evaporated under reduced pressure on a film evaporator. The residual yellow oily base weighed 1.2 g (64%). The base (1.1 g) was converted to the hydrogen oxalate salt that crystallized from absolute EtOH–absolute Et_2O (15 ml each) in a yield of 1.4 g, mp 114–119° dec. Further recrystallization from EtOH–Et_2O gave an analytical sample, mp 114–115° dec.

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

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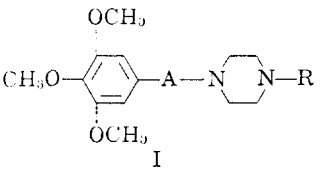
Fifty-two N^1,N^4-disubstituted piperazine derivatives, in which the N^1 substituents are 3,4,5-trimethoxybenzoyl or 3,4,5-trimethoxybenzoylalkyl and the N^4 substituents are methyl, 2-(2′-hydroxyethoxy)ethyl, cyclohexyl, benzyl, *m*-methyl- or *p*-*t*-butylbenzyl, 2-phenethyl, phenyl, chloro- or methoxyphenyl, tolyl, 2,6-xylyl, 2-pyridyl, 2-pyrimidyl, or 2-thiazolyl groups, have been synthesized and screened for CNS activity. The majority of the compounds produced CNS depressant effects as shown by gross observation of intact animals and confirmed by motor activity studies and in some cases by conditioned-avoidance behavior.

In the search for better CNS drugs, the synthesis and screening of compounds having a 3,4,5-trimethoxyphenyl group as an essential moiety have given encouraging results.[2-4] A considerable amount of literature has established the CNS activity of compounds containing a piperazine moiety.[5] A number of 3,4,5-trimethoxybenzamides,[6] and 3,4,5-trimethoxyacetophenone[7] have been reported to possess CNS depressant or tranquillizing activity. Recently, Mannich bases of 1-aryl-4-acetyl-5-methylpyrazoles[8] and different acetophenones[9] with N-substituted piperazines have been reported to have good sedative–tranquillizing activity. The butyrophenone derivatives of the general formula N^1-(aroylalkyl)-N^4-(substituted)piperazines[10] have also been studied, one of which, N^1-[γ-(*p*-fluorobenzoyl)propyl]-N^4-(*o*-methoxyphenyl)piperazine (haloanisone),[11] is at present undergoing clinical trials. Accordingly, the synthesis of the compounds having general formula I was undertaken.



I

A = CO, $COCH_2$, $COCH_2CH_2$, $CH(OH)CH_2CH_2$, $COCH_2CH_2CH_2$, or $CH(OH)CH_2CH_2CH_2$

R = CH_3, 2-(2′-hydroxyethoxy)ethyl, cyclohexyl, benzyl, *m*-methyl- or *p*-*t*-butylbenzyl, phenethyl, C_6H_5, *o*- or *p*-chlorophenyl, *o*-, *m*-, or *p*-methoxyphenyl, *o*-, *m*-, or *p*-tolyl, 2,6-xylyl, 2-pyridyl, 2-pyrimidyl, or 2-thiazolyl

Chemistry.—The requisite N-monosubstituted piperazines were prepared according to literature methods.[12] N-Alkyl-, N-cycloalkyl-, N-aralkyl-, and N-hetero-

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cyclic piperazines were prepared by the action of the corresponding halides on excess of piperazine. In general, N-arylpiperazines were prepared by heating stoichiometric amounts of hydrochlorides of diethanolamine and different anilines. However, N-methoxyphenylpiperazines which could not be obtained by the above method were prepared by the condensation of β,β'-dibromodiethylamine hydrobromide and the corresponding anisidines.

3,4,5-Trimethoxybenzoylpiperazines (I, A = CO) were made in good yields by condensing equimolecular proportions of 3,4,5-trimethoxybenzoyl chloride and the various N-monosubstituted piperazines in the presence of triethylamine.

α-[N^4-(Substituted)-N^1-piperazinyl]-3,4,5-trimethoxyacetophenones (I, A = $COCH_2$) were obtained by the condensation of α-bromo-3,4,5-trimethoxyacetophenone with various N-monosubstituted piperazines. α-Bromo-3,4,5-trimethoxyacetophenone was formed by bromination of 3,4,5-trimethoxyacetophenone, which in turn was synthesized by the action of trimethoxybenzoyl chloride on sodium ethyl acetoacetate and subsequent hydrolysis of the resulting ester.

