New Analgetic Agents. V.[1] 1-Butyryl-4-cinnamylpiperazine Hydrochloride and Related Compounds

TSUTOMU IRIKURA, KUNIYOSHI MASUZAWA, KEIGO NISHINO, MORIMICHI KITAGAWA, HIROAKI UCHIDA, NORIKO ICHINOSEKI, AND MASATOSHI ITO

Kyorin Chemical Laboratory, Kyorin Pharmaceutical Company, Ltd., Ukima, Kita-ku, Tokyo, Japan

Received February 12, 1968

The syntheses of 1-acyl-4-substituted piperazines are reported. All of these compounds were tested for analgetic activity in mice using both a pressure method and the D'Amour–Smith method. Their structure–activity relationship is discussed. In particular, the title compound showed promising analgetic activity.

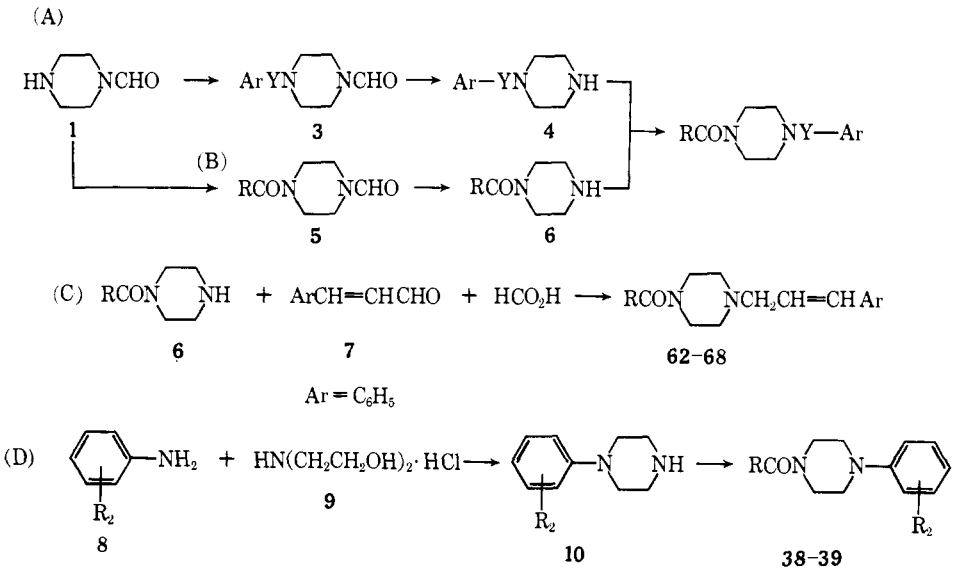
Recently, a wide variety of physiologically active compounds having a piperazine ring as a structural feature has been described. These include antihistaminic,[2] tranquilizing,[3] ganglion stimulating,[4] and antitumor agents.[5]

In the previous papers of this series,[6] it has been shown that 1,4-bis(aryloxyacetyl)piperazines obtained by the reactions of 1,4-bis(chloroacetyl)piperazine with phenols were interesting as antipyretic analgetic agents. In order to investigate a structure–activity correlation in the class of 1-acyl-4-substituted piperazines, 1,4-bis(acyl)piperazines and 1,4-bis(alkoxyacyl)piperazines were prepared by general methods and the analgetic activity measured with mice showed a great activity in 1,4-bis(butyryl)piperazine (**13**, Table II).

tivity of 1-acyl-4-cinnamylpiperazine hydrochlorides has never been described. These facts prompted us to investigate the structure–activity correlation of 1-acyl-4-phenyl-, 1-acyl-4-aralkyl-, and 1-acyl-4-cinnamylpiperazines. These piperazine derivatives were prepared by the four methods as illustrated in Chart I.

