Aq NaOH (30%) was added dropwise with vigorous stirring to maintain the pH between 10 and 10.5. After addn of about 10 ml of aq NaOH, the pH remained const and the Et_2O layer was removed to give an oil which crystd from heptane: 4-methoxy-1-naphthol, mp 126–128° (lit.[18] 124–125°); 5-methoxy-1-naphthol, mp 137–138° (lit.[19] 135–136°); 8-methoxy-1-naphthol, mp 55–57° (lit.[13] 55–56°); 3-methoxy-2-naphthol, mp 107–108° (lit.[20] 108°); 6-methoxy-2-naphthol, mp 148–149° (lit.[21] 136–137°) (*Anal.* ($C_{11}H_{10}O_2$) C, H); 7-methoxy-2-naphthol, mp 114–115° (lit.[22] 116–117°).

(b) By the method of Byrde,[23] 6-methoxy-1-naphthol, mp 82–84° (lit.[23] 85°), 7-methoxy-1-naphthol, mp 104–106° (lit.[23] 100–102°)(*Anal.* ($C_{11}H_{10}O_2$) C, H), and 5-methoxy-2-naphthol, mp 59–60° (lit.[24] unstable oil) (*Anal.* ($C_{11}H_{10}O_2$) C, H), were prepd by decompn of the appropriate methoxynaphthalene diazonium salt in dil acid under N_2. Purification of the crude phenol was effected by chromatog on acid-washed alumina with elution by C_6H_6–Et_2O (9:1), unlike the alk extn of Byrde;[23] it crystd from heptane as colorless needles.

(c) 2-Methoxy-1-naphthol was synthesized as an oil by treatment of 2-methoxy-1-naphthylmagnesium bromide with O_2 followed by decompn with dil acid.[25]

(d) Attempts to prep 3-methoxy-1-naphthol by decompn of the diazonium sulfate in dil H_2SO_4, by decompn of the diazonium fluoroborate in AcOH, by the action of O_2 or of trimethyl borate[26] on 3-methoxy-1-naphthylmagnesium bromide followed by acid decompn, yielded only small amts of 2-methoxy-1,4-naphthoquinone, yellow needles from aq EtOH, mp 183–184° (lit.[27] 184–185°). *Anal.* ($C_{11}H_8O_3$), C, H.

(e) 4-Acetamido-1-naphthol, mp 186–187° (lit.[28] 187°), and 4-methyl-1-naphthol, mp 82–83° (lit.[29] 85°), were prepd by the lit. methods.

Substituted Naphthyl Ethers of *N*-Acetyl-3,5-dinitro-L-tyrosine Ethyl Ester (Table I, 1–12).—A 2-fold excess of the appropriate substituted naphthol was condensed with *N*-acetyl-3,5-dinitro-L-tyrosine ethyl ester by standard methods.[2,10,11] Formation of the 8′-methoxy-1′-naphthyl ether (**6**) required γ-picoline as solvent heated under reflux for 1.5 hr, and a 1:1 molar ratio of phenols, in place of pyridine and standard reaction conditions. Crystd from aq EtOH.

Substituted Naphthyl Ethers of *N*-Acetyl-3,5-diiodo-L-tyrosine Ethyl Ester (Table I, 13–20).—The dinitro compds (**1–12**) were hydrogenated, bis-diazotized, and decompd in aq I_3^- soln by standard methods.[2,10,11] The crude products were chromatogd on acid-washed alumina and crystd from aq EtOH. All yields were low due to tar formation, and no diiodo compds could be isolated from the dinitro intermediates **1, 4, 6, 10**.

Substituted Naphthyl Ethers of 3,5-Diiodo-L-tyrosine (Table II, 21–28).—The diiodo methoxynaphthyl ethers (**13–15, 18–20**) were hydrolyzed to the amino acids (Table II, **21–23, 26–28**) using HI in AcOH.[2,10] Compds **16** and **17** were hydrolyzed with HCl in AcOH.[9] The free amino acids were isolated by isoelectric pptn.

