0.75H_2O$) C, H, N.

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Registry No. (±)-**5**, 102978-40-5; **10a**, 56670-20-3; **10c**, 109466-84-4; **10d**, 98276-57-4; **11d**, 109466-82-2; **11b**, 109466-83-3; **12a**, 109466-87-7; **12b**, 109466-88-8; **12d**, 59236-38-3; **13a**, 109466-91-3; **13b**, 109466-92-4; **14a**, 6228-86-0; **14b**, 20028-53-9; **14c**, 5858-28-6; **14d**, 109467-00-7; **15a**, 18002-41-0; **15b**, 109467-02-9; **15c**, 109467-03-0; (±)-**16**, 109581-95-5; (±)-**17**, 109581-96-6; (±)-**18**, 109581-97-7; (±)-**19**, 109466-89-9; (±)-**20**, 109466-90-2; (±)-**22**, 109466-93-5; (±)-**23**, 109466-94-6; (±)-**24**, 109466-95-7; (±)-**25**, 109466-96-8; (±)-**26**, 109466-97-9; (±)-**27**, 109466-98-0; (±)-**28**, 109494-80-6; (±)-**29**, 109494-81-7; (±)-**30**, 109466-99-1; (±)-**31**, 109581-98-8; (±)-**32**, 109467-01-8; (±)-**33**, 109467-04-1; (±)-**34**, 109467-05-2; (±)-**35**, 109494-82-8; (±)-**36**, 104155-88-6; 4-(trifluoromethyl)-2-nitrobenzenediazonium chloride, 109466-85-5; 4-amino-3-nitrobenzotrifluoride, 400-98-6; formaldoxime, 75-17-2; 4-(trifluoromethyl)-2-nitrobenzaldehyde oxime, 109466-86-6; aminoguanidine bicarbonate, 2582-30-1; 2-aminoisobutyric acid, 62-57-7.

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Synthesis and Structure–Activity Relationships of 1-Substituted 4-(1,2-Diphenylethyl)piperazine Derivatives Having Narcotic Agonist and Antagonist Activity[1]

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Received March 30, 1987

Racemates and enantiomers of 1-substituted 4-[2-(3-hydroxyphenyl)-1-phenylethyl]piperazine derivatives (**3**–**18**) were synthesized, and their analgesic and other pharmacological activities and structure–activity relationships were investigated. The *S*-(+) enantiomers of **2a**, **5**, **7**, **9**, **10**, and **15**–**18** had a stronger analgesic activity than their *R*-(−) enantiomers; analgesic activity of the strongest one [(*S*)-(+)-**10**] was 105 times as potent as that of morphine. The *S*-(+) enantiomers of these compounds had the opposite configuration to that of morphine with respect to its (C-9) asymmetric center but the same configuration to that of the tyrosine residue of Met^5-enkephalin. The *R*-(−) enantiomers of **16** and **18** showed narcotic antagonist activity, but the *S*-(+) enantiomers did not. (*R*)-(−)-**18** had analgesic and narcotic antagonist activities comparable to pentazocine but showed no significant physical dependence liability. From these results, it is suggested that these compounds show an uncommon enantioselectivity in comparison with morphine and its surrogates, and belong to a new series of compounds having a potent analgesic activity.

Previously, this laboratory found that (±)-1-cyclohexyl-4-(1,2-diphenylethyl)piperazine (**1**) (MT-45) has a central analgesic activity comparable to that of morphine.[2] The analgesic activity of the compound is predominantly

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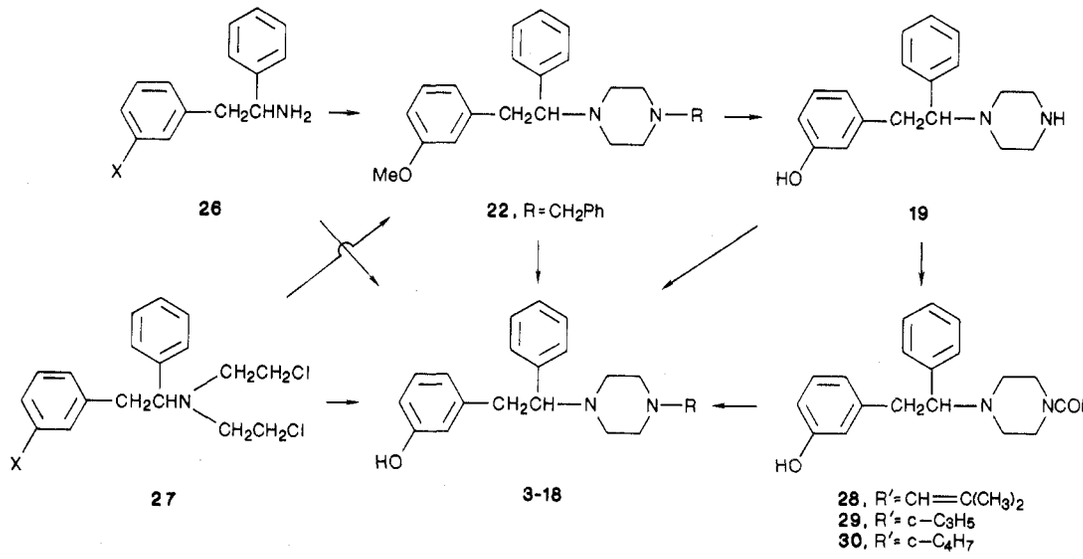
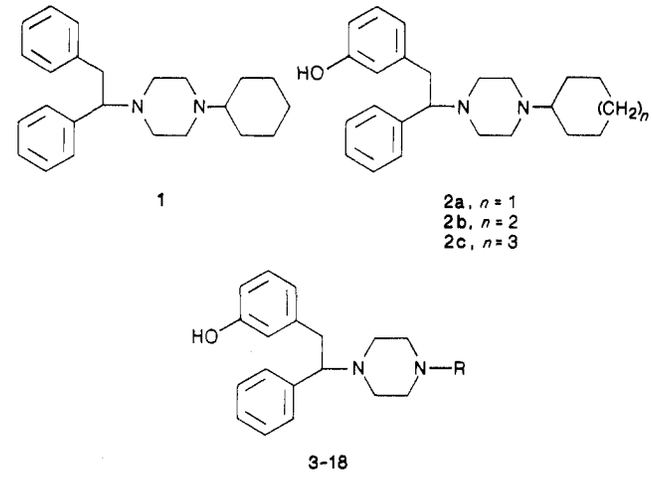
Scheme I



due to the *S*-(+) enantiomer, although the *R*-(−) enantiomer also has such activity at $^1/_{20}$ to $^1/_{30}$ of the level of the *S*-(+) enantiomer. However, the *S*-(+) enantiomer showed physical dependence liability (ED_{50} for the jumping test = 2.5 mg/kg, sc). Various aspects of the pharmacological properties of **1**, which are somewhat different from those of morphine, have been reported by us.[3] Morphine, enkephalin, and their analogues have commonly a tyramine moiety in their molecules, which appears to be related to the opiate–receptor interaction.[4] Since **1** also has the partial structure of tyramine in the molecule, the chemical structures of **1**, morphine, and Met[5]-enkephalin were compared, and various structural modifications were investigated to find a nonnarcotic analgesic.

Most potent analgesics with a morphine-like structure have an addictive effect as well as an analgesic effect. For the purpose of separating the drug dependency of morphine-like analgesics from the analgesic effect, two strategies are generally taken into consideration. Firstly, a narcotic antagonist group, or potential group from which such an effect would be expected, is introduced at the basic nitrogen atom in the morphine-like molecule, to furnish a narcotic antagonist with analgesic properties. Such cases include nalbuphine, pentazocine, butorphanol, and buprenorphine.[5] Secondly, a racemic compound having an analgesic effect is resolved into its corresponding enantiomers, and an enantiomer without physical dependency is used as the analgesic agent. Benzomorphan derivatives are one such case.[6] In the case of **1**, the weaker *R*-(−) enantiomer did not show any physical dependence liability in animal experiments (inactive in the jumping test). We therefore considered that nonnarcotic, strong analgesics might be derived from (*R*)-(−)-**1**.

Chart I



The possible sites in the structure of **1** for substitution by certain substituents are as follows: substitution on the 1- and 2-phenyl groups and at N-1 of the piperazinyl group (Chart I). Effects of substituents on the phenyl rings of **1** have been reported in a previous paper.[7] Compounds **2a–c** having a hydroxyl group at the meta position of the 2-phenyl group (Chart I) showed the most potent activity. In the present study, we tried another approach to modify the chemical structure of **1**, in which the 1-phenyl group and the 2-(*m*-hydroxyphenyl) group were generally kept constant, while various substituents were introduced into N-1 of the piperazinyl group, thus yielding compounds **3–18**. The pharmacological actions of these compounds were then examined, and the results showed that it was

(1) This work was presented in part (a) at the 3rd Symposium on Medicinal Chemistry, Osaka, Nov. 1981; Abstr, p 54 and (b) at the 1981 International Narcotic Research Conference, Kyoto, July 26–30, 1981 (In *Advances in Endogenous and Exogenous Opioids: Proceedings of the International Narcotic Research Conference*; Takagi, H., Simon, E. J., Ed.; Kodansha Ltd.: Tokyo, 1981; p 399).

