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Naphthoquinone Antimalarials. XXIX. 2-Hydroxy-3-(ω-cyclohexylalkyl)-1,4-naphthoquinones

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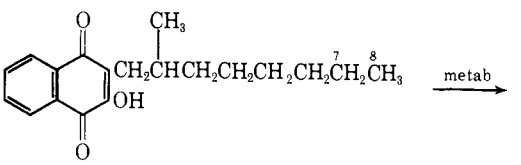
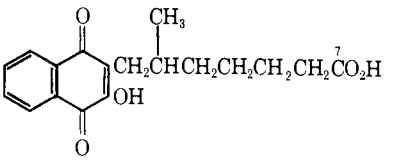
This investigation is a continuation of work started during World War II by the Harvard group. The series cited in the title has been extended to include members having very large hydrocarbon groups in the hope that they will undergo metabolic hydroxylation to give products of adequate antimalarial activity in man and resistant to further metabolic oxidation.

This work is an extension of a wartime research recorded in 24 initial papers[1] and in 4 supplementary publications.[2]

The typical 2-hydroxy-3-alkyl-1,4-naphthoquinones **1** and **3** have adequate activity in the suppression of *Plasmodium lophurae* in ducks, as indicated by their quinine equivalents (*Q*) of 2.1 and 0.5, and they also effectively destroy the exoerythrocytic forms of malaria parasites found in the reticulo-endothelial cells of chickens infected with *P. gallinaceum*. In a clinical trial of the two compounds in syphilitic patients undergoing malaria therapy (blood-induced *P. vivax* and *P. falciparum*), **1**, highly potent in ducks, proved to be completely inactive in man, whereas **3** showed definite, if weak, activity. A study of plasma and urine extracts from nonmalarial subjects given the drug established that both quinones are degraded rapidly in the human organism, whereas they are not metabolized by ducks or chickens. Compound **1** affords the carboxylic acid **2**, whereas **3** is degraded to two secondary alcoholic derivatives, one of which was identified by synthesis as **4**. The naphthoquinone antimalarials are powerful inhibitors of respiratory systems. At a concentration of 1×10^{-6} *M*, **3** effects 50% inhibition of the respiration of parasitized red blood cells drawn from a duck infected with *P. lophurae*. A close parallelism between antimalarial and antirespiratory activity for 158 quinones showed that the *in vitro* test can be used safely for evaluation of antimalarial activity on a microscale. Application of this technique established



1 (*Q* = 2.1)



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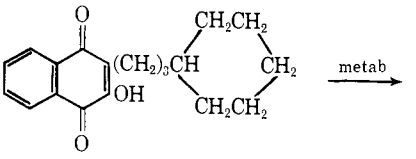
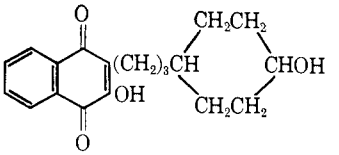


3 (*Q* = 0.5)



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that the metabolite of **1**, with two oxygens in the side chain, is completely devoid of activity, whereas the metabolite of **3** retains about one-tenth of the original activity.

Introduction of a hydroxyl group into the side chain renders the drug resistant to metabolic degradation but has the fault of reducing biological potency. However, a method of compensating for this loss was

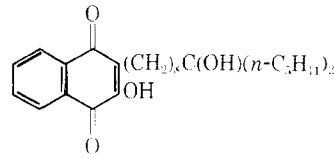
(1) L. F. Fieser, M. T. Leffler, *et al.*, *J. Am. Chem. Soc.*, **70**, 3151, 3174, 3181, 3186, 3195, 3197, 3203, 3206, 3213 (1948); M. T. Leffler, *et al.*, *ibid.*, **70**, 3222, 3224 (1948) (papers XIII, XIV); L. F. Fieser, *et al.*, *ibid.*, **70**, 3156 (paper II), 3215, 3228 (paper XV) (1948); **71**, 3615 (1949); **72**, 996 (1950); *J. Pharmacol. Exptl. Therap.*, **94**, 85, 97, 112 (1948); *J. Biol. Chem.*, **176**, 1359, 1363 (1948); L. F. Fieser, *J. Am. Chem. Soc.*, **70**, 3165, 3232, 3237 (1948).

