N-Isopropyl Derivatives of Dopamine and 5,6-Dihydroxy-2-aminotetralin

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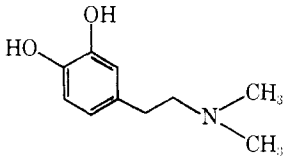
Secondary and tertiary amino homologs of the title compounds have been prepared, bearing an N-isopropyl group. In peripheral evaluation, certain members of the series exhibited β-adrenergic agonist effects of lower activity than isoproterenol. N-Methyl-N-isopropyl-5,6-dihydroxytetralin exhibited marked properties consistent with its being an α agonist, and it is concluded that introduction of considerable bulk about the nitrogen of a catecholamine does not a priori destroy α-agonist effects. The compounds qualitatively paralleled the effects of dopamine in assays based upon direct intrastriatal administration in rats, although they were less potent than dopamine.

There are conflicting reports on the nature of the changes in receptor agonist properties which result from the introduction of bulk about the nitrogen of catecholamine-like agents. In a prior communication[1] we have described the long-lasting, direct adrenergic α-receptor stimulating action of N,N-dimethyldopamine (1) and *dl*-1,2,3,4-tetrahydro-2-dimethylamino-5,6-dihydroxynaphthalene (2). These tertiary amines were more active than



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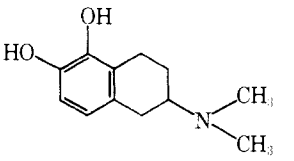
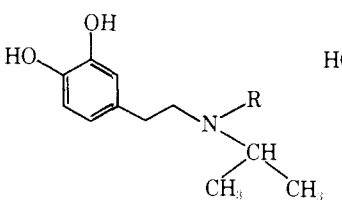


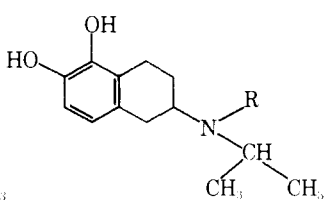
2

their primary and secondary amino congeners. These results contradict the proposal of Ariëns and Simonis[2] and of Pruss et al.[3] that introduction of bulk about the nitrogen of an adrenergic α agonist (as exemplified by norepinephrine–epinephrine–isoproterenol) decreases affinity for the α receptor and increases affinity for the β receptor. In particular, N-methylepinephrine was shown to be considerably less active an α agonist than epinephrine.[3] However, these studies have utilized only a limited number of compounds with N-substitution and, although there are reports of the preparation of a number of higher N-*n*-alkyl homologs of **2**, the agonist activity of these agents at the catecholamine receptor sites was not evaluated.[4]

The present studies were designed to extend these investigations and to resolve some of the anomalous findings. The N-isopropyl derivatives **3–6** were prepared, thus extending the series of N,N-dialkylated 2-amino-5,6-dihydroxytetralins begun in this laboratory[5] and continued by the McDermed group.[4]



3, R = H
4, R = Me



5, R = H
6, R = Me

Compound **3** was originally prepared by Breitschneider[6] by a tedious route beginning with isoproterenol. In the present work, **3** and **4** were prepared by catalytic alkylation of 3,4-dimethoxy-β-phenethylamine and of N-isopropyl-3,4-dimethoxy-β-phenethylamine, respectively. The tetralin systems **5** and **6** were prepared by reductive amination of 5,6-dimethoxy-β-tetralone by a modification of the method of Borch et al.[7] Spectral (ir and NMR) data on all compounds prepared were consistent with the proposed structures.

The ability of the compounds to stimulate catecholaminergic receptor sites was determined in pharmacological experiments designed to assess activity at the peripheral adrenergic α and β receptors and at central (neostriatal) dopaminergic receptor sites using tests established by Costall and colleagues.[8,9] Herein are presented results of a study of specific asymmetric behavior and hyperactive–stereotyped behavior induced by the direct stimulation of neostriatal dopaminergic mechanisms in the rat and preliminary data on certain peripheral actions in the dog.

