kynuramine[16,17] and 5-hydroxytryptamine.[18] In the case of kynuramine, the appearance of 4-hydroxyquinoline was measured, and in the case of 5-hydroxytryptamine, its disappearance. The endogenous 5-HT content of the brain was also measured, according to the method of Anden and Magnusson.[18]

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Antihypertensive and Monoamine Oxidase Inhibitory Activity of Some Derivatives of 3-Formyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine

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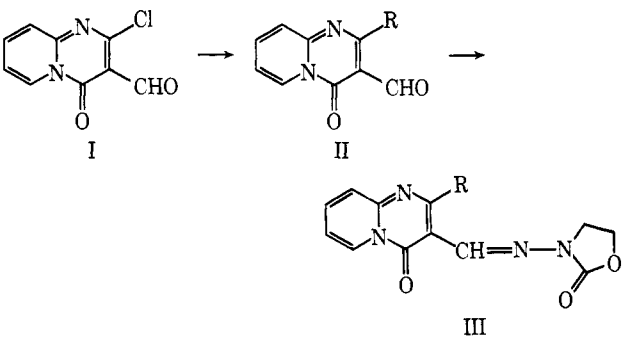
The antihypertensive and MAO-inhibitory activity of a variety of compounds derived from 2-chloro-3-formyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine are described. The most potent among these compds were the 3-amino-2-oxazolidinone derivatives of 2-piperidino-3-formyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine and its tetrahydro and hexahydro derivatives. The correlation between the MAO inhibition and antihypertensive response was not very good. The toxicity of the compds was very low as compared to other MAO inhibitors.

It has been previously reported[1] that 3-amino-2-oxazolidinone derivatives of some azacycloalkyl-substituted nitrobenzaldehydes showed marked antihypertensive and MAO-inhibitory activity. Compds wherein the NO_2 was replaced by NH_2 failed to show activity. Furazolidinone which is also known to produce slow and gradual reduction in arterial blood pressure, is also derived from a nitroheterocyclic aldehyde, namely, 5-nitrofurfural.[2]

We were interested in preparing a few derivatives of 2-chloro-3-formyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine[3] for biological evaluation. Treatment of this compd with secondary amines gave the corresponding ortho-substituted amino compds which on condensation with 3-amino-2-oxazolidinone showed pronounced antihypertensive and MAO-inhibitory activity. The structural pattern required for eliciting optimum antihypertensive and MAO-inhibiting properties in pyrido[1,2-*a*]pyrimidine series was found to be different from the one found in the series described earlier.[1] The toxicity of these compds was also found to be very low.

Chemistry.—2-Chloro-3-formyl-4-oxo-4*H*-pyrido-[1,2-*a*]pyrimidine (I)[3] was treated with an excess of primary and secondary amines to give the corresponding secondary and tertiary amino substituted aldehydes IIa–IIg which on condensation with 3-amino-2-oxazolidinone gave compds IIIa–IIIg. Direct condensation of I with the above reagent gave IIIh. Controlled catalytic hydrogenation of IIIa and IIIb with Pd/C until 2 moles of H_2 was absorbed, gave IVa and IVb, resp. Hydrogenation of IIIa using 10% Pd/C until 3 moles of H_2 was absorbed gave Va. Treatment of the latter with ethyl isocyanate gave Vb. Reaction of IIa and IIc with amioguanidine hydrogen carbonate in EtOH containing AcOH gave VIa and VIb, resp. Condensation of IIa with *N*-aminopiperidine and 4-amino-1,2,4-triazole gave VIIa and VIIb, resp.



