Studies on 1-Substituted 4-(1,2-Diphenylethyl)piperazine Derivatives and Their Analgesic Activities. 2.[1] Structure-Activity Relationships of 1-Cycloalkyl-4-(1,2-diphenylethyl)piperazines

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Forty-six 1-cycloalkyl-4-(1,2-diphenylethyl)piperazines were synthesized. The influence of substituents on phenyl groups of 1-cycloalkyl-4-(1,2-diphenylethyl)piperazines **4a–c** on the analgesic activity was investigated in experimental animals. The most active compounds, **5a–c**, in this series had a *m*-hydroxyl group on the 2-phenyl group of **4a–c**, while morphine has a phenolic hydroxyl group para to the aminoethyl moiety. Their activities were 23–56 and 23–38 times those of their original compounds **4a–c** and morphine, respectively, tested by the D'Amour–Smith method after subcutaneous administration.

In the previous paper[2,3] it was shown that 1-cycloalkyl-4-(1,2-diphenylethyl)piperazine derivatives **4a–c** have potent analgesic activity comparable to that of morphine, and the more active enantiomer, (*S*)-(+)-**4a**, has 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 methionine-enkephalin.[4]

It is well-known that the introduction of a phenolic hydroxyl group on a definite position of an analgetically active molecule frequently causes an increase in the activity and an enhancement of binding to the opiate receptor.[5] In order to investigate the influence of substituents on the two phenyl groups of **4a–c** on the analgesic activity, a series of compounds having various kinds of substituents on the phenyl groups were synthesized.[6] Consequently, it was found that the greatest enhancement of activity was caused by the introduction of a hydroxyl group to the meta position of the 2-phenyl group of **4a–c**. In contrast, morphine possesses a phenolic hydroxyl group para to the aminoethyl moiety.

Chemistry. Starting materials, 1,2-diphenylethylamines **1**, *N,N*-bis(2-hydroxyethyl)-1,2-diphenylethylamines **2**, and *N,N*-bis(2-chloroethyl)-1,2-diphenylethylamines **3**, were prepared in a manner similar to that described in the literature[2,7,8] (see Chart I and Table I).

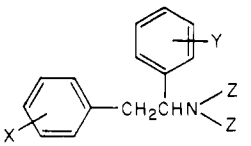
Compounds **5a**, **6a**, **7–10**, **17–19**, **20a**, **21–24**, and **29–31** were prepared from **1** or **3** in a manner similar to that described previously.[2] Phenolic derivatives **5**, **6**, **20**, and **25–28** were obtained by cleavage of the ether linkage of methoxy analogues with hydrobromic acid. Acylation of **5a**, **6a**, and **20a** afforded **12–15**, and alkylation afforded **11** and **16**. Further synthetic routes are described in the patent literature.[6] Synthesized compounds are shown in Tables II and III.

Pharmacological Results and Discussion. Analgesic activity of the synthesized compounds was measured by the method of D'Amour–Smith,[9] phenylquinone writhing,[10] or the Haffner[11] test in mice or rats. Analgesic ED_{50} values (mg/kg) were calculated by the method of Litchfield–Wilcoxon.[12]

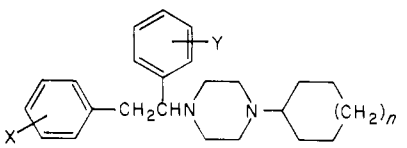
With regard to the analgesic activity (molar basis) measured by the D'Amour–Smith method after subcutaneous administration in mice, the following structure–activity relationships were deduced from the results shown in Table IV.

Compounds **1–3** did not show significant analgesic activity (Table IV).[13] The introduction of a hydroxyl group into the meta position of the 2-phenyl group (**5a–c**) enhanced the activity markedly, while the introduction of a hydroxyl group into the para or ortho position (**6a–c** or **20a–c**) weakened the activity except for **6b**, which was approximately **4b** in activity. The analgesic activity of

Chart I[a]



1, Z = H
2, Z = CH_2CH_2OH
3, Z = CH_2CH_2Cl



4a–c, X = Y = H
5a–c, X = 3-OH; Y = H
6a–c, X = 4-OH; Y = H
7–20, Y = H
21–31

[a] For additional data on compounds 1–31, see Tables I–III. For the a series, $n = 1$; b, $n = 2$; c, $n = 3$.

