(50 ml) was refluxed for 4 hr and evapd. Crystn from CH_3CN gave pure **8a** (3.5 g), mp 233–233.5°. A methiodide salt was prepared, mp 163–164°.

1-(2-Hydroxyphenethyl)-2-imino-3-methylimidazolidine (9a). A slurry of **7a** (30 g; 0.1 mole) in H_2O (250 ml) was maintained at 5° as $NaBH_4$ (4.2 g; 0.11 mole) was added portionwise. The mixt was stirred cold for 0.5 hr and the excess borohydride was destroyed with concd HCl. The soln was heated to boiling, cooled, basified to pH 11 with 10% NaOH and extd with $CHCl_3$. The organic phase was dried and evapd to give crude **9a** (18 g). Recrystn from cyclohexane gave pure **9a**, mp 88–90°.

1-(2-Hydroxy-2-thienylethyl)-2-imino-3-methylimidazolidine Hydrochloride (9b). A slurry of **7a** (20 g; 0.066 mole) in H_2O (125 ml) was maintained at 5° as $NaBH_4$ (2.5 g; 0.066 mole) was added portionwise. The mixt was stirred cold for 15 min and excess borohydride was destroyed with concd HCl. The soln was heated to boiling, cooled, basified to pH 11 with 10% NaOH, and evapd. The residue was treated with Me_2CO–Et_2O (1:1) and filtered to remove inorganic material. The filtrate was treated with ethereal HCl to ppt **9b** (9.6 g). Recrystn from abs EtOH gave pure **9b**, mp 203–206°.

1-Methyl-6-phenyl-2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]imidazole Dihydrochloride (10a). A soln of **9a** (7 g; 0.032 mole) in $SOCl_2$ (100 ml) was refluxed for 1.5 hr and evapd. Residual $SOCl_2$ was destroyed with H_2O (25 ml) and the aq phase was extd with $CHCl_3$. The organic phase was dried and evapd to give an oil which was dissolved in hot $MeNO_2$ and chilled. Filtration of the solid gave **10a** (3.4 g), first mp 176–178° with resolidification at 178°, second mp 300°.

2-Imino-3-methyl-1-(*trans*-styryl)imidazolidine Hydrochloride (11). Method A. A sample of **10a** (3.4 g; 0.012 mole) in a flask under N_2 was carefully melted over a flame so as to avoid charring. The gummy residue (2.8 g) was crystd from DMF to give pure **11** (0.6 g), mp 300° dec. The nmr spectrum [(DMSO-d_6)- δ 3.05 (3 H, singlet, CH_3N), 3.80 (4 H, singlet, imidazolidine ring protons), 5.98 (1 H, doublet, J = 14 cps, vinyl proton α to phenyl ring), 7.33 (5 H, multiplet, Ph ring protons), 8.03 (1 H, doublet, J = 14 cps, vinyl proton β to Ph ring), 9.13 (2 H broad singlet, exchangeable with D_2O, NH)] revealed the configuration.

Method B. A quantity of **10a** (7.1 g; 0.025 mole) was heated under vacuum (80 mm) at 100° for 65 hr to give a virtually quant yield (6.1 g) of **11**, mp 300° dec.

3-Methyl-2-nitroimino-1-phenacylimidazolidine (12). To a soln of Na (0.39 g; 0.017 g-atom) in abs EtOH (50 ml) was added **7a** (5 g; 0.017 mole), the mixt was heated to reflux and evapd. The residue was triturated with C_6H_6 (50 ml) which was filtered to remove NaBr and evapd. The oily free base (3 g) was taken up in Ac_2O (5 ml), chilled to 5°, and stirred as acetyl nitrate[10] (13.5 g) was slowly added. The soln was stirred at 25° for 1 hr, poured into cold Et_2O (200 ml), and refrigerated. The gummy ppt (3.3 g) was chromatographed on silica gel‡ (200 g) using CH_3CN as eluant. The initially eluted material (1.6 g) was recrystd from *i*-PrOH to give pure **12**, mp 150–153°.

