B. 1-Benzyloxyadenosine[7] (4.54 g, 10.0 mmoles) was converted to 5-amino-1-β-D-ribofuranosyl-4-carboxamidine by the published procedure.[7] A solution of the crude amidine (4b) in 100 ml of 0.1 *N* NaOH was refluxed for 2 hr before it was neutralized with HOAc, filtered, and treated with picric acid (2.29 g) in 50 ml of H_2O. The crystalline picrate was collected by filtration and converted back to the free base by treatment with Dowex 1-X8 (CO_3^{2-}) resin. The product was recrystallized from water, yield 452 mg (18% from 1-benzyloxyadenosine). This material was essentially identical with that prepared by method A described above.

C. A solution of 1-aminoinosine[9] (283 mg, 1.0 mmole) in 50 ml of 0.2 *N* NaOH was refluxed for 1 hr to give 8b before 1 g of Raney nickel catalyst was added and refluxing continued for an additional hr. The catalyst was removed by filtration, and the solution neutralized with HOAc and concentrated to *ca.* 10 ml before the addition of picric acid (1.0 mmole). The picrate was collected by filtration and converted back to the free base by treatment with Dowex 1-X8 (CO_3^{2-}). Concentration of the solution to about 2 ml caused the product to crystallize from solution, yield 95 mg (37%). It was essentially identical with that prepared by procedures A and B described above.

5-Amino-1-(2-deoxy-β-D-ribofuranosyl)imidazole-4-carboxamide (5c). A. A solution of 2′-deoxyinosine (630 mg, 2.5 mmoles) and hydroxylamine-*O*-sulfonic acid (425 mg, 3.75 mmoles) in 12.5 ml of 0.6 *N* NaOH was allowed to stand at 4° for 3 days to give 7c before 2 ml of 2 *N* NaOH was added and the resulting solution refluxed for 2 hr to give 8c. Raney nickel catalyst (W. R. Grace & Co.) (500 mg) was then added, and the solution was refluxed for another hr. The catalyst was removed by filtration and washed with water, and the combined filtrate and washings were neutralized with acetic acid before the addition of picric acid (2.5 mmoles). The resulting picrate was collected by filtration and converted back to the free base by treatment with Dowex 1-X8 (CO_3^{2-}) resin. The cream-colored glass that resulted was recrystallized from MeOH: yield 109 mg (18%); mp 174–176° (Mel-Temp); λ_{max} ($\epsilon \times 10^{-3}$) 0.1 *N* HCl, 245 (8.87), 268 (10.4), pH 7 and 0.1 *N* NaOH, 267 nm (12.6). *Anal.* ($C_9H_{14}N_4O_4$) C, H, N.

B. A solution of 5-amino-1-(2-deoxy-β-D-ribofuranosyl)imidazole-4-carboxamidine[7] (595 mg, 2.46 mmoles) in 10.5 ml of 0.24 *N* NaOH was refluxed for 2 hr, filtered, and treated with picric acid (563 mg) in MeOH (20 ml). The resulting picrate was treated with Dowex 1-X8 (CO_3^{2-}) to regenerate the free base which was further purified by chromatography on a silica gel G plate developed twice with 3:1 $CHCl_3$–MeOH. The product was eluted with methanol, yield 84 mg (14%). This material was essentially the same as that prepared by method A described above.

9-β-D-Arabinofuranosyl-1-hydroxyhypoxanthine (2d). To a solution of 9-β-D-arabinofuranosyladenine 1-oxide[11] (687 mg, 2.43 mmoles) in 25 ml of 29% HOAc was added $NaNO_2$ (1.68 g, 24.3 mmoles). After 4 days at room temperature, the solution was extracted twice with 400 ml of ether before evaporation to dryness several times with additions of water. The crude product was purified by water elution from a Dowex 50W-X4 (100–200 mesh) column (3.2 × 25 cm). The yield was 304 mg (44%). A small sample was recrystallized from water: mp 147°; λ_{max} ($\epsilon \times 10^{-3}$) 0.1 *N* HCl, 251 (9.15), pH 7 and 0.1 *N* NaOH, 227 (31.2), 256 (6.58), 291 nm (3.62). *Anal.* ($C_{10}H_{12}N_4O_6$) C, H, N.

9-β-D-Arabinofuranosyl-1-benzyloxyhypoxanthine (3d). A solution of 9-β-D-arabinofuranosyl-1-hydroxyhypoxanthine (774 mg, 2.7 mmoles) and benzyl bromide (465 mg, 2.7 mmoles) in 60 ml of DMA containing K_2CO_3 (376 mg, 2.7 mmoles) was heated at 70° for 16 hr. After filtration, the reaction mixture was evaporated to dryness *in vacuo*. A solution of the residue in acetonitrile was filtered before it was evaporated to a light orange syrup (1.0 g) that crystallized on standing. A small portion of this material was recrystallized from 50% EtOH: mp 241°; λ_{max} ($\epsilon \times 10^{-3}$) 0.1 *N* HCl and pH 7, 251 nm (9.35). *Anal.* ($C_{17}H_{18}N_4O_6$) C, H, N.