Results

Cannulae locations, determined in every fifth animal, were within the area of investigation and were indistinguishable from those reported by Costall and Naylor.[8] After peripheral saline pretreatment, the unilateral insertion of an injection cannula or unilateral administration of 1 or 2 μl of solvent or saline into the caudate–putamen caused a rat to circle to the contralateral side. The duration of this "injection behavior" never exceeded 90 sec. Following haloperidol pretreatment, the "injection behavior" was more intense, but its duration never exceeded 2–5 min. The behavior was considered to result from the physical disruption of the tissue and, as such, to be nonspecific. The results reported in Table I refer to motor asymmetries which developed after the period of injection artifact. Dopamine and compounds **3** and **5** were shown to be potent agents to induce contralateral asymmetries, but further N-methyl substitution (**4, 6**) markedly reduced this activity (see Table I). The bilateral injection of **1** or 2 μl of saline or solvent into the striatum of the nialamide-treated rats frequently induced an immediate but brief period of injection artifact (2–7 min), characterized by hyperactivity and occasional chewing. Again, the results of Table I refer to the behavior after this period of injection artifact. In this model, all compounds (**3–6**) were considerably less active than dopamine but, again, compounds **4** and **6** were less active than **3** and **5** (Table I).

Peripheral Effects. The compounds were bioassayed in dogs with bilateral vagotomy and anesthetized with barbital sodium. Blood pressure responses were measured from

Table I. Contralateral Asymmetric Behavior and Stereotyped-Hyperactive Behavior Caused by the Intrastriatal Injection of Dopamine and Analogs

		Contralateral asymmetric behavior								Hyperactive–stereotyped behavior			
		Solvent				Haloperidol				Nialamide			
Intrastriatal drug	Dose, μg/μl	No. of rats responding	Latency of onset, min	Intensity[a] (scored)	Duration, hr	No. of rats responding	Latency of onset, min	Intensity[a] (scored)	Duration, hr	No. of rats responding	Latency of onset, min	Intensity[a] (scored)	Duration, hr
Dopamine	100/1	6/6	18	+	2+	6/6		++		6/6	70	+++	
	50/1	0/4		0		6/6		++		6/6	65	+++	
	25/1					6/6	1M[b]	++	2+	6/6	88	+++	2+
	12.5/1					6/6		+		6/6	92	+(+)	
	6.25/1					2/6		+		3/8	121	(+)	
N-Isopropyldopamine (**3**)	100/1	6/6	1M	+	2+	6/6		++	2+	6/6	122	+	
	50/1	0/4		0		6/6		++	2+	6/6	96	+	2+
	25/1					6/6	1M	++	1.9	4/6	118	+	
	12.5/1					5/6		+	0.5				
	6.25/1					4/4		0					
N-Methyl-*N*-isopropyl-2-(3,4-dihydroxyphenyl)-ethylamine (**4**)	100/1	2/6	1M	+	0.4	4/6	1M	+	1.8	2/6	96	+	
	50/1	0/4		0		0/4		0		2/6	109	+	2+
	25/1									0/6		0	
2-(*N*-Isopropyl)amino-5,6-dihydroxy-1,2,3,4-tetrahydronaphthalene (**5**)	100/2	5/6	46	+	2+	6/6	22	++		5/6	84	+	
	50/1	4/6	80	+	1.2	6/6	1M	++	2+	6/6	92	+	2+
	25/1	0/6		0		6/6	1M	+		6/6	112	+	
	12.5/1					4/6	1M	+		3/6	100	+	
2-(*N*-Methyl-*N*-isopropyl)-amino-5,6-dihydroxy-1,2,3,4-tetrahydronaphthalene (**6**)	100/2	0/4		0		6/6	47	++		6/6	65	+	
	50/1	0/4		0		2/6	38	+	2+	6/6	57	+	2+
	25/1					0/6		0		5/6	98	+	
										0/6		0	

[a] See methods for assessment of intensity. [b] Immediate onset.

