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Syntheses and Analgesic Activities of 1-[2-Methyl-2-(*N*-propionyl-*p*- or *m*-substituted-phenylamino)ethyl]-4-phenethylpiperazines[1)]

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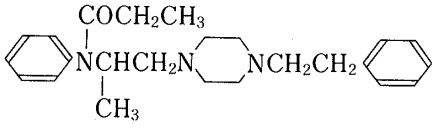
For the purpose of increasing the analgesic activity of *N*-[1-methyl-2-(4-phenethylpiperazino)ethyl]propionanilide (I), several substituent groups were introduced into both benzene rings of I. 1-[2-Methyl-2-(*N*-propionyl-*p*- or *m*-substituted-phenylamino)ethyl]-4-phenethylpiperazines (VIa—f, h) and 1-[2-methyl-2-(*N*-propionyl-*p*-methoxyphenylamino)ethyl]-4-(*p*-substituted-phenethyl)piperazines (XIIa—e) were prepared by substitution at the *p*- or *m*-position of the aniline moiety, and by substitution at the *p*-position of the phenethyl moiety, respectively.

Potent activity (92—100% inhibition of writhing at 30 mg/kg, *s.c.*) could be achieved by introducing alkoxyl groups into the benzene ring of the aniline moiety. Among such compounds, 1-[2-methyl-2-(*N*-propionyl-*p*-methoxyphenylamino)ethyl]-4-phenethylpiperazine (VIa) showed the highest activity (ED_{50}: 3.17 mg/kg, *s.c.*), which was equivalent to 1/2 of the activity of pentazocine (ED_{50}: 1.64 mg/kg, *s.c.*).

On the other hand, introduction of several substituents into the benzene ring of the phenethyl moiety resulted in low analgesic activities (2—58% inhibition of writhing at 30 mg/kg, *s.c.*).

Keywords——analgesic; sodium borohydride with alminium chloride; diazotization; piperazine; 1-[2-methyl-2-(*N*-propionyl-*p*-substituted-phenylamino)ethyl]-4-phenethylpiperazine; 1-[2-methyl-2-(*N*-propionyl-*m*-substituted-phenylamino)ethyl]-4-phenethylpiperazine; 1-[2-methyl-2-(*N*-propionyl-*p*-methoxyphenylamino)ethyl]-4-(*p*-substituted-phenethyl)piperazine

In a previous paper,[1)] we reported the syntheses and analgesic activities of *N*-[1-methyl-2-(4-substituted-piperazino)ethyl]propionanilides, one of which, *N*-[1-methyl-2-(4-phenethylpiperazino)ethyl]propionanilide (I), possessed *ca.* 1/3 of the analgesic activity of pentazocine in terms of the inhibition of writhing induced by acetic acid upon subcutaneous admin-



I

Chart 1

istration. This suggests that the benzene ring of the phenethyl moiety as well as that of the aniline moiety plays an important role in receptor-binding, just as in the cases of phenazocine,[2)] etonitazine,[3)] and fentanyl.[4)] Therefore, for the purpose of increasing the activity of I, we tried to introduce various substituent groups into both benzene rings of I and examined the resulting compounds for analgesic activities. In this paper, the syntheses and analgesic activities of these are reported.

We synthesized 1-[2-methyl-2-(*N*-propionyl-*p*- or *m*-substituted-phenylamino)ethyl]-4-

phenethylpiperazines (VIa—f, h) by substitution at the *p*-position (R_1) and *m*-position (R_2) of the aniline moiety and 1-[2-methyl-2-(*N*-propionyl-*p*-methoxyphenylamino)ethyl]-4-(*p*-substituted-phenethyl)piperazines (XIIa—e) by substitution at the *p*-position (R_3) of the phenethyl moiety.

The propionanilide derivatives (VIa—f, h) were prepared as shown in Chart 1. Namely, 1-phenethylpiperazine (II)[5] was used as the starting material for the following syntheses. Acylation of II with α-bromopropionyl bromide gave 1-(2-bromopropionyl)-4-phenethylpiperazine (III), which, without purification, was allowed to react with substituted anilines to give 1-[2-(*p*- or *m*-substituted)-phenylamino]propionyl-4-phenethylpiperazines (IVa—g). Lithium aluminium hydride reduction of IVa—g afforded 1-[2-methyl-2-(*p*- or *m*-substituted-phenylamino)ethyl]-4-phenethylpiperazines (Va—g) as viscous oils, which were transformed into oxalates. *N*-Propionylation by warming with propionic anhydride afforded 1-[2-methyl-2-(*N*-propionyl-*p*- or *m*-substituted-phenylamino)ethyl]-4-phenethylpiperazines (VIa—f, h). As it was difficult to purify VIa—f, h by vacuum distillation because of the occurrence of thermal decomposition, VIa—f, h were purified by extraction and alumina column chromatography with chloroform as the eluent. The free bases were viscous oils and were transformed into their oxalates in the usual manner.

