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, 1,4bis(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 = C₆H₅CH=CHCH₂) was synthesized by the deformylation of 1-cinnamyl-4-formylpiperazine (3a) which was obtained by the treatment of 1-formylpiperazine (1) with cinnamylhalide (2) in the presence of NaHCO₃. The nmr spectrum of 4a showed a doublet at τ 3.54 and a doublettriplet centered at τ 3.96 arising from the two olefinic





The analgetic activity of 3-cinnamyl-8-propionyldiazabicyclo [3.2.1]octane⁷ and the antihistaminic action of 1-benzhydryl-4-cinnamylpiperazine hydrochloride⁸ have been reported. However, the analgetic ac-

- (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,
- (6) (a) I. FIRURA, K. NISHINO, and N. ICHINOSEKI, Fakugaku 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).

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 NaBH₄ 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 Powers¹⁰ for N-formyldiethylamine.

- (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).



			Yield,	Pier	Picrate		
No.	R	Bp (mm), °C	67	Mp, °C	$Formula^{a}$		
6a	CH_3	110-112 (1.0) ^b	48.1	228 - 230	$\mathrm{C}_{12}\mathrm{H}_{15}\mathrm{N}_{5}\mathrm{O}_{8}$		
6b	$n-C_3H_7$	$117 - 121 \ (3.0)$	53.8	205 - 207	$C_{14}H_{19}N_5O_8$		
6c	n-C ₅ H ₁₁	131 - 136(2.0)	98.9	159 - 160.5	$\mathrm{C}_{16}\mathrm{H}_{23}\mathrm{N}_5\mathrm{O}_3$		
^a All	compou	ads 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 method¹² and the D'Amour-Smith's method.¹³ In the experiments to test the activity of the compounds by the pressure method of Green¹⁴ 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