β-[N^4-(Substituted)-N^1-piperazinyl]-3,4,5-trimethoxypropiophenones (I, A = $COCH_2CH_2$) resulted from Mannich reactions on 3,4,5-trimethoxyacetophenone and N-monosubstituted piperazine hydrohalides. When the Mannich reaction with N-(*m*-tolyl)piperazine dihydrochloride was carried out under the same conditions as with other N-arylpiperazines, β,β-bis[N^4-(*m*-tolyl)-N^1-piperazinyl]-3,4,5-trimethoxypropiophenone resulted, in place of the expected β-[N^4-(*m*-tolyl)-N^1-piperazinyl]-3,4,5-trimethoxypropiophenone.

γ-[N^4-(Substituted)-N^1-piperazinyl]-3,4,5-trimethoxybutyrophenones (I, A = $COCH_2CH_2CH_2$) were prepared by the fusion of γ-chloro-3,4,5-trimethoxybutyrophenone and the requisite N-monosubstituted piperazine. The required γ-chloro-3,4,5-trimethoxybutyrophenone, hitherto unknown, was formed in 85% yield from α-3,4,5-trimethoxybenzoyl-γ-butyrolactone by treatment with hydrochloric acid and fused $ZnCl_2$. The reduction of some ketonic Mannich bases and butyrophenones with sodium borohydride gave the corresponding alcohols. The physical constants, yields, recrystallization solvents, and analyses of the compounds synthesized are given in Table I.

Pharmacology.—Almost all the compounds reported in this paper were tested for their central nervous system (CNS) activity. The gross observation of intact mice revealed that some of these compounds possess good CNS depressant activity. This was confirmed by testing their effects on spontaneous motor activity (Actophotometer, MetroIndustries, U. S. A.), potentiation of barbital hypnosis,[13] and in some cases by their effect on classical avoidance behavior in rats.[14] The approximate LD_{50} of the compounds were determined on mice intraperitoneally as described by Litchfield, *et al.*[15] The results of these observations are summarized in Table I. All the compounds were also tested for analgetic, anticonvulsant, and monoamine oxidase inhibitory activities. None of the compounds had any analgetic activity (narcotic or nonnarcotic), when tested by the rat tail flick method,[16] clip method,[17] and Nilsen's electric shock method.[18] Similarly, there was no protection against convulsion produced by minimal electroshock and by pentylenetetrazole.[19] Also no MAO inhibition was seen by antireserpine activity.[20] All of the compounds were administered intraperitoneally in a suspension made with 0.5% carboxymethylcellulose (CMC). (The vehicle itself was tested in a control group with negative results.)

Structure–Activity Relationships.—In general, the CNS depression activity as seen by decrease in motor activity was in the following descending order according to the nature of –A–, the bridge joining the trimethoxyphenyl and the piperazine nucleus in the general formula I: $-COCH_2CH_2- > -COCH_2CH_2CH_2- > -CO- > -COCH_2-$. It was also noted that the nature of the substituent R on the N^4 position of piperazine affects the activity. In the two most active series, *viz.*, propiophenones (I, A = $COCH_2CH_2$) and the butyrophenones (I, A = $COCH_2CH_2CH_2$), a higher order of activity was observed when the N^4 substituent R was phenyl or substituted phenyl than when it was an alkyl, aralkyl, or heterocyclic group. Further, the substitution in the *ortho* position of the phenyl ring led to more active compounds (**34**, **35**, **39**) than *meta* or *para* substitution. When both the *ortho* positions of the N^4-phenyl ring were substituted with methyl groups (**42**), the activity was diminished considerably. The symmetrically substituted piperazine derivative (**45**) was completely devoid of activity.

In the trimethoxybenzoylpiperazine series (I, A = CO), however, the activity was found to be higher for N^4-heterocyclic-substituted piperazines than the N^4-aryl ones. Also the N^4-heterocyclic-substituted piperazines of this series were the least toxic. The reduction of the carbonyl group to the secondary alcoholic group slightly diminished the activity and increased the toxicity.

Compounds **13**, **35**, **39**, **40**, and **49** are undergoing a more extensive pharmacological evaluation.

Experimental Section[21]

Intermediates.—The required 3,4,5-trimethoxybenzoyl chloride,[22] 3,4,5-trimethoxyacetophenone,[23] and α-bromo-3,4,5-trimethoxyacetophenone[24] were prepared by literature methods.