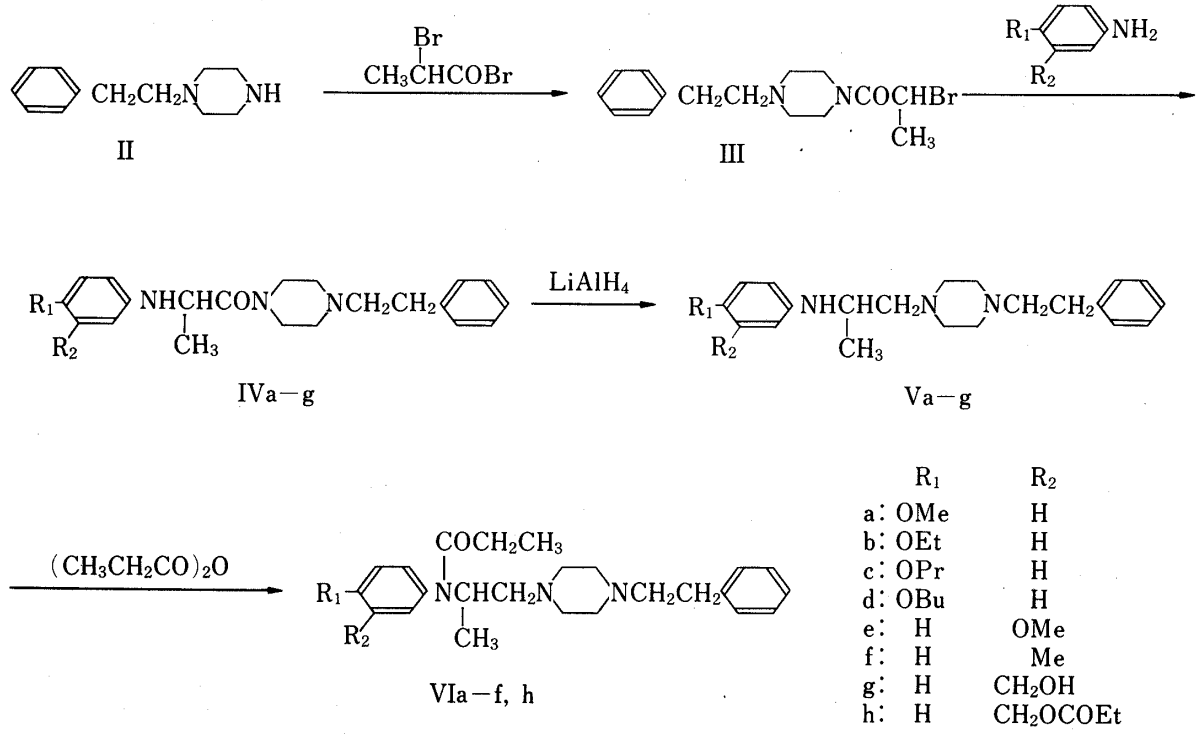


Chart 2

The substituted-phenethyl derivatives (XIIa—e) were prepared in a similar manner (Chart 2). *p*-Nitrophenethyl bromide (VII)[6] and piperazine hexahydrate were condensed in MeOH–dioxane to afford 1-(*p*-nitrophenethyl)piperazine (VIII). 1-(2-Bromopropionyl)-4-(*p*-nitrophenethyl)piperazine (IX) (obtained from VIII and α-bromopropionyl bromide) was condensed with *p*-anisidine to afford 1-[2-(*p*-methoxyphenylamino)propionyl]-4-(*p*-nitrophenethyl)piperazine (X). Next, reduction of the amide (X) was tried with lithium aluminium hydride. However, the desired amine was not obtained, because the amide (X) contained a nitro group, which was also easily reduced by lithium aluminium hydride. Therefore, selective reduction of the amide (X) was essential in this step. By using sodium

borohydride together with a Lewis acid ($AlCl_3$) (mole ratio 3 : 1) in diglyme–tetrahydrofuran (THF) (volume ratio 1 : 4),[7] the selective reduction of the amide (X) was achieved to give 1-[2-methyl-2-(*p*-methoxyphenylamino)ethyl]-4-(*p*-nitrophenethyl)piperazine (XI) satisfactorily (76.9%). *N*-Propionylation of XI gave 1-[2-methyl-2-(*N*-propionyl-*p*-methoxyphenylamino)ethyl]-4-(*p*-nitrophenethyl)piperazine (XIIa). In order to obtain several *p*-substituted phenethyl compounds, the nitro group of XIIa was catalytically reduced to an amino group on PtO_2. The amino derivative (XIIb) was converted to the bromo derivative (XIIc)