5-Amino-1-β-D-arabinofuranosylimidazole-4-carboxamide (5d). A. A solution of crude 9-β-D-arabinofuranosyl-1-benzyloxyhypoxanthine (938 mg, 2.5 mmoles) in 86 ml of EtOH and 10.6 ml of 1.0 *N* NaOH and enough H_2O to give a clear solution was refluxed for 3 hr before it was neutralized with 1.0 *N* HCl and then evaporated to dryness. The residue was dissolved in 150 ml of EtOH, and the solution filtered to remove salt before evaporation to an orange syrup, which was dissolved in 70 ml of 50% EtOH. Hydrogenolysis was carried out for 18 hr at room temperature and atmospheric pressure in the presence of *ca.* 200 mg of Raney nickel catalyst, which was then removed by filtration and washed with water. The combined filtrate and washings were evaporated to dryness *in vacuo* to give a residue which crystallized from methanol: yield 180 mg (28%); mp 191°; λ_{max} ($\epsilon \times 10^{-3}$) 0.1 *N* HCl, 245 (8.90), 267 (9.98), pH 7 and 0.1 *N* NaOH, 267 nm (12.3). *Anal.* ($C_9H_{14}N_4O_5$) C, H, N.

B. A solution of 5-amino-1-β-D-arabinofuranosylimidazole-4-carboxamidine[7] (224 mg, 0.87 mmole) in 10 ml of 0.1 *N* NaOH was refluxed for 1 hr before it was neutralized with HOAc and treated with picric acid (0.87 mmole). The picrate, which was collected by filtration, was converted back to the free base by treatment with Dowex 1-X8 (CO_3^{2-}) resin. The free base was recrystallized from methanol, yield 122 mg (55%). This material was essentially identical with that prepared by procedure A described above.

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Effects of Some Substituted Phenanthrenes on the Central Nervous System†

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A variety of substituted phenanthrenes were prepared by Mosettig and van de Kamp,[1] Fieser,[2] Mosettig and Burger,[3] and others and found by Eddy[4-8] to produce a variety of pharmacological effects when given orally to cats. Central nervous depression and analgesia were prominent effects seen with some compounds. 3-Substituted carboxylic acids were very active.

Such findings prompted us to synthesize a number of phenanthrenes monosubstituted in the 2, 3, and 9 positions and evaluate these for various central nervous system effects. Central nervous depressant, analgetic, and anticonvulsant properties were found among a number of agents in mice.

Synthesis. The novel phenanthrene compounds described herein were obtained by the reactions shown in Scheme I. The unstable ylide methoxymethylenetriphenylphosphorane was allowed to react with the various acetylphenanthrenes to give the cis-trans enol ether mixture a. Acid hydrolysis generated the aldehydes b in good yield, and oxidation or reduction of the latter compounds gave respectively the corresponding carboxylic acids c and the

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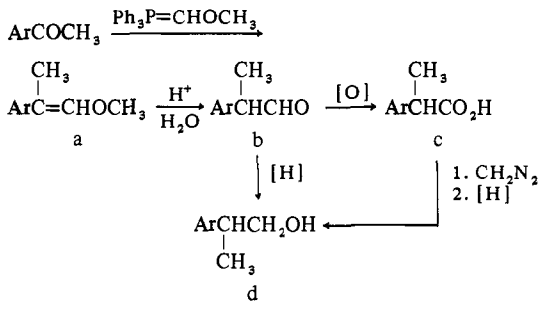
Scheme I



alcohols d, which could also be obtained by reduction of the esters obtained by methylation of c.

Pharmacology. The phenanthrenes used in this study were first evaluated for behavioral effects in mice by a procedure similar to one described by Irwin.[9] Some agents produced marked central nervous system (CNS) depression and were evalulated for their ability to induce a loss of righting in mice (the inability of a mouse to resume a normal posture within 30 sec of assuming a supine position). Estimates of loss of righting potency (PD_{50}) and LD_{50}'s are shown on Table I. Loss of righting only occurred with acids and phenanthrylpropionic acids were more active than corresponding carboxylic acids. Saturation of the 9,10 double bond reduced potency. 3-Substituted acids were more potent than the 2- or 9-substituted compounds. All of the acids, except phenanthrene-3-carboxylic acid (**9**), displayed a narrow margin between lethal and paralytic dose levels, *i.e.*, $LD_{50}/PD_{50} \leq 1.5$. With the exception of compound **9** deaths were usually delayed, *i.e.*, occurring hours or days after recovery of the animals from CNS depression.

