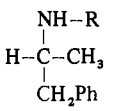
ine[8] resides in the *S* enantiomers. Pertinent to this observation are the reports that these three agents act at the same site of MAO.[9,10] A SAR study of 2-phenylcyclopropylamines has indicated that the major binding moieties of this class of MAO inhibitors are the phenyl and amino groups.[1] In this same study it was concluded that the degree of inhibitory activity of these compounds is related to the ability of the phenyl group to approach coplanarity with the C-2-C-3 atoms of the cyclopropane ring. A recent report[11] of the conformational analysis of amphetamine by nmr indicated a preferred trans disposition of the phenyl and amino groups. It is probable that pheniprazine exhibits a similar conformational preference although this has not yet been experimentally determined. Hence, the structural and stereochemical correlations found to exist for the MAO-inhibitory activity of tranylcypromine, amphetamine, and pheniprazine suggest a common mode of binding for these agents in their interactions with MAO. It is suggested that the phenyl and amino (hydrazino) groups primarily contribute to binding of the inhibitors to the site on the enzyme and that these moieties lie in distinctly different planes in the enzyme-inhibitor complex.



3a, R = H
3b, R = NH_2

It is of interest to note that similar pharmacophoric conformations have been proposed for tranylcypromine and amphetamine in their inhibition of the catecholamine uptake process in the CNS.[12] However, it is significant that the more active enantiomers of these agents as inhibitors of this process, (−)-2 and (+)-amphetamine, are of opposite stereochemistry at the common chiral center α to the amino group thereby suggesting dissimilarities in their modes of binding at the uptake process or perhaps different sites of action.

Studies of the steric aspects of the pharmacological actions of the cyclopropylamines are continuing in these laboratories.

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Antimalarial Activity of Clopidol, 3,5-Dichloro-2,6-dimethyl-4-pyridinol, and Its Esters, Carbonates, and Sulfonates†

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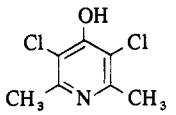
Clopidol,‡ 3,5-dichloro-2,6-dimethyl-4-pyridinol, **1**,[1] has been shown to possess antimalarial activity by the Walter Reed Army Institute of Research. It was active against the following strains of malaria: *Plasmodium berghei* in mice, *P. gallinaceum* in chicks, *P. cynomologi* in the *Macaca mulatta* monkey, and the *refractory* (chloroquine resistant) strain of *P. falciparum* in humans. It was considered a curative against *P. gallinaceum* at a dosage level of 160 mg/kg



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against *P. cynomologi* when given orally for 7 consecutive days. Studies with ^{36}Cl-labeled clopidol§ showed that clopidol is rapidly excreted from the body. Within 24 hr, 91% of the ^{36}Cl radioactivity was accounted for in the urine and feces of rats as unchanged clopidol.

Due to the rapid excretion of clopidol and its high insolubility in organic solvents as well as water, it was of interest to prepare derivatives of clopidol which would be more lipophilic and could in turn be hydrolyzed to clopidol *in vivo*. We have synthesized a series of esters, carbonates, and sulfonates of clopidol.

The esters and carbonates of clopidol, given in Table I, were prepared by treating the sodium salt of clopidol suspended in DMF with the corresponding acid chloride. It is of interest to note that the methyl and ethyl carbonates were prepared in high yields using this method even though ethyl chloroformate has been shown to have a half-life of only 9.5 min at 20° in DMF.[2] The sulfonates of clopidol, listed in Table II, were prepared by treatment of the sodium salt of clopidol with sulfonyl chlorides in a manner similar to the preparation of the esters and carbonates.

Antimalarial Data. Clopidol and its esters, carbonates, and sulfonates described herein have been tested for antimalarial activity against *P. berghei* in mice by Dr. Leo Rane at the University of Miami.# The results of these tests were furnished to us by Dr. E. A. Steck, Walter Reed Army Institute of Research. Three of the compounds were active: **1** at a dose level of 160 mg/kg, **9** at a level of 320 mg/kg, and **15** at 640 mg/kg. One may conclude that the greater lipophilicity of the derivatives of clopidol does not enhance the antimalarial activity. In as much as **9** and **15** were active, the synthesis of other hydrolyzable derivatives of clopidol is being carried out.

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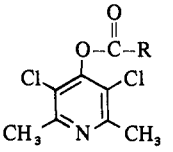
§The ^{36}Cl-labeled clopidol was prepared by New England Nuclear Corp., Boston, Mass. 02118.

‡Clopidol is the active component of Coyden, a commercial coccidiostat sold by The Dow Chemical Co.