γ-Chloro-3,4,5-trimethoxybutyrophenone.—A mixture of 8.4 g of α-(3,4,5-trimethoxybenzoyl)-γ-butyrolactone[25,26] and 25 ml of concentrated HCl was heated on a steam bath for 3 hr. After cooling, 8.0 g of fused $ZnCl_2$ was added and heating was continued for 2 hr. The reaction mixture was then cooled and extracted

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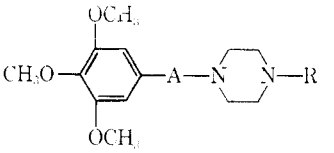
TABLE I

N^1,N^3-DISUBSTITUTED PIPERAZINES



No.	A	R	Cryst solvent[a]	% yield[b]	M.p.,[c] °C	Formula	Analyses[d]	Mouse LD50, mg/kg ip	CNS depression,[d] mg/kg	% decrease in motor activity of mice[e]
1	CO	Cyclohexyl	E_{70}	63	103–104	$C_{20}H_{30}N_2O_3$	N	200	50[f]	–
2	CO	*m*-Methylbenzyl	P	62	212–213	$C_{22}H_{28}N_2O_3 \cdot HCl$	C, H, N	300	60[g]	50
3	CO	*p*-*t*-Butylbenzyl	P	65	130–131	$C_{26}H_{36}N_2O_3$	N	800	200	69
4	CO	Phenyl	E–H	70	134–135[h]	$C_{20}H_{24}N_2O_4$	N	300	60	–
5	CO	*o*-Chlorophenyl	B–H	52	148–149	$C_{20}H_{23}ClN_2O_4$	C, H, N	*i*	*i*	*i*
			E–Et		156–158	$C_{20}H_{29}ClN_2O_4 \cdot HCl$	N			
6	CO	*p*-Chlorophenyl	E–H	73	138–139	$C_{20}H_{23}ClN_2O_4$	N	300	90[j]	57
			E		218–219	$C_{20}H_{23}ClN_2O_4 \cdot HCl$	N			
7	CO	*o*-Methoxyphenyl	H	66	115–116	$C_{21}H_{26}N_2O_5$	C, H, N	75	–[k]	68
8	CO	*m*-Methoxyphenyl	E	59	170–171	$C_{21}H_{26}N_2O_5 \cdot$ oxalate	N	*i*	*i*	*i*
9	CO	*p*-Methoxyphenyl	E	45	152–153	$C_{21}H_{26}N_2O_5$	N	300	90[l]	50
			E		223–225	$C_{21}H_{26}N_2O_5 \cdot HCl$	N			
10	CO	*p*-Tolyl	H	63	130–131	$C_{21}H_{26}N_2O_3$	N	300	90[l]	–
			E		155–157	$C_{21}H_{26}N_2O_4 \cdot HCl$	N			
11	CO	*m*-Tolyl	E_{70}	62	103–104	$C_{21}H_{26}N_2O_3$	N	400	50	56
12	CO	*p*-Tolyl	E_{70}	61	102–103	$C_{21}H_{26}N_2O_3$	N	400	50[f]	–
			E–Et		240–242	$C_{21}H_{26}N_2O_3 \cdot HCl$	N			
13	CO	2-Pyridyl	P	70	112–113	$C_{19}H_{23}N_3O_3$	C, H, N	800	60[m]	83
14	CO	2-Pyrimidyl	P	71	155–156	$C_{18}H_{22}N_4O_3$	N	800	60[n]	70
15	CO	2-Thiazolyl	P	68	141–142	$C_{17}H_{21}N_3O_3S$	N	800	100	91
16	$COCH_2$	2-(2-Hydroxyethoxy)ethyl	E–Ac	41	164–165 dec	$C_{19}H_{30}N_2O_6 \cdot HBr$	C, H, N	800	90	–
17	$COCH_2$	Benzyl	E	42	227–229 dec	$C_{22}H_{28}N_2O_3 \cdot 2HCl$	N	250	90	–
18	$COCH_2$	*m*-Methylbenzyl	E	48	228–230 dec	$C_{23}H_{30}N_2O_4 \cdot 2HCl$	N	150	–[o]	–
19	$COCH_2$	*p*-*t*-Butylbenzyl	E	45	237–239 dec	$C_{26}H_{36}N_2O_4 \cdot 2HCl$	C, H, N	75	–	–
20	$COCH_2$	Phenyl	E–Et	40	177–178	$C_{21}H_{26}N_2O_4 \cdot$ maleate	N	*i*	*i*	*i*
21	$COCH_2$	*o*-Chlorophenyl	...	37	*p*	$C_{21}H_{25}ClN_2O_4$	N	415	–	50
22	$COCH_2$	*o*-Methoxyphenyl	H	60	117–118	$C_{22}H_{28}N_2O_5$	N	100	30[n]	69
