mg. of semicarbazone, m. p. 219–221° (mixed m. p. undepressed), and 22 mg., m. p. 185–190°. The total amount of crude semicarbazone corresponded to a 12–20% over-all yield.

Summary

6-Cyclohexyl-Δ^{1-9}-octalone-2 (VIII) has been prepared from 4-cyclohexylcyclohexanone by the Robinson–Mannich base synthesis. The use of hydroxymethylene ketones in this synthesis has been found to be advantageous, with over-all yields of 60–65% in this example.

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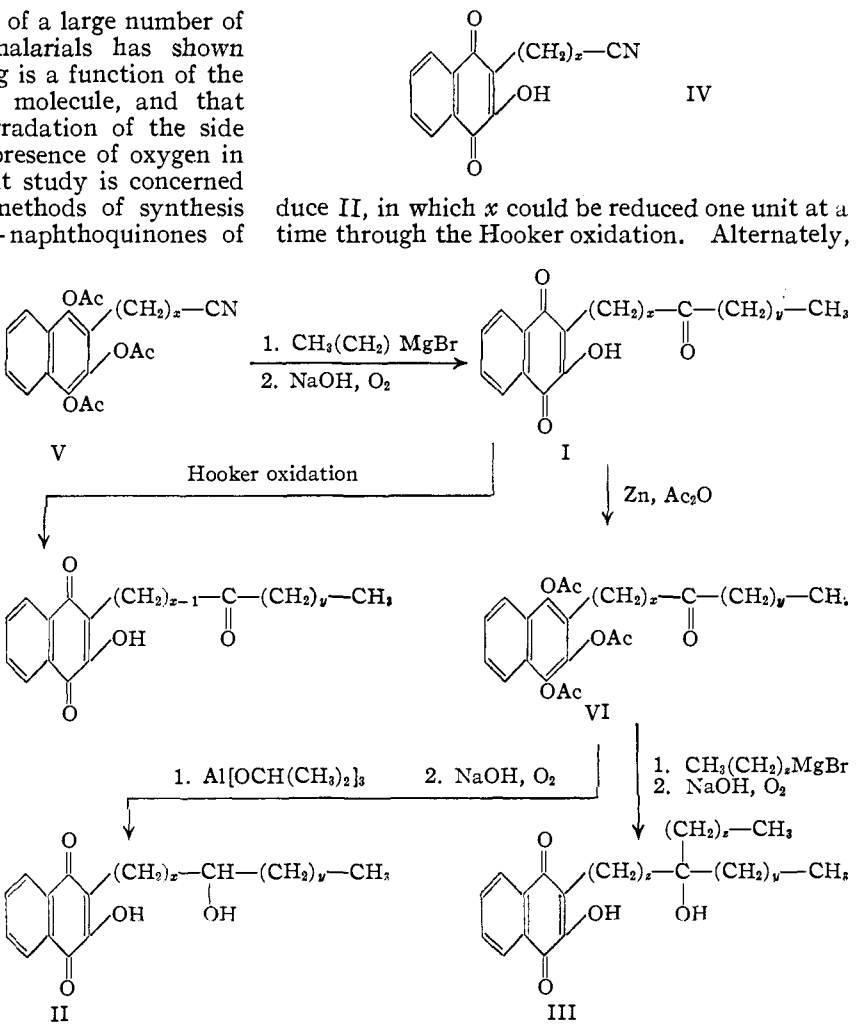
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Synthesis of 2-Alkyl-3-hydroxy-1,4-naphthoquinones with Oxygenated Side Chains[1]

BY DONALD J. CRAM[2]

The syntheses and testing of a large number of naphthoquinones[3] as antimalarials has shown that the potency of the drug is a function of the lipophilic character of the molecule, and that resistance to metabolic degradation of the side chain is dependent on the presence of oxygen in the side chain. The present study is concerned with the development of methods of synthesis of 2-alkyl-3-hydroxy-1,4-naphthoquinones of structures I, II and III, in which x, y and z can be varied independently. Such methods would permit a systematic approach to the balance of lipophilic character of the quinone against resistance to metabolic degradation of the molecule, these two variables working in opposition to each other.

The synthesis of IV (x = 10) by Fieser, *et al.*,[4] suggested the approach to the problem which has been worked out in the following fashion. Treatment of reductively acetylated nitrile quinones (V) with Grignard reagents produced ketones (I) in which x and y could be varied independently: x, by either starting with different nitriles or by applying the Hooker oxidation[5] to the ketones themselves; y, by using Grignard reagents prepared from different alkyl halides. The ketones were reductively acetylated and the ketonic group of the side chain reduced with aluminum isopropoxide to produce II, in which x could be reduced one unit at a time through the Hooker oxidation. Alternately,



the reductively acetylated ketones were treated with Grignard reagents of varying types to produce tertiary alcohols of type III.

