β-(p-Chloro-α-phenylbenzylamino)ethyl chloride hydrochloride was obtained in 71% yield by the action of $SOCl_2$ on β-(p-chloro-α-phenylbenzylamino)ethyl alcohol in $CHCl_3$ following the usual techniques; it was crystallized from EtOH, mp 230–232°.[14b] *Anal.* ($C_{15}H_{16}Cl_3N$) C, H, N.

β-[N-(Methyl)-N-(p-chloro-α-phenylbenzyl)amino]ethyl Alcohol.—A mixture of β-(p-chloro-α-phenylbenzylamino)ethyl alcohol (26.15 g, 0.1 mole), HCOOH (10 ml, 98%), and HCHO (41 ml, 37–41%) was refluxed for 6 hr. Most of the HCHO and HCOOH were removed by distillation under diminished pressure. The residue was made alkaline with cold 5 *N* NaOH and extracted with Et_2O. The combined Et_2O extracts were dried (Na_2SO_4) and concentrated and the residue was distilled *in vacuo*. The fraction distilling at 184–190° (6 mm) was collected, yielded 18 g (65%). *Anal.* ($C_{16}H_{18}ClNO$) N.

β-[N-(Methyl)-N-(p-chloro-α-phenylbenzyl)amino]ethyl chloride hydrochloride was obtained as an oil by the action of $SOCl_2$ on the corresponding alcohol and was used directly for further condensation.

β-(1,2-Diphenylethylamino)ethyl chloride hydrochloride was prepared in 91% yield by the action of $SOCl_2$ on the corresponding alcohol[15] as usual and crystallized (EtOH), mp 212–213° dec. *Anal.* ($C_{16}H_{19}Cl_2N$) N.

β-[N-(Methyl)-N-(1,2-diphenethyl)amino]ethyl chloride hydrochloride was prepared from β-(1,2-diphenylethylamino)ethyl alcohol hydrochloride, following the method described by Kerwin, *et al.*[16]

N^1-[β-(p-Chloro-α-phenylbenzyloxy)ethyl]-N^4-(2-pyridyl)piperazine Maleate (37).—To a mixture of N-(2-pyridyl)piperazine (1.63 g, 0.01 mole) and Et_3N (2.0 g, 0.02 mole) in EtOH (20 ml), was added a solution of β-(p-chloro-α-phenylbenzyloxy)ethyl chloride[17] (3.09 g, 0.11 mole) in EtOH (10 ml) and the reaction mixture was refluxed for 25 hr. The solvent was distilled off, and the residue was treated with cold 40% NaOH till alkaline and extracted with Et_2O. The combined Et_2O extracts were dried (Na_2SO_4) and concentrated. The resulting oil was taken up in 20 ml of EtOH and added to a solution of maleic acid in EtOH. The solid thus obtained was crystallized.

N-(p-Chloro-α-phenylbenzyl)-N′-(2,6-xylidino)ethylenediamine (97) was prepared by the condensation of β-(p-chloro-α-phenylbenzylamino)ethyl chloride [obtained by the basification of 9.5 g, 0.03 mole, of β-(p-chloro-α-phenylbenzylamino)ethyl chloride hydrochloride] with 2,6-xylidine (3.63 g, 0.03 mole) following the method described for **37**. The resulting oil was distilled *in vacuo* and the fraction distilling at bp 230–242° (7 mm) was collected. The free base was converted to its maleate salt.

N-(p-Chloro-α-phenylbenzyl)ethylenediamine (83).—A solution of p-chloro-α-phenylbenzyl chloride (23.7 g, 0.1 mole) in pyridine (25 ml) was added dropwise with stirring to an ice-cooled solution of ethylenediamine (24 g, 0.4 mole) in pyridine (50 ml). The reaction mixture was stirred at room temperature for 16 hr and then heated on a steam bath for 1 hr. Pyridine was distilled off at diminished pressure, cold H_2O was added to the residue, and the residue was extracted with Et_2O. The combined Et_2O extracts were dried (Na_2SO_4) and concentrated. The residual oil was distilled *in vacuo* and the portion distilling between 176 and 182° (2 mm) was collected.

The other compounds reported in Tables I–III were obtained by the condensation of appropriate halides with various N-monosubstituted piperazines or appropriate amines, following the method described for **37**. In case of amines having low boiling points, excess of amines was taken, eliminating the use of triethylamine. The resulting products were crystallized when solid or converted into the appropriate salts or distilled under vacuum when an oil.

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Synthesis and Central Nervous System Depressant Activity of New Piperazine and Related Derivatives. III

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Several N^1,N^4-disubstituted piperazine derivatives, in which N^1 substituents are 3,4,5-trimethoxybenzoylacetyl, 3,4,5-trimethoxycinnamoyl or -hydrocinnamoyl, 3,4,5-trimethoxyphenylpropyl, and 3,4,5-trimethoxybenzoylalkyl and N^4 substituents are benzyl, *m*-methyl- or *p*-*t*-butylbenzyl, *p*-chloro-α-phenylbenzyl, phenyl, chloro-, fluoro-, or methoxyphenyl, tolyl, α,α,α-trifluorotolyl, 2-pyridyl, 2-pyrimidyl, or 2-thiazoyl groups, have been synthesized. Analogous compounds with other alkyl and heterocyclic amines in place of piperazine have also been synthesized. All these compounds have been screened for CNS activity. A few of these compounds exhibited significant CNS depressant activity. The 3,4,5-trimethoxyphenyl moiety was found to be the most essential for CNS activity as stepwise omission of the methoxy groups of most active compounds resulted in loss of activity.

