from experiment 1 above. The material isolated from the third peak (K_3 = 0.52) moved 2.5 times as fast as fraction 2 on tlc in system B. The amino acid analysis revealed the same amino acid composition as fraction 2. This compound is most likely the acetoxy derivative of I. It was not studied further.

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4(1*H*)-Quinolones. 2. Antimalarial Effect of Some 2-Methyl-3-(1′-alkenyl)- or -3-alkyl-4(1*H*)-quinolones†

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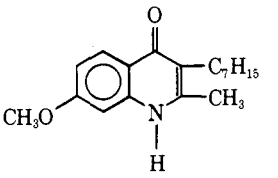
A large number of 4(1*H*)-quinolones have been prepared as intermediates in the synthesis of potential antimalarial agents of the 4-aminoquinoline series. However, except in isolated cases[1-3] the antimalarial potential of the 4-quinolones themselves have not been explored in great detail. This occurred despite the fact that the Schönhöfer theory of antimalarial action of aminoquinolines[4] would suggest that the prototropy postulated as necessary for high antimalarial activity in this class of compounds may lead *in vivo* to a 4-quinolone by hydrolysis of the 4-imino intermediate. Of the 4-quinolones reported to possess antimalarial activity, endochin (2-methyl-3-*n*-heptyl-7-methoxy-4(1*H*)-quinolone, **1**)‡ was considered a very promising lead.[6] **1** was found to have excellent prophylactic as well as therapeutic activity in canaries infected with *P. praecox;* however, it was reported to have failed in clinical trials.[6]

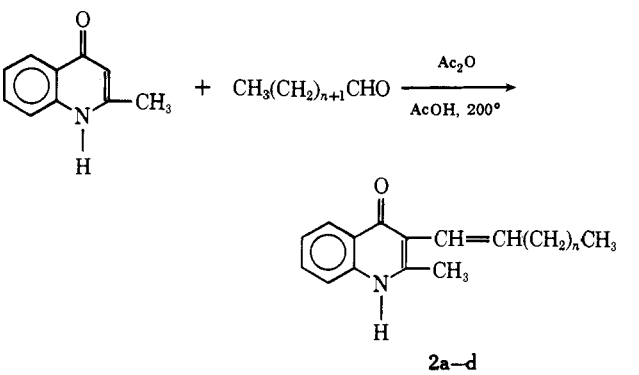


1

In connection with another investigation in progress in these laboratories, several 2-methyl-3-(1′-alkenyl)- or -3-alkyl-4(1*H*)-quinolones were prepared[7] which were structurally related to **1**. This report is concerned with the synthesis of some new 4-quinolones of the endochin type as well as their antimalarial activity.

Chemistry. The new 2-methyl-3-(1′-alkenyl)-4(1*H*)-quinolones (**2**) described in the present communication were prepared by the reaction of an appropriate *n*-aliphatic aldehyde with 2-methyl-4(1*H*)-quinolone in the presence of acetic anhydride and catalytic amounts of glacial acetic acid as described earlier[7] (Scheme I). The 2-methyl-3-*n*-alkyl-4(1*H*)-quinolones (**3**) were synthesized by the Conrad–Limpach method[8] which involves the condensation of aniline with an appropriately substituted β-keto ester, followed by cyclization of the 3-anilinocrotonate formed (Scheme II). 2-Methyl-3-(*N*-piperidinomethyl)-4(1*H*)-quinolone [**3h**, $R_1 = CH_2N(CH_2)_5$; $R_2 = R_3 = H$] was prepared by the method of Ghosh and Chaudhuri,[9] by treating 2-methyl-4(1*H*)-quinolone with paraformaldehyde and piperidine in a Mannich-type condensation. Compounds of type **2** and **3** are described in Table I.

Scheme I



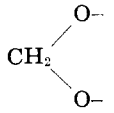
2a–d

Antimalarial Results. The antimalarial results described in the present report were obtained using the *P.*

†For paper 1 in this series, see ref 7.

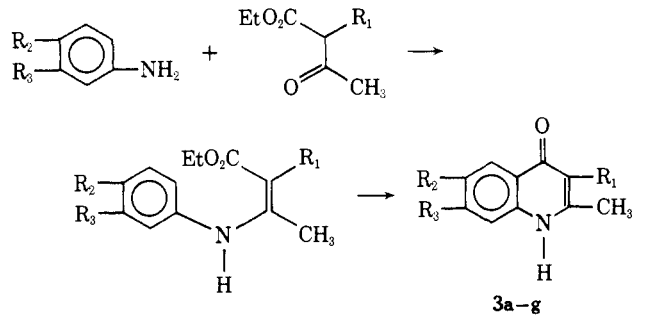
‡It is of interest that endochin is structurally reminiscent of the coenzyme Q and that a variety of coenzymes Q antimetabolites have been reported recently to exhibit antimalarial activity against *P. berghei* in mice. See ref 5.