(2) M. Paulshock and C. M. Moser, *ibid.*, **72**, 5073, 5419 (1950); D. J. Cram, *ibid.*, **71**, 3950, 3953 (1949) (papers XXVII XXVIII).

revealed by a study of distribution characteristics (paper XV[1]). Distribution of a hydroxynaphthoquinone between ether and an aqueous buffer and determination (by colorimetry) of the amount extracted permitted calculation of a logarithmic constant pE characteristic of each compound. The study revealed

$$pE = \log \frac{[\text{Quinone}]^{\text{ether}}}{[\text{Quinone}]^{\text{water}}} + \text{pH} - 2$$

the important relationship that for maximal antimalarial activity a naphthoquinone must have a hydrophilic–lipophilic balance such that the pE value falls in the range 10–12. Metabolic hydroxylation of the side chain produces a marked hydrophilic shift, as is evident from the pE value for **3** of 9.5 as compared to the value of 6.4 for its metabolite (**4**). However, in any series pE increases with increasing molecular weight and hence loss in activity from hydroxylation of the side chain can be compensated for by increasing the size of the hydrocarbon part of the chain. These considerations suggested synthesis of **5**, which contains a tertiary hydroxyl group to provide protection from metabolic degradation in a compensatingly large (C_{19}) side chain. Although only feebly active in ducks



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when given orally, intramuscularly administered **5** possesses high potency. Metabolism studies in man and in various animals were made by parenteral administration of drug, withdrawal of blood samples from time to time, and determination of the activity of the naphthoquinone present by measuring the antirespiratory activity by the Warburg technique. In the case of intravenously administered **3**, the activity of naphthoquinone extracted from plasma fell to one-third the original level after only 0.5 hr, and after 4 hr the activity revealed a level of one-tenth that of **3** and persisted at the same level for some 20 hr. Parenterally administered **5** afforded satisfactory levels of effective drug lasting for several hours. The laboratory evidence pointing to **5** as a promising drug was not complete until after the war, when formerly extensive facilities for clinical trial were no longer available. However, in a trial carried out in Lebanon, intravenously administered **5** proved to be both suppressive and curative, at least in the limited number of cases tried. That the compound did not subsequently find a place in practical therapy perhaps is because it is effective only when given by parenteral administration.

The other candidate antimalarials developed during the war such as pentaquine, primaquine, and chloroquine, are nitrogen-containing compounds related to the German-developed quinacrine and pamaquine. Chloroquine in particular gained widespread use; it has low toxicity and suppresses all usual forms of malaria. However, in 1964 drug resistance to chloroquine in malaria (*P. falciparum*) became a serious problem in Southeastern Asia and a potential threat in South America.[3] The naphthoquinone series seems particularly attractive because resistance of parasites to nitrogen heterocycles should not imply resistance to compounds containing only C, H, and O and probably acting by a different mechanism. The present extension of the earlier work is conducted as a joint project between the Harvard[4] and Sterling-Winthrop groups. One plan is to examine quinones similar to **3** but having larger hydrocarbon side chains. In the plot of activity against *P. lophurae* in ducks for 2-hydroxy-3-(ω-cyclohexylalkyl)-1,4-naphthoquinones (paper II[1]), quinone **3** is seen to be somewhat below the peak of the curve, which then rises a little to C_{16} C_{17} and then falls off abruptly. The highest member examined, 2-hydroxy-3-(ω-cyclohexylnonyl)-1,4-naphthoquinone, formerly seemed quite uninteresting because it is only feebly active in ducks. However, it now seems possible that the compound will be metabolized in man and probable that the metabolites are more potent than the **3** metabolites. Thus, our present aim is to find a compound which itself does not possess satisfactory drug action but which will yield a metabolite having this quality and resistant to further metabolic degradation.

Fortunate for our project is the fact that the method of assay against *P. lophurae* in ducks has given way to methods using *P. berghei* in mice[5] and *P. cynomolgi* in monkeys.[6] Our earlier work included exploratory experiments aimed at finding a test animal showing a response to administered naphthoquinone comparable to that of man and therefore suitable for examination of new compounds with respect to persistence and resistance to deactivation (paper XX[1]). Following intravenous administration of **3**, naphthoquinone pigment disappeared from the blood of dogs, cats, and rabbits in a matter of a few minutes after the injection; it persisted for longer periods in a guinea pig and in an anesthetized monkey, but very little drug degradation occurred. Intravenously injected **3** persisted in the blood of a duck for more than 1 hr and suffered no degradation. The mouse proved to be a particularly satisfactory test animal. Intravenously injected **3** and **5** both persisted in the blood for considerable periods and suffered metabolic deactivation comparable to that observed in man; **5** persisted better and was degraded less extensively than **3**.