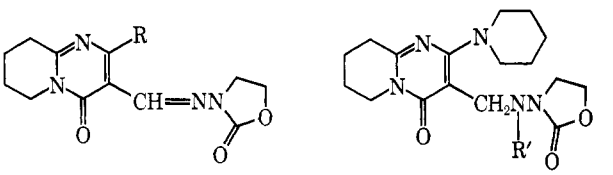
I II III

a, R = N⟨ ⟩

b, R = N⟨ ⟩

c, R = N⟨ ⟩NCH$_3$

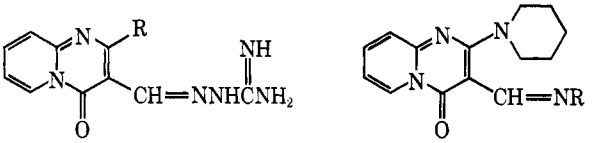
d, R = NEt$_2$
e, R = N(CH$_2$CH=CH$_2$)$_2$
f, R = NHCH$_2$CH$_2$N(CH$_3$)$_2$
g, R = NHCH$_3$
h, R = Cl



IVa, R = N⟨ ⟩

b, R = N⟨ ⟩

Va, R′ = H
b, R = CONHC$_2$H$_5$



VIa, R = N⟨ ⟩

b, R = N⟨ ⟩NCH$_3$

VIIa, R = N⟨ ⟩

b, R = N⟨N=N⟩

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TABLE I

ANTIHYPERTENSIVE AND MAO-INHIBITORY ACTIVITY OF SOME DERIVATIVES OF 3-FORMYL-4-OXO-4*H*-PYRIDO[1,2-*a*]PYRIMIDINE

Compound	Hypotensive act.[a] Cat	Dog	Antihypertensive effect	MAO-inhibition,[b] % Kynuramine	5-HT	LD_{50}, mg/kg po mice	Remarks
IIIa	0	0	−96 (100)	88	100	1820 ± 73	Orally absorbed epinephrine effect potentiated on blood pressure
			−49 (30)	51	80		
IIIb	−	0	−56 (30)	53		>3000	Orally absorbed epinephrine effect potentiated on blood pressure
				32		>1000 (rat)	
IIIc	−	+	−55 (100)	21	67	>3000	Orally absorbed epinephrine reversed in cat
			−13 (30)				
IIId	−	+	−67 (30)	84	99	1820 ± 304	Orally absorbed epinephrine effect potentiated on blood pressure
				71	81	>100 (rat)	
IIIe	0	0		63	70		
IIIf	0	0	0 (30)	0	18		
IIIg	0	−	−28 (30)	0			
IIIh	0	−	−10 (30)	66	73		
IVa	−	0	−75 (30)	91	100	1567 ± 131	Orally absorbed epinephrine effect potentiated on blood pressure
				82		>1000 (rat)	
IVb	−	0		93			Epinephrine effect potentiated on blood pressure
Va	−	0	−98 (30)	88			
Vb	−	0	0 (30)	0			
VIa	0	−	−27 (30)	0			
VIb	0	++	0 (100)	0	0		
VIIa	0	−	−13 (30)	0	0		
VIIb	−	0	0 (100)	0			
Pargyline	⊕	−	−25 (30 mg/kg po)	73	64	680	
			−47 (100 mg/kg po)	53	50	300 (rat)	

[a] By hypotensive activity is meant the fall of blood pressure was more than 15 mm and lasted for more than 15 min. (+) Activity at 9 mg/kg iv; (++) activity at 3 mg/kg iv; (0) no activity; (⊕) no activity up to 15 mg/kg iv. [b] For MAO-inhibition studies the compds were given at 100 mg/kg po and the animals were killed 16 hr later. Wherever there are 2 inhibitions reported in the table, the second one refers to 50 mg/kg po.

Results and Discussion

Most of the compds reported in this paper did not show any marked hypotensive activity in anesthetized animals up to 9 mg/kg iv. Pargyline did not produce any measurable fall of blood pressure in anesthetized animals when given at a dose of 15 mg/kg iv (Table I). Despite the fact that most of these compds were inactive in lowering blood pressure in acute experiments, they were very potent antihypertensives in renal hypertensive rats. Many of the compds were 2–4 times more potent than pargyline as regards their antihypertensive activity. The fall of blood pressure in renal hypertensive rats ranged from 30 to 100 mm at 30 to 100 mg/kg po given for 10 days.