5a–c was 23–56 and 23–38 times that of **4a–c** and morphine, respectively. The strongest activity in this series was found in **5b**. Acylation of the hydroxyl group of **5a** caused a slight decrease in the activity. The potency of methyl ethers (**7a–c**) of **5a–c** was comparable to that of **4a–c** and weaker than that of acylated analogues **12** and **14**. The substitution of a methyl or chloro group in the meta position of the 2-phenyl group caused a marked decrease in activity. Thus, the potency order for meta substituents on the 2-phenyl group where $n = 1$ was

$$OH \geq OAc \gg OMe \geq H \gg Me > Cl$$

The corresponding aromatic-substituent constants (π values)[15] are as follows: OH, –0.67; OAc, –0.64; OMe, –0.02; H, 0.00; Me, 0.56; Cl, 0.71. Accordingly, it is suggested that there may be an inverse correlation between the analgesic activity of the meta-substituted compounds and the contribution of their substituents to lipophilicity. In this connection, the inverse correlation in the central nervous system depressant activity has been reported by Yoshimoto et al.[14]

The most active compound among the para-substituted derivatives on the 2-phenyl group was **6b**, and its activity was only 1.4 and 0.93 times that of **4b** and morphine, respectively. The potency order for the para substituents on the 2-phenyl group where $n = 1$ or 2 was

$$H \geq OH \text{ (or OAc)} \gg OMe \geq Me > Cl$$

Unlike the meta substituents, activity of some compounds

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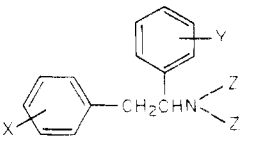
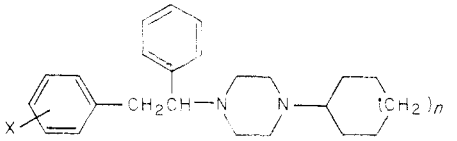
Table I. 1,2-Diphenylethylamine Derivatives



compd	X	Y	Z	salt	mp, °C	recrystn solvent	formula[a]
1b	3-OH	H	H	HCl[b]	187–188	EtOH-Et_2O	$C_{14}H_{15}NO\cdot HCl$
1c	2-OMe	H	H	HCl	242–245	*i*-PrOH-AcOEt	$C_{15}H_{17}NO\cdot HCl$
1d	2-OH	H	H	HBr	211–213	EtOH-Et_2O	$C_{14}H_{15}NO\cdot HBr$
1e	3-Me	H	H	HCl	245–248	EtOH-AcOEt	$C_{15}H_{17}N\cdot HCl$
2a	3-OMe	H	$(CH_2)_2OH$	HCl[c]	129–130	EtOH-Et_2O	$C_{19}H_{25}NO_3\cdot HCl$
2b	2-OMe	H	$(CH_2)_2OH$	HCl	168–169	EtOH	$C_{19}H_{25}NO_3\cdot HCl$
2c	4-Cl	H	$(CH_2)_2OH$		105–106	AcOEt	$C_{18}H_{22}ClNO_2$
2d	H	2-OMe	$(CH_2)_2OH$	HCl	155–157	EtOH	$C_{19}H_{25}NO_3\cdot HCl$
2e	H	4-Cl	$(CH_2)_2OH$	HCl	120–121	Me_2CO-Et_2O	$C_{18}H_{22}ClNO_2\cdot HCl$
3a	3-OMe	H	$(CH_2)_2Cl$	HCl	103–106.5	Me_2CO	$C_{19}H_{23}Cl_2NO\cdot HCl$
3b	4-OMe	H	$(CH_2)_2Cl$	HCl	121–124	Me_2CO	$C_{19}H_{23}Cl_2NO\cdot HCl$
3c	4-Me	H	$(CH_2)_2Cl$	HCl	142–145	Me_2CO	$C_{19}H_{23}Cl_2N\cdot HCl$
3d	4-Cl	H	$(CH_2)_2Cl$	HCl	136–137	Me_2CO	$C_{18}H_{20}Cl_3N\cdot HCl$
3e	H	2-OMe	$(CH_2)_2Cl$	HCl	136–140	Me_2CO	$C_{19}H_{23}Cl_2NO\cdot HCl$