TABLE II								
1,4-Bis(acyl)piperazines and Related	Compounds							



Group	No.	R	${{ m Mp}^a} { m or} {{ m bp (mm),}} {{ m oc}}$	Yield, %	Formula	$Analyses^i$	LD ₅₀ , mg/kg po	Pressure ^b ED ₅₀ , ip	D'Amour- Smith ^{b,c} ED50, ip
Δ.	11	CH_{a}^{h}	149-143	47 4	$C_{0}H_{1}N_{0}O_{0}$	CHN	5100	()d	0
	12	C.H.	88-90	52 3	CioHieNoOa	Č Ĥ Ň	1750	ŏ	ŏ
	13	$n - C_0 H_{\pi}$	29-31	60.0	CroHos NoOa	C H N	836	11 97	3 83
	14	$i = C_2 H_2$	131-132	54 1	CiaHaaNaOa	H N C_{θ}	1980	10.21	1.5
	15	$n - C H_{h}^{h}$	54-55	36.8	CuHasNaO	\mathbf{x}	300	6 78	7.0
	16	$i = C \cdot H \cdot h$	110_111	59.4	$C_{14}H_{26}H_{2}O_{2}$	Ĉнх	445	8 40	6 1
	17	n-C-H-h	79_{73}	62.4	$C_{14}H_{26}H_{2}O_{2}$	\vec{C} \vec{H} \vec{N}	228	4 72	4 6
	18	$n = C_5 \Pi_{11}$	41-43	40.6	$C_{16} H_{30} N_2 O_2$	N 11, 11	606 606	4 22	1 2
	10	$m C H_{i}$	64_66	45.0 85.8	$C_{18}H_{34}N_{2}O_{2}$	ê u x	>2000	2.02	1.0
	20	$C H_i$	102.104	09.0	$C_{20}H_{38}N_{2}O_{2}$	C H X	>1000	0.20	·t.0
	20	CHCI	190-194	70.2	$C_{13}\Pi_{18}\Pi_{2}O_{2}$ $C_{14}H_{18}\Pi_{2}O_{2}$	C H N	>1000	Ä	• • •
	21	245CH(0CH)	222 990	22 7	$C_{18}\Pi_{16}\Pi_{2}O_{2}O_{12}$	C H N	>1000	ň	• • •
D	22 09	CH OCH	210-220	00.1 90.4	C H N O	C H N	>1000	2.95	5 ÷
D	20	C H O C H	04-00 71 5 79	04.4	C H N O	C, H, N	/4000	0.19	15 9
	24	$C_2\Pi_5 OC\Pi_2$	(1.0~(0	00.1	$C \mathbf{U} \mathbf{N}_{2} \mathbf{O}_{4}$		1400	9.12	10.0
	20	$n - C_3 \Pi_7 O C \Pi_2$	00 5 100	07.1	C H N O		2400	0.04	2.4L
	20	$i - C_3 \Pi_7 O C \Pi_2$	99.0-100	0.0	$C_{14}\Gamma_{26}\Gamma_{20}V_{4}$	C, Π, N	100	2.00	1 = 0
	27	$n - C_4 H_9 O C H_2$	02-04	30.0	$C_{16} H_{30} N_2 O_4$	$(\underline{U}, \underline{U}, \underline{N})$	189	4.74	10.0
	28	$i - C_4 H_9 U C H_2$	120 - 128	51.8	$C_{16}H_{30}N_2O_4$		• • /	0	• • •
	29	$(UH_3)_3UUUH_2$	120-122	31.8	$C_{16}H_{30}N_2O_4$	$-0, \pm, \Sigma$		0	• • •
	30	$n-C_5H_{11}OCH_2$	280(10)	20.0	$C_{18}\Pi_{34}N_2O_1$	\bigcirc 11, N		<u> </u>	• • •
	31	$n-C_6H_{13}OCH_2$	250(2)	04.0	$C_{20}H_{38}N_2O_4$	N.	• •	0	• • •
~	32	$n-C_8H_{17}OCH_2$	27-31	18.8	$C_{24}H_{46}N_2O_4$	A H M		0	
C	33	$C_6H_5NHCH_2$	250	39.0	$C_{20}H_{24}N_4O_2$	C, H, N	>1000	0 0	9.4
	34	o-CIC ₆ H ₄ NHCH ₂	260	15.4	$C_{20}H_{22}N_4O_2Cl_2$	С, Н, N	>1000	0 0	9.2
	35	$C_6H_5NCH_2$	191-193	11.2	$\mathrm{C}_{22}\mathrm{H}_{28}\mathrm{N}_4\mathrm{O}_2$	С, Н, Х	>1000	U	9.0
	36	$\operatorname{C}_6H_5\operatorname{NCH}_2$	210-213	11.2	$\mathrm{C}_{24}\mathrm{H}_{32}\mathrm{N}_{3}\mathrm{O}_{2}$	Ν	>1000	0	20.2
	37	$\overset{\mathrm{C}_2\mathrm{II}_5}{\mathrm{C}_6\mathrm{H}_5\mathrm{SCH}_2}$	152-153	82.8	$C_{20}H_{22}N_2O_2S_2$	С, Н, Х	>1000	0	6.1

^a Crystallization solvents: 11 (Me₂CO); 20 (EtOH); 12-15 (Et₂O-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 ED₅₀ 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 $\pm 0.4\%$ of the theoretical values. ^a C: calcd, 63.68; found, 63.14. ^b 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). ⁱ A. W. Hofmass, Ber., 23, 3301 (1890).

In the methods A and D, acyl chlorides were treated with twice the theoretical amount of corresponding 1substituted piperazines (4 and 10) in benzene or with equimolar amount of corresponding 1-substituted piperazines (4 and 10) in the presence of NaHCO₃ in ethanol to give 1-acyl-4-substituted piperazines. In order to study the chemical and physiological properties of 1acyl-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 NaHCO₃ in benzene to give **62**, **64**, and **67**. In method C, the Leuckart amine alkylation¹¹ was carried out to furnish **62–68** in good yields. The majority of the 1-acyl-4-substituted pipermanometer. 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