Table I. Chemical and Analytical Data for 2-Methyl-3-(1′-alkenyl)- or -3-alkyl-4(1*H*)-quinolones

Compd no.	R_1	R_2	R_3	Yield, %	Mp, °C	Formula	Analyses[a]	Recryn solvent
2c	$CH{=}CH(CH_2)_9CH_3$	H	H	16	164–166	$C_{22}H_{31}NO$	C, H, N	MeOH
2d	$CH{=}CH(CH_2)_{15}CH_3$	H	H	26	103–106	$C_{28}H_{43}NO$	C, H, N	Hexane
3d	$(CH_2)_{11}CH_3$	H	H	47	214–215	$C_{22}H_{33}NO$	C, H, N	EtOH–H_2O
3e	$(CH_2)_8CH_3$	H	CF_3	15	253–254	$C_{20}H_{26}NOF_3$	C, H, N, F	MeOH
3f	$(CH_2)_8CH_3$			15	>300	$C_{20}H_{27}NO_3$	C, H, N	EtOH
3g	$(CH_2)_{11}CH_3$	H	CF_3	10	238–239	$C_{23}H_{32}NOF_3$	C, H, N	EtOH–H_2O

[a] Analytical results were within 0.3% of the theoretical values.

Scheme II



3a–g

berghei infection in mice.§ They are based on the relative response of infected mice to each of the submitted compounds as expressed by the mean survival time of the treated animals (MSTT) and the mean survival time of controls (MSTC).[10] A single dose of the test compound was given 72 hr after the mice were infected with *P. berghei*. Several doses were tested: 80, 160, 320, and 640 mg/kg. Untreated animals died within 6–8 days and had a mean survival time (MSTC) of 6.1 days. Treated animals were kept under observation for 60 days. The prolongation of life for 2.5 days was considered statistically significant. A minimum mean survival time of 12 days was required for compounds to be considered active. Animals which survived for 60 days were considered cured.

2-Methyl-4(1*H*)-quinolone (**3i**, $R_1 = R_2 = R_3 = H$), the parent compound of this series, was inactive at any of the doses tested as was **2a** ($n = 4$). Compounds **2b** ($n = 6$) and **2c** ($n = 9$) increased the mean survival time of the test mice (IMST) by 4.5 (320 mg/kg) and 10.3 days (320 mg/kg), respectively. In fact, compound **2c** was curative (two out of five mice) at a dose of 640 mg/kg and its activity compares with that of endochin (one cure at 320 mg/kg and three cures at 640 mg/kg). Compound **2d** ($n = 15$) increased the MSTT of the infected mice 4.7 days at 640 mg/kg. Elimination of the double bond in conjugation with the 4(1*H*)-quinolone ring, as in compounds **3a** ($R_1 = C_7H_{15}$; $R_2 = R_3 = H$), **3b** ($R_1 = C_8H_{17}$; $R_2 = R_3 = H$), **3c** ($R_1 = C_9H_{19}$; $R_2 = R_3 = H$), and **3d** ($R_1 = C_{12}H_{25}$; $R_2 = R_3 = H$), destroyed the activity. Compounds **3e** ($R_1 = C_9H_{19}$; $R_2 = H$; $R_3 = CF_3$), **3f** [$R_1 = C_9H_{19}$; R_2, $R_3 = CH_2(O\text{-})_2$], **3g** ($R_1 = C_{12}H_{25}$; $R_2 = H$; $R_3 = CF_3$), and **3h** ($R_1 = CH_2\text{-c-}NC_5H_{10}$; $R_2 = R_3 = H$) were also inactive. None of the compounds were toxic, except **3i** (four toxic deaths at a dose of 160 mg/kg).

§The antimalarial screening was carried out by Dr. Leo Rane of the University of Miami and the test results were kindly made available through the courtesy of Drs. S. T. R. Sweeney and R. Strube of the Walter Reed Army Institute of Research.

The mechanism of action at the molecular level of the 2-methyl-3-alkenyl-4(1*H*)-quinolone is not known. However, related compounds have been reported to interfere with DNA synthesis.[11]

Experimental Section

All melting points were taken in a Thomas-Hoover melting apparatus and are uncorrected. Analysis was performed by Spang Microanalytical Laboratory, Ann Arbor, Mich., and Galbraith Laboratories, Knoxville, Tenn. Ir spectra were determined with a Perkin-Elmer 21 spectrophotometer.

2-Methyl-3-(1′-dodecenyl)-4(1*H*)-quinolone (2c). In a typical procedure for the preparation of the 3-alkenyl derivatives in Table I, a mixture of 0.08 mol of dodecylaldehyde and 0.04 mol of 2-methyl-4(1*H*)-quinolone (**3i**) in a three-necked flask equipped with stirrer, condenser, and separatory funnel was heated to 200°. Acetic anhydride (2.1 g) and 6 drops of glacial acetic acid were then added and the reaction mixture was kept at this temperature for 7 hr while stirring. It was then poured into 250 ml of ice water and allowed to stand overnight. The mixture was warmed to 60° and extracted twice with 200 ml of benzene. The combined extracts were washed with 100 ml of water. On cooling and partial evaporation of the benzene layer, **2c** was obtained. Evaporation of the water layer gave unreacted **3i**.

2-Methyl-3-alkyl-4(1*H*)-quinolone (3a–g). Typically, the method described for the corresponding 2-methyl-4(*H*)-quinolone[8] was used, using aniline, *m*-trifluoromethylaniline, or 3,4-methylenedioxyaniline and ethyl 2-*n*-nonyl- or 2-*n*-dodecylacetoacetate[7] as starting materials. The intermediate anilinocrotonates were used for cyclization without further purification. Yields and recrystallization solvents are shown on Table I.

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