[a] All compounds were analyzed for C, H, N, and Br or Cl; analytical results were within ±0.4% of the theoretical values. [b] Base, mp 179–181 °C. Anal. ($C_{14}H_{15}NO$) C, H, N. [c] Base, mp 67–69 °C. Anal. ($C_{19}H_{25}NO_3$) C, H, N.

Table II. 1-Cycloalkyl-4-(1,2-diphenylethyl)piperazine Derivatives



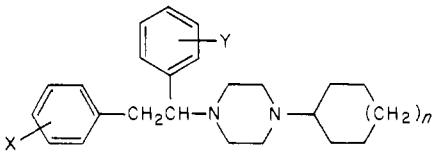
compd	X	*n*	salt	procedure[a]	mp, °C	recrystn solvent	yield, %	formula[b]
5a	3-OH	1	2HBr[c]	A	268–270	MeOH	60	$C_{24}H_{32}N_2O\cdot 2HBr$
5b	3-OH	2	2HBr	C	279–281	MeOH-H_2O	90	$C_{25}H_{34}N_2O\cdot 2HBr$
5c	3-OH	3	2HBr	C	274–276	MeOH	90	$C_{26}H_{36}N_2O\cdot 2HBr$
6a	4-OH	1	2HBr[d]	A	267–268.5	MeOH	57	$C_{24}H_{32}N_2O\cdot 2HBr$
6b	4-OH	2	2HBr	C	268–271	MeOH	89	$C_{25}H_{34}N_2O\cdot 2HBr$
6c	4-OH	3	2HBr	C	262–265	MeOH-H_2O	95	$C_{26}H_{36}N_2O\cdot 2HBr$
7a	3-OMe	1	2HCl	A	240–243	MeOH	58	$C_{25}H_{34}N_2O\cdot 2HCl$
7b	3-OMe	2	2HCl	B	242–247	MeOH	52	$C_{26}H_{36}N_2O\cdot 2HCl$
7c	3-OMe	3	2HCl	B	243–246	MeOH	53	$C_{27}H_{38}N_2O\cdot 2HCl$
8a	4-OMe	1	2HCl[e]	B	243–245	MeOH	74	$C_{25}H_{34}N_2O\cdot 2HCl$
8b	4-OMe	2	2HCl	B	241–244	MeOH	62	$C_{26}H_{36}N_2O\cdot 2HCl$
8c	4-OMe	3	2HCl	B	241–245	MeOH-H_2O	54	$C_{27}H_{38}N_2O\cdot 2HCl$
9a	3-Me	1	2HCl	A	244–247	MeOH	75	$C_{25}H_{34}N_2\cdot 2HCl$
9b	3-Me	2	2HCl	B	243–249	MeOH	64	$C_{26}H_{36}N_2\cdot 2HCl$
9c	3-Me	3	2HCl	B	238–240	MeOH	57	$C_{27}H_{38}N_2\cdot 2HCl$
10a	4-Me	1	2HCl	B	252–256	MeOH	58	$C_{25}H_{34}N_2\cdot 2HCl$
10b	4-Me	2	2HCl	B	253–256	MeOH	64	$C_{26}H_{36}N_2\cdot 2HCl$
10c	4-Me	3	2HCl	B	249–253	MeOH	60	$C_{27}H_{38}N_2\cdot 2HCl$
11	4-OEt	1	2HCl	D	246–249 dec	MeOH	62	$C_{26}H_{36}N_2O\cdot 2HCl$
12	3-OAc	1	2HCl	E	220–223	EtOH	45	$C_{26}H_{34}N_2O_2\cdot 2HCl$
13	4-OAc	1	2HBr	E	270–271 dec	MeOH	58	$C_{26}H_{34}N_2O_2\cdot 2HBr$
14	3-OCOEt	1	2HCl	E	219–222	EtOH	78	$C_{27}H_{36}N_2O_2\cdot 2HCl$
15	2-OCOEt	1	2HCl	E	222–227	EtOH	53	$C_{27}H_{36}N_2O_2\cdot 2HCl$
16	4-OCH_2Ph	1	$2HCl\cdot H_2O$[f]	D	236–243	EtOH-Et_2O	60	$C_{31}H_{38}N_2O\cdot 2HCl\cdot H_2O$
17	3-Cl	1	2HCl	B	238–241	MeOH	72	$C_{24}H_{31}ClN_2\cdot 2HCl$
18a	4-Cl	1	2HCl	B	247–249	MeOH	56	$C_{24}H_{31}ClN_2\cdot 2HCl$
18b	4-Cl	2	2HCl	B	245–250 dec	MeOH	76	$C_{25}H_{33}ClN_2\cdot 2HCl$
19a	2-OMe	1	2HCl	A	236–239	MeOH	54	$C_{25}H_{34}N_2O\cdot 2HCl$
19b	2-OMe	2	2HCl	B	244–249	MeOH	63	$C_{26}H_{36}N_2O\cdot 2HCl$
19c	2-OMe	3	2HCl	B	244–248	MeOH	65	$C_{27}H_{38}N_2O\cdot 2HCl$
20a	2-OH	1	2HBr[g]	A	245.5–247.5	EtOH	62	$C_{24}H_{32}N_2O\cdot 2HBr$
20b	2-OH	2	2HBr	C	260–262	MeOH	82	$C_{25}H_{34}N_2O\cdot 2HBr$
20c	2-OH	3	2HBr	C	261–263	MeOH	93	$C_{26}H_{36}N_2O\cdot 2HBr$