⁽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



										Pressure	Smith
						\$72-1-1			LD ₅₀ ,	ED₅o, ma/ka	ED50,
Group	No.	Rı	R2	Y	Mp. °C ^a	viela,	Formula	Analyses	ng/kg po	nig/kg po	111g/kg 200
D	38	CH	н	_	216-217	71 6	C.,H.,N.OCI	CHN	1200	00	0
D	39	C.H.	o-Cl		122 - 124	27.3	C ₁₂ H ₁₇ N ₂ OCl	$C H \cdot N'$	1=00 d	Õ	d
	40	C ₂ H ₃	н		205	89.7	CuHa NaOCl	CHN	1900	Õ	•••
	41	C4H4CH	н		200	31 0	C ₁₂ H ₂₁ N ₂ OCl	CHN	1000	Õ	
	42	C ₆ H ₅ OH ₂	н		90-945	32.3	C:-H:N:O	N, 11, 11		0	
	43	CeH5	a-Cl		131-133	74.8	C17H17NoOCl	C. H. N		Ő	
	44	o-CeH4Cl	н Н		200-202	22.6	C ₁₇ H ₁₈ N ₂ OCl ₂	C. H. N	••••	0	
	45	o-C ₆ H ₄ Cl	o-Cl		$165 - 166^{b}$	58.8	$C_{17}H_{16}N_{2}OCl_{2}$	C. H. N		0	
	46	m-C ₆ H ₄ Cl	н		207 - 209	59.8	C ₁₇ H ₁₈ N ₂ OCl ₂	C. H. N		0	
	47	$m-C_{6}H_{4}Cl$	o-Cl		135-137*	53.0	C ₁₇ H ₁₆ N ₂ OCl ₂	C. H. N		0	
	48	$p-C_{e}H_{4}Cl$	Н		$122 - 123^{b}$	65.3	C ₁₇ H ₁₇ N ₂ OCl	С. Н. N		0	
	49	$p-C_6H_4Cl$	o-Cl		$110 - 111^{b}$	58.8	C ₁₇ H ₁₆ N ₂ OCl ₂	С, Н, N		0	
\mathbf{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	$C_{2}H_{5}$	o-Cl	CH_2	198 - 200	87.3	$C_{14}H_{20}N_2OCl_2$	С, Н, N		0	
	52	$C_{3}H_{7}$	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	$C_{\circ}H_{5}$	Н	CH_2	247	67.3	$C_{18}H_{21}N_2OCl$	C, H, N		0	0
	55	$o-C_6H_4Cl$	Η	CH_2	257	54.5	$\mathrm{C}_{18}\mathrm{H}_{20}\mathrm{N}_{2}\mathrm{OCl}_{2}$	С, Н, N	>1000	0	• • •
	56	$o-C_6H_4Cl$	o-Cl	CH_2	234 - 235	40.5	$\mathrm{C}_{18}\mathrm{H}_{19}\mathrm{N}_{2}\mathrm{OCl}_{3}$	С, Н, N	442	0	• • •
	57	$o-C_6H_4OCH_3$	o-Cl	CH_2	223 - 224	42.0	$\mathrm{C_{19}H_{22}N_2O_2Cl_2}$	C, H, N	705	0	
	58	$3,4,5-C_6H_2(OCH_3)_3$	o-Cl	CH_2	233	47.8	$\mathrm{C_{21}H_{26}N_2O_4Cl_2}$	С, Н, N	586	0	
\mathbf{F}	59	C_2H_5	Н	$\mathrm{CH}_{2}\mathrm{CH}_{2}$	204 - 205	37.1	$\mathrm{C}_{15}\mathrm{H}_{23}\mathrm{N}_{2}\mathrm{OCl}$	С, Н, N	400	0	• • •
	60	C_3H_7	Cl	$\rm CH_2 \rm CH_2$	175 - 177	50.4	$\mathrm{C_{16}H_{24}N_2OCl_2}$	С, Н, N	400	0	
	61	C_2H_5	Η	$(CH_2)_3$	174 - 175	27 , 2	$\mathrm{C_{16}H_{25}N_2OCl}$	С, Н, N	400	0	
	62	CH_3	Н	$CH_2CH=CH$	205 - 206	46.3	$\mathrm{C}_{15}\mathrm{H}_{21}\mathrm{N}_{2}\mathrm{OCl}$	С, Н, N	1000	0	• • •
	63	C_2H_5	Η	CH₂CH==CH	184 - 187	55.0	$\mathrm{C}_{16}\mathrm{H}_{23}\mathrm{N}_{2}\mathrm{OCl}$	С, Н, N	715	28.9	58.2
	64	n-C ₃ H ₇	\mathbf{H}	$CH_2CH=CH$	207 - 209	52.3	$\mathrm{C}_{17}\mathrm{H}_{25}\mathrm{N}_{2}\mathrm{OCl}$	С, Н, N	882	38.5	17.6
	65	i-C ₃ H ₇	\mathbf{H}	$CH_2CH=CH$	214 - 217	43.7	$\mathrm{C}_{17}\mathrm{H}_{25}\mathrm{N}_{2}\mathrm{OCl}$	С, Н, N	693	79.5	135.0
	66	n-C ₄ H ₉	н	$CH_2CH=CH$	209-212	42.1	$\mathrm{C}_{18}\mathrm{H}_{27}\mathrm{N}_{2}\mathrm{OCl}$	С, Н, N	790	117.0	
	67	n-C ₅ H ₁₁	н	$CH_2CH=CH$	198 - 200	35.6	$\mathrm{C}_{19}\mathrm{H}_{29}\mathrm{N}_{2}\mathrm{OCl}$	С, Н, N	•••	0	
	68	n-C ₆ H ₁₃	Η	$CH_2CH=CH$	195 - 198	40.8	$\mathrm{C}_{23}\mathrm{H}_{31}\mathrm{N}_{2}\mathrm{OCl}$	С, Н, N		0	
Amino	nvrine									165	921

