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.

Acknowledgments.—We wish to thank Mr. W. F. Argall, Mrs. Esther Montero, Mrs. Kathleen Edelman, Miss Elizabeth Riddleberger, and Miss Paula Harris for excellent technical assistance. This investigation was supported by U. S. Army Medical Research and Development Command Contracts DA-49-193-MD-2587 and DA-49-193-MD-2784. This is Contribution No. 505 from the Army Research Program on Malaria.

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

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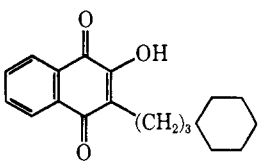
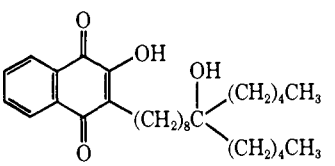
As based on the essentiality of coenzyme Q_8 in the metabolism of *Plasmodium*, new lipoidal quinones have been synthesized as potential inhibitors of the biosynthesis and/or function of coenzyme Q_8 in the metabolism of *Plasmodium* and as potential antimalarials. Twelve 7-alkyl-6-hydroxy-5,8-quinolinequinones 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."

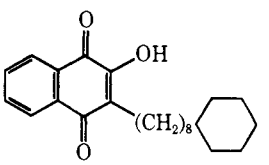
In 1967, Fieser and Archer[2] and their respective associates synthesized the new naphthoquinone III, which has been extensively investigated as an antimalarial according to information kindly made available to us through Walter Reed Army Institute of Research, Washington, D.C.



I



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.

(1) (a) L. F. Fieser, E. Berlinger, F. J. Bondhus, F. C. Chang, W. C. Dauben, M. G. Ettlinger, G. Fawaz, M. Fields, M. Fieser, C. Heidelberger, H. Heymann, A. M. Seligmann, W. R. Vaughan, A. G. Wilson, E. Wilson, M. Wu, and M. T. Leffler, K. E. Hamlin, R. J. Hathaway, E. J. Matson, E. E. Moore, M. B. Moore, R. T. Rapala, and H. E. Zaugg, *J. Amer. Chem. Soc.*, **70**, 3151 (1948); (b) *ibid.*, **70**, 3154 (1948); (c) *ibid.*, **70**, 3155 (1948).

(2) L. F. Fieser, J. P. Schirmer, S. Archer, R. R. Lorenz, and P. I. Pfaffenbach, *J. Med. Chem.*, **10**, 513 (1967).

(3) F. S. Skelton, P. J. Rietz, and K. Folkers, *ibid.*, **13**, 602 (1970).

labeling method using *in vitro* cultures of *P. knowlesi* incubated with [^{14}C]shikimic acid.

When coenzyme Q (ubiquinone, IV) became known in biochemistry, it was predicted that this quinone could exist in *Plasmodium* as an intrinsic component of metabolism; if so, the antimalarial activity of the naphthoquinones I, II, and III could, at least in part, be due to inhibition of coenzyme Q in the manner of antimetabolites.

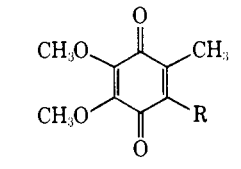
A search for the presence of coenzyme Q in *Plasmodium* was successful. The apparent occurrence of coenzymes 8 and 9 in *P. lophurae* was reported by Rietz, *et al.*[4] Skelton, *et al.*,[5] next demonstrated that *P. knowlesi* biosynthesizes [^{14}C]coenzymes Q_8, Q_9, and perhaps Q_7 from [^{14}C]*p*-hydroxybenzoic acid. Then, it was shown that coenzyme Q_8 was biosynthesized by *P. cynomolgi* and *P. berghei* by Skelton, *et al.*[3]

The biosynthesis of coenzyme Q was also demonstrated in blood cultures of monkeys infected with *P. alciparum* and *P. knowlesi* by Schnell, *et al.*[6]

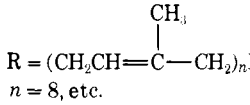
With the establishment of the presence and biosynthesis of the dominant coenzyme Q_8 in *Plasmodium* and the absence of vitamin K, it was appropriate to test established antimalarials and also the naphthoquinones to see if they actually do have antimetabolite activity for coenzyme Q.