[a] Capital letters refer to procedures in the Experimental Section. [b] See footnote *a* in Table I. [c] Base, mp 140–141 °C. Anal. ($C_{24}H_{32}N_2O$) C, H, N. [d] Base, mp 197–199 °C. Anal. ($C_{24}H_{32}N_2O$) C, H, N. [e] Base, mp 96–97 °C. Anal. ($C_{25}H_{34}N_2O$) C, H, N. [f] Mass spectrum (CI) *m/e* 455 (MH^+). [g] Base, mp 185–186 °C. Anal. ($C_{24}H_{32}N_2O$) C, H, N.

was only slightly potentiated in spite of the introduction of a hydroxyl group. The activity of **6a** especially, bearing the N^1-cyclohexyl group, clearly decreased compared with **4a**.

On the other hand, the introduction of the substituent Y into the 1-phenyl group (**21–25**) caused a marked decrease in the activity compared with each original compound, **4a–c**. The introduction of two substituents, X and

Table III. 1-Cycloalkyl-4-(1,2-diphenylethyl)piperazine Derivatives



compd	X	Y	n	salt	procedure[a]	mp, °C	recrystn solvent	yield, %	formula[b]
21	H	4-OMe	1	2HCl	A	242-245	MeOH	59	$C_{25}H_{34}N_2O\cdot 2HCl$
22	H	3-OMe	1	2HCl	B	253-256	MeOH	65	$C_{25}H_{34}N_2O\cdot 2HCl$
23a	H	2-OMe	1	2HCl	B	244-246	MeOH	67	$C_{25}H_{34}N_2O\cdot 2HCl$
23b	H	2-OMe	2	2HCl	B	250-255	MeOH	70	$C_{26}H_{36}N_2O\cdot 2HCl$
23c	H	2-OMe	3	2HCl	B	251-256	MeOH	61	$C_{27}H_{38}N_2O\cdot 2HCl$
24	H	4-Cl	1	2HCl	B	246-249	MeOH	60	$C_{24}H_{31}ClN_2\cdot 2HCl$
25	H	3-OH	1	2HBr	C	235-238	MeOH	74	$C_{24}H_{32}N_2O\cdot 2HBr$
26	3-OH	3-OH	1	2HBr	C	234-235	MeOH	85	$C_{24}H_{32}N_2O_2\cdot 2HBr$
27	2-OH	3-OH	1	2HBr	C	224-226	EtOH	75	$C_{24}H_{32}N_2O_2\cdot 2HBr$
28	2-OH	2-Me	1	2HBr·0.5-EtOH[c]	C	243-244	EtOH	49	$C_{25}H_{34}N_2O\cdot 2HBr\cdot 0.5EtOH$
29	3-OMe	3-OMe	1	2HCl	B	245-249	MeOH	57	$C_{26}H_{36}N_2O_2\cdot 2HCl$
30	2-OMe	3-OMe	1	2HCl	B	239-246	MeOH	63	$C_{26}H_{36}N_2O_2\cdot 2HCl$
31	2-OMe	2-Me	1	2HCl	B	246-249	MeOH	60	$C_{26}H_{36}N_2O\cdot 2HCl$

[a] See footnote *a* in Table II. [b] See footnote *a* in Table I. [c] Mass spectrum (EI) *m/e* 378 (M^+).

Y, into both phenyl groups resulted in a decrease of activity (**26–31**).