The intermediates required in this study were synthesized by the methods as depicted below. 1-Cinnamylpiperazine (**4a**) (ArY = $C_6H_5CH{=}CHCH_2$) was synthesized by the deformylation of 1-cinnamyl-4-formylpiperazine (**3a**) which was obtained by the treatment of 1-formylpiperazine (**1**) with cinnamyl halide (**2**) in the presence of $NaHCO_3$. The nmr spectrum of **4a** showed a doublet at τ 3.54 and a doublet–triplet centered at τ 3.96 arising from the two olefinic

CHART I



The analgetic activity of 3-cinnamyl-8-propionyldiazabicyclo[3.2.1]octane[7] and the antihistaminic action of 1-benzhydryl-4-cinnamylpiperazine hydrochloride[8] have been reported. However, the analgetic activity of 1-acyl-4-cinnamylpiperazine hydrochlorides has never been described. These facts prompted us to investigate the structure–activity correlation of 1-acyl-4-phenyl-, 1-acyl-4-aralkyl-, and 1-acyl-4-cinnamylpiperazines. These piperazine derivatives were prepared by the four methods as illustrated in Chart I.

The intermediates required in this study were synthesized by the methods as depicted below. 1-Cinnamylpiperazine (**4a**) (ArY = $C_6H_5CH{=}CHCH_2$) was synthesized by the deformylation of 1-cinnamyl-4-formylpiperazine (**3a**) which was obtained by the treatment of 1-formylpiperazine (**1**) with cinnamyl halide (**2**) in the presence of $NaHCO_3$. The nmr spectrum of **4a** showed a doublet at τ 3.54 and a doublet–triplet centered at τ 3.96 arising from the two olefinic protons with a large coupling constant (J = 16 cps), indicating that these two hydrogen atoms are *trans* to each other. In an attempt to obtain 1-substituted piperazines without using a protective group, we could not synthesize **4a** by the selective reduction of 4-cinnamyl-2-piperazinone with $NaBH_4$ in triethylamine.[9] 1-Acylpiperazines (**6**, Table I) were prepared by removing the formyl group from 1-acyl-4-formylpiperazines (**5**) using the technique of Powers[10] for N-formyldiethylamine.

(1) Part IV: K. Nishino, N. Ichinoseki, K. Shishido, and T. Irikura, *Yakugaku Zasshi*, **85**, 715 (1965).

(2) R. A. Marshall, H. P. Sawyer, Jr., and B. E. Lincoln, Jr., *J. Maine Med. Ass.*, **54**, 169 (1963).

(3) H. Fleischl, *J. Amer. Geriat. Soc.*, **13**, 253 (1965).

(4) S. Murayama and K. R. Unna, *J. Pharmacol. Exp. Ther.*, **140**, 183 (1963).

(5) B. W. Harrom and J. A. Carbon (Abbott Laboratories), German Patent 1,138,781 (Oct 31, 1962).

(6) (a) T. Irikura, K. Nishino, and N. Ichinoseki, *Yakugaku Zasshi*, **83**, 785 (1963); (b) T. Irikura, K. Masuzawa, M. Kitagawa, and H. Uchida, *ibid.*, **84**, 744 (1964).

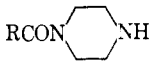
(7) G. Cignarella, E. Occelli, G. Crisliani, L. Paduano, and E. Testa, *J. Med. Chem.*, **6**, 764 (1963).

(8) Laboratoria Pharmaceutica DR. C. Janssen, N. V., British Patent 809,760 (March 25, 1956).

(9) K. Masuzawa, H. Uchida, and M. Kitagawa, *Bull. Chem. Soc. Japan*, **40**, 244 (1967).

(10) J. C. Powers, R. Seidner, and T. G. Parsons, *Tetrahedron Letters*, 1713 (1965).

TABLE I
1-ACYLPIPERAZINES



No.	R	Bp (mm), °C	Yield, %	Picrate Mp, °C	Picrate Formula[a]
6a	CH_3	110–112 (1.0)[b]	48.1	228–230	$C_{12}H_{15}N_5O_8$
6b	n-C_3H_7	117–121 (3.0)	53.8	205–207	$C_{14}H_{19}N_5O_8$
6c	n-C_5H_{11}	131–136 (2.0)	98.9	159–160.5	$C_{16}H_{23}N_5O_8$

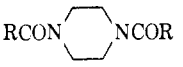
[a] All compounds showed a correct analysis for C, H, N. [b] Lit.[6b] bp 95–105° (0.5 mm).

azines synthesized were oils and therefore were isolated as hydrochlorides.