We have recently reported[2] the synthesis and CNS depressant activity of compounds incorporating 3,4,5-trimethoxyphenyl and piperazine groupings into a single molecule with appropriate variations in the connecting bridge and at the N^4 position of piperazine ring. In that series the $-COCH_2CH_2-$ linkage was found to furnish the most active compounds. The work has now been extended to include new linkages, restricting the length of the bridge to three carbon atoms. Analogous compounds replacing the piperazine with other biologi-

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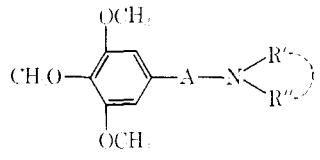
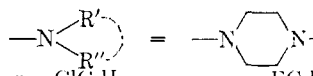
(2) R. B. Petigara, C. V. Deliwala, S. S. Mandrekar, and U. K. Sheth, *J. Med. Chem.*, **11**, 332 (1968).

cally active alkyl and heterocyclic amines have also been prepared. These compounds having the general formula I were studied for their CNS activity.



I

A = $COCH_2CO$, $CH(OH)CH_2CO$, $CH{=}CHCO$, CH_2CH_2CO, $CH_2CH_2CH_2$



(R = $PhCH_2$, *m*-Me- or *p*-*t*-$BuC_6H_3CH_2$, *p*-chloro-α-phenylbenzyl, Ph, *o*-, *m*-, or *p*-ClC_6H_4, *o*-, *m*-, or *p*-FC_6H_4, *o*- or *p*-$MeOC_6H_4$, *o*-, *m*-, or *p*-MeC_6H_4, α,α,α-trifluoro-*m*-tolyl, 2-pyridyl, 2-pyrimidyl, or 2-thiazolyl), $-NHCH(CH_3)CH_2C_6H_5$, cyclohexylamino, 2,6-xylidino, 2-aminopyridyl, morpholino, and piperidino

Some other compounds belonging to the earlier series,[2] *viz.*, acetophenones, propiophenones, and butyrophenones, prepared and studied, are also reported in the present publication.

Among all the compounds reported earlier[2] and here, the most active compounds were the Mannich bases derived from 3,4,5-trimethoxyacetophenone and N-(*o*-methoxy-, *o*-methyl-, *o*-chloro-, and *p*-fluorophenyl)-piperazines. To evaluate the role of the three MeO groups in the 3,4,5-trimethoxyphenyl moiety the 3,4-dimethoxyphenyl, 4-methoxyphenyl, and unsubstituted phenyl analogs of the first three of the active Mannich bases were also synthesized and studied.

Chemistry.—N^1-(3,4,5-Trimethoxybenzoylacetyl)-N^4-(substituted)piperazines and N-3,4,5-trimethoxybenzoylacetylamines (I, A = $COCH_2CO$) were obtained by the direct fusion of ethyl 3,4,5-trimethoxybenzoyl acetate and the requisite N-monosubstituted piperazines and other amines, respectively. Some of these β-ketoamides were catalytically reduced with Raney nickel to the corresponding β-hydroxyamides (I, A = $CH(OH)CH_2CO$).

N^1-(3,4,5-Trimethoxycinnamoyl)-N^4-(substituted)-piperazines (I, A = $CH{=}CHCO$) were obtained by heating 3,4,5-trimethoxycinnamic acid and N-monosubstituted piperazines in anhydrous xylene, with simultaneous removal of H_2O by azeotropic distillation according to the method adopted by Boissier and Ratouis.[3] Similarly, N^1-(3,4,5-trimethoxyhydrocinnamoyl)-N^4-(substituted)piperazines (I, A = CH_2CH_2CO) were obtained from 3,4,5-trimethoxyhydrocinnamic acid. These amides were reduced to the corresponding amines (I, A = $CH_2CH_2CH_2$) by LAH.

The acetophenones, propiophenones, and butyrophenones were prepared by the methods already reported in our previous publication.[2] However, when the Mannich reaction with N-(*m*-fluorophenyl)piperazine hydrochloride was carried out under the usual conditions, β,β-bis[N^4-(*m*-fluorophenyl)-N^1-piperazinyl]-3,4,5-trimethoxypropiophenone resulted, instead of the desired product.

The demethoxylated analogs of the active compounds were obtained by the Mannich reaction of the 3,4-dimethoxyacetophenone, 4-methoxyacetophenone, and acetophenone with the requisite N-arylpiperazines. Since Mannich bases from acetophenone were obtained in very poor yields, they were prepared in good yields by the condensation of β-bromopropiophenone and N-arylpiperazines.

The physical constants, yields, recrystallization solvents, and analyses are given in Tables I–III.

Pharmacology.—Almost all the compounds reported in this paper were tested for CNS activity. The study of gross behavior and spontaneous motor activity (Actophotometer, Metro Industries, U. S. A.) and potentiation of barbital hypnosis[4] in intact mice revealed that a few compounds in this series possessed good CNS depressant activity. The approximate LD_{50} (ip) values in mice of all the compounds were determined.[5] The results of these observations are summarized in Tables I–III. Some of the compounds were also studied for their hypotensive and adrenergic blocking activity in anesthetized dogs. The results of these studies are given as footnotes to the last column of Tables I and III.

Structure–Activity Relationships.—None of the compounds having the $COCH_2CO$ linkage showed CNS activity. Thus the replacement of the terminal CH_2 of $COCH_2CH_2$ with CO results in loss of activity. The reduction of the keto group of $COCH_2CO$ to a secondary alcoholic group ($CHOHCH_2CO$) did not bring about any change in activity. When the linkage $COCH_2CH_2$ of active compounds was inverted to CH_2CH_2CO (hydrocinnamides) the CNS activity was lost. The cinnamides (I, A = $CH{=}CHCO$) were also devoid of CNS activity. Further, when the hydrocinnamides were reduced to the corresponding amines (I, A = $CH_2CH_2CH_2$), significant CNS activity was noticed.

The compounds with alkyl or heterocyclic amines did not show any CNS depressant activity, except **46** (α-morpholino-3,4,5-trimethoxyacetophenone) which was moderately active.