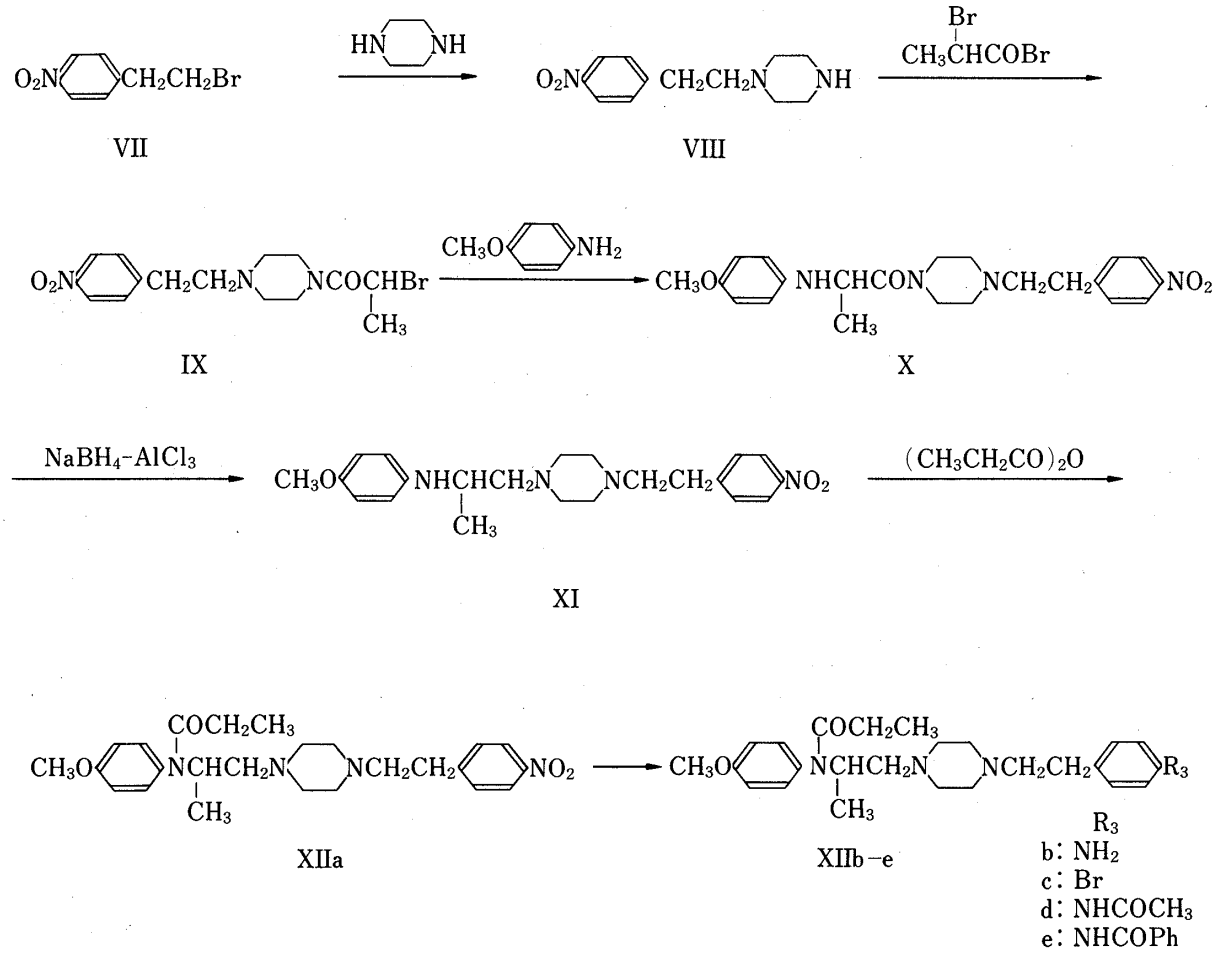


Chart 3

after diazotization of XIIb, followed by addition of CuBr in 47% hydrobromic acid. Acylation of XIIb with acetyl chloride and benzoic anhydride gave the *N*-acetyl derivative (XIId) and *N*-benzoyl derivative (XIIe), respectively. These free bases (XIIa—e) were all viscous oils, and were transformed into their oxalates in the usual manner.

Pharmacological Results and Discussion

The sixteen oxalates described above were examined by subcutaneous administration to mice for analgesic activity in terms of the inhibition of writhing induced by acetic acid[8] in comparison with pentazocine. These compounds were also tested for acute toxicity in mice. The pharmacological results are listed in Table I.

When the activities of compounds Va—d are compared with those of VIa—d, it is apparent that the propionyl moiety on the nitrogen atom of the aniline group is essential for the enhancement of analgesic activity. Potent analgesic activity (at 30 mg/kg, *s.c.*) could be

achieved by introducing an alkoxyl group into the *p*- or *m*-position of the phenyl ring of the aniline moiety: *p*-methoxypropionanilide derivative (VIa) 95%; *p*-ethoxypropionanilide derivative (VIb) 92%; *p*-propoxypropionanilide derivative (VIc) 100% and *m*-methoxypropionanilide derivative (VIe) 100%. This may suggest that less hydrophobic substituents attached to the phenyl ring of the aniline moiety are desirable for potent activity. In order to examine these analgesic activities in more detail, ED_{50} (50% effective dose) was estimated for four compounds, using five ddY male mice at each dose (2.5, 5.0, 10.0 mg/kg, *s.c.*). Among them, VIa showed the highest activity (ED_{50}: 3.17 mg/kg, *s.c.*), which was 1/2 of the activity of pentazocine (ED_{50}: 1.64 mg/kg, *s.c.*). Nevertheless, VIb and VIc are of interest, because they are less toxic than VIa and VIe.

On the other hand, introduction of substituents into the phenyl group of the phenethyl moiety resulted in low inhibitory activity, ranging from 2 to 58%. Since the use of various physicochemically different substituents all resulted in relatively low inhibitory activity, it appears that the unsubstituted phenyl ring is of importance for potent activity.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 260-10 spectrometer and proton nuclear magnetic resonance (^{1}H-NMR) spectra on a JEOL JMN-PMX 60 spectrometer operating at 60 MHz in $CDCl_3$ solution with tetramethylsilane as an internal standard. Mass spectra (MS) were measured with a JEOL JMS-01SG-2 mass spectrometer.

General Procedure for the Preparation of 1-[2-(*p*- or *m*-Substituted)-phenylamino]propionyl-4-phenethylpiperazines (IVa—g)——A Typical Example: 1-[2-(*p*-Methoxyphenylamino)propionyl]-4-phenethylpiperazine

Table I. Analgesic Activity

Compd. No.	mg/kg[a)]	Inhibition of writhing (%)	ED_{50} (mg/kg, *s.c.*)	Toxicity (mg/kg, *s.c.*)
I	30	78		30 No apparent change
Va	30	18		1000 Sedation
				Death within 24 h
Vb	30	12		1000 Myasthenia
				Sedation
Vc	30	28		1000 Sedation
Vd	30	30		1000 Myasthenia
VIa	30	95	3.17	300 Myasthenia
				Sedation
				Death within 24 h
VIb	30	92	5.64	1000 A little
				Sedation
VIc	30	100	5.32	1000 Sedation
VId	30	43		1000 No apparent change
VIe	30	100	10.00	1000 Death
VIf	30	48		1000 Death
VIh	30	0		
XIIa	30	2		300 Myasthenia
XIIb	30	52		300 Myasthenia
XIIc	30	35		1000 Myasthenia
XIId	30	15		300 Myasthenia
XIIe	30	58		
Pentazocine	10	85	1.64	

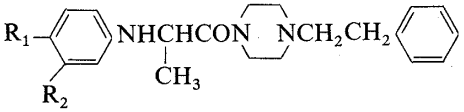
a) All compounds were injected subcutaneously.