Aminopyrine

^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-H₂O); **60**, **61** (*i*-PrOH); **62** (MeCN-Et₂O); **63** (EtOH-Et₂O). ^b Free base. ^c 0 = no effect. ^d Not done. ^c See footnote *f*, Table II. ^f N: caled, 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 phenylpropylsubstituted 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 un-Ir spectra were recorded on a Japan Spectroscopic corrected. Model DS-301 spectrometer and the nmr data (CCl₄) were obtained with a Hitachi Co., Ltd., Model R-20, with Me₄Si as an internal reference standard.

1,4-Bis(acyl)piperazines (11-22).--While most of the 1,4bis(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 CHCl₃ (150 ml) was added, drop by drop, to a suspension of piperazine hexahydrate (0.5 mole) and NaHCO3 (0.1 mole) in CHCl3 (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) ,

D'Amour-

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).

Cinamyl 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_s (300 ml) and the extract was washed with three 100-ml portions of 20% aqueous NaCl. The organic phase was dried (Na₂SO₄) 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 110° (17 mm)), p_{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.^{ir} bp 130° (10 mm)), $\nu_{\rm max}$ 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 118 (14.7 g. 0.129 mole) and NaHCO₃ (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 $90-100^{\circ}$ for 15 hr. The reaction mixture was extracted (C_6H_6) and the combined extracts were dried (Na₂SO₄). 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 II), 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. ($C_{25}H_{24}N_8O_{14}$) C, H, N.

1-Acylpiperazines (6).—A solution of acyl chloride (0.11 mole) in CHCl₃ (10 ml) was added dropwise to a mixture of **1** (0.1 mole) and NaHCO₃ (0.11 mole) in CHCl₃ (200 ml). After the addition was over, stirring was continued at room temperature for several more hours. The reaction mixture was washed (H₂O), dried (Na₂SO₄), 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 C₆H₆ (150 ml). The suspension was heated at 75–80° for 4–5 hr, by which time the evolution of CO and H₂ had ceased. The reaction mixture was poured into ice-water. The C₆H₆ layer was separated and the aqueous layer was saturated with Na₂CO₃. The resultant aqueous layer was extracted (C₆H₆), the combined extract was dried (Na₂SO₄) 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 Λ and D are listed in Table III. The preparation of 1-*n*-butyryl-4cinnamylpiperazine 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 C₆H₆ (3 ml) was added, drop by drop, to a suspension of 4a (4.3 g, 0.021 mole) and NaHCO₃ (2.1 g, 0.025 mole) in C₆H₆ (50 ml) at 0.5^o. After the addition was over, the mixture was stirred at room temperature for 3 hr. The reaction mixture was washed twice (2^C₄ aqueous NaHCO₃, H₂O) and then dried (Na₂SO₄). The solvent was removed under reduced pressure and the residue was distilled to give 4.4 g (75.8^C₄) of the free base of 64, bp 194-196° (0.1 mm). The free base was dissolved in C₆H₆ (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}^{KOR} 253 mµ (ϵ 20,100); ν_{max}^{KOR} 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 NaHCO₅ (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 (H₂O) and dried (Na₂SO₄). 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 einnamaldehyde (3.5 g, 0.027 mole), 6b (4.0 g, 0.027 mole), and HCO₂H (1.5 g, 0.032 mole) was heated at 120° for 1 hr, cooled to 20–25°, and poured into CHCl₃ (100 ml). The resultant solution was washed twice with H₂O and dried (Na₃SO₄). 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 encourgement.

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

⁽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. Watube, Yakugaku Zasshi, 74, 1049 (1954).