This paper reports synthesis of the three missing members of the 2-hydroxy-3-(ω-cyclohexylalkyl)-1,4-naphthoquinone series. Bioassay data are reserved for comparison with those for corresponding ω-adamantylalkyl compounds to be described in an accompanying paper.

Experimental Section[7]

Preliminary Trials.—One approach which seemed attractive was to use commercially available (Eastman, Fisher) 11-[Lewis]

(3) D. V. Moore and J. E. Lanier, *Am. J. Trop. Med. Hyg.*, **10**, 5 (1961); M. D. Young and D. V. Moore, *ibid.*, **10**, 317 (1961).

(4) We were advised of the situation and urged to resume work on the naphthoquinones by Dr. Leo Rane, University of Miami School of Medicine, and Dr. David P. Jacobus, Walter Reed Army Medical Center. Compound **5** is under active reexamination by the Miami and Walter Reed groups. The Harvard work was initially supported in part by grant CA-01636 from the National Institutes of Health (L. F. F.).

(5) D. G. Davey, *Exptl. Chemotherapy*, **1**, 198 (1963); see also J. P. Thurston, *Brit. J. Pharmacol.*, **5**, 409 (1950).

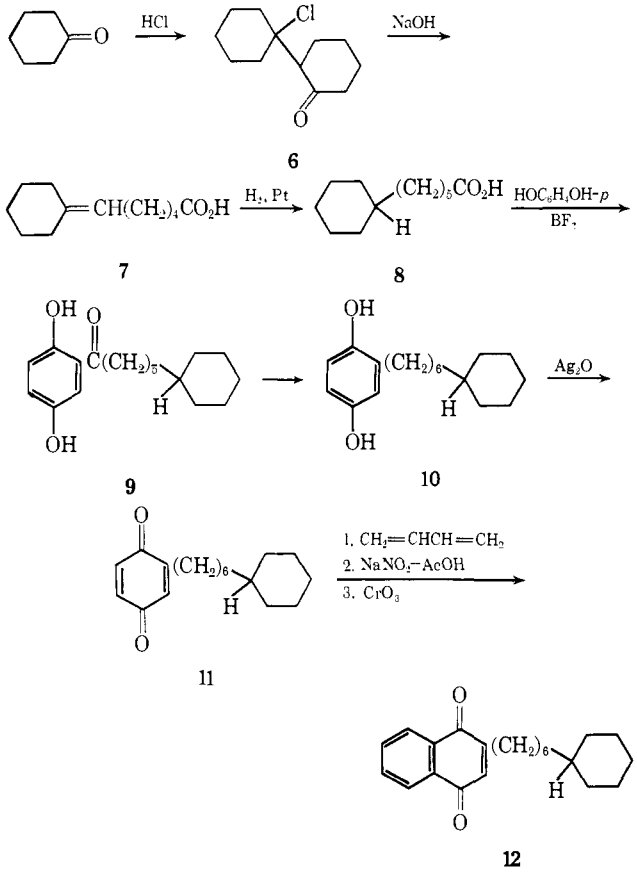
(6) J. P. Thurston, *ibid.*, **5**, 507 (1950).

(7) Experiments by J. P. S., Jr., except as noted.

undecanoic acid[8] as starting material for construction of the large side chain $(CH_2)_{10}C_6H_{11}$. Hydrogenation of the benzene ring and conversion through the acid chloride to the peroxide by the method of Silbert and Swern[9] gave material almost completely free of the carboxylic acid, but use of this for alkylation of 2-hydroxy-1,4-naphthoquinone gave a yellow product which remained an oil despite all attempts to induce crystallization. The plan to carry out successive Hooker oxidations was thus abandoned.

In another trial, the method of Plešek[10] (yield 41%) and hydrogenation[11] gave 6-cyclohexylhexanoic acid (**8**) (mp 32–33°) (Scheme I).