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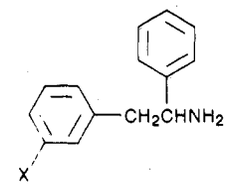
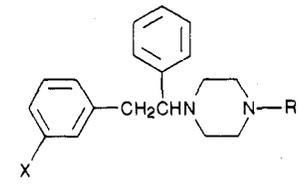
Table I. 1,2-Diphenylethylamine Derivatives



compd	X	salt	conf[a]	mp, °C	$[\alpha]^t_D$, deg (c, t)[b]	recrystn solvent	formula[c]
(+)-**26b**	OH	base	*S*	133–135	+54.2 (1.00, 24)	AcOEt	$C_{14}H_{15}NO$
(−)-**26b**	OH	base	*R*	132–134	−54.3 (1.00, 25)	EtOH–*n*-hexane	$C_{14}H_{15}NO$
(+)-**26c**	OMe	HCl	*S*	244–248	+86.5 (1.50, 26)	EtOH	$C_{15}H_{17}NO{\cdot}HCl$
		$^1/_2$(+)-DBT[d]		145–155	+127.0 (1.50, 27)	95% EtOH	$C_{15}H_{17}NO{\cdot}^1/_2C_{18}H_{14}O_8$
(−)-**26c**	OMe	HCl	*R*	244–248	−86.6 (1.50, 26)	EtOH	$C_{15}H_{17}NO{\cdot}HCl$
		$^1/_2$(−)-DBT		143–148	−128.0 (1.50, 26)	EtOH	$C_{15}H_{17}NO{\cdot}^1/_2C_{18}H_{14}O_8$
(±)-**26d**	NO_2	HCl		230–235		EtOH	$C_{14}H_{14}N_2O_2{\cdot}HCl$
(−)-**26d**	NO_2	$^1/_2$(−)-DBT	*R*		−92.7 (1.00, 27)	95% EtOH	$C_{14}H_{14}N_2O_2{\cdot}^1/_2C_{18}H_{14}O_8$

[a] Absolute configuration. [b] Solvent: MeOH. [c] All compounds were analyzed for C, H, N, and halogen; analytical results were within ±0.4% of the theoretical values. [d] DBT: dibenzoyltartaric acid.

Table II. 1-Substituted 4-(1,2-Diphenylethyl)piperazine Derivatives



compd	X	R	salt	conf[a]	procedure[b]	mp, °C	recrystn solvent	yield, %	formula[c]
(±)-**19**	OH	H	2HCl		C	214–215	EtOH	86	$C_{18}H_{22}N_2O{\cdot}2HCl$
(+)-**19**	OH	H	2HCl	*S*	C	227–232	EtOH	66	$C_{18}H_{22}N_2O{\cdot}2HCl$
(−)-**19**	OH	H	2HCl	*R*	C	227–232	EtOH	80	$C_{18}H_{22}N_2O{\cdot}2HCl$
			base			157–158	*i*-PrOH		$C_{18}H_{22}N_2O$
(±)-**20**	OMe	H	2HCl		D	214–218	EtOH	70	$C_{19}H_{24}N_2O{\cdot}2HCl{\cdot}^3/_2H_2O$
(−)-**20**	OMe	H	2HCl	*R*	D	216–221	MeOH	88	$C_{19}H_{24}N_2O{\cdot}2HCl$
(±)-**21**	OMe	Me	2HCl		A	224–227	EtOH	18	$C_{20}H_{26}N_2O{\cdot}2HCl$
(±)-**22**	OMe	$CH_2C_6H_5$	2HCl		B	211–214	EtOH	71	$C_{26}H_{30}N_2O{\cdot}2HCl$
(−)-**22**	OMe	$CH_2C_6H_5$	2HCl	*R*	A	179–183	EtOH–Et_2O	60	$C_{26}N_{30}N_2O{\cdot}2HCl{\cdot}^1/_2H_2O$
(−)-**23**	NO_2	c-C_6H_{11}	2HCl	*R*	A	233–238	MeOH	81	$C_{24}H_{31}N_3O_2{\cdot}2HCl$
(−)-**24**	NH_2	c-C_6H_{11}	$^5/_2$maleate[d]	*R*	G	141–143	EtOH	59	$C_{24}H_{33}N_3{\cdot}^5/_2(C_4H_4O_4){\cdot}^1/_2H_2O$
(−)-**25**	OMe	c-C_6H_{11}	2HCl	*R*	H	243–247	MeOH	32	$C_{25}H_{34}N_2O{\cdot}2HCl$
					A	243–247		53	
			2(−)-NTA[e]		H	150–151	95% EtOH		$C_{25}H_{34}N_2O{\cdot}2(C_{10}H_{10}N_2O_7)$
(±)-**28**	OH	$COCH{=}C(CH_3)_2$	base		F	186–187	MeOH	89	$C_{23}H_{28}N_2O_2$
(−)-**28**	OH	$COCH{=}C(CH_3)_2$	base	*R*	F	134–136	*i*-PrOH	90	$C_{23}H_{28}N_2O_2$
(±)-**31**	OMe	2-$MeOC_6H_4$	2HCl		B	225–228	EtOH	41	$C_{26}H_{30}N_2O_2{\cdot}2HCl{\cdot}C_2H_5OH$

[a] Absolute configuration. [b] Capital letters refer to the procedures in the Experimental Section. [c] See footnote *c* in Table I. [d] Mass spectrum, m/z 363 (M^+). [e] NTA: 2′-nitrotartranilic acid.

possible to obtain a compound having the desirable properties for which we were aiming. In the present paper, the synthesis and analgesic activity of such compounds are reported, and structure–activity relationships (SARs) are discussed.

Chemistry

Compounds **2a**, **3–25**, and **31** were synthesized by the routes shown in Scheme I. Thus, the racemats of **3–18** were synthesized from 1,2-diphenylethylamines (**26**) and *N*,*N*-bis(2-chloroethyl)-1,2-diphenylethylamines (**27**) according to the methods previously reported.[2] Some of the compounds were obtained by cleavage of the ether linkage of methoxy analogues with hydrobromic acid.[7] *N*-[2-(3-Hydroxyphenyl)-1-phenylethyl]piperazine (**19**) was prepared from **26c** via the *N*-benzyl derivative **22** by the catalytic reduction and the demethylation with aqueous hydrobromide. Compounds **15**, **16**, and **18** were synthesized from **19** via the *N*-acyl derivatives **29**, **30**, and **28**, respectively, by reduction with sodium bis(2-methoxyethoxy)aluminum hydride or lithium aluminum hydride.

The racemic compounds **2a** and **3–18** were resolved completely with (−)- or (+)-2′-nitrotartranilic acid, or partly with (−)- or (+)-dibenzoyltartaric acid, into their enantiomers. Racemate **26** was resolved with these compounds into the enantiomers [(+)-**26** and (−)-**26**] and then enantiomers of **2a**, **3–5**, **7**, **9**, **10**, **15–20**, and **22–25** were also prepared from (+)-**26** or (−)-**26**. Compounds thus obtained are listed in Tables I–IV. The enantiomeric purity of (*R*)-(−)-**18** was examined by Nobuhara et al.[8] on high-performance liquid chromatography using a β-cyclodextrin-containing mobile phase; no (+) enantiomer was detected. As the specific rotations of (*R*)-(−)-**18**·2HCl and (*S*)-(+)-**18**·2HCl were equal in magnitude but opposite in sign, (*S*)-(+)-**18**·2HCl was proved to be enantiomerically pure. Accordingly, it was deduced that the enantiomers