23	$COCH_2$	*p*-Methoxyphenyl	E–Et	55	240–241	$C_{22}H_{28}N_2O_5$	C, H, N	350	90[j]	50
24	$COCH_2$	*o*-Tolyl	E–Et	40	232–233 dec	$C_{22}H_{28}N_2O_4 \cdot 2HCl$	N	*i*	*i*	*i*
25	$COCH_2$	2-Pyridyl	E	64	238–239 dec	$C_{20}H_{25}N_3O_4 \cdot 2HCl$	C, H, N	800	–	–
26	$COCH_2$	2-Pyrimidyl	E	61	208–210 dec	$C_{19}H_{24}N_4O_4 \cdot 2HCl$	C, H, N	175	35[j]	56
27	$COCH_2$	2-Thiazolyl	E–Ac	57	229–230 dec	$C_{18}H_{23}N_3O_4S \cdot 2HCl$	C, H, N	350	90	–
28	$COCH_2CH_2$	Methyl	E	44	206–208 dec	$C_{17}H_{26}N_2O_4 \cdot 2HCl$	C, H, N	450	50	–
29	$COCH_2CH_2$	Cyclohexyl	E	40	238–240 dec	$C_{22}H_{34}N_2O_4 \cdot HCl$	C, H, N	100	20	56
30	$COCH_2CH_2$	Benzyl	P	40	238–239 dec	$C_{23}H_{30}N_2O_4 \cdot 2HCl$	C, H, N	250	–[p]	–
31	$COCH_2CH_2$	*m*-Methylbenzyl	E	30	236–238 dec	$C_{24}H_{32}N_2O_4 \cdot 2HCl$	C, H, N	150	–[q]	–
32	$COCH_2CH_2$	2-Phenethyl	E	38	237–238 dec	$C_{24}H_{32}N_2O_4 \cdot 2HCl$	N	100	40[j]	50
33	$COCH_2CH_2$	Phenyl	P–Et	40	193–194 dec	$C_{22}H_{28}N_2O_4 \cdot HCl$	C, H, N	450	60[n]	60[r]
34	$COCH_2CH_2$	*o*-Chlorophenyl	E	60	219–221 dec	$C_{22}H_{27}ClN_2O_4 \cdot HCl$	C, H, N	500	20[n]	60[r]
35	$COCH_2CH_2$	*o*-Methoxyphenyl	E	45	223–225 dec	$C_{23}H_{30}N_2O_5 \cdot HBr$	C, H, N	325	10[s]	98[n]
			E		89–90	$C_{23}H_{30}N_2O_5$	N			
			E		142–143	$C_{23}H_{30}N_2O_5 \cdot$ maleate	N			
36	$CHOHCH_2CH_2$	*o*-Methoxyphenyl	E	91	186–187 dec	$C_{23}H_{32}N_2O_5 \cdot 2HCl$	N	150	20[t]	72
37	$COCH_2CH_2$	*m*-Methoxyphenyl	E	35	193–194 dec	$C_{23}H_{30}N_2O_5 \cdot HCl$	N	400	50	50
38	$COCH_2CH_2$	*p*-Methoxyphenyl	E	45	210–211 dec	$C_{23}H_{30}N_2O_5 \cdot HBr$	N	80	20[n,u]	72
39	$COCH_2CH_2$	*o*-Tolyl	E	70	218–219 dec	$C_{23}H_{30}N_2O_4 \cdot HCl$	C, H, N	340	10[n,v]	95[r]
			E		111–112	$C_{23}H_{30}N_2O_4$	N			
			E		152–154	$C_{23}H_{30}N_2O_4 \cdot$ maleate	N			
40	$CHOHCH_2CH_2$	*o*-Tolyl	E–Et	92	155–156 dec	$C_{23}H_{32}N_2O_4 \cdot 2HCl$	C, H, N	150	20[n,w]	91
41	$COCH_2CH_2$	*p*-Tolyl	E	45	202–203 dec	$C_{23}H_{30}N_2O_4 \cdot HCl$	C, H, N	150	10[n,x]	50
42	$COCH_2CH_2$	2,6-Xylyl	E	55	217–219 dec	$C_{24}H_{32}N_2O_4 \cdot HCl$	C, H, N	200	50	–
43	$COCH_2CH_2$	2-Pyridyl	P	40	204–205 dec	$C_{21}H_{27}N_3O_4 \cdot 2HCl$	N	250	30	50[n,y]
44	$COCH_2CH_2$	2-Pyrimidyl	E	55	205–206 dec	$C_{26}H_{36}N_4O_9 \cdot 2HCl$	C, H, N	350	90	55
45	$COCH_2CH_2$	β-(3,4,5-Trimethoxybenzoyl)ethyl	E	46	216–217 dec	$C_{28}H_{38}N_2O_8 \cdot 2HCl$	C, H, N	1000	–[z]	–
46	$COCH_2CH_2CH_2$	Methyl	E	54	221–223 dec	$C_{18}H_{28}N_2O_4 \cdot 2HCl$	C, H, N	300	–	–
47	$COCH_2CH_2CH_2$	Phenyl	E–Et	32	175–177 dec	$C_{23}H_{30}N_2O_4 \cdot 2HCl$	N	200	40[n,a]	76
			H		75–76	$C_{23}H_{30}N_2O_4$	N			