Both chloroquine and menoctone were found to inhibit coenzyme Q–enzyme systems by Skelton, *et al.*[7]

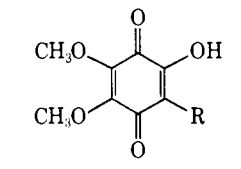
At this stage of progress, the synthesis of new quinones as potential antimalarials could be designed upon the new knowledge of the existence of coenzyme Q_8 in the metabolism of *Plasmodium*. Catlin, *et al.*, synthesized new hydroxyquinones, V, based on the structure of coenzyme Q and found that they do inhibit coenzyme Q–enzyme systems.[8] The synthesis of these new 2,3-dimethoxy-1,4-benzoquinones was described by Catlin, *et al.*[9]



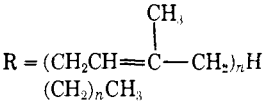
IV



$R = (CH_2CH{=}C(CH_3){-}CH_2)_nH$, $n = 8$, etc.



V



$R = (CH_2CH{=}C(CH_3){-}CH_2)_nH$, $(CH_2)_nCH_3$

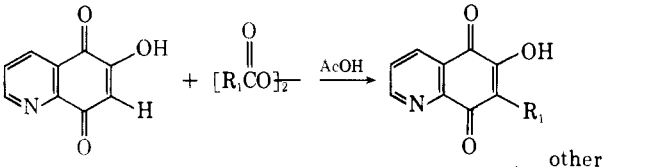
It is important to recognize that the coenzyme Q_8 of *Plasmodium* is a lipoidal substance largely because of the 40 C atoms in its isoprenoid side chain. Consequently, one may consider that effective inhibitors of coenzyme Q might also have to be lipoidal in nature. For this reason, the synthesis of several categories of lipoidal quinones is currently a part of our research toward new prophylactic and curative-type antimalarials.

One category of lipoidal quinones is represented by the 7-alkyl-6-hydroxy-5,8-quinolinequinones, VI, and the 6-alkyl-7-hydroxy-5,8-quinolinequinones, VII, compound types previously synthesized by Pratt and Drake.[10,11] In the present investigation it was of interest to prepare new additional alkylated 5,8-quinolinequinones with longer alkyl chains to increase the lipoidal character of the molecule. These compounds may be synthesized by alkylation with a diacyl peroxide of the 6- and 7-hydroxy-5,8-quinolinequinones, resp. Previously, 7-undecyl-6-hydroxy-5,8-quinolinequinone was shown to exhibit significant amebicidal activity against an induced *Entamoeba histolytica* infection in the guinea pig.[11,12] It was desirable to synthesize the corresponding N analogs of menoctone, 7-ω-cyclohexyloctyl-6-hydroxy-5,8-quinolinequinone and 6-ω-cyclohexyloctyl-7-hydroxy-5,8-quinolinequinone, in order to compare their *in vitro* inhibitory activities against coenzyme Q with that of monoctone and in order to determine their *in vivo* antimalarial activities in systems conducted by the Walter Reed Army Institute for Research.

These quinolinequinones have been found to inhibit mitochondrial reductase systems, and the inhibition is reversible by coenzyme Q. For example, Skelton, *et al.*,[13] reported that 7-ω-cyclohexyloctyl- and 7-*n*-pentadecyl-6-hydroxy-5,8-quinolinequinones, are not only inhibitors of coenzyme Q reductase systems but are more effective inhibitors than the exemplary menoctone.

