ranges employed were 5–320 μg for **3**, **9**, and **13**, 5–80 μg for **10**, and 50–500 ng for isoprenaline. Figure 2 is derived by drawing the best lines through the accumulated data points for increases in force and rate. All data points lie within 10% of the line for either dependent variable.

(b) Conscious Dogs.[20,21] Adult beagle dogs (Pfizer colony) were prepared, under aseptic recovery surgery, with a carotid artery loop and two subcutaneous titanium studs, designed to act as permanent ECG electrodes and placed, one each, in the dorsal neck and rump areas. Following adequate time for recovery and full wound healing, each dog was placed in a canvas support within the laboratory. A strain gauge was placed around the carotid loop and recording leads attached to the two electrodes. Recordings of both the arterial pulse and the ECG were made via appropriate interfacing onto a Grass polygraph. Measurements of QA interval (the time in milliseconds between the R wave of the ECG signal and the up-stroke of the arterial pressure pulse) were made by digital computer. To assess the activity of a test substance, recordings of QA interval were made every 0.16 h from 0.5 h before to up to 4 h after the oral administration, by gavage, of a solution of the test substance. Each value of QA interval, at a given time point, represents the mean of six consecutive sets of values, each set being the mean of the values recorded in an 8-s period. Results are expressed as the change in QA interval from the mean control (predose) value. In control animals ($n = 8$), changes in QA interval of 1.5 ± 2 and 0.5 ± 1.5 ms were observed at 1 and 3 h, respectively, after saline administration. Decreases in QA interval of 10, 15, and 20 ms correspond approximately to increases in dP/dt max of 20, 45, and 70%, respectively. A decrease in QA interval of 20 ms approaches the maximum change possible.

(20) Alabaster, C. T.; Henderson, C. G. *Br. J. Pharmacol.* **1982**, *76*, 251P.
(21) Cambridge, D.; Whiting, M. V. *Cardiovasc. Res.* **1986**, *20*, 444.
(22) Yamanaka, M.; Saito, I.; Yamatsu, K.; Fujimoto, T. Belgian Patent 4,880,020; *Chem. Abstr.* **1980**, *93*, 220743.

Acknowledgment. We gratefully thank D. J. Greenan for pK_a data and D. E. Balderson, J. Butler, S. I. Davis, T. L. Kidd, and A. G. Pomeroy for valuable technical assistance.

Registry No. **3**, 102791-36-6; **4**, 102791-49-1; **5**, 102791-44-6; **6**, 102791-50-4; **7**, 102791-51-5; **8**, 102791-60-6; **9**, 102791-39-9; **10**, 102791-41-3; **11**, 102791-42-4; **12**, 102791-48-0; **13**, 102791-47-9; **14**, 102791-45-7; **15**, 118111-92-5; **16**, 102791-55-9; **17**, 118111-93-6; **18**, 118111-94-7; **19**, 99584-29-9; **20**, 102791-92-4; **21**, 102792-12-1; **22**, 102791-96-8; **23**, 118111-95-8; **24**, 102792-31-4; **25**, 102792-14-3; **26**, 102791-93-5; **27**, 102791-94-6; **28**, 102791-95-7; **29**, 102792-11-0; **30**, 102792-10-9; **31**, 23309-18-4; **32**, 102792-15-4; **33**, 446-33-3; **34**, 118111-96-9; **35**, 102792-04-1; **36**, 102791-90-2; **37**, 102792-08-5; **38**, 102792-05-2; **39**, 102792-07-4; **40**, 102791-86-6; **41**, 102791-88-8; **42**, 102791-89-9; **43**, 102792-09-6; **44**, 102792-03-0; **45**, 102791-91-3; **46**, 102792-18-7; **47**, 102791-75-3; **48**, 102791-99-1; **49**, 102791-83-3; **50**, 102792-00-7; **51**, 102792-01-8; **52**, 102791-78-6; **53**, 102791-80-0; **54**, 102791-81-1; **55**, 102791-98-0; **56**, 102791-97-9; **57**, 102791-84-4; **58**, 102792-21-2; **59**, 102792-23-4; **60**, 108857-39-2; **61**, 102792-24-5; **62**, 108857-38-1; **63**, 102792-29-0; **64**, 102792-17-6; **65**, 118111-97-0; 4-methylimidazole, 822-36-6; 3-methyl-4-nitroaniline, 611-05-2; *trans*-3-ethoxyprop-2-enoyl chloride, 99471-66-6; triethyl phosphonoacetate, 867-13-0; *trans*-ethyl 3-[2-amino-3-(trifluoromethyl)-5-(2,4-dimethylimidazol-1-yl)phenyl]prop-2-enoate, 102791-70-8; 1,2-diformylhydrazine, 628-36-4; ethyl acrylate, 140-88-5; pyrazole, 288-13-1; 1,2,4-triazole, 288-88-0; 2*H*-tetrazole, 288-95-9; 2-methylimidazole, 693-98-1; 4-trifluoromethylimidazole, 33468-69-8; 2,4-dimethylimidazole, 930-62-1; 4-fluoronitrobenzene, 350-46-9; 4-fluoro-(2-trifluoromethyl)nitrobenzene, 393-09-9; 1-(3-acetyl-4-amino-5-methylphenyl)-2,4-dimethylimidazole, 118111-98-1.

Supplementary Material Available: X-ray data are available for 6-(2,4-dimethylimidazol-1-yl)-8-methyl-2(1*H*)-quinolinone (**13**) (9 pages). Ordering information is given on any current masthead page.

Acrylamide Derivatives as Antiallergic Agents. 2.[1] Synthesis and Structure–Activity Relationships of *N*-[4-[4-(Diphenylmethyl)-1-piperazinyl]butyl]-3-(3-pyridyl)acrylamides

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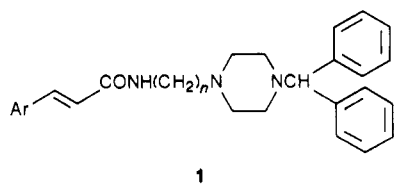
Research Laboratories, Dainippon Pharmaceutical Co., Ltd., Enoki 33-94, Suita, Osaka 564, Japan. *Received May 27, 1988*

A new series of 3-(3-pyridyl)acrylamides **16**, **17**, **19**, and **26**, and 5-(3-pyridyl)-2,4-pentadienamides **20–25** were prepared and evaluated for their antiallergic activity. Several of these compounds exhibited more potent inhibitory activities than the parent compound **1a** [(*E*)-*N*-[4-[4-(diphenylmethyl)-1-piperazinyl]butyl]-3-(3-pyridyl)acrylamide] against the rat passive cutaneous anaphylaxis (PCA) reaction and the enzyme 5-lipoxygenase. Particularly, (*E*)-*N*-[4-[4-(diphenylmethyl)-1-piperazinyl]butyl]-3-(6-methyl-3-pyridyl)acrylamide (**17p**) showed an ED_{50} value of 3.3 mg/kg po in the rat PCA test, which was one-fifth of ketotifen and oxatomide. As compared with ketotifen and oxatomide, compound **17p** (AL-3264) possessed a better balance of antiallergic properties due to inhibition of chemical mediator release, inhibition of 5-lipoxygenase, and antagonism of histamine.

The clinical success of disodium cromoglycate (DSCG)[2] as a therapeutic drug for the prophylactic treatment of asthma and allergic disease has stimulated a research interest that has led to the discovery of orally, more potent antiallergic agents with desirable biological properties. We have found new, orally active antiallergic compounds having (i) inhibitory activity against the enzyme 5-lipoxygenase, which catalyzes the generation of leukotrienes

Chart I



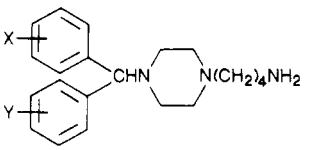
1

(LTA_4, LTB_4, LTC_4, LTD_4, and LTE_4), from arachidonic acid, (ii) inhibitory activity against the release of chemical mediators such as histamine and slow reacting substance of anaphylaxis (SRS-A) (LTC_4, LTD_4, and LTE_4) and (iii) antihistamine activity as well. Our previous paper reported[1] that some of the β-aryl- and β-heteroarylacryl-

(1) Part I of this series: Nishikawa, Y.; Shindo, T.; Ishii, K.; Nakamura, H.; Kon, T.; Uno, H. Submitted for publication to *Chem. Pharm. Bull.*
(2) Cox, J. S. G.; Beach, J. E.; Blair, A. M. J. N.; Clarke, A. J.; King, J.; Lee, T. B.; Loveday, D. E. E.; Moss, G. F.; Orr, T. S. C.; Ritchie, J. T.; Sheard, P. *Adv. Drug. Res.* **1970**, *5*, 115.

0022-2623/89/1832-0583$01.50/0

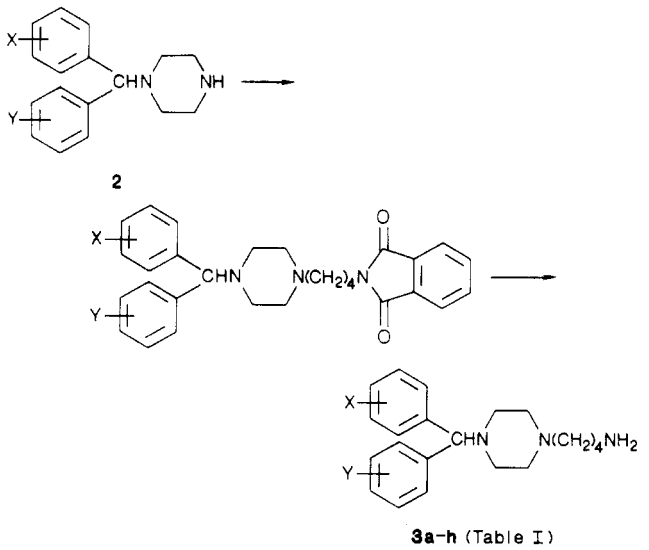
Table I. 1-(4-Aminobutyl)-4-[bis(substituted-phenyl)methyl]piperazines



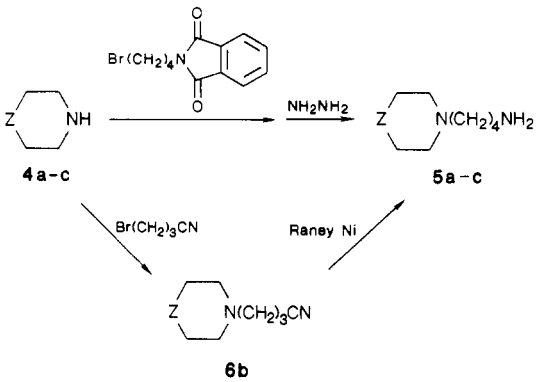
compd	X	Y	salt	mp, °C	recrystn solvent	yield,[a] %	formula[b]
3a	4-F	H	2 fumarate	190–193	EtOH	76	$C_{21}H_{28}FN_3 \cdot 2C_4H_4O_4$
3b	4-Cl	H	2.5 fumarate	165–170	EtOH	72	$C_{21}H_{28}ClN_3 \cdot 2.5C_4H_4O_4$
3c	4-OMe	H	2.5 fumarate	151–155	EtOH	79	$C_{22}H_{31}N_3O \cdot 2.5C_4H_4O_4$
3d	3-Me	H		oil[c]		66	
3e	4-Me	H	2.5 fumarate	159–163	EtOH	72	$C_{22}H_{31}N_3 \cdot 2.5C_4H_4O_4 \cdot 0.5H_2O$
3f	3,4-Me_2	H		oil[d]		85	
3g	4-Cl	4-Cl	2 fumarate	130–135	EtOH	70	$C_{21}H_{27}Cl_2N_3 \cdot 2C_4H_4O_4 \cdot H_2O$
3h	4-Me	4-Me	2 fumarate	121–125	EtOH	54	$C_{23}H_{33}N_3 \cdot 2C_4H_4O_4 \cdot 0.5H_2O$

[a] Total yields (%) of the crude free bases were based on the corresponding piperazines. [b] All compounds were analyzed for C, H, N, S, and halogen; analytical results were within ±0.4% of the theoretical values. [c] Mass spectrum (EIMS), m/z 337 (M^+). [d] EIMS, m/z 351 (M^+).

