Table II. Inhibition of Coenzyme Q Enzyme Systems by 6-Alkylamino-5,8-quinolinequinones

	In vitro assay systems[a]					
	DPNH-oxidase			Succinoxidase		
Compd No.[b]	Specific activity[c]	Inhibitor concn,[d] mμmoles	% reversal[e]	Specific activity[c]	Inhibitor concn,[d] mμmoles	% reversal[e]
CoQ_{10}	0.582			0.562		
1	0.302	41	90	0.292	15	
3	0.321	17	97	0.288	10	
5	0.320	17	98	0.286	11	
6	0.328	20	95	0.290	10	
7	0.326	20	95	0.288	10	
10	0.318	14	98	0.290	9	
11	0.320	17	98	0.291	10	

[a] *In vitro* assays were conducted by the Warburg method using heavy beef heart mitochondria. § [b] 100 mμmoles of CoQ_{10} was added in each case. [c] Microatoms of O/min per mg of protein. [d] For 50% inhibition. [e] After addn of a further 200 mμmoles of CoQ_{10}.

about 0.2 as active as inhibitors of the NADH-oxidase system, and only about 0.5 as active as inhibitors of the succinoxidase system.

The 7-*n*-tetradecylaminomethyl-6-hydroxy-5,8-quinolinequinone was inactive as an inhibitor of both the NADH-oxidase and succinoxidase systems up to a level of 200 mμmoles.

Experimental Section

General Procedures. All melting points were taken on a Thomas-Hoover melting point apparatus and 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.

6-Alkylamino-5,8-quinolinequinones. Fifteen new 6-alkylamino-5,8-quinolinequinones were prepd by treating the appropriate alkylamine with 6-methoxy-5,8-quinolinequinone in EtOH at room temp as previously described.[4] After stirring at room temp, the reaction mixt was dild with Et_2O or hexane and placed in the freezer. Generally a dark red ppt was then collected and recrystd repeatedly from EtOH-H_2O (charcoal) or occasionally Et_2O-hexane (charcoal) or EtOH-Et_2O (charcoal). When necessary, column chromatography on the crude reaction mixt followed by crystn was used to secure a pure product (Table I).

7-*n*-Tetradecylaminomethyl-6-hydroxy-5,8-quinolinequinone.[4] This new 7-alkylaminomethyl-6-hydroxy-5,8-quinolinequinone was prepd in a manner similar to previously published procedures[2,11] by adding a mixt of *n*-tetradecylamine (1.4 g) and 37% CH_2O soln (0.8 ml) in 5 ml of EtOH to a stirred suspension of 6-hydroxy-5,8-quinolinequinone (1 g) in EtOH at room temp. The 6-hydroxy-5,8-quinolinequinone rapidly dissolved upon addn of the amine soln, and the product pptd from the reaction mixt in about 10 min, although stirring was continued for about 6 hr. The product was recrystd from EtOH to yield the red cryst substance. An analytical sample was recrystd from EtOH-$CHCl_3$.

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Mechanism of Action of Amodiaquine. Synthesis of Its Indoloquinoline Analog†

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The relationship between structural modifications in the antimalarial amodiaquine (**1a**) and the corresponding ability to complex with DNA has been studied. This led to the synthesis of ring-closed amodiaquine or 3-chloro-8-methoxy-9-diethylaminomethyl-11*H*-indolo[3,2-*c*]quinoline (**3b**). Results from DNA binding and RNA polymerase inhibition suggest that the increased binding and activity of **3b** over that of amodiaquine (1a) results from the increased planar area afforded by **3b**. Similar considerations also suggest that the mechanism of action of amodiaquine differs from that of chloroquine.