(IVa): Acylation of 1-phenethylpiperazine (II)[5] (10 g) with α-bromopropionyl bromide (5.7 g) gave 1-(2-bromopropionyl)-4-phenethylpiperazine (III) (9.0 g). K_2CO_3 (3.8 g) and *p*-methoxyaniline (3.4 g) were added to a solution of III in EtOH (75 ml). The mixture was refluxed for 8 h. The precipitate was removed by filtration and the filtrate was concentrated *in vacuo* to afford crude IVa. Recrystallization from iso-PrOH gave IVa (8.16 g, 84.5%) as colorless prisms, mp 105—106 °C. IR ν_{max}^{Nujol} cm^{-1}: 3350 (NH), 1630 (C=O). NMR ($CDCl_3$) δ: 1.30 (3H, d, J=6 Hz, $CHC\underline{H}_3$), 3.70 (3H, s, OCH_3), 4.32 (1H, br s, NH), 7.21 (5H, s, $CH_2\underline{Ph}$). MS *m/e*: 367 (M^+). *Anal.* Calcd for $C_{22}H_{29}N_3O_2$: C, 71.94; H, 7.90; N, 11.44. Found: C, 71.89; H, 8.09; N, 11.23.

In a similar manner the following compounds were prepared: 1-[2-(*p*-ethoxyphenylamino)propionyl]-4-phenethylpiperazine (IVb), 1-[2-(*p*-propoxyphenylamino)propionyl]-4-phenethylpiperazine (IVc), 1-[2-(*p*-butoxyphenylamino)propionyl]-4-phenethylpiperazine (IVd), 1-[2-(*m*-methoxyphenylamino)propionyl]-4-phenethylpiperazine (IVe), 1-[2-(*m*-methylphenylamino)propionyl]-4-phenethylpiperazine (IVf), 1-[2-(*m*-hydroxymethylphenylamino)propionyl]-4-phenethylpiperazine (IVg). The data for these compounds are listed in Tables II and III.

General Procedure for the Synthesis of 1-[2-Methyl-2-(*p*- or *m*-substituted-phenylamino)ethyl]-4-phenethylpiperazines (Va—g)——A Typical Example: 1-[2-Methyl-2-(*p*-methoxyphenylamino)ethyl]-4-phenethylpiperazine (Va): A solution of IVa (5 g) in absolute Et_2O (35 ml) was added dropwise to a solution of $LiAlH_4$ (1.0 g)

TABLE II.



Compd. No.	R_1	R_2	Yield (%)	mp (°C)	Recryst. solv.	Formula	Analysis (%) Calcd (Found) C	H	N
IVa	OMe	H	84.5	105—106	iso-PrOH	$C_{22}H_{29}N_3O_2$	71.94 (71.89)	7.90 8.09	11.44 11.23)
IVb	OEt	H	68.3	103—104	iso-PrOH	$C_{23}H_{31}N_3O_2$	72.44 (72.57)	8.14 8.49	11.02 10.87)
IVc	OPr	H	72.2	87—88	iso-PrOH	$C_{24}H_{33}N_3O_2$	72.91 (73.15)	8.36 8.60	10.63 10.54)
IVd	OBu	H	43.2	102—103	Et_2O	$C_{25}H_{35}N_3O_2$	73.35 (73.56	8.56 8.82	10.27 10.50)
IVe	H	OMe	38.5	117—119	iso-PrOH	$C_{22}H_{29}N_3O_2$	71.91 (71.86	7.95 8.00	11.43 11.41)
IVf	H	Me	68.6	109—111	iso-PrOH	$C_{22}H_{29}N_3O$	75.18 (74.88	8.32 8.34	11.95 11.78)
IVg	H	CH_2OH	89.4	113—115 (Oxalate)	iso-PrOH (Oxalate)	$C_{22}H_{31}N_3O \cdot 1.1C_2H_2O_4 \cdot 0.1H_2O$	62.06 (61.87	6.76 6.77	8.97 9.15)

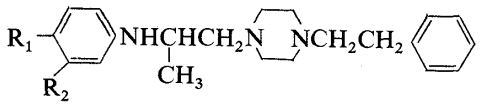
TABLE III. Instrumental Analysis Data

Compd. No.	MS *m/e* (M^+)	IR ν_{max}^{Nujol} cm^{-1} NH	IR C=O	^{1}H-NMR ($CDCl_3$) δ $CHC\underline{H}_3$ (d, J=6 Hz)	$\underline{Ph}CH_2$ (s)	Other protons
IVa	367	3350	1630	1.30	7.21	3.70 (3H, s, OCH_3) 4.32 (1H, br s, NH)
IVb	381	3370	1640	1.17	7.20	1.18 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$) 4.16 (1H, br s, NH)
IVc	395	3350	1636	1.30	7.20	0.97 (3H, t, J=7 Hz, $OCH_2CH_2C\underline{H}_3$) 4.10 (1H, br s, NH)
IVd	409	3360	1640	1.20	7.20	3.80 (1H, br s, NH)
IVe	367	3350	1640	1.35	7.10	3.69 (3H, s, OCH_3)
IVf	351	3350	1640	1.34	7.06	2.22 (3H, s, *m*-$C\underline{H}_3Ph$)
IVg	367	—	1640	1.34	7.04	4.47 (2H, s, $C\underline{H}_2OH$)

in absolute Et_2O (75 ml) at 2 °C over a period of 1 h with stirring. The mixture was refluxed for 3 h, then cooled, and H_2O (1.5 ml), 15% aqueous NaOH solution (4.0 ml) and H_2O (4.0 ml) were successively added to the reaction mixture at 0 °C with vigorous stirring. The precipitate was removed by filtration and the filtrate was dried over $MgSO_4$ and concentrated *in vacuo*. The oily residue was purified by alumina column chromatography with $CHCl_3$ as the eluent. The eluate was concentrated *in vacuo* to afford Va (3.0 g, 62.4%) as a deep red oil. IR ν_{max}^{Nujol} cm^{-1}: 3340 (NH). NMR ($CDCl_3$) δ: 1.31 (3H, d, J=6 Hz, $CH\underline{CH_3}$), 3.70 (3H, s, OCH_3), 4.20 (1H, br s, NH), 7.16 (5H, s, $CH_2\underline{Ph}$). MS *m/e*: 353 (M^+). Oxalate: mp 203—204 °C (MeOH). *Anal.* Calcd for $C_{22}H_{31}N_3O \cdot 2C_2H_2O_4$: C, 58.53; H, 6.57; N, 7.88. Found: C, 58.31; H, 6.48; N, 7.69.