Pharmacology. The methods used for evaluating the analgetic activity of the compounds in Tables II and III were the pressure method[12] and the D'Amour-Smith's method.[13] In the experiments to test the activity of the compounds by the pressure method of Green[14] as modified by Takagi, *et al.*, constant water pressure was applied to the tail of a 20-g mouse and the pressure was recorded on a smoked paper through a Hg manometer. The pain threshold was determined by the pressure at which the responses to pain (*e.g.*, writhing, squeaking, or trying to bite the pressed portion) were first observed. Normal pain threshold of untreated animals was about 40 mm. When the pain threshold of test animals exceeded 100 mm after the administration of a test compound, the dose of the test compound was considered to be effective.

1,4-Bis(acyl)piperazines and related compounds (**11–37**) were divided into three groups. In group A (**11–22**), 1,4-bis(butyryl)piperazine (**13**) was the most

TABLE II
1,4-BIS(ACYL)PIPERAZINES AND RELATED COMPOUNDS



Group	No.	R	Mp[a] or bp (mm), °C	Yield, %	Formula	Analyses[f]	LD_{50}, mg/kg *po*	Pressure[b] ED_{50}, ip	D'Amour-Smith[b,c] ED_{50}, ip
A	11	CH_3[h]	142–143	47.4	$C_8H_{14}N_2O_2$	C, H, N	5100	0[d]	0
	12	C_2H_5	88–90	52.3	$C_{10}H_{18}N_2O_2$	C, H, N	1750	0	0
	13	n-C_3H_7	29–31	60.0	$C_{12}H_{22}N_2O_2$	C, H, N	836	11.27	3.83
	14	i-C_3H_7	131–132	54.1	$C_{12}H_{22}N_2O_2$	H, N; C[g]	1980	0	1.5
	15	n-C_4H_9[h]	54–55	36.8	$C_{14}H_{26}N_2O_2$	N	390	6.78	7.9
	16	i-C_4H_9[h]	110–111	52.4	$C_{14}H_{26}N_2O_2$	C, H, N	445	8.49	6.1
	17	n-C_5H_{11}[h]	72–73	62.0	$C_{16}H_{30}N_2O_2$	C, H, N	338	4.72	4.6
	18	n-C_6H_{13}[h]	41–43	49.6	$C_{18}H_{34}N_2O_2$	N	696	4.32	4.3
	19	n-C_7H_{15}[i]	64–66	85.8	$C_{20}H_{38}N_2O_2$	C, H, N	>3000	3.23	4.3
	20	C_6H_5[j]	193–194	92.2	$C_{18}H_{18}N_2O_2$	C, H, N	>1000	0	...[e]
	21	o-C_6H_4Cl	222	70.2	$C_{18}H_{16}N_2O_2Cl_2$	C, H, N	>1000	0	...
	22	3,4,5-$C_6H_2(OCH_3)_3$	218–220	33.7	$C_{24}H_{30}N_2O_8$	C, H, N	>1000	0	...
B	23	CH_3OCH_2	82–83	82.4	$C_{10}H_{18}N_2O_4$	C, H, N	>4000	3.25	2.7
	24	$C_2H_5OCH_2$	71.5–73	88.7	$C_{12}H_{22}N_2O_4$	C, H, N	775	9.12	15.3
	25	n-$C_3H_7OCH_2$	55–57	67.1	$C_{14}H_{26}N_2O_4$	C, H, N	1490	3.64	2.4
	26	i-$C_3H_7OCH_2$	99.5–100	5.3	$C_{14}H_{26}N_2O_4$	C, H, N	3400	2.98	...
	27	n-$C_4H_9OCH_2$	52–54	30.6	$C_{16}H_{30}N_2O_4$	C, H, N	189	7.74	15.3
	28	i-$C_4H_9OCH_2$	125–128	31.8	$C_{16}H_{30}N_2O_4$	N	...	0	...
	29	$(CH_3)_3COCH_2$	120–122	31.8	$C_{16}H_{30}N_2O_4$	C, H, N	...	0	...
	30	n-$C_5H_{11}OCH_2$	280 (10)	20.6	$C_{18}H_{34}N_2O_4$	C, H, N	...	0	...
	31	n-$C_6H_{13}OCH_2$	250 (2)	54.5	$C_{20}H_{38}N_2O_4$	N	...	0	...
	32	n-$C_8H_{17}OCH_2$	27–31	18.8	$C_{24}H_{46}N_2O_4$	N	...	0	...
C	33	$C_6H_5NHCH_2$	250	39.5	$C_{20}H_{24}N_4O_2$	C, H, N	>1000	0	9.4
	34	o-$ClC_6H_4NHCH_2$	260	15.4	$C_{20}H_{22}N_4O_2Cl_2$	C, H, N	>1000	0	9.2
	35	$C_6H_5NCH_2$ (CH$_3$)	191–193	11.2	$C_{22}H_{28}N_4O_2$	C, H, N	>1000	0	9.0
	36	$C_6H_5NCH_2$ (C_2H_5)	210–213	11.2	$C_{24}H_{32}N_4O_2$	N	>1000	0	20.2
	37	$C_6H_5SCH_2$	152–153	82.8	$C_{20}H_{22}N_2O_2S_2$	C, H, N	>1000	0	6.1

