Table II. Effect of 5-Phenoxymethyl-2-oxazolidinethiones on Mouse Food Intake and Motor Activity[a]

Compd	Food intake, g/24 hr	Drug intake, mg/kg per 24 hr	Motor activity counts/10 min % of control
2	7	459	78
3	8	548	91
4	4	268	47[b]
5	13	858	83
7	20	1307	69
9	27	1765	99
11	11	714	49[b]
12	9	616	67
I	12	540	44[b]
Control	29		100[c]

[a] All drugs added as 1% of diet; see Experimental Section. [b] Significantly different from control, $p < 0.05$. [c] Spontaneous motor activity in control mice was 587 ± 122 counts/10 min (±S.D.); $n = 6$.

In vitro enzyme inhibitory activity was not predictive of *in vivo* activity as detd by depletion of NE concns from rat brain. Compd **5**, the most inhibitory of these oxazolidinethiones *in vitro*, did not deplete rat brain NE and did not affect food intake or spontaneous motor activity in mice. This lack of correlation between *in vitro* enzyme inhibition and *in vivo* effects may be due to several factors including (1) variable absorption of these compds after either ip (rat) or oral (mouse) administration, and (2) taste of the drug in the diet. Faiman, *et al.*, in detg the antithyroid activity of several 5-substituted 2-oxasolidinethiones in rats, found marked variability in the effect of these compds when ingested as part of the diet as compared to the effects of parenterally administered drug.[18] A similar difficulty in absorption of these compds by rats after ip administration could explain the latency in the onset of norepinephrine depleting activity. Absorption studies with **12** in rats showed max blood levels of drug 2 hr after dosing with 25 mg and the blood levels remained relatively constant over the 2- to 24-hr interval.[19] Although blood levels of circulating oxazolidinethione were not measured in this study, sustained blood levels would provide an explanation for the significant inhibition of brain dopamine β-hydroxylase as reflected in the depletion of brain NE at 16 hr with **2**, **3**, **4**, and **12**. The adverse effect of taste of drug when added to the diet cannot be detd. This factor may be responsible for the decreased food intake (**2**, **3**, and **12**) without an impairment of spontaneous activity.

Previous mention has been made of the antithyroid activity of numerous substituted 2-oxazolidinethiones.[18,20,21] Compd **12** also demonstrated thyroid toxicity in chronic studies in both rats (10 mg/kg per day) and in dogs (100 mg/kg per day).[22] The antithyroid effects of the remainder of these oxazolidinethiones have not been detd.

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Preparation of a Camoquine Derivative with Quaternary Carbon Side Chain

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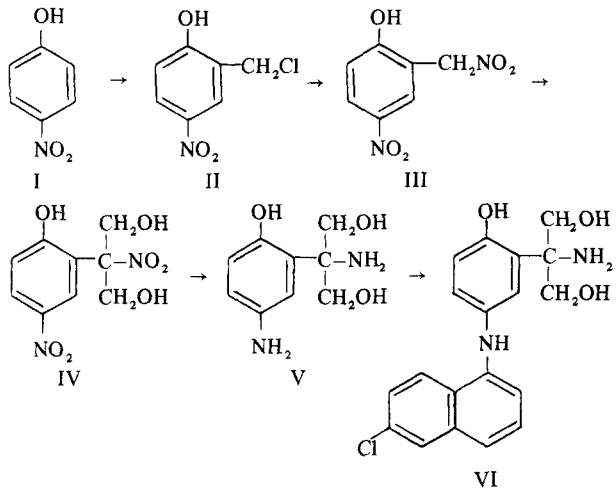
Since an enzymatic degradation of the terminal alkylamino function of chloroquine or camoquine might be the mechanism of plasmodial resistance to antimalarials, we synthesized a novel analog of camoquine: 4-[3′-(α,α-dihydroxymethylaminomethyl)-4′-hydroxyphenylamino]-7-chloroquinoline (VI), with the terminal amino function attached to a quaternary C. The nonbiodegradability of an amino function adjacent to a quaternary C is well known.[1] Though antimalarial compounds with quaternary side chains have been made previously,[2] compounds with a quaternary C adjacent to the terminal amino function have not been reported.