Scheme I



Scheme II[a]



[a] **a**, Z = >CHOCHPh$_2$; **b**, Z = >CHC(OH)Ph$_2$; **c**, Z = >C=CPh$_2$.

amides **1** with a piperazinyl group (Chart I) displayed a remarkably high activity in the rat passive cutaneous anaphylaxis (PCA) test by oral administration and, particularly, compound **1a** (Ar = 3-pyridyl, n = 4) was the most interesting compound having the desirable properties for which we aimed.

The present study was focused on enhancing the inhibitory activity of **1a** not only against the PCA reaction but also against 5-lipoxygenase. Several of the synthesized acrylamides and 2,4-pentadienamides were more active than the parent compound **1a** in the rat PCA test and in the in vitro inhibition of 5-lipoxygenase. The present paper deals with syntheses and the antiallergic activity of 3-(3-pyridyl)acrylamides and 5-(3-pyridyl)-2,4-pentadienamides; the structure–activity relationships (SARs) of these compounds are also discussed.

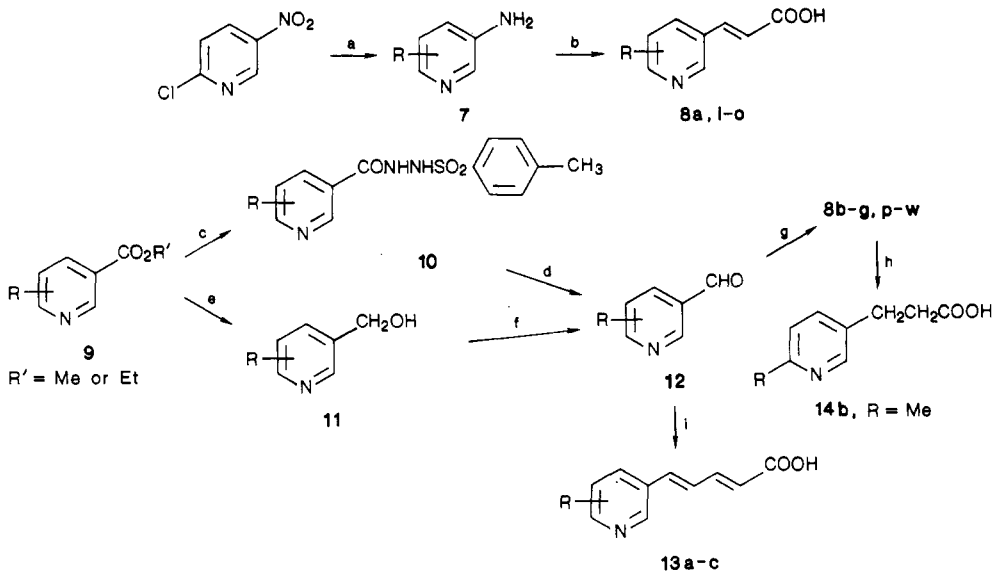
Chemistry

The requisite amines **3a–h** (Table I), **5a**, and **5c** were prepared from the corresponding piperazines **2** or piperidines **4** via the phthalimides according to the method reported previously[1] (Schemes I and II); the amine **5b** was prepared from the nitrile derivative **6b** by catalytic reduction with Raney nickel. The nitrile **6b** was in turn prepared from **4b** via alkylation with 4-bromobutyronitrile.

3-(3-Pyridyl)acrylic acids **8a–g** and **8i–w** (Table II) were synthesized by the routes shown in Scheme III. Thus, compounds **8a**, **8i**, **8j**, **8n**, and **8o** were prepared by an analogous method of Sohda et al.;[3] for the preparation of **8o**, reduction of 2-(ethylthio)-5-nitropyridine to the amino derivative **7o** was carried out by the use of reduced iron instead of catalytic reduction with 5% palladium-on-carbon. Compound **8b** was prepared by the Wittig reaction starting from 2-(methylamino)-3-pyridinecarbaldehyde (**12b**).[4] Compounds **8d**, **8e**, and **8f** were prepared from the corresponding ethyl nicotinates **9d**, **9e**, and **9f** by the McFadyne–Stevens reaction.[5] The acrylic acids **8c**,[6] **8g**, and **8p–v** were prepared starting from the respective methyl or ethyl nicotinates **9**, which were converted to the hydroxymethyl derivatives **11** by reduction with lithium aluminum hydride or sodium bis(2-methoxyethoxy)aluminum hydride, followed by oxidation with chromium trioxide, lead tetraacetate, or active manganese dioxide and then condensation with malonic acid. Other 3-(3-pyridyl)acrylic acids **8k–m**[3] and **8w**[7] were prepared according to known procedures. The 3-(3-pyridyl)acrylic acids **8** except **8b**, **8d**, and **8s** thus prepared were assigned the E configuration on the basis of coupling constants for the olefinic protons (J = 16 Hz) in their NMR spectra. Compounds **8b**, **8d**, and **8s** were deduced also to be E isomers from the NMR spectra of **17b**, **17d**, and **17s**, which

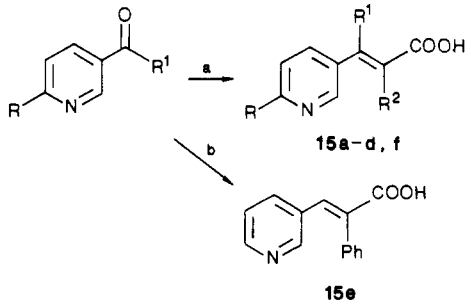
(3) Sohda, T.; Mizuno, K.; Imamiya, E.; Tawada, H.; Meguro, K.; Kawamatsu, Y.; Yamamoto, Y. *Chem. Pharm. Bull.* **1982**, *30*, 3601.
(4) Fadda, A. A.; Abdelrazek, F. M.; El-Habbal, M. M. *Indian J. Chem.* **1986**, *25B*, 194.
(5) McFadyne, J. S.; Stevens, T. S. *J. Chem. Soc.* **1936**, 584.
(6) Dornow, A.; Bormann, H. *Ber.* **1949**, *82*, 216.
(7) Korytnyk, W. *J. Med. Chem.* **1964**, *8*, 112.

Scheme III[a]



[a] (a) (1) RH, NaH, (2) H_2/Pd-C or reduced Fe; (b) (1) $NaNO_2$, (2) CH_2=CHCOOMe, Cu_2O, (3) 4 N KOH; (c) (1) NH_2NH_2, (2) *p*-$MeC_6H_4SO_2Cl$; (d) K_2CO_3; (e) $LiAlH_4$ or Vitride; (f) CrO_3, $Pb(OAc)_4$, or active MnO_2; (g) $CH_2(COOH)_2$ or (1) $(EtO)_2P(O)CH_2COOEt$, NaH, (2) dilute KOH; (h) H_2/Pd-C; (i) (1) $(EtO)_2P(O)CH_2CH$=$CHCOOEt$, NaH, (2) dilute KOH.

Scheme IV[a]



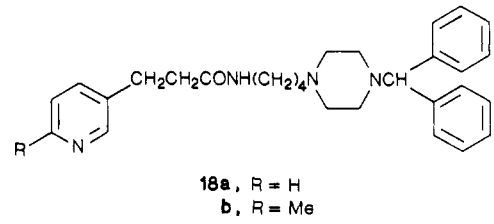
[a] (a) (1) $(EtO)_2P(O)CHR^2COOEt$, NaH, (2) dilute KOH; (b) $PhCH_2COOH$, Et_3N, Ac_2O.

were derived from **8b**, **8d**, and **8s**, respectively. 5-(3-Pyridyl)-2,4-pentadienoic acids **13a–c** (Table II) were prepared by the Wittig reaction of the corresponding 3-pyridinecarbaldehydes **12** with triethyl phosphonocrotonate (Scheme III). The stereochemistry of **13a–c** was assigned the *E,E* configuration by the coupling constants for the olefinic protons (J = nearly 15 Hz) in the NMR spectra. 3-(3-Pyridyl)propionic acids **14a** (R = H) and **14b** were prepared by catalytic reduction of the corresponding 3-(3-pyridyl)acrylic acids with 5% palladium-on-carbon.

3-(3-Pyridyl)acrylic acids **15a**, **15b**,[8] **15c**, **15d**, and **15f** (Table II) were prepared by the Wittig reaction of 3-acetylpyridine, 3-pyridinecarbaldehyde, and 6-methyl-3-pyridinecarbaldehyde (**12p**) (Scheme IV). (*E*)-2-Phenyl-3-(3-pyridyl)acrylic acid (**15e**) was prepared from 3-pyridinecarbaldehyde and phenylacetic acid according to the literature.[9] Compounds **15a–d** and **15f** were assigned the *E* configuration by quantitative analysis of the nuclear Overhauser effects in their NMR spectra.

3-(3-Pyridyl)acrylamides **16**, **17**, **19**, and **26**, 3-(3-pyridyl)propionamides **18a** and **18b** (Chart II), and 5-(3-pyridyl)-2,4-pentadienamides **20–25** listed in Tables III–VII were prepared by condensation of the corresponding

Chart II



amines with 3-(3-pyridyl)acrylic acid and the carboxylic acids **8** and **13–15**. 3-(3-Pyridyl)acrylamides **16**, **17**, and **26** were assigned the *E* configuration by their NMR spectra, which showed a coupling constant of 16 Hz for the olefinic protons. 5-(3-Pyridyl)-2,4-pentadienamides **20–25** were assigned the *E,E* configuration by their NMR spectra. 3-(3-Pyridyl)acrylamides **19a–f**, prepared from (*E*)-3-(3-pyridyl)acrylic acids **15a–f** under mild conditions, were deduced to be *E* isomers.

Pharmacological Results and Discussion

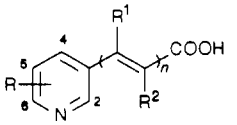
Compounds **16–26** (Tables III–VII) were evaluated for their antiallergic activity in the rat PCA assay by oral administration 1 h before antigenic challenge and compared with the parent compound **1a**.

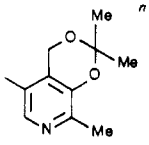
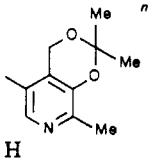
The effect of substitution at both phenyl groups of **1a** on the activity was frst examined (Table III). Introduction of a halogen such as fluoro (**16a**) or chloro (**16b**) or a methoxy (**16c**) group into the para position of one of the phenyl rings caused no increase in activity. On the other hand, introduction of a methyl group into the para position (**16e**) of one of the phenyl rings caused a marked increase in activity, whereas introduction of the methyl group into the meta position (**16d**) resulted in a decrease in activity. However, introduction of the methyl group into both para positions of the two phenyl groups (**16h**) lowered the activity. Besides, introduction of the methyl group into both meta and para positions of one of the phenyl rings (**16f**) reduced the activity not only below the *p*-methyl derivative **16e** but also below the *m*-methyl derivative **16d**.

The effect of substitution on the pyridine ring of **1a** is shown in Table IV. Although no clear SARs were observed, several compounds showed potent anti-PCA ac-

(8) Freemann, F.; Chang, G. A.; Kappos, J. C.; Sumarta, L. *J. Org. Chem.* **1987**, *52*, 1460.
(9) Clarke, F. H.; Felock, G. A.; Silvermann, G. B.; Watmick, C. M. *J. Org. Chem.* **1962**, *27*, 533.