Table I (*Continued*)

No.	A	R	Crystn solvent[a]	% yield[b]	Mp,[c] °C	Formula	Analyses[21]	Mouse LD_{50}, mg/kg ip	CNS depression,[d] mg/kg	% decrease in motor activity of mice[e]
48	$COCH_2CH_2CH_2$	*o*-Chlorophenyl	E–Ac	47	198–200 dec	$C_{23}H_{29}ClN_2O_4 \cdot 2HCl$	N	200	50	52
			H		84–86	$C_{23}H_{29}ClN_2O_4$	N			
49	$COCH_2CH_2CH_2$	*o*-Methoxyphenyl	E	52	185–187 dec	$C_{24}H_{32}N_2O_5 \cdot 2HCl$	C, H, N	150	50[hh]	79
			H		114–115	$C_{24}H_{32}N_2O_5$	N			
50	$CHOHCH_2CH_2CH_2$	*o*-Methoxyphenyl	E–Et	90	194–195 dec	$C_{24}H_{34}N_2O_5 \cdot 2HCl$	C, H, N	75	20	75
51	$COCH_2CH_2CH_2$	*o*-Tolyl	E–Et	48	191–192 dec	$C_{24}H_{32}N_2O_4 \cdot 2HCl$	N	200	50[ii]	58
			H		89–91	$C_{24}H_{32}N_2O_4$	N			
52	$COCH_2CH_2CH_2$	2-Pyridyl	E	55	229–231 dec	$C_{22}H_{29}N_3O_4 \cdot 2HCl$	C, H, N	150	10[ii]	55