Organic Synthesis.—The synthesis of the alkylated 6- or 7-hydroxy-5,8-quinolinequinones, VI and VII, respectively, was accomplished by treating the appropriate dialkanoyl peroxide with 6- or 7-hydroxy-5,8-quinolinequinone, resp, in AcOH as shown in Schemes I and II.[10,11]

SCHEME I



VI + other products

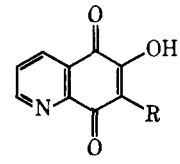
$R_1 = (CH_2)_4CH_3$; $CH_2C_6H_{11}$
$(CH_2)_7CH_3$; $(CH_2)_3C_6H_{11}$
$(CH_2)_{12}CH_3$; $(CH_2)_5C_6H_{11}$
$(CH_2)_{13}CH_3$; $(CH_2)_8C_6H_{11}$
$(CH_2)_{14}CH_3$; $(CH_2)_4C_6H_{11}$
$(CH_2)_{15}CH_3$;
$(CH_2)_{18}CH_3$;

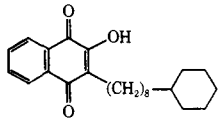
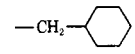
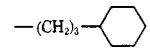
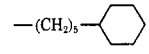
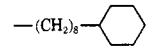
Each of the new alkylated quinolinequinone derivatives is a yellow substance with a relatively sharp melting point. The derivatives containing a cyclohexyl moiety crystallized more readily and were obtained in higher yields than the derivatives containing a straight alkyl chain.

(4) P. J. Rietz, F. S. Skelton, and K. Folkers, 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., M 23.
(5) F. S. Skelton, K. D. Lunan, K. Folkers, J. V. Schnell, W. A. Siddiqui, and Q. M. Geiman, *Biochemistry*, **8**, 1284 (1969).
(6) J. V. Schnell, W. A. Siddiqui, Q. M. Geiman, F. S. Skelton, K. D. Lunan, and K. Folkers, *J. Med. Chem.*, in press.
(7) F. S. Skelton, R. S. Pardini, J. C. Heidker, and K. Folkers, *J. Amer. Chem. Soc.*, **90**, 5334 (1968).
(8) J. C. Catlin, R. S. Pardini, G. D. Daves, Jr., J. C. Heidker, and K. Folkers, *ibid.*, **90**, 3572 (1968).
(9) J. C. Catlin, G. D. Daves, Jr., and K. Folkers, *J. Med. Chem.*, **14**, 45 (1971).
(10) Y. T. Pratt and N. L. Drake, *J. Amer. Chem. Soc.*, **77**, 4664 (1955).
(11) Y. T. Pratt and N. L. Drake, *ibid.*, **79**, 5024 (1957).
(12) D. J. Taylor and J. Greenburg, *Amer. J. Hyg.*, **56**, 58 (1952).
(13) F. S. Skelton, C. M. Bowman, T. H. Porter, K. Folkers, and R. S. Pardini, *Biochem. Biophys. Res. Commun.*, **43**, 102 (1971).

TABLE I

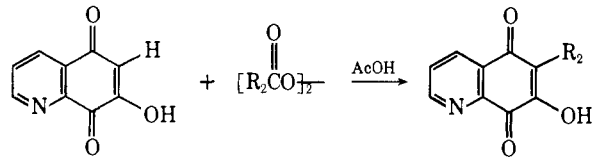
ANTIMALARIAL ACTIVITY OF CERTAIN 7-ALKYL-6-HYDROXY-5,8-QUINOLINEQUINONES IN THE *in Vivo* ANTIMALARIAL DRUG SCREEN



R	Mp,[f] °C	Yield, %	Mouse test (*P. berghei*) Activity,[a] mg/kg	Mouse test (*P. berghei*) $(T - C)$,[b] mg/kg	Mosquito test (*P. gallinaceum*)[c]
					
Reference compound			Active at 40; curative at 160	9.2 at 160	Complete suppression of oocysts and sporozoites
$(CH_2)_4CH_3$	102–104	14			
$(CH_2)_7CH_3$	103–104	33		1.3 at 640	
$(CH_2)_{12}CH_3$	93–94	22	Active at 320	9.3 at 320 11.3 at 640	
$(CH_2)_{13}CH_3$	101–102	13	Active at 320	8.2 at 320	25% suppression of oocysts and 75% suppression of sporozoites
$(CH_2)_{14}CH_3$	96–98	17	Active at 160; curative at 640	8.1 at 160 10.5 at 320 13.2 at 640	
$(CH_2)_{15}CH_3$	99–102	20[d]			
$(CH_2)_{18}CH_3$	97–99	14[d]	Inactive at 640[e]	0.4 at 320 0.6 at 640	Inactive
	181–182	23		0.1 at 320	
	124–125	23		1.7 at 320 3.3 at 640	
	129–131	30		2.5 at 320	
	119–121	24	Active at 320	6.2 at 320	
$(CH_2)_4C_6H_5$	143–144	36		0.5 at 320 0.7 at 640	