Chemistry. *p*-Nitrophenol (I) was chloromethylated to the corresponding chloromethyl derivative (II)[3] which when treated with $NaNO_2$ or $AgNO_2$ at low temp gave the nitro compound III. Using $AgNO_2$ the yield of III was 75% as compared with a 50% yield when $NaNO_2$ was used. The low reaction temp (0° or less) was designed to obviate the formation of nitrate ester.[4] The facile nitration of the alkyl chloride II appears to contradict the generally held view[5] that only alkyl bromides or iodides are suitable for the preparation of the nitro derivatives. III in dioxane reacted readily with HCHO in the presence of $Ca(OH)_2$ to give 2-nitro-2-(2-hydroxy-5-nitrophenyl)propane-1,3-diol (IV) (yield 75%). The yield of IV was lower when $(C_2H_5)_3N$ was used in place of $Ca(OH)_2$. Reduction of IV with Zn and H_2SO_4 gave the diamine V which, without isolation, was condensed with 4,7-dichloroquinoline to yield VI.

Though Balcom and Furst[6] have studied the reduction of aromatic nitro groups by NH_2NH_2 and Raney Ni, there are apparently no reports of similar reductions of the aliphatic nitro function, possibly because of the instability of aliphatic nitro compounds under the basic conditions of the experiment.[7] Thus when III, a compound with an aliphatic nitro side chain, was reduced by this method and condensed

Scheme I. Scheme of Syntheses



with 4,7-dichloroquinoline, a brownish intractable product was obtained. However when IV was treated similarly it gave VI in 33% yield. Apparently an aliphatic NO_2 can be reduced by hydrazine and Raney Ni, although in lower yield, provided the NO_2 is attached to a quaternary C.

Experimental Section†

2-(α-Nitromethyl)-4-nitrophenol (III). (a) Using $AgNO_2$. To a slurry of 40 g (0.264 mole) of $AgNO_2$ in 100 ml of dry Et_2O, cooled to 0° and stirred, was added dropwise over 1 hr 37.5 g (0.2 mole) of 2-hydroxy-5-nitrobenzyl chloride (II)[3] dissolved in 100 ml of dry Et_2O. Stirring was contd in the dark at 0° for a total of 25 hr. The reaction mixt was filtered, the Ag salt washed with dry Et_2O, and the combined filtrate was evapd under reduced pressure leaving a yellow solid residue which on recrystn from Et_2O–C_6H_6 gave 30 g of III (76%), mp 152.5°. *Anal.* ($C_7H_6N_2O_5$) C, H.

(b) Using $NaNO_2$. II (18.7 g, 0.1 mole) dissolved in 50 ml of DMF was added dropwise with stirring to 12 g (0.178 mole) of dry $NaNO_2$ and 13.3 g of dry urea dissolved in 150 ml of DMF and cooled to −60°. Stirring was contd for 5 hr after which the mixt was poured into 500 ml of ice H_2O and extd with three 50-ml portions of Et_2O. The combined ext was dried (Na_2SO_4), and the solvent was removed *in vacuo* giving 10 g of crude III (50%). Recrystn from Et_2O–C_6H_6 gave 9.6 g of III, mp 152°.

2-Nitro-2-(2-hydroxy-5-nitrophenyl)propane-1,3-diol (IV). (a) Eight grams (0.1 mole) of 40% HCHO in 8 ml of dry dioxane was added dropwise over 1 hr to 10 g (0.05 mole) of III in 24 ml of dry dioxane contg 40 mg of $Ca(OH)_2$ in fine suspension. After stirring for 40 hr at 29°, the dioxane soln was dild with H_2O and extd with three 10-ml portions of Et_2O. The Et_2O ext was washed with satd brine and dried (Na_2SO_4). When Et_2O was removed *in vacuo* a thick oily residue was obtd which on crystn from Et_2O–C_6H_6 gave 9.7 g (74%) of IV, mp 115°. *Anal.* ($C_9H_{10}N_2O_7$) C, H, N.