[a] Ac, Me_2CO; B, C_6H_6; E, EtOH; E_{70}, 70% EtOH; Et, Et_2O; H, *n*-C_6H_{14}; P, *i*-PrOH. [b] Yields reported are the results of single experiments and are based on the 3,4,5-trimethoxybenzoyl chloride (in case of **1–15**), N-substituted piperazines (in case of **16–27**), N-substituted piperazine hydrohalide salts (in case of **28–35**, **37–39**, and **41–45**), and γ-chloro-3,4,5-trimethoxybutyrophenone (in case of **46–49**, **51**, and **52**); yields are calculated for the materials melting not less than 2–3° below the highest melting point obtained. [c] Melting points were taken in capillary tubes 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 footnotes in this column. [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 to be significant and is indicated as negative (−). [f] Produced 60% potentiation of barbital hypnosis at 20 mg/kg. [g] Mild depression in cat at 5 mg/kg. [h] J. R. Boissier, R. Ratouis, and C. Dumont, *J. Med. Chem.*, **6**, 541 (1963), reported mp 133–135°. [i] Pharmacological testings not done. [j] Produced 60% potentiation of barbital hypnosis at 100 mg/kg. [k] Sleep in cat lasting for 5 hr at 5 mg/kg can be aroused easily but goes back to sleep if left undisturbed; normal in 24 hr. [l] Produced 80% potentiation of barbital hypnosis at 100 mg/kg. [m] Marked relaxation of nictitating membrane and marked sedation observed in cat which persisted for more than 2 hr at 20 mg/kg. Marked sedation and loss of righting reflex observed in mice at 135 mg/kg. Produced 60% potentiation of barbital hypnosis at 100 mg/kg. [n] Marked sedation in mice at 135 mg/kg. [o] Produced hyperactivity and irritability in mice at 60 mg/kg. Produced 80% potentiation of barbital hypnosis at 30 mg/kg. [p] Boiling point 155–158° (5 mm). [q] Mild sedation and relaxation of nictitating membrane observed in cat at 5 mg/kg. Produced 60% potentiation of barbital hypnosis at 50 mg/kg. [r] Produced 80% potentiation of barbital hypnosis at 35 mg/kg. [s] Marked salivation in cat at 5 mg/kg. [t] Urination, salivation, and limb paralysis observed in mice at 60 mg/kg. [u] Also has marked hypoteusive action. [v] 60% decrease in motor activity of mice at 20 mg/kg. [w] Produced catatonia in mice at 100 mg/kg. [z] Marked sedation and loss of righting reflex observed in mice at 10 mg/kg. Marked sedation (lasting for 6 hr) and marked relaxation of nictitating membrane observed in cat at 10 mg/kg. Produced catatonia in cat at 80 mg/kg. Produced 100% potentiation of barbital hypnosis at 20 mg/kg. Blocking of conditioned avoidance response (CAR) in rats at 20 mg/kg. 100% inhibition of orientation and amphetamine-induced hyperactivity. Also has marked hypotensive action. [y] 98% decrease in motor activity of mice at 10 mg/kg. [z] Produced 60% potentiation of barbital hypnosis at 50 mg/kg. Also has hypotensive action. [aa] Produced 80% potentiation of barbital hypnosis at 20 mg/kg. Marked sedation and relaxation of nictitating membrane (effect lasting for 4 hr) observed in cat at 5 mg/kg. [bb] Marked sedation and loss of muscle tone observed in mice at 50 mg/kg. Marked sedation and relaxation of nictitating membrane observed in cat at 5 and 20 mg/kg. At higher doses (120–160 mg/kg) catatonia was noticed. It has also marked hypotensive action. [cc] 95% decrease in motor activity of mice at 10 mg/kg. [dd] Produced 100% potentiation of barbital hypnosis at 20 mg/kg. [ee] Produced 100% potentiation of barbital hypnosis at 20 mg/kg. Mild sedation and loss of muscle tone were observed in mice at 10 mg/kg. [ff] 50% decrease in motor activity of mice at 10 mg/kg. [gg] Produced 60% potentiation of barbital hypnosis at 20 mg/kg. Also has marked hypotensive action. [hh] Marked sedation in mice at 50 mg/kg. Also has marked hypotensive action. [ii] Marked sedation and loss of muscle tone observed in mice at 50 mg/kg. [jj] Produced 90% potentiation of barbital hypnosis at 10 mg/kg.

with ether. The combined ether extracts were washed (H_2O), dried (Na_2SO_4), treated with active carbon, and concentrated under reduced pressure. The resulting solid residue on crystallization from hexane gave 7.0 g (85%) of product, mp 80–82°.

The **2,4-dinitrophenylhydrazone** derivative of this compound was crystallized (EtOH), mp 139–140°. *Anal.* ($C_{19}H_{21}ClN_4O_7$) N.

N-Monosubstituted Piperazines.—The following N-monosubstituted piperazines required for the present work were prepared by the methods described in literature: N-methyl,[12a] N-[2-(2-hydroxyethoxy)ethyl],[12b] N-cyclohexyl,[12c] N-benzyl,[12d] N-*m*-methylbenzyl,[12e] N-*p*-*t*-butylbenzyl,[12e] N-phenethyl,[12e] N-phenyl,[12f] N-*o*- and -*p*-chlorophenyl,[12g] N-*m*-, -*o*-, and -*p*-tolyl,[12g] N-*m*-, -*o*-, and -*p*-methoxyphenyl,[12h] N-(2,6-xylyl),[12i] N-(2-pyridyl),[12j] N-(2-pyrimidyl),[12i] and N-(2-thiazolyl).[12j]

m-Methylbenzyl bromide,[27] *p*-*t*-butylbenzyl bromide,[28] phenethyl chloride,[29] 2-bromopyridine,[30] 2-chloropyrimidine,[31] and 2-chlorothiazole[32] required for preparing the corresponding N-monosubstituted piperazines were obtained by literature methods.