Table II. 3-(3-Pyridyl)acrylic Acids and 5-(3-Pyridyl)-2,4-pentadienoic Acids



compd	R	R^1	R^2	n	procedure[a]	mp, °C	recrystn solvent[b]	yield,[c] %	formula[d]
8a	2-Cl	H	H	1	A	195–199	A	15[e]	$C_8H_6ClNO_2 \cdot 0.167H_2O$
8b	2-NHMe	H	H	1	B	*f*		18	$C_9H_{10}N_2O_2$
8c	2-Me	H	H	1	C	218–219[g]	A	25	$C_9H_9NO_2$
8d	5-F	H	H	1	D	*h*		8	$C_8H_6FNO_2$
8e	5-Cl	H	H	1	D	195–197	A	22	$C_8H_6ClNO_2$
8f	5-Br	H	H	1	D	207–210	A	12	$C_8H_6BrNO_2$
8g	5-OMe	H	H	1	C	280–281	A, B	33	$C_9H_9NO_3$
8h[i]	5-OH	H	H	1					
8i	6-Cl	H	H	1	A	241–244	A	9[e]	$C_8H_6ClNO_2$
8j	6-OMe	H	H	1	A	235–240	A, C	26	$C_9H_9NO_3 \cdot 0.25H_2O$
8k	6-OEt	H	H	1	A	175–177[j]	A	31	$C_{10}H_{11}NO_3$
8l	6-O-*n*-Pr	H	H	1	A	172–173[k]	C	23	$C_{11}H_{13}NO_3$
8m	6-O-*n*-pentyl	H	H	1	A	134–135[l]	C	22	$C_{13}H_{17}NO_3$
8n	6-OPh	H	H	1	A	204–206	A	21	$C_{14}H_{11}NO_3$
8o	6-SEt	H	H	1	A	157–159	A	11	$C_{10}N_{11}NO_2S$
8p	6-Me	H	H	1	E	213–214	A	39	$C_9H_9NO_2$
8q	6-*n*-Pr	H	H	1	E	140–141	B, D	9	$C_{11}H_{13}NO_2$
8r	6-*i*-Pr	H	H	1	F	179–181	D	57	$C_{11}H_{13}NO_2$
8s	6-*n*-Bu	H	H	1	E	*m*		48	$C_{12}H_{15}NO_2$
8t	6-Ph	H	H	1	C	204–206	A, B	39	$C_{14}H_{11}NO_2$
8u	2-Me, 6-Me	H	H	1	C	206–208	D	21	$C_{10}H_{11}NO_2$
8v	5-Me, 6-Me	H	H	1	F	230–234	A	68	$C_{10}H_{11}NO_2$
8w		H	H	1	F	228–231[o]	A	25	$C_{13}H_{15}NO_4$
13a	H	H	H	2	B	195–197	C	40	$C_{10}H_9NO_2$
13b	6-Me	H	H	2	B	249–250	C	38	$C_{11}H_{11}NO_2$
13c		H	H	2	B	230 dec	C	61	$C_{15}H_{17}NO_4$
15a	H	Me	H	1	B	146–147	A, B	23	$C_9H_9NO_2$
15b	H	H	Me	1	B	185–187[p]	C	74	$C_9H_9NO_2$
15c	H	H	Et	1	B	105–108	*q*	23	$C_{10}H_{11}NO_2$
15d	H	H	*n*-Pr	1	B	85–87	*q*	33	$C_{11}H_{13}NO_2 \cdot 0.5H_2O$
15e	H	H	Ph	1	G	190–192[r]	A	31	$C_{14}H_{11}NO_2$
15f	6-Me	H	Me	1	B	154–155	D	21	$C_{10}H_{11}NO_2$

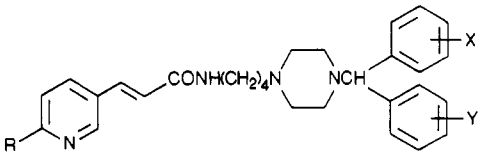
[a] Capital letters refer to the procedures in the Experimental Section. [b] A = EtOH, B = *n*-hexane, C = MeOH, D = *i*-PrOH, E = toluene, F = Et_2O, and G = MeCN. [c] Total yields (%) of the crude acids were based on the starting materials. [d] See footnote *b* in Table I. [e] Total yields (%) of the crude acids were based on the amino derivatives. [f] EIMS, 178 (M^+). [g] Lit.[6] mp 214 °C. [h] EIMS, 167 (M^+). [i] This compound was not synthesized because **17h** was derived from **17g**. [j] Lit.[3] mp 182–183 °C. [k] Lit.[3] mp 173–174 °C. [l] Lit.[3] mp 136–137 °C. [m] EIMS, 205 (M^+). [n] The structure of the 3-pyridyl moiety was illustrated. [o] Lit.[7] mp 220–221 °C. [p] Lit.[8] mp 189–191 °C. [q] Washed with water. [r] Lit.[9] mp 197–200 °C.

tivity. Introduction of the methyl group into the 2- and/or 6-position(s) of the pyridine ring (**17c**, **17p**, and **17u**) tended to enhance activity; particularly, compound **17p** bearing the methyl group at the 6-position showed the greatest activity in this series. The bulkier substituents at the 6-position such as propyl (**17q**), isopropyl (**17r**), and butyl (**17s**) groups, however, seemed to reduce the activity. We expected that **16i** (Table III) would be more active than **17p** because **16e** was more active than **1a**. However, introduction of the methyl group into the pyridine ring of **16e** caused no enhancement in activity. Decreasing order of activity for substituents at the 5-position of the pyridine ring was Cl, F ≥ H > Br > OH > OMe and at the 6-position was Me > H > Cl ≥ OPh, *n*-Pr ≥ OMe > *n*-Bu ≥ SEt ≥ O-*n*-pentyl > O-*n*-Pr, Ph. Compound **17p** showed the highest activity and the activities of **17d** and **17e** were comparable to that of **1a**; the others were less active than **1a**.

The effect of saturation of the double bond in the acryloyl moiety was examined (Table IV). The propionamides **18a** and **18b** (Chart II) had reduced activity when compared with **1a** and **17p**, respectively. In addition, **18b** did not show inhibitory activity against 5-lipoxygenase at a concentration of 10 μM. Accordingly, the acryloyl moiety in this series seems to play an important role in inhibition against the rat PCA reaction and 5-lipoxygenase.

The effect of substitution of alkyl and phenyl groups at the α- and β-positions of the acryloyl moiety is shown in Table V. Introduction of methyl (**19b**) and ethyl (**19c**) groups into the α-position increased the activity as compared with **1a**, whereas introduction of the methyl group (**19a**) into the β-position and a phenyl group into the α-position caused no increase in activity. Introduction of a bulkier alkyl group such as propyl (**19d**) into the α-position reduced the activity below **1a**. Therefore, we expected that introduction of the methyl group (**19f**) into the α-position

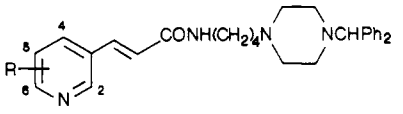
Table III. *N*-[4-[4-(Substituted-diphenylmethyl)-1-piperazinyl]butyl]-3-(3-pyridyl)acrylamides

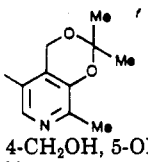


compd	R	X	Y	salt	procedure[a]	mp, °C	formula[b]	recrystn solvent[c]	yield, %	rat PCA test: % inhibition, 20 mg/kg po
1a	H	H	H							62.3[d]
16a	H	4-F	H	3 oxalate	H	97–100	$C_{29}H_{33}FN_4O{\cdot}3C_2H_2O_4{\cdot}H_2O$[e]	D	41	53.8[d]
16b	H	4-Cl	H	3 oxalate	H	83–86	$C_{29}H_{33}ClN_4O{\cdot}3C_2H_2O_4{\cdot}0.5H_2O$	A	31	19.9
16c	H	4-OMe	H	2 oxalate	H	94–97	$C_{30}H_{36}N_4O_2{\cdot}3C_2H_2O_4{\cdot}1.5H_2O$	A	24	40.9[d]
16d	H	3-Me	H	3 oxalate	H	82–85	$C_{30}H_{36}N_4O{\cdot}3C_2H_2O_4{\cdot}H_2O$	A	21	19.0[f]
16e	H	4-Me	H		H	114–117	$C_{30}H_{36}N_4O{\cdot}0.25H_2O$	E	57	82.9[d]
16f	H	3,4-Me_2	H		H	*g*	*h*		22	5.4
16g	H	4-Cl	4-Cl	2 oxalate	H	100–104	$C_{29}H_{32}Cl_2N_4O{\cdot}2C_2H_2O_4{\cdot}0.5H_2O$	A	29	5.4
16h	H	4-Me	4-Me		H	*g*	*h*		29	20.2
16i	Me	4-Me	H	4 oxalate	H	126–131	$C_{31}H_{38}N_4O{\cdot}4C_2H_2O_4{\cdot}H_2O$	A	44	73.9[d]
oxatomide										42.2[d]

[a] See footnote *a* in Table II. [b] See footnote *b* in Table I. [c] See footnote *b* in Table II. [d] $p < 0.01$, significantly different from the vehicle control. [e] N: calcd, 7.36; found, 6.86. [f] $p < 0.05$. [g] Isolated as an oil. [h] Satisfactory high-resolution mass spectral data were obtained.

Table IV. *N*-[4-[4-(Diphenylmethyl)-1-piperazinyl]butyl]-3-(3-pyridyl)acrylamides



compd	R	salt	procedure[a]	mp, °C	formula[b]	recrystn solvent[c]	yield, %	rat PCA test: % inhibition 20 mg/kg po
1a	H							62.3[d]
17a	2-Cl	3 oxalate	H	108–109	$C_{29}H_{33}ClN_4O{\cdot}3C_2H_2O_4{\cdot}0.5H_2O$	A, D	34	39.3[d]
17b	2-NHMe	2 tartrate	I	110–114	$C_{30}H_{37}N_5O{\cdot}2C_4H_6O_6{\cdot}H_2O$	A, F	64	45.2[e]
17c	2-Me	1.5 tartrate	H	99–103	$C_{30}H_{36}N_4O{\cdot}1.5C_4H_6O_6{\cdot}H_2O$	A, F	33	68.8[d]
17d	5-F		H	128–129	$C_{29}H_{33}FN_4O$	B, E	27	65.0[d]
17e	5-Cl		H	122–124	$C_{29}H_{33}ClN_4O$	G	37	66.4[d]
17f	5-Br		H	133–134	$C_{29}H_{33}BrN_4O$	G	25	47.5[d]
17g	5-OMe	1.5 tartrate	H	90–95	$C_{30}H_{36}N_4O_2{\cdot}1.5C_4H_6O_6$	A, F	32	7.6
17h	5-OH		J	186–188	$C_{29}H_{34}N_4O_2$	C, G	20	28.8[e]
17i	6-Cl		H	162–164	$C_{29}H_{33}ClN_4O$	B, D	38	49.3[d]
17j	6-OMe		H	153–155	$C_{30}H_{36}N_4O_2$	G	43	41.0[e]
17k	6-OEt	3 oxalate	H	100–105	$C_{31}H_{38}N_4O_2{\cdot}3C_2H_2O_4{\cdot}2.5H_2O$	D	33	33.9
17l	6-O-*n*-Pr		H	144–145	$C_{32}H_{40}N_4O_2$	G	24	7.5
17m	6-O-*n*-pentyl		K	80–81	$C_{34}H_{44}N_4O_2$	G	28	14.9[e]
17n	6-OPh		H	145–147	$C_{35}H_{38}N_4O_2$	D	13	45.6[e]
17o	6-SEt		H	137–140	$C_{31}H_{38}N_4OS$	E	35	18.6[e]
17p	6-Me		L	129–131	$C_{30}H_{36}N_4O$	G	70	81.9[d]
17q	6-*n*-Pr		K	138–140	$C_{32}H_{40}N_4O$	G	41	44.4
17r	6-*i*-Pr	2 tartrate	K	102–106	$C_{32}H_{40}N_4O{\cdot}2C_4H_6O_6{\cdot}3H_2O$	A, F	55	38.9
17s	6-*n*-Bu		K	121–123	$C_{33}H_{42}N_4O{\cdot}0.25H_2O$	G	26	22.2
17t	6-Ph		H	155–156	$C_{35}H_{38}N_4O$	G	44	3.2
17u	2-Me, 6-Me	2 tartrate	H	105–110	$C_{31}H_{38}N_4O{\cdot}2C_4H_6O_6{\cdot}0.5H_2O$	A, F	34	66.8[d]
17v	5-Me, 6-Me	2 tartrate	K	105–111	$C_{31}H_{38}N_4O{\cdot}2C_4H_6O_6{\cdot}2H_2O$	A, F	58	40.5[d]
17w		3 oxalate	H	163–166	$C_{34}H_{42}N_4O_3{\cdot}3C_2H_2O_2{\cdot}1.5H_2O$	A, B	40	17.0[e]
17x	4-CH_2OH, 5-OH, 6-Me		M	133–134	$C_{31}H_{39}N_4O_3$	C, G	24	53.7[d]
18a	H	fumarate	I	151–153	$C_{29}H_{36}N_4O{\cdot}C_4H_4O_4{\cdot}0.5H_2O$	C, G	68	28.1
18b	Me		I	126–127	$C_{30}H_{38}N_4O$	G	37	24.9
oxatomide								42.2[d]