Table I records the physical properties and analytical data obtained for the new compounds that were prepared as well as a reference to the procedure employed (typical procedures are given in the experimental section). All of the quinones were prepared from compound of type IV as a

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(3) Fieser, *et al.*, THIS JOURNAL, **70**, 3151–3244 (1948).

(4) Fieser, *et al.*, *ibid.*, **70**, 3208 (1948).

(5) Fieser, *et al.*, *ibid.*, **70**, 3215 (1948).

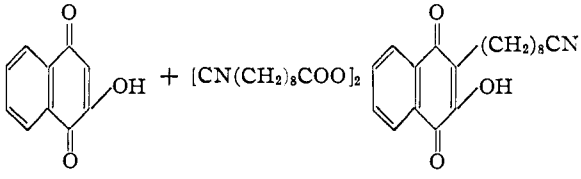
TABLE I

2-ALKYL-3-HYDROXY-1,4-NAPHTHOQUINONES AND DERIVATIVES

Compound		Procedure	Yield, %	M. p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
IV	$x = 8$	A	55	100–101	$C_{19}H_{21}O_3N$	73.29	6.80	73.44	6.74
IV[4]	$x = 10$	A	51	96–97	.....	...	..	...	..
V	$x = 8$	B	46	98–99	$C_{25}H_{29}O_5N$	68.32	6.65	68.62	6.47
V	$x = 10$	B	89	101	$C_{27}H_{33}O_5N$	69.36	7.11	69.48	6.95
I	$x = 8, y = 7$	C[a]	72	106–107	$C_{27}H_{38}O_4$	76.02	8.98	76.30	8.72
I	$x = 9, y = 0$	D	54	108–109	$C_{21}H_{26}O_4$	73.65	7.65	73.39	7.85
I	$x = 9, y = 7$	D	68	108–109	$C_{28}H_{40}O_4$	76.32	9.15	76.42	8.90
I	$x = 10, y = 0$	C	72	105–106	$C_{22}H_{28}O_4$	74.13	7.92	74.36	8.36
I	$x = 10, y = 1$	C	73	104–105	$C_{23}H_{30}O_4$	74.55	8.16	74.36	8.42
I	$x = 10, y = 2$	C	82	103–104	$C_{24}H_{32}O_4$	74.96	8.39	74.76	8.15
I	$x = 10, y = 3$	C	87	91–92	$C_{25}H_{34}O_4$	75.35	8.59	75.10	8.80
I	$x = 10, y = 7$	C	75	107–108	$C_{32}H_{42}O_4$	76.61	9.31	76.91	9.38
VI	$x = 8, y = 7$	B	81	81–82	$C_{33}H_{46}O_7$	71.71	8.39	71.70	8.46
VI	$x = 9, y = 0$	B	84	73–74	$C_{27}H_{34}O_7$	68.92	7.28	69.51	7.53
VI	$x = 10, y = 7$	B	92	79–80	$C_{38}H_{50}O_7$	72.13	8.65	72.07	8.42
II	$x = 8, y = 7$	E	88	95–96	$C_{27}H_{40}O_4$	75.66	9.41	75.52	8.33
II	$x = 9, y = 7$	D	25	109–110	$C_{28}H_{42}O_4$	75.97	9.56	76.25	9.86
II	$x = 10, y = 7$	E	86	95–96	$C_{29}H_{44}O_4$	76.27	9.71	76.37	9.91
III	$x = 8, y = 7, z = 0$	F	92	Oil	$C_{28}H_{42}O_4$	75.97	9.56	76.02	9.60
III	$x = 9, y = 7, z = 0$	F[b]	90	Oil	$C_{29}H_{44}O_4$	76.27	9.76	76.39	9.78
III	$x = 10, y = 7, z = 0$	F	93	Oil	$C_{30}H_{46}O_4$	76.55	9.85	76.37	9.91

[a] Also prepared by D, yield 53%, m. p. 106–107°. [b] Prepared by the action of octylmagnesium bromide on VI, $x = 9, y = 0$.

primary starting material. Compound VII was synthesized by methods analogous to the preparation of IV ($x = 10$).[4] The compound 9-amidononanoic acid,[6] was dehydrated and the product hydrolysed to give 9-cyanononanoic acid. This substance was converted to its solid peroxide (VIII), which was used to alkylate lawsone by procedures that have been developed by Fieser, *et al.*[3]