[a] Crystallization solvents: 11 (Me_2CO); **20** (EtOH); **12–15** (Et_2O–petroleum ether (bp 30–70°)); **16–19, 23–27** (ligroin); **21, 28, 29** (MeOH); **22, 33–37** (DMF); **30–32** (MeCN). [b] Potency ratio to sulpyrin (sodium methylaminoantipyrine methanesulfonate) (= 1). [c] The ED_{50} for sulpyrin by this method is 425.6 mg/kg ip. [d] 0 = no effect. [e] Not done. [f] Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for these elements or functions were within ±0.4% of the theoretical values. [g] C: calcd, 63.68; found, 63.14. [h] St. Groszkowski, A. Serper, N. Ionesco, A. Soresco, A. Hacic, and D. Panaitesc, *Ann. Pharm. Franc.*, **16**, 517 (1958). [i] A. L. Jacoby (to National Aluminate Corp.), U. S. Patent 2,541,584 (Feb 13, 1951). [j] A. W. Hofmass, *Ber.*, **23**, 3301 (1890).

In the methods A and D, acyl chlorides were treated with twice the theoretical amount of corresponding 1-substituted piperazines (**4** and **10**) in benzene or with equimolar amount of corresponding 1-substituted piperazines (**4** and **10**) in the presence of $NaHCO_3$ in ethanol to give 1-acyl-4-substituted piperazines. In order to study the chemical and physiological properties of 1-acyl-4-cinnamylpiperazines in detail, **62–68** were then synthesized through other two routes. In method B, 1-acylpiperazines (**6**) were treated with cinnamyl bromide (**2b**) in the presence of $NaHCO_3$ in benzene to give **62**, **64**, and **67**. In method C, the Leuckart amine alkylation[11] was carried out to furnish **62–68** in good yields. The majority of the 1-acyl-4-substituted piper-

(11) M. L. Moore, *Org. Reactions*, **5**, 301 (1949).

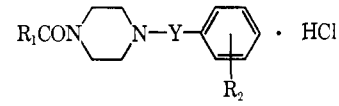
(12) K. Takagi and T. Kameyama, *Yakugaku Zasshi*, **78**, 553 (1958).

(13) F. E. D'Amour and D. L. Smith, *J. Pharmacol. Exp. Ther.*, **72**, 74 (1941).

(14) A. F. Green, P. A. Young, and E. I. Godfrey, *Brit. J. Pharmacol.*, **6**, 572 (1951).