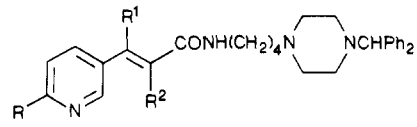
[a] See footnote *a* in Table II. [b] See footnote *b* in Table I. [c] See footnote *b* in Table II. [d] $p < 0.01$. [e] $p < 0.05$. [f] See footnote *n* in Table III.

of the acryloyl moiety of **17p** would cause an increase in activity. Compound **19f**, however, was weaker than **17p** and **19b**.

It is interesting to note that, as described above, single methyl substitution at the 4-position of one of the phenyl rings (**16e**), at the 2- or 6-position of the pyridine ring (**17c** and **17p**), or at the α-position of the acryloyl moiety (**19b**) increased the activity in comparison with **1a** but second methyl substitution at these positions (**16h**, **16i**, **17u**, and **19f**) caused no increase in activity when compared with the monomethyl compounds.

In Table VI are listed compounds with a 2,4-pentadienoyl moiety in the place of the acryloyl group. As in the earlier work[1] with *N*-[[4-(diphenylmethyl)-1-

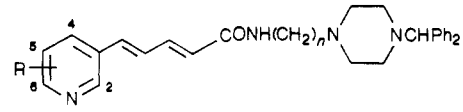
Table V. α- and β-Substituted *N*-[4-[4-(Diphenylmethyl)-1-piperazinyl]butyl]-3-(3-pyridyl)acrylamides



compd	R	R^1	R^2	salt	procedure[a]	mp, °C	formula[b]	recrystn solvent[c]	yield, %	rat PCA test: % inhibition 20 mg/kg po
1a	H	H	H							62.3[d]
19a	H	Me	H	2 fumarate	L	137–140	$C_{30}H_{36}N_4O \cdot 2C_4H_4O_4$	A	27	52.2[d]
19b	H	H	Me		L	120–122	$C_{30}H_{36}N_4O$	G	34	78.9[d]
19c	H	H	Et	1.5 fumarate	I	137–141	$C_{31}H_{38}N_4O \cdot 1.5C_4H_4O_4$	A, F	47	67.8[d]
19d	H	H	*n*-Pr		I	*e*	*f*		77	44.2[d]
19e	H	H	Ph	2 oxalate	I	82–85	$C_{35}H_{38}N_4O \cdot 2C_2H_2O_4 \cdot 2H_2O$	A, F	27	58.0[d]
19f	Me	H	Me		I	133–135	$C_{31}H_{38}N_4O$	G	39	58.2[d]
oxatomide										42.2[d]

[a] See footnote *a* in Table II. [b] See footnote *b* in Table I. [c] See footnote *b* in Table II. [d] $p < 0.01$. [e] See footnote *g* in Table III. [f] See footnote *h* in Table III.

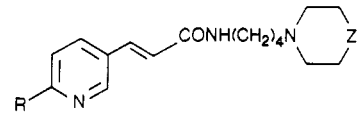
Table VI. *N*-[4-[4-(Diphenylmethyl)-1-piperazinyl]butyl]-5-(3-pyridyl)-2,4-pentadienamides



compd	R	*n*	salt	procedure[a]	mp, °C	formula[b]	recrystn solvent[c]	yield, %	rat PCA test: % inhibition 20 mg/kg po
1a									62.3[d]
20	H	3	fumarate	L	218–220	$C_{30}H_{34}N_4O \cdot C_4H_4O_4 \cdot 0.5H_2O$	C, G	37	40.4[e]
21	H	4		L	178–180	$C_{31}H_{36}N_4O$	G	42	66.4[d]
22	6-Me	3		L	192–194	$C_{31}H_{36}N_4O$	G	49	35.8[e]
23	6-Me	4		L	163–165	$C_{32}H_{38}N_4O$	G	56	68.8[d]
24	4-CH_2OH, 5-OH, 6-Me	3		M	153–155	$C_{32}H_{38}N_4O_3$	G	33	9.8
25	4-CH_2OH, 5-OH, 6-Me	4		M	216–217	$C_{33}H_{40}N_4O_3$	C	40	16.4
oxatomide									42.2[d]

[a] See footnote *a* in Table II. [b] See footnote *b* in Table I. [c] See footnote *b* in Table II. [d] $p < 0.01$. [e] $p < 0.05$.

Table VII. *N*-[4-(4-Substituted-1-piperidinyl)butyl]-3-(3-pyridyl)acrylamides



compd	R	Z	salt	procedure[a]	mp, °C	formula[b]	recrystn solvent[c]	yield, %	rat PCA test: % inhibition 20 mg/kg po
1a	H	$NCHPh_2$							62.3[d]
26a	H	$CHOCHPh_2$	2 oxalate	K	100–103	$C_{30}H_{35}N_3O_2 \cdot 2C_2H_2O_4 \cdot 2.5H_2O$	A	58	42.2
26b	H	$CHC(OH)Ph_2$	1.5 tartrate	I	109–113	$C_{30}H_{35}N_3O_2 \cdot 1.5C_4H_6O_6 \cdot 2H_2O$	A	19	35.1[e]
26c	H	$C{=}CPh_2$		I	155–157	$C_{30}H_{33}N_3O$	G	52	85.9[d]
26d	Me	$C{=}CPh_2$		I	129–132	$C_{31}H_{35}N_3O$[f]	G	44	99.5[d]
oxatomide									42.2[d]

[a] See footnote *a* in Table II. [b] See footnote *b* in Table I. [c] See footnote *b* in Table II. [d] $p < 0.01$. [e] $p < 0.05$. [f] C: calcd, 79.96; found, 79.38.

piperazinyl]alkyl]cinnamamides, a higher activity was observed for compounds **21**, **23**, and **25** with a four-methylene chain ($n = 4$) in comparison with compounds **20**, **22**, and **24** with a three-methylene chain ($n = 3$), respectively. Regardless of introduction of the methyl group at the 6-position of the pyridine ring, compounds **21** and **23** were equal or somewhat superior to **1a** in activity.

The effect of replacement of the 4-(diphenylmethyl)-piperazine group by piperidines substituted with a diphenylmethyl or diphenylmethylene group at the 4-position was examined (Table VII). Compounds **26c** and **26d** having the diphenylmethylene group showed a marked increase in activity over the corresponding **1a** and **17p**, respectively. Compounds **26a** and **26b** bearing (di-

Table VIII. Inhibitory Activity against 5-Lipoxygenase

compd	5-lipoxygenase[a] % inhibition
16e	25.1[b]
17b	80.4[c]
17p	45.7[c]
17x	72.7[b]
19b	43.5[c]
20	60.3[c]
23	73.8[c]
26d	51.7[c]
1a	2.3
caffeic acid	22.7[c,d]

[a] Inhibitory activity at 10 μM. [b] $p < 0.05$. [c] $p < 0.01$. [d] Inhibitory activity at 30 μM.

Table IX. Antiallergic Activities of Compound **17p** (AL-3264) and Reference Compounds

compd	PCA test rat: ED_{50}, mg/kg po[e]	hist release[a] human basophil: IC_{50}, μM[e]	5-lipoxygenase[b] GP[d] leukocyte: IC_{50}, μM[e]	anti-hist[c] GP trachea: IC_{50}, μM[e]
17p	3.3	34	4.86	0.12
ketotifen	16.3	>100 (19.3%)	>100	0.0016
oxatomide	18.2	>10 (8.2%)	15.2	0.056
caffeic acid	NT[f]	NT	16.7	NT

[a] Inhibitory activity against histamine release. [b] Inhibitory activity against 5-lipoxygenase. [c] Anti-histamine activity. [d] Guinea pig. [e] ED_{50} and IC_{50} values were calculated from the regression lines and were significant at $p < 0.05$. [f] NT = not tested.

phenylmethyl)oxy and hydroxydiphenylmethyl groups, respectively, had reduced activity.

The compounds possessing potent anti-PCA activity were then tested for their in vitro 5-lipoxygenase inhibitory activity. As shown in Table VIII, compounds **17p**, **19b**, and **26d** were more active than **1a** in both anti-PCA and 5-lipoxygenase inhibitory activities. Compound **17b**, bearing the methylamino group at the 2-position of the pyridine ring, and **17x** showed potent inhibitory activity against 5-lipoxygenase but they were weaker inhibitors of the rat PCA reaction. Compound **16e**, however, was equipotent to **17p** and **19b** in the rat PCA test although it was a weaker inhibitor of 5-lipoxygenase than **17p** and **19b**. The replacement of the acryloyl moiety by the 2,4-pentadienyl moiety (**20** and **23**) caused a remarkable increase in inhibitory activity against 5-lipoxygenase. Compound **23**, which had potent inhibitory activities against 5-lipoxygenase and the PCA reaction, showed no antihistamine activity in vitro at a concentration of 1 μM. Compound **26d** possessed the greatest inhibitory activity against the PCA reaction and potent inhibitory activity against 5-lipoxygenase. However, it showed an undesirable effect (ptosis) in gross behavior at a dose of 100 mg/kg po in mice. Therefore, compound **17p** (AL-3264), which had potent inhibitory activities against 5-lipoxygenase and the rat PCA reaction, was selected as worthy of further evaluation.

Compound **17p** was further tested for inhibitory activity against mediator release from human basophils and in vitro antihistamine activity. In addition, the inhibitory activity of **17p** against 5-lipoxygenase was tested by various experimental conditions; the conversion rate of arachidonic acid to 5-hydroxy-6,8,11,14-eicosatetraenoic acid (5-HETE) in the absence of inhibitors was lowered to 20–30% from 40–50%. Table IX gives the results from these tests for **17p** as compared with other antiallergic drugs. Compound **17p** was five times as potent as ketotifen[10] and oxatomide[11] in inhibitory activity against the rat PCA reaction by oral administration. Unlike ketotifen, **17p** had in vitro 5-lipoxygenase inhibitory activity, which was three times as potent as that of oxatomide; its in vitro antihistamine activity was comparable to that of oxatomide. In addition, **17p** had a potent inhibitory activity against histamine release from healthy human basophils induced by anti-human IgE antibody.