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Biosynthesis of Coenzymes Q by Malarial Parasites. 2. Coenzyme Q Synthesis in Blood Cultures of Monkeys Infected with Malarial Parasites (*Plasmodium falciparum* and *P. knowlesi*)†

JEROME V. SCHNELL, WASIM A. SIDDIQUI, QUENTIN M. GEIMAN,

Department of Preventive Medicine, Stanford University School of Medicine, Stanford, California 94305

FREDERICK S. SKELTON, KENNETH D. LUNAN, AND KARL FOLKERS*

Stanford Research Institute, Menlo Park, California 94025

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The incorporation of [^{14}C]*p*-hydroxybenzoic acid into coenzymes Q by cultures of normal monkey blood and monkey blood infected with malarial parasites has been measured. The host blood cells and the corresponding parasites are: rhesus monkey blood with *Plasmodium knowlesi*, and night monkey (*Aotus trivirgatus*) blood with *P. falciparum*. Only coenzyme Q_{10} was labeled in normal *Aotus* blood cultures, while coenzymes Q_8, Q_9, and Q_{10} were labeled in *Aotus* blood cultures infected with *P. falciparum*. Effects of incubation time and of parasitemia on incorporation were compared for rhesus blood cultures infected with *P. knowlesi* and *Aotus* blood cultures infected with *P. falciparum*. No correlation of extent of incorporation with growth stage could be demonstrated for rhesus blood infected with *P. knowlesi*.

It was demonstrated[1] that rhesus monkey blood cells which are infected with *Plasmodium knowlesi* incorporate [^{14}C]*p*-hydroxybenzoic acid into coenzymes Q_8, Q_9, and Q_{10} (I, n = 8, 9, and 10) while normal rhesus blood cells synthesize only coenzyme Q_{10} from the same labeled precursor. These data agreed with the results on the identification of coenzymes Q from normal duck blood and duck blood infected with *P. lophurae*.[2] The recent discovery that a new world monkey (*Aotus trivirgatus*) is susceptible to infection with *P. falciparum*[3] provided an opportunity to study the biosynthesis of coenzyme Q by this important human parasite. This

* To whom correspondence should be addressed at the Institute for Biomedical Research, The University of Texas at Austin, Austin, Texas 78712.
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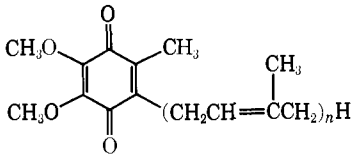
report concerns the nature of the incorporation of labeled *p*-hydroxybenzoic acid into coenzymes Q by cultures of normal monkey blood cells and blood cells infected with either *P. falciparum* or *P. knowlesi*.



I

Results

The data on the activity and identity of the [^{14}C]-coenzymes Q biosynthesized from labeled *p*-hydroxybenzoic acid upon incubation with aliquots of normal *Aotus* blood cells and cells infected with *P. falciparum* are in Table I. These data show that only coenzyme

TABLE I

INCORPORATION OF [^{14}C]*p*-HYDROXYBENZOIC ACID INTO COENZYMES Q BY BLOOD CULTURES OF NORMAL AND INFECTED (*P. falciparum*) NIGHT MONKEYS (*Aotus trivirgatus*)

Incubation time, hr	Parasitemia, %	[^{14}C]Coenzymes Q isolated by tlc, total dpm	Side chain length by reversed-phase paper chromatog
1	5	40	
8	5	281	(7), 8, 9, 10[a]
1	0	5	
8	0	93	10

[a] Relative radioactivity 8 ≫ 10 > 9 > 7.

Q_{10} is biosynthesized in the normal blood, and that coenzymes Q_8, Q_9, and probably Q_7 are biosynthesized by blood cells infected with *P. falciparum*. Coenzyme Q_8 was the most highly labeled, and coenzymes Q_{10} and Q_9 showed progressively lower activity. This relative activity also showed that coenzyme Q_8 is the dominant coenzyme Q of *P. falciparum*.

