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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References

(1) (a) R. B. Petigara, C. V. Deliwala, S. S. Mandrekar, and U. K. Sheth, *J. Med. Chem.*, 11, 332 (1968); (b) R. B. Petigara, C. V. Deliwala, S. S. Mandrekar, N. K. Dadkar, and U. K. Sheth, *ibid.*, 12, 865 (1969).
(2) (a) R. C. Fuson, *Chem. Rev.*, 16, 1 (1935); (b) J. H. Burkhalter and S. H. Johnson, Jr., *J. Amer. Chem. Soc.*, 73, 4835 (1951); (c) W. L. Nobles and J. H. Burkhalter, *J. Amer. Pharm. Ass. Sci. Ed.*, 47, 86 (1958).
(3) L. Kalb and O. Gross, *Ber.*, **59B**, 729 (1926).
(4) C. H. Bruening and W. L. Nobles, *J. Pharm. Sci.*, 54, 925 (1965).
(5) N. L. Drake and P. Allen, Jr., "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1941, p 69.

Heterocycles. 5. Oxazole N-Oxides[1]

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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

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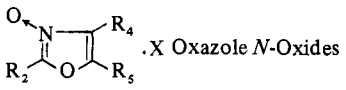
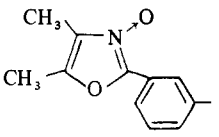
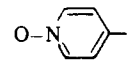
†All melting points were determined in open capillary tubes on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Ir spectra were recorded on a Beckman IR-5 or IR-8 spectrophotometer (KBr or pressed smears of neat liquid). Pmr spectra were run on a Varian H60 (s = singlet, d = doublet, 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.

Table I.



.X Oxazole *N*-Oxides

Compd	R_2	R_4	R_5	X	Mp, °C	Formula[a]	Pmr, δ
1	C_6H_5	CH_3	CH_3	$4H_2O$	61-62[b]	$C_{11}H_{19}NO_6$	2.10(s,3), 2.35(s, 3), 3.52(s,6, shifts to 3.97 on addn of D_2O), 7.42-7.70(m, 3), 8.30-8.53(m,2)[g]
2	5-NO_2-2-C_4H_2O	CH_3	CH_3		162-163	$C_9H_8N_2O_5$	2.24(s,3), 2.48(s,3), 7.55(d,1,J = 4 Hz), 7.77(d,1,J = 4 Hz)[f]
3	5-NO_2-2-C_4H_2OCH=CH	CH_3	CH_3		197-198 dec	$C_{11}H_{10}N_2O_5$	2.18(s,3), 2.35(s,3), 6.70(d,1,J = 4 Hz), 7.18 (d,1,J = 16.25 Hz), 7.37(d,1,J = 4 Hz), 7.95(d,1,J = 16.25 Hz)[f]
4	2-C_4H_3S	CH_3	CH_3		135-137	$C_9H_9NO_2S$	2.20(s,3), 2.33(s,3), 7.11,7.18(pr d,1,J's = 5 Hz), 7.50(AMXq,1,J_{am} = 5 Hz, J_{ax} = 1.25 Hz), 7.79(AMXq,1,J_{am} = 5 Hz,J_{ax} = 1.25 Hz)[f]
5	C_6H_5	$CO_2C_2H_5$	CH_3	HCl	93-95[c]	$C_{13}H_{14}NO_4Cl$	1.30(t,3,J = 7 Hz), 2.52(s,3), 4.37(q,2,J = 7 Hz), 7.27-7.67(m,3), 7.73-8.00(m,2), 8.10(br s,1, disappears on addn of D_2O)[f]
6	3-$NO_2C_6H_4$	CH_3	CH_3		166-167[d]	$C_{11}H_{10}N_2O_4$	2.25(s,3), 2.47(s,3), 7.70(t,1,J = 8 Hz), 8.33 (d,1,J = 4 Hz), 8.93(d,1,J = 4 Hz), 9.27(s,1)[f]
7		CH_3	CH_3	$0.5H_2O$	211 dec	$C_{16}H_{17}N_2O_{4.5}$	2.48, 2.62(pr s,3), 8.65(s,1)[h]
8	4-$(CH_3)_2NC_6H_4$	CH_3	CH_3	H_2O	190-191 dec	$C_{13}H_{18}N_2O_3$	2.23,2.33(pr s,6), 3.07(s,6), 6.76(d,2,J = 9 Hz), 8.28(d,2,J = 9 Hz)[f]
9	$C_6H_5CH_2$	C_6H_5	C_6H_5	HCl	128	$C_{22}H_{18}NO_2Cl$	4.78(s,2), 7.22-7.88(m,15), 14.43(s,1,disappeared on addn of D_2O) peak at 4.78 splits to 4.63(s,0.35) and 5.27 (s,1.53)[f]
10	H	C_6H_5	C_6H_5	HCl	130-131 dec	$C_{15}H_{12}NO_2Cl$	7.55, 7.63(pr s,10), 9.75(s,1)[h,i]
11	$C_6H_5C_6H_4$	CH_3	C_6H_5		161-163	$C_{22}H_{17}NO_2$[k]	2.51(s,3), 7.28-7.88(m,12), 8.63(½ABq, 2,J = 9 Hz)[f]
	$C_6H_5C_6H_4$	CH_3	C_6H_5	HCl	190-193 dec	$C_{22}H_{18}NO_2Cl$[l]	2.72(s,3), 7.38-7.95(m + ½ABq, 12.7,J = 9 Hz), 8.48(½ABq, 2,J = 9 Hz)[h]
12	4-$NO_2C_6H_4$	H	C_6H_5		152, 184-186[e]	$C_{15}H_{10}N_2O_4$	7.50-8.07(m, 5), 8.30(s,1),8.47-8.92(m,4)[h]
13		CH_3	CH_3	HCl	210 dec	$C_{10}H_{11}N_2O_3Cl$	2.33(s,3), 2.60(s,3), 5.07(s,2), 8.66 + 8.70(d + s with sidebands, 4, J = 1 Hz)[j]
14	C_2H_5	$C_6H_5CH_2$	C_6H_5	HCl	122-123	$C_{18}H_{18}NO_2Cl$	1.53(t,3,J = 7.5 Hz), 3.40(q,2,J = 7.5 Hz), 4.40(s,2), 7.32(s,5), 7.57(s,5), 13.88(s,1, disappears on addn of D_2O)[f]
15	3-$NO_2C_6H_4$	H	C_6H_5		130, 168-171[e]	$C_{15}H_{10}N_2O_4$	7.50-8.23(m,6), 823(s,1), 8.60(d,1,J = 8 Hz), 8.87(d,1,J = 8 Hz), 9.25(s,1)
	3-$NO_2C_6H_4$	H	C_6H_5	HCl	165-166 dec	$C_{15}H_{11}N_2O_4Cl$	7.50-8.20(m,6), 8.30(s,1), 8.67(d,1,J = 8 Hz), 8.87(d,1,J = 8 Hz), 9.33(s,1)[h]
16	C_6H_5	H	C_6H_5	HCl	153-154	$C_{15}H_{12}NO_2Cl$	7.53-7.87(m,7), 7.92-8.15(m,2), 8.42-8.65(m,2), 8.92(s,1), 10.27(s,2)[g]