Some selected compounds were tested for their analgesic activities by the Haffner method after subcutaneous administration in rats (Table V). In this test, it was found that **5a** and **5b** showed potent analgesic activity. Their potencies were 33 and 42 times that of morphine, respectively. The analgesic activity of **5a**, tested by the method of D'Amour–Smith[9] was antagonized completely by the simultaneous administration of naloxone hydrochloride (0.1 mg/kg sc) in mice.

In general, it is considered that the phenolic hydroxyl group of opiates plays an important role in binding to the opiate receptor,[5a-c] and morphinelike analgesics are highly stereoselective in their interaction with receptors.[16] The analgesic activity of **4a–c** was enhanced markedly by the introduction of a *m*-hydroxyl group on the 2-phenyl group, and their compounds having the hydroxyl group among the substituents examined were the most active. From these results it is suggested that the 2-phenyl group may play a more significant role in the interaction with analgesic receptors than the 1-phenyl group, though the 1-phenyl group is necessary for an appearance of analgesic activity. Opiates such as morphine and racemorphan have a phenolic hydroxyl group on the para position to their aminoethyl moieties or on the meta position with respect to their quaternary carbon atoms. This hydroxyl group is necessary for the appearance of potent analgesic activity.[5a-c] In contrast, 2- (or 4-) hydroxy-*N*-methylmorphinan does not show any analgesic activity.[5c,17,18] In the derivatives of 4-phenylpiperidine,[5c,d] 3,5-propanopiperidine,[5e] phenylmorphan,[5d] 1-phenyl-6-azabicyclo[3.2.1]octane,[5f] 1-phenyl-2-aminomethylcyclohexanole,[5g] and 6,7-benzomorphan,[5c] the position of the phenolic hydroxyl group corresponds to that of the phenolic hydroxyl group of morphine (meta to the quaternary carbon; only in 6,7-benzomorphans para to the aminoethyl moiety).[5a] Furthermore, methionine-enkephalin has a phenolic hydroxyl group on the para position to the aminoethyl moiety.[4,5b] Thus, although introduction of a hydroxyl group into the 2-phenyl group of **4a–c** causes a marked increase in analgesic activity, the position of the hydroxyl group in the most active compounds is meta with respect to the β-phenethylamine moiety and may not correspond, at least structurally (but not clear conformationally), to that of the phenolic hydroxyl group of morphine.