[a] All compds were administered sc in graded doses to groups of 5 mice. [b] $(T - C)$ = change in survival time in days of treated and nontreated (control) mice. [c] All concns of compds administered (in sucrose) were at 0.1%. [d] Yield of crude product. [e] Mp, 90–93°, test sample; [f] Anal. sample.

SCHEME II



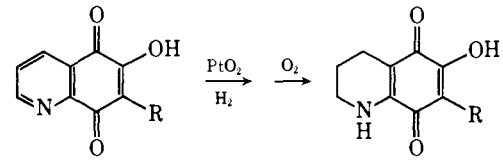
VII

+

other products

$R_2 = (CH_2)_7CH_3$; $(CH_2)_5C_6H_{11}$
$(CH_2)_{13}CH_3$ $(CH_2)_8C_6H_{11}$

SCHEME III



$R = (CH_2)_8C_6H_{11}$
$(CH_2)_{13}CH_3$

Hydrogenation of representative 7-alkyl-6-hydroxy-5,8-quinolinequinones, VI, using PtO_2 as catalyst followed by air oxidation, yielded the corresponding 1,2,3,4-tetrahydro-5,8-quinolinequinone derivatives in good yield as indicated in Scheme III.

The intermediate hexahydroquinones could not be isolated because of their extreme susceptibility to air oxidation. The tetrahydro derivatives are dark purple crystalline materials.

Antimalarial Activity.—Most of these compounds were tested for antimalarial activity against *Plasmodium berghei* in mice,[14] and representative compounds were tested against *P. gallinaceum* in the mosquito (*Aedes aegypti*).[15] A single dose at the desired level is given sc 72 hr after the mice are infected with *P. berghei*. A minimum mean survival time of 13.0 days is required for the compound to be declared active. Mice

(14) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).

(15) E. J. Gerberg, L. T. Richard, and J. B. Poole, *Mosquito News*, **26**, 359 (1966).

living 60 days or more after treatment are considered as cured.

As seen in Table I, the *in vivo* activities of the 7-alkyl-6-hydroxy-5,8-quinolinequinones seem generally to increase as the length of the side chain is increased to 15 CH_2 units; with a longer side chain, as exemplified by 7-*n*-nonadecyl-6-hydroxy-5,8-quinolinequinone, a decrease in activity is observed. Changes in survival time ($T - C$) for the alkylated 6-hydroxy-5,8-quinolinequinones show that 5 mice treated with the pentadecyl analog at a 640 mg/kg dose level survived for 13.2 days, and one of them was cured at this dose level. Mice treated with the ω-cyclohexyloctyl, tridecyl, tetradecyl, pentadecyl, and nonadecyl analogs survived for 6.2, 9.3, 8.2, and 10.5, and 0.4 days, resp, at a dose level of 320 mg/kg. The decrease in activity of the nonadecyl derivative is probably due to inadequate functional characteristics at inhibition sites imposed on the molecule by the longer side chain and shows that a critical lipophilic–hydrophilic balance[2,16] may be necessary for optimum *in vivo* antimalarial activity.

A comparison of the *in vivo* antimalarial activity of 3-ω-cyclohexyloctyl-2-hydroxy-1,4-naphthoquinone (menoctone, III) with the antimalarial activity of 7-*n*-pentadecyl-6-hydroxy-5,8-quinolinequinone is of particular interest. Menoctone exhibited a survival time of 9.2 days (160 mg/kg), and the pentadecyl analog exhibited a comparable survival time of 8.1 days (160 mg/kg). However, menoctone showed toxicity at a higher dose level (3/5 deaths at 640 mg/kg), while the pentadecyl derivative was not toxic at this level. The quinolinequinone analog of menoctone, 7-ω-cyclohexyloctyl-6-hydroxy-5,8-quinolinequinone, shows activity ($T - C = 6.2$) with no toxicity at the highest level tested (320 mg/kg). These data are limited, but do indicate that there may be effective antimalarial activity and less toxicity in these quinolinequinones than in menoctone; however, additional compounds and comparisons would be necessary to determine such a possible advantage.