3-Methyl-1-phenacyl-2-imidazolidinone (13). A soln of **12** (2.6 g; 0.01 mole) in 20% NaOH (50 ml) was refluxed for 10 min, cooled, and extd with $CHCl_3$. The $CHCl_3$ was dried and evapd to give a crude oil (1.9 g) which was shown by tlc (silica gel, CH_3CN) to be primarily one compd. Crystn from heptane gave pure **13**, mp 113–116°.

5,5′-Bis(2,3-dihydro-1-methyl-6-phenyl-1*H*-imidazo[1,2-*a*]imidazole) (14). A soln of **8a** (14.5 g; 0.073 mole) as the free base in $CHCl_3$ (350 ml) was stirred at 25° for 4.5 hr with excess active MnO_2[7] (42 g). The MnO_2 was filtered off and the filtrate evapd to give **14** (7.7 g). Recrystn from acetone gave pure **14**, mp 217–220°, mass spectrum, M^+ = 396.

Reduction of 4a. A soln of **4a** (1 g; 4.6 mmoles) in abs EtOH (30 ml) was reduced under atm pressure with prereduced PtO_2 (0.1 g) for 19 days. Uptake of H_2 was measured as 120 ml; theoretical uptake for 1 equiv of H_2, *ca.* 115 ml. The catalyst was filtered off and the solvent evapd. Recrystn from cyclohexane gave white needles, mp 92–94°, whose ir spectrum was identical with that of **9a**. Mmp with **9a** showed no depression.

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‡Silica gel was purchased from Gebr. Hermann, D5000 Köln Ehrenfeld, West Germany, under the name kieselgel.

Synthesis and Central Nervous System Activity of New Piperazine Derivatives. 4

J. A. Fernandez, R. A. Bellare, C. V. Deliwala,*

Department of Chemotherapy, Haffkine Institute, Bombay 12, India

N. K. Dadkar, and U. K. Sheth

Department of Pharmacology, Seth G. S. Medical College, Bombay 12, India.

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Earlier, we reported the synthesis and CNS depressant activity of compounds incorporating the 3,4,5-trimethoxyphenyl and piperazine groupings linked by various connecting bridges.[1] The most active compounds obtained were Mannich bases having $COCH_2CH_2$ linkage. The presence of the 3,4,5-trimethoxycinnamoyl group in rescinnamine (another important therapeutically active alkaloid of *Rauwolfia*) and the interesting physiological properties exhibited by vinylogs[2] of various drugs suggested the extension of the work. The present note describes the synthesis and study of Mannich bases and related compounds having the general formula I (see Table I).

Chemistry. The title compounds were prepared by Mannich reaction of 3,4,5-trimethoxy- or unsubstituted benzalacetone and various N-monosubstituted piperazines. However, when the Mannich reaction with *N*-(α,α,α-trifluoro-*m*-tolylpiperazine hydrochloride was carried out under the same conditions, α,α-bis-N^4-(α,α,α-trifluoro-*m*-tolyl) piperazinyl-N^1-methyl 3,4,5-trimethoxystyrylmethyl ketone resulted instead of the desired product.

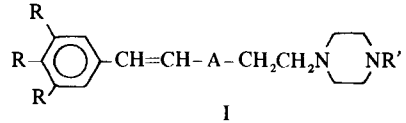
Some Mannich bases were reduced to the corresponding alcohols with $NaBH_4$ in order to see the effect on the activity.

The structures of compounds described are assigned on the basis of known synthetic route, elemental analyses, and spectral measurements. The ir and uv spectra of the compounds are in accordance with these assignments.

Pharmacology. The CNS activity of the compounds was studied in mice by methods described earlier.[1] The gross observation of intact mice, spontaneous motor activity, and potentiation of barbital hypnosis revealed that few of the compounds (**5**, **7**, **8**, **11**) possessed good CNS depressant activity. Compounds having aryl substitution in the N^4 position of the piperazine displayed better activity than the rest. Further, the compounds having F in the ortho or para position of the N^4 Ph ring exhibited significant CNS depressant activity.