Experimental Section

All melting points, determined on a Yanagimoto micromelting point apparatus, are uncorrected. Mass spectra were recorded on a Hitachi RMU-6L mass spectrometer (EI, 70 eV) or a JMS-D300 mass spectrometer (CI, methane) with a direct inlet system. Organic extracts were dried over anhydrous Na_2SO_4.

2-(3-Methoxyphenyl)-1-phenylethylamine (**1a**), 2-(4-methoxyphenyl)-1-phenylethylamine, 2-(4-hydroxyphenyl)-1-phenylethylamine, and 1-(4-methoxyphenyl)-2-phenylethylamine were prepared according to the literature.[7b,c] 1,2-Diphenylethylamines **1b–e** (Table I) were prepared in a manner similar to that described in the literature.[7a] *N,N*-Bis(2-hydroxyethyl)-1,2-diphenylethylamines **2a–e** (Table I) and their 2-chloroethyl derivatives **3a–e** (Table I) were prepared in a manner similar to that described in the literature.[2,8]

1-Cycloalkyl-4-(1,2-diphenylethyl)piperazines 5–31 (Tables II and III). Procedure A. Compounds **5a–9a, 19a, 20a,** and **21** were prepared by the reactions of **1** and *N,N*-bis(2-chloroethyl)cyclohexylamine hydrochloride in a manner similar to that described previously.[2]

Procedure B. Compounds **7–10, 17–19, 22–24,** and **29–31** were prepared by the reaction of **3**·HCl with an appropriate cycloalkylamine in a manner similar to that described previously.[2]

Procedure C. Cleavage of the Ether Linkage (5, 6, 20, and 25–28). A mixture of 1-cycloheptyl-4-[2-(3-methoxyphenyl)-1-phenylethyl]piperazine (**7b**) dihydrochloride (10.6 g, 22.8 mmol), 47% hydrobromic acid (106 mL), and glacial acetic acid (53 mL) was refluxed for 3–5 h and then allowed to cool. The precipitated crystals were collected by filtration, washed with acetone, and recrystallized from aqueous MeOH to give 11.2 g of **5b**·2HBr.

Compounds **5a,c, 6, 20,** and **25–28** were prepared from **7a,c, 8, 19, 22,** and **29–31**, respectively, in a manner similar to that described above.

Procedure D. Alkylation (11 and 16). A mixture of 1-cyclohexyl-4-[2-(4-hydroxyphenyl)-1-phenylethyl]piperazine (**6a**) (14.5 g, 39.8 mmol), K_2CO_3 (15.5 g, 112 mmol), and acetone (400 mL) was refluxed for 2 h with stirring. To the mixture was added dropwise diethyl sulfate (7.2 g, 46.6 mmol), and the mixture was refluxed for 16 h with stirring. After being cooled, the inorganic materials were filtered off, the solvent was removed in vacuo, and to the residue was added 28% NH_4OH. The mixture was extracted with Et_2O, and the Et_2O extract was dried. After the solvent was removed, the oily residue was purified by chromatography on a column of silica gel. The product was eluted with 50% (v/v) Et_2O–$CHCl_3$. The oily base was converted to its