In a similar manner the following compounds were prepared: 1-[2-methyl-2-(*p*-ethoxyphenylamino)ethyl]-4-phenethylpiperazine (Vb), 1-[2-methyl-2-(*p*-propoxyphenylamino)ethyl]-4-phenethylpiperazine (Vc), 1-[2-methyl-2-(*p*-butoxyphenylamino)ethyl]-4-phenethylpiperazine (Vd), 1-[2-methyl-2-(*m*-methoxyphenylamino)ethyl]-4-phenethylpiperazine (Ve), 1-[2-methyl-2-(*m*-methylphenylamino)ethyl]-4-phenethylpiperazine (Vf), 1-[2-methyl-2-(*m*-hydroxymethylphenylamino)ethyl]-4-phenethylpiperazine (Vg). The data for these compounds are listed in Tables IV and V.

TABLE IV.



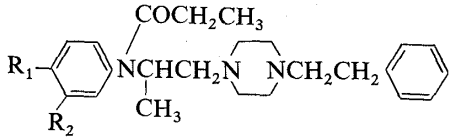
Compd. No.	R_1	R_2	Yield (%)	mp (°C)	Recryst. solv.	Formula	Analysis (%) Calcd (Found)		
							C	H	N
Va	OMe	H	62.4	203—204	MeOH	$C_{22}H_{31}N_3O \cdot 2C_2H_2O_4$	58.53	6.57	7.88
							(58.31	6.48	7.69)
Vb	OEt	H	98.6	200—201.5	MeOH–H_2O	$C_{23}H_{33}N_3O \cdot 2C_2H_2O_4$	59.22	6.81	7.67
							(59.51	6.74	7.61)
Vc	OPr	H	99.5	212—214	MeOH–H_2O	$C_{24}H_{35}N_3O \cdot 2C_2H_2O_4$	59.89	6.95	7.49
							(59.95	6.90	7.36)
Vd	OBu	H	89.4	214—216	MeOH–H_2O	$C_{25}H_{37}N_3O \cdot 2C_2H_2O_4$	59.59	7.19	7.19
							(59.93	7.20	7.32)
Ve	H	OMe	26.0	203—205	EtOH	$C_{22}H_{31}N_3O \cdot 2C_2H_2O_4$	58.53	6.61	7.87
							(58.27	6.54	7.81)
Vf	H	Me	25.3	201—203	EtOH	$C_{22}H_{31}N_3 \cdot 2C_2H_2O_4$	60.34	6.81	8.12
							(60.08	6.96	8.08)
Vg	H	CH_2OH	20.8	203—205	EtOH	$C_{22}H_{31}N_3O \cdot 2C_2H_2O_4$	56.99	6.73	7.67
						$\cdot 0.8H_2O$	(57.05	6.68	7.77)

TABLE V. Instrumental Analysis Data

Compd. No.	MS *m/e* (M^+)	IR ν_{max}^{film} cm^{-1} (NH)	^{1}H-NMR ($CDCl_3$) δ		
			$CH\underline{CH_3}$ (d, J=6 Hz)	$Ph\underline{CH_2}$ (s)	Other protons
Va	353	3340	1.31	7.16	3.70 (3H, s, OCH_3)
					4.20 (1H, br s, NH)
Vb	367	3340	1.18	7.20	1.33 (3H, t, J=7 Hz, $OCH_2C\underline{H_3}$)
					3.40 (1H, br s, NH)
					3.90 (1H, q, J=7 Hz, $C\underline{H}CH_3$)
Vc	381	3340	1.20	7.20	1.00 (3H, t, J=7 Hz, $OCH_2CH_2C\underline{H_3}$)
					3.83 (1H, br s, NH)
Vd	395	3340	1.16	7.10	0.95 (3H, t, J=7 Hz, $OCH_2CH_2CH_2C\underline{H_3}$)
					3.80 (1H, br s, NH)
Ve	353	3370	1.17	7.01	3.65 (3H, s, OCH_3)
Vf	337	3350	1.15	7.04	2.20 (3H, s, *m*-$C\underline{H_3}Ph$)
Vg	353	—	1.17	7.03	4.50 (2H, s, $C\underline{H_2}OH$)

General Procedure for the Synthesis of 1-[2-Methyl-2-(*N*-propionyl-*p*- or *m*-substituted-phenylamino)ethyl]-4-phenethylpiperazines (VIa—f, h)——A Typical Example: 1-[2-Methyl-2-(*N*-propionyl-*p*-methoxyphenylamino)ethyl]-4-phenethylpiperazine (VIa): A mixture of Va (2 g) and propionic anhydride (8 ml) was heated at 100 °C for 3 h. The mixture was poured over ice and neutralized with $NaHCO_3$. The solution was adjusted to pH 2 with 20% aqueous HCl solution and washed with Et_2O. Then, the acidic solution was adjusted to pH 9 and extracted with Et_2O. The Et_2O extract was dried over $MgSO_4$ and concentrated *in vacuo*. The oily residue was purified by alumina column chromatography with $CHCl_3$ as the eluent to afford VIa (1.0 g, 43.2%) as a yellowish red oil. IR ν_{max}^{Nujol} cm^{-1}: 1645 (C=O). NMR ($CDCl_3$) δ: 1.01 (3H, t, J=6 Hz, $CH_2\underline{CH_3}$), 1.07 (3H, d, J=6 Hz, $CH\underline{CH_3}$), 3.80 (3H, s, OCH_3), 7.20

TABLE VI.