The butyrophenones displayed moderate activity, whereas the Mannich bases (I, A = $COCH_2CH_2$) exhibited marked CNS depressant activity confirming earlier findings.[2] Of the Mannich bases, **31** possessed a very high order of CNS depressant activity with comparatively low toxicity. From all the Mannich bases, including those reported earlier,[2] it is evident that the compounds having a MeO, Me, or Cl substituent in the *ortho* position of the N^4-phenyl ring were the most active. However, when the substituent was F, *para*-substituted **31** proved to be superior to the corresponding *p*-F (**30**) and *m*-CF_3 (**32**) analogs.

As seen from the comparative CNS activity (Table III), the stepwise omission of the MeO groups in three active compounds (**51, 55,** and **59**) resulted in loss of CNS depressant activity, which establishes the importance of the 3,4,5-trimethoxyphenyl moiety in imparting CNS depressant activity to these organic molecules.

A few of the piperazine derivatives (**18, 20, 22, 24, 27, 30, 31, 61**) showed marked hypotensive or/and adrenergic blocking activity. The cinnamides, *viz.*, **18** and **20,** exhibited a high order of hypotensive and adrenergic blocking activity, respectively. The hydrocinnamides were devoid of both the activities. When these

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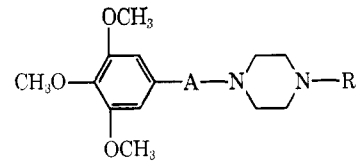
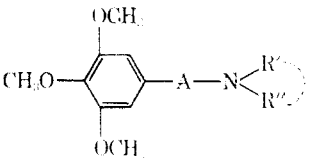
TABLE I

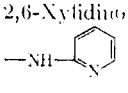
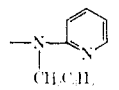


No.	A	R	Crystn solvent[a]	% yield[b]	Mp,[c] °C	Formula	Analyses[a]	Mouse LD_{50}, mg/kg ip	CNS depres,[d] mg/kg	% ↓ in motor act. of mice[e]
1	$COCH_2CO$	$PhCH_2$	E_{70}	52	102–103	$C_{23}H_{28}N_2O_5$	C, H, N	800	60	(−)
2	$COCH_2CO$	m-$MeC_6H_4CH_2$	E_{70}	50	90–92	$C_{24}H_{30}N_2O_5$	C, H, N	800	45	(−)
3	$COCH_2CO$	p-t-$BuC_6H_4CH_2$		40	[f]	$C_{27}H_{36}N_2O_5$	N	[g]	[g]	[g]
4	$COCH_2CO$	p-Cl-α-phenylbenzyl	H	75	100 (softens at 72°)	$C_{29}H_{31}ClN_2O_5$	N	500	135	(−)[h]
5	$COCH_2CO$	Ph	E_{70}	63	104–105	$C_{22}H_{26}N_2O_5$	C, H, N	400	(−)	(−)
6	$COCH_2CO$	o-ClC_6H_4	E_{70}	68	125–127	$C_{22}H_{25}ClN_2O_5\cdot H_2O$	C, H, N	800	(−)	(−)
7	$COCH_2CO$	o-$MeOC_6H_4$	P	63	137–139	$C_{23}H_{28}N_2O_6$	C, H, N	800	(−)	(−)
8	$CH(OH)CH_2CO$	o-$MeOC_6H_4$	H	71	56–58	$C_{23}H_{30}N_2O_6$	C, H, N	400	(−)	(−)
9	$COCH_2CO$	p-$MeOC_6H_4$	E_{70}	55	112–113	$C_{23}H_{28}N_2O_6\cdot H_2O$	C, H, N	400	(−)	(−)
10	$COCH_2CO$	o-MeC_6H_4	E	58	143–144	$C_{23}H_{28}N_2O_5$	C, H, N	400	50	50
11	$CH(OH)CH_2CO$	o-MeC_6H_4	H	63	115–116	$C_{23}H_{30}N_2O_5$	C, H, N	400	(−)	(−)
12	$COCH_2CO$	m-Tolyl	E_{70}	80	95–97	$C_{23}H_{28}N_2O_5$	C, H, N	400	(−)	(−)
13	$COCH_2CO$	p-Tolyl	E_{70}	59	106–108	$C_{23}H_{28}N_2O_5$	N	400	50	67
14	$COCH_2CO$	2-Pyridyl	E_{70}	65	112–113	$C_{21}H_{25}N_3O_5$	N	800	(−)	(−)
15	$COCH_2CO$	2-Pyrimidyl	E_{70}	62	143–144	$C_{20}H_{24}N_4O_5$	C, H, N	800	(−)	(−)
16	$COCH_2CO$	2-Thiazolyl	E	61	137–139	$C_{19}H_{23}N_3O_5S$	C, H, N	800	90	(−)
17	$CH{=}CHCO$	o-ClC_6H_4	E	65	180–181	$C_{22}H_{25}ClN_2O_4$	C, H, N	150	(−)	(−)
18	$CH{=}CHCO$	o-$MeOC_6H_4$	E	58	170–172	$C_{23}H_{28}N_2O_5$	C, H, N	150	50	(−)[i]
19	$CH{=}CHCO$	o-Tolyl	H	54	138–139	$C_{23}H_{28}N_2O_4$	C, H, N	>800	100	(−)
20	$CH{=}CHCO$	2-Pyridyl	E–Et	63	142–144	$C_{21}H_{25}N_3O_4$	C, H, N	200	(−)	(−)[j]
21	CH_2CH_2CO	o-ClC_6H_4	E	46	153–154	$C_{22}H_{27}ClN_2O_4$	C, H, N	>200	(−)	(−)
22	$CH_2CH_2CH_2$	o-ClC_6H_4	E–Et	69	165–167	$C_{22}H_{29}ClN_2O_3\cdot HCl$	C, H, N	300	20	76[i]
23	CH_2CH_2CO	o-$MeOC_6H_4$			[k]	$C_{23}H_{30}N_2O_5$	N	200	(−)	(−)
24	$CH_2CH_2CH_2$	o-$MeOC_6H_4$	E	69	181–182	$C_{23}H_{32}N_2O_4\cdot$oxalate	C, H, N	150	20	86[l,m]
25	CH_2CH_2CO	o-Tolyl	E	67	125–126	$C_{23}H_{30}N_2O_4$	C, H, N	>800	(−)	(−)
26	CH_2CH_2CO	2-Pyridyl	E_{80}	56	115–116	$C_{21}H_{27}N_3O_4$	C, H, N	>800	(−)	(−)
27	$CH_2CH_2CH_2$	2-Pyridyl	E–Et	37	163–164	$C_{21}H_{29}N_3O_3\cdot$oxalate	C, H, N	>200	50	(−)[n]
28	$COCH_2CH_2$	m-ClC_6H_4	E	20	205–207 dec	$C_{22}H_{27}ClN_2O_4\cdot HCl$	C, H, N	>400	40	80
29	$COCH_2CH_2$	p-ClC_6H_4	E	32	184–185 dec	$C_{22}H_{27}ClN_2O_4\cdot HCl$	C, H, N	>400	(−)	(−)
30	$COCH_2CH_2$	o-FC_6H_4	E	30	196–198 dec	$C_{22}H_{27}FN_2O_4\cdot HCl$	C, H, N	>400	20	(−)[o,m]
31	$COCH_2CH_2$	p-FC_6H_4	E	38	188–189 dec	$C_{22}H_{27}FN_2O_4\cdot HCl$	C, H, N	>500	5	93[p,q]
			E		110–111	$C_{22}H_{27}FN_2O_4$	C, H, N			
			E		147–148 dec	$C_{22}H_{27}FN_2O_4\cdot$mal[v]	N			
32	$COCH_2CH_2$	F_3-Tolyl[u]	E	44	197–198 dec	$C_{23}H_{27}F_3N_2O_4\cdot HCl$	C, H, N	>800	100	60[r]
33	$COCH_2CH_2CH_2$	o-FC_6H_4	H	51	122–123	$C_{23}H_{29}FN_2O_4$	N			
			E		161–163 dec	$C_{23}H_{29}FN_2O_4\cdot HCl$	N	>600	20[s]	(−)[o,t]
34	$COCH_2CH_2CH_2$	m-FC_6H_4	H	46	113–114	$C_{23}H_{29}FN_2O_4$	N			
			E		156–158 dec	$C_{23}H_{29}FN_2O_4\cdot HCl$	C, H, N	300	50	(−)
35	$COCH_2CH_2CH_2$	p-FC_6H_4	E	56	216–218 dec	$C_{23}H_{29}FN_2O_4\cdot HCl$	N	150	10[s]	(−)
36	$COCH_2CH_2CH_2$	F_3-Tolyl[u]	H	61	81–82	$C_{24}H_{29}F_3N_2O_4$	N			
			E		226–227 dec	$C_{24}H_{29}F_3N_2O_4\cdot HCl$	C, H, N	600	100	(−)