N¹-(3,4,5-Trimethoxybenzoyl)-N⁴-(2-pyridyl)piperazine (13).—To a solution of 3.26 g (0.02 mole) of N-(2-pyridyl)piperazine and 4.0 g (0.04 mole) of triethylamine in 20 ml of anhydrous $CHCl_3$, 4.6 g (0.02 mole) of 3,4,5-trimethoxybenzoyl chloride dissolved in 20 ml of anhydrous $CHCl_3$ was added slowly. The reaction mixture was refluxed for 7 hr. It was then cooled, washed (H_2O), and dried (Na_2SO_4), and $CHCl_3$ was removed *in vacuo*. The residue solidified when triturated with hexane. The solid was then recrystallized twice from *i*-PrOH to give 5.0 g of pure **13**.

Other members of this series (I, A = CO) were prepared, following the above procedure. The resulting products were either recrystallized, when solid, from the appropriate solvents or converted, when oily, to appropriate salts.

N¹-(3,4,5-Trimethoxyphenacyl)-N⁴-[2-(2-hydroxyethoxy)-ethyl]piperazine Hydrobromide (16).—A solution of 5.8 g (0.02 mole) of α-bromo-3,4,5-trimethoxyacetophenone and 3.5 g (0.02 mole) of N-[2-(2-hydroxyethoxy)ethyl]piperazine in 40 ml of Me_2CO was refluxed for 3 hr and concentrated to half of its volume. The reaction mixture was left overnight at 10°. The resulting white solid was filtered, dried, and recrystallized.

N¹-(3,4,5-Trimethoxyphenacyl)-N⁴-(*p*-methoxyphenyl)piperazine (23).—A solution of 3.18 g (0.011 mole) of α-bromo-3,4,5-trimethoxyacetophenone, 1.92 g (0.01 mole) of N-(*p*-methoxyphenyl)piperazine, and 2.0 g (0.02 mole) of triethylamine in

(27) A. F. Titley, *J. Chem. Soc.*, 514 (1926).

(28) (a) *t*-Butyl chloride: J. F. Norris and A. W. Olmsted, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p 138; (b) *t*-butylbenzene: D. Nightingale, R. G. Taylor, and H. W. Smelser, *J. Am. Chem. Soc.*, **63**, 258 (1941); (c) *t*-butylbenzyl bromide: P. Mamalis, H. Green, D. J. Outred, and M. Rix, *J. Chem. Soc.*, 3915 (1962).

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(30) C. F. H. Allen and J. R. Thirtle, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 136.

(31) I. C. Kogon, R. Minin, and C. G. Overberger, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p 182.

(32) K. Ganapathi and A. Venkataraman, *Proc. Indian Acad. Sci.*, **22a**, 343 (1945); *Chem. Abstr.*, **40**, 4059[8] (1946).

60 ml of EtOH was refluxed for 8 hr. The reaction mixture was concentrated *in vacuo*, made alkaline with 40% NaOH, and extracted ($CHCl_3$). The extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The resulting solid residue was recrystallized three times.

Other members of this series (I, A = $COCH_2$) were prepared following the above procedure. The resulting products were either crystallized from the appropriate solvents, when solid, or, when oily, converted to the maleate or dihydrochloride salts by addition of acetone solution of the base to the ethanolic maleic acid or to the excess 5 *N* 2-propanolic–HCl.

N¹-[β-(3,4,5-Trimethoxybenzoyl)ethyl]-N⁴-(*o*-tolyl)piperazine Monohydrochloride (39).—To a solution of 5.0 g (0.02 mole) of N-(*o*-tolyl)piperazine dihydrochloride in 100 ml of EtOH, 3 ml (~0.03 mole) of aqueous formaldehyde (37–41%), and 5.0 g (0.024 mole) of 3,4,5-trimethoxyacetophenone was added and the mixture was refluxed for 7 hr. Additional aqueous formaldehyde (3 ml) was added and reflux continued further for 7 hr. The reaction mixture was concentrated to half of its volume and allowed to cool, when a white shining crystalline compound separated out. This was collected by filtration, 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 ether to the calculated amount of maleic acid in EtOH.