Table II. Biological Effects of β Agonists

Compd	Relative potencies (95% C.I.) Diastolic pressure decrease	Heart rate increase
Isoproterenol	1.0[a]	1.0
5	0.019 (0.006–0.05)	0.01 (0.005–0.03)
3	0.001[b]	0.001[b]
M-8[c]	0.08 (0.05–0.3)	0.006[d]

[a]Minimal dose for bioassay was 0.05 μg/kg. [b]Estimated maximum relative potencies from dose-response curves. [c]5,6-Dihydroxy-2-methylaminotetralin hydrobromide.[5] [d]Estimated from response to 1 μg/kg; 2 and 4 μg/kg produced no additional increase.

the right femoral artery using a P-23AA Statham transducer. Changes in heart rate were monitored using a Beckman cardiotachometer. Recordings of the response were made using a Beckman Type R recorder. Solutions of the compounds were administered into the left femoral vein by rapid injection. The order of compound injection was randomized. Succeeding doses of each compound were increased by 0.3 log intervals. The relative potencies were calculated by a 3 × 3 parallel line bioassay as outlined by Finney.[11] Compound **4** produced only a relatively weak pressor response (0.002 times as active as epinephrine) and little, if any, action on heart rate. Compounds **3** and **5** were compared to isoproterenol for their ability to lower the diastolic pressure and induce tachycardia. These responses were blocked by propranolol (2 mg/kg). Also included in this assay was 5,6-dihydroxy-2-methylaminotetralin ("M-8"), the secondary amine analog of **2** (see Table II). Compound **6** produced a pressor response in five dogs in doses of 10 μg/kg and higher. Doses less than 10 μg/kg did not produce a depressor response. The dose–response curves for **6** and for epinephrine were nonlinear. The dose levels used for **6** produced a slowing of the heart that appears to be similar in magnitude to that observed for **2**.[12]

A series of experiments was done using anesthetized and bilaterally vagotomized cats. Compounds **4** and **6** showed only pressor effects, which were abolished after phentolamine (5 mg/kg), an α-adrenoceptor blocking agent. Compounds **3** and **5** produced a decrease in blood pressure which was blocked by propranolol (2 mg/kg), a β-adrenoceptor blocking agent. Only M-8 showed both α- and β-adrenergic activity. Small doses of M-8 decreased blood pressure, and this effect was reversed after propranolol; higher doses of M-8 increased blood pressure, and this effect was potentiated after phentolamine. Bretylium tosylate (10 μg/kg) did not alter blood pressure responses to these compounds.

Discussion

Costall and Naylor[8] have found that pretreatment of rats with haloperidol, nialamide, or a combination of the two in the intrastriatal administration assay increased the sensitivity of caudate tissue to the dopamine effect, and these workers have advanced possible explanations for these seemingly paradoxical effects. Using the intrastriatal administration assays, it has been shown that increasing substitution on the nitrogen atom of dopamine reduces dopamine-like activity.[9] Thus, it is not understood why *N*-isopropyldopamine (**3**) with a relatively larger substituent is more active than epinine (*N*-methyldopamine). However, the results obtained using the compounds with *N*,*N*-dialkyl substitution clearly indicate that further increases in bulk about the nitrogen do reduce dopamine-like effectiveness (compare **3** to **4** and **5** to **6**, Table I). These results at a behavioral level are at variance with observations from the snail neurone assay[13] and with a biochemical analysis of dopamine-like activity in the caudate nucleus, for Sheppard and Burghardt[14] have reported that *N*-methyl-*N*-isopropyldopamine (**4**) is 0.018 times as active as dopamine in a rat caudate nucleus adenylate cyclase assay, whereas *N*-isopropyldopamine was completely inert. However, it should be noted that, using cebus monkey caudate adenylate cyclase, *N*-isopropyldopamine shows an efficacy at least as great as that of dopamine.[15]

In peripheral studies, Derouaux[16] has reported that *N*-isopropyldopamine (**3**), in doses of 100–250 μg in the rabbit, produces occasional very slight hypertension and that 500–1000-μg doses cause a marked tendency to hypotension. Lands et al.[17] found that, in the dog, a 730-μg dose caused a marked rise in blood pressure, followed by a fall in 5 of 13 animals. This group noted that "Sympathin-I-mimetic (inhibitory) effects are not prominent with hydroxytyramine derivatives that do not contain the alcoholic OH of norepinephrine". More recently, Tuttle and Mills[18] have demonstrated that *N*-isopropyldopamine produces blood pressure lowering and heart rate increase in the dog, but this compound was much weaker than isoproterenol.