[a] Ac, Me_2CO; B, C_6H_6; E, EtOH; E_{70}, 70% EtOH; Et, Et_2O; H, hexane; P, i-PrOH. [b] Yields reported are the results of single experiments and are calculated for the material melting not less than 2–3° below the highest melting point obtained. [c] Melting points were taken in capillary tubes sealed at one end with a partial immersion thermometer and are uncorrected. [d] Mice were observed during the toxicity tests. The lowest dose at which significant depression was noted in mice is recorded in this column. Depression at doses greater than 40% of the LD_{50} is not considered to be significant and is indicated as negative (—). Any other significant effects on the CNS of mice, rats, or cats are also noted in this column as footnotes. The significant cardiovascular effects are also given in this column as footnotes. [e] The study of motor activity of a group of six mice was done on an actophotometer for 10 min before and 1, 2, and 4 hr after drug administration (dose one-tenth of the LD_{50}). The peak effect is given here. Less than 50% decrease in motor activity was not considered significant and is indicated as negative (—). [f] Bp 165–170° (13 mm). [g] Pharmacological testings was not done. [h] Produced 60% potentiation of barbital hypnosis at 45 mg/kg. Decrease in motor activity and constriction of pupil were observed in the cat at 5 mg/kg ip. [i] Showed marked hypotensive and mild adrenergic blocking activity at 10 mg/kg. [j] Showed marked adrenergic blocking activity at 1.5–5.0 mg/kg, but did not show any hypotensive activity. [k] Bp 260–270° (15 mm). [l] 86% decrease in motor activity was observed in mice at 20 mg/kg. Marked sedation at 50 mg/kg and marked loss of muscle tone, traction, and placing as well as righting reflexes were observed in mice. Produced 100% potentiation of baribtal hypnosis at 20 mg/kg. [m] Showed marked hypotensive and adrenergic blocking activity at 2.5 mg/kg. [n] Showed mild hypotensive and marked adrenergic blocking activity at 2.5 mg/kg. [o] Due to the paralytic effect more than a 90% decrease in motor activity was observed at one-tenth of the LD_{50}; when SMA was studied at 10 mg/kg, the per cent decrease of motor activity was too low to be significant. [p] 93% decrease in motor activity of mice was observed at 10 mg/kg (ED_{50} = 4.3 mg/kg). Marked sedation and loss of muscle tone were observed in mice at 20 mg/kg; when the dose was increased only duration of action was prolonged. Marked sedation (lasting for 3 hr) and relaxation of the nictitating membrane were observed in the cat between 20 and 40 mg/kg. The cat did not show any aggressiveness toward mice. Produced catatonia in the cat between 80 and 100 mg/kg. Produced 100% potentiation of barbital hypnosis at 15 mg/kg. Produced 100% blocking of CAR in rats at 30 mg/kg. Effects similar to those seen in cats were also observed in dogs and monkeys. The compound possesses a high order of muscle relaxation activity. [q] Showed mild hypotensive activity at 2.5 mg/kg, and at 10 mg/kg marked hypotensive and mild adrenergic blocking activity. [r] Produced 60% potentiation of barbital hypnosis at one-tenth of the LD_{50}. [s] Mild to marked sedation and loss of muscle tone were observed between 20 and 100 mg/kg. [t] Produced 100% potentiation of barbital hypnosis at 60 mg/kg. [u] α,α,α-Trifluoro-m-tolyl. [v] mal, maleate.