These results on *P. falciparum* agree with the labeling of the coenzymes Q observed[1] for cultures of rhesus monkey blood cells with and without *P. knowlesi*. In these experiments, the radioactivity of the coenzymes Q formed by *Aotus* blood cells infected with *P. falciparum* was less than that formed by rhesus blood cells infected with *P. knowlesi*. Also, the radioactivity of the coenzymes Q varied considerably from one experiment to another throughout these studies.

If the biosynthesis of coenzymes Q in infected blood is principally due to the parasites, then the extent of incorporation of [^{14}C]*p*-hydroxybenzoic acid should increase directly with the parasitemia. The results of experiments to test this possibility for *P. knowlesi* and *P. falciparum* are summarized in Table II. In both cases the infected blood cultures showed greater incorporation of [^{14}C]*p*-hydroxybenzoic acid than was observed for the control cultures. Increased incorporation was observed as the infection of *P. falciparum* in the *Aotus* blood increased from 5 to 15%, but a linear response was not evident. Increasing the level of erythrocytes containing *P. knowlesi* from 6 to 17% did not lead to a significantly increased level of incorporation.

The effect of incubation time on the extent of [^{14}C]*p*-hydroxybenzoic acid incorporation was investigated in

TABLE II

INCORPORATION OF [^{14}C]*p*-HYDROXYBENZOIC ACID INTO COENZYMES Q BY BLOOD CULTURES IN RELATION TO LEVEL OF PARASITEMIA

Blood cultures[a]	Parasitemia, %	[^{14}C]Coenzymes Q, total dpm
Normal rhesus blood	0	200
Infected rhesus blood[b]	6	1692
Infected rhesus blood[b]	17	1700
Normal *Aotus* blood	0	98
Infected *Aotus* blood[c]	5	172
Infected *Aotus* blood[c]	15	352

[a] Incubation time of 6 hr. [b] Infected with *P. knowlesi*. [c] Infected with *P. falciparum*.

TABLE III

INCORPORATION OF [^{14}C]*p*-HYDROXYBENZOIC ACID INTO COENZYMES Q BY BLOOD CULTURES IN RELATION TO INCUBATION TIME

Incubation time, hr	[^{14}C]Coenzymes Q, total dpm: Rhesus blood, Normal	Rhesus blood, Infected[a]	*Aotus* blood, Normal	*Aotus* blood, Infected[b]
1	0	858	0	40
3	20	1020	22	112
6	80	1353	98	172

[a] Infected with *P. knowlesi*; parasitemia, 5%. [b] Infected with *P. falciparum*; parasitemia, 5%.

the experiments summarized in Table III. The rapid incorporation of label in rhesus monkey blood infected with *P. knowlesi* is evident from these data since the level of radioactivity in the coenzymes Q at 1 hr was 63% of that observed after 6 hr incubation. The level of incorporation of label in *Aotus* blood infected with *P. falciparum* progressively increased with incubation time, but a linear relationship was not observed. In these two experiments, the level of incorporation of label in the normal blood cultures of the 2 host species was comparable.

Since *P. knowlesi* infections in rhesus monkeys are synchronous, it was possible to study the biosynthesis of coenzymes Q in a given morphologic form of the parasite. This made it possible to compare the level of incorporation of [^{14}C]*p*-hydroxybenzoic acid when the parasites present at the start of 2 experiments were at different growth stages. Two experiments are summarized in Table IV. In experiment A 90% of the parasites were ring forms, and in experiment B 81% of the parasites were trophozoite forms. The results in the last column of Table IV indicate that most of the incorporation occurred during the first 8 hr of incubation for both forms. The higher level of incorporation observed for trophozoite forms in relation to ring forms is probably due to variations other than growth stages.