Table III

1-Acyl-4-substituted Piperazine Hydrochlorides



Group	No.	R_1	R_2	Y	Mp, °C[a]	Yield, %	Formula	Analyses[e]	LD_{50}, mg/kg po	Pressure ED_{50}, mg/kg po	D'Amour-Smith ED_{50}, mg/kg po
D	38	CH_3	H		216–217	71.6	$C_{12}H_{17}N_2OCl$	C, H, N	1200	0[c]	0
	39	C_2H_5	*o*-Cl		122–124	27.3	$C_{13}H_{18}N_2OCl_2$	C, H; N[f]	...[d]	0	...[d]
	40	C_3H_7	H		205	89.7	$C_{14}H_{21}N_2OCl$	C, H, N	1900	0	...
	41	$C_6H_5CH_2$	H		214	31.0	$C_{18}H_{21}N_2OCl$	C, H, N	...	0	...
	42	C_6H_5	H		90–94[b]	32.3	$C_{17}H_{18}N_3O$	N	...	0	...
	43	C_6H_5	*o*-Cl		131–133[b]	74.8	$C_{17}H_{17}N_2OCl$	C, H, N	...	0	...
	44	*o*-C_6H_4Cl	H		200–202	22.6	$C_{17}H_{18}N_2OCl_2$	C, H, N	...	0	...
	45	*o*-C_6H_4Cl	*o*-Cl		165–166[b]	58.8	$C_{17}H_{16}N_2OCl_2$	C, H, N	...	0	...
	46	*m*-C_6H_4Cl	H		207–209	59.8	$C_{17}H_{18}N_2OCl_2$	C, H, N	...	0	...
	47	*m*-C_6H_4Cl	*o*-Cl		135–137[b]	53.0	$C_{17}H_{16}N_2OCl_2$	C, H, N	...	0	...
	48	*p*-C_6H_4Cl	H		122–123[b]	65.3	$C_{17}H_{17}N_2OCl$	C, H, N	...	0	...
	49	*p*-C_6H_4Cl	*o*-Cl		110–111[b]	58.8	$C_{17}H_{16}N_2OCl_2$	C, H, N	...	0	...
E	50	CH_3	*o*-Cl	CH_2	198–199	76.4	$C_{13}H_{18}N_2OCl_2$	C, H, N	1190	0	...
	51	C_2H_5	*o*-Cl	CH_2	198–200	87.3	$C_{14}H_{20}N_2OCl_2$	C, H, N	...	0	...
	52	C_3H_7	*o*-Cl	CH_2	196–199	53.8	$C_{15}H_{22}N_2OCl_2$	C, H, N	1860	43.39	68.0
	53	$C_6H_5CH_2$	*o*-Cl	CH_2	218	58.2	$C_{19}H_{22}N_2OCl_2$	N	205	0	0
	54	C_6H_5	H	CH_2	247	67.3	$C_{18}H_{21}N_2OCl$	C, H, N	...	0	0
	55	*o*-C_6H_4Cl	H	CH_2	257	54.5	$C_{18}H_{20}N_2OCl_2$	C, H, N	>1000	0	...
	56	*o*-C_6H_4Cl	*o*-Cl	CH_2	234–235	40.5	$C_{18}H_{19}N_2OCl_3$	C, H, N	442	0	...
	57	*o*-$C_6H_4OCH_3$	*o*-Cl	CH_2	223–224	42.0	$C_{19}H_{22}N_2O_2Cl_2$	C, H, N	705	0	...
	58	3,4,5-$C_6H_2(OCH_3)_3$	*o*-Cl	CH_2	233	47.8	$C_{21}H_{26}N_2O_4Cl_2$	C, H, N	586	0	...
F	59	C_2H_5	H	CH_2CH_2	204–205	37.1	$C_{15}H_{23}N_2OCl$	C, H, N	400	0	...
	60	C_3H_7	Cl	CH_2CH_2	175–177	50.4	$C_{16}H_{24}N_2OCl_2$	C, H, N	400	0	...
	61	C_2H_5	H	$(CH_2)_3$	174–175	27.2	$C_{16}H_{25}N_2OCl$	C, H, N	400	0	...
	62	CH_3	H	$CH_2CH{=}CH$	205–206	46.3	$C_{15}H_{21}N_2OCl$	C, H, N	1000	0	...
	63	C_2H_5	H	$CH_2CH{=}CH$	184–187	55.0	$C_{16}H_{23}N_2OCl$	C, H, N	715	28.9	58.2
	64	*n*-C_3H_7	H	$CH_2CH{=}CH$	207–209	52.3	$C_{17}H_{25}N_2OCl$	C, H, N	882	38.5	17.6
	65	*i*-C_3H_7	H	$CH_2CH{=}CH$	214–217	43.7	$C_{17}H_{25}N_2OCl$	C, H, N	693	79.5	135.0
	66	*n*-C_4H_9	H	$CH_2CH{=}CH$	209–212	42.1	$C_{18}H_{27}N_2OCl$	C, H, N	790	117.0	...
	67	*n*-C_5H_{11}	H	$CH_2CH{=}CH$	198–200	35.6	$C_{19}H_{29}N_2OCl$	C, H, N	...	0	...
	68	*n*-C_6H_{13}	H	$CH_2CH{=}CH$	195–198	40.8	$C_{20}H_{31}N_2OCl$	C, H, N	...	0	...
Aminopyrine										165	221

