(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%).

(22) L. F. Fieser, *J. Am. Chem. Soc.*, **48**, 2922 (1926).
(23) L. F. Fieser and M. Fieser, *ibid.*, **70**, 3215 (1948).

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

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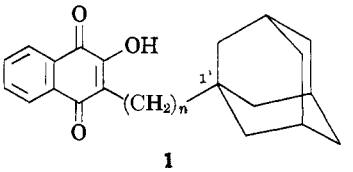
The naphthoquinones formulated were synthesized as candidate antimalarials of interest because of their analogy to the promising ω-cyclohexylalkyl derivatives.[1] The preparation of some of the acids required for diacyl peroxide alkylation of 2-hydroxy-1,4-naphthoquinone involved expansion of the already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

(1) For paper XXIX see L. F. Fieser, J. P. Schirmer, S. Archer, R. R. Lorenz, and P. I. Pfaffenbach, *J. Med. Chem.*, **10**, 513 (1967).

(2) The Harvard work was supported in part by a grant from the National Institutes of Health, CA-01696.

(3) R. C. Fort, Jr., and P. von R. Schleyer, *Chem. Rev.*, **64**, 277 (1964).

(4) K. Gerzon, E. V. Krunkalns, R. L. Brindle, F. J. Marshall, and M. A. Root, *J. Med. Chem.*, **6**, 760 (1963).

(5) R. T. Rapala and R. J. Kraay, Abstracts, 148th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1964, p 220.

(6) W. L. Davis, R. R. Grunert, R. F. Hoff, J. W. McGahen, E. M. Neumayer, M. Paulshock, J. W. Watts, T. R. Wood, E. C. Hermann, and C. E. Hoffmann, *Science*, **144**, 862 (1964).

(7) P. von R. Schleyer, M. M. Donaldson, R. D. Nicholas, and C. Cupas, *Org. Syn.*, **42**, 8 (1962).

TABLE I
2-HYDROXY-3-[ω-(1-ADAMANTYL)ALKYL]-1,4-NAPHTHOQUINONES (1)

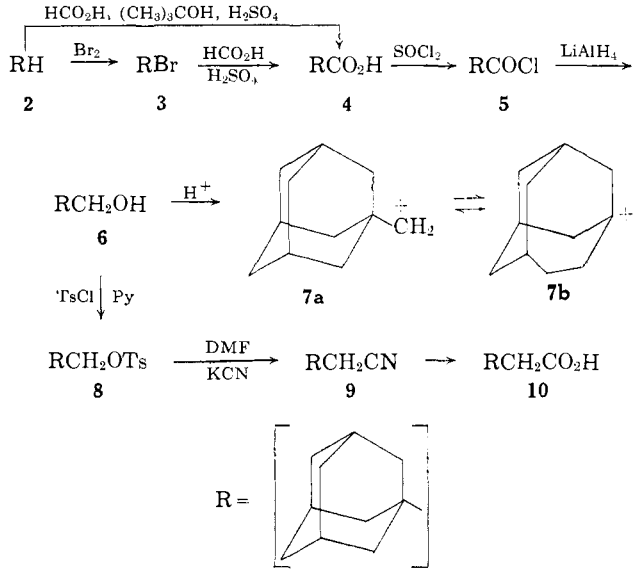
n	Mp, °C	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found
1	178–179	$C_{21}H_{22}O_3$	78.23	78.22	6.88	6.83
2	156–157	$C_{22}H_{24}O_3$	78.54	78.40	7.19	7.24
3	117–118	$C_{23}H_{26}O_3$	78.82	78.75	7.48	7.54
4	120–121[a]					
5	126–127	$C_{25}H_{30}O_3$	79.33	78.91	7.99	8.06

[a] Crude.

Pont group[6] that discovered the striking antiviral activity of 1-aminoadamantane.