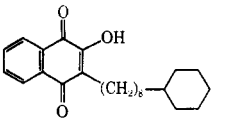
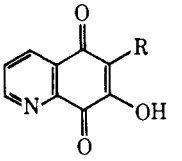
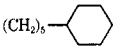
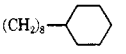
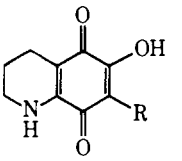
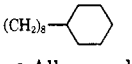
A comparison of the values of $T - C$ for 7-ω-cyclohexylpentyl-6-hydroxy-5,8-quinolinequinone (2.5 at 320 mg/kg, Table I) with its isomer, 6-ω-cyclohexylpentyl-7-hydroxy-5,8-quinolinequinone (1.3 at 320 mg/kg, Table II) indicates that the 7-alkyl-6-hydroxy derivative is about twice as active as its isomer in the *in vivo* malaria assay. However, 6-ω-cyclohexyloctyl-7-hydroxy-5,8-quinolinequinone cured 5/5 mice at the 640 mg/kg dose level, while exhibiting no apparent toxicity. 7-ω-Cyclohexyloctyl-6-hydroxy-5,8-quinolinequinone shows a ($T - C$) value of 6.2 at 320 mg/kg, the highest level tested; and menoctone, 3-ω-cyclohexyloctyl-2-hydroxy-1,4-naphthoquinone, shows 4/5 cures at 160 mg/kg and 320 mg/kg, but only 2/5 cures and 3/5 toxicity at a 640 mg/kg dose level.

Reduction of the pyridine moiety of representative 7-alkyl-6-hydroxy-5,8-quinolinequinones destroys the *in vivo* antimalarial activity of these compounds as seen in Table II. Apparently changes in the conformations of the pyridine ring and/or alterations in the oxidation–reduction potential of the quinone upon reduction of the pyridine moiety result in the elimination of antimalarial activity.

A number of these 7-alkyl-6-hydroxy-5,8-quinolinequinones are being evaluated in mitochondrial NADH oxidase and succinoxidase systems for inhibition of coenzyme Q (CoQ).[17] Preliminary results indicate that reasonably good correlation exist in the 7-alkyl-6-hydroxy-5,8-quinolinequinone series between the inhibitor concentration in the *in vitro* systems and the *in vivo* antimalarial activity in the *P. berghei* mouse test.

TABLE II

ANTIMALARIAL ACTIVITY OF CERTAIN 6-ALKYL-7-HYDROXY-5,8-QUINOLINEQUINONES AND 1,2,3,4-TETRAHYDRO-7-ALKYL-6-HYDROXY-5,8-QUINOLINEQUINONES IN THE ANTIMALARIAL DRUG SCREEN

R	Mp,[c] °C	Yield, %	Mouse test (*P. berghei*) activity,[a] mg/kg	Mouse test (*P. berghei*) ($T - C$),[b] mg/kg
 Reference compound			Active at 40; curative at 160	9.2 at 160
				
$(CH_2)_7CH_3$	108–109	20		0.5 at 640
$(CH_2)_{13}CH_3$[d]	111–112	5		
	133–134	26		1.3 at 320 3.7 at 640
	116–117	21		3.5 at 320 5/5 cures at 640
				
$(CH_2)_{13}CH_3$	136–137	79		0.4 at 640
	158–159	74		0.4 at 640

[a] All compds were administered sc in graded doses to groups of 5 mice. [b] ($T - C$) = change in survival time in days of treated and nontreated (control) mice. [c] Anal. sample. [d] Purified by silica gel column chromatography and recrystallization from ether–hexane and then ether–ethanol–benzene (charcoal).