Amodiaquine[1] (**1a**) is, along with chloroquine, one of the most widely used drugs both for the treatment of acute malaria and for suppression.[2,3] Generally, it is pharmacologically not differentiated from chloroquine, and an analogous mechanism of action is assumed because it contains the same number of C atoms between the two side-chain nitrogens. It is our belief, however, that the side chain in amodiaquine confers special steric and electronic properties to the molecule. When ω Hückel MO calculations were performed on chloroquine and amodiaquine models,[4,§] we found a difference between the corresponding energy levels of the highest occupied molecular orbital (HOMO) and the lowest empty molecular orbital (LEMO), as seen in Table I. Amodiaquine and chloroquine differ in chemical reactivity as evidenced by the fact that the former does not form a

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§MO calculations on chloroquine have been performed previously.[5]

Table I. Molecular Orbital Energy Levels in β Units and Melting Temperature of Native DNA in the Presence of Drugs

	Free base		Ring proton		pH 7.5[a]		pH 5.9[b]	
Compound	HOMO	LEMO	HOMO	LEMO	T_m, °C	ΔT_m, °C	T_m, °C	ΔT_m, °C
Chloroquine	+0.648	−0.549	+0.803	−0.332	80	12	80	12
1b					85	17	81	13
Amodiaquine	+0.566	−0.561	+0.679	−0.354	79.5	11.5	79.5	11.5
2					73	5	73.5	5.5
3b	+0.579	−0.576	+0.675	−0.367	80.5	12.5	85	17

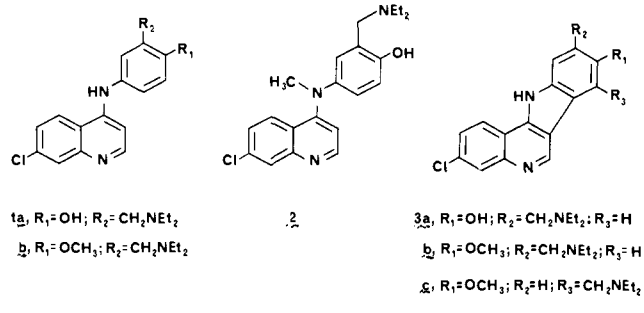
[a]pH value used in evaluating chloroquine activity in ref 9. [b]pH value used in evaluating chloroquine activity in ref 15. [c]ΔT_m values are calcd with respect to the T_m of calf thymus DNA (T_m = 68°).

complex with ferrihemic acid while the latter does.[6,7] Furthermore, in the proposed model for the interaction of chloroquine with its biological target molecule, DNA, it is difficult to envisage how the amodiaquine side chain would fit this model.[8,9] As demonstrated for some analogs of chloroquine with unsaturated side chains, the conformation of the side chain is a very important factor, with an influence beyond that of simple additive bond distances.[10]

In amodiaquine, the relative conformation of the two rings in the molecule might be of importance for its interaction with DNA; thus, in order to study this effect, we decided to compare it with 2 analogs in which the relative conformation of the 2 rings is fixed. One of them, N^4-methylamodiaquine# (**2**), is a compound with antimalarial activity (0.2 that of amodiaquine)[11] and is one in which, for steric reasons, the 2 rings are twisted out of plane. The other analog, with a totally flat structure that more closely resembles amodiaquine, is **3a** in which the extra bond connecting the 2 rings gives an indoloquinoline system.

The conformation of amodiaquine may lie in between the 2 extremes represented by these 2 compounds, and a rationale is proposed to the effect that the compound whose capacity to interact with DNA approaches or exceeds that of amodiaquine should give an indication of the conformation that is best suited for such interaction. The introduction of an extra bond in amodiaquine, as in **3a** or **b**, presents a different system but one which electronically is very similar to that of amodiaquine, as seen from the energy levels in Table I, and, therefore, the main variable is the steric one. In this system there are 2 possible positions for the diethylaminoethyl moiety, namely, **3a** or **b** and **3c**, when one considers it as derivable from ring closure of amodiaquine. Of these 2 possible configurations, that of **3a** or **b** is the desired one based on the postulate that the quinoline ring will interact with DNA through an intercalating mechanism taking place from the quinoline side, while **3c** would offer some steric hindrance to a close approach. Fortunately **3b** was the only compound isolated from the Fischer indole synthesis, in 45% yield, starting with **4** and **5b** (Scheme I).