Discussion

The results, in Table I, demonstrate that [^{14}C]*p*-hydroxybenzoic acid is incorporated into coenzymes Q to a greater extent by *Aotus* blood cells which are infected with *P. falciparum* than by normal *Aotus* blood cells. In the infected blood cultures there was incorporation of [^{14}C]*p*-hydroxybenzoic acid into coenzymes Q_8, Q_9, and probably Q_7 as well as into coenzyme Q_{10}. It is believed that [^{14}C]coenzyme Q_{10} in the control cultures is biosynthesized by the *Aotus* leucocytes as was found, previously, for rhesus leucocytes.[1] The higher

TABLE IV

INCORPORATION OF [^{14}C]*p*-HYDROXYBENZOIC ACID INTO COENZYMES Q BY BLOOD CULTURES IN RELATION TO GROWTH STAGE OF *P. knowlesi*

Experiment[a]	Incubation time, hr	Differential parasite count,[b] % R	T	S	G	[^{14}C]Coenzymes Q, total dpm
A	0	90	8	2		
	8	15	82	3		676
	16	6	89	5		866
	24	6	73	20	1	876
B	0	2	81	14	3	
	8	10	14	76		1439
	18	82	11	5	2	1321
	24	38	56	16		1439

[a] Initial parasitemia in both experiments was 3%. [b] R = rings, T = trophozoites, S = schizonts and segmenters, and G = gametocytes. The sequence of events following invasion of the host erythrocyte by the parasite involves progressive development through ring, trophozoite, schizont, and segmenter stages. Gametocytes are sexual forms which may differentiate from trophozoite stages.

radioactivity of coenzyme Q_8, relative to the other labeled coenzymes Q, shows that coenzyme Q_8 may be the dominant coenzyme Q in the metabolism of the parasite. This essential role of coenzyme Q_8 may pertain to all malarial parasites since coenzyme Q_8 is apparently the dominant coenzyme Q for *P. knowlesi*,[1] *P. lophurae*,[2] and *P. cynomolgi*.[4]

Tables II, III, and IV show that the total incorporation varied in these experiments. There may be several reasons for this variability. The biosynthesis of coenzyme Q_8 from *p*-hydroxybenzoic acid by malarial parasites represents a pathway of lipid metabolism, and the intermediates in the sequence are not yet established for these organisms. The blood samples employed in these experiments could have contained precursors, intermediates, or other products which could affect the utilization of the labeled *p*-hydroxybenzoic acid. The levels of such substances could vary with parasite species, host species, host diet, and other factors. The variability of this experimental system is perhaps indigenous; the blood cells are a mixture of cell types having a variety of functions and characteristics. Also the malarial parasite has a complex growth cycle (see footnote to Table IV). Despite these uncertainties it is both possible and informative to compare the incorporation data from these experiments with blood infected with *P. knowlesi* and *P. falciparum*.

Comparison of the data presented in Tables II and III shows clearly that rhesus erythrocytes infected with *P. knowlesi* incorporated the labeled *p*-hydroxybenzoic acid more rapidly than did *Aotus* blood infected with *P. falciparum*. There are at least two reasons why this result is plausible: (1) *P. knowlesi* has a 24-hr life cycle, while *P. falciparum* has a 48-hr life cycle; (2) the growth medium employed for these studies[5] was formulated for *P. knowlesi* and may not be optimal for the growth of *P. falciparum*. The rapid incorporation rate for rhesus blood infected with *P. knowlesi* may account for the results in Table II, where increased parasitemia did not produce increased incorporation, and in Table III, where prolonged incubation times produced only moderate increases in incorporation. Perhaps lower levels of parasitemia and shorter incubation times are required before the predicted responses can be observed.

The data of Table IV show that most of the incorporation occurred during the first 8 hr of incubation and that the label incorporated was conserved throughout the remainder of the incubation period. These two points suggest that the extent of biosynthesis of coenzyme Q_8 does not depend upon the morphologic stages present at the start of these experiments. When [^{14}C]*p*-hydroxybenzoic acid was added to the cultures after 8 hr of incubation in the growth medium, the extent of incorporation was only about 10–15% of that incorporation observed when the labeled *p*-hydroxybenzoic acid was added at the start of the incubation. This effect was also independent of the nature of the starting growth stages. This observation suggests that the biosynthesis of coenzyme Q_8 may be impaired after 8 hr incubation *in vitro* or that coenzyme Q biosynthesis may have proceeded from unlabeled materials present in the blood cells or the growth medium. Elucidation of the biosynthetic sequence between *p*-hydroxybenzoic acid and coenzyme Q_8 by malarial parasites may be necessary before interpretation of these observations is possible.