In the present studies, *N*-isopropyl substitution of dopamine analogs and congeners yields two different responses. In dopamine itself, β-receptor agonist properties were seen only with the secondary amine **3** and were very weak. The tertiary amine **4** exhibited only very weak pressor response and was virtually devoid of any cardiac stimulating properties. The aminotetralins **5** and M-8 (Table II) were much more active than **3** as β agonists, but both were much less active than isoproterenol in ability to lower blood pressure and increase heart rate. Compound **5** exhibited only β-receptor activation, while M-8 activated β receptors at lower doses and simultaneously activated α receptors at higher doses. Compound **6** appeared similar in activity to **2**, in its ability to induce pressor responses by activating α receptors, and also in inducing bradycardia (probably by inhibiting the cardioaccelerator nerves innervating cardiac muscle). It thus appears that introduction of some little bulk about the nitrogen of a catecholamine does not a priori destroy α-agonist affects. It may be significant that the tertiary amino and bulky secondary amino α agonists reported thus far do now bear a benzyl OH group and, hence, they are congeners, not of norepinephrine, but rather of dopamine.

Experimental Section

Melting points were determined in open glass capillaries on a Thomas-Hoover Unimelt apparatus and are corrected. Boiling points are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Where analyses are indicated by symbols of the elements, the analytical results were within ±0.4% of the theoretical values.

Pharmacology. Intracerebral Injection Effects. Methods. All experiments utilized Sprague–Dawley (C.F.E.) rats weighing 300–350 g at the time of the operation.

Intracerebral Injection Technique. Stainless steel cannulae (0.65 mm in diameter) were stereotaxically implanted in the brains of rats anesthetized with chloral hydrate (300 mg/kg ip). Cannulae were fixed to the skull using retaining screws and acrylic cement and constructed to allow the administration of drug solution into each hemisphere. Stainless steel stylets (0.3 mm in diameter), extending 1 mm beyond the tip of the guide cannulae, prevented the occlusion of the lumen by blood and tissue. The tips of the guide cannulae were implanted at anterior 8.0, vertical +3.0, and lateral ±3.0;[10] the stainless steel injection units (0.3 mm in diameter) were made to extend 1.5 mm beyond the tips of the guides and thus de-

posit drug at the center of the caudate–putamen complex. Animals were used two occasions only during the second to fourth postoperative weeks. During the injection procedure the rats were manually restrained, the stylet(s) withdrawn, and the injection cannula(e) inserted. Drugs were administered in a volume of 1 or 2 μl over a 5-sec period from an Agla micrometer syringe and the injection cannula(e) remained in position for a further 55 sec to allow deposition of the drug. The stylets were replaced immediately after withdrawal of the injection unit.

Behavioral Observations. Experiments were carried out between 09:00 and 21:00 hr in a sound-proofed, diffusely illuminated room maintained at 21 ± 1°C.

Contralateral Asymmetric Behavior. In experiments to determine the ability of the drug to cause contralateral asymmetric behavior following unilateral intrastriatal application, animals were treated with solvent or with haloperidol (2 mg/kg ip) 30 min before intrastriatal injection. The possible explanations for the effect of haloperidol have been discussed previously.[8] Immediately following the intrastriatal injection, rats were placed in an "open field" and closely observed. Contralateral asymmetries were assessed according to the system: 0 = no asymmetry; + = periodic holding of the head to one side with movements of the body in the same direction when disturbed, able to move straightforward; ++ = head and body held continuously to one side, resistance to manual turning of the body in opposite direction.