Preparation of the Required Acids.—One key starting material, adamantane-1-carboxylic acid (**4**), was prepared in good yield both by carboxylation of adamantane with formic acid, *t*-butyl alcohol, and 96% H_2SO_4[8] and from 1-bromoadamantane, formic acid, and 96% H_2SO_4[9] (Scheme I). The next product desired, 1-adamantylacetic acid (**10**), was obtained by Stetter, *et al.*,[9] by submitting acid **4** to the Arndt–Eistert reaction, but since their yield was only 25% we sought an alternative synthesis. The route through the hydroxymethyl, bromomethyl, and cyanomethyl derivatives suffers from the fact that displacements of 1-hydroxymethyladamantane (**6**) involve major participation of either the adamantylmethyl carbonium ion **7a** or the rearranged ion **7b** and hence can yield either the normal adamantylmethyl bromide from **7a** or the homoadamantyl derivative from **7b**, depending upon the conditions.[10,11] Thus, in the reverse reaction, 1-homoadamantanol reacts with hydrogen bromide in acetic acid at 25° to give 1-bromohomoadamantane, whereas at 150° the product is 1-bromomethyladamantane. However, we found that this difficulty can be obviated by proceeding through the tosylate (**8**).

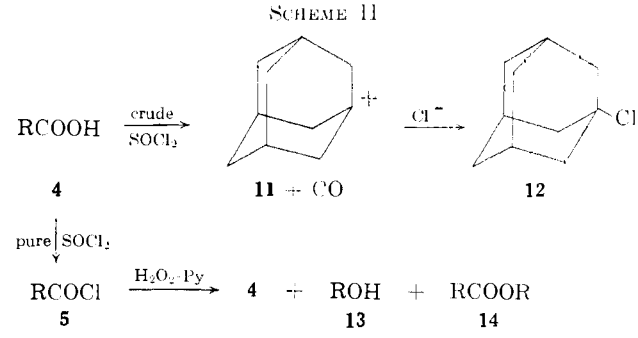
SCHEME I



1-Hydroxymethyladamantane (**6**) has been prepared previously[10] by the sequence: acid → acid chloride → ethyl ester → **6**. We tried direct reduction of the free acid with $LiAlH_4$ in tetrahydrofuran (THF) (reflux 24 hr), a method which proved highly satisfactory with the next two higher homologs, but obtained the alcohol **6** in only 15–20% yield. However, 1-adamantanecarboxylic acid chloride (**5**) when pure was reduced quantitatively to **6** by the same method. In his synthesis of twistane, Whitlock[12] displaced a mesylate group by cyanide in DMF at 120°; we applied the same procedure to the tosylate **8** and obtained the desired 1-cyanomethyladamantane in a yield of 92–96%. In contrast, acetolysis of the tosylate **8** at 120° is reported to give 1-acetoxyhomoadamantane in a yield of 94% and only 6% of 1-acetoxymethyladamantane.[11] There was no difficulty in effecting alkaline hydrolysis to the desired 1-adamantylacetic acid (**10**) in ethylene glycol at 150° and the over-all yield from acid **4** was 75%, or three times that previously realized. That no rearrangement had occurred was established by reduction of **10** with $LiAlH_4$ to a substance shown to be 1-hydroxyethyladamantane by the nmr spectrum (triplet for CH_2OH at τ 6.5).

In the course of the above work one interesting finding resulted from an attempt to convert crude adamantane-1-carboxylic acid (**4**) into the acid chloride by heating it with $SOCl_2$ without solvent at 50–60°. The product contained chlorine but showed no infrared carbonyl absorption, and analysis and comparison with an authentic sample showed it to be 1-chloroadamantane (**12**) (Scheme II). On repetition with acid **4** which had been purified by precipitation from a filtered solution in dilute alkali the product was the acid chloride **5**. The altered course of the reaction in the initial trial probably was due to the presence of a trace of sulfuric acid in the crude acid employed. Thus crude acid washed liberally with hot H_2O until the washings gave a negative test for sulfate ion on treatment with $SOCl_2$ gave the acid chloride. When pure acid was dissolved in concentrated H_2SO_4, recovered by addition of ice, filtered, dried, and treated with $SOCl_2$, the product was 1-chloroadamantane. Reaction of the pure acid (1 g) and concentrated H_2SO_4 (1 drop) with $SOCl_2$ (2 ml) afforded 1-chloroadamantane. The driving force for the acid-catalyzed decarboxylation apparently is the formation of the highly stabilized adamantyl carbonium ion **11**.[3]