[a] All new compds were analyzed for C, H, and N and results are within ±0.4%. [b] Lit. mp 58-62. [c] Mp varies with rate of heating. [d] Lit mp 159-160 dec. [e] Double mp. [f] Run in $CDCl_3$. [g] Run in DMSO-d_6. [h] Run in CF_3CO_2H-$CDCl_3$. [i] The sample seems to decomp in DMSO-d_6 as evidenced by a change in spectrum; *e.g.*, immediate run 7.3-8.2 (m), 11.13 (s), 13.57 (broad m); on standing overnight 7.3-8.3 nature of m has changed), 13.57 (broad m). [j] Run in D_2O. [k] Calcd C, 80.71; found C, 81.27. [l] Calcd C, 72.62; found C, 71.28.

in H_2O and making basic (to about pH 8) with solid $NaHCO_3$, followed by standard work-up. See Table I for the results.

References

(1) P. M. Weintraub, *Chem. Ind. (London)*, 1296 (1970) (part 4).

(2) E. Ochiai, "Aromatic Amine Oxides," Elsevier Publishing Company, New York, N.Y., 1967, pp 424-442; M. H. Bickel, *Pharm. Rev.*, **21**, 325 (1969).

(3) (a) D. Diels and D. Riley, *Ber.*, 48, 897 (1915); (b) W. Dilthey and J. Friedrichsen, *J. Prakt. Chem.*, 127, 292 (1930); (c) J. W. Cornforth and R. H. Cornforth, *J. Chem. Soc.*, 96 (1947); (d) C. M. Selwitz and A. I. Kosak, *J. Amer. Chem. Soc.*, 77, 5370 (1955); (e) K. Bodendorf and H. Towliati, *Arch. Pharm. (Weinheim)*, 298, 293 (1965).

Antiviral Agents. 2. Analogs of 2-(α-Hydroxybenzyl)benzimidazole

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A large number of analogs of the antiviral agent, 2-(α-hydroxybenzyl)benzimidazole (**HBB**), have been synthesized and evaluated for their effects on various viruses. One of the more recent publications[1] reported on the antiviral

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