Hyperactive–Stereotyped Behavior. This was assessed after the bilateral intrastriatal application of the drug to animals treated 2 hr previously with nialamide (100 mg/kg ip). The rationale behind the use of nialamide has been discussed previously.[9] For observation, animals were placed in individual perspex observation cages measuring 30 × 20 × 15 cm high, and hyperactive–stereotyped behavior was assessed according to the system: 0 = behavior indistinguishable from control rats; (+) = hyperactive exploration of the cage; + = repetitive head and front limb movements, periodic activity; ++ = repetitive head and front limb movements, infrequent biting movements and infrequent periods of activity; +++ = continuous chewing or biting at the shavings, cage, or body.

Drugs. Nialamide (Sigma) was dissolved in a minimum quantity of hydrochloric acid and was made up to volume with distilled water. Haloperidol (Janssen) was dissolved in 1% lactic acid. All doses were calculated as the base and were administered in a volume of 1 ml/kg ip. Dopamine hydrochloride (Koch-Light) and the dopamine analogs **3–6** were prepared in nitrogen-bubbled distilled water containing 0.1% sodium metabisulfite.

***N*-Isopropyl-β-(3,4-dimethoxyphenyl)ethylamine Hydrochloride (7).** 3,4-Dimethoxy-β-phenethylamine (20.0 g, 0.11 mol) and 20.0 g (0.34 mol) of reagent-grade acetone in 100 ml of anhydrous EtOH were hydrogenated in the presence of 1.0 g of Pt black in a Parr shaker at an initial pressure of 55 psig. After 0.5 hr, the calculated amount of H_2 was absorbed. The reaction mixture was filtered; volatiles were removed from the filtrate under reduced pressure (steam bath) and the residue was distilled at 105° (0.005 mm) to afford 21.0 g (85%) of product. This was converted to its HCl salt, mp 197–198° (EtOH–Et_2O). Anal. ($C_{13}H_{22}ClNO_2$) C, H, N.

***N*-Methyl-*N*-isopropyl-β-(3,4-dimethoxyphenyl)ethylamine Hydrochloride (8).** The free base of **7** (7.0 g, 0.031 mol) and 15 ml of 37% aqueous formaldehyde were hydrogenated in the presence of 1.0 g of 10% Pd/C in 100 ml of anhydrous EtOH in a Parr shaker at an initial pressure of 55 psig. After 45 min, the calculated amount of H_2 was absorbed. The reaction mixture was filtered and volatiles were removed from the filtrate under reduced pressure (steam bath). The residue was treated with excess 5% KOH and this mixture was extracted with Et_2O. The volatiles were removed from this extract; the oily residue was taken up in 10% HCl, and this solution was extracted with Et_2O, which was discarded. The aqueous phase was treated with excess KOH and was extracted with Et_2O. The extract was dried ($MgSO_4$) and the Et_2O was removed to leave an oil: bp 106–107° (0.005 mm); yield, 7.0 g (95%). This was converted to its HCl salt, mp 161–162° (EtOH–Et_2O). Anal. ($C_{14}H_{24}ClNO_2$) C, H, N.

1,2,3,4-Tetrahydro-2-isopropylamino-5,6-dimethoxynaphthalene Hydrochloride (9). 1,2,3,4-Tetrahydro-5,6-dimethoxy-2(1*H*)-naphthalene[19] (7.0 g, 0.038 mol) in 45 ml of MeOH was added with stirring to 13.5 g (0.22 mol) of isopropylamine in 45 ml of MeOH and 15 ml of 5 *N* methanolic HCl, and the resulting mixture was cooled under N_2 in an ice bath. Sodium cyanoborohydride (1.52 g, 0.0228 mol) was added to give a purple reaction mixture. Methanolic HCl was added carefully until the purple color changed to yellow brown, and during the course of the reaction, more was added to maintain the yellow-brown color. At the end of 3 hr of stirring at room temperature, the reaction mixture was brought to pH 2 with concentrated HCl. Volatiles were removed under reduced pressure, and the residue was taken up in water. This solution was extracted three times with Et_2O, then was basified with KOH, and extracted with Et_2O. This extract was dried (Na_2SO_4) and filtered, and the filtrate was treated with ethereal HCl. The solid which separated was recrystallized three times from EtOH–Et_2O and once from 2-PrOH–Et_2O to yield 2.1 g (19%) of material, mp 251–252°. Anal. ($C_{15}H_{24}ClNO_2$) C, H, N.