SCHEME II



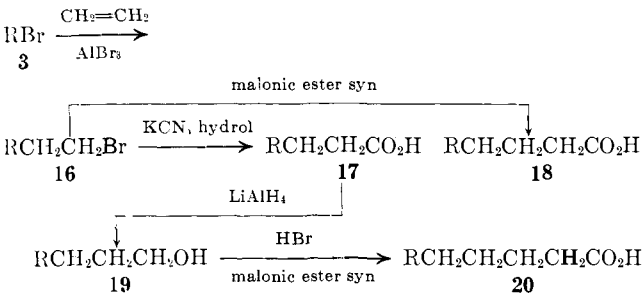
A further unusual reaction was encountered in an attempt to convert adamantane-1-carboxylic acid chloride

(8) H. Koch and W. Haaf, *Org. Syn.*, **44**, 1 (1964).
(9) H. Stetter, M. Schwarz, and A. Hirshhorn, *Ber.*, **92**, 1629 (1959).
(10) H. Stetter and P. Goebel, *ibid.*, **96**, 550 (1963).
(11) J. E. Norlander, S. P. Jindal, P. von R. Schleyer, and R. C. Fort, Jr., Abstracts, 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965.
(12) H. W. Whitlock, Jr., *J. Am. Chem. Soc.*, **84**, 3412 (1962).

(**5**) into the corresponding diacyl peroxide according to Silbert and Swern[13] by reaction with H_2O_2 and pyridine. The product was a mixture which on extraction of an ethereal solution with dilute alkali afforded adamantane-1-carboxylic acid as one component. The neutral fraction, obtained on evaporation of the ether on being sublimed and then crystallized, afforded 1-hydroxyadamantane (**13**). Further processing afforded also the ester **14**.

An attractive route to acids higher in the series than **10** was suggested by a report by Stetter and Goebel[14] that, under catalysis by $AlBr_3$, 1-bromoadamantane can be added to ethylene to give 1-(β-bromoethyl)-adamantane (**16**) (Scheme III). A slight modification of a procedure[9] for bromination of adamantane raised the yield of 1-bromoadamantane to 96%; the amount of bromine was reduced to half (added at once) and in the work-up sodium bisulfite was replaced by SO_2. Stetter and Goebel[14] conducted the addition to ethylene at −20 to −30° and obtained 1-(β-bromoethyl)adamantane (**16**) in 57% yield. In operating in this temperature range we experienced the difficulty that the product contained appreciable amounts of by-products, one of which appeared from nmr and ir spectra of the mixtures to be 1-(α-bromoethyl)adamantane. This difficulty was virtually eliminated when the reaction temperature was lowered to −75°, excess ethylene was avoided, and high-quality $AlBr_3$ was used. Under these conditions the yield usually was 65–70%. The β-bromoethyl derivative **16** was converted in 70% yield *via* the nitrile to β-(1-adamantyl)-propionic acid (**17**), which was obtained in only 10–20% yield by carbonation of a reaction mixture from lithium and the bromide **16** (and a few drops of *n*-butyl bromide). By application of the standard malonic ester synthesis,[15] the β-bromoethyl derivative **16** afforded γ-(1-adamantyl)butyric acid (**18**). Still higher acids were obtained by further application of the two synthetic sequences cited.

SCHEME III



The acids in this series exhibit an interesting alternation in melting point. Figure 1 shows that the melting points of the acids with an odd number of methylene groups are on a line below the line for the acids of the n = even series.