[a] Crystallization solvents: **38**, **40**, **41**, **44**, **46**, **48**, **54–58** (EtOH); **39**, **50–53**, **59**, **64–68** (MeCN); **42** (DMF); **43**, **45**, **47**, **49** (EtOH–H_2O); **60**, **61** (*i*-PrOH); **62** (MeCN–Et_2O); **63** (EtOH–Et_2O). [b] Free base. [c] 0 = no effect. [d] Not done. [e] See footnote *f*, Table II. [f] N: calcd, 9.68; found, 9.16.

active compound; replacing the butyryl group of **13** by a lower or a higher acyl group led to a considerable diminution of the activity. No analgetic activity was found in the benzoyl derivatives (**20–22**). In group B (**23–32**), 1,4-bis(ethoxyacetyl)- and 1,4-bis(butoxyacetyl)piperazine (**24**, **27**) were active compounds. In group C (**33–37**), all of the compounds showed profound analgetic activity in the D'Amour–Smith test but were inactive when tested by the pressure method. 1-Acyl-4-substituted piperazines were divided next into three groups. In group D (**34–49**), no active compounds were found. In group E (**50–58**), only **52** was active. In group F (**59–68**), the phenethyl- and phenylpropyl-substituted compounds (**59–61**) were inactive. On the other hand, the compounds substituted with a cinnamyl group at N^4 of the piperazine ring in 1-acyl-4-substituted piperazines showed a potent analgetic activity. Among them, 1-propionyl- and 1-butyryl-4-cinnamylpiperazines (**63**, **64**) were the most potent. The potency of **64** was 4.3 times that of aminopyrine. The pharmacological screening data for these compounds (**11–68**) are given in Tables II and III.

Experimental Section

Melting points were measured on a micro hot stage and are uncorrected. Ir spectra were recorded on a Japan Spectroscopic Model DS-301 spectrometer and the nmr data (CCl_4) were obtained with a Hitachi Co., Ltd., Model R-20, with Me_4Si as an internal reference standard.

1,4-Bis(acyl)piperazines (11–22).—While most of the 1,4-bis(acyl)piperazines were already known, some which were unknown were prepared by the general method outlined below. A solution of the appropriate acyl chloride (0.1 mole) in $CHCl_3$ (150 ml) was added, drop by drop, to a suspension of piperazine hexahydrate (0.5 mole) and $NaHCO_3$ (0.1 mole) in $CHCl_3$ (100 ml), and the mixture was stirred at room temperature for 5 hr. The reaction mixture was filtered, and the filtrate was then dried (Na_2SO_4) and concentrated under reduced pressure. The residue was recrystallized from a suitable solvent to give colorless crystals; the yields were 50–80% (Table II).