1,2,3,4-Tetrahydro-2-methylisopropylamino-5,6-dimethoxynaphthalene Hydrochloride (10). To 0.43 g (0.0015 mol) of **9** and 1.5 ml of 37% aqueous formaldehyde in 10 ml of MeOH was added 0.13 g (0.0002 mol) of sodium cyanoborohydride. The initially basic solution was neutralized (to pH paper) with 5 *N* methanolic HCl. Additional methanolic HCl was added from time to time to maintain a pH of 5–6 as the mixture was stirred under N_2 for 12 hr. The mixture was then brought to pH 2 with concentrated HCl, the volatiles were removed under reduced pressure, and the residue was taken up in a small amount of water. This solution was washed with Et_2O, which was discarded, and then with two 70-ml portions of $CHCl_3$. The oil obtained from evaporation of the pooled $CHCl_3$ extracts was dissolved in water, the solution was treated with excess $NaHCO_3$, and the resulting mixture was extracted several times with benzene. The benzene extracts were concentrated to ca. 20 ml, and 0.5 ml of phenyl isocyanate was added. After standing at room temperature for 10 min, this solution was warmed for 0.25 hr, 1 ml of MeOH was added to destroy the unreacted phenyl isocyanate, and heating was continued for 0.25 hr. The cooled solution was extracted with an equal volume of 5% HCl. The HCl extract was extracted with two 120-ml portions of $CHCl_3$. Evaporation of the $CHCl_3$ left an oil which was induced to crystallize by treatment with benzene and evaporation of the benzene under reduced pressure. The resulting solid was recrystallized from MeOH–benzene to give 0.2 g (44%) of a white solid, mp 165–167°. Anal. ($C_{16}H_{26}ClNO_2$) C, H, N.

Ether Cleavage Reactions. The appropriate dimethyl ether was heated in excess 48% HBr under N_2 for 3 hr at 150°. Volatiles were removed under reduced pressure (steam bath) and the crude HBr salt was recrystallized (see Table III).

Table III. Hydrobromide Salts of *N*-Isopropyl Derivatives of Dopamine and 5,6-Dihydroxy-2-aminotetralin

Compd	Mp, °C	Yield, %	Formula	Analyses
3	166–167[a,b] dec	94	$C_{11}H_{18}BrNO_2$	C, H, N
4	165–166[a] dec	95	$C_{12}H_{20}BrNO_2$	C, H, N
5	129–130[a] dec	84	$C_{13}H_{20}BrNO_2$	C, H, N
6	188–192[c] dec	83	$C_{14}H_{22}BrNO_2$	C, H, N

[a] From EtOH–Et_2O. [b] Breitschneider[6] reported the HCl salt of this compound. [c] From *n*-BuOH–hexane.

Acknowledgment. This investigation was supported by Grant NS04349, National Institute of Neurological Diseases and Stroke, and by the Medical Research Council of the United Kingdom.

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Antimalarials. Synthesis and Antimalarial Activity of 1-(4-Methoxycinnamoyl)-4-(5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine and Derivatives