Alkylation of 2-Hydroxy-1,4-naphthoquinone.—For conversion of the new acids to the corresponding diacyl peroxides the procedures used previously by Fieser, Leffler, *et al.*,[16] proved less satisfactory than the newer method of Silbert and Swern[13] involving treatment of the acid chloride with H_2O_2 and pyridine. The diacyl peroxide alkylations proceeded essentially as in the earlier work, that is, peroxides from unhindered acids afforded 2-hydroxy-3-alkyl-1,4-naphthoquinones of satisfactory purity in moderate but adequate yield. Our attempts to prepare the first member of the series, 2-hydroxy-3-(1-adamantyl)-1,4-naphthoquinone, have been unsuccessful. The result of attempted conversion of **5** to the diacyl peroxide has been described. Attempted Hooker[17] oxidation of the next higher homolog (**1**, n = 1) likewise was unsuccessful. One of us previously encountered difficulty in attempted preparation of 2-hydroxy-3-cyclohexyl-1,4-naphthoquinone and obtained this compound only by a synthesis starting with the addition of butadiene to cyclohexyl-1,4-benzoquinone.[18]

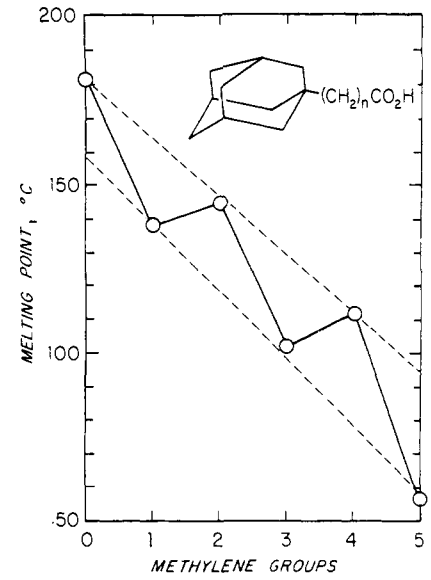


Figure 1.

Assays for Antimalarial Activity.[19]—The 2-hydroxy-3-(ω-cyclohexylalkyl)-1,4-naphthoquinones described in paper XXIX[1] and the 2-hydroxy-3-[ω-(1-adamantyl)-alkyl]-1,4-naphthoquinones were tested for antimalarial activity in *Plasmodium berghei* infected mice using the method of Thurston.[20] All medications were administered orally in graded doses once a day for 5 days to groups of five mice at each dose level.

Chloroquine, the control drug, consistently cleared the blood of parasites of all the mice for the entire test period of 28 days at a dose of 5 mg/kg. Similar results were achieved with 25 mg/kg of 2-hydroxy-3-cyclohexylheptyl- and 2-hydroxy-3-cyclohexyloctyl-1,4-naphthoquinone. The cyclohexylnonyl homolog was less active, since 100 mg/kg was required for complete clearance.

The best of the adamantane derivatives were **1**, n = 2, and **1**, n = 3. The former cleared the blood of all five mice at 40 mg/kg for 1 week but at 20 mg/kg only two of the five were cleared. Compound **1**, n = 2, cleared parasites in four of five mice at the 20

(13) L. S. Silbert and D. Swern, *J. Am. Chem. Soc.*, **81**, 2364 (1959).
(14) H. Stetter and P. Goebel, *Ber.*, **95**, 1039 (1962).
(15) R. Adams and R. M. Kamm, "Organic Syntheses," Coll. Vol. 1, John Wiley and Sons, Inc., New York, N. Y., 1941, p 250; E. E. Reid and J. R. Ruhoff, *ibid.*, Coll. Vol. II, 1943, p 474.
(16) L. F. Fieser, M. T. Leffler, *et al.*, *J. Am. Chem. Soc.*, **70**, 3178 (1948).
(17) L. F. Fieser and M. Fieser, *ibid.*, **70**, 3215 (1948).
(18) L. F. Fieser, *ibid.*, **70**, 3165 (1948).
(19) By D. A. Berbeiian and R. G. Slighter of the Sterling-Winthrop Research Institute.
(20) J. P. Thurston, *Brit. J. Pharmacol.*, **5**, 409 (1950).

mg/kg level for only 1 week; complete relapse was noted by the end of the 14th day. The other adamantane derivatives were even less active. In addition, some toxicity was noted in the case **1**, $n = 5$, at the 50-mg/kg level. Three of five mice died but the blood of the survivors was cleared of parasites for 1 week.