SCHEME I



2-(6-Cyclohexylcaproyl)hydroquinone (**9**).—A mixture of 0.1 mole of the acid chloride from **8** ($SOCl_2$) and 0.1 mole of hydroquinone in 50 ml of CCl_4 was saturated with gaseous BF_3 and refluxed on the steam bath overnight. The BF_3-addition product was decomposed with either aqueous sodium acetate or aqueous Na_2CO_3, and the substituted hydroquinone was obtained by ether extraction; yield of crude product 74%. Crystallization from ligroin gave golden yellow platelets, mp 76–77°.

Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: C, 74.60; H, 8.96.

The same product was obtained by the procedure of Armstrong, *et al.*,[12] for C-acylation of hydroquinone with a carboxylic acid and BF_3. A product of inferior quality was obtained in higher yield, but purification led to the same yield as reported above.

2-(6-Cyclohexylhexyl)hydroquinone (**10**).—Reduction of the carbonyl group of **9** was attempted by several methods but none proved fully satisfactory. A modified Clemmensen procedure of Adams, *et al.*,[13] seemed promising, but catalytic reduction, although erratic, gave the only satisfactory batch of **10**. A mixture of 7.25 g of the ketone **9**, 0.5 g of 30% Pd–C, and 200 ml of absolute ethanol showed no uptake of hydrogen overnight at 4.2 kg/cm². Addition of 3 drops of concentrated HCl and further shaking for 20 hr effected complete reduction (yield quantitative). An analytical sample was obtained by boiling a portion with a large volume of petroleum ether (bp 38–52°) and drawing off and concentrating the solution. This gave white flakes, mp 77–79°.

Anal. Calcd for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.41; H, 10.14.

2-(6-Cyclohexylhexyl)-1,4-benzoquinone (**11**).—A mixture of 1 g of the hydroquinone **10**, 2.3 g of freshly prepared Ag_2O,[14] and 30 ml of anhydrous ether was stirred and filtered. Removal of the ether *in vacuo* gave 1 g of a yellow solid, mp 64–65°. A sample recrystallized from acetic acid–water melted at 65.5–67.5°.

Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 79.01; H, 9.54.

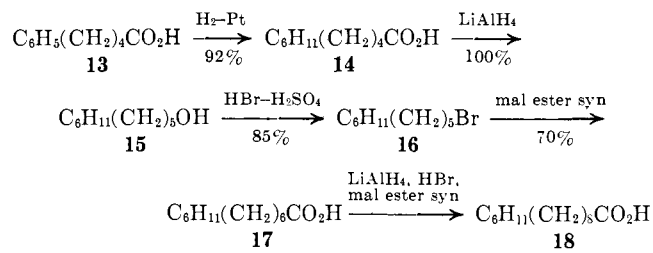
2-(6-Cyclohexylhexyl)-1,4-naphthoquinone (**12**).—The procedure for conversion of the benzoquinone **11** to the naphthoquinone **12** was patterned after one described.[15] A Carius tube charged with 5.1 g of **12**, 2.5 ml of butadiene, and 40 ml of AcOH was sealed and heated at 80° for 48 hr. The reddish yellow solution was filtered by suction through a pad of Norit and the light orange filtrate was heated on the steam bath to eliminate butadiene. A solution of 3.5 g of $NaNO_2$ in a little H_2O was added, and the mixture was warmed briefly on the steam bath to give a wine-colored solution. After addition of a solution of 5 g of CrO_3 and 1 ml of concentrated H_2SO_4 in 5 ml of H_2O, the mixture was heated on the steam bath for 45 min and then poured onto ice and H_2O. The flocculent precipitate was collected and washed well with H_2O. Crystallization from methanol gave 2.0 g of the yellow naphthoquinone, mp 78–79°.

Anal. Calcd for $C_{22}H_{28}O_2$: C, 81.44; H, 8.70. Found: C, 81.05; H, 8.53.

The plan was to hydroxylate **12** in the quinone ring by BF_3-catalyzed bromination and alkaline hydrolysis,[16] but the product obtained in poor yield in the first step was anomalous (*Anal.* Calcd: Br, 19.81. Found: Br, 46.98). Although on hydrolysis it afforded the expected product, we report below a more reliable route to this compound.