The cardiovascular effect of most of these compounds were studied in normotensive dogs under pentobarbital

Table I

No.	R'	Crystn solvent[a]	% yield[b]	Mp,[c] °C	Formula	Analyses[d]	Approx LD_{50} (mouse), mg/kg ip	CNS depresn,[e] mg/kg	%↓ in motor act.[f]	Adreno-lytic activity[g]	Blood pressure change[h,i]
					 I						
	R = OCH_3; A = CO										
1	Cyclohexyl	P	44	230–233 dec	$C_{24}H_{36}N_2O_4 \cdot 2HCl$	N	300	50[j]	+		
2	*m*-$MeC_6H_4CH_2$	P	33	201	$C_{26}H_{34}N_2O_4 \cdot 2HCl$	C, H, N	150	0[k]	0		
3	β-$C_6H_5C_2H_4$	E	36	205–206 dec	$C_{26}H_{34}N_2O_4 \cdot 2HCl$	N	200	0	0		
4	Ph	E	30	175	$C_{24}H_{30}N_2O_4 \cdot HCl \cdot H_2O$	C, H, N	150	0	0		
5	*o*-ClC_6H_4	E	38	188	$C_{24}H_{29}ClN_2O_4 \cdot HCl \cdot H_2O$	C, H, N	800	50[l]	+++	++	++++
6	*p*-ClC_6H_4	E	51	175	$C_{24}H_{29}ClN_2O_4 \cdot HCl \cdot H_2O$	C, H, N	800	100[l]	0		
7	*o*-FC_6H_4	E	67	189	$C_{24}H_{29}FN_2O_4 \cdot HCl \cdot H_2O$	C, H, N	800	50[l]	++++	+++	++
8	*p*-FC_6H_4	E	62	188	$C_{24}H_{29}FN_2O_4 \cdot HCl \cdot H_2O$	C, H, N	600	50[l]	++++	+	+
9	*o*-$MeOC_6H_4$	E	35	209[d]	$C_{25}H_{32}N_2O_5 \cdot HBr$	C, H, N	300	50[l]	++		
10	*p*-$MeOC_6H_4$	E	66	178–180 dec	$C_{25}H_{32}N_2O_5 \cdot HBr$	N	800	200	+		
11	*o*-Tolyl	P	30	180	$C_{25}H_{32}N_2O_4 \cdot HCl$	C, H, N	800	50	++++		
12	2-Pyridyl	P–Et	47	174–176	$C_{23}H_{29}N_3O_4 \cdot 2HCl$	N	800	0[m,n]	0	++	±
13	2-Pyrimidyl	E	53	199	$C_{22}H_{28}N_4O_4 \cdot HCl$	C, H, N	150	50[m,o]	0		
	R = OCH_3; A = CHOH										
14	*o*-FC_6H_4	E–Et	35	184–185	$C_{24}H_{31}FN_2O_4 \cdot 2HCl$	C, H, N	300	50	++	++++	+++
15	*p*-FC_6H_4	P	41	202–205 dec	$C_{24}H_{31}FN_2O_4 \cdot 2HCl$	C, H, N	200	50	+	+++	+++
16	*p*-$MeOC_6H_4$	E–Et	43	214 dec	$C_{25}H_{34}N_2O_5 \cdot 2HCl$	C, H, N	300	100	+	+++	+++
	R = H; A = CO										
17	*o*-FC_6H_4	P	30	167–170	$C_{21}H_{23}FN_2O \cdot 2HCl$	C, H, N	150	15	+	+++	++
18	*p*-FC_6H_4	E	42	178	$C_{21}H_{23}FN_2O \cdot 2HCl$	C, H, N	300	50	0	+	+++
19	2-Pyridyl		51	Oil	$C_{20}H_{23}N_3O$	N	300	50[m]	0	+++	±
	R = H; A = CHOH										
20	2-Pyridyl		38	Oil	$C_{20}H_{25}N_3O$	N	400	50	+	+++	++