Scheme I



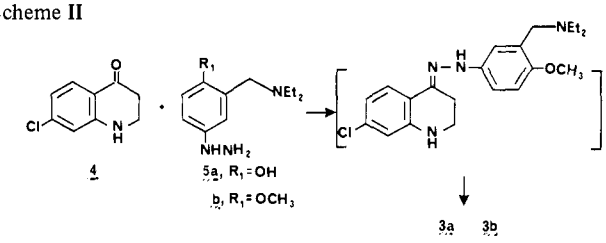
1a, R_1=OH; R_2=CH_2NEt_2
b, R_1=OCH_3; R_2=CH_2NEt_2

2

3a, R_1=OH; R_2=CH_2NEt_2; R_3=H
b, R_1=OCH_3; R_2=CH_2NEt_2; R_3=H
c, R_1=OCH_3; R_2=H; R_3=CH_2NEt_2

#We are grateful to Dr. L. M. Werbel, Parke Davis & Co., for a sample of this compound.

Scheme II



Based on steric arguments in the course of the indolization of the intermediate phenylhydrazone compound, **3b** is actually what one would expect. In this reaction indolization is followed by spontaneous dehydrogenation.[12,13] The structure of **3b** was confirmed by nmr spectroscopy, as indicated in Figure 1.

Synthesis of the indoloquinoline analog **3a** containing the phenolic group of amodiaquine was our first objective; however, owing to the instability of the hydrazine precursor **5a**, synthesis of **3a** was not feasible. Owing to the fact that amodiaquine (**1a**) and its Me ether (**1b**) possess the same antimalarial activity,[14] little or no difference in biological activity was expected between **3a** and **3b**.

Biological Activity. The activity is expressed in terms of the increase of the melting temp of native DNA (T_m). As seen from Table I, N^4-methylamodiaquine (**2**) has the lowest activity at both pH values customarily employed.[9,15] Chloroquine and amodiaquine are of comparable activity and are insensitive to changes in pH. The Me ether of amodiaquine (**1b**) and the indoloquinoline analog (**3b**) are both susceptible to changes in pH and surprisingly their activity is reversed; **1b** is as active at pH 7.5 as **3b** is at pH 5.9 and *vice versa*. Possibly these results stem from differences in pK_a values between **1b** and **3b**. Further studies will be made.

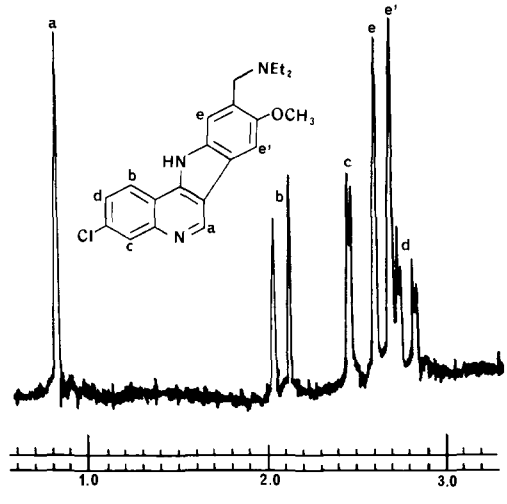


Figure 1. Nmr spectrum (100 MHz) of **3b** in CH_3OD. Chemical shifts in τ.

Table II. Per Cent Inhibition of RNA Polymerase.

Compound	% inhib of RNA polymerase
Chloroquine	20
Amodiaquine	12
2	6.8
1b	33.9
3b	55.7

However, our data appear to confirm that planarity of the molecules or the possibility of a planar transition state (such is the case in amodiaquine and **1b**) is an important factor in the interaction of 4-arylaminoquinolines with DNA. Therefore, the aromatic side chain of amodiaquine might be involved in the process of intercalation along with the quinoline ring contrasting with the role of the chloroquine side chain which is thought to fall outside the contour of the DNA molecule after intercalation of the quinoline ring has taken place.[8,9,**]

The 2 most active compounds in Table I, based upon T_m values, are also the 2 most effective compounds in the *in vitro* inhibition of *Escherichia coli* RNA polymerase (Table II). In addition, the hypochromic effect observed in the uv spectra of drug–DNA complexes with respect to the uv of the drug alone (Figures 2 and 3) provides further evidence of strong interaction of **1b** and **3b** with DNA.