Experimental Section[21]

1-Bromoadamantane.[9]—A mixture of 25 g of adamantane and 35 ml of bromine was stirred and warmed gradually in an oil bath to a bath temperature of 110° and this temperature was maintained for 3 hr. A solution of the cooled mixture in 100 ml of CCl_4 was poured into ice–water (100 ml) and the flask was rinsed with 50 ml of this solvent. SO_2 was bubbled into the organic layer with swirling until the aqueous layer was colorless and the organic layer was only lightly colored. The aqueous layer was extracted with CCl_4 and the combined organic extracts were dried and evaporated at the water pump at 50°. A solution of the solid residue in 40 ml of methanol when cooled in Dry Ice–acetone deposited 36–37.5 g of crystals of satisfactory quality, mp 115–117° (sealed tube). Concentration of the mother liquor to a volume of 15 ml and ice cooling afforded an additional 1.5–2 g of 1-bromoadamantane; total yield about 96%. Sublimation gave 33 g of product, mp 118–119°.

Adamantane-1-carboxylic Acid.—The preparation of this acid from 1-bromoadamantane was carried out according to Stetter, *et al.*,[9] except that a solution of the bromide in hexane was added at once before dropwise addition of formic acid. Purification by extraction with 5% NaOH solution and acidification gave material satisfactory for the subsequent reactions (mp 181°[9]).

When 1-chloroadamantane was substituted for 1-bromoadamantane in this reaction the yield of the acid was less than 50%, but the unreacted chloro compound was all recovered.

Adamantane-1-carboxylic Acid Chloride.[9,22]—A mixture of 18 g of mineral acid free adamantane-1-carboxylic acid and 20 g of $SOCl_2$ was warmed in an oil bath to 50–60° and kept at that temperature for 1 hr. Excess reagent was distilled at the pressure of the water pump, benzene (20 ml) was added and distilled (water pump), and vacuum distillation of the residue gave 19 g of white solid, mp 54–56°. This hindered acid chloride shows remarkable stability. It can be suspended in aqueous alkali for some time with only minor hydrolysis. An ethereal solution can be shaken with aqueous alkali without appreciable decomposition. Hydrolysis can be effected by refluxing with aqueous alkali and acidifying the solution. Addition of H_2O to a solution of the acid chloride in pyridine gives a mixture of the acid and its anhydride separable by careful treatment with cold aqueous alkali to extract the carboxylic acid. The residue, mp 229–231°, was identified as the anhydride by comparison with a sample prepared by boiling the acid with acetic anhydride.[22]

Reaction of Acid Chloride 5 with H_2O_2 in Pyridine.—A solution of 5 g of **5** in 70 ml of ether was stirred at 0°, treated with 3 ml of 30% H_2O_2, and then 4 ml of pyridine was added by drops, with stirring at 0°, which was continued for 2 hr. The ethereal layer was washed with H_2O and on extraction with 5% NaOH afforded, after acidification, adamantane-1-carboxylic acid. The neutral fraction obtained after evaporation of the ether was sublimed and then crystallized from petroleum ether to yield **1-hydroxyadamantane,** mp 275–280°, identical with an authentic sample.[9]

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.59. Found: C, 78.65; H, 10.33.

The residue from the sublimation on crystallization from petroleum ether afforded **adamantane-1-carboxylic acid anhydride,** mp 229–230°, described above.

Evaporation of the petroleum ether mother liquor and crystallization of the residue from methanol gave a further product identified as the **ester** RCOOR (**14**): mp 275–277°; ir ester bands at 5.75, 8.1 μ.

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.05; H, 9.50.

In the nmr spectrum of this substance the proton bands are essentially the sum of those of 1-hydroxyadamantane and adamantane-1-carboxylic acid. The ester resisted alkaline hydrolysis but was hydrolyzed readily by pouring a solution in concentrated H_2SO_4 onto ice. The identity of the ester was later confirmed by its synthesis in pyridine.