Table IV. Analgesic Activity in Mice

compd	salt	ED_{50}, mg/kg (95% confidence limits) D'Amour-Smith method, sc	phenylquinone method, po
5a	2HBr	0.143 (0.082-0.247)	3.53 (1.44-8.69)
5b	2HBr	0.107 (0.071-0.160)	2.71 (1.26-5.84)
5c	2HBr	0.182 (0.129-0.256)	2.76 (1.16-6.53)
6a	2HBr	13.1 (9.36-16.4)	58.3 (29.9-114)
6b	2HBr	4.32 (2.56-7.28)	35.9 (23.2-55.4)
6c	2HBr	5.37 (3.07-9.41)	14.6 (8.26-25.7)
7a	2HCl	3.22 (2.63-4.68)	9.18 (4.95-17.0)
7b	2HCl	2.81 (1.29-6.16)	2.51 (0.95-6.64)
7c	2HCl	7.91 (4.09-15.3)	3.41 (2.04-5.68)
8a	2HCl	74.2 (57.9-94.8)	39.0 (26.4-53.4)
8b	2HCl	117 (71.5-190)	23.6 (17.3-32.0)
8c	2HCl	301 (240-377)	17.2 (5.93-49.7)
9a	2HCl	49.1 (31.8-75.6)	14.5 (6.47-32.4)
9b	2HCl	92.0 (47.4-179)	17.8 (9.18-34.6)
9c	2HCl	250 (181-345)	
10a	2HCl	115 (83.9-150)	51.7 (25.6-104)
10b	2HCl	134 (93.3-194)	>100
10c	2HCl	~320	50.3 (17.1-148)
11	2HCl	101 (80.2-132)	40.1 (20.6-78.2)
12	2HCl	0.159 (0.117-0.216)	1.84 (1.04-3.27)
13	2HBr	14.1 (10.2-19.6)	
14	2HCl	0.210 (0.123-0.359)	
15	2HCl	16.3 (10.5-25.3)	24.1 (7.20-80.9)
16	$2HCl \cdot H_2O$	67.3 (56.2-80.6)	91.7 (43.1-195)
17	2HCl	219 (148-323)	
18a	2HCl	>160[a] (inactive)	
18b	2HCl	>320	
19a	2HCl	4.63 (3.08-6.96)	9.70 (5.08-18.6)
19b	2HCl	6.02 (3.78-9.56)	16.4 (11.3-23.9)
19c	2HCl	14.9 (7.18-30.9)	
20a	2HBr	11.6 (4.65-29.1)	18.8 (7.70-46.1)
20b	2HBr	70.7 (40.9-122)	14.3 (7.77-26.5)
20c	2HBr	40.8 (19.4-85.6)	8.66 (3.88-19.3)
21	2HCl	~160	38.3 (23.4-62.7)
22	2HCl	22.0 (15.3-27.6)	41.4 (25.5-67.0)
23a	2HCl	47.8 (25.5-89.3)	31.6 (11.7-107)
23b	2HCl	138 (108-178)	41.6 (21.3-81.1)
23c	2HCl	≥320	
24	2HCl	>80[a] (inactive)	
25	2HBr	23.0 (16.2-32.0)	32.8 (15.7-68.6)
26	2HBr	7.53 (5.70-9.96)	>100
27	2HBr	>320	
28	2HBr·0.5-EtOH	76.2 (48.9-133)	18.5 (10.3-33.4)
29	2HCl	12.3 (8.99-16.9)	12.4 (4.69-32.7)
30	2HCl	37.3 (26.0-53.6)	21.1 (17.7-25.1)
31	2HCl	32.6 (21.2-50.2)	
1a	HCl	>320	
1b	HCl	>320	
2a	HCl	>320	
2d	HCl	>160[a] (inactive)	
3a	HCl	28.3 ip[b] (20.2-39.6)	
3e	HCl	>160[a] (inactive)	
4a[d]	2HCl	3.09 (2.21-4.95)	12.5 (6.29-21.8)
4b	2HCl	4.79[c] (2.64-8.54)	10.4[d] (6.21-17.4)
4c[d]	2HCl	3.45 (2.06-5.80)	8.98 (4.03-20.0)
morphine	HCl	2.39 (1.78-3.20)	4.20 (2.61-6.77)

[a] Toxic dose. [b] Insoluble (suspension). [c] $n = 50$. [d] See ref 2.

Table V. Analgesic Activity in Rats

compd	salt	ED_{50}, mg/kg (95% confidence limits), Haffner method, sc
5a	2HBr	0.0588 (0.0356-0.0969)
5b	2HBr	0.0464 (0.0345-0.0623)
6a	2HBr	6.95 (4.73-9.70)
morphine	HCl	1.17 (0.65-2.28)

hydrochloride with methanolic HCl, and the resulting crystals were recrystallized from MeOH to give 11.5 g of 11·2HCl.

Compound **16** was prepared in a manner similar to that described above by using benzyl bromide.