[a] E, EtOH; P, *i*-PrOH; Et, Et_2O. [b] Yields reported are the results of single experiments and are calcd for a material melting not less than 2–3° below the highest mp obtd. [c] Melting points were taken with a partial immersion thermometer in capillary tubes sealed at one end and are uncor. [d] Where analyses are indicated only by the symbol of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. [e] Depression at doses greater than 40% of the LD_{50} is considered insignificant and is indicated as 0. Chlorpromazine and reserpine as reference compounds produced CNS depression at 5 and 2 mg/kg, respectively, under these conditions. [f] Up to 50% decrease is indicated at 0, 50–60% as +, 60–70% as ++, 70–80% as +++, and 80–90% as ++++. [g] Reversal lasting for not less than 30 min after administration of the drug with 10.0 mg/kg is indicated as +, expressed as follows: fall in blood pressure by 5% is indicated as ±, by 5–15% as +, by 15–25% as ++, by 25–40% as +++ and 40% or more as ++++. [i] None of the compds tested for hypotensive activity showed antihistaminic or anticholenergic activity when tested *in vivo*. [j] Produced 60% potentiation of barbital hypnosis at 0.1 of LD_{50} dose. [k] Produced hyperactivity at 50 mg/kg. [l] Produced mild analgetic effect at 100 mg/kg. [m] Produced 60% potentiation of barbital hypnosis at 100 mg/kg. [n] Showed mild antiinflammatory activity at 100 mg/kg. [o] Loss of muscle tone at 100 mg/kg.

anesthesia. The drugs were administered in doses of 1.0, 2.5, 5.0, and 10.0 mg/kg in suspension in CM-cellulose. The animals were observed for a period of 4–6 hr after the administration of drugs and blood pressure responses and respiration recorded. Only an actual reversal of the blood pressure to epinephrine was selected as the criterion of adrenergic blocking activity.

A few of the compounds (**5**, **7**, **14–20**) showed hypotensive and/or adrenergic blocking activity; **19** produced very specific adrenolytic activity at 2.5 mg/kg lasting for 60 to 120 min.

The reduction of CO group to the CHOH brought about a decrease in CNS depressant activity. Similarly, while the importance of 3,4,5-trimethoxy groups in the Ph ring for the CNS depressant activity is confirmed, they do not seem to contribute significantly toward adrenolytic and hypotensive activity.

Experimental Section

Ir spectra were recorded on Model 137 Perkin-Elmer Infracord while uv spectra were measured on Zeiss PMQ II spectrophotometer. N-Monosubstituted piperazines were prepd by literature methods cited earlier.[1] 3,4,5-Trimethoxybenzaldehyde was obtained from the corresponding benzhydrazide by treatment with ammoniacal ferricyanide.[3]

3,4,5-Trimethoxybenzalacetone. Bruening and Nobles[4] have mentioned the prepn of 3,4,5-trimethoxybenzalacetone but the physical constants were not stated. We have prepared it by the Drake and Allen's method[5] as follows. To a mixt of 3,4,5-trimethoxybenzaldehyde (9.8 g, 0.05 mole) and Ac_2O (22.5 ml, 0.3 mole) was added gradually 10% NaOH (2 ml, 0.005 mole). The flask was stoppered, shaken for 4 hr, and extd 3 times with 50-ml portions of C_6H_6. After drying (Na_2SO_4), C_6H_6 was removed under reduced pressure and the residue crystd (*n*-C_6H_{14}), mp 88° (softens at 80°), yield 5.28 g (44%). *Anal.* ($C_{13}H_{16}O_4$) C, H.

N^1-[2-(3,4,5-Trimethoxycinnamoyl)ethyl]-N^4-(*m*-methylbenzyl)piperazine Dihydrochloride. To a soln of 2.63 g (0.01 mole) of *N*-(*m*-methylbenzyl)piperazine dihydrochloride in 50 ml of EtOH, 3 ml (approx 0.03 mole) of aq CH_2O (37–41%) and 2.6 g (0.011 mole) of 3,4,5-trimethoxybenzalacetone were added and the mixt was refluxed for 7 hr. Addl CH_2O (3 ml) was added and the refluxing contd for a further 7 hr. The product sepg on concn to one-third vol and cooling was collected and crystd (EtOH). Other Mannich bases were prepd similarly.