Like pargyline many of the compds produced irreversible inhibition of MAO of the rat tissue (brain and liver homogenate). Some of them were more potent than pargyline. These compds exhibited more inhibitory activity toward hepatic than cerebral MAO (details will be published elsewhere). Out of this whole series, 5 compds, namely, IIIa, IIIb, IIId, IVa, and Va, were very active as regards both properties (MAO inhibition as well as antihypertensive activity).

Despite the fact that 4 compds (IIIa, IIId, and IVa) were very potent MAO inhibitors *in vivo* they were not very effective *in vitro* up to a dose of 1×10^{-4} *M* (using 5-hydroxytryptamine as a substrate). In the case of IIIa, however, some inhibition of MAO was seen in both liver and brain homogenates with 1×10^{-4} *M* (approximately 30%) (see ref 1).

Since the antihypertensive effects of these compds were seen on prolonged treatment, IIIa and pargyline were given to dogs at 30 mg/kg po for 8 days. The blood pressure, ECG, heart rate, and response to epinephrine and norepinephrine (NE) were investigated before and after treatment with IIIa. Unlike pargyline, IIIa on chronic feeding produced a 20-mm fall of blood pressure. The response to epinephrine and NE was potentiated in these dogs. The heart rate was slightly reduced. In the case of pargyline, however, no significant effect was observed on any parameters studied.

Like many other MAO inhibitors, IIIa showed weak and transient ganglionic blocking activity as measured by the inhibition of the contraction of cat nictitating membrane following cervical sympathetic nerve stimulation (48% inhibition of preganglionic and 13% inhibition of postganglionic fibres at 3 mg/kg iv). There was no significant effect on the inotropic and chronotropic effect of the isolated cat heart up to a dose of 1 mg. However, the coronary flow was increased significantly.

The 5 compds listed above (excluding Va) depicted typical effects of MAO inhibitors in animals. They potentiated the effects of epinephrine, NE, and tyramine on the blood pressure, antagonized reserpine-induced hypothermia (24–40% at 25 mg/kg po) and gave a positive dopa test (++++ at 25 mg/kg po). They all significantly increased the levels of brain NE and 5-hydroxytryptamine in the rat brain.

In general, the aminoxazolidinones derived from

TABLE II

Compd	Method	Mp, °C	Recrystn solvent	Yield, %	Formula[a]
IIa	A	157	EtOH	59	$C_{14}H_{15}N_3O_2$
IIIa	B	231	MeOH	62	$C_{17}H_{19}N_5O_3$
IIIb	A, B	120	*i*-PrOH	51	$C_{18}H_{21}N_5O_3 \cdot H_2O$
IIIc	A, B	260	MeOH	43	$C_{17}H_{20}N_6O_3 \cdot HCl \cdot H_2O$
IIId	A, B	135	*i*-PrOH	46	$C_{16}H_{19}N_5O_3 \cdot H_2O$
IIIe	A, B	102	CH_2Cl_2	38	$C_{18}H_{19}N_5O_3$
IIIf	A, B	220	MeOH	32	$C_{16}H_{20}N_6O_3$
IIIg	A, B	312	MeOH	43	$C_{13}H_{13}N_5O_3$
IIIh	B	239	MeOH	65	$C_{12}H_9ClN_4O_3$
IVa	C	190	*i*-PrOH	67	$C_{17}H_{22}N_5O_3$
IVb	C	150	CH_2Cl_2–Et_2O	59	$C_{18}H_{25}N_5O_3$
Va	C	132	*i*-PrOH	47	$C_{17}H_{25}N_5O_3$
Vb	B	218	CH_2Cl_2–Et_2O	42	$C_{20}H_{30}N_6O_4$
VIa	D	217	EtOH	44	$C_{15}H_{19}N_7O$
VIb	D	220	MeOH	37	$C_{15}H_{20}N_8O$
VIIa	B	217	MeOH	69	$C_{19}H_{25}N_5O \cdot HCl \cdot 0.5H_2O$
VIIb	B	268	MeOH	61	$C_{16}H_{17}N_7O$