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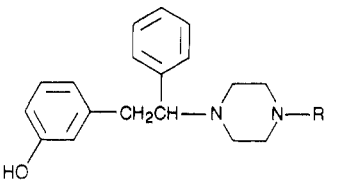
Table III. 1-Substituted 4-[2-(3-Hydroxyphenyl)-1-phenylethyl]piperazine Derivatives



compd	R	salt	conf[a]	procedure[b]	mp, °C	recrystn solvent	yield, %	formula[c]
(±)-3	Me	2HCl		C	251–254 dec	MeOH	52	$C_{19}H_{24}N_2O\cdot2HCl$
(+)-3	Me	2HCl	*S*	C	259–260	MeOH	55	$C_{19}H_{24}N_2O\cdot2HCl$
(−)-3	Me	2HCl	*R*	C[d]	259–260	MeOH	53	$C_{19}H_{24}N_2O\cdot2HCl$
(±)-4	Et	2HCl		C	216.5–218	MeOH	55	$C_{20}H_{26}N_2O\cdot2HCl$
(−)-4	Et	2HCl	*R*	E	231–232	MeOH	52	$C_{20}H_{26}N_2O\cdot2HCl$
(±)-5	*n*-Pr	2HCl		C	212–214	EtOH	60	$C_{21}H_{28}N_2O\cdot2HCl\cdot{}^1/_2H_2O$
(−)-5	*n*-Pr	2HCl	*R*	E	229–233	MeOH	51	$C_{21}H_{28}N_2O\cdot2HCl$
(±)-6	$(CH_2)_4CH_3$	2HCl		E	226–230	MeOH	56	$C_{23}H_{32}N_2O\cdot2HCl$
(±)-7	$CH_2C_6H_5$	2HCl		A	226–229	H_2O–MeOH	54	$C_{25}H_{28}N_2O\cdot2HCl$
(−)-7	$CH_2C_6H_5$	2HBr	*R*	C	193–196	EtOH	84	$C_{25}H_{28}N_2O\cdot2HBr$
(±)-8	$CH_2CH_2C_6H_5$	2HBr		C	235–236	MeOH	55	$C_{26}H_{30}N_2O\cdot2HBr$
(±)-9	C_6H_5	2HBr		C	240–245	MeOH	64	$C_{24}H_{26}N_2O\cdot2HBr\cdot{}^1/_2H_2O$
(−)-9	C_6H_5	2HCl	*R*	C	177–180	MeOH	60	$C_{24}H_{26}N_2O\cdot2HCl$
(±)-10	2-$MeOC_6H_4$	2HCl		B	185–188	MeOH	22[e]	$C_{25}H_{28}N_2O_2\cdot2HCl\cdot{}^1/_2H_2O$
(+)-10	2-$MeOC_6H_4$	2HCl	*S*	A	194–201	MeOH	20	$C_{25}H_{28}N_2O_2\cdot2HCl$
(−)-10	2-$MeOC_6H_4$	2HCl	*R*	A	194–200	MeOH	24	$C_{25}H_{28}N_2O_2\cdot2HCl$
(±)-11	3-$MeOC_6H_4$	2HCl		B	190–195	MeOH	15[e]	$C_{25}H_{28}N_2O_2\cdot2HCl$
(±)-12	4-$MeOC_6H_4$	2HCl		B	187–191	MeOH	20[e]	$C_{25}H_{28}N_2O_2\cdot2HCl$
(±)-13	2-HOC_6H_4	2HBr		C	219–224	MeOH	65	$C_{24}H_{26}N_2O_2\cdot2HBr$
(±)-14	2-ClC_6H_4	HCl		B	202–205	MeOH	20[e]	$C_{24}H_{25}ClN_2O\cdot HCl\cdot{}^1/_2H_2O$
(±)-15	CH_2-c-Pr	2HCl		F	207–209	EtOH	25[f]	$C_{22}H_{28}N_2O\cdot2HCl\cdot{}^1/_2H_2O$
(−)-15	CH_2-c-Pr	2HCl	*R*	F	210–214	EtOH	26[g]	$C_{22}H_{28}N_2O\cdot2HCl$
(±)-16	CH_2-c-Bu	2HCl		F	228–232	EtOH	21[f]	$C_{23}H_{30}N_2O\cdot2HCl$
(+)-16	CH_2-c-Bu	2HCl	*S*	F	230–234	EtOH	18[h]	$C_{23}H_{30}N_2O\cdot2HCl\cdot{}^1/_2H_2O$
(−)-16	CH_2-c-Bu	2HCl	*R*	F	230–234	EtOH	15[g]	$C_{23}H_{30}N_2O\cdot2HCl\cdot{}^1/_2H_2O$
(±)-17	$CH_2CH{=}CH_2$	2HCl		B	216–219	MeOH	22	$C_{21}H_{26}N_2O\cdot2HCl$
(−)-17	$CH_2CH{=}CH_2$	2HCl	*R*	E	221–223	MeOH	33	$C_{21}H_{26}N_2O\cdot2HCl$
(±)-18	$CH_2CH{=}C(CH_3)_2$	2HCl[i]		F	221–225 (241–242 dec[j])	MeOH	72[f]	$C_{23}H_{30}N_2O\cdot2HCl$
(+)-18	$CH_2CH{=}C(CH_3)_2$	2HCl[i]	*S*	H	220–224 (228.5–230 dec[j])	EtOH	22	$C_{23}H_{30}N_2O\cdot2HCl$
				F	228.5–230 dec[j]		75[h]	
		2(+)-NTA[k]		H	126.5–128	EtOH		$C_{23}H_{30}N_2O\cdot2(C_{10}H_{10}N_2O_7)$
(−)-18	$CH_2CH{=}C(CH_3)_2$	2HCl[i]	*R*	H	221–224 (228.5–230 dec[j])	EtOH	28	$C_{23}H_{30}N_2O\cdot2HCl$
				F	228.5–230 dec[j]		76[g]	
		2(−)-NTA		H	126.5–128	EtOH		$C_{23}H_{30}N_2O\cdot2(C_{10}H_{10}N_2O_7)$
(+)-2a	c-C_6H_{11}[l]	2HCl[i]	*S*	H	275–280 dec (283–284[j])	MeOH	23	$C_{24}H_{32}N_2O\cdot2HCl$
				A	275–280 dec		37	
		2(+)-NTA		H	157–158	95% EtOH		$C_{24}H_{32}N_2O\cdot2(C_{10}H_{10}N_2O_7)$
(−)-2a	c-C_6H_{11}	2HCl[i]	*R*	H	275–280 dec (283–284[j])	MeOH	32	$C_{24}H_{32}N_2O\cdot2HCl$
				A	275–280 dec		41	
		2(−)-NTA[k]		H	157–158	95% EtOH		$C_{24}H_{32}N_2O\cdot2(C_{10}H_{10}N_2O_7)$

[a] Absolute configuration. [b] See footnote *b* in Table II. [c] See footnote *c* in Table I. [d] Starting material, (−)-**21** (crude), was prepared from (−)-**26c** (procedure A). [e] Based on **27a** (X = OMe)·HCl. [f] Based on (±)-**19**. [g] Based on (−)-**19**. [h] Based on (+)-**19**. [i] See ref 10. [j] Melting points (uncorrected) taken in a capillary. [k] NTA: 2′-nitrotartranilic acid. [l] Cyclohexyl.