Acids Required for Alkylation.—5-Phenylvaleric acid (**13**), available from the Aldrich and Fisher Chemical Companies, served as starting material for the preparation of ω-cyclohexylnonanoic acid (**18**) (Scheme II). Hydrogenation of the benzene ring with platinum catalyst in acetic acid at 4.2 kg/cm² proceeded readily.[17] The product **14**, which distilled at 130° (1 mm) [lit.[11] 151–153° (4 mm)], was obtained in 92% yield. The cyclohexylvaleric acid was reduced quantitatively by $LiAlH_4$ to the alcohol **15** which afforded the bromide **16** in 85% yield of distilled material, bp 80° (0.3–0.4 mm). Alkylation of malonic ester, hydrolysis, and decarboxylation afforded ω-cyclohexylheptanoic acid[11] **17** (mp 25–26°) in 70% over-all yield (the intermediate malonic acid, crystallized from petroleum ether, melted at 111–112°). A portion of the acid **17** was used for an alkylation and the remainder was used to synthesize the known[11] ω-cyclohexylnonanoic acid (**18**). The bromide boiled at 113–115° (0.2 mm); the malonic acid was obtained in 68% over-all yield; ω-cyclohexylnonanoic acid (**18**) was crystallized from petroleum ether and melted at 44.5–45.5° (lit.[10] 45.5–46.5°).

SCHEME II



(8) S. A. Dmitriev, N. M. Karavaev, and A. V. Smirnova, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1800 (1961); *Chem. Abstr.*, **56**, 7207 (1962).

(9) L. S. Silbert and D. Swern, *J. Am. Chem. Soc.*, **81**, 2364 (1959).

(10) J. Plešek, *Collection Czech. Chem. Commun.*, **21**, 902 (1956).

(11) G. S. Hiers and R. Adams, *J. Am. Chem. Soc.*, **48**, 2392 (1926).

(12) E. C. Armstrong, R. L. Bent, A. Loria, J. R. Thirtle, and A. Weissberger, *ibid.*, **82**, 1928 (1960).

(13) R. Adams, C. K. Cain, and B. R. Baker, *ibid.*, **62**, 2201 (1940).

(14) I. A. Pearl, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p. 972.

(15) L. F. Fieser, *J. Am. Chem. Soc.*, **70**, 3165 (1948).

(16) L. F. Fieser, *ibid.*, **70**, 3172, 3173 (1948).

(17) P. A. Levene and R. E. Marker, *J. Biol. Chem.*, **110**, 311 (1935).

ω-Cyclohexyloctanoic acid was prepared similarly (Scheme III). A suspension of 12 g of $LiAlH_4$ in 100 ml of tetrahydrofuran (THF) was stirred until most of the hydride had dissolved; a solution of 19.8 g of ω-cyclohexylhexanoic acid (**8**) in THF was added in 1–1.5 hr, and the mixture was refluxed overnight. The mixture was cooled in ice and the complex decomposed by the

SCHEME III

$$C_6H_{11}(CH_2)_5CO_2H \xrightarrow[98\%]{LiAlH_4} C_6H_{11}(CH_2)_6OH \xrightarrow{HBr\text{-}H_2SO_4}$$

8 **19**

$$C_6H_{11}(CH_2)_6Br \xrightarrow[72\%]{\text{mal ester syn}} C_6H_{11}(CH_2)_7CO_2H$$

20 **21**

addition of 1–2 ml of 10% NaOH solution. The heating mantle was replaced, the mixture was brought to reflux, and additional alkali was added by drops until hydrolysis was complete. The LiOH settled as a fine powder which was easily removed by filtration through a sintered-glass funnel, which was then washed with ether. Removal of solvent in a flash evaporator gave alcohol **19** which from the ir spectrum was found to be pure enough for the next step. A mixture of 22.3 g of **19**, 50 g of 48% HBr, and 7 ml of concentrated H_2SO_4 was refluxed for 5–6 hr, cooled, diluted, and extracted with ether.[18] The yield of bromide **20**, bp 113° (2 mm), was 22 g (74%). For alkylation of malonic ester by a standard procedure,[19] 200 ml of absolute ethanol was distilled into a dry round-bottomed flask, 2.1 g of sodium was added, and the mixture was stirred and refluxed until solution was complete. Then 26 g of diethyl malonate was added, followed by 22 g of the bromide **20**. The mixture was stirred and refluxed overnight (NaCl separated) and a solution of 26 g of KOH in 25 ml of H_2O was added to hydrolyze the ester. The mixture was heated to boiling and the condenser was removed. As the ethanol boiled off, H_2O was added to keep the salt in solution. When removal of ethanol was complete, the mixture was rinsed into a mixture of 52 g of concentrated H_2SO_4 and 300–400 ml of ice water. The malonic ester soon separated as a white solid and was collected by suction filtration. A sample crystallized from petroleum ether melted at 114–115°.[11] Heating the malonic acid at 140° for 4 hr gave 19.4 g of ω-cyclohexyloctanoic acid (**22**).