Yields in this reaction were variable but all products reported above were always obtained. The results were the same with 30 or 90% H_2O_2. When no H_2O_2 was used no alcohol or ester were obtained.

1-Chloroadamantane was obtained by reaction of $SOCl_2$ as above with 5 g of unpurified adamantane-1-carboxylic acid. After removal of excess reagent, sublimation gave 4 g of product melting at 158–162°. Recrystallization from ethanol and resublimation raised the melting point to 169–170°.

Anal. Calcd for $C_{10}H_{15}Cl$: C, 70.36; H, 8.86; Cl, 20.78. Found: C, 70.22; H, 8.91; Cl, 20.87.

Conversion to adamantane-1-carboxylic acid is described above.

1-Hydroxymethyladamantane (6).—A solution of 10 g of adamantane-1-carboxylic acid chloride in 120 ml of THF was stirred with ice cooling during gradual addition of 2 g of powdered $LiAlH_4$. The mixture was then stirred and refluxed for 5 hr, cooled, and 5% NaOH solution was added dropwise to destroy excess $LiAlH_4$. The white precipitate was filtered off, the filtrate was concentrated to 50 ml, and H_2O was added to precipitate the alcohol **6**. The product, 8.1 g (97.5%), melted at 113–115° and was satisfactory for the next step. Recrystallization from aqueous methanol raised the melting point to 115–116°.[9]

1-Adamantylacetic Acid (10).—Treatment of the alcohol 6 with *p*-toluenesulfonyl chloride in pyridine gave 1-hydroxymethyladamantane tosylate,[9] mp 76–77°, in yield of 90–95%. A mixture of 16 g of the tosylate, 8 g of KCN, and 60 ml of DMF was stirred in an oil bath at 120° for 1 day. The reaction mixture was poured onto ice and the solid precipitate was collected and dried: 8.31 g (95%), mp 68–69°. Sublimation at atmospheric pressure gave 1-cyanomethyladamantane, mp 72–73°.

Anal. Calcd for $C_{12}H_{17}N$: C, 82.23; H, 9.78; N, 7.99. Found: C, 82.18; H, 9.78; N, 7.70.

A mixture of 10 g of the cyanomethyl compound, 15 g of KOH, and 50 ml of ethylene glycol was stirred and heated at 150° for 30 hr. The solution was poured into 300 ml of hot H_2O, 1 g of Norit was added, and the hot mixture was filtered. Acidification of the filtrate precipitated a solid which on crystallization from methanol afforded 9.7 g of adamantyl-1-acetic acid, mp 137–138°, lit.[9] 136°). The over-all yield from adamantane-1-carboxylic acid was 75%.

Reaction of the tosylate **8** with potassium acetate in DMF for 1 day at 120° gave unchanged **8** and 1-acetoxymethyladamantane: ir, 5.75 (acetate), 8.4, 8.5 μ (tosylate); nmr, τ 6.45 (CH_2OTs), 6.3 (CH_2OAc).

1-(β-Bromoethyl)adamantane (16).[9]—A flask was charged with 30 g of 1-bromoadamantane and 60 ml of hexane. The mixture was stirred magnetically in a Dry Ice–acetone bath at −75° and 15 g of freshly pulverized $AlBr_3$ of high quality was introduced (best results were obtained with hard yellow lumps supplied in a sealed ampoule). The weight of the flask with the three necks stoppered was recorded and ethylene was bubbled in with stirring at −75° until the gain in weight was 4.2 g (15–30 min). Addition of ethylene was then stopped but stirring was continued for 5 min longer. The mixture was transferred to a separatory funnel containing 50 g of ice and 25 ml of ether, with use of hexane and ether for rinsing. On shaking, both layers became nearly colorless. The water layer was separated and extracted with ether, the combined extract was washed (Na_2CO_3 solution) and dried ($CaCl_2$), and the solvent was evaporated. The residue, about 35 g (occasionally solid, contains 2–5 g of adamantane) on vacuum distillation afforded 26–28 g of material boiling at 90–115° (0.2–0.5 mm) and solid at room temperature. This was dissolved in hot methanol (125–150 ml) and allowed to cool to room temperature and then to −5° for several hours. The product, 18–20 g, mp 68–69°, was satisfactory 1-(β-bromoethyl)adamantane. More material (3–5 g) was obtained in a second crop after distillation and recrystallization; over-all yield 67%.