TABLE II

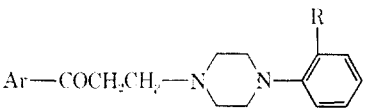


No.	A	—N<R'/R''>	Cryst solvent[a]	% yield[b]	Mp,[c] °C	Formula	Analyses[d]	Mouse LD_{50}, mg/kg ip	CNS depres,[d] mg/kg	% ↓ in motor act. of mice[e]
37	CO	—NHCH(CH₃)CH₂C₆H₅	H	68	165–166	$C_{19}H_{25}NO_4$	C, H, N	800	200	56
38	$COCH_2$	—NHCH(CH₃)CH₂C₆H₅	P	66	218–219 dec	$C_{20}H_{25}NO_4 \cdot HBr$	C, H, N	800	(—)	(—)
39	$COCH_2CO$	—NHCH(CH₃)CH₂C₆H₅	P	77	133–135	$C_{21}H_{25}NO_5$	C, H, N	800	300	64
40	$COCH_2$	Cyclohexylamino	E	65	228–230	$C_{17}H_{25}NO_4 \cdot HBr$	N	150	(—)	(—)
			E	56	225–226	$C_{17}H_{25}NO_4 \cdot HCl$	C, H, N			
41	$COCH_2CO$	Cyclohexylamino	Ac	62	177–178	$C_{18}H_{25}NO_5$	C, H, N	800	(—)	(—)
42	$CH(OH)CH_2CO$	Cyclohexylamino	E_{70}	61	125–126	$C_{18}H_{27}NO_5$	C, H, N	800	(—)	(—)
43	$COCH_2CO$	2,6-Xylidino	Ac	86	189–190	$C_{20}H_{23}NO_5$	C, H, N	800	135	60
44	$COCH_2CO$		Ac	63	170–171	$C_{16}H_{18}N_2O_5$	C, H, N	350	(—)	60
45	$COCH_2CO$		E	49	192–194 dec	$C_{23}H_{34}N_2O_4 \cdot HBr$	C, H, N	150	(—)	(—)
46	$COCH_2$	Morpholino	E	72	226–227 dec	$C_{15}H_{21}NO_5 \cdot HBr$	C, H, N	800	135	73[f]
			E	70	218–220 dec	$C_{15}H_{21}NO_5 \cdot HCl$	N			
47	$CH(OH)CH_2$	Morpholino	E	70	208–209 dec	$C_{15}H_{23}NO_5 \cdot HCl$	C, H, N	800	60	*g*
48	$COCH_2CO$	Morpholino	B–H	58	123–124	$C_{16}H_{21}NO_6$	C, H, N	800	90	(—)
49	$CH(OH)CH_2CO$	Morpholino	Ac–H	63	101–102	$C_{16}H_{23}NO_6$	C, H, N	800	135	(—)
50	$COCH_2CO$	Piperidino	P	43	128–130	$C_{16}H_{23}NO_5$	C, H, N	*g*	*g*	*g*

[a–c] See corresponding footnotes in Table I. [d] See footnote *r*, Table I. [e] Pharmacological testing was not done.

TABLE III

COMPARATIVE CNS DEPRESSANT ACTIVITY OF THE DEMETHOXYLATED ANALOGS



No.	Ar	R	Cryst solvent[a]	% yield[b]	Mp,[c] °C	Formula	Analyses[c]	Mouse LD_{50}, mg/kg ip	CNS depres,[d] mg/kg	% ↓ in motor act. of mice[e]
51[f]	3,4,5-$(MeO)_3C_6H_2$	MeO	E		223–224 dec	$C_{23}H_{30}N_2O_6 \cdot HBr$		325[g]	5	98[h,i]
52	3,4-$(MeO)_2C_6H_3$	MeO	E	39	209–210 dec	$C_{22}H_{28}N_2O_4 \cdot HBr$	C, H, N	100	(—)	(—)
53	4-$MeOC_6H_4$	MeO	E	40	192–193 dec	$C_{21}H_{26}N_2O_3 \cdot HBr$	C, H, N	150	50	58[j]
54	Ph	MeO	E	71	192–194 dec	$C_{20}H_{24}N_2O_2 \cdot HCl$	C, H, N	150	50	(—)[k]
55[f]	3,4,5-$(MeO)_3C_6H_2$	MeO	E		218–219 dec	$C_{23}H_{30}N_2O_4 \cdot HCl$		340[m]	60	95[h,n]
56	3,4-$(MeO)_2C_6H_3$	Me	E	42	239–240 dec	$C_{22}H_{28}N_2O_3 \cdot HCl$	C, H, N	400	20	*p*
57	4-$MeOC_6H_4$	Me	E	38	207–208 dec	$C_{21}H_{26}N_2O_2 \cdot HCl$	C, H, N	500	(—)	(—)
58	Ph	Me	H	63	96–97	$C_{20}H_{24}N_2O$	N			
					204–205 dec	$C_{20}H_{24}N_2O \cdot HCl$	C, H, N	600	20	(—)
59[f]	3,4,5-$(MeO)_3C_6H_2$	Cl	E		219–221 dec	$C_{22}H_{27}ClN_2O_4 \cdot HCl$		500	20[o]	66[h,p]
60	4-$MeOC_6H_4$	Cl	E	42	192–194 dec	$C_{20}H_{23}ClN_2O_3 \cdot HCl$	C, H, N	800	50	*p*
61	Ph	Cl	H	65	121–122	$C_{19}H_{21}ClN_2O$	N			
			E		184–185 dec	$C_{19}H_{21}ClN_2O \cdot HCl$	C, H, N	700	100	(—)[k,q]