N^1-[2-(3-Hydroxy-3,4,5-trimethoxycinnamyl)ethyl]-N^4-(*p*-fluorophenyl)piperazine. A soln of 1.93 g (0.0045 mole) of N^1-[3,4,5-trimethoxycinnamoyl)ethyl]-N^4-(*p*-fluorophenyl)piperazine in 75 ml of MeOH was made alk to pH 10 with 50% NaOH and cooled to 0°. $NaBH_4$ (0.3 g) was added with stirring over a period of 15 min and the mixt stirred for addnl 2 hr at room temp. It was then cooled to 5° and acidified to pH 2 with concd HCl. After stirring for 15 min the pH was again adjusted to 10 with 50% NaOH. The MeOH was removed and the residue dild with about 75 ml of H_2O and extd with $CHCl_3$. The ext was dried (Na_2SO_4), and the $CHCl_3$ was removed under reduced pressure. The oily residue obtd was taken up in Et_2O and HCl salt was prepd by the usual method. Other OH compds were prepd by the same method.

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Heterocycles. 5. Oxazole *N*-Oxides[1]

P. M. Weintraub*

Hess & Clark, Division of Richardson-Merrell, Ashland, Ohio 44805.
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The growing body of biological data on aromatic *N*-oxides[2] prompted us to synthesize some oxazole *N*-oxides. These compounds were made from α-oximino ketones and aldehydes.[3] Surveying the literature, we found only trisubstituted derivates had been prepared using substituted benzaldehydes as the aldehyde component. We wished to extend the reaction to aliphatic aldehydes, to α-ketoaldoximes, and to ascertain the biological activity of the resulting compounds. Our results are summarized in Table I.

We found aliphatic aldehydes such as phenylacetaldehyde, CH_2O, and propionaldehyde give oxazole *N*-oxides, for example, **9**, **10**, and **14**. However, Ph groups at C_4 and C_5 seem necessary substituents since phenylacetaldehyde, 2,2-dimethylpropionaldehyde, and 1-methyl-1-formyl-3-cyclohexene, did not give adducts with 2,3-butanedione monoxime. Phenylacetaldehyde and heptaldehyde did not give adducts with α-oximinopropiophenone, and, surprisingly, propionaldehyde did not give an adduct with benzil *anti*-monoxime.

Three 2,5-disubstituted oxazole oxides were prepared using α-oximinoacetophenone with 3- and 4-nitrobenzaldehyde or benzaldehyde to give **15**, **12**, and **16**, respectively. Formaldehyde and benzil *anti*-monoxime readily gave the 4,5-disubstituted derivative **10**.

Several heterocyclic aldehydes were employed in this reaction to give a wider range of derivatives for biological evaluation, *e.g.*, **2**,**3**, **4**, and **13**. For some reason amine bases such as pyridine-2-carboxaldehyde, *N*-methylpyrrole-2-carboxaldehyde, and 2-formyl-3-methylquinoxaline did not undergo this reaction, while 4-dimethylaminobenzaldehyde gave **8** without incident.

Biological Evaluation. The compounds were screened against *Eimeria acervulina*, *E. tenella*, and *Salmonella typhimurium* in chickens; *Histomonas meleagridis* and *Pasteurella multocida* in turkeys; and Asian influenza, *Escherichia coli*, *Staphococcus aureus*, and *Salmonella choleraesuis* in mice. Only **2** showed any activity being active against *S. choleraesuis*, *P. multocida*, *S. aureus*, *S. typhimurium*, *E. coli*, and *H. meleagridis*. This activity can be accounted for by the nitrofuryl portion of the molecule.

Experimental Section†

General Procedure. A stream of HCl gas was bubbled into a soln of aldehyde (0.1 mole) and oximino ketone (0.11 mole) in AcOH (20 ml) for 2 hr. The reaction mixt (sometimes solidified) was poured into a large vol of Et_2O. An oil separated which generally solidified on stirring. The solvent was decanted and the residue crystallized to give an oxazole *N*-oxide hydrochloride. The free base was obtained by dissolving the crude hydrochloride

*Address correspondence to Merrell National Laboratories, Division of Richardson-Merrell, Inc., Cincinnati, Ohio 45215.

†All melting points were determined in open capillary tubes on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Ir spectra were recorded on a Beckman IR-5 or IR-8 spectrophotometer (KBr or pressed smears of neat liquid). Pmr spectra were run on a Varian H60 (s = singlet, d = doublet, t = triplet, m = multiplet, v br = very broad) in $CDCl_3$ (unless otherwise stated) (Me_4Si). Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. The standard drying agent used was $MgSO_4$ and solvents were removed on a rotary evaporator.