VIII VII

Experimental

9-Cyanononanoic Acid.—A mixture of 50 g. of the ethyl ester[5] of 9-amidononanoic acid and 25 g. of phosphorus pentachloride were heated at 100° under reduced pressure for one-half hour. The liquid was cooled, dissolved in benzene, and the solution was washed first with water, then with sodium carbonate solution, and again with water. The organic layer was dried, and evaporated under reduced pressure to an oil, which was dissolved in 245 cc. of a 0.78 *N* barium hydroxide solution in methanol; the mixture was allowed to stand for fifteen hours. The barium salt was then collected, dissolved in a minimum amount of water, and acidified with an excess of acetic acid. The product was crystallized from an ether–petroleum ether mixture; yield of half acid, 26 g., m. p. 49–50°. The melting point did not change on recrystallization.

Anal. Calcd. for $C_{10}H_{17}O_2N$: C, 65.54; H, 9.35. Found: C, 65.72; H, 9.22.

(6) This substance was prepared according to the procedure of Flaschentrager, *Z. physiol. Chem.*, **159**, 297–308 (1926).

2-(8′-Cyanoöctyl)-3-hydroxy-1,4-naphthoquinone (Procedure A).—A solution of 72 g. of 9-cyanononanoic acid, 70 g. of thionyl chloride (Eastman White Label), and two drops of pyridine in 300 cc. of dry ether was refluxed for three hours. The solution was evaporated to an oil under reduced pressure. Dry ether (300 cc.) was added to the oil, and the mixture was again evaporated to an oil, which was dissolved in 300 cc. of dry ether, treated with 10 g. of Darco and filtered.

The filtrate was cooled to −15°, and to the chilled solution, 97 g. of a cold solution of 33% hydrogen peroxide was added. The temperature was again brought to −15°, and a solution of 34 g. of sodium hydroxide in 165 cc. of water was added at such a rate that the temperature of the stirred mixture never went above −5°. When the addition was complete, the mixture was stirred for one-half hour at −10°, and the white solid that separated was collected, washed with cold water, and pressed as dry as possible. This substance was dissolved in a minimum amount of chloroform, the solution dried with magnesium sulfate and filtered. The filtrate was evaporated to one-third of the original volume, and five volumes of low-boiling petroleum ether was added. The peroxide that separated was dried (45 g.).

The peroxide was mixed with 23 g. of lawsone and 450 cc. of glacial acetic acid, and the mixture was heated to 95° for two hours. The solvent was then evaporated under reduced pressure, and the residue was dissolved in ether. The ether solution was washed first with a solution of sodium bicarbonate, then with water, and the quinone was extracted into a 2% sodium hydroxide solution, which was washed with petroleum ether and acidified. Crystallization of the quinone that separated (glacial acetic acid) produced 22.5 g. of yellow needles, m. p. 99–100°. The substance formed yellow staffs, m. p. 100–101°, when crystallized from ethanol.

This quinone formed a red color in alkaline solution (addition of sodium hydrosulfite dispelled the color), and a red-orange color in a solution of concentrated sulfuric acid.

2-(10′-Cyanodecyl)-1,3,4-triacetoxynaphthalene (Procedure B).—A mixture of 22.5 g. of 2-(10′-cyanodecyl)-3-hydroxy-1,4-naphthoquinone, 22.5 g. of zinc dust,

135 cc. of acetic anhydride and two drops of triethylamine were mixed, and allowed to stand for two days at room temperature. The mixture was warmed to 50°, filtered, and the cake was washed with boiling acetic acid. To the combined filtrates was added enough water to decompose the excess acetic anhydride, the mixture was cooled, and the product was crystallized; 27.5 g. of hard white granules, m. p. 101°.

2-(11'-Ketononadecyl)-3-hydroxy-1,4-naphthoquinone (Procedure C).—Octylmagnesium bromide Grignard reagent was made in the usual way from 21.2 g. of magnesium turnings, 170 g. of octyl bromide, and 300 cc. of dry ether. To this mixture, stirred in an atmosphere of nitrogen, 27.5 g. of 2-(10'-cyanodecyl)-1,3,4-triacetoxynaphthalene (dissolved in 300 cc. of dry benzene) was added over a period of one-half hour. Ether was distilled from the reaction mixture until the volume had dropped to 400 cc. and the solution was refluxed for three hours, cooled, and poured into a mixture of ice and 50% hydrochloric acid. The two layers were well mixed, separated, and the ether–benzene layer was extracted with a sodium hydroxide-saturated solution of 50% methanol and water. The aqueous layer was washed with petroleum ether, and an excess of brine was added. The sodium salt that separated was collected, washed with water and suspended in glacial acetic acid; 20 g. of canary-yellow needles separated: m. p. 107–108°. Further crystallization of the quinone did not alter the melting point. The color reactions of this substance are identical with those of other 2-alkyl-3-hydroxy-1,4-naphthoquinones.