Scheme II

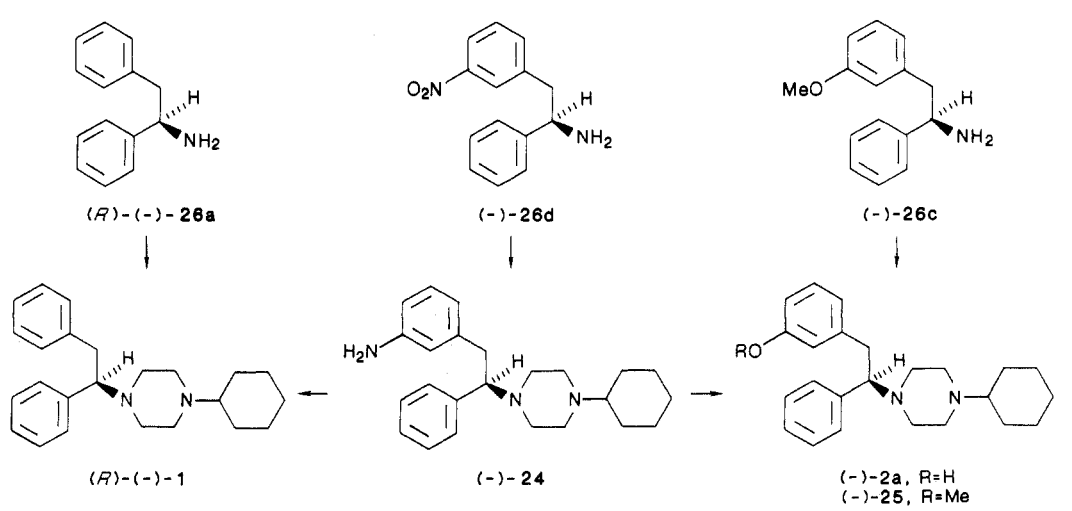


Table IV. Data of Optical Rotation

compd	salt	procedure[a]	$[\alpha]^t_D$, deg (c, t)[b]
(+)-**2a**	2HCl[c]	H	+51.5 (0.55, 27)
		A	+51.6 (0.55, 26)
	2(+)-NTA[d]	H	+63.8 (2.00, 32)
(−)-**2a**	2HCl[c]	H	−51.6 (0.55, 28)
		A	−51.5 (0.55, 26)
	2(−)-NTA	H	−63.9 (1.99, 30)
(+)-**3**	2HCl	C	+64.5 (0.50, 26)
(−)-**3**	2HCl	C	−64.6 (0.50, 25)
(−)-**4**	2HCl	E	−58.3 (0.50, 28)
(−)-**5**	2HCl	E	−54.8 (0.50, 29)
(−)-**7**	2HBr	C	−37.5 (1.00, 28)
(−)-**9**	2HCl	C	−48.3 (0.34, 26)
(+)-**10**	2HCl	A	+44.6 (0.50, 27)
(−)-**10**	2HCl	A	−44.8 (0.50, 27)
(−)-**15**	2HCl	F	−59.9 (1.50, 24)
(+)-**16**	2HCl	F	+57.5 (1.50, 24)
(−)-**16**	$2HCl \cdot {}^1/_2H_2O$	F	−57.3 (1.50, 24)
(−)-**17**	2HCl	E	−64.0 (1.00, 23)
(+)-**18**	2HCl[c]	H	+60.2 (2.00, 28)
		F	+60.3 (2.00, 22)
	2(+)-NTA	H	+65.3 (2.00, 26)
(−)-**18**	2HCl[c]	H	−60.1 (2.00, 29)
		F	−60.3 (2.00, 27)
	2(−)-NTA	H	−65.5 (2.00, 28)
(+)-**19**	2HCl	C	+69.9 (0.50, 28)
(−)-**19**	2HCl	C	−70.1 (1.00, 28)
	base		−96.2 (1.00, 22)
(−)-**20**	2HCl	D	−69.5 (1.00, 26)
(−)-**22**	$2HCl \cdot {}^1/_2H_2O$	A	−45.2 (1.00, 28)
(−)-**23**	2HCl	A	−4.8 (1.00, 29)
(−)-**24**	${}^5/_2$maleate$\cdot {}^1/_2H_2O$	G	−13.2 (1.00, 26)
(−)-**25**	2HCl	H	−49.5 (0.50, 29)
		A	−49.4 (0.50, 27)
	2(−)-NTA	H	−62.0 (2.00, 26)
(−)-**28**	base	F	−31.3 (1.00, 29)

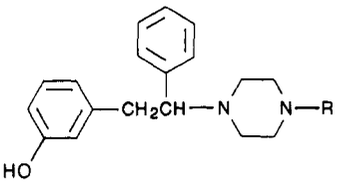
[a] See footnote *b* in Table II. [b] Solvent: MeOH. [c] See ref 10. [d] NTA: 2′-nitrotartranilic acid.

prepared from (+)- or (−)-**26c** in a manner nearly similar to the preparation of (*R*)-(−)-**18** were enantiomerically pure.

Determinations of the absolute configurations of enantiomers of **2a**, **3–5**, **7**, **9**, **10**, and **15–19** were carried out by the following synthetic procedures and by optical rotatory dispersion (ORD). Determination of the absolute configuration of (−)-2-(3-methoxyphenyl)-1-phenylethylamine [(−)-**26c**] is shown in Scheme II: (−)-1,2-diphenylethylamine [(−)-**26a**] and (−)-**1** have the *R* configuration,[2,9] and correlation of (−)-**26c** and (−)-**1** was attempted. (−)-1-Cyclohexyl-4-[2-(3-aminophenyl)-1-phenylethyl]piperazine [(−)-**24**] was derived from (−)-2-(3-nitrophenyl)-1-phenylethylamine [(−)-**26d**]. (−)-1-Cyclohexyl-4-[2-(3-methoxyphenyl)-1-phenylethyl]piperazine [(−)-**25**] and (−)-**1** were prepared by methanolysis and decomposition, respectively, of the diazonium derivatives prepared from (−)-**24**. As (−)-**1** had the *R* configuration, (−)-**24**, (−)-**25**, and (−)-**26d** were proved to be the *R* configuration. Compound (−)-**25** was derived from (−)-**26c**. Therefore, the absolute configuration of (−)-**26c** was proved to be the *R* configuration, and thus the compounds **2a**, **3–5**, **7**, **9**, **10**, and **15–19** obtained from (−)-**26c** by the routes shown in Scheme I were proved to be the *R* configuration (refer to Table III). As shown in Table V, the ORD of (−)-**26c** and (*R*)-(−)-**26a** showed negative plain curves, so that the absolute configuration of (−)-**26c** was assigned to the *R* configuration. The ORD of (−)-**2a**, (−)-**18**, and (*R*)-(−)-**1** showed negative plain curves, so that the absolute configurations of these compounds were assigned to the *R* configuration.

(9) Nakazaki, M.; Mita, I.; Toshioka, N. *Bull. Chem. Soc. Jpn.* **1963**, *36*, 161.

Chart II. Analgesic Potency Order in Mice: Tail-Flick Test (Molar Basis, Sc)



(1) R = H, alkyl
n-$C_5H_{11} > n$-Pr $\geq$ M*[b] $\gg$ Me > Et, H

(2) R = cycloalkyl[a]
c-$C_7H_{13} \geq$ c-$C_6H_{11} \cong$ c-$C_8H_{15} >$ M*

(3) R = -C_6H_4X'
(a) X′ = OMe, 2-OMe > 3-OMe $\cong$ H $\cong$ 4-OMe > M*
(b) X′: ortho, OH $\cong$ OMe > H > Cl > M*

(4) R: 2-HOC_6H_4, 2-$MeOC_6H_4 \geq$ c-C_nH_{2n-1} (n = 6-8) $\geq$ $(CH_2)_2C_6H_5 >$ n-$C_5H_{11} \geq CH_2CH{=}C(CH_3)_2 \cong$ 3-$MeOC_6H_4$, $C_6H_5 \geq CH_2$-c-$C_4H_7 \cong$ 4-$MeOC_6H_4$ > M*

(5) R = 2-$MeOC_6H_4$, c-C_6H_{11}, $CH_2C_6H_5$, $(CH_2)_nCH_3$ (n = 0-2), $CH_2CH{=}C(CH_3)_2$, CH_2-c-C_4H_7
S-(+) > (±) $\gg$ R-(−)

[a] See ref 7. [b] M* = morphine.

Pharmacological Results and Discussion

The analgesic activity of the compounds synthesized was tested in mice in the tail-flick and phenylquinone-writhing tests by subcutaneous injection. The analgesic activities obtained in both tests are shown in Table VI.

The effect of the substituent R at N-1 of the piperazinyl group of **2a** and **3–18** on the analgesic activity is shown in Chart II. The unsubstituted compound **19** was almost inactive in the tail-flick test. Compounds with R as a small alkyl group, like methyl or ethyl, were weaker than morphine, but compounds with an *n*-propyl or *n*-amyl group were more potent. Compounds with R as an aralkyl group, such as a β-phenethyl group, showed strong analgesic activity; compounds with R as an aryl group, such as a phenyl group, showed weaker activity than compounds with R as a cyclohexyl group; compounds with an oxygen functionality at the ortho position of the phenyl group showed stronger analgesic activity. Thus, (*S*)-(+)-**10** showed the most potent analgesic activity (105 times as strong as that of morphine) in the present series of compounds. When R was a 3-methyl-2-butenyl group or cyclobutylmethyl group, which might introduce narcotic antagonist activity, stronger analgesic activity than morphine was obtained. When R was a cycloalkyl group, a strong analgesic activity was shown when the carbon numbers were 6–8, as already reported in the previous paper.[7] As shown above, when such bulky lipophilic groups as the cycloalkyl groups of carbon 6–8, and *o*-hydroxyphenyl or *o*-methoxyphenyl group were introduced into N-1, a much stronger analgesic activity was obtained. No such effect of substitution at the N-position on analgesic activity was observed with the known morphine-like analgesics. In **2a**, **10**, **16**, and **18**, the order of analgesic potency of the enantiomers was *S*-(+) > (±) $\gg$ *R*-(−). The potency order in **5**, **7**, **9**, **15**, and **17** is apparently *S*-(+) > (±) $\gg$ *R*-(−) since the racemates were much stronger than the *R*-(−) enantiomers. The activities depended predominantly on the *S*-(+) enantiomers and in some compounds the *R*-(−) enantiomers were practically inactive. However, in the compounds with strong activity, the *R*-(−) enantiomers still retained the activities. For example, no analgesic effect was shown in (*R*)-(−)-**16** in the tail-flick and phenylquinone-writhing tests. On the other hand, a weak analgesic activity was shown by (*R*)-(−)-**18** in the tail-flick test, but a stronger activity comparable to that of pentazocine was shown in the phenylquinone-writhing test.