1,4-Bis(alkoxyacyl)piperazines (23–32) were obtained by the treatment of 1,4-bis(chloroacetyl)piperazine with sodium alkoxides in a manner analogous to the procedure reported earlier[6b] (Table II).

1,4-Bis(N-phenylglycyl)piperazines (33–36).—A mixture of 1,4-bis(chloroacetyl)piperazine (0.1 mole) and the appropriate aniline (0.4 mole) in EtOH (50 ml) was heated with stirring under reflux for 3 hr. After cooling, the crystals which separated from the solution were collected by filtration, washed (H_2O),

and recrystallized from DMF to give colorless crystals; the yields were 10–40% (Table II).

1,4-Bis(phenylthioacetyl)piperazine (37) was synthesized by the reaction of 1,4-bis(chloroacetyl)piperazine with thiophenol in a fashion analogous to the method of synthesizing 1,4-bis(phenoxyacetyl)piperazine[6b] (Table II).

Cinnamyl Chloride (2a).—A mixture of styrene (60 g, 0.57 mole), paraformaldehyde (46.6 g, 1.55 moles), and 35% HCl (300 ml) was heated with stirring at 80° for 3.5 hr. The reaction mixture was extracted with $CHCl_3$ (300 ml) and the extract was washed with three 100-ml portions of 20% aqueous NaCl. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure, and then the residue was distilled to yield 33.6 g (38.3%) of a colorless oil, bp 57–59° (0.07 mm) (lit.[15] bp 119° (17 mm)), ν_{max} 962 (*trans*-CH=CH-)[16] and 1659 cm^{-1}.

Cinnamyl bromide (2b) was prepared by the published procedure and had bp 110–112° (3 mm) (lit.[15] bp 130° (10 mm)), ν_{max} 963 (*trans*-CH=CH-)[16] and 1640 cm^{-1}.

1-Cinnamylpiperazine (4a).—Cinnamyl halide (**2a** or **2b**, 0.129 mole) was added, drop by drop, to a stirred suspension of 1[18] (14.7 g, 0.129 mole) and $NaHCO_3$ (11.6 g, 0.138 mole) in EtOH (100 ml) and the mixture was heated under reflux for 4 hr. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to give 27.8 g of 1-cinnamyl-4-formylpiperazine as an amber oil, bp 184–188° (0.18 mm). To the oil was added 30% aqueous NaOH (100 ml) and the mixture was heated at 90–100° for 15 hr. The reaction mixture was extracted (C_6H_6) and the combined extracts were dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was distilled under N_2 to yield 12.8 g (49.0%) of viscous liquid, bp 129–135° (1 mm). Nmr on the purified material showed a multiplet at τ 2.62–2.96 (5 H), a doublet at 3.54 (1 H), a doublet–triplet centered at 3.96 (1 H), a doublet at 7.04 (2 H), a multiplet at 7.22–7.84 (8 H), and a singlet at 8.14 (1 H, >NH).

The picrate was isolated as yellow needles, mp 247° dec. *Anal.* ($C_{23}H_{24}N_8O_{14}$) C, H, N.

1-Acylpiperazines (6).—A solution of acyl chloride (0.11 mole) in $CHCl_3$ (10 ml) was added dropwise to a mixture of **1** (0.1 mole) and $NaHCO_3$ (0.11 mole) in $CHCl_3$ (200 ml). After the addition was over, stirring was continued at room temperature for several more hours. The reaction mixture was washed (H_2O), dried (Na_2SO_4), and concentrated under reduced pressure; the residue was distilled to give 1-acyl-4-formylpiperazine (**5**) as a crude yellow oil; the yields were 35–47%, ν_{max} 1645 (>NCOR) and 1675 cm^{-1} (>NCHO). It was used for the next step without further purification. The crude **5** (0.1 mole) was added to NaH (4.8 g in 50% oil, 0.1 mole) in refluxing C_6H_6 (150 ml). The suspension was heated at 75–80° for 4–5 hr, by which time the evolution of CO and H_2 had ceased. The reaction mixture was poured into ice-water. The C_6H_6 layer was separated and the aqueous layer was saturated with Na_2CO_3. The resultant aqueous layer was extracted (C_6H_6), the combined extract was dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was distilled to give 1-acylpiperazine of colorless product, ν_{max} 1635 (>NCOR) and 3300 cm^{-1} (>NH). The products were identified as the picrates (Table I).