Experimental Section

General Procedures.—Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Pmr spectra were obtd using a Varian Associates A-100 spectrometer; absorptions are given in τ units. The solvent and internal standard were $CDCl_3$ and TMS, resp, unless otherwise noted. Tlc was performed using glass plates coated with silica gel G. Elemental analyses were carried out by Chemalytics, Inc., Tempe, Ariz. The values were within 0.4%.

Alkylated 6- or 7-hydroxy-5,8-quinolinequinones.—The 6- or 7-hydroxy-5,8-quinolinequinone was prepd in a manner similar to previously published procedures.[18,19] The new alkylated 6- or 7-hydroxy-5,8-quinolinequinones were synthesized by a procedure similar to that described by Pratt and Drake.[10,11] However, in

(16) F. J. Bullock, *J. Med. Chem.*, **11**, 419 (1968).

(17) K. Folkers, unpublished work.

(18) K. N. Campbell, J. F. Kerwin, A. H. Sommers, and B. K. Campbell, *J. Amer. Chem. Soc.*, **68**, 1559 (1946).

(19) Y. T. Pratt and N. L. Drake, *ibid.*, **77**, 37 (1955).

this case the alkylated 6- or 7-hydroxy-5,8-quinolinequinones were generally purified by crystn from Et_2O–hexane. Purification by salt formation was not necessary. The melting points and yields of the new quinolinequinone derivatives are listed in Table I and II along with their corresponding antimalarial activity. Pmr spectra for these new derivatives were consistent with the proposed structures.

1,2,3,4-Tetrahydro-7-*n*-tetradecyl-6-hydroxy-5,8-quinolinequinone.—7-*n*-Tetradecyl-6-hydroxy-5,8-quinolinequinone (500 mg) in EtOH (100 ml) was reduced (PtO_2) with the Parr hydrogenator at an initial pressure of 3.1 kg/cm². After 6 hr, the reaction mixt was filtered (Celite); the filtrate was air oxidized for several hr and then evapd *in vacuo* to a purple solid. Repeated recrystn from Et_2O–$CHCl_3$–EtOH yielded purple crystals (400 mg, 79% yield): mp 136–137°; R_f 0.16 (Et_2O–hexane, 1:1), 0.65 (Et_2O); pmr absorptions 6.27 (m, 1 H), 6.61 (t, 2 H), 7.60 (m, 4 H), 8.17 (t, 3 H), 8.75 (s, ≅24 H), and 9.12 (m, 3 H).

1,2,3,4-Tetrahydro-7-ω-cyclohexyloctyl-6-hydroxy-5,8-quinolinequinone.—7-ω-Cyclohexyloctyl-6-hydroxy-5,8-quinolinequinone (1 g) in EtOH (100 ml) was reduced (PtO_2) with the Parr hydrogenator. After 4 hr the reaction mixt was filtered (Celite); the filtrate was air oxidized for several hr and then evapd *in vacuo*. The purple solid was repeatedly recrystd from EtOH–$CHCl_3$ to yield purple crystals (750 mg, 74% yield): mp 158–159°; R_f 0.18 (Et_2O), 0.83 (ether–ethanol, 1:1); pmr absorptions 6.58 (t, 2 H), 7.58 (q, 4 H), and 8.0–9.0 (m, ≅27 H).

Acknowledgments.—Appreciation is expressed to the U.S. Army Medical Research and Development Command. Their contract No. DADA 17-69-C-9067 contributed to the support of this research. This is Contribution No. 924 from the Army Research Program on Malaria.