Table V. ORD Data of (−)-1,2-Diphenylethylamine Derivatives and (−)- or (+)-1-Substituted 4-(1,2-Diphenylethyl)piperazine Derivatives

compd	salt	conf[b]	ORD[φ][24-29] (×10², deg) (*c* 0.10,[a] MeOH) 650 nm	589 nm	400 nm	300 nm
(−)-**2a**	2HCl	*R*	−1.6	−1.7	−5.4	−21.0
(−)-**18**	2HCl	*R*		−1.9	−5.3	−20.5
(−)-**26a**	HCl	*R*[c]		−2.4	−6.4	−19.7
(−)-**26c**	HCl	*R*	−1.9	−2.4	−5.1	−19.7
(−)-**1**	2HCl	*R*[d]	−1.5	−2.0	−6.2	−17.2
(+)-**1**	2HCl	*S*[d]	+1.5	+2.1	+6.2	+17.3

[a] (−)-**26c**, (−)-**18**, *c* 0.05. [b] Absolute configuration. [c] See ref 9. [d] See ref 2.

Table VI. Analgesic Activity of 1-Substituted 4-[2-(3-Hydroxyphenyl)-1-phenylethyl]piperazine Derivatives in Mice

compd	salt	ED_{50}, mg/kg, sc (95% confidence limits) tail-flick test	phenylquinone test	compd	salt	ED_{50}, mg/kg, sc (95% confidence limits) tail-flick test	phenylquinone test
(±)-**3**	2HCl	77.1	15.1 (10.1–22.5)	(−)-**15**	2HCl	>16 (inactive)	11.9 (5.68–24.9)
(+)-**3**	2HCl	43.1	14.2 (7.71–26.3)	(±)-**16**	2HCl	0.613 (0.486–0.774)	0.0864 (0.0320–0.233)
(−)-**3**	2HCl	>80	10.3 (5.01–21.1)	(+)-**16**	2HCl·$^1/_2H_2O$	0.522 (0.0786–0.879)	0.0478 (0.0182–0.125)
(±)-**4**	2HCl	>80	13.9 (10.4–18.6)				
(−)-**4**	2HCl	>80	ca. 60	(−)-**16**	2HCl·$^1/_2H_2O$	>40 (inactive)	>10
(±)-**5**	2HCl·$^1/_2H_2O$	1.87 (1.20–2.91)	0.506 (0.309–0.830)				
				(±)-**17**	2HCl	8.68 (4.85–15.2)	1.75 (0.576–5.35)
(−)-**5**	2HCl	>40	≥40	(−)-**17**	2HCl	>80	46.5
(±)-**6**	2HCl	0.297 (0.148–0.593)		(±)-**18**	2HCl[a]	0.426 (0.361–0.504)	0.0197 (0.0100–0.0391)
(±)-**7**	2HCl	15.7 (8.19–30.0)		(+)-**18**	2HCl[a]	0.162 (0.127–0.207)	0.0055 (0.0018–0.0168)
(−)-**7**	2HBr	>80		(−)-**18**	2HCl[a]	41.1	1.87 (1.08–3.25)
(±)-**8**	2HBr	0.200 (0.101–0.396)		(±)-**19**	2HCl	>80	13.5 (7.73–23.4)
(±)-**9**	2HBr	0.649 (0.415–1.01)		(+)-**19**	2HCl	>80	30.3 (9.20–99.6)
(−)-**9**	2HCl	13.9 (10.4–18.6)		(−)-**19**	2HCl	>80	14.0 (8.31–23.5)
(±)-**10**	2HCl·$^1/_2H_2O$	0.065 (0.037–0.115)	0.016 (0.0103–0.0253)	(±)-**2a**	2HBr[a]	0.126 (0.076–0.208)	0.0037 (0.0014–0.0102)
				(+)-**2a**	2HCl[a]	0.054 (0.039–0.075)	0.0030 (0.0012–0.0080)
(+)-**10**	2HCl	0.028 (0.020–0.040)	0.0077 (0.00366–0.0163)	(−)-**2a**	2HCl[a]	4.24 (3.32–5.81)	0.0275 (0.0084–0.0896)
(−)-**10**	2HCl	0.568 (0.443–0.728)	0.113 (0.0517–0.246)	morphine	HCl	2.39 (1.78–3.20)	0.58 (0.43–0.77)
(±)-**11**	2HCl	0.467 (0.249–0.875)		pentazocine		>80	1.87 (0.826–4.07)
(±)-**12**	2HCl	0.761 (0.533–1.088)					
(±)-**13**	2HBr	0.071 (0.044–0.113)	0.0116 (0.00480–0.0281)				
(±)-**14**	HCl·$^1/_2H_2O$	1.41 (1.11–1.80)					
(±)-**15**	2HCl·$^1/_2H_2O$	14.8 (7.84–28.0)	1.42 (0.353–5.08)				

[a] See ref 10.

Narcotic antagonist activity and physical-dependence liability of the more potent compounds were then examined. Narcotic antagonist activity was determined in the tail-flick test by measuring antagonist effect against morphine analgesia, and physical dependence liability was determined in the jumping test in mice, by administering the test compounds subcutaneously. As shown in Table VII, no narcotic antagonist activity was shown in the *S*-(+) enantiomers, but stronger activity than that of pentazocine was shown by the *R*-(−) enantiomers, like **2a**, **16**, and **18**. Compound (−)-**16** showed the strongest narcotic antagonist activity in the present series, but did not show analgesic activity and physical-dependence liability, suggesting that it is a pure narcotic antagonist. On the other hand, compound (−)-**18** (AD-1211) has analgesic and narcotic antagonist activities comparable to those of pentazocine, while its physical-dependence liability is weaker than that of pentazocine.[10] Compound (−)-**2a**, having a strong analgesic activity and weak physical dependence liability, has a stronger narcotic antagonist activity than that of pentazocine. On the other hand, (−)-**10**, which showed a potent analgesic activity and some physical-dependence liability, has no narcotic antagonist activity.

Compounds **2a**, **5**, **7**, **9**, **10**, and **15**–**18** have two basic nitrogen atoms and lack conformational rigidity, which suggests a chemical nature different from morphine. The *S*-(+) enantiomers of these compounds are the more potent of the enantiomers, but the *R*-(−) enantiomers of **9**, **10**, and **18** still retained some analgesic activity. The (C-9) asym-

Table VII. Narcotic Antagonist and Jumping-Producing Activities of 1-Substituted 4-[2-(3-Hydroxyphenyl)-1-phenylethyl]piperazine Derivatives in Mice

compd	salt	ED_{50}, mg/kg, sc (95% confidence limits) narcotic antagonist act.	jumping-producing act.
(±)-**10**	2HCl·$^1/_2H_2O$	inactive	0.185 (0.00668–0.515)
(+)-**10**	2HCl	inactive	0.10 (0.0280–0.358)
(−)-**10**	2HCl	inactive	1.0 (0.206–4.86)
(±)-**16**	2HCl	inactive	2.6
(+)-**16**	2HCl·$^1/_2H_2O$	inactive	1.17 (0.542–2.53)
(−)-**16**	2HCl·$^1/_2H_2O$	0.78 (0.357–1.71)	>50
(±)-**18**	2HCl	>4 (40%)[a]	2.0
(+)-**18**	2HCl	>2	0.647 (0.280–1.49)
(−)-**18**	2HCl[b]	3.54 (1.52–8.20)	>100 (14%)[c]
(±)-**2a**	2HBr	>2	1.16 (0.630–2.13)
(+)-**2a**	2HCl	>1	0.24 (0.147–0.408)
(−)-**2a**	2HCl[b]	2 (50%)[a]	>20 (40%)[c]
morphine	HCl		5.68 (3.31–9.72)
pentazocine		3.79 (1.47–9.74)	>80 (17%)[c]

[a] Maximum reversing rate (percent of number of mice reversed/tested). [b] See ref 10. [c] Maximum jumping rate (percent of number of mice jumped/tested) among doses tested.

(10) Nakamura, H.; Ishii, K.; Yokoyama, Y.; Motoyoshi, S.; Natsuka, K.; Shimizu, M. *J. Pharm. Pharmacol.* **1980**, *32*, 635.

metric center of morphine or the corresponding position of morphine-like analgesics has the *R* configuration. However, in **2a**, **5**, **7**, **9**, **10**, and **15–18** the absolute configuration of the enantiomers with a stronger analgesic activity is opposite to this, but is identical with that of the tyrosine residue in Met[5]-enkephalin.[11] When any group producing narcotic antagonist activity was introduced at N-1 of the piperazinyl group, the *S*-(+) enantiomer with a stronger analgesic activity did not show narcotic antagonist activity, but the *R*-(−) enantiomer had a narcotic antagonist activity. The effect of such substitutions was different from that of nalbuphine, butorphanol, and other mixed narcotic antagonists. Among these compounds, (*R*)-(−)-**18** showed an excellent analgesic activity. From further pharmacological evaluation, it has been found that (*R*)-(−)-**18** has stronger analgesic and narcotic antagonist activity than does pentazocine, with lower physical-dependence liability; thus, (*R*)-(−)-**18** is somewhat distinct pharmacologically from pentazocine.[10,12]

As described above, the compounds of this study represent a novel structural class of analgesics, and their enantioselectivity for the analgesic activity is different from that of the known morphine-like potent analgesics.