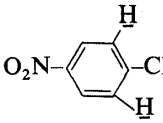
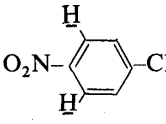
Compd. No.	R_1	R_2	Yield (%)	mp (°C)	Recryst. solv.	Formula	Analysis (%) Calcd (Found) C	H	N
VIa	OMe	H	43.2	197—198	Dioxane–H_2O	$C_{25}H_{35}N_3O_2 \cdot 2C_2H_2O_4$	59.08	6.62	7.13
							(58.84	6.53	7.09)
VIb	OEt	H	81.0	209—212	Dioxane–H_2O	$C_{26}H_{37}N_3O_2 \cdot 2C_2H_2O_4 \cdot 0.5H_2O$	58.83	6.86	6.86
							(58.84	6.67	6.98)
VIc	OPr	H	69.7	198—199	Dioxane–H_2O	$C_{27}H_{39}N_3O_2 \cdot 2C_2H_2O_4$	60.29	6.97	6.81
							(60.49	7.03	6.70)
VId	OBu	H	63.1	204—206	Dioxane–H_2O	$C_{28}H_{41}N_3O_2 \cdot 2C_2H_2O_4$	60.85	7.13	6.66
							(60.61	7.08	6.66)
VIe	H	OMe	43.2	185—187	EtOH	$C_{25}H_{35}N_3O_2 \cdot 1.9C_2H_2O_4 \cdot 0.9H_2O$	57.95	6.86	7.04
							(57.65	6.62	7.49)
VIf	H	Me	77.2	214—216	EtOH	$C_{25}H_{35}N_3O \cdot 2C_2H_2O_4$	60.72	6.85	7.33
							(60.47	6.84	7.32)
VIh	H	CH_2OCOEt	37.1	179—182	EtOH	$C_{28}H_{39}N_3O_3 \cdot 2.6C_2H_2O_4 \cdot H_2O$	55.55	6.49	5.86
							(55.23	6.58	6.23)

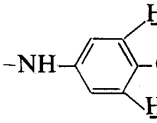
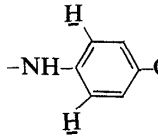
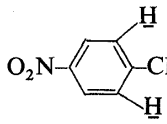
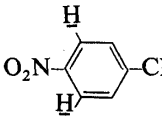
TABLE VII. Instrumental Analysis Data

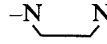
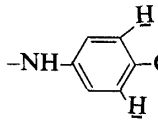
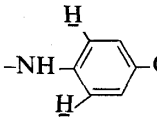
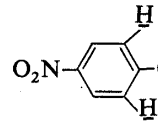
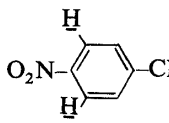
Compd. No.	MS m/e (M^+)	IR ν_{max}^{film} cm^{-1} (C=O)	^{1}H-NMR ($CDCl_3$) δ $\underline{Ph}CH_2$ (s)	Other protons
VIa	409	1645	7.20	1.01 (3H, t, J=6 Hz, $CH_2C\underline{H_3}$)
				1.07 (3H, d, J=6 Hz, $CHC\underline{H_3}$)
				3.80 (3H, s, OCH_3)
VIb	423	1640	7.20	4.05 (1H, q, J=6 Hz, $C\underline{H}CH_3$)
VIc	437	1640	7.20	
VId	451	1640	7.20	
VIe	409	1660	7.10	1.03 (3H, d, J=8 Hz, $CHC\underline{H_3}$)
				1.03 (3H, t, J=7 Hz, $CH_2C\underline{H_3}$)
				3.73 (3H, s, OCH_3)
VIf	393	1650	7.05	1.00 (3H, t, J=6 Hz, $CH_2C\underline{H_3}$)
				1.01 (3H, d, J=6 Hz, $CHC\underline{H_3}$)
				2.32 (3H, s, *m*-$C\underline{H_3}$Ph)
VIh	465	1660	7.06	1.07 (3H, d, J=6 Hz, $CHC\underline{H_3}$)
		1740		1.15 (6H, t, J=6 Hz, $CH_2C\underline{H_3}$)
		(OC=O)		5.02 (2H, s, $C\underline{H_2}OCOCH_2CH_3$)

(5H, s, CH_2Ph). MS *m/e*: 409 (M^+). Oxalate: mp 197—198 °C (dioxane–H_2O). *Anal.* Calcd for $C_{25}H_{35}N_3O_2 \cdot 2C_2H_2O_4$: C, 59.08; H, 6.62; N, 7.13. Found: C, 58.84; H, 6.53; N, 7.09.

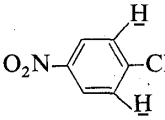
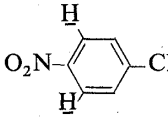
In a similar manner the following compounds were prepared: 1-[2-methyl-2-(*N*-propionyl-*p*-ethoxyphenylamino)ethyl]-4-phenethylpiperazine (VIb), 1-[2-methyl-2-(*N*-propionyl-*p*-propoxyphenylamino)ethyl]-4-phenethylpiperazine (VIc), 1-[2-methyl-2-(*N*-propionyl-*p*-butoxyphenylamino)ethyl]-4-phenethylpiperazine (VId), 1-[2-methyl-2-(*N*-propionyl-*m*-methoxyphenylamino)ethyl]-4-phenethylpiperazine (VIe), 1-[2-methyl-2-(*N*-propionyl-*m*-methylphenylamino)ethyl]-4-phenethylpiperazine (VIf), 1-[2-methyl-2-(*N*-propionyl-*m*-propionyloxymethylphenylamino)ethyl]-4-phenethylpiperazine (VIh). The data for these compounds are listed in Tables VI and VII.