Since compound **9** displayed a favorable ratio ($LD_{50}/PD_{50} > 2$), it was evaluated intravenously in two mongrel dogs for anesthetic effects. In the dog, unlike the mouse, anesthesia was slow in onset; disorientation, confusion, and extreme uncontrolled movements occurred. Although loss of righting occurred, the animals never seemed to fully lose consciousness. This, and the finding that hemolysis and hematuria occurred, precluded further consideration of its use as an anesthetic.

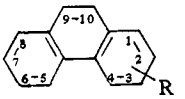
Eddy's findings,[4,7] which indicated that phenanthrene carboxylic acids are vested with analgetic properties prompted an evaluation of these compounds's ability to significantly depress responsiveness in 50% of mice (AD_{50}) to a thermal stimulus (hot plate).[10] Responses were measured 1, 1.5, and 2 hr after intraperitoneal administration of the compound. Most 2- or 3-substituted phenanthryl acids (compounds **4**, **5**, **7-9**) appear to be highly active (Table II). However, since they are CNS depressants, the unresponsiveness to pain may be due to general CNS depression and not analgesia. The ratio between depressant and analgetic dose levels (PD_{50}/AD_{50}) for all agents is 4 or less, as with chlorpromazine, a nonanalgetic.

2′-Phenanthryl-2-propionaldehyde (**2**) and the corresponding alcohol **3** appear to be true analgetics since both are devoid of CNS depressant effects. Both are weak, being respectively $^1/_{48}$ and $^1/_{45}$ as active as morphine.

These agents were also appraised as antagonists of maximal electroshock-induced seizures (MES).[11] All phenanthrene-substituted acids, alcohols, and aldehydes antagonized MES, though only four compounds (**3-6**) showed significant activity at subdepressant dose levels. Only 2′-phenanthryl-2-propan-1-ol (**3**) produced a more favorable PD_{50}/CD_{50} than phenobarbital but possessed only $^1/_{16}$ of phenobarbital's potency.

Thus, a number of agents were found which are as potent as some clinically useful drugs. Compounds **6** and **9** produce the same degree of CNS depression as phenobarbital or chlordiazepoxide and are much more active than meprobamate.[12] Likewise, a number are moderately potent analgetics and anticonvulsants. Unfortunately, none display a decisive superiority over existing drugs.

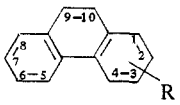
Table I. Paralytic Potency (PD_{50}) and Toxicity (LD_{50}) of Various Alkyl-Substituted Phenanthrenes



No.	R	Mouse, intraperitoneal route: PD_{50}[a] (mg/kg)	Mouse, intraperitoneal route: LD_{50} (mg/kg)	LD_{50}/PD_{50}
1	2-$CH(CH_3)CO_2H$	167 (149-187)[b]	<100[c]	<1
2	2-$CH(CH_3)COH$	No effect at 1000	>500 < 1000	
3	2-$CH(CH_3)CH_2OH$	No effect at 1000	>500 < 1000	
4	9,10-Dihydro-2-$CH(CH_3)CO_2H$	257 (236-280)	120 (96-149)[c]	<1
5	9,10-Dihydro-2-$CH(CH_3)CH_2OH$	~500	~500	~1
6	3-$CH(CH_3)CO_2H$	85 (75-93)	129 (107-165)[c]	1.5
7	9-$CH(CH_3)CO_2H$	257 (175-289)	288 (110-750)[c]	1.1
8	9,10-Dihydro-2-CO_2H	230 (205-258)	259 (199-299)[c]	1.1
9	3-CO_2H	111 (96-119)	263 (223-302)	2.4
10	3-$CONH_2$	~500	>900	
11	9-CN	No effect at 1000	>1000	
	Chlorpromazine	13 (10-16)	85 (77-153)	6.5
	Chlordiazepoxide	98 (38-123)	227 (202-260)	2.3
	Phenobarbital	103 (72-114)	222 (188-349)	2.2

[a] PD_{50} and LD_{50} estimates were obtained through use of the method of J. T. Litchfield, Jr., and F. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949). At least 30 mice in groups of 10/dose level were used for each determination. [b] 95% confidence limits. [c] Many deaths were delayed; *i.e.*, many fatalities occurred at various times after recovery of mice from the central nervous depressant actions of the compounds.