[a] E, EtOH; H, hexane. [b–c] See corresponding footnotes in Table I. [f] Reported earlier by us.[2] [g] Mouse LD_{50} = 380 mg/kg *po*. [h] Detailed pharmacological findings will be published separately and hence only salient points are given here. [i] Produced 98% decrease in motor activity of mice at 10 mg/kg (ED_{50} = 3 mg/kg). Marked sedation and loss of righting reflex were observed in mice at 10 mg/kg. Marked sedation (lasting for 6 hr) and marked relaxation of nictitating membrane were observed in the cat at 5 mg/kg. Produced catatonia in the cat at 80 mg/kg. Produced 100% potentiation of barbital hypnosis at 5 mg/kg, 100% inhibition of orientation, and amphetamine-induced hyperactivity. Produced 100% blocking of conditioned avoidance response (CAR) in rats at 20 mg/kg. Effects were similar to those seen in cats were also noticed in dogs and monkeys. [j] Showed marked hypotensive and adrenergic blocking activity at 2.5 mg/kg. [k] Ptosis was observed in mice at 10 mg/kg. [l] Produced 60% potentiation of barbital hypnosis at 15 mg/kg. [m] Mouse LD_{50} = 540 mg/kg *po*. [n] Produced 95% decrease in motor activity of mice at 10 mg/kg (ED_{50} = 4 mg/kg). Marked sedation and loss of muscle tone were observed in mice at 50 mg/kg. Marked sedation and relaxation of the nictitating membrane were observed in the cat at 5 and 20 mg/kg. Produced catatonia in the cat at 80 mg/kg. Produced 100% potentiation of barbital hypnosis at 5 mg/kg, 100% inhibition of orientation, and amphetamine-induced hyperactivity. Produced 100% blocking of CAR in rats at 20 mg/kg. Effects similar to those seen in cats were also noticed in dogs and monkeys. [o] Showed marked hypotensive and adrenergic blocking activity at 4.0 mg/kg. [p] Due to the paralytic effect more than an 85% decrease in motor activity was observed at one-tenth of the LD_{50}; when SMA was studied at 10 mg/kg the per cent decrease of motor activity was too low to be significant. [q] Produced catatonia in the cat at 100 mg/kg. [r] Produced 66% decrease in motor activity at 20 mg/kg.

hydrocinnamides were reduced to the corresponding amines (**22**, **24**, and **27**), marked adrenergic blocking activity was observed; **24** had also marked hypotensive activity. The propiophenone derivatives **30**, **51**, **55**, **59**, and **61** have marked hypotensive and adrenergic blocking activity. When the *o*-F of **30** was shifted to the *para* position (**31**), the adrenergic blocking activity was diminished to a great extent, whereas the hypotensive property was retained.

Compound **31** has been selected for more extensive pharmacological evaluation; **20** and **22** are undergoing detailed cardiovascular studies.

Experimental Section

Pharmacological Methods.—The studies of CNS activity were performed by administering intraperitoneally the suspension of the test compounds made with 0.5% carboxymethoxycellulose (CMC). The vehicle itself was tested in a control group with negative results. For the studies of hypotensive and adrenergic blocking activity, healthy mongrel dogs (10–15 kg) were anesthetized with sodium pentobarbital (35 mg/kg iv). The blood pressure was recorded by a Hg manometer. The test compound was administered intravenously in different dosages. The effects of test compounds on blood pressure and epinephrine-induced pressor response were studied.

Chemistry.[6] **Intermediates.**—The requisite 3,4,5-trimethoxybenzaldehyde,[7] 3,4,5-trimethoxycinnamic acid,[8] 3,4,5-trimethoxyhydrocinnamic acid,[8] 3,4,5-trimethoxybenzoyl chloride,[9] ethyl 3,4,5-trimethoxybenzoylacetate,[10] 3,4,5-trimethoxyacetophenone,[10] α-bromo-3,4,5-trimethoxyacetophenone,[11] 3,4-dimethoxyacetophenone (Fries migration[12] of guaicol acetate followed by methylation[13]), 4-methoxyacetophenone,[14] β-bromopropiophenone,[15] and 2-benzylaminopyridine[16] were prepared by known methods. γ-Chloro-3,4,5-trimethoxybutyrophenone was obtained as described previously.[2]

N-(Monosubstituted)piperazines.—The following N-monosubstituted piperazines were prepared according to known methods: N-benzyl-,[17a] N-*m*-(methylbenzyl)-,[17b] N-(*p*-*t*-butylbenzyl)-,[17b] N-(*p*-chloro-α-phenylbenzyl)-,[17c] N-phenyl-,[17d] N-*m*-, -*o*-, and -*p*-chlorophenyl-,[17e] N-*o*-fluorophenyl-,[17f] N-*m*- and -*p*-fluorophenyl-,[17g] N-*o*- and -*p*-methoxyphenyl-,[17h] N-*m*-, -*o*-, and -*p*-tolyl-,[17e] N-(2-pyridyl)-,[17i] N-(2-pyrimidyl)-,[17i] and 2-(thiazolyl)-.[17i]

N-(α,α,α-Trifluoro-*m*-tolyl)piperazine which could not be obtained according to a patent method,[18] was prepared in 35% yield by heating a stoichiometric amount of hydrochlorides of diethanolamine and *m*-trifluoromethylaniline with simultaneous removal of H_2O following the method of Pollard and MacDowell described for the preparation of N-phenylpiperazine;[17d] bp 120° (1 mm). *Anal.* ($C_{11}H_{13}F_3N_2$) N. The free base (5.0 g) was taken up in 15 ml of EtOH and added to 15 ml of *i*-Pr-HCl (22%). This on dilution with Et_2O gave a white solid, which on recrystallization from EtOH afforded the monohydrochloride, mp 232–233° dec. *Anal.* ($C_{11}H_{13}F_3N_2 \cdot HCl$) C, H, N.