β-(1-Adamantyl)propionic Acid (17). A.—Excess Li (flakes) was added to an ethereal solution of 2 g of 1-(β-bromoethyl)-adamantane (**16**) and 2 drops of *n*-butyl bromide and the solution was decanted into a flask containing crushed Dry Ice. Work-up and crystallization from aqueous ethanol afforded about 100 mg of a carboxylic acid, mp 142–144°.

B.—A mixture of 10 g of **16**, 30 ml of ethanol, and 6 g of KCN was refluxed for 36 hr. KOH (15 g) was added and refluxing was

(21) Analyses by Elek Microanalytical Laboratories, Torrance, Calif.

(22) H. Stetter and E. Rauscher, *Ber.*, **93**, 1161 (1960).

continued for 36 hr. The mixture was added to hot H_2O and cooled, and the turbid aqueous solution was extracted with ether and acidified. A solid separated and on crystallization from aqueous methanol afforded 6 g (70%) of **17**, mp 142–144°. The analytical sample melted at 144–145°.

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.75; H, 9.59.

Use of triethylene glycol or DMF in place of ethanol reduced the reaction time to a total of 10 hr but gave an inferior product.

γ-(1-Adamantyl)butyric Acid (18).—Sodium (2.5 g) was dissolved in absolute ethanol (50 ml, distilled over Mg) with stirring and protection from moisture and 15 ml of redistilled malonic ester was added dropwise, followed by 15 g of 1-(β-bromoethyl-adamantane). After stirring and refluxing for 5 hr, most of the ethanol was distilled, a solution of 20 g of KOH in 30 ml of H_2O was added, and the mixture was refluxed for 5 hr. More ethanol was removed by distillation and the mixture was cooled, acidified (H_2SO_4), and extracted with ether. The residue from evaporation of the ether was heated in an oil bath at 170–180° for 1 hr for decarboxylation and a solution of the crude acid in dilute KOH was decolorized with Norit, precipitated, and crystallized from aqueous methanol to give 11 g of **18**, mp 100–102°.

Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.56; H, 9.89.

δ-(1-Adamantyl)valeric Acid (20).—Three grams of β-(1-adamantyl)propionic acid (**17**) was reduced with $LiAlH_4$ and the resulting alcohol (oil) was refluxed with 48% HBr (8 g) and H_2SO_4 (2 g) for 4 hr. The mixture was extracted with hexane, and the extract was washed with Na_2CO_3, dried, and evaporated. Distillation of the residue gave 2.9 g of the bromide, bp 105° (0.15 mm). The malonic ester synthesis, performed as for **18**, gave 2.1 g of **20**, mp 111–112° (aqueous methanol).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.27; H, 10.15.

ε-(1-Adamantyl)hexanoic Acid.—Application to γ-(1-adamantyl)butyric acid of the above sequence: acid → alcohol → bromide [bp 118° (0.18 mm)] → malonic acid derivative gave the hexanoic acid in about 75% yield. After decolorization of a petroleum ether (bp 38–52°) solution with Norit and slow evaporation of solvent, the acid was obtained as soft solid melting at 61–64°.

Anal. Calcd for $C_{16}H_{26}O$: C, 76.75; H, 10.47. Found: C, 77.46; H, 10.39.

Synthesis of 2-Hydroxy-3-(ω-adamantylalkyl)-1,4-naphthoquinones.—Each acid chloride was obtained by reaction of the acid with 20–30% excess $SOCl_2$ in ether and removal of the ether and excess reagent at 50° (water pump). Addition of benzene and redistillation removed traces of reagent. Thionyl chloride was also used without solvent.