Experimental Section

Melting points were taken in open capillary tubes by use of a Mel-Temp electric block. They are uncorrected. Uv spectra were detd in a 5×10^{-3} *M* Tris-HCl buffer solution at pH 7.5 by means of a Cary 14 recording spectrophotometer. Ir spectra were obtd with a Perkin-Elmer infracord spectrophotometer. Nmr spectra were obtd with either a Varian Associates HA-100 MHz or A-60A spectrometer. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. When indicated, all analytical results were within less than 0.4% of the calcd figures. Hückel MO calcns were carried out by means of an IBM 360/67 computer through use of a Fortran IV program for ω Hückel MO calcns. The parameters used are those recommended by Kier and Roche.[16] Calf thymus DNA was purchased from Worthington Biochemical Corp., Freehold, N. J. The melting temps of DNA and drug–DNA complexes were detd in either a 1.5×10^{-2} *M* potassium phosphate buffer at pH 5.9 or in a 5×10^{-3} *M* Tris-HCl buffer at pH 7.5 by means of a Gilford Model 2400 spectrophotometer equipped with a thermostatically regulated bath. The concn was 20 μg/ml. RNA polymerase was prepd by the method of Chamberling and Berg[17] as modified by Richardson.[18] Calf thymus DNA (20 μg) was preincubated with each agent (4×10^{-4} *M*) in 0.4 ml of Tris-HCl (5×10^{-3} *M*, pH 7.5) for 10 min at 37° prior to assay of polymerase activity. The assay mixt (0.4 ml) contd: 28.5 μmoles of Tris-HCl

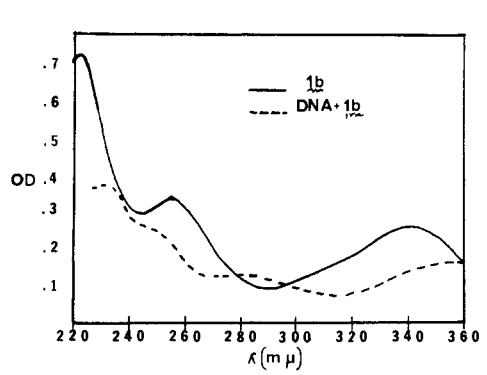


Figure 2.

**After this manuscript was written, Dr. L. H. Schmidt of Southern Research Institute in a personal communication stated that, unlike chloroquine, both amodiaquine and amopyroquine, which contain benzene rings in the side chain, cure the owl monkey of chloroquine-resistant *falciparum* malaria (human strains).

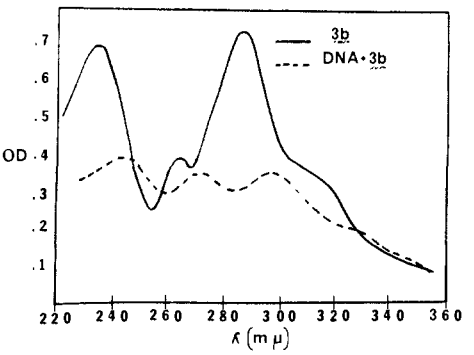


Figure 3.

(pH 8.0); 42.0 μmoles of KCl; 0.84 μmole of dithiothreitol; 0.4 μmole of $MnCl_2$; 100 mμmoles each of CTP, GTP, and UTP; 25 mμmoles of ATP; 0.1 μCi of ATP-^{14}C; 15 μg of polymerase protein; 5 μg of preincubated DNA; and 10^{-4} *M* of each agent to be tested. The assay mixts were incubated for 10 min at 37°, and the reactions were stopped by the addn of 3.0 ml of cold 5% TCA. The ppt was then collected on Millipore filters (0.45 μ pore size) washed 3 times with 2.5% TCA, dried, and assayed for radioactivity in a Packard Tri-Carb liquid scintillation spectrometer.