1-(*p*-Nitrophenethyl)piperazine (VIII)——A solution of piperazine hexahydrate (28 g) in MeOH was neutralized with aqueous HCl solution, then a solution of *p*-nitrophenethyl bromide (VII)[6] (11.1 g) in MeOH (20 ml) and dioxane (20 ml) was added dropwise with stirring. After the addition, the reaction mixture was heated at 60 °C for 1.5 h and then cooled. It was made acidic with aqueous HCl solution and washed with benzene. The acidic solution was then made alkaline and extracted with benzene. The benzene extract was dried over $MgSO_4$ and concentrated *in vacuo* to afford VIII (3.5 g, 72.0%) as yellowish crystals, mp 78—81.5 °C. From the acidic benzene extract, VII (6.3 g) was recovered. IR ν_{max}^{Nujol} cm^{-1}: 3270 (NH), 1345 (NO_2). NMR ($CDCl_3$) δ: 1.72 (1H, s, NH), 7.25 (2H, d, J=8 Hz, ), 7.99 (2H, d, J=8 Hz, ). MS *m/e*: 235 (M^+). Hydrochloride: mp 181—183 °C (EtOH). *Anal.* Calcd for $C_{12}H_{17}N_3O_2 \cdot 2HCl \cdot 1/2H_2O$: C, 45.43; H, 6.36; N, 13.25. Found: C, 45.26; H, 6.19; N, 13.32.

1-[2-(*p*-Methoxyphenylamino)propionyl]-4-(*p*-nitrophenethyl)piperazine (X)——A solution of α-bromopropionyl bromide (61.0 g) in benzene (150 ml) was added dropwise to a solution of VIII (43.2 g) in benzene (200 ml) at 0—3 °C with stirring. The reaction mixture was stirred for 1.5 h, then made alkaline and extracted with benzene. The benzene extract was dried over $MgSO_4$ and concentrated *in vacuo* to afford IX as a pale yellow oil. A mixture of IX, K_2CO_3 (25.4 g), *p*-anisidine (22.6 g) and EtOH (300 ml) was refluxed for 10 h. The precipitate was removed by filtration and the filtrate was concentrated to afford crude X. Recrystallization from iso-PrOH gave X (38.9 g, 65.2%) as yellow crystals; mp 130—131 °C. IR ν_{max}^{Nujol} cm^{-1}: 3310 (NH), 1630 (C=O), 1345 (NO_2). NMR ($CDCl_3$) δ: 1.32 (3H, d, J=6 Hz, $CHCH_3$), 3.67 (3H, s, OCH_3), 4.19 (1H, br s, NH), 6.46 (2H, d, J=9 Hz, ), 6.63(2H, d, J=9 Hz, ), 7.26 (2H, d, J=8 Hz, ), 7.99 (2H, d, J=8 Hz, ). MS *m/e*: 412 (M^+). *Anal.* Calcd for $C_{22}H_{28}N_4O_4$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.99; H, 6.89; N, 13.49.

1-[2-Methyl-2-(*p*-methoxyphenylamino)ethyl]-4-(*p*-nitrophenethyl)piperazine (XI)——A solution of $AlCl_3$ in absolute THF (20 ml), a solution of X in absolute THF (30 ml), and diglyme (15 ml) were successively added dropwise to a suspension of $NaBH_4$ in absolute THF (30 ml) at room temperature with stirring. The mixture was refluxed for 20 h then made alkaline and extracted with ethyl acetate. The ethyl acetate extract was dried over $MgSO_4$ and concentrated *in vacuo*. The oily residue was purified by alumina column chromatography with a mixed solvent of $CHCl_3$ and benzene (volume ratio 1 : 6) as the eluent to afford XI (0.54 g, 76.9%) as a red-brown oil. IR ν_{max}^{film} cm^{-1}: 3330 (NH), 1345 (NO_2). NMR ($CDCl_3$) δ: 1.17 (3H, d, J=6 Hz, $CHCH_3$), 2.47 (3H, s, ), 3.67 (3H, s, OCH_3), 6.56 (2H, d, J=9 Hz, ), 6.63 (2H, d, J=9 Hz, ), 7.20 (2H, d, J=9 Hz, ), 7.96 (2H, d, J=9 Hz, ). MS *m/e*: 398 (M^+). Oxalate: mp 194—196 °C (EtOH). *Anal.* Calcd for $C_{22}H_{30}N_4O_3 \cdot 2C_2H_2O_4$: C, 53.97; H, 5.92; N, 9.68. Found: C, 53.99; H, 5.94; N, 9.63.

1-[2-Methyl-2-(*N*-propionyl-*p*-methoxyphenylamino)ethyl]-4-(*p*-nitrophenethyl)piperazine (XIIa)——A solution

of XI (0.45 g) and propionic anhydride (1.35 ml) was heated at 100 °C for 3 h. The reaction mixture was made acidic and washed with $CHCl_3$. The acidic solution was then made alkaline and extracted with $CHCl_3$. The $CHCl_3$ extract was concentrated and purified by alumina column chromatography with $CHCl_3$ as the eluent to afford XIIa (0.33 g, 64.6%) as a yellowish-brown oil. IR ν_{max}^{film} cm^{-1}: 1640 (C=O), 1350 (NO_2). NMR ($CDCl_3$) δ: 0.97 (3H, d, J=7 Hz, $CH\underline{CH_3}$), 1.00 (3H, t, J=7 Hz, $CH_2\underline{CH_3}$), 3.75 (3H, s, OCH_3), 5.10 (1H, s, CH), 7.22 (2H, d, J=8 Hz,  7.97 (2H, d, J=8 Hz,  MS m/e: 454 (M^+). Oxalate: mp 203—205 °C (EtOH). *Anal.* Calcd for $C_{25}H_{34}N_4O_4 \cdot 2C_2H_2O_4$: C, 54.88; H, 6.04; N, 8.83. Found: C, 55.17; H, 6.00; N, 8.80.