Alkylation of 2-Hydroxy-1,4-naphthoquinone.—In a typical case, a mixture of 5 g of ω-cyclohexylheptanoic acid (**17**), 9 ml of $SOCl_2$, and 100 ml of benzene was refluxed overnight, and excess reagent and solvent were distilled under reduced pressure; additional benzene was added and distilled. The infrared spectrum then indicated the residue to be of satisfactory purity. Following the procedure of Silbert and Swern,[9] a solution of the acid chloride in 100 ml of ether was stirred at 0° and 0.5 ml of 90% H_2O_2 was added. After 10–15 min 2.25 ml of pyridine was added dropwise; the solution became turbid and a precipitate separated. The mixture was stirred at room temperature for 1 hr and then washed with H_2O, 5% HCl, H_2O, 2% NaOH, and H_2O. The solution was then dried and evaporated at 40° in a flash evaporator. The material solidified on standing and the infrared spectrum indicated satisfactory purity; yield 4.5 g. This material, together with 1.7 g of 2-hydroxy-1,4-naphthoquinone, was heated with 140 ml of acetic acid and stirred at 95–100° (oil bath) overnight. The acetic acid was removed by distillation from the oil bath at reduced pressure and then in a flash evaporator. A solution of the residue in 100 ml of benzene was washed with three 50 ml portions of aqueous $NaHCO_3$ to remove 2-hydroxy-1,4-naphthoquinone (0.7 g) and then with three 50-ml portions of aqueous Na_2CO_3 solution (discarded). The alkylated quinone was then extracted with several portions of 2% NaOH solution. Acidification of the combined red extracts gave an oil which solidified and which on collection by ether extraction gave 1.5 g of yellow-orange solid. Chromatography on silica gel and crystallization from ligroin gave 1.2 g of 2-hydroxy-ω-cyclohexylhexyl-1,4-naphthoquinone, mp 106–106.5°.

Anal. Calcd for $C_{22}H_{30}O_4$: C, 77.61; H, 8.29. Found: C, 77.42; H, 8.18.

(18) The procedure is based on that for dodecyl alcohol by O. Kamm and C. S. Marvel, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p 29.

(19) R. Adams and J. R. Johnson, "Laboratory Experiments in Organic Chemistry," 4th ed, The Macmillan Co., New York, N. Y., 1953, pp 417, 421.

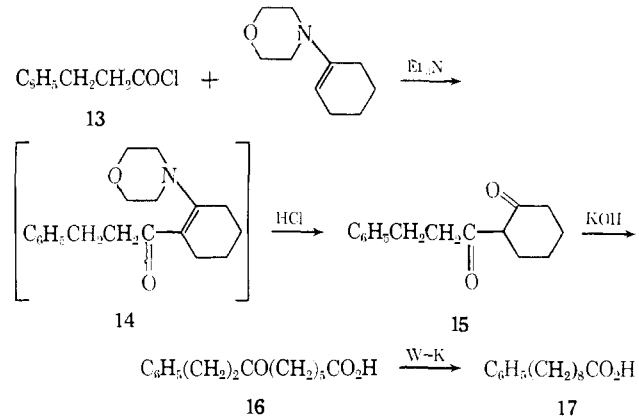
The following homologs were prepared initially in the same way from acids **21** and **18**.

2-Hydroxy-3-(ω-cyclohexylheptyl)-1,4-naphthoquinone, mp 102.5–103°. *Anal.* Calcd for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53. Found: C, 77.73; H, 8.44.

2-Hydroxy-3-(ω-cyclohexyloctyl)-1,4-naphthoquinone, mp 78–79°. *Anal.* Calcd for $C_{24}H_{32}O_3$: C, 78.22; H, 8.75. Found: C, 77.97; H, 8.52.

Large-Scale Preparations.[20]—ω-Phenylnonanoic acid (**17**) was prepared initially according to Huisgen, *et al.*,[21] by condensation of bis(3-phenylpropyl)cadmium with adipic acid ester chloride followed by Wolff–Kishner reduction. Although the yields were good, a synthesis preferred because of the ready availability of the starting materials and the ease of running the reactions starts with the condensation of hydrocinnamoyl chloride with 1-morpholinocyclohexene, basic cleavage of the β-diketone **15**, and Wolff–Kishner reduction (Scheme IV).