5-Hydrazino-2-methoxy-*N,N*-diethylbenzylamine (5b). To a soln of 8 g (0.0383 mole) of 5-amino-2-methoxy-*N,N*-diethylbenzylamine[1] in 50 ml of concd HCl, 2.64 g of $NaNO_2$, dissolved in 10 ml of H_2O, was added dropwise with the temp of the mixt between −5° and 0°. Excess HNO_2 was immediately destroyed with sulfamic acid, which was added in small portions until the reaction with starch-iodine paper was neg. With the temp maintd between −5° and 0°, 28 g of $SnCl_2 \cdot 2H_2O$ dissolved in 15 ml of concd HCl was added, and the mixt was stirred for 2 hr. The solid formed was collected and treated with 25% NaOH which caused the sepn of a bright yellow oily layer. It was extd with Et_2O and was dried (Na_2SO_4). Removal of the solvent *in vacuo* gave 4.4 g (50%) of **5b** as an oil. This oil was unstable in air but it was kept safely in a sealed ampoule under N_2: ir (neat) 2.90–3.20 (medium, broad, $NHNH_2$), 8.10 (strong, OCH_3), 11.45 (weak, broad, arom CH bending), 12.40 μ (medium, broad, arom CH bending); nmr ($CDCl_3$) τ 8.95 (t, 6, $N[CH_2CH_3]_2$), 7.35 (q, 4, $N[CH_2CH_3]_2$), 6.40 (s, 2, CH_2NEt_2, after D_2O exchange), 6.30 (s, 3, OCH_3, after D_2O exchange), and 3.10 (m, 3, arom protons).

3-Chloro-8-methoxy-9-diethylaminomethyl-11*H*-indolo[3,2-*c*]-quinoline (3b) Dihydrochloride Monohydrate. To a soln of 1.75 g (0.0096 mole) of 4[19] and 2.42 g (0.0108 mole) of the hydrazine **5b** in 20 ml of EtOH, 5 ml of concd HCl was added, and the mixt was refluxed for 18 hr. Cooling caused pptn of a yellow compd. It was collected on a filter, washed with $CHCl_3$, and dried. The mother liquid after standing and the addn of $CHCl_3$ produced a small second crop. Compd **3b** was obtd: 1.55 g (45%), mp 205–215°, which was recrystd from EtOH; mp 350° dec; ir (KBr) 2.95 (strong, NH), 6.80 (strong), 6.95 (strong), 8.10 (medium, OCH_3), 11.90 (medium, broad, arom CH bending), and 12.20 μ (medium, broad, arom CH bending); nmr (D_2O) τ 8.55 (t, 6, $N[CH_2CH_3]_2$), 6.60 (q, 4, $N[CH_2CH_3]_2$), 6.10 (s, 3, OCH_3), 5.75 (s, 2, CH_2NEt_2), 2.80 (m, 5, arom protons), and 1.20 (s, 1, arom 6H); 100-MHz nmr (CH_3OD), only the arom region, see Figure 1. *Anal.* ($C_{21}H_{22}ClN_3O \cdot 2HCl \cdot H_2O$) C, H, N.

Free Base. One half of the HCl salt obtd was dissolved in H_2O and the free base was pptd out by adding a small amt of 25% NaOH. The solid was washed with H_2O, filtered, dried, and recrystd from PhH as white needles: mp 284–285°; ir (KBr) 2.95 (medium, NH), 6.45 (strong), 6.70 (strong), 6.85 (strong), 8.00 (medium, OCH_3), 9.00 (strong), 12.00 (medium, arom CH bending), and 12.25 μ (strong, arom CH bending). *Anal.* ($C_{21}H_{22}ClN_3O$) C, H, N.