As a result of the present study, compound **17p** (AL-3264) was found to possess a better balance of antiallergic properties (inhibition of the chemical mediator release and of 5-lipoxygenase and antagonistic action of histamine) compared with ketotifen and oxatomide. This compound, therefore, seems more promising as an antiallergic candidate than **1a** reported previously.[1]

Experimental Section

All melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. ^1H NMR spectra were taken at 60 MHz with a Varian EM-360 spectrometer, at 80 MHz with a Varian FT-80A spectrometer, or at 300 MHz with a Varian XL-300 spectrometer. Chemical shifts are expressed in δ (ppm) values with tetramethylsilane as an internal standard. Electron impact mass spectra (EIMS) were recorded on a JEOL JMS D-300 or a Hitachi RMU-6L spectrometer. Elemental analyses are given only by symbols of the elements; analytical results were within ±0.4% of theoretical values. Organic extracts were dried over anhydrous $MgSO_4$.

The following known intermediates were prepared according to the cited literature: 1-(*p*-fluorobenzhydryl)-,[12] 1-(*p*-chlorobenzhydryl)-,[13] 1-(*m*-methylbenzhydryl)-,[14] and 1-(*p,p'*-dichlorobenzhydryl)piperazines;[14] 4-(diphenylmethoxy)-,[15] 4-(hydroxydiphenylmethyl)-,[16] and 4-(diphenylmethylene)piperidines;[17] ethyl 2-methyl-,[18] ethyl 5-fluoro-,[19] ethyl 5-chloro-,[19] ethyl 5-bromo-,[20] methyl 5-methoxy-,[21] ethyl 6-methyl-,[22] methyl 6-phenyl-,[23] and ethyl 2,6-dimethylnicotinates.[24]

1-(*p*-Methoxybenzhydryl)- (2c), 1-(*p*-Methylbenzhydryl)- (2e), 1-(*m,p*-Dimethylbenzhydryl)- (2f), and 1-(*p,p'*-Dimethylbenzhydryl)piperazines (2h). These compounds were prepared according to the method described in the literature.[13]

1-(4-Aminobutyl)-4-(diphenylmethyl)piperazines 3a–h (Table I), 1-(4-Aminobutyl)-4-(diphenylmethoxy)piperidine (5a), and 1-(4-Aminobutyl)-4-(diphenylmethylene)piperidine (5c). These compounds were prepared in a manner similar to that described previously.[1] The crude **5a** and **5c** were prepared from the corresponding piperidines **4a**[15] and **4c**;[17] the overall yields were 92% and 74%, respectively.

1-(4-Aminobutyl)-4-(hydroxydiphenylmethyl)piperidine (5b). A mixture of 4-(hydroxydiphenylmethyl)piperidine (**4b**)[16] (8.0 g, 0.030 mol), 4-bromobutyronitrile (4.4 g, 0.030 mol), K_2CO_3 (6.2 g, 0.045 mol), NaI (6.2 g, 0.041 mol), and methyl ethyl ketone (240 mL) was heated at reflux temperature for 5 h with stirring. After the mixture was cooled, the insoluble materials were removed by filtration and washed with $CHCl_3$. The filtrate and the washings were combined and concentrated to dryness in vacuo. To the residue was added 200 mL of $CHCl_3$. The $CHCl_3$ layer was washed with water, dried, and concentrated in vacuo. The residue was chromatographed on silica gel with $CHCl_3$ as eluent to give 9.5 g (95%) of 1-(3-cyanopropyl)-4-(hydroxydiphenylmethyl)piperidine (**6b**). Compound **6b** (9.5 g, 0.028 mol) was hydrogenated in 200 mL of CH_3OH containing 60 mL of 28%

(10) Martin, U.; Römer, M. *Arzneim.-Forsch.* **1978**, *28*, 770.
(11) Emanuel, K. B.; Towse, G. D. W. *Drugs Today* **1980**, *16*, 219.
(12) Janssen Pharmaceutica, N. V. Ger. Offen. 1,929,330; *Chem. Abstr.* **1970**, *73*, 14874g.
(13) Fujii, K.; Tomino, K.; Watanabe, H. *Yakugaku Zasshi* **1954**, *74*, 1049.
(14) Morren, H. G. Brit. Patent 817,231; *Chem. Abstr.* **1960**, *54*, 9970.
(15) Ciba-Geigy Corp. U. S. Patent 4,261,990; *Chem. Abstr.* **1981**, *95*, 80209z.
(16) Macarty, F. J.; Tilford, C. H.; Van Campen, M. G., Jr. *J. Org. Chem.* **1961**, *26*, 4084.
(17) Union Chimique-Chemische Bedrijven, S. A. Ger. Offen. 2,016,667; *Chem. Abstr.* **1971**, *74*, 13015m.
(18) Baumgarten, P.; Dormow, A. *Ber.* **1939**, *72*, 563.
(19) Aktiebolaget Astra, U. S. Patent 3,637,714; *Chem. Abstr.* **1976**, *84*, 43861h.
(20) Bachman, G. B.; Micucci, D. D. *J. Am. Chem. Soc.* **1948**, *70*, 2381.
(21) Urban, R.; Schnider, O. *Helv. Chim. Acta* **1964**, *47*, 363.
(22) Castle, R. N.; Whittle, C. W. *J. Org. Chem.* **1959**, *24*, 1189.
(23) Plattner, J. J.; Gless, R. D.; Cooper, G. K.; Rapoport, H. *J. Org. Chem.* **1974**, *39*, 303.
(24) Kato, T.; Noda, M. *Chem. Pharm. Bull.* **1976**, *24*, 303.

ammonium hydroxide and 1.0 g of Raney nickel at room temperature. The mixture was filtered and the filtrate was concentrated to dryness in vacuo. The residue was crystallized from a mixture of toluene (100 mL) and $(CH_3)_2CHOH$ (30 mL) to give 6.2 g (65%) of **5b**: EIMS, m/z 338 (M^+).

The crude **3a–h** and **5a–c**, without further purification, were used for the preparation of the corresponding 3-(3-pyridyl)-acrylamides **16a–i** and **26a–d**.

Ethyl 6-Propylnicotinate (9q). A mixture of 3-cyano-6-propyl-2-pyridone[25] (13.8 g, 0.085 mol) and phosphorus pentachloride (17.7 g, 0.085 mol) was heated at reflux temperature for 1 h with stirring. The mixture was then poured into 500 mL of ice water. The solution was adjusted to pH 7 with $NaHCO_3$ and extracted with two 150-mL portions of $CHCl_3$. The combined extracts were dried, and the solvent was removed by distillation in vacuo. The residue was chromatographed on silica gel and eluted with toluene to give 13.7 (89%) of 2-chloro-3-cyano-6-propylpyridine.

2-Chloro-3-cyano-6-propylpyridine (13.7 g, 0.076 mol) was hydrogenated in 150 mL of CH_3OH containing 7.7 g (0.076 mol) of $(C_2H_5)_3N$ and 1.2 g of 5% Pd/C until an equivalent volume of hydrogen was absorbed. The mixture was filtered and the filtrate was concentrated to dryness in vacuo. To the residue was added 50 mL of 10% K_2CO_3. The mixture was extracted with two 150-mL portions of $CHCl_3$. The combined extracts were dried and concentrated to dryness in vacuo to give 9.3 g (84%) of crude 5-cyano-2-propylpyridine, which was then combined with 50% H_2SO_4 (80 mL). The stirred mixture was heated at reflux temperature overnight. After being cooled, the mixture was adjusted to pH 3–3.5 with $NaHCO_3$ and concentrated in vacuo. To the residue was added 100 mL of CH_3OH, and the insoluble materials were removed by filtration and the filtrate was concentrated to dryness in vacuo. To the residue were added 90 mL of absolute C_2H_5OH and 6.8 mL of concentrated H_2SO_4. The mixture was heated at reflux temperature for 20 h and then concentrated in vacuo. The residue was neutralized with 10% K_2CO_3. The mixture was extracted with three 100-mL portions of $CHCl_3$. The extracts was dried and concentrated in vacuo to give 10.5 g of an oil, which was chromatographed on silica gel and eluted with $CHCl_3$ to give 9.6 g (78%) of **9q**: EIMS, m/z 193 (M^+).

Ethyl 6-Isopropylnicotinate (9r) and Ethyl 6-Butylnicotinate (9s). 3-Cyano-6-isopropyl-2-pyridone and 6-butyl-3-cyano-2-pyridone were prepared from methyl isopropyl ketone and methyl butyl ketone, respectively, in a manner similar to that described in the literature.[25] The overall yields of the 3-cyano-2-pyridone derivatives were 26% and 14%, respectively. Compounds **9r** and **9s** were prepared from the 3-cyano-2-pyridone derivatives in a manner similar to that described above. The overall yields of **9r** and **9s** were 24% and 48%, respectively.

Ethyl 5,6-Dimethylnicotinate (9v). The mixture of 3-cyano-5,6-dimethyl-2-pyridone and 3-cyano-6-ethyl-2-pyridone were prepared from methyl ethyl ketone in a manner similar to that described in the literature;[25] the NMR spectrum proved that these compounds were in the ratio 1:1. The overall yield was 27%.

The mixture (19.7 g, 0.13 mol) of 3-cyano-5,6-dimethyl-2-pyridone and 3-cyano-6-ethyl-2-pyridone was added slowly to phenylphosphoric dichloride (59.7 g, 0.30 mol). The reaction mixture was heated at 180 °C for 2 h with stirring. The resulting solution was then poured into 340 mL of ice water. After being stirred for 2 h, the resulting suspension was extracted with two 150-mL potions of $CHCl_3$. The combined extracts were dried, and the solvent was removed by distillation in vacuo. The residue was chromatographed on silica gel and eluted with toluene to give an oily product. To the oily product was added 20 mL of $(C_2H_5)_2O$–*n*-hexane (1:1), and the resultant solid was collected and washed with $(C_2H_5)_2O$ to give 4.9 g (22%) of 2-chloro-3-cyano-5,6-dimethylpyridine: mp 92–94 °C; ^1H NMR (60 MHz, $CDCl_3$) δ 2.31 (3 H, s, CH_3), 2.54 (3 H, s, CH_3), 7.68 (1 H, s, C-4 H).

Compound **9v** was prepared from 2-chloro-3-cyano-5,6-dimethylpyridine in a manner similar to that described above. The overall yield of **9v** was 45%.

(25) Mariella, R. P.; Stansfield, R. *J. Am. Chem. Soc.* **1951**, *73*, 1368.

3-(3-Pyridyl)acrylic Acids 8a–g, 8i–w, and 15a–f and 5-(3-Pyridyl)-2,4-pentadienoic Acids 13a–c (Table II). Procedure A. 3-(6-Methoxy-3-pyridyl)acrylic Acid (8j). To a stirred solution of 2-chloro-5-nitropyridine (10 g, 0.063 mol), absolute CH_3OH (2.0 g, 0.063 mol), and anhydrous tetrahydrofuran (THF) (40 mL) was added 2.8 g of NaH (about 60%, in oil) under cooling in an ice-water bath. The mixture was stirred at room temperature for 1 h, and 30 mL of water was added. The mixture was extracted with three 40-mL portions of $CH_3CO_2C_2H_5$, and the combined extracts were dried. The solvent was removed by distillation in vacuo to give 8.0 g (82%) of crude 2-methoxy-5-nitropyridine.

The crude 2-methoxy-5-nitropyridine (8.0 g, 0.052 mol) was hydrogenated in 80 mL of CH_3OH containing 1.7 g of 5% Pd/C at room temperature under atmospheric pressure. After removal of the catalyst by filtration, 100 mL of acetone was added to the filtrate. To the stirred and ice-cooled solution was added 18 mL of concentrated HCl. Then a solution of $NaNO_2$ (3.3 g, 0.048 mol) in water (7 mL) was added dropwise below 5 °C. To the mixture was added slowly 22.4 g (0.26 mol) of methyl acrylate with stirring at 5 °C. The temperature was raised to 35 °C, and 0.7 g of Cu_2O was added to the mixture in small portions with vigorous stirring. After the nitrogen gas evolution had ceased, the reaction mixture was concentrated in vacuo, diluted with water, neutralized with 28% ammonium hydroxide, and extracted with three 100-mL portions of $CH_3CO_2C_2H_5$. The combined extracts were dried and concentrated in vacuo. The residue was chromatographed on silica gel and eluted with $CHCl_3$ to give 4.5 g (38%) of methyl 2-chloro-3-(6-methoxy-3-pyridyl)propionate.