SCHEME IV



2-Hydrocinnamoylcyclohexanone (**15**).—A solution of 250 g (1.49 moles) of hydrocinnamoyl chloride in 650 ml of $CHCl_3$ was added over a period of 2 hr to a solution of 213.6 g (1.27 moles) of 1-morpholinocyclohexene[21] and 155 g (1.53 moles) of Et_3N in 1.6 l. of $CHCl_3$ while maintaining a temperature of 35°. The resulting light red solution was allowed to stand at room temperature for 20 hr and then refluxed with 640 ml of 18% HCl for 5 hr to eliminate the enamine group. After cooling, the organic layer was separated, washed well with water, and concentrated under vacuum. Distillation of the residue afforded 201 g (69%) of the 1,3-diketone **15**, bp 152–160° (0.5 mm), $n^{25}D$ 1.557. The distillate crystallized on standing and a sample recrystallized from methanol melted at 42–42.5°.

Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.30; H, 7.58.

7-Keto-9-phenylnonanoic Acid (**16**).—Potassium hydroxide solution (4 *N*, 640 ml) was heated to boiling and to it was added 201 g of 2-hydrocinnamoylcyclohexanone. The mixture was stirred, refluxed for several minutes until homogeneous and cooled, and the light yellow solution was acidified with concentrated HCl and stirred to hasten crystallization. The product was collected, washed with H_2O, and dried *in vacuo* at room temperature for 16 hr to yield 207 g (96%) of white crystals, mp 38–40°.

Anal. Calcd for $C_{15}H_{24}O_3$: C, 72.55; H, 8.12. Found: C, 73.00; H, 8.03; neut equiv, 247.8.

ω-Phenylnonanoic Acid (**17**).—A solution of 395 g of the keto acid **16** and 270 ml of 85% hydrazine hydrate in 1600 ml of diethylene glycol was heated at 120° for 4 hr. Water and excess hydrazine were removed under vacuum, the vacuum being maintained until the pot temperature had again risen to 120°. The mixture was cooled to 70°, 410 g of KOH was added, and the temperature was gradually raised to 220° in 2.5 hr and held at this point for 5 hr. After cooling, the dark paste was dissolved in 6 l. of hot H_2O, acidified with concentrated HCl, and extracted three times with ether. The combined ether extracts were dried (Na_2SO_4), charcoaled, and evaporated. Distillation gave 245 g

(20) By S. Archer, R. R. Lorenz, and P. I. Pfaffenbach.

(21) R. Huisgen, W. Rapp, I. Ugi, H. Walz, and I. Glogger, *Ann.*, **586**, 52 (1954).

(67%) of **17**, bp 170–177° (0.3 mm); the colorless oil quickly crystallized.

ω-Cyclohexylnonanoic Acid (18).—A solution of 361 g of ω-phenylnonanoic acid in 1450 ml of AcOH was hydrogenated in the presence of 4 g of PtO_2 at 80° and 155.5 kg/cm² pressure. The catalyst was filtered and the acetic acid was removed under vacuum. Distillation of the residue afforded 354 g (96%) of a fraction boiling at 160–169° (0.5 mm). The distillate crystallized on standing and a sample recrystallized from methanol melted at 45–47°.

Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 75.17; H, 11.84.

2-Hydroxy-3-(ω-cyclohexyloctyl)-1,4-naphthoquinone.—A solution of 562 g of acid **18** in 550 ml of $CHCl_3$ was added to 325 g of $SOCl_2$ at such a rate as to maintain reflux. After refluxing for 2 hr, the $CHCl_3$ was removed under vacuum and the residue distilled. The fraction of ω-cyclohexylnonoyl chloride boiling at 141–144° (0.1 mm), a colorless oil, amounted to 540 g (90%).