Experimental Section

All melting points were determined on a Yanagimoto micro melting point apparatus unless otherwise specified and are uncorrected. Optical rotations were obtained with a digital polarimeter (Model DIP-4, Japan Spectroscopic Co., Ltd). IR spectra were recorded on a Hitachi 215 grating infrared spectrometer. ^{1}H NMR spectra were taken with a Varian HA-100 spectrometer using Me_4Si as an internal standard. Mass spectra were recorded on a Hitachi RMU-6L mass spectrometer using the direct inlet system at 70-eV ionization potential. Optical rotatory dispersion measurements were carried out with an automatic recording spectropolarimeter (Model ORD/UV-5, Japan Spectroscopic Co., Ltd). Elemental analysis are indicated only by symbols of the elements; analytical results were within ±0.4% of theoretical values. Organic extracts were dried over anhyrous Na_2SO_4.

(±)-2-(3-Nitrophenyl)-1-phenylethylamine (26d) (Table I). This compound was prepared from 3-nitrobenzyl phenyl ketone[13] in a manner similar to that described in the literature.[14]

(−)-2-(3-Methoxyphenyl)-1-phenylethylamine [(−)-26c] (Table I). To a solution of dibenzoyl-L-(+)-tartaric acid monohydrate (133 g, 0.354 mol) in 95% (v/v) EtOH (530 mL) was added (±)-**26c**[15] (160 g, 0.704 mol) with stirring. The mixture was heated at about 95 °C with stirring, by which the mixture was dissolved. After the mixture was cooled for 2–3 days, the precipitates were collected, washed with EtOH, and recrystallized twice or thrice from EtOH to give 99.7 g (35%) of (−)-**26c**·$^1/_2$dibenzoyl-L-(+)-tartrate as colorless needles. To the above salt was added 20% NaOH and the mixture was extracted with AcOEt. The AcOEt layer was washed with water and dried, and the solvent was removed in vacuo. The oily residue [(−)-**26c**] was converted to its hydrochloride with ethanolic HCl, and the resulting crystals were recrystallized from EtOH to give (−)-**26c**·HCl: ORD (Table V).

(+)-2-(3-Methoxyphenyl)-1-phenylethylamine [(+)-26c] and (−)-2-(3-Nitrophenyl)-1-phenylethylamine [(−)-26d] (Table I). These compounds were prepared from (±)-**26c** and (±)-**26d**, respectively, in a manner similar to that described above.

(−)-2-(3-Hydroxyphenyl)-1-phenylethylamine [(−)-26b] (Table I). A mixture of (−)-**26c** (7.5 g, 33.0 mmol) and 47% HBr (75 mL) was refluxed for 2.5 h, and then the mixture was concentrated in vacuo. To the residue was added water and the mixture was made alkaline with ammonia. The alkaline mixture was extracted with AcOEt. The AcOEt layer was dried and the solvent was removed in vacuo. The crystals were recrystallized from EtOH–*n*-hexane to give 5.5 g (78%) of (−)-**26b**.

(+)-2-(3-Hydroxyphenyl)-1-phenylethylamine [(+)-26b] (Table I). This compound was prepared from (+)-**26c** in a manner similar to that described above.

1-Substituted 4-(1,2-Diphenylethyl)piperazines 2a, 3–25, 28, and 31 (Tables II–IV). Procedure A. (a) (−)-1-Cyclohexyl-4-[2-(3-nitrophenyl)-1-phenylethyl]piperazine [(−)-23] Dihydrochloride. In DMF (60 mL) were dissolved (−)-**26d** (10.0 g, 41.3 mmol) and *N*,*N*-bis(2-chloroethyl)cyclohexylamine hydrochloride (11.2 g, 43.0 mmol), and $NaHCO_3$ (11.7 g, 139 mmol) was added to the solution. The mixture was refluxed for 10 h with stirring and the solvent was removed in vacuo. To the residue was added 10% Na_2CO_3 and the alkaline mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water and dried. The solvent was removed in vacuo. The residue was treated with ethanolic HCl, and the resulting crystals were recrystallized from MeOH to give 15.7 g of (−)-**23**·2HCl: IR (KBr) 1530, 1350 cm^{-1} (NO_2).

(b) (−)-1-Cyclohexyl-4-[2-(3-methoxyphenyl)-1-phenylethyl]piperazine [(−)-25] Dihydrochloride. In EtOH (30 mL) were dissolved (−)-**26c** (1.2 g, 5.3 mmol) and *N*,*N*-bis(2-chloroethyl)cyclohexylamine hydrochloride (1.3 g, 5.0 mmol), and $NaHCO_3$ (1.4 g, 16.7 mmol) was added to the solution. The alkaline mixture was refluxed for 24 h with stirring and the solvent was removed in vacuo. To the residue was added 5% Na_2CO_3 and the mixture was extracted with AcOEt. The AcOEt layer was washed with water and dried. The solvent was removed in vacuo. The residue was treated with methanolic HCl, and the resulting crystals were recrystallized from MeOH to give 1.2 g of (−)-**25**·2HCl as colorless needles.

(c) (+)-1-Cyclohexyl-4-[2-(3-hydroxyphenyl)-1-phenylethyl]piperazine [(+)-2a] Dihydrochloride. From (+)-**26b** (1.1 g, 5.2 mmol), *N*,*N*-bis(2-chloroethyl)cyclohexylamine hydrochloride (1.3 g, 5.0 mmol), and $NaHCO_3$ (1.4 g, 16.7 mmol) 0.8 g of (+)-**2a**·2HCl was obtained as colorless needles by the above procedure A (b).

Procedure B. (±)-1-(2-Methoxyphenyl)-4-[2-(3-methoxyphenyl)-1-phenylethyl]piperazine (31) Dihydrochloride. In DMF (50 mL) was dissolved *N*,*N*-bis(2-chloroethyl)-2-(3-methoxyphenyl)-1-phenylethylamine (**27a**) hydrochloride (5.6 g, 14.4 mmol) and *o*-anisidine (7.3 g, 59.2 mmol) was added to the solution. The mixture was refluxed for 5 h with stirring. The solvent was removed, and to the residue was added 28% NH_4OH. The mixture was extracted with Et_2O. The Et_2O extract was washed with water and dried. Then the solvent was removed, and the oily residue was distilled under reduced pressure to remove excess of *o*-anisidine. The residue was treated with ethanolic HCl, and the resulting crystals were recrystallized from EtOH to give 2.8 g of **31**·2HCl.

Procedure C. (a) (−)-1-Cyclohexyl-4-[2-(3-hydroxyphenyl)-1-phenylethyl]piperazine [(−)-2a] Dihydrochloride. A mixture of (−)-**25**·2HCl (0.45 g, 1.0 mmol), 47% HBr (4.5 mL), and acetic acid (1.5 mL) was refluxed for 0.5 h. The solvent was removed in vacuo, and to the residue was added 5% Na_2CO_3. The alkaline mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was dried and the solvent was removed. The residue was treated with ethanolic HCl and the resulting crystals were recrystallized from MeOH to give 0.30 g (69%) of (−)-**2a**·2HCl as colorless needles: mp 275–280 °C dec; $[\alpha]^{28}_D$ −51.5° (*c* 0.55, MeOH); ORD (Table V). By mixture melting point measurement, specific rotation, and IR spectrum, this compound was identical with (−)-**2a**·2HCl prepared by procedure A.

(b) (−)-*N*-[2-(3-Hydroxyphenyl)-1-phenylethyl]piperazine [(−)-19]. A mixture of (−)-**20**·2HCl (37.0 g, 100 mmol) and 47% HBr (370 mL) was refluxed for 1.5 h. After being cooled, the reaction mixture was poured into cold 25% ammonia, and the mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was dried and the solvent was removed. The residue was recrystallized from *i*-PrOH to 25.0 g (89%) of (−)-**19**.