A mixture of methyl 2-chloro-3-(6-methoxy-3-pyridyl)-propionate (4.5 g, 0.020 mol), 4 N KOH (46 mL), and C_2H_5OH (46 mL) was heated at reflux temperature for 2 h. The mixture was concentrated in vacuo. To the residue was added 30 mL of water, and the mixture was adjusted to pH 4 with 10% HCl. The resulting precipitate was collected to give 2.9 g (83%) of **8j**: EIMS, m/z 179 (M^+); ^1H NMR (60 MHz, $(CH_3)_2SO$-d_6) δ 3.89 (3 H, s, OCH_3), 6.54 (1 H, d, J = 16 Hz, -CH=C*H*CO-), 7.53 (1 H, d, J = 16 Hz, -C*H*=CHCO-).

Procedure B. 5-(3-Pyridyl)-2,4-pentadienoic Acid (13a). To a solution of triethyl phosphonocrotonate (10 g, 0.040 mol) in DMF (100 mL) were added slowly 1.6 g of NaH (about 60%, in oil) and then 4.3 g (0.040 mol) of 3-pyridinecarbaldehyde. The resulting mixture was stirred at room temperature for 40 min and then at 80 °C for 16 h and concentrated in vacuo. To the residue was added 50 mL of water, and the aqueous mixture was extracted with three 80-mL portions of $CHCl_3$. The combined extracts were dried and concentrated in vacuo. The residue was chromatographed on silica gel and eluted with $CHCl_3$ to give 5.7 g (70%) of ethyl 5-(3-pyridyl)-2,4-pentadienoate.

A mixture of ethyl 5-(3-pyridyl)-2,4-pentadienoate (5.7 g, 0.028 mol), 2 N KOH (20 mL), and C_2H_5OH (20 mL) was heated at reflux temperature with stirring for 1 h. The C_2H_5OH was removed by distillation in vacuo. The aqueous solution was adjusted to pH 4 with 10% HCl. The resulting precipitate was collected and washed with cold water to give 2.8 g (57%) of **13a**: EIMS, m/z 175 (M^+); ^1H NMR (300 MHz, $(CH_3)_2SO$-d_6) δ 6.08 (1 H, d, J = 14.7 Hz, -CH=CHCH=C*H*CO-), 7.09 (1 H, d, J = 15.4 Hz, -C*H*=CHCH=CHCO-), 7.25 (1 H, dd, J = 15.4, 10.7 Hz, -CH=C*H*CH=CHCO-), 7.38 (1 H, dd, J = 14.7, 10.7 Hz, -CH=CHC*H*=CHCO-).

Procedure C. 3-(2-Methyl-3-pyridyl)acrylic Acid (8c). To a stirred suspension of lithium aluminum hydride (3.1 g, 0.082 mol) in dry $(C_2H_5)_2O$ (140 mL) was added dropwise a solution of ethyl 2-methylnicotinate[18] (9.0 g, 0.055 mol) in dry $(C_2H_5)_2O$ (70 mL) at room temperature, and the mixture was heated at reflux temperature for 1.5 h. After the reaction mixture was cooled to 0 °C, the remaining lithium aluminum hydride was allowed to decompose by the cautious addition of 15 mL of water. The $(C_2H_5)_2O$ layer was decanted, and the residual solid was extracted with three 30-mL portions of $(C_2H_5)_2O$. The combined extracts were dried and concentrated in vacuo to give 6.4 g (96%) of crude 2-methyl-3-pyridinemethanol (**11c**).

Chromium trioxide (7.4 g, 0.074 mol) was slowly added to 110 mL of pyridine at 20 °C, and a solution of 6.4 g of the crude **11c** in 45 mL of pyridine was added in one portion to the complex. The temperature was raised to the reflux temperature over a

period of 2 h, and the mixture was heated at reflux temperature for 1.5 h. To the cooled mixture was added 220 mL of water, and the mixture was extracted with five 20-mL portions of $(C_2H_5)_2O$. The combined extracts were dried and concentrated in vacuo to give 2.3 g (37%) of crude 2-methyl-3-pyridinecarbaldehyde (**12c**).

A mixture of the crude **12c** (2.3 g), malonic acid (3.0 g, 0.029 mol), piperidine (0.3 mL), and pyridine (14 mL) was stirred at 100 °C for 3 h. The reaction mixture was concentrated in vacuo, and 2.5 mL of water was added to the residue. The resulting precipitate was collected to give 2.2 g (71%) of **8c**: EIMS, m/z 163 (M^+); ^1H NMR (60 MHz, $(CH_3)_2SO$-d_6) δ 2.58 (3 H, s, CH_3), 6.51 (1 H, d, J = 16 Hz, -CH=C*H*CO-), 7.80 (1 H, d, J = 16 Hz, -C*H*=CHCO-).

Procedure D. 3-(5-Chloro-3-pyridyl)acrylic Acid (8e). A mixture of ethyl 5-chloronicotinate[19] (9.0 g, 0.049 mol) and hydrazine monohydrate (7.3 g, 0.15 mol) was stirred at 110 °C for 1 h and then cooled. To the mixture was added 30 mL of cold water. The resulting precipitate was collected and washed with cold water to give 7.9 g (95%) of crude 5-chloro-3-pyridinecarbohydrazonic acid.

To a stirred mixture of 7.9 g of the crude hydrazonic acid in 50 mL of pyridine was added slowly 9.7 g (0.051 mol) of *p*-toluenesulfonyl chloride. After the mixture became a clear solution, the pyridine was removed by distillation in vacuo and 30 mL of water was added to the residue. The resulting precipitate was collected and washed with water to give 14.3 g (95%) of the crude *p*-toluenesulfonyl derivative **10e**.

The crude **10e** (14.3 g) was added to 70 mL of ethylene glycol at 120 °C, and 14 g (0.13 mol) of anhydrous Na_2CO_3 was added to the stirred mixture. The reaction mixture was heated at 160 °C for 10 min. The mixture was cooled, diluted with water, and extracted with three 100-mL portions of $(C_2H_5)_2O$. The combined extracts were dried and concentrated in vacuo to give 3.5 g (56%) of crude 5-chloro-3-pyridinecarbaldehyde (**12e**).

The crude **8e** was derived from the crude **12e** in 44% yield in a manner similar to that described in procedure C: EIMS, m/z 183 (M^+): ^1H NMR (60 MHz, $(CH_3)_2SO$-d_6) δ 6.79 (1 H, d, J = 16 Hz, -CH=C*H*CO-), 7.65 (1 H, d, J = 16 Hz, -C*H*=CHCO-).

Procedure E. 3-(6-Methyl-3-pyridyl)acrylic Acid (8p). 6-Methyl-3-pyridinemethanol (**11p**) was prepared from ethyl 6-methylnicotinate in 89% yield by the use of sodium bis(2-methoxyethoxy)aluminum hydride instead of lithium aluminum hydride as in procedure C.

A suspension of lead tetraacetate (110.8 g, 0.25 mol) in dry toluene (470 mL) was stirred at 80 °C for 20 min. To the suspension was added dropwise over a period of 25 min a solution of **11p** (30 g, 0.24 mol) in dry toluene (100 mL). The reaction mixture was heated at reflux temperature with stirring for 2.5 h. After the mixture was cooled, the insoluble materials were removed by filtration and washed with toluene. The filtrate and the washings were combined, washed successively with 10% Na_2CO_3 and water, dried, and concentrated in vacuo to give 16.9 g (57%) of crude 6-methyl-3-pyridinecarbaldehyde (**12p**).

The crude **8p** was derived from the crude **12p** in 77% yield by procedure C: EIMS, m/z 163 (M^+); ^1H NMR (300 MHz, $(CH_3)_2SO$-d_6) δ 2.49 (3 H, s, CH_3), 6.68 (1 H, d, J = 16.0 Hz, -CH=C*H*CO-), 7.60 (1 H, d, J = 16.0 Hz, -C*H*=CHCO-).

Procedure F. 3-(6-Isopropyl-3-pyridyl)acrylic Acid (8r). 6-Isopropyl-3-pyridinemethanol (**11r**) was prepared from ethyl 6-isopropylnicotinate in 91% yield by procedure C.

To a solution of **11r** (5.1 g, 0.034 mol) in 70 mL of $CHCl_3$ was added active manganese dioxide (35 g), and the mixture was heated at reflux temperature with stirring for 1 h. The insoluble materials were removed by filtration and washed with $CHCl_3$. The filtrate and the washings were concentrated in vacuo to give 3.7 g (74%) of crude 6-isopropyl-3-pyridinecarbaldehyde (**12r**).

The crude **8r** was derived from the crude **12r** in 85% yield by procedure C: EIMS, m/z 177 (M^+); ^1H NMR (60 MHz, $(CH_3)_2SO$-d_6) δ 1.25 (6 H, d, $CH(CH_3)_2$), 6.60 (1 H, d, J = 16 Hz, -CH=C*H*CO-), 7.57 (1 H, d, J = 16 Hz, -C*H*=CHCO-).

Procedure G. 2-Phenyl-3-(3-pyridyl)acrylic Acid (15e). To a stirred mixture of 3-pyridinecarbaldehyde (4.3 g, 0.040 mol), phenylacetic acid (5.4 g, 0.039 mol), and acetic anhydride (11.4 mL) was added $(C_2H_5)_3N$ (5.6 g, 0.039 mol). The mixture was stirred at 100 °C for 4 h. After being cooled, the mixture was alkalized with 10% $NaHCO_3$. The aqueous mixture was warmed to 60 °C and filtered. The filtrate was adjusted to pH 4.5 with 10% HCl, and the resulting precipitate was collected and recrystallized from C_2H_5OH to give 2.7 g (31%) of **15e**.

The crude **8a–g**, **8i–w**, **13a–c**, **15a–d**, and **15f**, without further purification, were used for the preparation of the corresponding amides **17a–x**, **19a–d**, **19f**, **20–25**, and **26d**. These acids recrystallized from the solvent given in Table II were subjected to elemental analyses.

3-(3-Pyridyl)propionic Acid (14a). A mixture of 3-(3-pyridyl)acrylic acid[26] (5.0 g, 0.034 mol), 10% Pd/C (0.4 g), CH_3OH (150 mL), and DMF (50 mL) was hydrogenated at room temperature under atmospheric pressure until an equivalent volume of hydrogen was absorbed. After removal of the catalyst by filtration, the filtrate was concentrated to dryness in vacuo and recrystallized from C_2H_5OH to give 4.5 g (88%) of **14a**: mp 149–151 °C; EIMS, m/z 151 (M^+). Anal. ($C_8H_9NO_2$) C, H, N.

3-(6-Methyl-3-pyridyl)propionic Acid (14b). This compound was prepared from **8p** in 75% yield in a manner similar to that described above: mp 114 °C (from C_2H_5OH–*n*-hexane); EIMS, m/z 165 (M^+). Anal. ($C_9H_{11}NO_2$) C, H, N.

3-(3-Pyridyl)acrylamides 16, 17, 19, and 26, 3-(3-Pyridyl)propionamides 18a and 18b, and 5-(3-Pyridyl)-2,4-pentadienamides 20–25 (Tables III–VII). Procedure H. *N*-[4-[4-(Diphenylmethyl)-1-piperazinyl]butyl]-3-(5-fluoro-3-pyridyl)acrylamide (17d). Compound **17d** was prepared by the use of ethyl chlorocarbonate in a manner similar to that described previously:[1] EIMS, m/z 472 (M^+); ^1H NMR (80 MHz, $(CH_3)_2SO$-d_6) δ 4.26 (1 H, s, C*H*Ph_2), 6.73 (1 H, d, J = 16 Hz, -CH=C*H*CO-).