(b) Using $(C_2H_5)_3N$. To a stirred soln contg 2 g (0.01 mole) of III and 1.6 g (0.02 mole) of 40% HCHO in 5 ml of dioxane was added dropwise over 30 min 0.1 ml of $(C_2H_5)_3N$ in 2 ml of dry dioxane. The color of the soln during addn changed from yellow to orange. Stirring was contd for 1.5 hr at 29°. IV was isolated as in a, yield 1.43 g (54%), mp 115°.

4-[3′-(α,α-Dihydroxymethylaminomethyl)-4′-hydroxyphenylamino]-7-chloroquinoline (VI). Using Zn and H_2SO_4. H_2SO_4 (112 ml, 30%) was added with vigorous stirring over 10 hr to a mixt of 5.2 g (0.02 mole) of IV and 24 g of Zn dust in 64 ml of 95% EtOH. Agitation was contd for another 1–2 hr. Excess Zn was filtered off and the pH of the filtrate was adjusted to 3 with NH_3. An equiv quantity of 4,7-dichloroquinoline (3.9 g) was added to the filtrate and the mixt was heated on a water bath for 1.5 hr. After cooling, the soln was made alk with NH_3 pptg the free amine and $Zn(OH)_2$. The gel-like ppt was filtered, washed with H_2O, and extd twice with cold EtOH, and once by digestion with hot EtOH. The combined EtOH ext was concd to 15 ml *in vacuo* and on addn of H_2O, VI sepd as a yellow solid, yield 3.8 g (52%). The solid was recrystd from EtOH–H_2O, mp 130–132°. The sulfate had mp 241–245° dec. *Anal.* ($C_{18}H_{18}ClN_3O_3 \cdot SO_4 \cdot 3H_2O$) C, H, N.

(b) Raney Ni(W_2) (1.5 g) was added to 5 ml of an EtOH soln of 0.5 g of IV (0.0012 mole) and 0.4 ml of NH_2NH_2 (0.008 mole) and the mixt was gradually brought to reflux. Successive portions of Raney Ni were added over 1.5 hr and finally excess Ni to decomp unreacted NH_2NH_2. The soln was filtered, the pH was adjusted to 3 with EtOH–HCl, and the amine, without isolation, was condensed with 4,7-dichloroquinoline as in a. The condensed product (0.23 g, 33%) as a free base was isolated with an ir spectrum identical with that of VI obtd by method a.

Pharmacology. Antimalarial Activity. The minimum effective dose of VI (HCl salt) against *Plasmodium berghei* in mice, detd according to the method of Thurston,[8] was found to be 10 mg/kg. The quinine equivalent is 5.8.

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†All melting points are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

Hill Reaction Inhibitors. 3. Conformational Aspects of Ureas†

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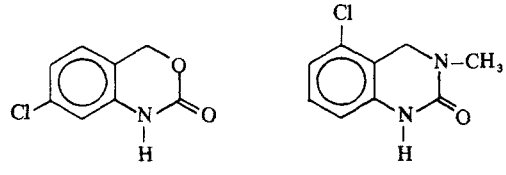
In earlier reports,[1,2] efforts were described to assess the conformational requirements of carbamate and urea inhibitors of the Hill reaction. The previous chemical systems (1, 2) involved fixed geometry of the carbamate and ureido groups. In each case the Ph ring, the N atom, and the C=O carbon atom were essentially coplanar, thus defining the overall shape of the molecule. The cyclic carbamate and urea (1, 2) were inactive while the corresponding linear systems *m*-$ClC_6H_4NHCOXCH_3$ (X=O; NCH_3) were active. The inactivity of 1 and 2 may be attributed



1 2

to the fact that the carbamate and ureido groups are in a conformation that prevents them from binding to the receptor. An alternative explanation involves the conformation of th Ph ring which is restricted in the cyclic

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