In the next step 255 g of 50% H_2O_2 was added with external cooling to a solution of 129 g of ω-cyclohexylnonoyl chloride in 1 l. of ether. The reaction mixture was stirred at −5° during addition of 47 g of pyridine over a period of 1 hr. The mixture was then warmed to room temperature and allowed to stand for 1 hr, and then the ethereal solution was washed with 5% $NaHCO_3$ solution and then with H_2O. The solution was dried (Na_2SO_4) and added carefully over a period of 2 hr to a well-stirred solution of 52.5 g of 2-hydroxy-1,4-naphthoquinone in 500 ml of acetic acid while maintaining the temperature of 100–110°. Heating was continued for 1 hr and the AcOH was removed under vacuum. The residue was slurried with 1 l. of pentane and filtered to remove unreacted hydroxynaphthoquinone, and more of this quinone was removed by several extractions with 5% $NaHCO_3$ solution. The residue remaining on evaporation of the pentane contained both product and considerable ω-cyclohexylnonanoic acid. To permit recovery of the acid, the residue was esterified by refluxing it in 600 ml of ethanol and 4 ml of concentrated H_2SO_4 for 6 hr (2-hydroxy-1,4-naphthoquinone is converted into the ether under conditions of Fischer esterification but 3-alkyl derivatives are too hindered to react).[22] The ethanol was removed *in vacuo* and a solution of the residue in pentane was extracted alternately with 2% NaOH and H_2O. After several extractions a red gum of the sodium salt of the product began to adhere to the walls of the separatory funnel and could be brought into the aqueous layer by addition of small amounts of methanol. The red water and water–methanol extracts were combined and acidified with HCl and extracted with ether. After removal of the ether, crystallization from methanol yielded 37.0 g of crude 2-hydroxy-3-alkyl-1,4-naphthoquinone. Two recrystallizations gave 30.0 g (31%) of product, mp 79–80°.

The above pentane layer containing ethyl ω-cyclohexylnonoate was concentrated and distillation of the residue gave 45.5 g of the ester, bp 113–117° (0.3 mm); this represents a recovery of 34%, based on the acid chloride.

2-Hydroxy-3-(ω-cyclohexylheptyl)-1,4-naphthoquinone (Hooker Oxidation[23]).—A mixture of 11.1 g of 2-hydroxy-3-(ω-cyclohexyloctyl)-1,4-naphthoquinone, 3.6 g of Na_2CO_3, 75 ml of dioxane, and 75 ml of H_2O was heated with 6 ml of 30% H_2O_2 under N_2 at 70° until the solution was colorless. The solution of ketol was cooled in an ice bath and treated with concentrated HCl and then H_2O saturated with SO_2 until the odor was retained. Nitrogen was passed in to eliminate excess SO_2 and 60 ml of 25% NaOH was added, followed by a solution of 30 g of $CuSO_4$ in 150 ml of H_2O. The mixture was heated on the steam bath for 30 min and filtered through Filter-Cel, and the residue was washed well with H_2O and dioxane until the filtrate came through colorless. The red filtrate was cooled in ice and acidified with concentrated HCl. On further cooling and stirring the product crystallized. The bright yellow crystalline product was collected and recrystallized from methanol (Norit). The yield of quinone, mp 102–103°, was 8.6 g (81%).

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Naphthoquinone Antimalarials. XXX.[1] 2-Hydroxy-3-[ω-(1-adamantyl)alkyl]-1,4-naphthoquinones[2]

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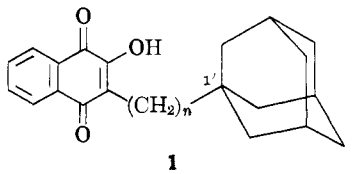
The naphthoquinones formulated were synthesized as candidate antimalarials of interest because of their analogy to the promising ω-cyclohexylalkyl derivatives.[1] The preparation of some of the acids required for diacyl peroxide alkylation of 2-hydroxy-1,4-naphthoquinone involved expansion of the already interesting chemistry of adamantane.

The unique properties of adamantane, which have aroused considerable interest in the hydrocarbon and its derivatives on the part of both chemists and pharmacologists,[3–6] prompted us to explore as possible antimalarial drugs the five ω-(1-adamantylalkyl) derivatives (**1**) of hydroxynaphthoquinone formulated



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(Table I). Each of these was prepared either by diacyl peroxide alkylation of 2-hydroxy-1,4-naphthoquinone or by the Hooker oxidation of the next higher homolog. The starting material, adamantane (**2**), is now available by the Schleyer synthesis[7] and is supplied by Aldrich Chemical Co.; for the gift of a first trial batch, we are indebted to Dr. Marvin Paulshock of the Du

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