Procedure I. *N*-[4-[4-(Diphenylmethyl)-1-piperazinyl]-butyl]-2-ethyl-3-(3-pyridyl)acrylamide Sesquifumarate (19c). A mixture of **15c** (0.80 g, 4.5 mmol), 1-(4-aminobutyl)-4-(diphenylmethyl)piperazine[1] (2.2 g), 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (0.87 g, 4.5 mmol), and CH_2Cl_2 (30 mL) was stirred at room temperature overnight. The reaction mixture was washed successively with 10% K_2CO_3 and water, dried, and concentrated to dryness in vacuo. The residue was chromatographed on silica gel and eluted with $CHCl_3$–CH_3OH (30:1) to give a brown oil, which was dissolved in 5 mL of C_2H_5OH containing 1.0 g of fumaric acid. To the resulting solution was added 15 mL of $(C_2H_5)_2O$. The solid separated was collected and recrystallized from C_2H_5OH–$(C_2H_5)_2O$ to give 1.4 g (47%) of **19c**: EIMS, m/z 482 (M^+); ^1H NMR (80 MHz, $(CH_3)_2SO$-d_6) δ 4.27 (1 H, s, C*H*Ph_2), 1.01 (3 H, t, CH_2CH_3).

Procedure J. *N*-[4-[4-(Diphenylmethyl)-1-piperazinyl]-butyl]-3-(5-hydroxy-3-pyridyl)acrylamide (17h). To a solution of the free base of **17g** (0.5 g, 1.0 mmol) in CH_2Cl_2 (20 mL) was added BBr_3 (1.3 g, 5.3 mmol) under cooling in an ice-water bath. The reaction mixture was stirred at room temperature overnight. To the mixture was added 10 mL of water under cooling in an ice-water bath, and the resulting mixture was adjusted to pH 7 with 1 N NaOH. The aqueous mixture was extracted with three 25-mL portions of $CHCl_3$. The extracts were dried and concentrated to dryness in vacuo. The residue was recrystallized from CH_3OH–CH_3CN to give 0.1 g (20%) of **17h**: EIMS, m/z 470 (M^+); ^1H NMR (80 MHz, $(CH_3)_2SO$-d_6) δ 4.22 (1 H, s, C*H*Ph_2), 6.61 (1 H, d, J = 16 Hz, -CH=C*H*CO-).

Procedure K. *N*-[4-[4-(Diphenylmethyl)-1-piperazinyl]-butyl]-3-(6-propyl-3-pyridyl)acrylamide (17q). A mixture of **8q** (0.71 g, 3.7 mmol), *N*-hydroxysuccinimide (0.47 g, 4.1 mmol), *N*,*N*′-dicyclohexylcarbodiimide (1.22 g, 5.9 mmol), and dioxane (20 mL) was stirred at room temperature overnight. The insoluble materials were removed by filtration and washed with dioxane. The filtrate and the washings were concentrated to dryness in vacuo. The residue was dissolved in 20 mL of anhydrous THF, and 1.2 g of 1-(4-aminobutyl)-4-(diphenylmethyl)piperazine[1] was added thereto. The mixture was stirred at room temperature for 5 h, and 40 mL of 10% K_2CO_3 was added. The mixture was extracted with three 50-mL portions of $CH_3CO_2C_2H_5$. The combined extracts were dried and the solvent was removed by distillation in vacuo. The residue was chromatographed on silica gel and eluted with $CHCl_3$–CH_3OH (40:1) to give an oily product,

(26) Marvel, C. S.; Coleman, L. E. Jr.; Scott, G. P. *J. Org. Chem.* **1955**, *20*, 1785.

which was crystallized from CH_3CN to give 0.77 g (41%) of **17q**: EIMS, m/z 496 (M^+); ^1H NMR (80 MHz, $(CH_3)_2SO$-d_6) δ 0.91 (3 H, t, $CH_2CH_2CH_3$), 4.26 (1 H, s, $CHPh_2$), 6.68 (1 H, d, J = 16 Hz, -CH=CHCO-).

Procedure L. N-[4-[4-(Diphenylmethyl)-1-piperazinyl]-butyl]-3-(6-methyl-3-pyridyl)acrylamide (17p). To a stirred suspension of **8p** (2.7 g, 0.017 mol) in anhydrous THF (70 mL) was added a solution of $(C_2H_5)_3N$ (1.7 g, 0.017 mol) in anhydrous THF (5 mL) at room temperature. The resulting mixture was cooled to −5 °C, and a solution of pivaloyl chloride (2.0 g, 0.017 mol) in anhydrous THF (5 mL) was added slowly. After the mixture was stirred at the same temperature for 30 min and cooled to −10 °C, a solution of 6.4 g of 1-(4-aminobutyl)-4-(diphenylmethyl)piperazine[1] in anhydrous THF (5 mL) was added slowly. The reaction mixture was stirred for 30 min at −10 to −5 °C and then at room temperature overnight. The insoluble materials were removed by filtration and washed with $CH_3CO_2C_2H_5$. The filtrate and the washings were concentrated in vacuo. To the residue was added 50 mL of 10% K_2CO_3, and the reaction mixture was extracted with 150 mL of $CH_3CO_2C_2H_5$. The extract was washed with water and dried. The solvent was removed by distillation in vacuo. The residue was recrystallized from CH_3CN to give 5.6 g (70%) of **17p**: EIMS, m/z 468 (M^+): ^1H NMR (80 MHz, $CDCl_3$) δ 2.57 (3 H, s, CH_3), 4.19 (1 H, s, $CHPh_2$), 6.39 (1 H, d, J = 16 Hz, -CH=CHCO-).

Procedure M. N-[4-[4-(Diphenylmethyl)-1-piperazinyl]butyl]-3-[5-hydroxy-4-(hydroxymethyl)-6-methyl-3-pyridyl]acrylamide (17x). A mixture of the free base of **17w** (1.7 g, 3.0 mmol) and 0.1 N HCl (600 mL) was heated at 85 °C for 40 min. The mixture was alkalized with 10% K_2CO_3 and extracted with three 100-mL portions of $CHCl_3$. The extracts were dried and concentrated to dryness in vacuo. The residue was recrystallized from CH_3OH–CH_3CN to give 0.53 g (34%) of **17x**: EIMS, m/z 514 (M^+); ^1H NMR (80 MHz, $(CH_3)_2SO$-d_6) δ 4.25 (1 H, s, $CHPh_2$), 4.71 (2 H, s, CH_2OH), 6.51 (1 H, d, J = 16 Hz, -CH=CHCO-), 7.64 (1 H, d, J = 16 Hz, -CH=CHCO-).

Reference Compounds. Oxatomide[27] and ketotifen[28] were prepared according to known procedures. Caffeic acid is commercially available (Nakalai Tesque, Japan).

Rat Passive Cutaneous Anaphylaxis (PCA) Assay.[29] Male Std:Wistar rats (140–200 g) were injected with 0.1 mL of a dilute solution of mouse antiserum to egg albumin in two sites of the shaved ventral skin. Forty-eight hours later each rat was challenged by an intravenous injection of 2 mg of the antigen together with 1 mL of a 0.5% Evan's blue saline solution. The rats were sacrificed 30 min after the challenge. The dimension (shortest × longest diameters) of the blueing lesions was measured on the undersurface of the skin. Test compounds were dissolved or suspended in a 0.5% gum tragacanth aqueous solution and administered orally to the rats 1 h before antigen challenge. Each group of three or four rats was used for each test compounds. The antiallergic activity of the compounds was expressed as percent inhibition of the dimension compared with the control group. Mouse anti-egg albumin antiserum was produced by the method of Levine and Vaz.[30]

5-Lipoxygenase Assay. The test was carried out according to the method of Ochi et al.[31] and Miyamoto and Obata[32] with minor modifications. In brief, the cytosol fraction of peritoneal exudate cells of guinea pigs was used as 5-lipoxygenase. The reaction mixture was incubated for 5 min at 30 °C after addition of (1-^{14}C)arachidonic acid (0.02 μCi). 5-Lipoxygenase activity was expressed as the conversion rate of arachidonic acid to 5-HETE for 5 min. Each group of three tubes was used for each test compound. The effect of test compounds was expressed as percent inhibition of the conversion rate compared with the control.

Histamine Release Assay. Basophils from nonallergic volunteers were collected by the method of Levy and Osler[33] with minor modifications. The cells were washed once with a cold Tris-A buffer at pH 7.4 (25 mL Tris, 120 mM NaCl, 5 mM KCl, and 0.03% human serum albumin) containing 4 mM EDTA and twice with Tris-A buffer. After washing, the cells were resuspended at 5–10 × 10^6 leukocytes/mL in Tris-ACM buffer at pH 7.6 (Tris-A buffer, 0.6 mM $CaCl_2$ and 1 mM $MgCl_2$). One milliliter of the cell suspension was incubated with 0.1 mL of a solution of the test compound or vehicle for 15 min at 37 °C and then for an additional 45 min with 0.1 mL of anti-human IgE antibody. After ice-cooling, the reaction mixture were centrifuged at 1200 rpm for 8 min at 4 °C. The supernatant fluids and the cells were analyzed separately for histamine by a modified method of the spectrophotofluorometric technique of Shore et al.[34] Inhibitory rate was calculated from histamine release rated without vs with test compound. IC_{50} values were determined from the best fit linear regression line of the inhibitory rates (average values of 2 experiments in each concentration).

Antihistamine Assay. Zig-zag strips of guinea pig trachea were prepared by the method of Emmerson and Mackay.[35] Dose–response curves for histamine were obtained before and 60 min after the addition of test compounds. Inhibitory rate was calculated from contraction heights in 3 × 10^{-5} M histamine without vs with test compound. IC_{50} values were determined from the best fit linear regression line of the inhibitory rates of histamine response.