The diacyl peroxides were made by reaction of the acyl chloride with 90% H_2O_2 in the presence of pyridine.[13] The yields were generally above 90% but in a few instances some acid accompanied the peroxide. In such a case the acid was recovered in usable form by extraction of an ethereal solution with dilute alkali. The peroxides are solids melting in the range 90–110° with evolution of CO_2.

The first step in the synthesis involves decomposition of a diacyl peroxide in the presence of an equivalent amount of 2-hydroxy-1,4-naphthoquinone (obtainable from commercially available 1,4-naphthoquinone by the method of Fieser).[18] Thus a mixture of the diacyl peroxide and hydroxynaphthoquinone in acetic acid was heated at 100–110° for 4 hr, the acetic acid was distilled *in vacuo*, and the residue was digested with ether. Filtration of the ether left a residue consisting chiefly of hydroxynaphthoquinone. The ether layer was extracted several times with 1% Na_2CO_3 to recover acid derived from hydrolysis of the diacyl peroxide. Further extraction with 2% NaOH and acidification afforded the alkylated quinone, which was purified by crystallization from methanol or ethanol or by chromatography on silica gel. Yields were generally 40–50%. However, the major by-product of an alkylation is the acid precursor, which can be recovered and recycled with substantial increase in yield. The fourth member of the series (n = 4, mp 120–121°) was obtained by Hooker oxidation and an analysis reported after termination of the work indicated too high an oxygen content, probably due to the presence of some of the intermediate ketol.

Potential Antimalarial Compounds.[1] IX.[2] Pyrimidine Derivatives of Urea and Guanidine

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Several substituted derivatives of arylbiguanide and arylamidineurea were prepared and cyclized to the corresponding pyrimidines as additional proof of the structure of arylamidineurea derivatives. Cyclization of the amidineurea moiety to pyrimidine reduces both the toxicity and the antimalarial activity in mice when compared with the starting compounds.

Some substituted amidineureas are active against *Plasmodium gallinaceum in vivo*.[2a,b] One of these compounds, 1-(*p*-nitrophenyl)-3-amidineurea hydrochloride[3] (I), was assessed for its toxicity and subsequently used in a field trial in Tanganyika by Dr. D. F. Clyde on more than 500 subjects infected with *P. falciparum*, *P. malariae*, *P. vivax*, and *P. ovale;* it gave fairly satisfactory results though it showed no advantage in comparison with proguanil.[4] A detailed investigation of this compound, the method of produc-

$$p\text{-}NO_2C_6H_4NHCONHC(=NH)NH_2 \cdot HCl$$
I

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(2) Parts I–VIII are as follows, respectively: (a) Y. Ch. Chin, Y. Y. Wu, B. Skowrońska-Serafin, T. Urbański, and J. Venulet, *Nature*, **186**, 170 (1960); (b) Y. Ch. Chin, Y. Y. Wu, B. Skowrońska-Serafin, T. Urbański, J. Venulet, and K. Jakimowska, *Bull. Acad. Polon. Sci.*, **8**, 109 (1960); (c) B. Skowrońska-Serafin and T. Urbański, *Tetrahedron*, **10**, 12 (1960); (d) T. Urbański, B. Serafin, and D. Księżna, Polish Patent, 48,020 (1962); (e) T. Urbański, B. Serafin, D. F. Clyde, K. Jakimowska, M. Wutkiewicz, P. Nantka-Namirski, J. Venulet, G. O. Schlütz, J. Splawiński, and T. Potaczek, *Tetrahedron*, **20**, *Suppl. 1*, 463 (1964); (f) B. Serafin, T. Urbański, and J. Żylowski, *ibid.*, 469 (1964); (g) K. Jakimowska, M. Wutkiewicz, and J. Venulet, *Acta Physiol. Polon.*, **15**, 701 (1964); (h) M. Wutkiewicz and J. Venulet, *ibid.*, **16**, 885 (1965).

(3) Nitroguanil, T 72.

(4) *World Health Organ. Tech. Rept. Ser.*, **320**, 9 (1961).