2-(10'-Ketoöctadecyl)-3-hydroxy-1,4-naphthoquinone (Procedure D).—This procedure is modeled after that developed by Fieser[5] as an improvement of the Hooker reaction.

A solution of 1.2 g. of sodium carbonate in 25 cc. of water was mixed with 50 cc. of dioxane, the solution was warmed to 70°, and 4.54 g. of 2-(11'-ketononadecyl)-3-hydroxy-1,4-naphthoquinone was added. Nitrogen was swept over the surface of the liquid, and after five minutes, 2 cc. of a 33% solution of hydrogen peroxide was added. The solution was held at 70° with nitrogen sweeping over the surface until it turned colorless. The solution was then cooled, acidified with 30% hydrochloric acid (3 cc.), mixed with 3 cc. of water saturated with sulfur dioxide, and the excess sulfur dioxide was removed by bubbling nitrogen through the mixture. Ethanol (100 cc.), 35 cc. of 25% sodium hydroxide solution, and 10 g. of cupric sulfate dissolved in 50 cc. of water were added. This mixture was stirred for one hour, heated to 60° for ten minutes, filtered and acidified with acetic acid. The product was crystallized twice from glacial acetic acid; 3.0 g. (fine canary-yellow needles), m. p. 108–109°.

2-(11'-Hydroxynonadecyl)-3-hydroxy-1,4-naphthoquinone (Procedure E).—To a solution (130 cc.) of 1 *M* aluminum isopropoxide through which nitrogen was bubbling, 13 g. of 2-(11'-ketononadecyl)-1,3,4-triacetoxynaphthalene was added. The solution was heated to the boiling point and then slowly fractionated through a short column. Both acetone and isopropyl acetate, as well as some isopropyl alcohol, distilled. A total of 50 cc. of distillate was collected in a period of six hours. At the end of that time the solution in the flask was cooled, and poured into a mixture of 35 cc. of concentrated hydrochloric acid, 100 cc. of water and 100 g. of ice. After the aluminum salt had decomposed, the mixture was extracted with 150 cc. of ether, and the ether layer was washed with water. To the ether layer, 100 cc. of a 50% ethanol–water mixture saturated with sodium hydroxide was then added. Oxygen was bubbled through the solution for one-half hour, an excess of glacial acetic acid was added, and the product that separated was crystallized (glacial acetic acid); 8.7 g. (86% yield) of fine yellow needles of product was obtained; m. p. 95–96°. Further recrystallization of the compound did not alter the melting point. The color reactions of the substance are the same as those of other 2-alkyl-3-hydroxy-1,4-naphthoquinones.

2-(9'-Hydroxy-9'-methylheptadecyl)-3-hydroxy-1,4-naphthoquinone (Procedure F).—The methyl Grignard reagent was prepared in the usual way from 2 g. of magnesium turnings, 12 g. of methyl iodide and 200 cc. of dry ether. To this solution (stirred in an atmosphere of nitrogen), 3 g. of 2-(9'-ketoheptadecyl)-1,3,4-triacetoxynaphthalene dissolved in 200 cc. of dry benzene was added over a period of one-half hour. The mixture was refluxed for four hours, cooled and poured slowly into a mixture of saturated ammonium chloride solution and ice. The two layers were well shaken, and the ether–benzene layer was washed with dilute alkaline solution. The ether–benzene solution was then extracted with several portions of a 65% ethanol–water mixture saturated with sodium carbonate. The extracts were combined and washed three times with low-boiling petroleum ether. To this alkaline solution was then added two volumes of brine, and the quinone was extracted into pure ethyl ether. The ether layer was washed twice with distilled water, then with two portions of 5% sulfuric acid solution, and finally with four portions of distilled water. The solution was dried thoroughly with magnesium sulfate and filtered through hard paper into a weighed flask. The ether was evaporated under reduced pressure, and the last traces of solvent were removed by heating the oil under 1 mm. of pressure at 50° for three hours. The product (2.2 g.) was obtained in the form of a viscous yellow-orange oil. The color reactions of this compound are the same as those of other 2-alkyl-3-hydroxy-1,4-naphthoquinones.

Acknowledgment.—The author is indebted to Dr. L. F. Fieser for many suggestions regarding this problem.

Summary

Procedures have been developed for the preparation of 2-alkyl-3-hydroxy-1,4-naphthoquinones in which ketonic carbonyl groups, and secondary and tertiary hydroxyl groups can be placed in the alkyl side chains in any desired position, the alkyl side chains being of any desired length.

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