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Registry No. **2a**, 27064-89-7; **2b**, 303-26-4; **2c**, 54041-93-9; **2d**, 68240-65-3; **2e**, 68240-63-1; **2f**, 118419-87-7; **2g**, 27469-61-0; **2h**, 68240-67-5; **3a**, 118419-73-1; **3a**·2fumarate, 118419-80-0; **3b**, 101620-08-0; **3b**·2.5fumarate, 118419-81-1; **3c**, 118419-74-2; **3c**·2.5fumarate, 118419-82-2; **3d**, 118419-75-3; **3e**, 118419-76-4; **3e**·2.5fumarate, 118419-83-3; **3f**, 118419-77-5; **3g**, 118419-78-6; **3g**·2fumarate, 118419-84-4; **3h**, 118419-79-7; **3h**·2fumarate, 118419-85-5; **4a**, 58258-01-8; **4b**, 115-46-8; **4c**, 50706-57-5; **5a**, 101620-78-4; **5b**, 117830-22-5; **5c**, 117830-21-4; **6b**, 118419-86-6; **8a**, 118419-93-5; **8b**, 118419-94-6; **8c**, 118419-95-7; **8d**, 118419-96-8; **8e**, 118419-97-9; **8f**, 118419-98-0; **8g**, 118419-99-1; **8i**, 118420-00-1; **8j**, 118420-01-2; **8k**, 118420-02-3; **8l**, 118420-03-4; **8m**, 118420-04-5; **8n**, 118420-05-6; **8o**, 118420-06-7; **8p**, 117830-17-8; **8q**, 118420-07-8; **8r**, 118420-08-9; **8s**, 118420-09-0; **8t**, 118420-10-3; **8u**, 118420-11-4; **8v**, 118420-12-5; **8w**, 118420-13-6; **9q**, 118419-90-2; **9r**, 118419-91-3; **9s**, 118419-92-4; **9v**, 77629-53-9; **10e**, 118420-18-1; **11c**, 56826-61-0; **11p**, 34107-46-5; **11r**, 107756-02-5; **12b**, 32399-08-9; **12c**, 60032-57-7; **12e**, 113118-82-4; **12p**, 53014-84-9; **12r**, 107756-03-6; **13a**, 118420-15-8; **13b**, 118420-16-9; **13c**, 118420-17-0; **14a**, 3724-19-4; **14b**, 118420-23-8; **15a**, 118420-19-2; **15b**, 106988-33-4; **15c**, 118420-20-5; **15d**, 118420-21-6; **15e**, 32986-89-3; **15f**, 118420-22-7; **16a**, 118420-24-9; **16a**·3oxalate, 118420-65-8; **16b**, 118420-25-0; **16b**·3oxalate, 118420-66-9; **16c**, 118420-26-1; **16c**·2oxalate, 118420-67-0; **16d**, 118420-27-2; **16d**·3oxalate, 118420-68-1; **16e**, 118420-28-3; **16f**, 118420-29-4; **16g**, 118420-30-7; **16g**·2oxalate, 118420-69-2; **16h**, 118437-09-5; **16i**, 118420-31-8; **16i**·4oxalate, 118420-70-5; **17a**, 118420-32-9; **17a**·3oxalate, 118420-75-0; **17b**, 118420-33-0; **17b**·2tartrate, 118420-76-1; **17c**, 118420-34-1; **17c**·1.5tartrate, 118420-77-2; **17d**, 118420-35-2; **17e**, 118420-36-3; **17f**, 118420-37-4; **17g**, 118420-38-5; **17g**·1.5tartrate, 118420-78-3; **17h**, 118420-39-6; **17i**, 118420-40-9; **17j**, 118420-41-0; **17k**, 118420-42-1; **17k**·3oxalate, 118420-79-4; **17l**, 118420-43-2; **17m**, 118420-44-3; **17n**, 118420-45-4; **17o**, 118420-46-5; **17p**, 118420-47-6; **17q**, 118420-48-7; **17r**,

(27) Janssen Pharmaceutica N. V. U. S. Patent 4,250,176; *Chem. Abstr.* **1978**, *88*, 50920n.
(28) Waldvogel, E.; Schwarb, G.; Bastian, J. M.; Bourquin, J. P. *Helv. Chim. Acta* **1976**, *59*, 866.
(29) Nakamura, H.; Motoyoshi, K.; Ishii, K.; Kadokawa, T. *Nippon Yakurigaku Zasshi* **1988**, *92*, 29.
(30) Levine, B. B.; Vaz, N. M. *Int. Archs Allergy Appl. Immun.* **1970**, *39*, 156.
(31) Ochi, K.; Yoshimoto, T.; Yamamoto, S. *J. Biol. Chem.* **1983**, *258*, 5754.
(32) Miyamoto, T.; Obata. T. *Perspectives in Prostaglandin Research*; Shiokawa, Y., Katori, M., Mizushima, Y., Ed.; Excepta Medica: Amsterdam, Oxford, and Princeton, 1983; p 78.
(33) Levy, D. A.; Osler, A. G. *J. Immunol.* **1966**, *97*, 203.
(34) Shore, P. A.; Burkhalter, A.; Cohn, V. H., Jr. *J. Pharmacol. Exp. Ther.* **1959**, *127*, 182.
(35) Emmerson, J.; Mackay, D. *J. Pharm. Pharmacol.* **1979**, *31*, 798.

118420-49-8; **17r**·2tartrate, 118420-80-7; **17s**, 118420-50-1; **17t**, 118420-51-2; **17u**, 118420-52-3; **17u**·2tartrate, 118420-81-8; **17v**, 118420-53-4; **17v**·2tartrate, 118420-82-9; **17w**, 118420-54-5; **17w**·3oxalate, 118420-83-0; **17x**, 118437-10-8; **18a**, 107755-78-2; **18a**·fumarate, 118420-84-1; **18b**, 107755-79-3; **19a**, 107755-62-4; **19a**·fumarate, 107755-63-5; **19b**, 107755-60-2; **19c**, 118420-55-6; **19c**·1.5fumarate, 118420-71-6; **19d**, 107755-68-0; **19e**, 107755-64-6; **19e**·2oxalate, 107755-65-7; **19f**, 107755-61-3; **20**, 118420-56-7; **20**·3fumarate, 118420-72-7; **21**, 118420-57-8; **22**, 118420-58-9; **23**, 118420-59-0; **24**, 118420-60-3; **25**, 118420-61-4; **26a**, 118420-62-5; **26a**·2oxalate, 118420-73-8; **26b**, 118420-63-6; **26b**·1.5tartrate, 118420-74-9; **26c**, 118420-64-7; **26d**, 117830-04-3; $(EtO)_2P(O)CHMeCO_2Et$, 3699-66-9; $(EtO)_2P(O)CHEtCO_2Et$, 17145-91-4; $(EtO)_2P(O)CH_2CO_2Et$, 867-13-0; $(EtO)_2P(O)CHPrCO_2Et$, 35051-49-1; $(EtO)_2P(O)CHPhCO_2Et$, 31641-78-8; 3-acetylpyridine, 350-03-8; 3-pyridinecarbaldehyde, 500-22-1; 4-bromobutyronitrile, 5332-06-9; 3-cyano-6-propyl-2-pyridone, 24049-25-0; 2-chloro-3-cyano-6-propylpyridine, 118419-88-8; 5-cyano-2-propylpyridine, 118419-89-9; 3-cyano-6-isopropyl-2-pyridone, 5782-69-4; 6-butyl-3-cyano-2-pyridone, 118420-86-3; 3-cyano-5,6-dimethyl-2-pyridone, 72716-80-4; 3-cyano-6-ethyl-2-pyridone, 4241-20-7; 2-chloro-3-cyano-5,6-dimethylpyridine, 65176-93-4; 2-chloro-5-nitropyridine, 4548-45-2; 2-methoxy-5-nitropyridine, 5446-92-4; methyl acrylate, 96-33-3; methyl 2-chloro-3-(6-methoxy-3-pyridyl)propionate, 107756-04-7; triethyl phosphonocrotonate, 10236-14-3; ethyl (*E,E*)-5-(3-pyridyl)-2,4-pentadienoate, 118420-14-7; ethyl 2-methylnicotinate, 1721-26-2; malonic acid, 141-82-2; ethyl 5-chloronicotinate, 20825-98-3; 5-chloro-3-pyridinecarbohydrazonic acid, 117830-18-9; ethyl 6-methylnicotinate, 21684-59-3; phenylacetic acid, 103-82-2; 3-(3-pyridyl)acrylic acid, 1126-74-5; 1-(4-aminobutyl)-4-(diphenylmethyl)piperazine, 101620-10-4; (2-(4-bromobutyl)-1*H*-isoindole-1,3(2*H*)-dione, 5394-18-3; ethyl 5-methoxynicotinate, 20826-01-1; ethyl 6-phenylnicotinate, 57443-68-2; ethyl 2,6-dimethylnicotinate, 1721-13-7; ethyl 5-fluoronicotinate, 22620-29-7; ethyl 5-bromonicotinate, 20986-40-7; 4-(diphenylmethyl)-1-piperazinepropanamine, 50971-75-0.

5-(1-Piperazinyl)-1*H*-1,2,4-triazol-3-amines as Antihypertensive Agents[1]

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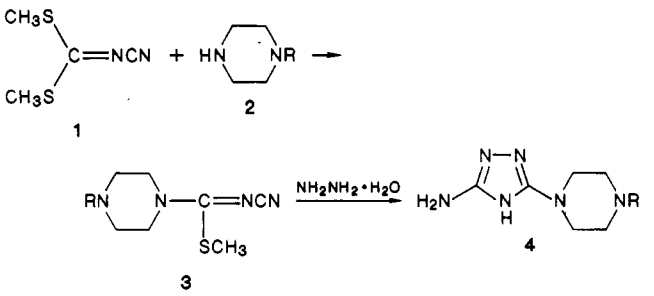
A series of 5-(1-piperazinyl)-1*H*-1,2,4-triazol-3-amines was synthesized and screened for antihypertensive and diuretic activity in spontaneously hypertensive rats (SHR). One compound, 5-[4-[(3-chlorophenyl)methyl]-1-piperazinyl]-1*H*-1,2,4-triazol-3-amine (**8**), was selected to define the mechanism of its antihypertensive activity. Studies in SHR suggest ganglionic blocking activity. Short-lived antihypertensive activity was observed in conscious renal hypertensive dogs.

During an ongoing search for effective drugs for the management of hypertension, the piperazinyltriazolamine **5** was synthesized. When administered orally to the conscious, spontaneously hypertensive rat, compound **5** significantly lowered blood pressure without affecting urinary output. The ubiquitous presence of the piperazine nucleus in cardiovascular drugs such as prazosin,[2] lidoflazine,[3] and urapidil[4] encouraged us to undertake, as one aspect of our investigation of this heterocyclic system, the synthesis and biological evaluation of a series of 4-N′-substituted piperazinyltriazolamines related to **5**, which we report in this paper.

Chemistry

The compounds listed in Table I were synthesized by the two-step route outlined in Scheme I. Dimethyl cyanocarboximidodithioate (**1**) reacted smoothly with 1 equiv of **2** in either ethanol or acetonitrile to give thioic acid **3** in high yield. Although **3** could be isolated as a crystalline solid, it was usual to proceed to the final step without isolation of this intermediate. The cessation of methyl mercaptan evolution indicated the completion of step 1. A slight excess of hydrazine hydrate was added and refluxing continued until evolution of the second mole of methyl mercaptan was complete. Ethanol reacted slowly with **1** to give, after reaction with hydrazine hydrate, small quantities of 5-ethoxy-1*H*-1,2,4-triazol-3-amine, which interfered with the purification of the final product; therefore, acetonitrile was the solvent of choice.

Scheme I



Discussion

Blood pressure lowering and diuretic activity was assessed in spontaneously hypertensive rats (SHR). As may be seen from Table I, a number of *N′*-benzyl- and *N′*-alkyl-substituted piperazines show blood pressure lowering properties. Alkyl (**36**, **37**), phenylalkyl (**5**, **6**, **7**, **42**), and phenoxyalkyl (**44**) derivatives, with the exception of those alkyl groups containing nitrogen (**41**, **43**), lower blood pressure as much as 75 mmHg below control levels. Cycloalkyl derivatives **38**, **39**, and **40** show significant but less blood pressure lowering capabilities. Benzylic derivatives indicate varying degrees of potency depending on the substituent and substitution pattern of the phenyl ring.

Thus, while the halogenated benzyl derivatives **8**, **19**, and **20** lower blood pressure markedly, ortho-substituted derivatives **9**, **11**, **14**, **15**, **21**, **29**, **32**, and **47** showed diminished potency. Ring deactivating groups, such as cyano (**24**) and nitro (**33**), suppress activity, whereas the effect of ring activation is less clear. While the *p*-amino (**27**), *p*-dimethylamino (**28**), and 3-bromo-*p*-(dimethylamino)benzyl (**31**) piperazine compounds exhibit blood pressure lowering

(1) Tomcufcik, A. S.; Meyer, W. E.; Dusza, J. P. U.S. Patent 4,421,753, 1983.
(2) Scriabine, A.; Constantine, J. W.; Hess, H.-J.; McShane, N. K. *Experientia* **1968**, *24*, 1150.
(3) Schaper, W. K. A.; Xhonneux, R.; Jageneau, A. H. M.; Janssen, P. A. J. *J. Pharmacol. Exp. Ther.* **1966**, *152*, 265.
(4) Schoetensack, V. W.; Bischler, P.; Dittmann, E. Ch.; Steinijans, V. *Arzneim.-Forsch.* **1977**, *27*(II), 1908.
(5) Servier, J. *Chem. Abstr.* **1964**, *60*, 2972*h*.

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