Procedure D. (−)-*N*-[2-(3-Methoxyphenyl)-1-phenylethyl]piperazine [(−)-20] Dihydrochloride. In AcOH (500 mL)

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was dissolved (−)-1-benzyl-4-[2-(3-methoxyphenyl)-1-phenylethyl]piperazine [(−)-**22**] dihydrochloride (94.0 g, 201 mmol), and 5% Pd/C (10.0 g) was added to the solution. The mixture was subjected to catalytic reduction. After about 1 equimolar amount of hydrogen was absorbed, the mixture was filtered to remove the catalyst. The solvent was removed in vacuo and the crystalline residue was recrystallized from MeOH to give 65.2 g of (−)-**20**·2HCl.

Procedure E. (−)-1-Allyl-4-[2-(3-hydroxyphenyl)-1-phenylethyl]piperazine [(−)-17] Dihydrochloride. In EtOH (50 mL) were dissolved (−)-**19** (3.7 g, 13 mmol) and allyl bromide (1.6 g, 13 mmol), and $NaHCO_3$ (1.6 g, 19 mmol) was added to the solution. The mixture was refluxed for 7 h with stirring. The solvent was removed in vacuo, and to the residue was added 5% Na_2CO_3. The mixture was extracted with AcOEt. The organic layer was washed with water and dried, and the solvent was removed. The oily residue was dissolved in AcOEt and the solution was subjected to silica gel column chromatography. The eluates of AcOEt were collected and treated with ethanolic HCl to give the dihydrochloride, which was recrystallized from MeOH to give 1.7 g of (−)-**17**·2HCl.

Procedure F. (−)-1-(3-Methyl-2-butenyl)-4-[2-(3-hydroxyphenyl)-1-phenylethyl]piperazine [(−)-18] Dihydrochloride. (1) In MeOH (340 mL) was dissolved (−)-**19** (20.0 g, 70.8 mmol), and water (9.1 mL) and K_2CO_3 (powder) (19.0 g, 137 mmol) were added to the solution. The mixture was stirred at room temperature for 30 min. To the stirred mixture was added dropwise 3,3-dimethylacryloyl chloride (17.0 g, 143 mmol) over a period of about 2 h. The mixture was stirred at room temperature for 1 h, and then the solvent was removed in vacuo. To the residue was added 10% Na_2CO_3 (160 mL), and the mixture was extracted with $CHCl_3$. The organic layer was washed with water and dried, and the solvent was removed in vacuo. The residue was recrystallized from *i*-PrOH to give 23.3 g of (−)-1-(3-methylcrotonyl)-4-[2-(3-hydroxyphenyl)-1-phenylethyl]-piperazine [(−)-**28**]: IR (KBr) 1650 cm^{-1} (amide).

(2) In THF (anhydrous) (230 mL) was dissolved (−)-**28** (20.0 g, 54.9 mmol). The solution was added dropwise at about 20 °C to a mixture of Vitride [sodium bis(2-methoxyethoxy)aluminum hydride; 70% toluene solution] (30.1 g, 104 mmol) in THF (anhydrous) (65 mL) over a period of about 1 h. The mixture was stirred at room temperature for 2.5 h. After the mixture was cooled, water was added dropwise and the solvent was removed in vacuo. To the residue was added water and the mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water and dried, and the solvent was removed in vacuo. The oily residue was dissolved in EtOH and the resulting solution was treated with 5% ethanolic HCl (165 mL) while the temperature was kept below 5 °C, and then pyridine (1.2 mL) and Et_2O (90 mL) were added to the mixture. The resulting crystals were collected, dried, and recrystallized from EtOH to give 19.7 g of (−)-**18**·2HCl: mass spectrum, *m/z* 350 (M^+), 243 ($M^+ - HOC_6H_4CH_2$); ORD (Table V). Free base: bp 201 °C (0.04 mmHg); ^1H NMR ($CDCl_3$) δ 1.61 (3 H, s, CH_3), 1.69 (3 H, s, CH_3), 2.94 (2 H, m, $>NCH_2CH{=}C<$), 5.21 (1 H, m, $>NCH_2CH{=}C<$).

Procedure G. (−)-1-Cyclohexyl-4-[2-(3-aminophenyl)-1-phenylethyl]piperazine [(−)-24] $^5/_2$Maleate. (−)-**23**·2HCl (8.0 g, 17.1 mmol) was dissolved in AcOH (160 mL), and 5% Pd/C (0.8 g) was added to the solution. The mixture was subjected to catalytic reduction. After about a 3 equimolar amount of hydrogen was absorbed, the mixture was filtered to remove the catalyst. The filtrate was concentrated in vacuo. To the residue was added 10% NaOH and the mixture was extracted with AcOEt. The AcOEt extract was washed with water and dried, and the solvent was removed in vacuo. The resulting oily base was converted to its maleate with maleic acid, and the resulting crystals were recrystallized from EtOH to give 6.7 g of (−)-**24**·$^5/_2$maleate.

Procedure H. Optical Resolution of (+)-1-(3-Methyl-2-butenyl)-4-[2-(3-hydroxyphenyl)-1-phenylethyl]piperazine (18). A mixture of (±)-**18** (20.5 g, 58.5 mmol) and (−)-2′-nitrotartranilic acid (33.4 g, 124 mmol) in EtOH (60 mL) was warmed to give a clear solution. After the solution was cooled, the precipitates were collected and recrystallized six or seven times from EtOH (allowed to stand overnight at room temperature) to give 15.0 g of (−)-**18**·2(−)-2′-nitrotartranilate as yellow needles. To the salt thus obtained was added water and the mixture was made alkaline with 10% Na_2CO_3 and extracted with AcOEt. The AcOEt extract was washed with water and dried, and the solvent was removed in vacuo. The residue was treated with 5% ethanolic HCl (60 mL) while the temperature was kept below 5 °C, and then pyridine (0.5 mL) and Et_2O (30 mL) were added to the mixture. The resulting crystals were recrystallized from EtOH to give 7.0 g of (−)-**18**·2HCl. The first mother liquid from the (−)-2′-nitrotartranilate formation was concentrated to dryness. To the residue was added 10% Na_2CO_3 and the alkaline solution was extracted with AcOEt. The AcOEt layer was washed with water and dried, and the solvent was removed in vacuo. A mixture of the oily free base and (+)-2′-nitrotartranilic acid (17.0 g, 62.9 mmol) in EtOH (25 mL) was warmed to give a clear solution. After the resulting solution was cooled, the precipitates were collected and recrystallized six or seven times from EtOH to give 10.0 g of (+)-**18**·2(+)-2′-nitrotartranilate. Treatment of the salt with alkali in a similar manner as described above gave the free base, which was converted to its hydrochloride. The hydrochloride was recrystallized from EtOH to give 5.4 g of (+)-**18**·2HCl.

Synthesis of (*R*)-(−)-1-Cyclohexyl-4-(1,2-diphenylethyl)-piperazine [(*R*)-(−)-1] from (−)-1-Cyclohexyl-4-[2-(3-aminophenyl)-1-phenylethyl]piperazine [(−)-24]. To a stirred solution of (−)-**24** (2.0 g, 5.50 mmol) in 31.5% H_2SO_4 (23.4 g) was added dropwise a solution of $NaNO_2$ (0.38 g, 5.51 mmol) in water (2.5 mL) while the temperature was maintained at 0–5 °C. After complete addition, a small amount of urea was added to the mixture. After an additional 10-min stirring, the reaction mixture was poured into 30% hypophosphorous acid (H_3PO_2) (30 mL). The mixture was made alkaline with 10% NaOH and the alkaline mixture was extracted with AcOEt. The AcOEt extract was washed with water and dried, and the solvent was removed in vacuo. The crystalline residue was purified by chromatography on a column of silica gel. The product was eluted with $CHCl_3$ and recrystallized from *n*-hexane to give 1.1 g (58%) of (−)-1; mp 95–97 °C; $[\alpha]^{29}_D$ −64.3° (*c* 0.50, MeOH). By mixture melting point measurement, specific rotation, and IR spectrum, this compound was identical with (*R*)-(−)-1, previously described.[2]

Synthesis of (−)-1-Cyclohexyl-4-[2-(3-methoxyphenyl)-1-phenylethyl]piperazine [(−)-25] Dihydrochloride from (−)-1-Cyclohexyl-4-[2-(3-aminophenyl)-1-phenylethyl]-piperazine [(−)-24]. To a stirred solution of (−)-**24**·3HCl (1.2 g, 3.30 mmol) in MeOH (10 mL) was added dropwise a solution of isoamyl nitrite (0.30 g, 2.56 mmol) in MeOH (2 mL) at about 0 °C. After 30 min of stirring, the reaction mixture was maintained at 50 °C for 1 h. The solvent was evaporated in vacuo. The crystalline residue was recrystallized from MeOH to give 0.67 g (58%) of (−)-**25**·2HCl: mp 243–247 °C; $[\alpha]^{29}_D$ −43.0° (*c* 0.50, MeOH). Anal. ($C_{25}H_{34}N_2O$·2HCl) C, H, Cl, N. The IR spectrum of this compound was identical with that of an authentic sample prepared by procedure A.