Table II. Analgetic (AD_{50}) and Anticonvulsant (CD_{50}) Potency of Various Alkyl-Substituted Phenanthrenes



No.	R	Mouse (mg/kg), intraperitoneal route PD_{50}	AD_{50}[a]	CD_{50}[a]	PD_{50}/AD_{50}	PD_{50}/CD_{50}
1	2-$CH(CH_3)CO_2H$	167	>100	122 (100-141)[b]	~1	1.4
2	2-$CH(CH_3)COH$	Inactive	305 (218-427)	~500		
3	2-$CH(CH_3)CH_2OH$	Inactive	285 (170-479)	253 (186-316)		
4	9,10-Dihydro-2-$CH(CH_3)CO_2H$	257	101 (84-123)	113(96-125)	2.5	2.3
5	9,10-Dihydro-2-$CH(CH_3)CH_2OH$	~500	~200	157 (126-188)	~2.5	~3.2
6	3-$CH(CH_3)CO_2H$	85	>90	>100	<1	<1
7	9-$CH(CH_3)CO_2H$	257	~200	142 (124-165)	1.3	1.8
8	2-CO_2H	230	124 (34-155)	257 (196-325)	1.9	<1
9	3-CO_2H	111	27 (16-45)	134 (97-162)	4.1	<1
10	3-$CONH_2$	~500	247 (190-301)	>750	~2	<1
11	9-CN	Inactive	>400	>750		
	Morphine		6.4 (2.4-9.0)			
	Phenobarbital	103	>100	15.4 (10.6-22.4)	>1	6.7
	Chlordiazepoxide	98	38 (27-49)	33.6 (26.2-43.0)	2.6	2.9
	Chlorpromazine	13	3.3 (2.2-4.7)	>20	3.9	<1

[a] AD_{50} and CD_{50} estimates were obtained through use of the method of J. T. Litchfield, Jr., and F. Wilcoxon [*J. Pharmacol. Exp. Ther.*, **96**, 99 (1949)]. At least 30 mice in groups of 10/dose level were used for each determination. [b] 95% confidence limits.

Table III. Data for New Compounds

	1	2	3	4	5	6	7
Yield, %	51[a]	54[b]	72[c]	47[a]	78[a]	43[a]	55[a]
Mp,[d] °C	172-175	58-61	120-122.5	118-120	81.5-82.5	136-138	182-184
Solvent	Aq MeOH	C_6H_6-hexane	Hexane	Aq MeOH	Et_2O-hexane	Aq MeOH	Aq MeOH
Anal.[e]	C, H	C, H	C, H	C, H	C, H	C, H	C, H

[a] From the aldehyde. [b] From the acetylphenanthrene. [c] From the methyl ester. [d] Kofler block. [e] Within ±0.4% of theory.

Experimental Section

The general procedure for conversion of an acetylphenanthrene into the corresponding alcohol, aldehyde, and acid is given below. Physical data and yields are shown on Table III.

Preparation of the Aldehydes. Methoxymethyltriphenylphosphonium chloride (0.125 *M*) was suspended in dry Et_2O (500 ml) at 0° under nitrogen. PhLi solution (*ca.* 2 *M*) was added until a faint yellow color persisted; then a further 0.125 *M* was added quickly. The blood-red ylide color developed immediately. Acetylphenanthrene (0.1 *M*) in a minimum amount of dioxane was added quickly. The red color was immediately discharged and water (200 ml) was added to the yellow reaction mixture. The separated organic layer was washed, dried, and evaporated to give an oil containing the enol ether mixture, which was dissolved in dioxane (200 ml) to which 2 *N* H_2SO_4 (20 ml) was added. The mixture was refluxed until tlc examination showed hydrolysis to the aldehyde was complete (1-24 hr). The cooled mixture was poured into water and the crude aldehyde isolated by Et_2O extraction; the pure aldehydes were obtained by column chromatography on silica gel (600 g) using C_6H_6 as an eluent.

Preparation of the Acids. Jones reagent was added to a solution of the aldehyde (2.0 g) in Me_2CO (100 ml) at 0° under nitrogen until a permanent yellow-brown color persisted. The mixture was poured into water and the product extracted with EtOAc. The extract was washed (water, two times) and then extracted with aqueous Na_2CO_3. Acidification of the carbonate extract then yielded the acids which were filtered off and recrystallized from aqueous MeOH.

Preparation of the Alcohols. (1) By Reduction of the Aldehydes. Excess ethanolic sodium borohydride was added to the aldehyde (2.0 g) in EtOH-THF (1:1, 20 ml). After 1 hr the mixture was poured into dilute HCl and the product was extracted with Et_2O. The dried Et_2O solution was passed through a small amount of silica gel and then evaporated to give the alcohol.

(2) By Reduction of the Ester. The methyl ester, derived by the action of diazomethane on the acid, was reduced using excess $LiAlH_4$ in Et_2O.

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