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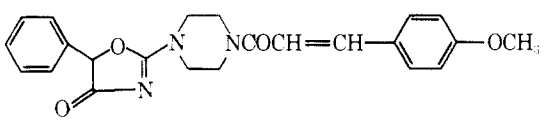
The preparation and activity against *Plasmodium berghei* of derivatives of 1-(4-methoxycinnamoyl)-4-(5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine are described. Replacement of the cinnamoyl group was accomplished by acylation or alkylation of 1-(5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine. Modifications of the 5-phenyl group were prepared either by a sequence of reactions involving mandelic ester–pemoline–piperazine pemoline or by the reaction of 5-aryl-2-thio-2,4-oxazolidinedione with piperazine or N-substituted piperazines. In a similar manner, pemoline was allowed to react with *N*-arylpiperazine, hexahydro-1*H*-1,4-diazepine, and 2,6-dimethylpiperazine to provide *N*-arylpiperazine pemoline derivatives and variations in the piperazine moiety. Several compounds in which the 2-oxazolin-4-one ring was replaced with other heterocyclic rings were prepared as were several open-chain analogs. Five compounds (three of them substituted in the para position of the 5-phenyl group and two *N*-arylpiperazine pemoline derivatives) were found to be active against *Plasmodium berghei*. The remaining active compound possessed changes in the cinnamoyl group and substitution on the 5-phenyl group.

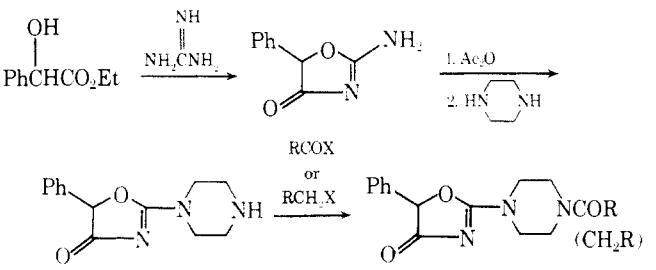
In an agreement with Walter Reed, compounds from Abbott were screened for blood schizonticidal activity against *Plasmodium berghei* in mice. Compound 1 was found to possess sufficient activity to warrant further interest. While 2-amino-5-phenyl-4-oxo-2-oxazoline (pemoline) is a constituent of the clinically useful drug Cylert in the treatment of minimal brain dysfunction in children,[1] compounds containing the (4-oxo-2-oxazolin-2-yl)piperazine moiety and possessing antimalarial activity have not to our knowledge been reported.[2] Structural variations of 1 and



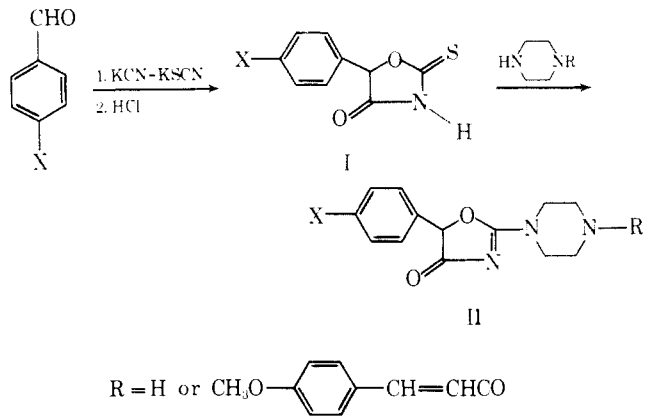
1

their activity against *P. berghei* are the subject of this paper.

Chemistry. The starting material for the compounds listed in Tables I–III containing the (5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine moiety was 1-(5-phenyl-4-oxo-2-oxazolin-2-yl)piperazine (piperazine pemoline). Condensation of mandelic ester with guanidine gave 2-amino-5-phenyl-2-oxazolin-4-one (pemoline).[3] Using the unpublished procedure of C. Lee (this laboratory), pemoline was activated by acylation with acetic anhydride to yield a monoacetyl derivative which reacted smoothly with piperazine to give piperazine pemoline. Acylation or alkylation with epoxides of α-bromo ketones of piperazine pemoline gave the corresponding compounds listed in Tables I–III. In the preparation of compounds **50–52**, the reaction of piperazine pemoline with the α-bromo ketones did not give an isolable compound. As the desired compounds were β-hydroxyethylpiperazine pemoline compounds, piperazine pemoline was alkylated with the epoxide to give the desired compounds directly.



The 5-aryl-4-oxo-2-oxazolinyl derivatives, compounds **15, 16, 19–21, 23,** and **25,** were prepared by allowing 5-aryl-2-thio-2,4-oxazolidinedione (I) to react with piperazine to



II