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Synthesis and Biological Activity of Some 4-Aryl-Substituted 4-Oxazolin-2-ones†

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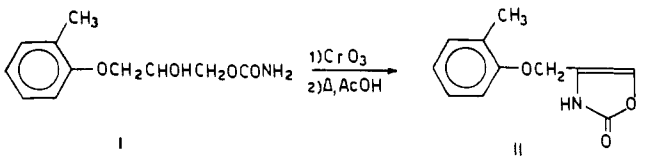
A series of 4-aryl-substituted 4-oxazolin-2-ones has been prepared by a method involving cyclization of carbamates of aryl hydroxymethyl ketones. On preliminary biological evaluation, some compounds produced myotonic symptoms and antagonized the barbiturate-induced sleep, while others showed mild to significant muscle relaxant and sedative activity. One of the "myotonic–analeptic" compounds, *viz.*, 4-phenyl-4-oxazolin-2-one, was obtained, through oxidation and cyclization, from the muscle relaxant drug, 2-hydroxy-2-phenylethyl carbamate (styramate).

During investigations on 5-unsubstituted 4-oxazolin-2-ones,[1] we have described[2] the conversion of the muscle relaxant drug mephenesin carbamate (I) into one such oxazolinone, namely, 4-(*o*-toloxymethyl)-4-oxazolin-2-one (II). The significant sedative properties displayed by II prompted us to investigate the preparation of analogous 4-substituted 4-oxazolin-2-ones, with the aim of establishing structure–activity relationships for this class of compounds. Another mephenesin-like muscle relaxant 1,2-glycol monocarbamate, 2-hydroxy-2-phenylethyl carbamate (styramate, V) appeared as an interesting starting material for our study, since it might easily lend itself to cyclization.

The present paper is concerned with the synthesis and preliminary pharmacological evaluation of a series of 5-aryl-substituted 4-oxazolin-2-ones (VII, and Table I) whose simplest member, 4-phenyl-4-oxazolin-2-one (**11**) was obtained from styramate.



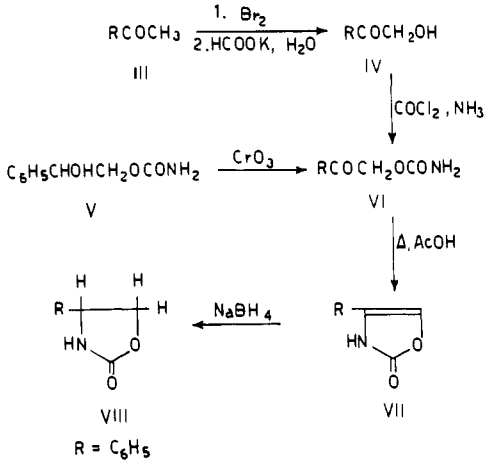
I II

Chemistry. The synthesis of all 4-monosubstituted-4-oxazolin-2-ones was accomplished by our previously described method.[1a]

The carbamates **1–10** were obtained on treatment with $COCl_2$ and NH_3 of the α-hydroxy ketones IV, which in turn were prepared from the aryl methyl ketones III by the procedure outlined in Scheme I. Phenacyl carbamate (**1**) was either obtained from phenacyl alcohol (IV, R = Ph) or, in slightly better yield, by CrO_3 oxidation of styramate. All hydroxy ketones, with the exception of *p*-fluorophenacyl and 2,5-dimethoxyphenacyl alcohol (IV, R = *p*-FC_6H_4 and 2,5-$(CH_3O)_2C_6H_3$, respectively) were known.

Structure proof for 4-phenyl-4-oxazolin-2-one (**11**), taken as a model for the whole group, was obtained as indicated in the Experimental Section. The structure of all other

Scheme I



compounds rests on analogous ir and nmr data, and on the similarity of the preparative method.

Biological Evaluation. All compounds listed in Table I and the 4,5-dihydro derivative of **11**, 4-phenyloxazolidin-2-one (VIII), for which pharmacological data were not found in the literature, were originally submitted for acute toxicity and behavioral studies in mice. This preliminary dose range testing evidenced two opposite types of activity: some of the compounds (**11**, **16**, **17**, and VIII) produced

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