Procedure E. Acylation (12–15). A mixture of **5a**·2HCl (5.2 g, 11.9 mmol), propionic anhydride (10.0 g, 76.8 mmol), and pyridine (100 mL) was refluxed for 4 h, and the solvent was removed in vacuo. To the residue was added acetone, and the precipitate was collected and recrystallized from EtOH to give 4.5 g of 14·2HCl.

Compounds **12**, **13**, and **15** were prepared from **5a**, **6a**, and **20a**, respectively, in a manner similar to that described above by using acetic anhydride or propionic anhydride.

Analgesic Assay. The compounds listed in Tables II and III were tested for analgesic activity by the method of D'Amour-Smith,[39] phenylquinone writhing,[10] or the Haffner[11] test described previously.[2,3] Five to fifteen animals for a dose and three to five doses for each compound were used, and the values of ED_{50} were calculated according to the Litchfield-Wilcoxon method.[12]

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Synthesis and Antihypertensive Activity of 5-Thio-2-pyridinecarboxylic Acid Derivatives

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Synthesis of various substituted 5-thio-2-pyridinecarboxylic acids and their derivatives is described by three methods, i.e., displacement of nitrite from methyl 5-nitro-2-pyridinecarboxylate (**10**) by a thiol anion, alkylation of methyl 5-thio-2-pyridinecarboxylate derived from reaction of the diazotized methyl 5-amino-2-pyridinecarboxylate (**5**) with thiocyanate followed by borohydride reduction of the product, and alkylation of 5-thio-2-pyridinecarbonitrile followed by hydrolysis. 5-Thio-2-pyridinecarbonitrile was obtained from butyl 6-methyl-3-pyridyl sulfoxide (**2**) by nitrosation and dehydration of the oxime. Many of these 5-thio-2-pyridinecarboxylic acid derivatives were orally active antihypertensive agents in the spontaneously hypertensive rat. Optimization of the structural parameters for this activity yielded 5-[(*m*-trifluorobenzyl)thio]-2-pyridinecarboxylic acid (**41**) and its sulfoxide, **42**. Further biological studies with these compounds are described.

Vasodilators are of growing importance in the therapy of cardiovascular diseases. Their use as antihypertensive agents has increased since concomitant administration of β-adrenergic drugs has become recognized as an excellent regimen.[1] More recently, interest has developed in the use of vasodilators for cardiac failure.[2]

Fusaric acid, 5-butyl-2-pyridinecarboxylic acid (**11**), has been shown to be a dopamine β-hydroxylase inhibitor in man,[3] although the antihypertensive effect seen in man and animals from both fusaric acid (**11**) and its amide seems better explained by direct peripheral arteriolar relaxation.[4] Therefore we concluded that certain substituted 5-thio-2-pyridinecarboxylic acids, **1**, might also be useful peripheral vasodilators.

Chemistry. The synthesis of 5-thio-2-pyridinecarboxylic acid (**1**, R = H) has been described by Delarge,[5] but only one derivative, **1** [R = $-C(=S)N(CH_3)_2$], has since been reported.[6] Extensive work has been carried out on the isomeric 3-thio-2-pyridinecarboxylic acids because of their hypoglycemic activity.[7] The paucity of work on 5-substituted 2-pyridinecarboxylic acids reflects the synthetic difficulties inherent in the 2,5 orientation of substituents in the pyridine ring. We have recently described a new route to such compounds.[8] Butyl 6-methyl-3-pyridyl sulfoxide[8] (**2**) prepared by this route could be nitrosated to the oxime of 5-(butylsulfinyl)-2-pyridinecarboxaldehyde (**3**). The oxime **3** could be dehydrated to 5-(butylsulfinyl)-2-pyridinecarbonitrile (**4**). The Pummerer rearrangement of the sulfoxide **4** then provided an intermediate which could be alkylated directly to provide a wide range of 5-thio-2-pyridinecarbonitrile derivatives. Hydrolysis of these derivatives with base provided the acids **1**. This procedure (Scheme I) is illustrated in the Experimental Section for 5-(benzyl-

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