1-Arylpiperazines (**10**) were prepared by the condensation of the appropriate anilines (**8**) with diethanolamine hydrochloride (**9**) essentially according to the method of Ishiguro, *et al.*[19]

The 1-acyl-4-substituted piperazines prepared by methods A and D are listed in Table III. The preparation of 1-*n*-butyryl-4-cinnamylpiperazine hydrochloride (**64**) described below is typical.

1-*n*-Butyryl-4-cinnamylpiperazine Hydrochloride (64). Method A.—A solution of *n*-butyryl chloride (2.6 g, 0.024 mole) in C_6H_6 (3 ml) was added, drop by drop, to a suspension of **4a** (4.3 g, 0.021 mole) and $NaHCO_3$ (2.1 g, 0.025 mole) in C_6H_6 (50 ml) at 0–5°. After the addition was over, the mixture was stirred at room temperature for 3 hr. The reaction mixture was washed twice (2% aqueous $NaHCO_3$, H_2O) and then dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was distilled to give 4.4 g (75.8%) of the free base of **64**, bp 194–196° (0.1 mm). The free base was dissolved in C_6H_6 (50 ml) and dry HCl was introduced into the solution to yield 6.3 g of colorless needles. They were recrystallized from MeCN to give 3.44 g of **64**: λ_{max}^{EtOH} 253 mμ (ε 20,100); ν_{max}^{Nujol} 955 (-CH=CH-), 1645 (>NCO-), and 2700–2300 cm^{-1} (broad).

Method B.—A mixture of **6b** (4.68 g, 0.03 mole), **2b** (6 g, 0.03 mole), and $NaHCO_3$ (2.6 g, 0.031 mole) in C_6H_6 (100 ml) was heated under reflux for 5 hr. After NaBr was filtered off, the filtrate was washed (H_2O) and dried (Na_2SO_4). Dry HCl was introduced into the solution to yield crystalline precipitates. The product was washed twice with C_6H_6 and recrystallized from MeCN to give 6.5 g (70.5%) of **64**, mp 207–208°, mixture melting point undepressed with an authentic sample prepared by method A. The ir spectra of the two samples were identical.

Method C.—A mixture of cinnamaldehyde (3.5 g, 0.027 mole), **6b** (4.0 g, 0.027 mole), and HCO_2H (1.5 g, 0.032 mole) was heated at 120° for 1 hr, cooled to 20–25°, and poured into $CHCl_3$ (100 ml). The resultant solution was washed twice with H_2O and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure and distillation of the residue gave 3.7 g (53.0%) of colorless liquid, bp 176–181° (0.06 mm); hydrochloride, colorless needles, mp 207–209°. The product was easily identified as **64** by mixture melting point with an authentic sample and by its ir spectrum.

Acknowledgment.—The authors wish to thank Dr. S. Ogihara, President of Kyorin Pharmaceutical Co., Ltd., for his interest and encouragement.

(15) M. F. Carroll, *J. Chem. Soc.*, 1266 (1940).

(16) G. Valkanas and E. S. Waight [*ibid.*, 2720 (1959)] reported that 1-phenylallyl chloride, the isomer of **2a**, rearranges rapidly and quantitatively to *trans*-cinnamyl chloride and exhibits strong infrared bands characteristic of a vinyl group (983 and 930 cm^{-1}).

(17) S. Gabriel, *Ber.*, **43**, 134 (1910).

(18) K. Fujii, K. Tomino, and H. Watabe, *Yakugaku Zasshi*, **74**, 1049 (1954).

(19) T. Ishiguro, E. Kitamura, and M. Matsumura, *ibid.*, **73**, 1110 (1953).