[a] All compds were analyzed for C, H, N.

products obtained by treating chloraldehyde I with cyclic and acyclic secondary amines showed high levels of antihypertensive and MAO-inhibiting activity. This is illustrated in the case of IIIa, IIIb, and IIId which contain piperidino, hexahydroazepino, and Et_2N groups, resp, as the tertiary amino residue ortho to the aminoxazolidinone group. IIIc, the *N*-methylpiperazino analog, showed an activity of a lower order. IIIf, the $Me_2NCH_2CH_2N$ analog, showed neither significant antihypertensive nor MAO-inhibiting properties. IIIg, the MeNH analog, showed some antihypertensive effect with no MAO inhibition. IIIh, the aminoxazolidinone derivative in which Cl occupies the ortho position, showed MAO-inhibiting properties but was devoid of antihypertensive activity. The tetrahydro derivative of IIIa (IVa) showed antihypertensive activity as well as MAO-inhibitory activity. The hexahydro derivative of IIIa (Va), obtained by hydrogenation under conditions in which azomethine double bond is also reduced, showed a high degree of antihypertensive and MAO-inhibitory activity. The urea derivative Vb, derived from Va, showed neither antihypertensive nor MAO-inhibitory activity. Guanyl hydrazones VIa and VIb were inactive. Condensation of IIa with other *N*-aminoheterocycles gave inactive products as illustrated by VIIa and VIIb.

In general, many of the compds in this series which showed antihypertensive activity did inhibit MAO *in vivo*. There were however a few which showed either antihypertensive activity or MAO inhibition (VIa, IIIh). For a discussion of this discrepancy see ref 1.

Experimental Section†

2-Chloro-3-formyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine (I), mp 226–227°, was prepd in 76% yield, essentially according to the method described by earlier workers, lit.[3] mp 224–226°.

General Methods. A. Synthesis of IIa–IIg.—The β-chloroaldehyde I (1 mole) was refluxed with the appropriate amine (3 moles) in dioxane for 4 hr. The solvent was removed *in vacuo*, the residue was treated with dil $NaHCO_3$ and extd with CH_2Cl_2, and the ext was dried (Na_2SO_4). Removal of solvent gave a residue which was crystd from the appropriate solvent.

B. Condensation of 2-Substituted Pyrido[1,2-*a*]pyrimidines with 3-Amino-2-oxazolidinone and Other *N*-Aminoheterocycles.—The aldehyde (1 mole) was refluxed with the appropriate *N*-aminoheterocycle (1.1 moles) in EtOH contg concd HCl (2 drops) for 3 hr. The prod obtd on cooling was filtered, washed with dil $NaHCO_3$, and worked up in the usual way. In some cases the corresponding hydrochlorides were prepd using a satd soln of HCl in *i*-PrOH.

C. Synthesis of Perhydro Derivatives.—Tetrahydro derivatives IVa and IVb were prepd the following way. Compds IIa and IIb were mixed with Pd/C (5%) in MeOH and shaken in a hydrogenation apparatus until 2 moles of H_2 was absorbed. Filtration of the catalyst and evapn of the solvent gave IVa and IVb, resp. The hexahydro deriv Va was prepd using Pd/C (10%) and carrying out the hydrogenation until 3 moles of H_2 was absorbed.

D. Guanyl Hydrazones VIa and VIb.—The aldehyde (1 mole) was refluxed with aminoguanidine hydrogen carbonate (1.1 moles) in EtOH contg AcOH (3 drops) for 4 hr. Evapn of the solvent and work-up in the usual way gave the desired compd.

For details of pharmacological experiments see ref 1.

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† Melting points were taken in soft glass capillary tubes and are uncor.