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

β,β-Bis[N⁴-(*m*-tolyl)-N¹-piperazinyl]-3,4,5-trimethoxypropiophenone.—To a solution of 3.73 g (0.015 mole) of 1-(*m*-tolyl)-piperazine dihydrochloride in 70 ml of EtOH, 1.5 ml (~0.015 mole) of aqueous formaldehyde, and 3.45 g (0.0165 mole) of 3,4,5-trimethoxyacetophenone were added and the mixture was refluxed for 7 hr. Aqueous formaldehyde (1.5 ml) was again added and reflux continued for another 7 hr. The reaction mixture was concentrated to one-third of its volume and added to 200 ml of dry acetone; the resulting solid on filtration was hygroscopic. It was dissolved in water, and the free base was liberated with 10% aqueous NaOH and extracted with $CHCl_3$. The extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The oily residue, on keeping for 2 days over anhydrous $CaCl_2$ in a vacuum desiccator, turned into a fine yellow solid, mp 89° dec (softens at 70°). *Anal.* ($C_{32}H_{40}N_2O_4$) C, H, N.

N¹-[γ-Hydroxy-γ-(3,4,5-trimethoxyphenyl)propyl]-N⁴-(*o*-tolyl)-piperazine Dihydrochloride (40).—A suspension of 6.52 g (0.015 mole) of **39** in 250 ml of MeOH was adjusted to pH 10 with 50% aqueous NaOH and cooled in an ice bath. While stirring at 0°, 0.9 g of $NaBH_4$ was added over a period of 15 min. The reaction mixture was stirred for 3 hr at room temperature. It was then cooled to 5° and acidified to pH 2 with concentrated HCl. After stirring for 15 min the pH was again adjusted to 10, with 50% aqueous NaOH. The reaction mixture was evaporated to half of its volume, diluted with 250 ml of H_2O, and extracted ($CHCl_3$). The extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The resulting yellow oily residue was taken up in 60 ml of Me_2CO and added to 30 ml of 5 *N* 2-propanolic–HCl. The white granular solid thus obtained was recrystallized.

N¹-[γ-(3,4,5-Trimethoxybenzoyl)propyl]-N⁴-(*o*-methoxyphenyl)piperazine Dihydrochloride (49).—γ-Chloro-3,4,5-trimethoxybutyrophenone (2.73 g, 0.01 mole) and 3.84 (0.02 mole) of N-(*o*-methoxyphenyl)piperazine were mixed and warmed. The mixture was kept for 6 hr at room temperature and then heated at 100° for 4 hr. After cooling, water 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 to give base which was also converted to its dihydrochloride salt.

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

N¹-[δ-Hydroxy-δ-(3,4,5-trimethoxyphenyl)butyl]-N⁴-(*o*-methoxyphenyl)piperazine dihydrochloride (50) was obtained from **49** by reduction with $NaBH_4$, following the procedure described for **40**.

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Transformations in the Morphine Series. II.[1a] A New Position Isomer of Dihydromorphinone[1b]

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The transformation of dihydrocodeinone (I) to a new position isomer (VII) of dihydromorphinone is described. In mice, VII elicited roughly one-third the analgetic activity of codeine. These data further demonstrate how critical are the relative points of linkage of the ethanamine system in respect to analgetic activity.

The numerous attempts at structural modification of morphine and its congeners with the view to enhancing pharmacological utility while concomitantly depressing less desirable side effects have been fully documented.[3] Recently[1a] we reported a novel transformation of codeine to an analog of the potent synthetic analgetic phenazocine in which a 14-fold increase in analgetic power over codeine was achieved. The present communication deals with another approach in this area.

Well known is the fact that in the morphine group of alkaloids the nitrogen end of the ethanamine system is linked to C-9 while the carbon terminus (normally at C-13) may, in certain instances, be rearranged to another position, *e.g.*, C-14 in metathebainone.[4] It occurred to us that useful chemical as well as pharmacological information would accrue if it were possible to shift the nitrogen end of the basic chain to a position other than C-9 without disturbing the remaining salient features of the molecule. To this end, dihydrocodeinone (I) was selected as the starting material for the envisaged transformation. Utilizing standard procedures, I-methiodide was degraded (Hofmann) to the corresponding methine and the latter was reduced to the dihydro derivative (II). Treatment of a warm,

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(3) See, for example, (a) Collected Papers—Report of Committee on Drug Addiction 1929–1941, National Research Council, Washington, D. C., 1941; (b) N. B. Eddy, H. Halbach, and O. J. Braenden, *Bull. World Health Organ.*, **17**, 569 (1957), and previous papers in this series.

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