Experimental Section

A. *In Vitro* **Culture Methods.**—The blood samples were obtained from normal rhesus monkeys (*Macaca mulatta*) and rhesus monkeys infected with *P. knowlesi*,‡ which was maintained by weekly iv inoculation of erythrocytic stages into rhesus monkeys. *P. falciparum* was first transmitted to the night monkey (*Aotus trivirgatus*) in our laboratory,[3] and the two strains of *P. falciparum* used for these studies were regularly maintained by serial blood passages in this host. In 4 experiments, the blood cultures were incubated with the modified synthetic medium,[6] and stearic acid was used as a plasma replacement.[7] The techniques for maintaining, counting, and evaluating the parasites were based on those described.[8] All cultures were maintained under bacterial free conditions.

B. Incorporation of ^{14}C-Labeled *p*-Hydroxybenzoic Acid into Coenzymes Q.—The normal (control) and infected blood samples (1.5 ml of blood cells in 9 ml of medium) were incubated (in duplicate) at 37° for a specified length of time. [^{14}C]*p*-Hydroxybenzoic acid[9] (9.0×10^4 cpm/sample, specific activity 282 mCi/mmole) was added at the start of incubation. At the end of the specified incubation period, the cells from each sample were collected by centrifugation (1500–2000 rpm), washed with modified Ringer's soln,§ and frozen in a Dry Ice–acetone bath. These cells were stored frozen until they were processed.

C. Isolation and Identification of the Coenzymes Q from Blood Cells.—The frozen blood cells were lyophilized and extd for 9 hr on a table shaker with 25 ml of hexane. After filtration, the hexane exts were evapd to dryness *in vacuo*. Unlabeled coenzyme Q_{10} (140 μg) was added to the residue as a carrier, and the mixt was twice chromatogd (multiple pass) to constant specific

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‡ The strain used for these studies was originally isolated from a monkey (*Macaca irus*) from Malaya and was given to Q. M. Geiman in 1965 by E. H. Sadun of the Walter Reed Army Institute of Research, Washington, D. C.

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§ Composition of modified Ringer's soln used for washing blood cells: NaCl, 8.21 g; KCl, 0.30 g; $CaCl_2$, 0.20 g; $MgCl_2$, 0.10 g; and H_2O, 1 l.

activity# on tl silica gel G plate** using Et_2O–hexane (10:90 v/v) as the solvent. The coenzyme Q area adjacent to a coenzyme Q_{10} reference was scraped from the plate and eluted with Et_2O. The radioactivity in the residue, after evapn of Et_2O, was measured using a Nuclear Chicago liquid scintillation spectrophotometer.

In an identical experiment, the residue contg the isolated coenzymes Q with the coenzyme Q_{10} carrier and the appropriate reference coenzymes Q were applied to a Whatman No. 3 MM chromatographic paper impregnated with Dow Corning No. 550 silicone oil. Reversed-phase paper chromatog in *n*-PrOH–H_2O (70:30 v/v), which will sep coenzymes Q with isoprenyl side chain lengths 10 through 7 (1, n = 7), was performed.

The coenzymes Q_9 and Q_7 areas from the reversed-phase paper chromatogram were rechromatogd in order to determine if these coenzymes Q were actually present or if the radioactivities in these areas were fringes of the more highly labeled coenzymes Q_{10} and Q_8, resp. In a typical procedure the coenzymes Q_9 and Q_7 areas, cut from the original paper chromatogram, were eluted with Et_2O; and each residue, after evapn of Et_2O, was applied to separate strips of silicone-impregnated paper. Reversed-phase paper chromatog was performed, as above, and strips corresponding to the areas of reference coenzyme Q_9 and Q_7, as well as narrow strips immediately above and below each area, were cut from the paper while still damp with solvent. Coenzymes Q were eluted from each strip with Et_2O and the radioactivity in each residue, after evapn of Et_2O, was measured by liquid scintillation counting.