#For a description of test method see Osdene, *et al.*[3]

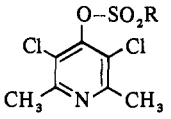
Table I. Esters and Carbonates of Clopidol



No.	R	Yield, %	Crystn solvent	Mp[a] or bp (mm), °C	Formula	Analyses[b]
2	CH_3	93	Hexane	56.5–57	$C_9H_9Cl_2NO_2$	C, H, Cl, N
3	CH_2Cl	15	Hexane	62–63	$C_9H_8Cl_3NO_2$	C, H, Cl, N
4	CH_2CH_3	39	Hexane	46.5–47	$C_{10}H_{11}Cl_2NO_2$	C, H, Cl, N
5	$CH(CH_3)_2$	62		78–79 (0.05)	$C_{11}H_{13}Cl_2NO_2$	C, H, Cl, N
6	$C(CH_3)_3$	81	Hexane	54–55	$C_{12}H_{15}Cl_2NO_2$	C, H, Cl, N
7	$(CH_2)_7CH{=}CH(CH_2)_7CH_3$	50	Me_2CO	<25	$C_{25}H_{39}Cl_2NO_2$	C, H, N
8	1-Adamantyl	41	Hexane	97.5–98.5	$C_{18}H_{20}Cl_2NO_2$	C, H, Cl, N
9	C_6H_5	88	Me_2CO	142–142.5	$C_{14}H_{11}Cl_2NO_2$	C, H, Cl, N
10	p-ClC_6H_4	82	Me_2CO	178–179	$C_{14}H_{10}Cl_3NO_2$	C, H, Cl, N
11	p-$CH_3OC_6H_4$	82	Me_2CO–$CHCl_3$	181–182	$C_{15}H_{13}Cl_2NO_3$	C, H, Cl, N
12	OCH_3	85	Hexane	67–68	$C_9H_9Cl_2NO_3$	C, H, Cl, N
13	OCH_2CH_3	87	Hexane	67.5–68.5	$C_{10}H_{11}Cl_2NO_3$	C, H, N[c]

[a] All melting points are uncorrected. [b] All analyses were within ±0.3% of the calcd values. [c] Cl: calcd, 26.85; found, 27.3.

Table II. Sulfonates of Clopidol



No.	R	Yield, %	Crystn solvent	Mp, °C[a]	Formula	Analyses[b]
14	CH_3	65	Hexane	111–112	$C_8H_9Cl_2NO_3S$	C, H, Cl, N, S
15	$CH_2CH_2CH_2Cl$	12	Me_2CO	67.5–68.5	$C_{10}H_{12}Cl_3NO_3S$	C, H, Cl, N, S
16	$(CH_2)_{15}CH_3$	66	Hexane	83.5–84	$C_{23}H_{39}Cl_2NO_3S$	C, H, Cl, N, S
17	C_6H_5	43	Me_2CO	117.5–118.5	$C_{13}H_{11}Cl_2NO_3S$	C, H, Cl, N, S
18	p-ClC_6H_4	53	Me_2CO–$CHCl_3$	146.5–147.5	$C_{13}H_{10}Cl_3NO_3S$	C, H, Cl, N[c]
19	p-FC_6H_4	54	Me_2CO	131–133 dec	$C_{13}H_{10}Cl_2FNO_3S$	C, H, Cl, N, S

[a] All melting points are uncorrected. [b] All analyses were within ±0.3% of the calcd values. [c] S: calcd, 8.75; found, 9.11.

Experimental Section

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Ir spectra were recorded on an Infracord spectrophotometer and nmr on a Varian Associates A-60 instrument (Me_4Si) and are in accord with proposed structures. The synthesis of the propionate ester, 4, and the p-chlorobenzenesulfonate, 18, serves as typical examples.

3,5-Dichloro-2,6-dimethyl-4-pyridylpropionate (4). Clopidol (19.2 g, 0.10 mole) was added slowly to a slurry of NaH (5.4 g, 0.11 mole, 50% mixture in oil) in 50 ml of DMF under N_2. The resulting mixture was cooled to 15° and to it was added CH_3CH_2COCl (9.2 g, 0.11 mole), dissolved in 25 ml of DMF. The reaction mixture was stirred for 1.5 hr and filtered. The filtrate was extracted with hexane, and the hexane solution was washed with H_2O and evaporated yielding the desired material.

3,5-Dichloro-2,6-dimethyl-4-pyridyl p-Chlorobenzenesulfonate (18). To a slurry of NaH (10.8 g, 0.22 mole, 50% mixture in oil) in 100 ml of DMF was added 38.4 g (0.20 mole) of clopidol. The mixture was cooled to 3° and to it was added 46.4 g (0.22 mole) of p-$ClC_6H_4SO_2Cl$, dissolved in 75 ml of DMF. The reaction mixture was stirred 1.5 hr and filtered, and the salt washed with $CHCl_3$. The filtrate was partially reduced *in vacuo* and the remaining solution cooled in ice H_2O causing the desired product to precipitate.

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N-Alkyl Derivatives of Purine-6(1*H*)-thione†

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A number of 9-alkylpurines are cytotoxic to H.Ep.-2 cells in culture, both the wild strain and a strain resistant to purine-6(1*H*)-thione (6-mercaptopurine).[1] Among the most active compounds are the 9-butyl, 9-cyclopentyl, and 9-cyclohexyl derivatives of purine-6(1*H*)-thione. Since these compounds are toxic to H.Ep.-2/MP cells, their mechanism of action, although still not defined, must be different from that of 6-mercaptopurine and could be due to binding to nucleic acid since it is known that the structurally related caffeine does bind to nucleic acids.[2] To shed some light on this activity, we decided to prepare derivatives of 6-mercaptopurine in which the alkyl groups are attached to nitrogens other than N-9.

7-Cyclopentylpurine-6(1*H*)-thione (**3**) was prepared by the route previously used for the preparation of other 7-alkylpurines including the 7-butyl derivatives.[3] *N*-(4-Amino-6-chloro-5-pyrimidinyl)formamide (**1**) was alkylated with

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