Analgesic Assay. The compounds listed in Table VI were tested for analgesic activity by the following methods. A tail-flick response was induced by heat radiation on the blackened tail of male mice (9–12 g) of ddN strain by using an apparatus and procedure as described by Nakamura and Shimizu.[3] Mice showing a response time of 4–6 s were used. After subcutaneous administration of compounds, the response time was measured six times at 30-min intervals with an arbitrary cutoff time of 15 s. When the response time was 10 s or more, the compound was considered to be effective. Five mice were used for each dose. Phenylquinone writhing was induced by phenylquinone (0.03% in 5% ethanol aqueous solution), 10 mL/kg, ip, in female mice (18–22 g) of ddN strain.[3,16] The number of writhes was counted for 15 min beginning from 5 min after phenylquinone challenge. Each compound was administered subcutaneously 30 min before phenylquinone. When number of writhes decreased by more than 50% compared with the vehicle control group, the compound was considered to be effective. Five mice were used for each dose.

Narcotic-Antagonist Assay. The compounds listed in Table VII were tested for narcotic antagonist activity by the following methods.[10] In the tail-flick test, the antagonist ED_{50} value was calculated from the number of positive mice showing the response time of less than 10 s at 30 or 60 min after a single subcutaneous

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injection of 5 mg/kg of morphine hydrochloride, that was effective (14–15 s) in prolonging the response time to thermal stimulus in 95% of animals. Each compound was administered subcutaneously just before morphine injection. Five mice were used for each dose.

Analgesic and narcotic antagonist ED_{50} values and 95% confidence limits were calculated according to the method of Litchfield and Wilcoxon.[17]

Physical-Dependence Assay. Male mice (19–23 g) of ddN strain received seven subcutaneous administrations of each compound in increasing doses of 8, 16, 25, 50, 100, 100, and 100 mg/kg for 2 days; five doses were given on the first day at 0900, 1000, 1100, 1300, 1500 h, and two were given on the second day at 0900 and 1100 h. Two hours after the last dose, the animals received a single intraperitoneal injection of 50 mg/kg nalorphine hydrochloride, and jumping behavior and other withdrawal signs were observed for 30 min in a separate cylinder (40 cm high and 15 cm in diameter).[18] Ten to 30 mice were used for each dose.

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Registry No. (–)-**1**, 57377-70-5; (+)-**2a**, 61310-95-0; (+)-**2a**·2(+)-NTA, 61331-59-7; (–)-**2a**·2HCl, 61310-94-9; (–)-**2a**·2(–)-NTA, 109364-66-1; (±)-**3**·2HCl, 109364-55-8; (+)-**3**·2HCl, 109364-56-9; (–)-**3**·HCl, 109364-57-0; (±)-**4**·2HCl, 109364-58-1; (–)-**4**·2HCl, 109430-82-2; (±)-**5**·2HCl, 61311-32-8; (–)-**5**·2HCl, 109430-83-3; (±)-**6**·2HCl, 109364-59-2; (±)-**7**·2HCl, 109364-60-5; (–)-**7**·2HBr, 109430-84-4; (±)-**8**·2HBr, 109364-61-6; (±)-**9**·2HBr, 109364-62-7; (–)-**9**·2HCl, 109430-85-5; (±)-**10**·2HCl, 61311-21-5; (+)-**10**·2HCl, 61341-38-6; (–)-**10**·2HCl, 109364-63-8; (±)-**11**·2HCl, 61311-26-0; (±)-**12**·2HCl, 61311-29-3; (±)-**12**·2HBr, 61311-25-9; (±)-**14**·HCl, 109364-64-9; (±)-**15**·2HCl, 67279-40-7; (–)-**15**·2HCl, 109430-86-6; (±)-**16**·2HCl, 67279-41-8; (+)-**16**·2HCl, 109364-65-0; (–)-**16**·2HCl, 67279-43-0; (±)-**17**·2HCl, 61311-40-8; (–)-**17**·2HCl, 61311-31-7; (±)-**18**, 83374-58-7; (±)-**18**·2HCl, 61311-22-6; (+)-**18**·2HCl, 61311-23-7; (+)-**18**·2(+)-NTA, 61311-54-4; (–)-**18**·2HCl, 61311-01-1; (–)-**18**·2(–)-NTA, 61311-52-2; (±)-**19**·2HCl, 109364-49-0; (+)-**19**·2HCl, 109364-50-3; (–)-**19**, 83434-62-2; (–)-**19**·2HCl, 109364-51-4; (±)-**20**·2HCl, 61311-63-5; (–)-**20**·2HCl, 109430-79-7; (±)-**21**·2HCl, 109364-52-5; (±)-**22**·2HCl, 61311-75-9; (–)-**22**·2HCl, 109430-80-0; (–)-**23**·2HCl, 109390-25-2; (–)-**24**, 109364-53-6; (–)-**24**·$^5/_2$maleate, 109364-54-7; (–)-**24**·3HCl, 109364-68-3; (–)-**25**·2(–)-NTA, 61311-50-0; (–)-**25**·2HCl, 61311-00-0; (+)-**26b**, 61311-58-8; (–)-**26b**, 65017-62-1; (±)-**26c**, 65017-65-4; (+)-**26c**, 109430-87-7; (+)-**26c**·HCl, 109525-57-7; (+)-**26c**·$^1/_2$(+)-DBT, 109525-58-8; (–)-**26c**, 65017-66-5; (–)-**26c**·HCl, 109525-59-9; (–)-**26c**·$^1/_2$(+)-DBT, 109525-60-2; (±)-**26d**, 109364-67-2; (±)-**26d**·HCl, 109364-48-9; (–)-**26d**, 109430-88-8; (–)-**26d**·$^1/_2$(–)-DBT, 109525-61-3; (±)-**27a**·HCl, 61311-70-4; (±)-**28**, 61311-66-8; (–)-**28**, 109430-81-1; (±)-**31**, 61311-35-1; 2-$MeOC_6H_4NH_2$, 90-04-0; $BrCH_2CH{=}CH_2$, 106-95-6; $Me_2C{=}CHCOCl$, 3350-78-5; *c*-$C_6H_{11}N((CH_2)_2Cl)_2$·HCl, 879-61-8.

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Studies on Histamine H_2 Receptor Antagonists. 2. Synthesis and Pharmacological Activities of *N*-Sulfamoyl and *N*-Sulfonyl Amidine Derivatives

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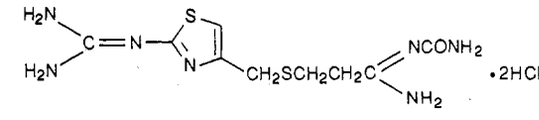
A series of *N*-sulfamoyl and *N*-sulfonyl amidines have been prepared and tested in vitro for H_2 antihistamine activity on guinea pig atrium. In addition, several selected compounds were assessed as inhibitors of gastric acid secretion induced by histamine in anesthetized dogs. Structure–activity relationship studies showed that those compounds containing 2-[(diaminomethylene)amino]thiazole exhibited potent H_2-receptor antagonist activity. Introduction of alkyl or aralkyl groups to the terminal nitrogen of the sulfamoyl moiety reduced biological activities. Sulfamoyl amidines were more potent in both tests than sulfonyl amidines. Of these compounds, 3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio]-N^2-sulfamoylpropionamidine (**2e**, famotidine) showed extremely high potency in both assays and was selected for clinical trials as an antiulcer agent. Acid-catalyzed hydrolysis of famotidine gave the sulfamoyl amide **6** at room temperature and the carboxylic acid **7** at elevated temperatures. ^{15}N NMR spectrum showed that famotidine in solution existed in only one of several possible tautomers derived from the amidine and the guanidine moieties. Nitrosation of famotidine was performed under mild condition and proved to occur on the 5-position of the thiazole ring.

In the preceding paper[1] we described the synthesis and histamine H_2 receptor antagonist activities of *N*-cyano and *N*-carbamoyl amidine derivatives related to cimetidine, ranitidine, and tiotidine. Structure–activity correlations of the amidine derivatives were different from those of the guanidine derivatives in two important respects, viz. The cyano amidines were less active than the corresponding carbamoyl amidines and introduction of a methyl group to the nitrogen at the terminal amidine moiety reduced the activity, the converse of the case for the guanidine series.[2,3] The most active compound of those derivatives, 3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio]-N^2-carbamoylpropionamidine dihydrochloride (I), when tested in vitro, is 30 times more active than cimetidine. This encouraging result prompted us to prepare



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compounds structurally related to the carbamoyl amidine to investigate the effect of structural modification on histamine H_2 receptor antagonist activity. It was of in-

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