Constant specific activity of the coenzymes Q was usually attained after the first tlc sepn. Relative specific activities of the product coenzymes Q were not indicated due to the nature of [^{14}C]*p*-hydroxybenzoic acid as a specific precursor of coenzyme Q.[9]

** Brinkman precoated silica gel G tl plates (20 × 20 cm) were marked into halves, and each half marked into 4 individual tl segments (5 × 10 cm). Four samples could be chromatographed at one time, and the coenzyme Q isolated from a min quantity of silica gel.

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Synthesis of New 5,8-Quinolinequinones as Inhibitors of Coenzyme Q and as Antimalarials†

THOMAS H. PORTER, FREDERICK S. SKELTON, AND KARL FOLKERS*

Institute for Biomedical Research, The University of Texas at Austin, Austin, Texas 78712

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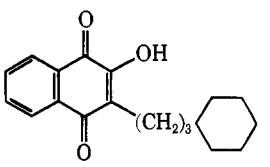
As based on the essentiality of coenzyme Q_8 in the metabolism of *Plasmodium*, new lipoidal quinones have been synthesized as potential inhibitors of the biosynthesis and/or function of coenzyme Q_8 in the metabolism of *Plasmodium* and as potential antimalarials. Twelve 7-alkyl-6-hydroxy-5,8-quinolinequinones and four 6-alkyl-7-hydroxy-5,8-quinolinequinones have been synthesized. Most of these derivatives were tested for antimalarial activity against *Plasmodium berghei* in the mouse, and representative compounds were tested against *P. gallinaceum* in the mosquito. Four of the substituted 6-hydroxy-5,8-quinolinequinones were active by the criterion (100% increase in survival) for antimalarial activity against *P. berghei*. Activity was lost when the 6-hydroxy-5,8-quinolinequinones were reduced to the tetrahydro derivatives. One of the substituted 7-hydroxy-5,8-quinolinequinones cured the mouse of malaria due to *P. berghei* and without evidence of toxicity.

The prodigious research on antimalarials during World War II included extensive studies by Fieser and by Leffler and their many respective coworkers on naphthoquinones.[1a] Emerging from all this effort were data on two naphthoquinones (I and II) which showed antimalarial activity in men.[1b] For II, it was stated that "two patients with primary vivax infection were given 2 g . . . for 4 days . . .. The results were dramatic. . . . The patients left the hospital in perfect condition with no parasites in the blood . . . or without relapse."[1c] For I, it was said that the "effect was not satisfactory, but enough to show . . . definite antimalarial activity in man."

In 1967, Fieser and Archer[2] and their respective associates synthesized the new naphthoquinone III, which has been extensively investigated as an antimalarial according to information kindly made available to us through Walter Reed Army Institute of Research, Washington, D.C.



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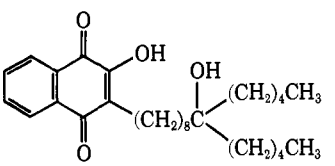
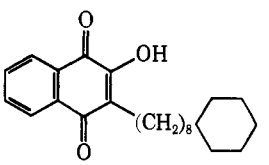


II



III

All of this research during World War II on naphthoquinones as potential antimalarials was apparently based on the concept that vitamin K was intrinsic in the metabolism of *Plasmodium*. Such a concept was not unreasonable at that time since it was known that vitamin K is intrinsic in the metabolism of many microorganisms. A search for the presence of vitamin K in *Plasmodium* by Skelton, *et al.*,[3] was unsuccessful, and they could not detect vitamin K by reversed-phase paper chromatography or mass spectral analysis or by a

† Coenzyme Q. 136.

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