Schistosomicides. 1.[1] Derivatives of 2-Aminomethyl-1,2,3,4-tetrahydroquinoline

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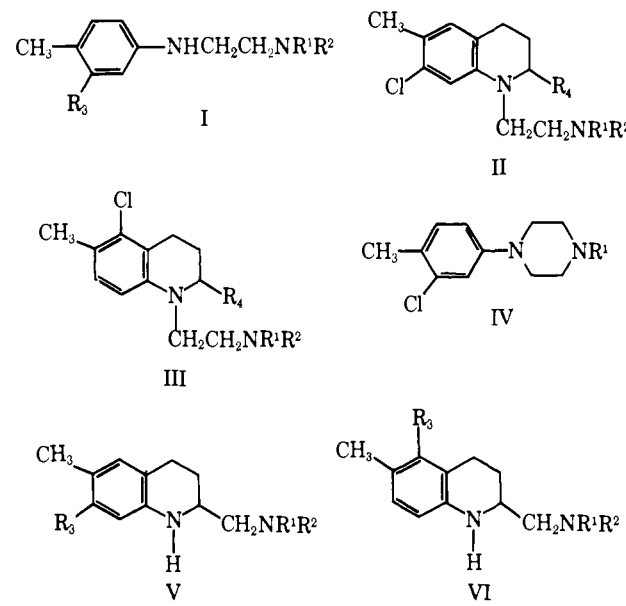
The synthesis and structure–activity relationships of a novel series of schistosomicidal 2-aminomethyl-1,2,3,4-tetrahydroquinoline derivatives (V) are described. The activity pattern of these conformationally constrained compounds is compared with that of the mirasan series of schistosomicides (I). Thus, in mice, for I decreasing activity is in the order R^3 = halogen, CN, and NO_2, whereas in V the reverse is the case, and an explanation based on lipophilicity considerations is proposed. The isomeric series VI is devoid of activity whereas members of series V display marked activity in single oral doses against *Schistosoma mansoni*, especially **10**, 2-*N*-isopropylaminomethyl-6-methyl-7-nitro-1,2,3,4-tetrahydroquinoline [V; R^1 = H; R^2 = $CH(CH_3)_2$; R^3 = NO_2]; the dextro form of **10** was the more active enantiomer. Members of series V show a distinct advantage over the mirasan series in that they display activity against *S. mansoni* in monkeys; thus, **10** is active in a single oral dose of 50 mg/kg. It is metabolized in mouse and monkey to the corresponding 6-hydroxymethyl derivative, 6-hydroxymethyl-2-*N*-isopropylaminomethyl-7-nitro-1,2,3,4-tetrahydroquinoline [XX&III; R^1 = H; R^2 = $CH(CH_3)_2$; R^3 = NO_2], which has been shown to be curative in monkeys in single im doses of 5–7.5 mg/kg.

Several examples are known in which structural modification of a biologically active compound has yielded analogs of constrained molecular conformation without consequent loss of biological activity, and a study of such compounds has provided useful information regarding structure–activity relationships.[2] 1-Substituted tetrahydroquinolines[3,4] (II and III) and 1-phenylpiperazines[5] (IV), may be regarded as examples of constrained molecules which retain the schistosomicidal activity displayed by the prototype mirasan series[3] (I), of which mirasan (I; R^1 = R^2 = C_2H_5; R^3 = Cl) is the parent member.

As an extension of this principle, we have synthesized 2-aminomethyltetrahydroquinolines of type V and VI which represent a new class of cyclic analogs of series I. A prime objective was the development of novel agents that would display worthwhile activity against schistosome infections in primates, since this is a property which is lacking in the earlier series I–IV.[4,6]



Chemistry.—The following general account describes the main methods of synthesis; the particular synthesis employed for each individual compound is indicated in the appropriate table.

(1) **Nitro Compounds.**—Three synthetic routes that have been used to prepare the key precursor XIII are

(1) A preliminary paper describing these compds has appeared: H. C. Richards and R. Foster, *Nature (London)*, **222**, 581 (1969).

(2) R. B. Barlow, "Introduction to Chemical Pharmacology," 2nd ed, Wiley, New York, N. Y., 1964.

(3) H. Mauss, H. Kölling, and R. Gönnert, *Med. Chem., Abhandl. Med. Chem. Forschungsstaetten Farbenfabriken Bayer*, **5**, 185 (1956).

(4) R. Gönnert, *Bull. W. H. O.*, **25**, 702 (1961).

(5) Hoechst, U. S. Patent, 2,830,056 (1958); *Chem. Abstr.*, **53**, 3253*d* (1959).

(6) O. D. Standen in "Experimental Chemotherapy," R. J. Schnitzer and F. Hawking, Ed., Vol. I, Academic Press, London, p 773 1963.