1-[2-Methyl-2-(*N*-propionyl-*p*-methoxyphenylamino)ethyl]-4-(*p*-aminophenethyl)piperazine (XIIb)——XIIa (14.8 g) was hydrogenated over platinum oxide (140 mg) catalyst in EtOH (200 ml) at normal temperature and pressure. After 3—4 h, absorption of hydrogen gas ceased. The precipitate was removed by filtration and the filtrate was concentrated to afford a pale yellow oil (14.0 g). The oily residue was washed with Et_2O and solidified to afford XIIb (11.5 g, 82.9%) as pale yellow crystals. IR ν_{max}^{Nujol} cm^{-1}: 3440, 3360, 3230 (NH_2), 1635 (C=O). NMR ($CDCl_3$) δ: 1.01 (3H, t, J=7 Hz, $CH_2\underline{CH_3}$), 1.03 (3H, d, J=7 Hz, $CH\underline{CH_3}$), 3.36 (2H, br s, NH_2), 3.70 (3H, s, OCH_3). MS m/e: 424 (M^+). Oxalate: mp 163—165 °C (EtOH). *Anal.* Calcd for $C_{25}H_{36}N_4O_2 \cdot 3C_2H_2O_4 \cdot H_2O$: C, 52.22; H, 6.22; N, 7.87. Found: C, 52.41; H, 6.32; N, 7.99.

1-[2-Methyl-2-(*N*-propionyl-*p*-methoxyphenylamino)ethyl]-4-(*p*-bromophenethyl)piperazine (XIIc)——A solution of $NaNO_2$ (0.64 g) was gradually added to a solution of XIIb (3 g) in 47% aqueous HBr solution (3 ml) below 5 °C; the reaction was followed by the use of KI-starch paper. The mixture was stirred for 1—2 h. The reaction was stopped and urea was added to the mixture. Next, CuBr (0.56 g) and 47% aqueous HBr solution (3 ml) were added. The reaction mixture was stirred overnight at room temperature, made alkaline, and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$ and concentrated to afford a dark brown oil (2.6 g). The oily residue was purified by alumina column chromatography with $CHCl_3$ as the eluent to afford XIIc (1.0 g, 29.0%) as a yellowish-brown oil. IR ν_{max}^{film} cm^{-1}: 1640 (C=O). NMR ($CDCl_3$) δ: 1.00 (3H, d, J=7 Hz, $CH\underline{CH_3}$), 1.03 (3H, t, J=7 Hz, $CH_2\underline{CH_3}$), 3.74 (3H, s, OCH_3). MS m/e: 487 (M^+), 489 (M^++2). Oxalate: mp 214—215 °C (EtOH). *Anal.* Calcd for $C_{25}H_{34}BrN_3O_2 \cdot 2C_2H_2O_4$: C, 52.10; H, 5.73; N, 6.29. Found: C, 52.37; H, 5.77; N, 6.31.

1-[2-Methyl-2-(*N*-propionyl-*p*-methoxyphenylamino)ethyl]-4-(*p*-acetamidophenethyl)piperazine (XIId)——Excess acetyl chloride was added to a solution of XIIb (2.0 g) in benzene (20 ml) with stirring. H_2O was added to the reaction mixture, which was then made alkaline with aqueous NaOH solution and extracted with benzene. The benzene extract was dried over $MgSO_4$ and concentrated to afford XIId (1.8 g, 81.9%) as a dark brown oil. IR ν_{max}^{film} cm^{-1}: 1620 (C=O). NMR ($CDCl_3$) δ: 0.97 (3H, d, J=7 Hz, $CH\underline{CH_3}$), 1.00 (3H, t, J=7 Hz, $CH_2\underline{CH_3}$), 2.24 (3H, s, CH_3CONH), 3.67 (3H, s, OCH_3). MS m/e: 466 (M^+). Oxalate: mp 184—185 °C (EtOH). *Anal.* Calcd for $C_{27}H_{38}N_4O_3 \cdot 2C_2H_2O_4 \cdot 1/2H_2O$: C, 59.79; H, 6.61; N, 8.54. Found: C, 57.00; H, 6.47; N, 8.40.

1-[2-Methyl-2-(*N*-propionyl-*p*-methoxyphenylamino)ethyl]-4-(*p*-benzamidophenethyl)piperazine (XIIe)——One equivalent of benzoic anhydride was added to a solution of XIIb (2 g) in acetone (20 ml) with stirring. The mixture was made acidic and washed with $CHCl_3$. The acidic solution was then made alkaline and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$ and concentrated to afford XIIe (2.0 g, 80.3%) as a reddishbrown oil. IR ν_{max}^{film} cm^{-1}: 3300 (NH), 1630 (C=O). NMR ($CDCl_3$) δ: 0.94 (3H, d, J=7 Hz, $CH\underline{CH_3}$), 0.99 (3H, t, J=7 Hz, : $CH_2\underline{CH_3}$), 3.73 (3H, s, OCH_3), 8.11 (1H, s, NH). MS m/e: 528 (M^+). Oxalate: mp 211—212 °C (EtOH). *Anal.* Calcd for $C_{32}H_{40}N_4O_3 \cdot 2C_2H_2O_4 \cdot 1/2H_2O$: C, 60.24; H, 6.32; N, 7.81. Found: C, 60.48; H, 6.21; N, 7.93.

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