N¹-[(3,4,5-Trimethoxybenzoyl)acetyl]-N⁴-(*o*-tolyl)piperazine (10).—A mixture of 11.28 g (0.04 mole) of ethyl 2,4,5-trimethoxybenzoyl acetate and 7.04 g (0.04 mole) of N-(*o*-tolyl)piperazine was heated in an oil bath at 120° for 2 hr and at 150° for 3 hr. It was then cooled and treated with H_2O. The solid thus obtained was filtered and crystallized (EtOH).

Other members of the series (I, A = $COCH_2CO$) were obtained in a similar manner by taking the appropriate N-monosubstituted piperazines or other amines. The ir spectra of the representative compounds were as expected.

N¹-[β-Hydroxy-β-(3,4,5-trimethoxyphenyl)propionyl]-N⁴-(*o*-tolyl)piperazine (11).—To a solution of 2.06 g (0.005 mole) of **10** in 120 ml of EtOH (or MeOH), freshly prepared Raney Ni W-7 (2.0 g) was added and the mixture was shaken for 10 hr under H_2 at 0.42 kg/cm². The mixture was then filtered and the filtrate was concentrated under reduced pressure. The resulting semisolid mass on crystallization (hexane) gave the desired product.

The other β-ketoamides were reduced in a similar manner. The ir spectra of a representative compound were as expected.

N¹-(3,4,5-Trimethoxycinnamoyl)-N⁴-(2-pyridyl)piperazine (20).—To a solution of 5.0 g (0.021 mole) of 3,4,5-trimethoxycinnamic acid in 50 ml of *o*-xylene, was added a solution of 3.26 g (0.02 mole) of N-(2-pyridyl)piperazine in 25 ml of *o*-xylene. The mixture was refluxed for 10 hr with azeotropic removal of H_2O using a Dean–Stark water separator. The solvent was removed under diminished pressure (10 mm). The residue solidified when treated with Et_2O (or hexane). This on recrystallization (EtOH–Et_2O) gave the desired compound.

N¹-(3,4,5-Trimethoxyhydrocinnamoyl)-N⁴-(*o*-chlorophenyl)piperazine (21) was obtained from 5.05 g (0.021 mole) of 3,4,5-trimethoxyhydrocinnamic acid and 3.93 g (0.02 mole) of N-(*o*-chlorophenyl)piperazine by following a procedure similar to the one above. It was crystallized twice (EtOH).

Other compounds of both these series were obtained as above. The absorption peaks of ir spectra of a representative hydrocinnamide were as expected.

N¹-[γ-(3,4,5-Trimethoxyphenyl)propyl]-N⁴-(*o*-chlorophenyl)-piperazine Hydrochloride (22).—To 250 ml of Na-dried Et_2O, 2.0 g of LAH was added and refluxed for 30 min. To this a solution of 1.5 g of **21** in 30 ml of THF was added dropwise and refluxed for 24 hr. Excess of LAH and metallic complex were decomposed by the slow addition of 5 ml of H_2O while stirring. The precipitates were filtered off and washed with Et_2O. The filtrate was dried (Na_2SO_4) and the solvent was removed. The oily residue was taken up in 20 ml of Me_2CO and added to 7 ml of *i*-Pr-HCl (22%) diluted with 200 ml of dry Et_2O. The white solid was filtered and recrystallized (EtOH–Et_2O).

The other amides (I, A = CH_2CH_2CO) were also reduced similarly to the corresponding amines and the resulting oily bases were converted to the appropriate salts. The ir spectra of a representative compound (as free base) were as expected.

N-[(1-Methyl-2-phenyl)ethyl]-3,4,5-trimethoxybenzamide (37).—To a solution of 2.7 g (0.02 mole) of *d*-amphetamine and 4.0 g (0.04 mole) of Et_3N in 20 ml of anhydrous $CHCl_3$, a solution of 4.61 g (0.02 mole) of 3,4,5-trimethoxybenzoyl chloride in 20 ml of anhydrous $CHCl_3$ was added slowly. The reaction mixture was refluxed for 5 hr. It was then cooled, washed (H_2O), and dried (Na_2SO_4) and $CHCl_3$ was removed *in vacuo*. The residue solidified when treated with hexane. The solid was then recrystallized twice from boiling hexane.

α-(Morpholino)-3,4,5-trimethoxyacetophenone Hydrobromide (46).—To a solution of 8.67 g (0.03 mole) of α-bromo-3,4,5-trimethoxyacetophenone in 40 ml of *i*-PrOH, was added dropwise a solution of 2.61 g (0.03 mole) of morpholine in 20 ml of *i*-PrOH. The reaction mixture was refluxed for 3 hr and left overnight after concentrating it to half of its volume. The solid was filtered and

(6) Ir spectra were determined in $CHCl_3$ using a Perkin-Elmer Infracord spectrophotometer. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

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recrystallized (*i*-PrOH) to give the desired compound. The free base was liberated and converted to its hydrochloride salt, mp 218–220° dec.

N-[β-Hydroxy-β-(3,4,5-trimethoxyphenyl)ethyl]morpholine Hydrochloride (47).—To a solution of 5.64 g (0.015 mole) of **46** in 120 ml of dry *i*-PrOH, 45 ml of molar Al(*i*-PrO)$_3$ solution in *i*-PrOH was added. The reaction mixture was refluxed for 3 hr and the distillate was tested for the presence of acetone (2,4-dinitrophenylhydrazone test). Reflux was continued (7 hr) till the acetone test became negative. The solvent was removed under diminished pressure (100 mm), and the reaction mixture was basified with 40% aqueous NaOH and extracted with Et_2O. The combined extracts were dried (Na_2SO_4) and added to 15 ml of *i*-Pr-HCl (22%). The resulting white solid on crystallization (EtOH) gave the product.

N^1-[β-(3,4,5-Trimethoxybenzoyl)ethyl]-N^4-(*p*-fluorophenyl)piperazine Hydrochloride (31).—To a solution of 3.25 g (0.015 mole) of N-(*p*-fluorophenyl)piperazine hydrochloride in 60 ml of EtOH, 2.2 ml (~0.022 mole) of aqueous CH_2O (37–41%) and 3.78 g (0.018 mole) of 3,4,5-trimethoxyacetophenone were added and the mixture was refluxed for 7 hr. Additional aqueous CH_2O (2.2 ml) was added and reflux continued for 7 hr. The reaction mixture was concentrated to one-fourth of its volume and allowed to cool overnight, when a white shiny crystalline compound separated out. This was filtered, dried, and recrystallized. The hydrochloride was converted quantitatively to the free base which was recrystallized from EtOH. The maleate salt of this base was prepared by the addition of its solution in EtOH to the calculated amount of maleic acid in EtOH followed by dilution with Et_2O.

The rest of the ketonic Mannich bases (1, A = $COCH_2CH_2$) were prepared by following this method.

β,β-Bis[N^4-(*m*-fluorophenyl)-N^1-piperazinyl]-3,4,5-trimethoxypropiophenone.—To a solution of 3.25 (0.015 mole) of 1-(*m*-fluorophenyl)piperazine hydrochloride in 70 ml of EtOH, 2.2 ml (~0.022 mole) of aqueous CH_2O and 3.47 g (0.0165 mole) of 3,4,5-trimethoxyacetophenone were added and the mixture was refluxed for 7 hr. Additional aqueous CH_2O (2.2 ml) was added and reflux continued for additional 7 hr. The reaction mixture was concentrated to one-fourth of its volume and left overnight. The resulting solid was filtered and recrystallized (EtOH); mp 190–192° dec. *Anal.* ($C_{33}H_{40}F_2N_4O_4 \cdot 2HCl$) C, H, N.

N^1-(β-Benzoylethyl)-N^4-(*o*-methoxyphenyl)piperazine Hydrochloride (54).—To a solution of 1.92 g (0.01 mole) of N-(*o*-methoxyphenyl)piperazine in 30 ml of EtOH were added 2 g (0.02 mole) of Et_3N and a solution of 2.13 g (0.01 mole) of β-bromopropiophenone in 15 ml of EtOH. The reaction mixture was refluxed for 9 hr and then concentrated. To the ice-cooled residue 15 ml of H_2O and 5 ml of 40% aqueous NaOH were added. It was then extracted with Et_2O, and the extracts were dried (Na_2SO_4) and concentrated. The residual oil, after warming under vacuum for some time and then cooling, did not solidify. It was taken up into Me_2CO and was added to 7 ml of *i*-Pr-HCl (22%). The resulting white solid was filtered and recrystallized twice.

N^1-[γ-(3,4,5-Trimethoxybenzoyl)propyl]-N^4-(α,α,α-trifluoro-*m*-tolyl)piperazine Hydrochloride (36).—A mixture of 2.73 g (0.01 mole) of γ-chloro-3,4,5-trimethoxybutyrophenone and 4.6 g (0.02 mole) of N-(α,α,α-trifluoro-*m*-tolyl)piperazine was warmed and kept for 6 hr at room temperature and then heated at 100° for 4 hr. After cooling, H_2O was added and the reaction mixture was extracted twice with 40 ml of $CHCl_3$. The extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The resulting solid residue was recrystallized from hexane to give the free base of **36**. The base was converted to the desired monohydrochloride salt by the usual procedure.

Other members of this series (1, A = $COCH_2CH_2CH_2$) were prepared following the above method. The resulting products were either crystallized, when solid, from the appropriate solvents, or converted, when oily, to the HCl salts.

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Synthesis and Pharmacological Activity of Alkylaminoalkyl Esters and Amides of 2-Hydroxy- (or Alkoxy-) 3-methoxybenzoic Acid

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A series of alkylaminoalkyl esters and amides of 2-hydroxy- (or alkoxy-) 3-methoxybenzoic acid were synthesized and their hydrochloride, methiodide, or oxalate salts were tested for local anesthetic activity. Only the diethylamino and *n*-butylamino ethyl esters of 2-butoxy-3-methoxybenzoic acid and morpholinoethyl 2-ethoxy-3-methoxybenzoate exhibited greater local anesthetic activity than lidocaine. However, these compounds were highly irritating and generally more toxic.

As a continuation of our investigation on local anesthetics,[2-5] studies of the well-known local anesthetic activity of alkylaminoalkyl esters and amides of substituted benzoic acids and the reported physiological activity of the ester, amides, and alkoxy derivatives of vanillic acid[6-9] suggested that an exploration of the activity of alkylaminoalkyl esters and amides of 2-hydroxy- (or alkoxy-) 3-methoxybenzoic acid might result in the discovery of potentially useful local anesthetic agents.

Chemistry.—The ester derivatives synthesized were the dimethylamino-, diethylamino-, piperidino-, and morpholinoethyl esters of 2-hydroxy-3-methoxybenzoic acid, 2,3-dimethoxybenzoic acid, 2-ethoxy-3-methoxybenzoic acid, 2-propoxy-3-methoxybenzoic acid,

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